Real-time electrogram Analysis for Drivers of AtRial fibrillation (RADAR)
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Real-time electrogram Analysis for Drivers of AtRial fibrillation (RADAR)

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PROTOCOL SUMMARY

Title:	**Real-time electrogram Analysis for Drivers of AtRial fibrillation (RADAR)**
Objective:	This study will assess the ability of real time electrogram processing to identify driver domains to target for ablation in persistent AF patients
Design:	This is a prospective, multi-center, non-randomized, un-blinded, observational trial.
Enrollment:	Eligible subjects will be consented for participation in the trial prior to undergoing AF ablation. Patients are considered eligible if they have 1. ≥ 18 years of age. 2. Symptomatic or drug-refractory patients who are planned to undergo a catheter ablation procedure for persistent AF (ether a first procedure or a redo procedure). Patients may have either persistent AF (AF > 7 days) or long-standing persistent AF (AF > 1 year's duration). 3. Ability to understand the requirements of the study and sign the informed consent form. 4.Willingness to adhere to study restrictions and comply with all post-procedural follow-up requirements 5. Projected lifespan greater than 1 year. Patients will be excluded from the trial if: 1. Rheumatic heart disease, 2. Current intra-cardiac thrombus, 3. History of MI or CABG within 6 weeks 4. Unstable angina 5. CVA or TIA within 3 months 6. Contraindication to anticoagulation 7. Class IV HF; 8. Unable to sign consent 9. Projected lifespan of < 1 year 10. Women known to be pregnant or to have positive beta-HCG. 11. Participation in another study that would interfere with this study. Patients are considered enrolled once consented. Patients who do not undergo AF ablation within 90 days of enrolling will be considered to be screen failures. Sixty-five subjects are expected to be enrolled in the study.
Clinical Sites:	1. Mount Sinai Hospital, New York, NY 2. University of Colorado Hospital, Denver, CO 3. University of Kansas Medical Center, Kansas City, KS 4. Seton Medical Center, Austin, TX 5. Porter Adventist Hospital, Denver, CO 6. Massachusetts General Hospital, Boston, MA
Time Course:	Expected duration of patient enrollment is approximately 8 months to 1 year.
Subject Description:	Subjects will only be eligible for this study if they are ≥ 18 years of age and have a history or suspected history of AF
Primary Endpoints:	1. Acute Procedural Outcome Analysis: after performing procedures on the 65 patients 2. Clinical Outcome Analysis - Freedom from recurrent AF after one

	procedure at 12 months. 3. Clinical Outcome Analysis – Freedom of recurrent AF after two procedures at 12 months.
Additional Endpoints:	1. Clinical Outcome Analysis – Freedom from recurrent AT after one procedure at 12 months. 2. Clinical Outcome Analysis – Freedom from recurrent AT after two procedures at 12 months. 3. Total duration of RF ablation/Fluoro time/exposure/ procedure time 4. Procedure-related adverse events 5. Major Adverse Cardiac Events (MACE) 6. Serious Adverse Events
Follow-Up	1. Post-Ablation blanking period = 3 months 2. AAD use during blanking: Any AAD is permitted, but should be stopped by 8 weeks post-procedure. 3. Any documented post-blanking AF episode > 30 seconds would be considered as a failure 4. Patients will undergo continuous 7-14 day ambulatory monitoring at 3, 6 and 12 months 5. A second ablation procedure using the CMA software is allowed should a patient have recurrence of AF at any time during the 1 year follow-up period.
Principal Investigator:	Vivek Reddy , M.D. Icahn School of Medicine at Mount Sinai One Gustave L Levy Place, Box 1030 New York, NY 10029, USA
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1 CONTACT INFORMATION

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1.1 STUDY SITES & INVESTIGATORS

Site	Principal Investigator
1. Mount Sinai Hospital	Vivek Reddy, MD
2. University of Colorado Hospital	Duy Nguyen, MD
3. University of Kansas Medical Center	Dhanunjay Lakkireddy, MD
4. Seton Medical Center	Kristopher Heinzmann, MD
5. South Denver Cardiology	Sri Sunduram, MD
6. Massachusetts General Hospital	Moussa Mansour, MD

2 STUDY OBJECTIVE

This prospective, multicenter observational study will examine the ability of real time electrogram processing mapping to identify driver domains to target for ablation in persistent AF patients.

3 INTRODUCTION, RATIONALE

Catheter ablation targeting the PVs and/or PV antrum has been recognized as the cornerstone of AF catheter ablation. But for non-PV sources of AF, ablation strategies remain controversial although several types of targets have been proposed: non-PV triggers, continuous fragmented atrial electrograms, ganglionated plexi, and linear lesions. Of note, in a recent multicenter trial, STAR AF-2, PV isolation (PVI) alone resulted in successful maintenance of SR in only 59% of patients with persistent AF.[1] This clearly reveals the need for establishing strategies to address non-PV sources of AF in non-paroxysmal AF. However, extensive atrial ablation lesion sets, such as ablation of CFAE sites or linear lesions, have not proven effective. In the STAR AF-2 trial, after 18 months, the freedom from recurrent AF in patients assigned to PVI alone (59%) was not improved by the addition of either CFAE ablation (49%) or linear ablation (46%), p=0.15.[1] Accordingly, PV isolation is now the most commonly performed procedure for not only paroxysmal AF, but also for persistent AF. However, there is little consensus as to what one should do beyond PV isolation.

Localized driver domains perpetuating AF have been difficult to detect with conventional techniques because of the limits of sequential temporospatial mapping, intermittent firing, and, presumably, spatial meandering of rotor-like activity. Accordingly, we propose to use a new software Computational Mapping Algorithm (CMA) that enables high resolution temporospatial mapping of atria for the identification of drivers of AF. CMA receives data from standard of care, commercially available 3D Mapping Systems (St. Jude Ensite System) and catheters and processes the data in a unique way. Electrogram and anatomy data are fed from the commercially available 3D Mapping

System to an adjacent laptop computer, via an Ethernet connection, that is running CMA. Commercially available 3D Mapping Systems track the position (X,Y,Z) of catheters and each electrode on the catheters in a 3D coordinate system. Further, these 3D Mapping Systems measure the electrical activity (electrograms) of the heart tissue with which each electrode comes in contact, much like an oscilloscope. These 3D Mapping Systems draw the position of the catheters in 3D on a computer screen to allow the physician to see their position without the use of ionizing radiation (x-ray). These 3D Mapping Systems then facilitate a process of "painting" the inside of a heart chamber with a catheter to create a cloud of X-Y-Z points that is used to create a 3D geometry (anatomic image) of the heart chamber. Concurrently, the 3D Mapping System is continuously displaying on the computer screen the electrograms measured on the electrodes, enabling the physician to see and diagnose arrhythmia within the context of the 3D geometry and the position of all the catheters.

The electrogram data and the 3D geometry data gathered by the 3D mapping system are passed to the laptop running CMA via an established communication protocol and an Ethernet cable. CMA then processes the electrogram data and generates a map of where the potential AF driver domains are located and superimposes those potential AF driver domain targets onto the 3D geometry of the anatomy (provided by the 3D mapping system). This AF driver domain map is displayed on the laptop computer that sits next to the 3D mapping system. This process is referred to as AF Mapping throughout the rest of this document. CMA employs a unique pattern recognition technology on electrograms recorded by a standard coronary sinus catheter to sequence and synchronize electrograms recorded throughout a particular atrial chamber of the heart with a standard spiral or loop catheter. CMA then stitches together electrograms panoramically throughout a particular atrial chamber, enabling the operator physician to visualize all the electrical activity of a particular chamber and thus identify drivers of AF. Further, CMA amalgamates and overlays physiologic data gathered by the standard catheters such as tissue voltage, enabling the physician operator to integrate information and holistically interrogate the patient's condition to decide on a catheter ablation treatment strategy. This approach using CMA has the potential to reduce the amount of catheter ablation performed in a particular patient while focusing and targeting ablation on removing and/or isolating drivers of AF. This approach using CMA also has the potential to provide meaningful therapy options for patients with persistent AF that have undergone standard of care pulmonary vein isolation and still suffer from AF.

Extensive retrospective evaluation of CMA has been performed and published[3,4]. A total of 70 patients have been mapped using CMA at Mercy Hospital in St. Louis, MO, University of Kansas Medical Center in Kansas City, KS, and Mount Sinai Hospital in New York, NY. No adverse events were associated with the mapping process. Fifty-five of the 70 mapped patients produced analysis that was usable. The unusable patient data can be attributed to initial tuning of the signal processing algorithms. In this 55 patient series of data, patients were mapped using CMA and subsequently ablated with standard of care ablation at the operator's discretion, without the benefit of the CMA generated maps. Ablation techniques included Wide Area Circumferential Ablation (WACA), empiric Complex Fractionated Atrial Electrogram (CFAE) Ablation and empiric linear lesion Ablation. Retrospectively, the data was analyzed to see the effects of incidental ablation of CMA identified AF Driver domains. Ultimately, the use of CMA generated maps of AF driver domains may serve to reduce the amount of empiric CFAE and linear lesion ablation and improve outcomes in persistent AF patients.

The Abstract and Conclusion sections from the journal article entitled ***"Characterization of Drivers in Patients with Persistent Atrial Fibrillation to Identify Substrate Based Rotor Ablation Targets"*** serve as a good overview of CMA and associated retrospective clinical findings:

ABSTRACT: *Recent clinical trials have shown that targeting rotors and focal impulses (FIs) during atrial fibrillation (AF) ablation improves outcomes. This study evaluated whether a novel computational mapping algorithm (CMA) could identify FIs and rotors, and characterize rotors when incidental ablation resulted in rhythm changes. Three-dimensional (3D) left atrial electroanatomic maps were created from signals recorded from multipolar circular mapping catheters in 61 patients undergoing persistent AF ablation. Forty of 61acquired patient datasets were of adequate quality for analysis CMA, employing an AF pattern recognition algorithm, creating 3D panoramic AF maps identifying drivers of AF (FI and rotors) post procedure. Rotors were further classified as substrate (SBR) or non-substrate based (NSBR) on the basis of rotor stability, proximity to voltage transition zones and complex fractionated atrial electrograms (CFAEs). Incidentally ablated identified AF drivers, including SBRs and NSBRs, were evaluated for rhythm changes. A total of 172 drivers were identified in 40 patients (4.3± 2.2 drivers/patient). Seventy percent were rotors (120/172) and 30% were FIs (52/172). Sixty-seven percent of rotors were classified as SBR vs 33% as NSBR. Incidental ablation of SBRs resulted in rhythm change 91% of the time versus only 24% of the time for NSBR ($p<0.0001$).*
CONCLUSIONS: *Incidental ablation of SBRs resulted in rhythm change significantly more frequently than ablation of NSBRs. Identification of drivers and classification of rotors based on substrate properties may allow a more tailored ablation approach in patients with persistent AF.*

The following is a description of what each Mapping System will perform during Persistent Atrial Fibrillation cases:

St. Jude Ensite System:

1. Tracking the position of the catheters as they travel through the heart and displaying them on a screen in 3D so that X-Ray is not needed (or reduced).
2. Create a shell of the heart chamber and display on a screen so that the physician knows where the catheters are in relation to the anatomy (shell of heart chamber).
3. Display electrogram signals from all the electrodes on the different catheters in the heart.

