Advances in Atrial Fibrillation Treatment: Ablation and Left Atrial Occlusion Strategies

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Disclosures

- Research Grants: Medtronic, Boston Scientific, St. Jude Medical, CardioFocus
- Advisory Board: Medtronic, CardioFocus
- Speaker: Medtronic, CardioFocus, St. Jude Medical

Outline

- AF introduction
- AF ablation
- LAA occlusion
Atrial Fibrillation: Facts

- Single most common sustained cardiac dysrhythmia
- In 2010, estimated 2.6 million Americans had AF and predicted 12 million in 2050
- Men have a 1.5 fold higher risk of developing AF
- Risk of AF increases with age. (Note: only 1% of patients with AF are less than 60 years old)
- Stroke is 5X more common in patients with AF
- About 1 in 7 strokes are caused by AF
- Hypertension is the most notable risk factor for developing AF
- The estimated cost of treating Americans with AF is $26 billion per year

Definitions

- Paroxysmal AF
  - AF that terminates spontaneously or with intervention within 7 days of onset
- Early Persistent AF
  - AF sustained beyond 7 days but < 3 months in duration
- Persistent AF
  - AF sustained beyond 7 days
- Long-standing Persistent AF
  - Continuous AF of greater than 12 months duration
- Permanent AF
  - Decision made to remain in AF with no further attempts at rhythm control
Indications for Catheter Ablation of Atrial Fibrillation

• Symptomatic AF refractory/intolerant to at least one class I or III antiarrhythmic medication
  - Paroxysmal
  - Persistent
  - Long-standing persistent

• Symptomatic AF prior to initiation of class I or III antiarrhythmic medication
  - Paroxysmal
  - Persistent
  - Long-standing persistent
Indications for Surgical Ablation of Atrial Fibrillation: concomitant open (such as mitral valve)

• Symptomatic AF refractory/intolerant to at least one class I or III antiarrhythmic medication
  • Paroxysmal
  • Persistent
  • Long-standing persistent

• Symptomatic AF prior to initiation of class I or III antiarrhythmic medication
  • Paroxysmal
  • Persistent
  • Long-standing persistent

Indications for Surgical Ablation of Atrial Fibrillation: concomitant closed (such as CABG or AVR)

• Symptomatic AF refractory/intolerant to at least one class I or III antiarrhythmic medication
  • Paroxysmal
  • Persistent
  • Long-standing persistent

• Symptomatic AF prior to initiation of class I or III antiarrhythmic medication
  • Paroxysmal
  • Persistent
  • Long-standing persistent

Indications for Surgical Ablation of Atrial Fibrillation: stand-alone or hybrid

• Symptomatic AF refractory/intolerant to at least one class I or III antiarrhythmic medication and failed one or more attempts at catheter ablation or prefer a surgical approach
  • Paroxysmal
  • Persistent
  • Long-standing persistent

The resulting concept... is based on that of a maze in which there is one entrance point into the box (SAN), one true conduction route between the entrance and exit, and several blind alleys along the route. Thus we refer to this surgical procedure as the maze procedure.

Between 1987-91, 22 pts underwent this procedure.

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>Paroxysmal atrial fibrillation after the three types of maze procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure</td>
<td>Post</td>
</tr>
<tr>
<td>Maze</td>
<td>572</td>
</tr>
<tr>
<td>Maze</td>
<td>415</td>
</tr>
<tr>
<td>Maze</td>
<td>482</td>
</tr>
</tbody>
</table>

Multiple electrode catheter

- 14 coil electrodes
- 2 thermocouples per electrode

- AF ocal Source of Atrial Fibrillation treated by Discrete Radiofrequency Ablation

- Pulmonary Vein Isolation (PVI)

Cardiac Ablation for Atrial Fibrillation

- **Goals**
  - High clinical efficacy
  - Low complication rates
  - Achieve durable pulmonary vein isolation with least amount of tissue damage/destruction

- **How to achieve durable pulmonary vein isolation?**
  - Lesions to be contiguous and transmural

- **Why is there re-connection?**
  - Role of edema or inefficient energy deliver?
  - Lack of energy titration based on patients’ anatomy?

