MHIF FEATURED STUDY:
VISITAG SURPOINT

DESCRIPTION:
Primary objective of study is to demonstrate safety and 12-month effectiveness of Tag Index-guided ablation using VISITAG SURPOINT™ Module with External Processing Unit when used with THERMOCOOL SMARTTOUCH® SF (STSF) and THERMOCOOL SMARTTOUCH® (ST) catheters for pulmonary vein isolation (PVI) in the treatment of subjects with drug refractory symptomatic paroxysmal AF.

CRITERIA LIST/QUALIFICATIONS:

Inclusion
1. Symptomatic paroxysmal AF; had at least 1 AF episode electrocardiographically documented within 1 year prior to enrollment
   Documentation may include ECG, TTM, Holter monitor or telemetry strip
2. Failed at least 1 antiarrhythmic drug (AAD Class I or III) as evidenced by recurrent symptomatic AF, or intolerable to the AAD

Exclusion
1. Previous surgical or catheter ablation for AF
2. Previous cardiac surgery (including CABG) within past 6 months (180 days)
3. Valvular cardiac surgical/percutaneous procedure (i.e., ventriculotomy, atriotomy, and valve repair or replacement and presence of a prosthetic valve)

AF is the most common sustained arrhythmia.
It affects 0.4% to 1% of the general population, and increases in prevalence with age.
Afib: Demographics

- An estimated 2.7–6.1 million people in the United States have AFib. With the aging of the U.S. population, this number is expected to increase.
- Approximately 2% of people younger than age 65 have AFib, while about 9% of people aged 65 years or older have AFib.
Afib: Demographics by Age


Afib: Hospitalization common

Fee-For-Service Medicare Beneficiaries
Ages 65 Years and Older 2009-2014

Atrial Fibrillation Hospitalization Rates
Total Population
Afib: Risk factors

- High blood pressure accounts for 14% to 22% of AFib cases.²
- Other risk factors for AFib include²:
  - Obesity
  - European ancestry
  - Diabetes
  - Heart failure
  - Ischemic heart disease
  - Hyperthyroidism
  - Chronic kidney disease
  - Heavy alcohol use
  - Left atrial or left ventricular chamber enlargement
  - Obstructive Sleep Apnea

Afib: Costs and Consequences

- More than 750,000 hospitalizations occur each year because of AFib.
- The condition contributes to an estimated 130,000 deaths each year.
- The death rate from AFib as the primary or a contributing cause of death has been rising for more than two decades.³,⁴
- AFib costs the United States about $6 billion each year.
- Medical costs for people who have AFib are about $8,705 higher per year than for people who do not have AFib.¹,²

Afib: Costs and consequences

- 2007 Report on 154,070 patients in France
  - Mean Follow-up 15.2 years
- In patients with atrial fibrillation
  - HR for all cause mortality
    - Men 1.5 / Women 1.8
  - HR for cardiovascular mortality
    - Men 2.2 / Women 3.4
- ALLHAT Trial Analysis (42,000pts)
  - Baseline AF
    - Mortality HR 2.8, CHF HR 3.16

J Am Coll Cardiol. 2009 Nov 24;54(22):2023-31

Afib: Treatment goals

Adverse Event Prevention
- Anticoagulation
- ? Other tx

Symptom Control
- Heart rate control
- Rhythm control
Afib: Adverse event prevention

- Anticoagulation for thromboembolic prophylaxis
  - CHA2DS2-Vasc Risk score based
  - CHF
  - Hypertension
  - Age ≥ 75 = 2
  - Diabetes
  - Stroke/TIA/Thromboembolism = 2
  - Vascular disease
  - Age 65-74
  - Female

Annualized stroke rate

Afib: Anticoagulation, warfarin versus apixababan

A Primary Outcome: Stroke or Systemic Embolism

B Major Bleeding

NNT 300 to prevent one CVA, 240 to prevent one death

NNT 100 to prevent one major bleed, 50 to prevent minor bleed

Afib: Adverse event prevention

- Aside from anticoagulation
- No other definitive treatment to reduce other adverse events
- *Except those with reduced LVEF – ablation significantly reduces mortality and CHF progression

Afib Treatment: Progression over time

- Rate control drugs
- Antiarrhythmic drugs
- Ablation

Time:
- 1940
- 2019
Atrial Fibrillation: Sinus Rhythm or Rate Control

**AFFIRM Trial**

**All-cause mortality**

- Cumulative mortality (%)

Years after randomization

- 0
- 1
- 2
- 3
- 4
- 5

- 0
- 5
- 10
- 15
- 20
- 25
- 30

4060 pts, CHADS 1

Rhythm control

Rate control

P = 0.08

*No difference in quality of life


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**AFFIRM TRIAL RESULTS**

- Death (NS): 25.9 vs 26.7
- Stroke (NS): 5.5 vs 7.1
- Hospitalization (p < 0.001): 73 vs 80.1