These three features will be used for the entire case to determine where to ablate tissue.

AFTx System:

1. Receive the heart chamber shell from St Jude Ensite.
2. Receive the electrogram signals from St Jude Ensite.
3. Use proprietary software algorithms to create a map of where the potential sources causing AF are within the chamber and highlight them on the heart chamber shell.

The physician will then navigate a catheter to those highlighted areas (using St Jude Ensite) and further interrogate the areas for suspicious electrograms and decide if it is appropriate to ablate the tissue. Ultimately, St. Jude Ensite is the final tool used to decide whether to ablate or not.

5 SCHEDULE OF TREATMENT AND TESTS

TABLE 1: SCHEDULE OF TREATMENTS AND TESTS:

	Baseline	Procedure	Discharge	Event monitor 3 months	Event monitor 6 months	Event monitor 12 months
Type of visit	Office	Hospital		Office	Office	Office
Informed Consent	X					
Brief History & Physical	X			X	X	X
TTE	X					
EKG	X		X	X	X	X
1-wk Ambulatory Monitoring				X	X	X
Medications	X	X	X	X	X	X
Adverse Events		X	X	X	X	X

6 ENDPOINTS

6.1 Primary Endpoint

Primary Endpoints:	1. Acute Procedural Outcomes as defined by termination of Atrial Fibrillation into NSR or AT > 5min. 2. Clinical Outcome Analysis - Freedom from recurrent AF after one procedure at 12 months. 3. Clinical outcome Analysis – Freedom from recurrent AF after two procedures at 12 months.
Additional Endpoints:	1. Clinical outcome Analysis – Freedom from recurrent AT after one procedure at 12 months. 2. Clinical outcome Analysis – Freedom from recurrent AT after two procedures at 12 months. 3. Total duration of RF ablation/Fluoro time/exposure/ procedure time 4. Procedure-related adverse events 5. Major Adverse Cardiac Events (MACE) 6. Serious Adverse Events

7 STUDY SUBJECTS

7.1 INCLUSION CRITERIA

1. ≥ 18 years of age.
2. Patients are considered eligible if they have symptomatic or drug-refractory AF and are planned to undergo a catheter ablation procedure for persistent AF (ether a first procedure or a redo procedure). Patients may have either persistent AF (AF > 7 days) or long-standing persistent AF (AF > 1 year's duration).
3. Ability to understand the requirements of the study and sign the informed consent form.
4. Willingness to adhere to study restrictions and comply with all post-procedural follow-up requirements
5. Projected lifespan greater than 1 year.

7.2 EXCLUSION CRITERIA

1. Rheumatic heart disease
2. Current intra-cardiac thrombus
3. History of MI or CABG within 6 weeks
4. Unstable angina
5. CVA or TIA within 3 months
6. Contraindication to anticoagulation
7. Class IV HF
8. Unable to sign consent
9. Projected lifespan of < 1 year
10. Women known to be pregnant or to have positive beta-HCG.
11. Participation in another study that would interfere with this study.

8 SAMPLE SIZE

This safety and efficacy study will enroll 65 patients across 1-5 US centers and 1-2 OUS centers. This number has been determined on the basis of study feasibility and not by statistical means. This is a feasibility study of the mapping system performance in which the sample size of the clinical investigation is intended to provide preliminary estimates of safety and performance.

The study will involve two cohorts. The first cohort will be composed of patients with persistent AF > 7 days but < 1 year's duration. The second cohort will be composed of up to 15 patients with long-standing persistent AF (AF > 1 year's duration).

9 PATIENT ENROLLMENT AND WITHDRAWAL

Patients meeting the study inclusion criteria will be identified in the outpatient or inpatient setting by investigators. Patients will be followed by one of the study site principal or co-investigators.

The study will typically be described (including the risks and benefits) during the initial clinic or hospital visit. Consent will typically be obtained at the time of the initial assessment if it is clear that the patient truly understands the nature of the study. Alternatively, the patient will be encouraged to take a copy of the consent form home to contemplate whether he/she would like to be enrolled in the study. Only patients who voluntarily provide consent will be included in this study. Consent will be obtained prior to undergoing the ablation procedure. Patients will be able to withdraw from the study at any point without compromising their medical care. All data will be de-identified and protected in accordance with institutional and HIPAA guidelines, including 1) de-identification of all geographic subdivisions smaller than a state; 2) all elements of dates related to the individual; 3) telephone and fax numbers; 4) email addresses; 5) social security number, medical record, health plan beneficiary, account, and certificate/license numbers; 6) vehicle identifiers; 7) device identifiers; 8) URLs and IP addresses; 9) biometric identifiers; and 10) photographic images.

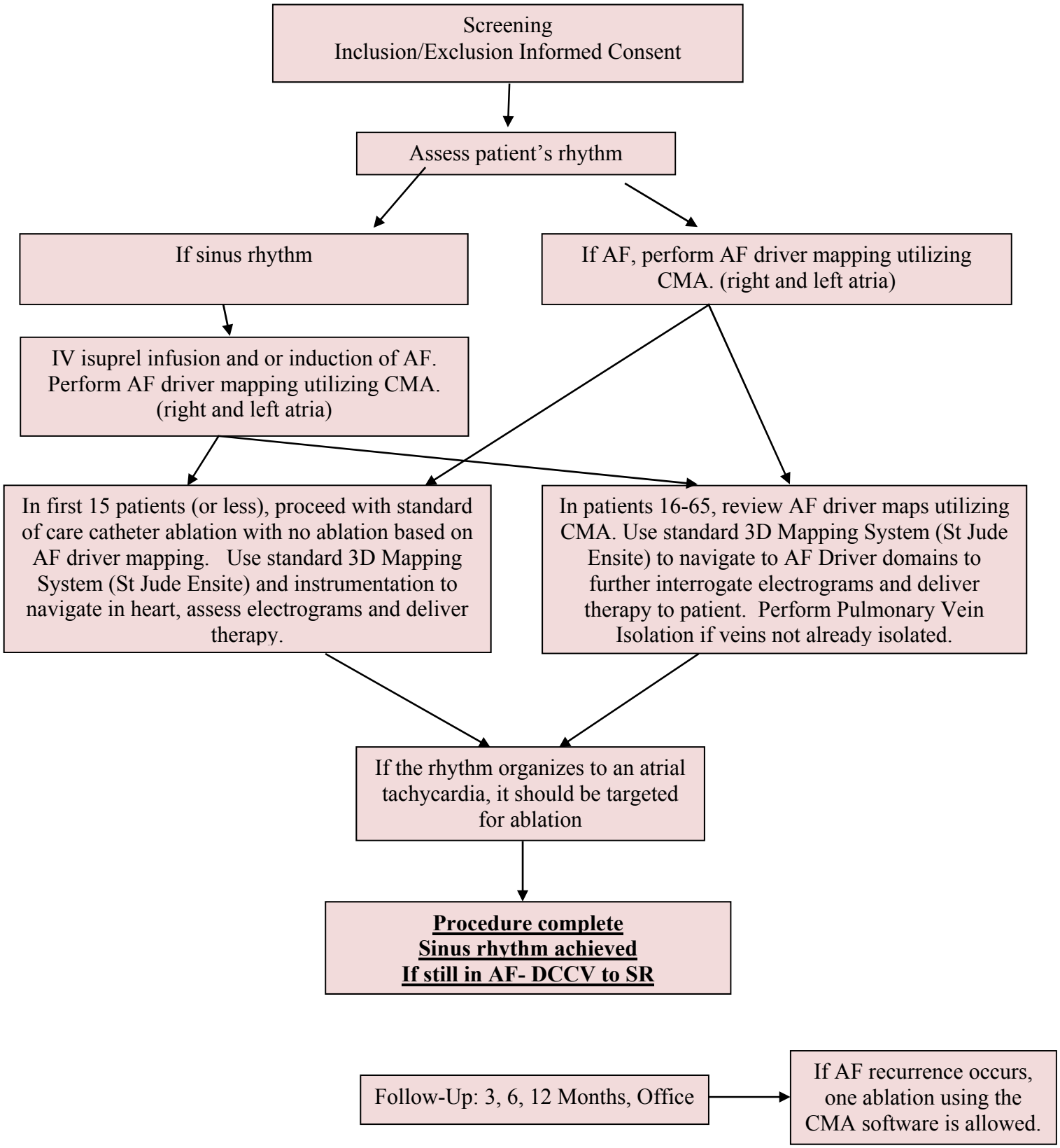
Eligible subjects will be consented for participation in the trial prior to undergoing AF ablation. Patients are considered enrolled once consented. Patients will be followed for 12 months. Patients who do not undergo an ablation procedure within 90 days of enrolling will be considered to be screen failures. Additionally, if a patient does not have any ablation performed that is a result of the mapping completed by the CMA software, the patient will be considered a screen failure. Patients who are deemed to be screen failures may be considered for re-enrollment should they require a later AF ablation procedure.