Tools for PVI in US

- **Radiofrequency (point-by-point ablation)**
- **Cryoballoon**
- **Laser**

**HeartLight Technology – Main components**

- Console
- Balloon Catheter
- Sheath
- Endoscope
Case (UVA 8.15.17)

- Mr. G is a 52 y.o. male with a 3 year h/o PAF. Current AF episodes monthly
- Med Hx: HTN
- Meds: Failed flecainide and metoprolol
- ECHO: Normal LV function; LA size 4.1 cm
- Plan: PVI
Case (UVA 8.15.17)

- RIPV not isolated
- Would like more antral RPV lesions
- LPVs limited by esophageal temperature rise

- Re-deployed balloon in RPVs
- Increased the balloon size
- Ablated more on periphery of endoscopic view
Importance of energy titration

Without energy titration, there will likely be regions without transmural lesions or there will be injury to adjacent structures.
Ablation Strategies for Persistent AF

- PVI only
- PVI + non-PV triggers
- PVI + linear lesions (Eg: 2C3L)
- PVI + CFAE
- PVI + linear lesions + CFAE
- Step-wise approach
- PVI + "catheter MAZE" (including RA ablation)
- PVI + entire posterior wall
- Rotor/driver domain ablation
- PVI + rotor/driver domain ablation
- Hybrid AF ablation

Percent change in wall thickness post ablation

RF = 29.5%
Laser = 8.5%
Substrate and Trigger Ablation for Reduction in Atrial Fibrillation Trial II [STAR AF II]

- 589 persistent AF patients randomized in 1:4:4 ratio to PVI only (67pts); PVI + CFAE (203pts); PVI + linear (259pts)
- FU 18 months
- Primary endpoint: Freedom from any AF > 30 seconds after 1 procedure


Substrate and Trigger Ablation for Reduction in Atrial Fibrillation Trial II [STAR AF II]

- 48 centers from 12 countries
- Persistent AF patients. (Excluded if paroxysmal, persistent AF > 3 years, or LA > 6.0 cm)
- Ablation performed with:
  - Open irrigated ablation
  - EnSite Velocity, St. Jude Medical*
- Post-procedure
  - 3-month “blanking” period and drugs then stopped
  - If recurrence post 3-months, could start (or re-start) AA drug and if appropriate re-ablation (same randomized strategy) at 3-6 months post initial procedure
- Monitoring
  - Clinical Assessment. 12 lead ECGs, 24 HR Holters at 3,6,9,12, and 18 months, and transtelephonic monitoring weekly for 18 months and with any symptom


*Funded the study
Why the result?

- Additional ablation result in new iatrogenic areas of arrhythmogenesis where the tissue is incompletely ablated or linear block not achieved?
- Perhaps neither CFAE or lines are the correct supplemental targets?
- Automated CFAE maps may not be accurate?
- Can we be assured of durable PVI?
- Ablation endpoint was not AF termination.
- For persistent AF, is total elimination of AF necessary or is AF burden reduction an acceptable endpoint?

**Driver Domains in Persistent Atrial Fibrillation (Haissaguerre M, et al. Circulation 2014;130:530-538)**

**Aim:** Evaluate use of non-invasive 3D Mapping (ECM) to identify drivers in distinct categories of persistent atrial fibrillation (AF).

**Methods:**
- Prospective, non-randomized
- RF ablation times compared to matched controls
- n=103
- Driver ablation + PVI + linear lesions if AF not terminated

**Results:**
- Acute results: 82/103 patients experienced AF termination (80%).
- Outcomes:
  - 58/90 (64%) in stable sinus rhythm at 12 mos
  - 16/90 repeat ablations for atrial tachycardia (12) or AF (4)
  - 85% with AF termination free from AF at 12 mos
### Aims
To evaluate the utility of ECG mapping as a practical tool prior to ablation for persistent AF in centers with no practical experience of the system.