Rate-Control  Rhythm-Control
Cabana Trial: AA drugs v. Ablation

Estimates of All-Cause Mortality Risk (ITT)

Ablation vs. Drug
Hazard ratio: 0.85 (95% CI, 0.60–1.21)
P=0.377

Cabana Trial

Primary Endpoint (Death, Disabling Stroke, Serious Bleeding, or Cardiac Arrest) (ITT)

Ablation vs. Drug
Hazard ratio: 0.86 (95% CI, 0.65–1.15)
P=0.303
Cabana Trial: Caveats

- 27.5% of the drug therapy arm underwent ablation
- 9.2% of the ablation arm did not undergo ablation
- By Treatment received analysis, ablation arm showed:
  - All cause mortality reduced 40% (7.5% versus 4.4%, p=0.005)
  - Death or CV hospitalization reduced 33% (74.9% to 41.2%, p=0.002)
  - 47% reduction in AF
- Only ~50% of patients post ablation were free of AF
- Only ~25% of patient on AAD were free of AF

Afib: Symptom control

- Rate Control
  - Resting HR <80 no better than <110bpm *if no symptoms
Afib: symptom control

- Maintenance of NSR
  - Antiarrhythmic drugs
  - Ablation

AA drug efficacy over time


Afib: Symptom control

- Ablation superior to medications

ThermoCool: Trial of Ablation vs. Alternative Antiarrhythmic Medication

N = 167 with paroxysmal AF
- Randomized to catheter ablation (n = 166) or AAD (n = 61)
  - Single procedure
  - Mean age 55.7 yrs
  - 33.5% women
MHI Research: Local contributions to national outcomes

- 2014-

- Success rates improved to 88%
Background – Atrial fibrillation mechanism

- Multiple wavelet hypothesis of Atrial fibrillation
  - Moe proposed in 1959
  - AF is a self-sustaining arrhythmia independent of focal discharges
  - Multiple independent reentrant wavelets are necessary to maintain fibrillation. These wavelets are always changing in position, shape, size and number with each successive excitation
  - Experimentally demonstrated by Allessie in 1985

- Factors allowing for development of multiple wavelets
  - Atrial size – Sufficient surface area necessary for critical number of multiple wavelets to develop
  - Heterogeneous conduction velocity and tissue refractory periods allow for functional reentry

- Led to the MAZE surgical procedure
Background –
Atrial fibrillation mechanism

- 1997 - Haissaguerre et al described focal discharges that initiate AF
  - 94% of AF triggers observed from within the pulmonary veins

Background
Trigger ablation for AF

- PV antral isolation
  - In paroxysmal AF
    - PV isolation can achieve approximately 80% 12-month freedom from AF with optimal contact-force radiofrequency ablation or second generation cryoballoon ablation
  - In persistent AF
    - PV isolation can achieve approximately 60% 12-month freedom from AF
    - Less successful likely due to the presence of non-PV drivers.

- Insufficient success rates have led to further investigation into methods to identify AF drivers
**Leading Circle Model of Atrial Fibrillation**

**Functional Reentry**
- Differs from simple reentry around a fixed barrier
- No excitable gap
- Central core of constant activation becomes refractory and unexcitable
- Small size, highest rotation frequency


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**Functional reentry**
- Allessie, et al. Rabbit model
- Membrane potential recordings
- D3 and D4 indicate refractory central core activated twice as often
- Low amplitude potential cannot propagate out of the center. Functionally unexcitable due to continual membrane depolarization


Rotors as form of functional reentry

- Rotors are specific form of functional reentry
- Described in 1992 with optical mapping
- Curved or spiral form
- Wavefront and wavetail meet at a focal point
  - Phase singularity
- Wavefront velocity is not constant
- Standard functional reentry has fixed unexcitable core
- Rotor core
  - At the phase singularity wavefront curvature is extreme and conduction velocity very slow
  - Unable to penetrate refractory core
  - Phase singularity rotates around core
  - Rotor is able to move through space as no fixed barrier and no center of completely unexcitable tissue

Rotor initiation with PAC

- In certain instances Rotors may anchor in place
  - Often to areas around the pulmonary veins and in areas of heterogeneous atrial tissue

https://doi.org/10.1371/journal.pone.0149695
Complex Rotors

- Spatial and propagation instability is observed
- As the rotating wavefronts spread away from the PS and core, they interact with other in areas of anatomic or functional inhomogeneity fragment.
- They can then induce multiple disorganised ‘fibrillatory’ waves which then induce the chaotic atrial activation associated with AF