9.1 MAPPING COHORTS

In the first cohort of up to 15 patients, AF mapping (utilizing CMA) will be performed but will not be utilized to guide the ablation procedure. That is, ablation will be based on standard approaches only. The purpose of this initial cohort is to validate the software and mapping procedure. Brief operator learning curve relating to the mapping procedure is expected. Proper sampling is necessary in order to achieve full spatial coverage of an entire chamber. The benefit of the technology includes infinite spatial resolution with unlimited multiple synchronized sample locations throughout the atria, but that unlimited sampling must be balanced with time added to the procedure for sampling and software computation. The first cohort of patients is designed to allow for this learning curve to be normalized between the catheter operators and the software operators. Performing the mapping alone, Kurian T, et al. have seen no procedure related adverse events in over 61 patients. As such, it is safe and worthwhile to take an initial cohort of patients to normalize the mapping process in persistent AF patients where the chambers are often diseased, complex and dilated requiring operator skill to

sample an entire chamber appropriately. The consistent convergence of the CMA software within five minutes signifies that a balance has been struck between the amount of sampling data supplied to the software and the operator's satisfaction in adequate sampling of the patient's anatomy. Over the course of these cases, if the software algorithm is converging to a solution consistently within five minutes of processing time, the size of this validation cohort may be reduced to less than 15.

In the second cohort of patients (potentially patients 16-65), AF mapping (utilizing CMA) will be performed and used to point the operator to regions within a heart chamber that should be interrogated further for suspicious electrogram activity, as measured by the St. Jude Ensite System, and ablated if the suspicious electrogram activity persists.



- **Empiric ablation (CFAE or linear ablation) is not permitted**

10 STUDY PROCEDURES

10.1. PRE-PROCEDURE EVALUATION

Patients will be consented for the study in either the inpatient or outpatient setting. The following tests and procedures will occur before the ablation as a routine part of pre-procedural medical assessment:

- Recording of patient medical history (including details of previous ablation)
- Recording of patient AF/AT recurrences
- Recording medication history (including all anti-arrhythmic drugs used and duration of use)
- Obtain β-HCG in females of child bearing age the morning of the procedure as per usual clinical practice
- Baseline assessment of arrhythmia burden and type: Office/inpatient records, ICD interrogation report
- Collect any pre-procedural echocardiograms
- Baseline laboratory, including complete blood count, standard electrolyte panel, renal function
- Baseline TTE to assess any adverse conditions.
- Consent must be obtained before the procedure.

10.2 PRE-PROCEDURE MEDICATION MANAGEMENT

It will be recommended that all subjects take therapeutic doses of anticoagulation for at least 3 weeks prior to their catheter ablation procedure. For those who are not taking anticoagulation for this length of time prior to their procedure, a pre-procedural transesophageal echocardiogram will be recommended if the subject presents in atrial fibrillation and has CHA2DS2-VASc score ≥1.

For subjects who are taking warfarin at the time of the ablation, it will be continued uninterrupted through the procedure. For subjects who are taking novel oral anticoagulants (NOACs) with twice daily dosing (dabigatran, apixaban), the morning dose on the day of the ablation will be held, and the NOAC will be resumed the evening after the procedure at the primary operator's discretion. For subjects who are taking NOACs with once daily dosing (rivaroxaban), the last dose will be the night prior to the procedure, and the NOAC will be resumed the evening after the procedure at the primary operator's discretion.

Every effort will be made to discontinue AADs prior to ablation.

10.3 PROCEDURAL DETAILS

- Patients will be brought to the electrophysiology laboratory in a fasting state

- Patients will under ECG to determine rhythm – i.e. Sinus rhythm v Atrial fibrillation

- Patients will undergo electrophysiology study using a mapping system and ablation as per standard practice. Placement of trimmed patches will be placed in standardized locations.

- The AF ablation procedure will be performed using any of the following marketed catheters: (Note: the first 3 catheters listed below are FDA approved for the treatment of paroxysmal

atrial fibrillation but not persistent The FlexAbility is only approved for treatment of typical atrial flutter.)

  - Biosense-Webster Smart Touch SF
  - Biosense-Webster Thermocool SF
  - St. Jude Medical TactiCath Quartz
  - St. Jude Therapy FlexAbility

- Intraprocedural anticoagulation will be administered with intravenous heparin, with target ACT levels ≥350 sec during any period in which catheters are positioned in the left atrium.

- For all patients, the initial ablation lesion set will consist of pulmonary vein isolation, assessed by entrance block during electrode recordings in the PV and by exit block during pacing from the PV.

- It will be suggested to operators that energy and duration of any RF lesions delivered either during PV isolation or subsequent ablation of drivers should be titrated to a goal tissue impedance drop ≥10 ohms from baseline during each lesion. Additionally, acute elimination of all local electrograms at ablation sites will be encouraged.

Presenting rhythm - Sinus

- AF is induced by pacing
- Electro anatomic maps of right and left atria are created and PV isolation is assessed with multielectrode mapping catheter.
- Once this occurs - **Map** $_{\textbf{inducedAF}}$ is obtained using the CMA software running on the laptop adjacent to the 3D Mapping System.
- Ablation of drivers can be initiated in chamber with faster CL or with greater number of identified drivers
- Drivers can be addressed in order of importance as suggested by maps.
- Periodic reassessment of TCL in LAA and RAA to be done to help direct operator to chamber of interest- e.g. if there is significant gradient between RAA and LAA such that RAA is faster then drivers can be pursued in RAA prior to completion of all driver regions of LA
- All drivers are to be sequentially ablated or isolated using the St Jude Ensite system to navigate ablation catheter to the anatomic region identified by the AF mapping as a potential driver domain, assessing the local electrograms via St. Jude Ensite system and delivering ablation via St. Jude ablation catheter. If rhythm is still not organized then ablation sites are visited again to ensure adequate ablation.
- Then, Re-assess rhythm
- If AF persists, Real time electrogram processing mapping should be repeated (**Map**$_{\textbf{Re1,2....}}$) and additional driver regions targeted.

- If the rhythm organizes to an atrial tachycardia, it should be targeted for ablation

- If rhythm is still is in AF despite elimination of all drivers based on repeated Maps or if no drivers are localized- the patient will be cardioverted to sinus rhythm (Number of remaps is at the discretion of operator)

- If during AF or AT ablation- the patient reverts to sinus rhythm- ablation is complete at that site as per operator definition of sufficient ablation. Additional drivers localized during mapping will also be targeted despite sinus rhythm

- Empiric ablation (CFAE or linear ablation) is not permitted

Presenting rhythm - Atrial fibrillation

- Electro anatomic maps of right and left atria are created and PV isolation is assessed with multielectrode mapping catheter.
- **Map** $_{\text{spontAF}}$ will be acquired CMA software running on the laptop adjacent to the 3D Mapping System.
- Prior to ablation- LAA and RAA cycle length are to be measured over 10 beats.
- Ablation of drivers can be initiated in chamber with faster CL or with greater number of identified drivers
- Drivers can be addressed in order of importance as suggested by maps.
- Periodic reassessment of TCL in LAA and RAA to be done to help direct operator to chamber of interest- e.g. if there is significant gradient between RAA and LAA such that RAA is faster then drivers can be pursued in RAA prior to completion of all driver regions of LA
- All drivers are to be sequentially ablated or isolated using the St Jude Ensite system to navigate ablation catheter to the anatomic region identified by the AF mapping as a potential driver domain, assessing the local electrograms via St. Jude Ensite system and delivering ablation via St. Jude ablation catheter. If rhythm is still not organized then ablation sites are visited again to ensure adequate ablation.
- Then, re-assess rhythm
- If AF persists, real time electrogram processing mapping should be repeated (**Map**$_{\text{Re1,2....}}$) and additional driver regions targeted. (previous driver regions may be revisited to ensure elimination of complex EGMs)
- If the rhythm organizes to atrial tachycardia this will be ablated and if rhythm converts to sinus – then procedure is deemed complete. Additional drivers are to be targeted based on **Map** $_{\text{Re1,2}}$
- If presenting rhythm is AF- and M**ap** $_{\text{spontAF}}$ has been acquired; induced AF map based driver ablation is not required unless this occurs spontaneously
- Empiric ablation (CFAE or linear ablation) is not permitted

10.4 POST-PROCEDURE

10.4.1 POST-PROCEDURE FOLLOW UP

- Discharge criteria decisions will be made at the discretion of the primary operator per current guidelines.
- Medication and adverse event review will be performed prior to discharge.
- Complications including vascular, stroke, heart failure, pericardial effusion, tamponade, bleeding, and death will be documented.
- The post ablation blanking period will last 3 months only - any AAD is permitted but should be stopped by 8 weeks after the study procedure
- The total number of episodes of post-blanking AT or AF episode > 30 seconds will be recorded

- Patients will undergo continuous 7 day ambulatory monitoring at 3, 6 and 12 months
- Review of medications and adverse events will be performed at the 3, 6 and 12 month follow up
- At any time during the follow-up period, patients will be allowed a second ablation procedure using the CMA software should recurrence of AF occur. Data from the second procedure will be recorded.

10.4.2 POST-PROCEDURE MEDICATION MANAGEMENT

- Standard cardiovascular medications are left up to the discretion of the investigator.
- Therapeutic anticoagulation beyond the requisite 2 month post-procedure time point will be at the discretion of the patient's physician.
- The post ablation blanking period will last 3 months only - any AAD is permitted but should be stopped by 8 weeks after the study procedure

11 SAFETY

The local site Principal Investigator will oversee the safety of the study at his/her site. The Data Coordinating Center will provide on-site and remote monitoring to assess safety issues at each site. Additionally, a Data Monitoring Committee will review safety data on a 6 month basis or as needed. A detailed tally of adverse events will be kept and are defined below.

Adverse Events

An adverse event is any undesirable clinical occurrence in a study patient, whether or not it is related to the study intervention. Any condition that was recorded as pre-existing is *not* an adverse event unless there is a change in the nature, severity or degree of the condition.

Serious Adverse Event

Serious adverse events are defined by FDA regulation as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; results in a congenital anomaly/birth defect; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization.

12 RISKS

Patient confidentiality risks associated with any research study are minimal and include: breach of confidentiality and loss of personal data.