### Methods
- Multicenter (8 centers), prospective non-randomized
- N=118, PsAF <1 year, refractory to >1 AAD, LA diameter <55mm

### Results
- Driver-only ablation resulted in AF termination in 64% of the patients (75/118)
- Acute termination rates were not significantly different across all 10 centers.
- At 1 year, 77% of patients were free from AF recurrence after only a single procedure (78% off AADs)
- 14/25 recurrences were persistent, of which 4 could not be managed by DC cardioversion ± new AADs ± repeat ablation
- 3 month blanking period (Failure=AF or AT >30secs)
- Holters at 3, 6*, 9, & 12* months (*=72 hours)

### Noninvasive mapping
1. Prep patient and apply vest
2. Obtain CT scan for heart-torso geometry
3. Record cardiac signals from vest
4. Select beats and create maps

### Phase Mapping (Atrial Fibrillation)
- Phase Map
- Composite Map
AF Recording and map generation

Define phase intervals
Identify intervals with >1000ms (recommend 1200ms) over enough samples (e.g., 30+) to be representative of rhythm under investigation. (Segment ET and combine AF recordings)

Phase maps
Create a composite phase map for each processed map interval

Composite map
Create composite of all detected phase map activity

Termination while ablating posterior left atrium around the left PVs
Initial experience at UVA compared to European experience

- All types of atrial fibrillation (PAF, persistent, long-standing persistent)
- Both index cases and Repeat ablation cases
- Did mapping both pre-procedure and intra-procedure
- Modified 7 segment model to subsegments (total of 19)
- Endpoint was ablation to sinus rhythm
- Used contact force sensing ablation catheters

University of Virginia Experience

- Initial Experience (February, 2017 – November, 2017)
  - Atrial – 48
  - Atrial (Persistent) – 18 (Index cases – 6, Repeat cases – 12)
  - Atrial (Long-standing Persistent) – 2 (Index cases – 2)
  - Atrial (Paroxysmal) – 1 (Index cases – 1)
  - Note: 2 patient non-inducible, 2 patient arrhythmia not mapped
  - PVC – 5
  - CRT – 5
  - CardioInsight™ Mapping System was used pre-procedure and intra-procedure

- For the above Atrial Arrhythmia patients, the ablation strategy was to ablate to sinus rhythm
  - Achieved in 28/38* (*All CardioInsight™ cases
  - Presented in AlBAF [27], 18/27 (67%) ablated to SR
  - Presented in SR [13], Induced 11/13 (85%) ablated to SR

*Could not induce sustained Arrhythmia in 1 case and unable to map the flutter in 1 case
Indications for Surgical Ablation of Atrial Fibrillation: stand-alone or hybrid

- Symptomatic AF refractory/intolerant to at least one class I or III antiarrhythmic medication and failed one or more attempts at catheter ablation or prefer a surgical approach

- Paroxysmal: Class IIb
- Persistent: Class IIa
- Long-standing persistent: Class IIa

Hybrid Cardiac Ablation

Table 1. Advantages of the hybrid AF approach

<table>
<thead>
<tr>
<th>Surgical component</th>
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</thead>
<tbody>
<tr>
<td>LA appendage exclusion</td>
<td></td>
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</tr>
<tr>
<td>Direct visualization of atrium of pulmonary veins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoidance of adjacent structures: esophagus, phrenic nerve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Access to epicardial structures: ganglionic plexi, ligament of Marshall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mapping to ensure PVI and block across lines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;Touch up&quot; gaps and complete epicardial lines of ablation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potential for complex mapping of rotors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ablation of sites inaccessible from epicardium: CS, cavitricuspid isthmus</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; LA, left atrial; PVI, pulmonary vein isolation; CS, coronary sinus.

