Atrial Fibrillation in the 21st Century

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Disclosures: none
Citations in slide notes
Why is this relevant?

• Atrial fibrillation is:
  • Common – the most common arrhythmia
  • Significant – stroke, heart failure, early mortality, etc etc
  • Complicated – spectrum of pathogenesis, clinical relevance, and management options – *timing is critical!*

• Does not have to be tolerated!!
Objectives

• Pathogenesis of atrial fibrillation
• Stroke prevention
• Rhythm vs rate control – is there a difference?
• Options for medical management
• Options for invasive management
Pathogenesis of AF

- A probabilistic phenomenon
- More of a syndrome than a disease
  - Spectrum of conditions which predispose to the possibility of AF
    - Genetically determined AF
    - Related to traditional risk factors: HTN, DM, CAD, CHF
    - Related to: valvular heart disease, HCM/amyloid/metabolic myopathies
    - Vagal tone, hyperthyroidism, lung disease, sleep apnea, anemia, alcohol/drugs, etc etc etc
  - Spectrum of patients who present with AF
    - Prognosis
    - Options for treatment

- Predictable progression of disease
  - Paroxysmal
  - Persistent
  - Long-standing persistent/permanent
Pathogenesis of AF

• Reentry 101:
  • In order for stable reentry to occur, the “wavelength” of the action potential must fit within the available path length
  • Wavelength: $\Lambda = CV \times ERP$
  • Path length is usually defined by structural or functional barriers
Pathogenesis of AF

- Caused by "random reentry" of multiple, complex wavelets
- No structural boundaries to define the reentry path
  - Shortest possible path to allow for reentry
Pathogenesis of AF

• Stability of AF is favored by:
  • Slowed conduction velocity
  • Shortened atrial ERP
  • Mass and character of atrial tissue
Pathogenesis of AF

• **AF begets AF!**
  • Acute and chronic remodeling
  • Shortened atrial ERP and slowed conduction velocity (shortened wavelength)
  • Increased atrial surface area and fibrosis (longer path length)
  • Increased heterogeneity in atrial conduction (“anchor points” for wavelet reentry)

• Paroxysmal: short-lasting, self-terminating
  • Increasing frequency/duration over time

• Persistent: stable, requires intervention
  • Early – may maintain SR without specific measures
  • Late – requires substrate modification

• Long-standing persistent/chronic/permanent: exceedingly low likelihood of maintaining SR
Stroke prevention

• ...it’s important
• More to come at the next talk
• ...but it’s important!
Rate vs rhythm control

• Does it even matter?

• AFFIRM trial (2002):
  • Rate control:
    • HR 80-110
    • >80% adequate rate control (5% required AVN ablation)
  • Rhythm control:
    • Amiodarone (>60%), sotalol (41%), others (<15%)
      • Ablation strategy in 14/2033 after multiple failed drugs

• Warfarin use:
  • 85% in rate control group
  • 70% in rhythm control group

• 1/3 of patients enrolled after first diagnosed episode of AF

• 20% 5-year mortality??

• Crossovers:
  • Rate control – heart failure, AF symptom
  • Rhythm control – failure of drug, side effects

• 5-year SR rates:
  • 35% in rate control group
  • 62% in rhythm control group
Rate vs rhythm control

• Does it even matter?

• SAMURAI-NVAF (2016)
  • Patients admitted with stroke and paroxysmal vs persistent AF
  • Sustained AF was independent risk factor for:
    • Mortality
    • Recurrent stroke
    • Long-term disability from index stroke

• Possible confounders:
  • More HTN, DM in persistent group
  • More warfarin (vs NOAC) use in persistent group
Rate vs rhythm control

• Definition of “symptomatic” AF:
  • Palpitations are of least concern!
  • *Fatigue/dyspnea/exercise intolerance*
  • Chest pain/pressure
  • Lightheadedness/orthostasis/”syncope”

Cardioversion

“Best I’ve felt in months!”

Onset of dyspnea, no relief with diuretics
Management options – rate control

• Beta blockers
• Calcium channel blockers (non-DHP)
  • ** do not use if systolic dysfunction!
• Digoxin??
  • Less effective
  • ?increased all-cause mortality
• Don’t forget AV node ablation + pacing!
Management options – rhythm control

- Therapeutic goals:
  - Extended “wavelength”
  - Less available atrial tissue
Management options – rhythm control