<u>Potential Risks Associated with AF Ablation</u>

- Death: End of Life
- Stroke (also called Cardiovascular Accident or CVA): may cause an interruption in the blood supply to a part of the brain
- Pericarditis: inflammation may occur in the outer lining of the heart (<1%).
- Cardiac perforation causing pleural effusion or tamponade: fluid build-up around the heart. A hole in your heart wall (*perforation*) could result in bleeding into the sac, called the pericardium, which surrounds your heart (*cardiac tamponade*). This may be treated by insertion of a needle, through your chest wall, into the sac and removal of the blood. This type of hole sometimes requires surgical repair
- Heart Valve injury (also called Valvular Damage/Insufficiency): an injury to a valve structure resulting in a loss and/or worsening of function (e.g., worsening of regurgitation score or prolapse) (<1%).
- Acute Pulmonary edema: fluid accumulation (build-up) in the lungs (<1%).
- Pulmonary embolism: blockage of a pulmonary artery; a blood clot from a vein may get stuck in the lungs. This is usually treated with drugs (<1%).
- Vascular access complications: an obstruction or perforation or damage to the vascular (blood vessel) system (2%).
- Arterial/venous thrombus: clot formation in the artery or vein (1.5%).
- AV fistula: an abnormal passageway (such as a hole) between an artery and a vein; this may allow blood to go between the arteries and veins and not through the entire body. This may cause some part of the body to not receive the usual amount of blood. This may heal on its own, but may require surgical repair (1.5%).
- Catheter insertion site hematoma: bleeding or bruising from the site of catheter placement. This may go away without treatment, but may require manual compression or surgical repair. If excessive bleeding at the site of the catheter placement continues, this could result in anemia requiring medical intervention (2%).
- Hypoxia: reduced oxygen supply to tissue (<1%).
- Infection, Localized or systemic: an infection may occur anywhere an incision or cut is made during the procedure (<1%).
- Peripheral venous thrombosis: blood clots in the vein (<1%).
- Phrenic nerve damage: damage to the nerve that controls the diaphragm and may affect your breathing. Symptoms may be temporary but in some cases can be permanent (respiratory arrest) (<1%).
- Pneumonia: infection of lungs or gathering of fluid in the lungs (<1%).
- Pseudoaneurysm: development of a false pouch in the vessel wall. This can be caused by movement of catheters in the blood vessels. This may heal on its own, but sometimes need surgical repair (<1%).
- Radiation injury resulting in dermatitis (skin burns): (<1%).
- Respiratory failure: damage to breathing that can be permanent (respiratory arrest) (<1%).
- Radiation exposure during the fluoroscopic imaging of the catheters during ablation: this may slightly increase the lifetime risk of developing a fatal malignancy or a genetic defect in offspring (<1%).
- Fluid overload: excessive fluid built up could result in pulmonary (lung) edema; congestive heart failure (CHF) may occur or may be exacerbated (worsened) due to delivery of sterile salt water (saline) during the procedure (these risks are specific to open irrigated ablation catheters) (1.5%).

<u>Potential Risks Associated with investigational mapping system:</u>

- The additional investigational mapping done for this study may cause patients to have a prolonged procedure time. The patients may be exposed to additional anesthesia as a

result of this prolonged procedure time.

- Potential harms of a more extensive bi-atrial lesion set over PV isolation include prolonged procedure time and atrial stunning.

13 STUDY MANAGEMENT

13.1 Study Data Collection and Processing

The Case Report Form (CRF) is an integral part of the study and subsequent reports. The CRF must be used to capture all study data recorded in the patient's medical record. The CRF must be kept current to reflect patient status during the course of the study. Patients will be identified by a 5-digit number and their initials. The investigator must keep a separate log of patient names and medical record numbers (or other personal identifiers) for their own reference. All study-related documents (CRFs, source medical records, regulatory binder) must be kept in a secure, locked environment with access limited to study personnel only.

The PI is responsible for ensuring the following: 1) adherence to the protocol; 2) verifying adherence to local regulations on the conduct of clinical research; and 3) ensuring completeness, accuracy, and consistency of the data entered in the CRF.

Final CRFs in human readable format must be reviewed and verified for accuracy by the study site Principal Investigator and signed-off. A copy of the final CRF will remain at the investigator's site at the completion of the study.

The CRF numbering convention is as follows:

_01_-_2_ _3__4_ A -B -A
_01_: Site # must be 2 digits (use leading zero) --- (sites 01-05)

_2_ _3__4_: patient screening/enrollment # (001 – 065)—must be 3 digits

A-B-A: Patient initials (if no middle initial, use dash)

Total 5 digits and initials for enrolled patients.

13.2 Confidentiality

Patient information will be kept confidential and managed according to the 1996 HIPAA guidelines. Each patient will be given a unique subject number and will be identified by this number and their initials. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient. Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidential and that the patient's privacy is protected.

13.3 Role of the Data Coordinating Center

As Principal Investigator and study sponsor of this clinical study, Vivek Reddy, MD assumes the overall responsibility for the conduct of the study, including assurance that the study meets national and institutional guidelines for study conduct. In this study, Vivek Reddy, MD will have certain direct

responsibilities and will delegate other responsibilities to his staff at the Data Coordinating Center at the Electrophysiology Clinical Research Group at the Icahn School of Medicine at Mount Sinai. The Data Coordinating Center (DCC) will: 1) ensure adherence to the national and institutional regulations; 2) develop and distribute protocols and case report forms; 3) coordinate data organization; 4) perform statistical analyses; 5) provide on-site and remote monitoring.

13.4 Withdrawal of Subjects

A subject may withdraw from the study at any time should he/she choose to do so. Additionally, subjects may be withdrawn by the investigator if deemed appropriate due to safety or compliance issues.

13.6 Economic Impact on Subjects

There are no additional costs related to involvement in this study. Since the cost of the procedure will be included within the Disease Related Group (DRG) charge, neither patient nor insurance provider will incur additional cost.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Maintaining Records (21 CFR 812. 140 (B))

All clinical sites will maintain study records for two years after research termination. The Data Coordinating Center will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the clinical trial.

14.2 Institutional Review Board (IRB) / Ethics Committee (EC) Information

This protocol and the informed consent must be reviewed and approved by the appropriate IRB/EC where the trial is to be conducted before enrollment of patients. Changes to the protocol that may increase the risk or present new risks to the patient, or may adversely affect the validity of the trial, must be approved in writing by the IRB/EC before the change is made.

The study site Principal Investigator(s) is responsible for submitting and obtaining initial and continuing review (at intervals not greater than once a year) of the trial by their IRB/EC.

15 CLINICAL CENTERS

The study will be conducted in up to 5 sites in the United States and 1-2 OUS sites. Each clinical center will be required to obtain IRB/EC approval for the protocol and consent (and their revisions) in a timely fashion, to recruit patients, to collect data and enter it accurately in the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP). In addition, centers will be required to provide the DCC with the information necessary for interim, annual, and final reports, to provide source documents, data and regulatory documents for study monitors, provide prompt responses to DCC inquiries, and to participate in analyses and reporting of study results.

15.1 Investigator Profile

All cardiologists, coordinators and other investigators in the study must complete the Investigator Profile form, including hospital affiliation, address, telephone, fax, beeper and email information. The

cardiologist and coordinator must email or fax their CV, Conflict of Interest Statement and Financial Disclosure Certification, and Institutional Health Insurance Portability and Accountability Act (HIPAA) Certificates to the DCC.

15.2 Qualifications and Training

Clinical investigators will be electrophysiologists with expertise in AF ablation. The certified operator will either perform the ablation on their own patient, or participate in the ablation of an enrolled patient. The clinical site Principal Investigator will be responsible for overseeing the ongoing performance of the other participating investigators at that site over the course of the study.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol at a site initiation visit in advance of patient enrollment. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the electronic data capture system.

16 DATA HANDLING

Information about patients will be kept confidential and managed according to the requirements of the United States of American Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed patient authorization informing the patient of the following:

1. What protected health information (PHI) will be collected from patients.
2. Who will have access to that information and why.
3. Who will use or disclose that information.
4. The rights of a research patient to revoke their authorization for use of their PHI.

In order to ensure patient confidentiality, all case report forms and patient information (CT/MRI, if reviewed), fluoroscopic and endoscopic images, ECGs) will be de-identified and replaced with a unique patient identifier. Information will be stored in the office of the local study coordinator, which will be kept in a secure, locked location. The research study coordinators, principal investigator and co-investigators will be the only personnel with access to this data. All data will be stored without any patient information apart from the unique three digit patient identifier. Electronic data will be encrypted and password-protected.

17 DATA ANALYSIS

This clinical study is a proof of concept study intended to assess the feasibility of the study mapping system. Baseline clinical characteristics (e.g. age, gender, renal function) and procedural characteristics (e.g. surface intracardiac electrogram and imaging findings) of the patients will be collected and analyzed.

Descriptive statistical data will be used to draw up the characteristics of subjects at the time of enrollment (demographics, baseline data). Quantitative parameters will be described using the following summary descriptive statistics: mean, standard deviation, median, and minimum and maximum values. Qualitative parameters will be described overall using frequencies and percentages. Percentages will be calculated on the number of non-missing observations. In all cases, the number of missing values will be specified.

Wilcoxon's test or Student's test for pairwise comparisons will be used, depending on the normality of the distribution, to study evolution in time.

17.1 Data Monitoring Committee

To meet the study's ethical responsibility to its subjects, an independent Data Monitoring Committee (DMC) will monitor results during the study. The committee will consist of a cardiologist who has no formal involvement or conflict of interest with the subjects, the investigators, the sponsor or the DCC. The DMC will act in a senior advisory capacity to the DCC regarding data and safety matters throughout the duration of the study. In addition, the DMC will review interim safety and endpoint data every 6 months or on an as needed basis depending on enrollment figures. These safety data include adverse events (e.g., infection, bleeding, right heart failure) and mortality. They will communicate their findings directly with the DCC. The FDA will be provided a copy of any written communication from the DMC to the study sponsor related to safety concerns, or changes to the study protocol, procedures or informed consent document. The DMC will be provided a copy of any letter from the FDA to the study sponsor related to safety concerns, or changes to the study protocol, procedures or informed consent document. The clinical centers will have no contact with the members of DMC regarding this trial and no voting member of the committee may participate in the study as an investigator. Non-DMC members will not be allowed during DMC closed meetings.

DMC membership:
David Park, MD - Electrophysiologist
NYU Medical Center
New York, NY

18 REFERENCES

[1] Approaches to catheter ablation for persistent atrial fibrillation: Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P; STAR AF II Investigators.