1 = PVI
2 = Roof
3 = Interior
4 = Anterior
5 = LSPV to LAA
6 = Interior to CS
7 = SVC
8 = Intercaval

a = mitral isthmus
b = CTI
Persistent Patients (45 pts)

<table>
<thead>
<tr>
<th></th>
<th>Surgery + Catheter (15)</th>
<th>Repeat Catheter (10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60±12</td>
<td>59±14</td>
<td>ns</td>
</tr>
<tr>
<td>Male (%)</td>
<td>66</td>
<td>67</td>
<td>ns</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>45±7</td>
<td>51±10</td>
<td>ns</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>20</td>
<td>16</td>
<td>ns</td>
</tr>
<tr>
<td>LA Diameter</td>
<td>4.8±0.9</td>
<td>4.5±0.8</td>
<td>ns</td>
</tr>
<tr>
<td># of Failed Ablations</td>
<td>1.7±0.5</td>
<td>1.8±1.2</td>
<td>ns</td>
</tr>
<tr>
<td># of AAD (%)</td>
<td>2.1±0.6</td>
<td>1.7±1.8</td>
<td>ns</td>
</tr>
<tr>
<td>BMI &gt;30 (%)</td>
<td>47</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>


Table 3. Post-Procedural Outcomes for All Patients Undergoing Catheter Alone versus Sequential Atrial Fibrillation Ablation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sequential (n = 93)</th>
<th>Catheter Alone (n = 20)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total procedure time (minutes)</td>
<td>400 ± 20</td>
<td>305 ± 15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial catheter time (minutes)</td>
<td>18.6 ± 3.1</td>
<td>15.0 ± 3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluoroscopy time (minutes)</td>
<td>17.6 ± 3.1</td>
<td>22.3 ± 3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td>15.7 ± 3.5</td>
<td>18.1 ± 1.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (4.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Tumour resected</td>
<td>4 (4.0%)</td>
<td>3 (15.0%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Hematomas (cm)</td>
<td>4 (4.0%)</td>
<td>2 (15.7%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>4 (4.7) ± 6.3</td>
<td>13 (16.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>On anti-arrhythmic drug at follow-up</td>
<td>1 (16.7%)</td>
<td>2 (16.7%)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Port Placement

- **Right Side**
- **Left Side**

Bipolar clamp
GP Mapping and Ablation
High Frequency Stimulation

Positive Vagal Response

Epicardial Exit Block

Ligament of Marshall

Left Pulmonary Artery

Ligament of Marshall

Ligament Insertion of Ligament of Marshall

LAA

LSPV
Atricure Exclude Appendage Device

- Multipolar catheter in each PV
  - Entrance block
  - Exit block with pacing
  - Often Roof Line gap
  - Li-Mi line includes CS burn
  - Use fluoro to confirm place Li-Mi line same place as surgeon
  - Isoproterenol run limited by pressure
Track Atrial Flutters
Oral Anticoagulation is Standard of Care, but Not Ideal for All
NOAC = Novel Oral Anticoagulants

- Bleeding risk
- Daily or 2x/daily regimen
- High non-adherence rates
- Complicates surgical procedures
- Limited reversal agents
- High cost

Novel Oral Anticoagulants:
- Warfarin
- Food and drug interaction issues
- Regular INR monitoring
- Complicates surgical procedures

Despite NOAC Adoption and Ability to Switch NOACs, Adherence to Anticoagulation Remains a Challenge

-30% of NOAC patients stop taking any drug at 2 years

Connection Between Non-Valvular AF-Related Stroke and the Left Atrial Appendage

- Stasis-related LA thrombus is a predictor of TIA and ischemic stroke.
- In non-valvular AF, >90% of stroke-causing clots that come from the left atrium are formed in the LAA.