AF Driver Mapping

- 2012 Narayan - Focal Impulse and Rotor Modulation
  - CONFIRM trial
    - 92 Patients
    - 72% Persistent AF
    - 86% Acute AF termination
    - 82.4% single procedure freedom from AF
- 2017 Seitz – Spatiotemporal Electrogram Dispersion
  - 96 patients
  - 77.2% persistent AF
  - 95% Acute AF termination
  - 89% single procedure freedom from AF
  - 55% single procedure freedom from AF/AT
AF Driver Mapping
Spatiotemporal Dispersion

- 2017 Seitz, et al
  - Spatiotemporal dispersion mapping
    - During optical mapping of isolated LA tissue
    - Pseudo-multipolar electrograms demonstrated dispersion in regions of AF drivers

AF Driver Mapping
Ripple Map

- Ripple display corresponds directly to the recorded electrogram
  - No interpolation between points or other processing
- An acquired point is not assigned just a single activation time value
- Allows display of all electrical events per acquired point

Fractionated electrogram as displayed by Ripple map
Ripple Map: Macroeentrant AT example

- There is no interpolation between points, as all data presented is "real''.

Courtesy of Drs Kanagaratnam, Luther & Linton from Imperial College Healthcare, London, UK

AF Driver Mapping Ripple Map

- Potential benefits
  - Allows complete chamber evaluation
  - High density, long duration, time continuous point display
    - depolarization frequency, EGM fractionation, and voltage
  - Voltage/substrate display in combination with depolarization characteristics
  - Easily and rapidly performed using currently available catheters and software
    - Pentaray
    - Confidense
    - Ripple map
  - It is possible these attributes may demonstrate AF driver sites which have proven challenging to otherwise display
AF Driver Mapping
Ripple Map

- Definition: High Frequency Ripple Activation (HFRA)
  - Atrial sites with near continuous, and high frequency atrial depolarization as displayed by Ripple map
- Hypothesis:
  - 1) regions on Ripple with HFRA would correspond to bipolar electrograms demonstrating CFAE and / or spatiotemporal dispersion
  - 2) ablation of HFRA sites would terminate AF and lead to improved freedom from AF.

AF Ripple Mapping
AF Example, Trigger and AF driver map

- Patient with prior PVI, now with recurrent AF
- AF Trigger observed
  - Isoproterenol
  - 15mcg/min
  - Spontaneous left atrial
- Sustained AF initiated with left atrial PACs
- Left PV reconnected
  - Pulmonary vein-initiated AF

Figure: Sustained AF initiated with PACs
AF Ripple Mapping
AF Example, Trigger and AF driver map

- PV initiated AF
- PVI performed, AF did not terminate
- AF driver map performed using Ripple

Figure: Sustained AF initiated with PACs

AF Driver Map with Ripple

2 AF Drivers located
Inferior posterior LA
Adjacent Right Inferior Pulmonary Vein
AF Driver Map with Ripple

- AF terminates with HFRA sites
- AF Trigger eliminated with PV isolation
  - Isoproterenol 1.5mcg no spontaneous PACs or AF
- AF Drivers modified
  - Noninducible atrial pacing 200ms

AF Driver Map with Ripple - Persistent AF Driver – Left PV antrum

- AF present for prior 4 months
- Trigger not revealed while in sustained AF
- AF Ripple map performed for AF drivers
Ripple Map Study

- A total of 161 consecutive patients underwent a first-time ablation for persistent AF
  - Ripple map guided (n=56)
  - standard stepwise (n=105) approach

Ripple map approach
- PV antral isolation • Ablation of HFRA locations
- Up to 3 Remaps performed if needed
- Ablation proceeded until AF termination or loss of all HFRA sites within LA and RA

Stepwise approach
- Haïssaguerre technique
- PV antral isolation • Posterior LA • LA roof • CFAE • Mitral isthmus