[2] Driver domains in persistent atrial fibrillation. Haissaguerre M, Hocini M, Denis A, Shah AJ, Komatsu Y, Yamashita S, Daly M, Amraoui S, Zellerhoff S, Picat MQ, Quotb A, Jesel L, Lim H, Ploux S, Bordachar P, Attuel G, Meillet V, Ritter P, Derval N, Sacher F, Bernus O, Cochet H, Jais P, Dubois R.

[3] Characterization of Drivers in Patients with Persistent Atrial Fibrillation to Identify Substrate Based Rotor Ablation Targets: Kurian T, Janardhan A, Doshi A, Kessman P, Nguyen B, Atkinson J, Edwards J, Efimov I, Sanchez M; The Journal of Innovations in Cardiac Rhythm Management, 6 (2015), 2153-2161.

[4] Rotors in Patients with Persistent Atrial Fibrillation; Case Report of a Left Atrial Appendage Rotor Identified by a Novel Computational Mapping Algorithm Integrated into 3-Dimensional Mapping and Termination of Atrial Fibrillation with Ablation: Kurian T, Doshi A, Kessman P, Nguy en B, Edwards J, Pieper S, Efimov I, Janardhan A, Sanchez M; Cardiac Electrophysiology Clinics 7 (2015) 157-163.

[5] Identification of Drivers in Patients with Persistent Atrial Fibrillation Using a Novel Spatiotemporal Computational Algorithm Integrated with Electroanatomic Mapping: Kurian T, Sanchez M, Doshi A, Kessman B, Edwards J, Pieper S, Efimov I, Janardhan A; 2014 Atrial Fibrillation Symposium Scientific Abstract Poster.

[6] Characterization Rotors in Patients with Persistent Atrial Fibrillation to Guide substrate Based Rotor Ablation Therapy; Kurian T, Doshi A, Kessman P, Nguyen B, Edwards J, Pieper S, Efimov I, Janardhan A, Sanchez M; 2014 Heart Rhythm Society Congress Scientific Abstract Poster.

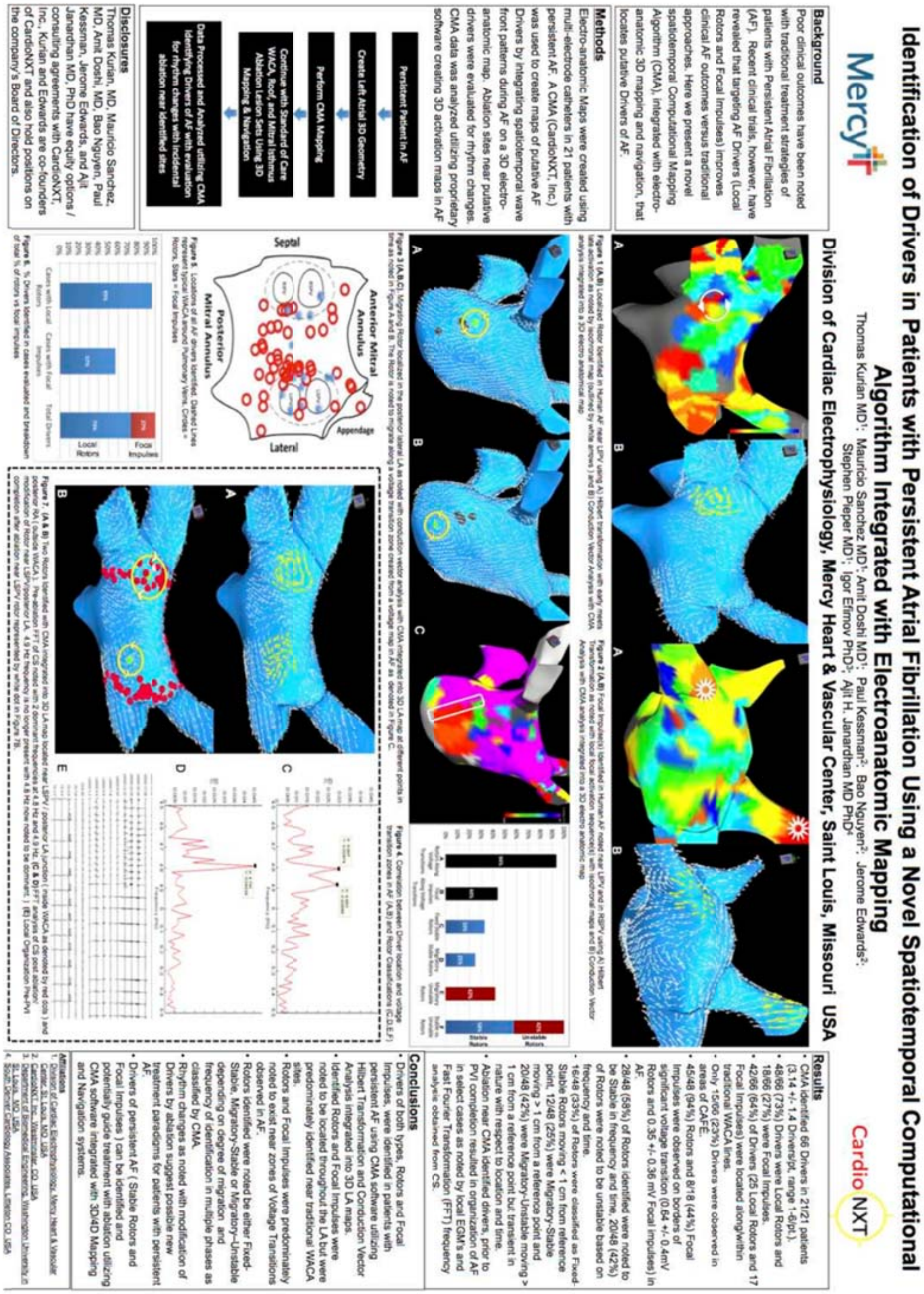
[7] Acute Termination of Atrial Fibrillation is Highly Correlated with Incidental Modification of Drivers Identified by Probabilistic AF Driver Analysis (PADA) Mapping: Kurian T, Janardhan A, Edwards J, Nguyen B, Kessman P, Doshi A, Pieper S, Efimov I, Sanchez M; 2015 Atrial Fibrillation Symposium Scientific Abstract Poster.

[8] Rotor Probability Index Predicts Rhythm Changes After Incidental Ablation of Identified Rotors in Persistent AF Patients; Kurian T, Janardhan A, Edwards J, Nguyen B, Kessman P, Doshi A, Pieper S, Efimov I, Sanchez M; 2015 Heart Rhythm Society Congress Scientific Abstract Poster.

[9] Outcomes after Incidental Ablation of Identified Rotors using Novel 3D Computational Mapping Algorithm in Persistent AF Patients; Kurian T, Janardhan A, Edwards J, Nguyen B, Kessman P, Doshi A, Lakkireddy DJ, Sanchez M; 2016 Atrial Fibrillation Symposium Published Scientific Abstract Poster.

[10] Incidence of Left Atrial Appendage Rotors in patients with Persistent Atrial Fibrillation using a Novel Computational Mapping Algorithm; Kurian T, Janardhan A, Edwards J, Nguyen B, Kessman P, Doshi A, Lakkireddy DJ, Sanchez M; 2016 Heart Rhythm Society Congress Scientific Abstract Poster.

APPENDIX 1A: 2014 Atrial Fibrillation Symposium Poster



Characterization of Rotors in Patients with Persistent Atrial Fibrillation to Guide Substrate Based Rotor Ablation Therapy

Thomas Kurian MD[1]; Amit Doshi MD[1]; Paul Kessman[2]; Bao Nguyen[2]; Jerome Edwards[2]; Stephen Pieper MD[1]; Igor Efimov PhD[3]; Ajit H. Janardhan MD PhD[1]; Mauricio Sanchez MD[1]

Division of Cardiac Electrophysiology, Mercy Heart & Vascular Center, Saint Louis, Missouri USA

Background

Recent clinical trials targeting AF Rotors have shown to improve clinical AF outcomes versus standard PVI & linear ablation. Selection of ideal Rotor targets, however, remains controversial. We recently presented a unique spatiotemporal Computational Mapping Algorithm (CMA), integrated with electro-anatomic 3D mapping and navigation, that identifies Rotors. Here we present a novel Rotor Characterization Algorithm (RCA) that classifies Rotors as Substrate Based Rotors (SBR) or Non Substrate Based Rotors (NSBR) utilizing relationships based on Rotor stability, proximity to voltage transition zones in AF, presence of CFAE and rotational pattern of wavefronts. We then determined whether ablation of SBR versus NSBR resulted in major rhythm changes.

Methods

Electro-anatomic Maps were created using multi-electrode catheters in 28 patients with persistent AF. A CMA (CardioNXT, Inc.) was used to identify putative AF Rotors by integrating spatiotemporal wave front patterns during AF on a 3D electro-anatomic map. Rotors were then subjected to a unique RCA (CardioNXT, Inc.) algorithm that classified Rotors as Substrate Based (SBR) versus Non Substrate Based (NSBR) based on (1) Rotor stability, (2) proximity to voltage transition zones in AF, (3) presence of CFAE and (4) rotational pattern of wavefronts. Ablation of RCA classified SBR and NSBR was evaluated for rhythm changes, defined as significant change in FFT (6X FFT Resolution Shift), organization into AT/AFL, or conversion to NSR.

Disclosures

Thomas Kurian MD, Mauricio Sanchez MD, Amit Doshi MD, Bao Nguyen, Paul Kessman, Jerome Edwards, Stephen Pieper MD, Igor Efimov PhD, and Ajit Janardhan MD PhD have equity options / consulting agreements with CardioNXT, Inc. Kurian and Edwards are co-founders of CardioNXT and also hold positions on the company's Board of Directors.

Figure 1 (A-B) Migrating SBR along lower left posterior wall, and NSBR, adjacent to RIPV, as noted with CMA Conduction Vector analysis integrated into 3D electro-anatomical map. (C) SBR depicted by green dots migrating along line of high voltage transition zone as measured in AF. NSBR depicted by white dots in low voltage transition zone (D) SBR depicted by green dots in region of Low CFAE and NSBR depicted by white dot in region adjacent to High CFAE.

Figure 2A Locations of all CMA identified drivers. Stars depict Foci, Rings depict Rotors.

Figure 2B Locations of all CMA identified SBRs versus NSBRs.

Figure 3. Rotor Statistics (A-E), presenting findings of identified and modified SBRs and NSBRs. Patient Statistics (F-J), presenting findings of rhythm change, organization and cardioversions.