Left Atrial Appendage Closure Devices
(FDA Approved Devices as of January, 2018)

Endocardial

- Watchman™

Epicardial

- Lariat™
- Atriclip™

WATCHMAN™ LAAC Device

Indications for Use

The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Procedure

- One-time implant that does not need to be replaced
- Performed in a cardiac cath lab/EP suite, does not need hybrid OR
- Performed by a Heart Team
- ICE/EP or ICEP, TEE, General Anesthesia, Surgical Back-up, WATCHMAN Clinical Specialist
- Transfemoral Access: Catheter advanced to the LAA via the femoral vein

* General anesthesia*
* 1 hour procedure*
* 1-2 day hospital stay*

* Typical patient treatment in U.S. clinical trial.
WATCHMAN™ - Most Studied LAAC Device

<table>
<thead>
<tr>
<th>Key Trials</th>
<th>N</th>
<th>Highlights</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF1*</td>
<td>707</td>
<td>Prospective, randomized 2:1, noninferiority trial of LAA closure vs. warfarin</td>
</tr>
<tr>
<td>CAPF</td>
<td>545</td>
<td>Prospective registry allowing continued access to the WATCHMAN Device and gain further information prior to FDA approval</td>
</tr>
<tr>
<td>PREVAIL1*</td>
<td>457</td>
<td>Prospective, randomized 2:1, noninferiority trial to collect additional information on the WATCHMAN Device</td>
</tr>
<tr>
<td>CAPF</td>
<td>579</td>
<td>Prospective registry allowing continued access to the WATCHMAN Device prior to FDA approval</td>
</tr>
<tr>
<td>EWOLUTION*</td>
<td>1019</td>
<td>Prospective registry following all patients receiving a WATCHMAN Device at participating centers in Europe, Middle East and Russia</td>
</tr>
</tbody>
</table>

Total patients >3,000 ~9,000 Patient-Years of Follow-up

* The EWOLUTION Registry is a European prospective registry which reflects CE Mark indications for use which differ from the FDA indications for use.

Procedural Success

Favorable Procedural Safety Profile:
All Device and/or Procedure-related Serious Adverse Events within 7 Days


* The EWOLUTION Registry is a European prospective registry which reflects CE Mark indications for use which differ from the FDA indications for use.

**The performance and timing of TEE to re-evaluate the LAA seal is left to physician discretion.**

Typical to patient treatment in U.S. clinical trials:

<table>
<thead>
<tr>
<th>Warfarin Cessation with WATCHMAN*</th>
<th>45 Days</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF*</td>
<td>87%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>CAP†</td>
<td>97%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>PREVAIL†</td>
<td>85%</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>


WATCHMAN Enables Patients to Discontinue Long-term OAC

92% of patients were able to discontinue warfarin after 45 days, with 99% able to discontinue after 1 year.

LARIAT Procedure
LARIAT Suture Delivery Device

- **FDA Indications:** The LARIAT Suture Delivery Device facilitates suture placement and knot tying for use in surgical applications where soft tissue are being approximated and/or ligated with a pre-tied polyester suture.

PLACE Procedure

- **Procedure:** PERMANENT LIGATION APPROXIMATION CLOSURE & EXCLUSION

  - ACCESS
  - CREATEАОNS
  - EXPANDABLE
  - ENDOCATH
  - BANDAGE

Spontaneous echo contrast or thrombus seen in incompletely ligated LAA in 9 of 18 (50%) patients.

4 patients with incompletely ligated LAA had thromboembolic events.
The Future

The most successful programs in the future might be those that employ an interdisciplinary, collaborative team approach to the treatment of AF, resulting in higher success rates for patients.

AF/LAA Collaborative Team Approach

- Team Members
  - EP, IC (structural heart interest), surgeon
- Individualize Patient
  - Ablation Strategy and/or device?
  - Are there contraindication to anticoagulation?
  - Arrhythmia management
    - Ablation
  - Other AF treatment
  - Concomitant surgical needs
    - CABG
    - Valve