Ripple Map Study: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ripple map (n=56)</th>
<th>Standard stepwise (n=105)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean in yr ±SD)</td>
<td>65.1 ± 10.3</td>
<td>64.8 ± 9.2</td>
<td>0.90</td>
</tr>
<tr>
<td>Male - no. (%)</td>
<td>67.8</td>
<td>85.7</td>
<td>0.008</td>
</tr>
<tr>
<td>Structural Heart Disease* (%)</td>
<td>14.3</td>
<td>17.1</td>
<td>0.64</td>
</tr>
<tr>
<td>Diabetes - no. (%)</td>
<td>16.1</td>
<td>21.0</td>
<td>0.45</td>
</tr>
<tr>
<td>Hypertension - no. (%)</td>
<td>46.4</td>
<td>52.3</td>
<td>0.045</td>
</tr>
<tr>
<td>Baseline LA dimension (cm ±SD)</td>
<td>4.3 ± 0.5</td>
<td>4.5 ± 0.6</td>
<td>0.068</td>
</tr>
<tr>
<td>Baseline LVEF (%±SD)</td>
<td>53.4 ± 11.3</td>
<td>55.2 ± 10.7</td>
<td>0.32</td>
</tr>
<tr>
<td>Prior BB or CCB use (%)</td>
<td>91.1</td>
<td>90.5</td>
<td>0.90</td>
</tr>
<tr>
<td>Failed AAD (class Ic or III) (%)</td>
<td>89.3</td>
<td>78.1</td>
<td>0.078</td>
</tr>
<tr>
<td>Duration since 1st AF diagnosis (months)</td>
<td>30.9 ± 41.6</td>
<td>41.2 ± 49.4</td>
<td>0.19</td>
</tr>
<tr>
<td>Duration continuous AF prior to RFA (months)</td>
<td>5.00 ± 5.7</td>
<td>7.3 ± 10.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Cha2ds2-Vasc score</td>
<td>2.3 ± 1.5</td>
<td>2.4 ± 1.6</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of patients who underwent Ripple map guided AF ablation. **SHD=Congestive heart failure, Constrictive pericarditis, Amyloid cardiomyopathy, Cardiac surgery.**
Ripple Map Study Results – Acute Termination All AF Types

- Paroxysmal AF: 95.8% termination (N=75)
- Persistent AF: 91.4% termination (N=56)

Ripple Map Study Results - HFRA characteristics

- Persistent AF:
  - 4.2 Mean HFRA Regions
- Paroxysmal AF:
  - 1.9 Mean HFRA Regions

Most Common HFRA Regions in Persistent AF:

- PV Antrum
- LA Roof
- LA Septum
- Inferior LA
- Posterior LA
Ripple Map Study Results – 18 Month Single Procedure

- After a single procedure, at 18 months significantly more patients in the Ripple map guided strategy were free of AF, compared to the standard stepwise strategy (98.2% versus 81.9, p=0.009).
- This difference remained after adjusting for gender and presence of HTN.

Best Randomized Study for Persistent AF – Single Procedure Freedom from AF

P=0.13 for the overall comparison, by the log-rank test
Ripple Map Study Results – 18 Month Single Procedure

- There was no difference in freedom from AT (53.6% versus 52.4%, p=0.89) or freedom from any atrial arrhythmia (51.8 versus 40.0, p=0.12).

![Graph showing freedom from arrhythmia over time](image)

Ripple Map Study Multiple procedure outcome

- After an average of 1.4 ablations procedures
  - Freedom from any AF was significantly higher in the Ripple group compared to the standard group (100% versus 88.6%, p=0.015)
  - There was no difference in freedom from AT (86.9% Ripple versus 76.2% standard, p=0.11) or any atrial arrhythmia (83.4% versus 70.5, p=0.09).
- 19 patients with AF or AT Recurrence in Ripple map group underwent second ablation
  - After 2 ablations, 17 of 19 (89.5%) were free of AF/AT
MHIF CV Grand Rounds – Jan. 14, 2019

MHI Research: Improving outcomes national ablation outcomes -

2000-14  
65% success

2016-17  
88% success

2014  
81% success

2018 93-95+% success

MHI Research: 2019 and beyond

- Improved accuracy of afib ablation targets using Ripple map technique developed at MHI
- Manuscript of 18 month follow up nearly complete for submission
- Research Version of Biosense Carto Mapping system under development with engineers in Israel
- Multicenter national trial proposed for 2019
MHI Research: 2019 and beyond

- Biosense Visitag SurePoint Study
  - Enrolling Now
  - National Multicenter Study
  - Paroxysmal Afib, Failed AAD
  - New Method for accurately estimating lesion size
    - First Ever Available
  - May demonstrate consistently high success rates due to improved lesion consistency

MHI Research: 2019 and beyond

- Biosense QDOT Study
  - Expected March 2019 Initial enrollment
  - National Multicenter Study
  - New Catheter for Afib ablation
    - Allows for surrogate lesion temperature assessment
    - QMODE: Automatic adjustment of power and tip cooling flow to keep temperature under char and steam pop zone
    - First Ever Available
    - QMODE +: Allows for safe high power, short duration ablation (90Watts, 4 Seconds versus current 30-35watts, 25-35 seconds)
    - In Europe, PAFib left atrial procedure times were reduced to from 120 to 45 minutes
  - Paroxysmal Afib, Failed AAD
Conclusions

- Afib is common, and associated with increased risk of stroke, mortality, and CHF
- Anticoagulation reduces stroke rate
- No treatment definitively reduces mortality
- For symptom control, ablation more effective than AA drugs
- With current research avenues, improved treatment options are emerging