Figure 4 (A) Anterior view of left atrium identifying two NSRBs (black arrows) and one SBR were identified (yellow arrows). **(B)** Voltage transition zone as measured in AF. **(C)** Global organization to atrial tachycardia occurred at ablation region near white dots as observed in CS Electrograms.

Figure 5 (A) Anterior view of left atrium identifying one SBR within the Left Atrial Appendage (yellow arrows). **(B)** Patchy voltage transition zones in LAA as measured in AF. **(C)** Global organization to normal sinus rhythm occurred at ablation region near white dots as observed in CS Electrograms.

Results

- CMA identified 100 Drivers in 28/28 patients (3.6 +/- 1.5 Drivers/pt, range 1-7/pt).
- 74/100 (74%) Drivers were Rotors.
- 26/100 (26%) were Focal Impulses.
- 39/74 (47%) of Rotors were Stable
- 39/74 (53%) of Rotors were Unstable.
- 50/74 (68%) Rotors were in areas of significant voltage transition (0.55 +/- 0.47mV Rotors) in AF.
- Only 17/74 (23%) Local Rotors were observed in areas of CFAE
- 50/74 (68%) were SBR. 24/74 (32%) were NSBR
- 7 SBRs were in/near the Left Atrial Appendage
- 23/27 (85%) of ablated SBRs in 18 cases resulted in rhythm changes.
- Only 2/11 (18%) of ablated NSBRs in 2 cases resulted in rhythm changes.
- 19/28 (68%) of cases where Rotors were modified resulted in rhythm change.
- Incidental ablation of 3 SBRs located in/near the LAA resulted in organization of AF.
- 10/12 (83%) cases that resulted in cardioversion had non-ablated SBR(s) identified via CMA.

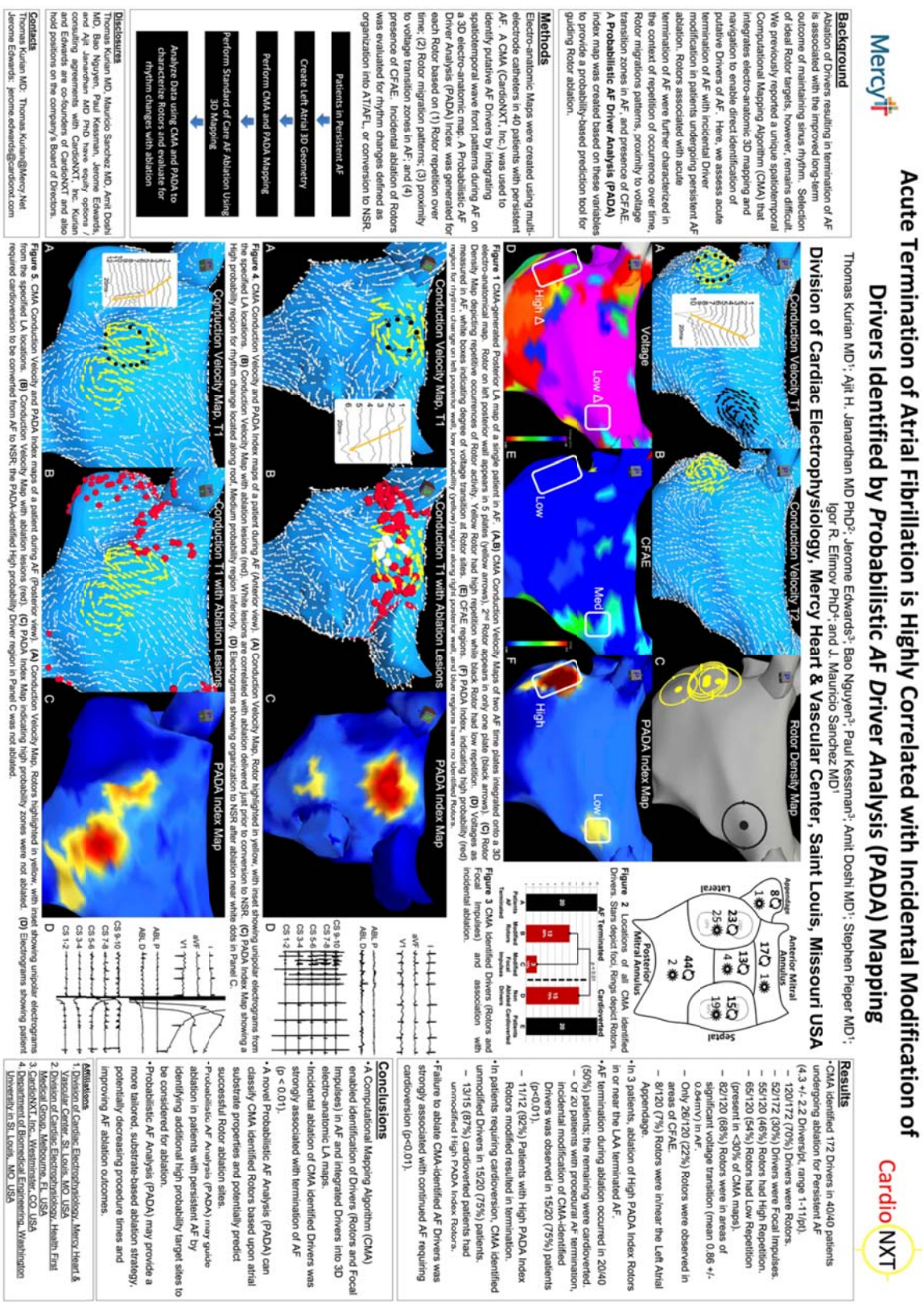
Conclusions

- A novel Computational Mapping Algorithm (CMA) can identify Rotors in AF integrated into 3D electro-anatomic mapping systems.
- A novel Rotor Characterization Algorithm (RCA) can classify CMA-identified rotors as Substrate Based (SBR) or Non Substrate Based (NSBR) based on Voltage Transition Zones, CFAE, Stability and Wavefront Pattern, integrated into 3D electro-anatomic mapping systems.
- Ablation near RCA-identified SBR's but NOT NSBR were strongly associated with rhythm changes (n < 0.0001)
- Rhythm changes associated with modification of SBRs vs. NSBRs suggest a new treatment paradigm in targeting rotors for AF ablation.
- RCA guided SBR vs. NSBR ablation may prevent unnecessary therapy by identifying ideal target sites in patients undergoing persistent AF ablation.
- CMA guided SBRs vs. NSBRs ablation can provide a tailored, substrate based approach for patients undergoing persistent AF ablation, potentially decreasing procedure times and improving AF ablation outcomes.

Affiliations

1. Division of Cardiac Electrophysiology, Mercy Heart & Vascular Center, St. Louis, MO, USA
2. CardioNXT, Inc., Westminster, CO, USA
3. Department of Biomedical Engineering, Washington University in St. Louis, MO, USA

APPENDIX 1C: 2015 Atrial Fibrillation Symposium Poster



VERSION 2.3, - December 2017 26

Mercy

Rotor Probability Index Predicts Rhythm Changes After Incidental Ablation of Identified Rotors in Persistent AF Patients

AF Therapeutics

Thomas Kurian MD[1]; Ajit H. Janardhan MD PhD[2]; Jerome Edwards[3]; Bao Nguyen[3]; Paul Kessman[3]; Jeffrey Atkinson[3]; Amit Doshi MD[1]; Stephen Pieper MD[1]; Igor R. Efimov PhD[4]; and J. Mauricio Sanchez MD[1]

Division of Cardiac Electrophysiology, Mercy Heart & Vascular Center, Saint Louis, Missouri USA

Background

Ablation of Drivers (Focal Impulses and Rotors) is associated with improved long-term outcomes in maintaining sinus rhythm post-ablation. Selection of ideal Rotor targets, however, remains challenging. We previously reported a unique spatiotemporal Computational Mapping Algorithm (CMA) that integrates electro-anatomic 3D mapping and navigation to enable direct identification of putative Drivers of AF. Here, we assess rhythm changes from AF with incidental Driver modification in patients undergoing persistent AF ablation. Rotors associated with rhythm changes from AF were further characterized in the context of repetition of occurrence over time, Rotor migration patterns, proximity to voltage transition zones in AF, and CFAE. A **Probabilistic AF Driver Analysis (PADA)** index map was created based on these variables to provide a probability-based prediction tool for guiding Rotor ablation.

Methods

Electro-anatomic Maps were created using multi-electrode catheters in 46 patients with persistent AF. A CMA (AF Therapeutics, Inc.) was used to identify putative AF Drivers by integrating spatiotemporal wave front patterns during AF on a 3D electro-anatomic map. A Probabilistic AF Driver Analysis (PADA) index was generated for each Rotor based on (1) Rotor repetition over time, (2) Rotor migration patterns, (3) proximity to voltage transition zones in AF, and (4) CFAE. Incidental ablation of Rotors was evaluated for rhythm changes defined by a change in FFT (6X FFT resolution shift) organization into AT/AFL, or conversion to NSR.

Patient in Persistent AF
↓
Create Left Atrial 3D Geometry
↓
Perform CMA and PADA Mapping
↓
Perform Standard of Care AF Ablation Using 3D Mapping
↓
Analyze Data using CMA and PADA to characterize Rotors and evaluate for rhythm changes with ablation

Disclosures

Thomas Kurian MD, Mauricio Sanchez MD, Amit Doshi MD, Stephen Pieper MD, Bao Nguyen, Paul Kessman, Jeffrey Atkinson, Jerome Edwards, and Ajit Janardhan MD PhD have equity options / consulting agreements with AFTX, Inc. Kurian and Edwards are co-founders of AFTX and also hold positions on the company's Board of Directors.

Contacts

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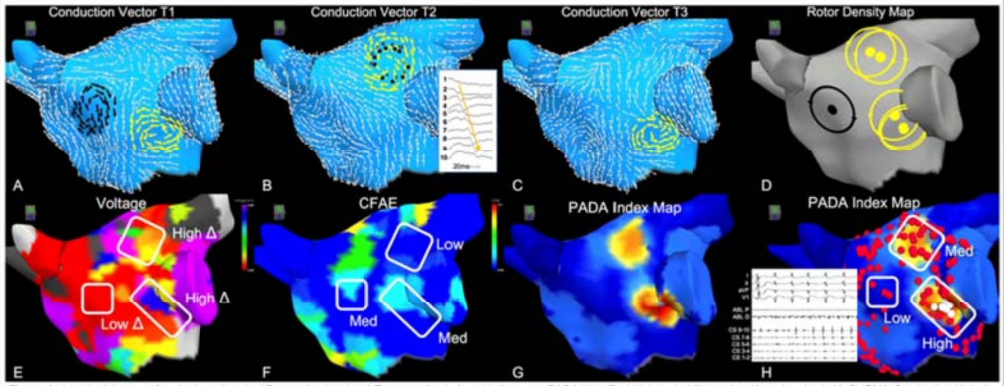

Figure 1. Anterior LA map of a single patient in AF organized to Atrial Tachycardia during ablation near PADA identified high probability region (Anterior view). **(A-C)** CMA Conduction Velocity Maps of three AF time plates integrated onto a 3D electro-anatomical map. Rotor on Roof appears in two plates (yellow arrows). Rotor adjacent to Appendage appears in three plates (yellow arrows). Rotor on Right Anterior Wall appears in only one plate (black arrows). **(D)** Rotor Density Map depicting repetitive occurrences of Rotor activity. Yellow Rotors have high repetition while black Rotor has low repetition. **(E)** Voltages as measured in AF, white boxes indicate voltage transitions at Rotor sites. **(F)** CFAE regions. **(G)** PADA index, red regions indicate high probability for rhythm change, as shown on Roof (FFT Change not shown) and Appendage (Atrial Tachycardia). Blue regions have no identified Rotors or low repetition and no voltage change. **(H)** PADA map and electrograms showing organization to Atrial Tachycardia after ablation near white dots.

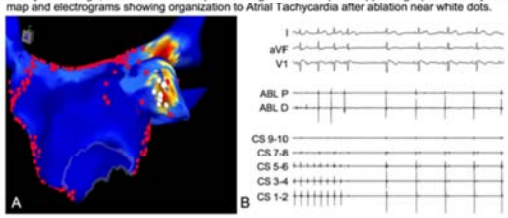

Figure 2. PADA index map of a patient during AF which terminated during ablation (white dots) near PADA identified high probability region (Anterior view). **(A)** PADA index map showing a high probability regions for rhythm change located within Appendage and LSPV. **(B)** Electrograms showing AF termination after ablation near white dots in Panel A.

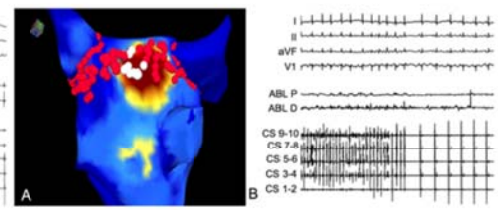

Figure 3. PADA index map of a patient during AF which terminated during ablation (white dots) near PADA identified high probability region (Anterior view). **(A)** PADA index map showing a high probability region for rhythm change. **(B)** Electrograms showing AF termination after ablation near white dots in Panel A.

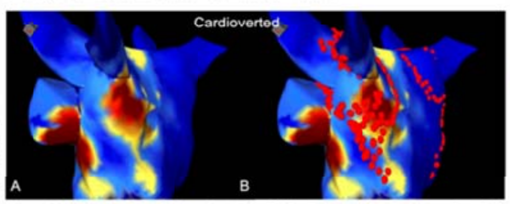

Figure 4. PADA index maps of a patient during AF in which a high probability region (Left Posterior Wall) was ablated, resulting in a change in CS FFT. A high probability region (LAA) was not ablated requiring cardioversion. **(A)** PADA Index map showing high probability regions for rhythm change located on LAA and Left Posterior Wall. **(B)** PADA map with lesions (red dots) showing only one high probability region ablated.

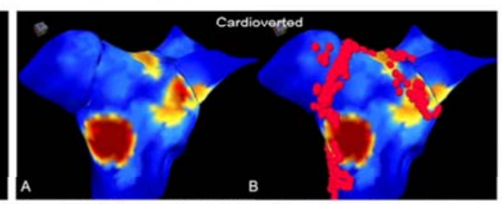

Figure 5. PADA index maps of a patient during AF in which one mid-level probability region (Roof) was ablated and one high probability region (RIPV) was ablated, both resulting in changes in CS FFT. One high probability region was not ablated requiring cardioversion (Posterior Wall view). **(A)** PADA index map showing two high probability regions for rhythm change located on the Posterior Wall and one mid-level probability region located on Roof. **(B)** PADA map with lesions (red dots) showing both ablated and non-ablated probability regions.

Results

- CMA identified 203 Drivers in 46 patients undergoing ablation for Persistent AF(4.4±2.1 Drivers/pt).
  - 145/203 (71.4%) Drivers were Rotors.
  - 58/203 (28.6%) Drivers were Focal Impulses.
  - 62/145 (42.8%) Rotors had High Repetition within a location (present in > 30% of CMA maps).
  - 73/145 (50.3%) Rotors had Low Repetition within a location (present in < 30% of CMA maps).
- Of 145 CMA identified rotors, 96 (66.2%) were incidentally ablated of which 71 (74.0%) resulted in rhythm change, defined by change of FFT/conversion to AT, AFL or SR.
- Rotors associated with rhythm change after ablation were located along high voltage gradients in AF (84.5% high vs. 15.5% low, $p < 0.0001$).
- Rotors near high CFAE were not associated with rhythm change (16.9% CFAE vs. 83.1% no CFAE, p=NS).
- High PADA index ablated rotors were associated with rhythm changes (6X FFT change, AT, AFL, SR) 53/71 (74.6%), while Low PADA index rotors resulted in rhythm changes in only 18/71 (25.4%). $p < 0.0005$.
- In 3 patients, ablation of High PADA index Rotors in or near the LAA terminated AF.
- AF termination to AFL, AT or SR during ablation occurred in 23/46 (50.0%) patients; the remaining were cardioverted.
  - Incidental modification of CMA-identified Drivers was observed in 17/23 (73.9%) patients with AF termination ($p<0.01$).
  - 14/15 (93.3%) Patients with High PADA index Identified Rotors incidentally modified resulted in termination.
- In patients requiring cardioversion, CMA identified unmodified Drivers in 17/23 (73.9%) patients.
  - 15/18 (83.3%) cardioverted patients had unmodified High PADA index Rotors ($p<0.01$).
- Failure to ablate High PADA index Rotors was strongly associated with continued AF, requiring cardioversion. ($p<0.01$).

Conclusions

- A Computational Mapping Algorithm (CMA) enables the identification of Drivers (Rotors and Focal Impulses) in AF, integrated into 3D electro-anatomic LA maps.
- A novel Probabilistic AF Analysis (PADA) classifies CMA identified Rotors based upon atrial substrate properties to predict successful Rotor ablation sites.
- Incidental Ablation of High PADA index Rotors were more likely to result in rhythm change than ablation of low PADA index Rotors
- Failure to ablate High PADA index Rotors was strongly associated with continued AF, requiring cardioversion. ($p<0.01$).
- Probabilistic AF Analysis (PADA) may provide a more tailored, substrate-based ablation strategy, potentially decreasing procedure times, and improving AF ablation outcomes.

Affiliations

1. Division of Cardiac Electrophysiology, Mercy Heart & Vascular Center, St. Louis, MO USA
2. Division of Cardiac Electrophysiology, Health First Medical Group, Melbourne, FL USA
3. AF Therapeutics, Inc., Westminster, CO USA
4. Department of Biomedical Engineering, Washington University in St. Louis, MO USA

Outcomes after Incidental Ablation of Identified Rotors using Novel 3D Computational Mapping Algorithm in Persistent AF Patients

Thomas Kurian MD[1]; Ajit H. Janardhan MD PhD[2]; Jerome Edwards[3]; Bao Nguyen[3]; Paul Kessman[3]; Jeffrey Atkinson[3]; Amit Doshi MD[1]; Dhanunjaya Lakkireddy MD[4]; and J. Mauricio Sanchez MD[1]

Division of Cardiac Electrophysiology, Mercy Heart & Vascular Center, Saint Louis, Missouri USA

Background

Ablation of Drivers (Focal Impulses and Rotors) is associated with improved long-term outcomes in maintaining sinus rhythm post-ablation. Selection of Ideal Driver targets, however, remains challenging. We previously reported a unique spatiotemporal Computational Mapping Algorithm (CMA) that integrates **electro-anatomic** 3D mapping and navigation to enable direct identification of putative Drivers of AF. Drivers associated with rhythm changes during AF were further characterized in the context of repetition of occurrence over time, Rotor migration patterns, proximity to voltage transition zones in AF, and CFAE. A **Probabilistic AF Driver Analysis (PADA)** index map was created based on these variables to provide a probability-based prediction tool to guide future real-time Driver ablation. Here, we assess one year follow up of patients whom undergone ablation correlated with incidental modification of identified Drivers.

Methods

Electro-anatomic Maps were created using multi-electrode catheters in 46 patients with persistent AF. A CMA (AF Therapeutics, Inc.) was used to identify putative AF Drivers by integrating spatiotemporal wave front patterns during AF on a 3D electro-anatomic map. A Probabilistic AF Driver Analysis (PADA) index was generated for each Rotor based on (1) Rotor repetition over time, (2) Rotor migration patterns, (3) proximity to voltage transition zones in AF, and (4) CFAE. Incidental ablation of each Rotor was evaluated for rhythm change defined by a change in FFT (8X FFT resolution shift), organization into AT/AFL, or conversion to NSR.

Disclosures

Thomas Kurian MD, Mauricio Sanchez MD, Amit Doshi MD, Dhanunjaya Lakkireddy MD, Bao Nguyen, Paul Kessman, Jeffrey Atkinson, Jerome Edwards, and Ajit Janardhan MD PhD have equity options / consulting agreements with AFTX, Inc. Kurian and Edwards are co-founders of AFTX and also hold positions on the company's Board of Directors.

Contacts

Thomas Kurian MD: Thomas.Kurian@Mercy.Net
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Figure 1. A) Anterior View of patient in AF with on phase CMA Conduction Vector analysis integrated onto a 3D electro-anatomical map. **B)** Rotor Density map noting driving locations identified via CMA conduction vector phase maps. **C)** Voltage transition zone as measured in AF. **D)** PADA Index, indicating high probability regions as noted by heat index map.

Figure 2. A) 3 PADA identified high probability region incidentally ablated during AF Procedure along the roof of LA. **B.)** Electrograms showing organization to NSR After ablation within PADA Region.

Figure 3. Locations of Identified Drivers, both Rotors and Focal Impulses.

Figure 4. A) 2 PADA Identified high probability regions incidentally ablated. Change of FFT was noted with ablation near roof / LSPV junction (not shown / white dots) **B.)** Electrograms showing organization to Atrial Tachycardia after incidental ablation in PADA regions.

Figure 5. 83% of patients had freedom from AF in 12 months. 31% of patients were in NSR with continued use of AADs or required redo procedures and 52% of patients had NSR off AADs. 17/19 (89%) of NSR Patients off AADs had 1 or more 1 High Probability PADA Region ablated.

Results

- CMA identified 223 Drivers in 46 patients undergoing ablation for Persistent AF(4.4±2.1 Drivers/pt).
  - 145/203 (71.4%) Drivers were Rotors.
  - 58/203 (28.6%) Drivers were Focal Impulses.
  - 62/145 (42.8%) Rotors had High Repetition within a location (present in > 30% of CMA maps).
  - 73/145 (50.3%) Rotors had Low Repetition within a location (present in < 30% of CMA maps).
- Of 145 CMA identified rotors, 96 (66.2%) were incidentally ablated of which 71 (74.0%) resulted in rhythm change, defined by change of FFT/conversion to AT/AFL or SR
- Twelve month follow-up showed 19/35 (54.%) cases in NSR without AADs or redo procedures.
- Atypical AFL/AT was noted in 13/35 (37.14%) cases requiring AADs/redo procedures.
- Recurrent AF was noted in 3/35 (8.6%) cases.
- 17/19 (89.5%) cases in NSR at 12 months without AAD's or redo's occurred when one or more identified High PADA Rotors were incidentally ablated

Conclusions

- A novel Probabilistic AF Analysis (PADA) classifies CMA identified Rotors based upon atrial substrate properties to predict successful Rotor ablation sites.
- Incidental Ablation of High PADA index Rotors were more likely to result in rhythm change than ablation of low PADA index Rotors
- Incidental Ablation of High PADA Rotor regions is associated with a high correlation of NSR maintenance at 12 months without AAD's/redo procedures.
- Recurrent AF Patients were noted to have a higher incidence of non-ablation of PADA Rotors
- Probabilistic AF Driver Analysis (PADA) may enable a patient specific, substrate-based ablation strategy, potentially decreasing procedure times and improving AF ablation outcomes.

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Incidence of Left Atrial Appendage Rotors in patients with Persistent Atrial Fibrillation using a Novel Computational Mapping Algorithm

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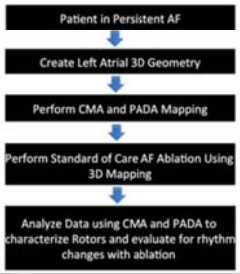
Background

Localized electrical rotors and focal impulse sources are postulated sustaining mechanisms for human atrial fibrillation (AF). Novel technologies developed to target these specific AF Drivers may fail to include the left atrial appendage (LAA). The LAA may be important in sustaining persistent AF as noted by previous clinical studies. We utilized a novel computational mapping algorithm integrating electro-anatomic 3D mapping and navigation to enable direct identification of putative Drivers of AF. Drivers associated with rhythm changes during AF were characterized by a **Probabilistic AF Driver Analysis (PADA)** index providing a probability-based prediction tool to help identify and characterize the number of rotors near / within the appendage and the effects of incidental ablation of those driver sites in our study population

Methods

Electro-anatomic Maps were created using multi-electrode catheters in 46 patients with persistent AF. A CMA (AF Therapeutics, Inc.) was used to identify putative AF Drivers by integrating spatiotemporal wave front patterns during AF on a 3D electro-anatomic map. A Probabilistic AF Driver Analysis (PADA) index was generated for each Rotor based on (1) Rotor repetition over time, (2) Rotor migration patterns, (3) proximity to voltage transition zones in AF, and (4) CFAE. Incidental ablation of each Rotor was evaluated for rhythm change defined by a change in FFT (6X FFT resolution shift), organization into AT/ AFL, or conversion to NSR. Rotors in / near the appendage were further characterized



Disclosures
Thomas Kurian MD, Mauricio Sanchez MD, Amit Doshi MD, Dhanunjaya Lakkireddy MD, Bao Nguyen, Paul Kessman, Jeffrey Atkinson, Jerome Edwards, and Ajit Janardhan MD PhD have equity options / consulting agreements with AFTX, Inc. Kurian and Edwards are co-founders of AFTX and also hold positions on the company's Board of Directors.

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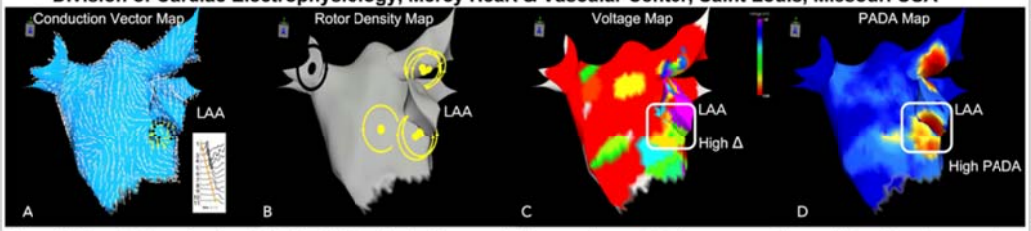
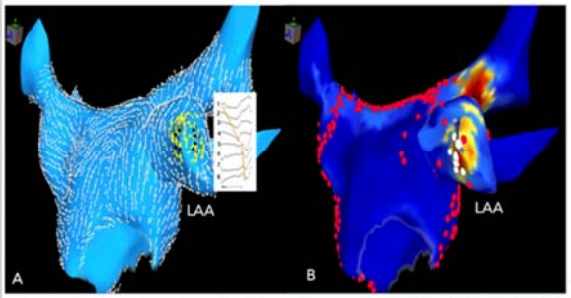


Figure 1. A) Anterior View of patient in AF with CMA Conduction Vector analysis integrated onto a 3D electro-anatomical map. B) Rotor Density map noting driving locations identified via CMA conduction vector phase maps. C) Voltage transition zone as measured in AF. D) PADA Index, indicating high probability regions inside/near the LAA as noted by heat index map.



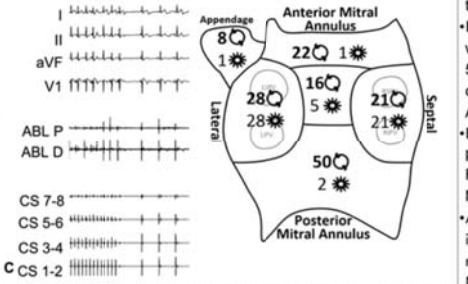
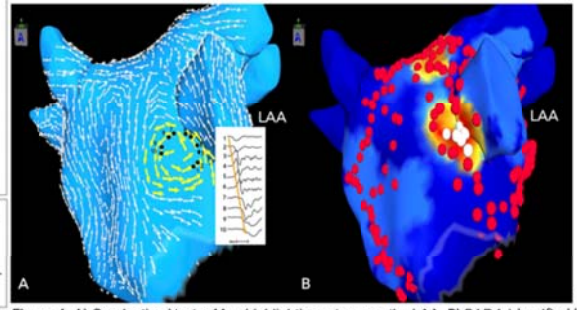


Figure 2. A.) Conduction Vector Map highlighting rotor in LAA B) I PADA identified high probability region incidentally ablated during AF Procedure inside the LAA. C.) Electrograms showing organization to NSR after ablation within PADA Region in LAA.

Figure 3. Locations of Identified Drivers, both Rotors and Focal Impulses.



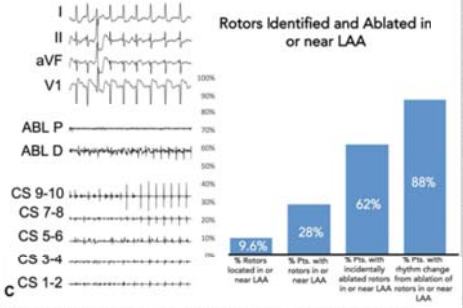


Figure 4. A) Conduction Vector Map highlighting rotor near the LAA. B) PADA Identified high probability region near the LAA incidentally ablated. C.) Electrograms showing organization to Atrial Tachycardia after incidental ablation in PADA regions near LAA.

Figure 5.) Statistics of incidental ablation of rotors in or near the LAA.

Results

- CMA identified 203 Drivers in 46 patients undergoing ablation for Persistent AF(4.4±2.1 Drivers/pt).
  - 145/203 (71.4%) Drivers were Rotors.
  - 58/203 (28.6%) Drivers were Focal Impulses.
  - 62/145 (42.8%) Rotors had High Repetition within a location (present in > 30% of CMA maps).
  - 73/145 (50.3%) Rotors had Low Repetition within a location (present in < 30% of CMA maps).
- CMA mapping identified 13 patients, of 46 in our series (28%), with rotors in or near the LAA.
- Of 145 CMA Identified rotors, 14 (9.6%) were located within (8/14) 57% or near the LAA (6/14) 42%.
- Incidental ablation of identified rotors within or near the LAA occurred in (8/14) 57% and was associated with a rhythm change (7/8) 87.5% as noted with FFT, AT/AFL or NSR.
- Rhythm change was noted in (7/8) 87.5% patients with incidental ablation LAA Rotors with change of FFT/AT/AFL/ or NSR
- AF Terminated to NSR / AT or AFL with incidental ablation of identified LAA rotors in or near the LAA to AT/AFL or NSR in (3/8) 37.5% patients.

Conclusions

- A novel Probabilistic AF Analysis (PADA) classifies CMA identified Rotors based upon atrial substrate properties to predict Ideal Rotor ablation sites.
- Identification of rotors within/ near the LAA may be important for patients undergoing ablation of persistent AF.
- Failure to identify Left Atrial Appendage rotors may affect outcomes in select patients with persistent atrial fibrillation.
- Probabilistic AF Driver Analysis (PADA) may enable a patient specific, substrate-based ablation strategy to identify ideal Rotor ablation sites including within / around the LAA

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