Black Box Warning:
- Mortality/SCA in ischemic heart disease

Black Box Warning:
- Torsades de Pointes

Black Box Warning:
- Death/stroke/heart failure in CHF

Black Box Warning:
- Pulm toxicity
- Hepatotoxicity
- Bradyarrhythmias

No Structural Heart Disease

Structural Heart Disease

Catheter Ablation

Dofetilide†
Dronedarone
Flecainide
Propafenone
Sotalol

Dofetilide†
Dronedarone
Sotalol

Amiodarone

CAD

HF

CYP3A4
CYP2D6
Renally cleared
Management options - rhythm control

• How does ablation work?
  • Radiofrequency (RF) ablation
  • Cryoablation

• Pulmonary vein isolation – most dependable strategy for AF control
  • Pulmonary vein “trigger” sites
    • Isolate source of PACs which may initiate reentry
  • Atrial “debulking”
    • Less atrial tissue available for random reentry
  • Ganglionic plexus modification
    • Pause-dependent/ vagally mediated AF
  • Complex, heterogenic atrial tissue
    • Common anchor sites for stable “rotors”

• LOTS of other “add-on” strategies...
Management options – rhythm control

• But doesn’t ablation fail in 1/3 of patients?

• Depends on how you define failure
  • Clinical AF – presentations to ED/clinic
  • Monitoring – ECG @ 12mo? 24h Holter? ILR?
  • Any AF? Some AF? Less AF?

• AFFIRM (2002): 82% SR at 1 year in medically treated pts
  • No specific AF burden monitoring

• DISCERN-AF (2013):
  • Ablation trial
  • 46% SR at 1 year by ILR monitoring
  • 58% symptom-free at 1 year
  • Nearly universal burden reduction
Management options – rhythm control

• What if we applied the same rigor to meds vs ablation?

• STOP-AF (2013)
  • Cryoablation vs drug (flecainide/propafenone/sotalol)
  • TTM monitors – weekly, Sx
  • Holter at 6+12 months

• CABANA (2018?)
  • Ablation vs drug
  • Mortality/stroke/bleeding/SCA
Management options – rhythm control

• But doesn’t ablation fail in 1/3 of patients?

• Depends on AF subtype

• STAR-AF (2010)
  • Paroxysmal (64%), persistent (36%)
  • 74% success rate at 1 year

• STAR-AF2 (2015)
  • All persistent
  • 46%-59% success rate at 1 year
Management options – rhythm control

• Ablation is a rapidly evolving field

• STAR-AF (2010)
  • Paroxysmal (64%), persistent (36%)
  • PVI-only success: 48% at 1 year

• STAR-AF2 (2015)
  • All persistent
  • PVI-only success: 59% at 1 year

• Better mapping, better catheters, better understanding of ablation targets

• FIRE vs ICE (2016) – already (somewhat) outdated
A structured approach to AF

• All patients!!
  • Education
  • Stroke prevention
  • Upfront discussion of options
  • A trial of sinus rhythm
  • Risk factor modification

• Early paroxysmal
  • Younger, healthier patients
  • Minimal disease burden
  • Rate control
    • Baseline + PRN
  • Pill-in-pocket
    • Only class 1c agents

• Late paroxysmal
  • Frequent, self-terminating episodes
  • Rhythm control
    • Class 1c, class 3
    • Amiodarone (older patients)
    • Ablation

• Early persistent
  • Able to maintain SR with minimal intervention
  • Rhythm control
    • Class 1c, class 3, amiodarone (older)
    • Ablation

• Late persistent
  • Unable to maintain SR without specific intervention
  • Rhythm control
    • Class 1c, class 3, amiodarone (older)
    • Ablation (more extensive)

• Chronic/permanent
  • Rate control
    • Often AVN ablation + pacing
  • Rhythm control
    • Extensive ablation – convergent procedure
Summary

• Atrial fibrillation is common

• Complex range of presentations
  • Risk factors, demographics, prognosis, management options
  • Not a single disease!

• Lots of management options, which aren’t mutually exclusive
  • Stroke prevention is highest priority!
  • Rate control – medical vs AVN ablation + pacing
  • Rhythm control – medical/catheter-based/surgical

• Ablation is not a four-letter word
  • Better rhythm control than antiarrhythmic drugs
  • Nearly universal reduction in AF burden
  • May be used in conjunction with drugs

• Complex, actively evolving data set
Conclusions

• You are getting sleepy...
• Very, very sleepy....
• You will not treat AF with a “one size fits all” approach...

• THANK YOU!
• Questions/comments?

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ABLATION TARGETS: ANATOMY

• Tubes/catheters inserted into veins in groin (sometimes 1 from neck)
• Using either radiofrequency (heat) energy, or cryo (cold) energy, the areas that cause fibrillation are targeted
Paroxysmal afib

• 80% or more originating from pulmonary veins
• Induce “fibrillatory conduction”
• Elimination of triggers is current goal of ablation, by electrical isolation of PVs
• Triggers may be modified by multiple factors especially neural activity (ganglionated plexi) which have effects on conduction, and initiation of afib
Catheter Ablation afib: PAC triggers AF
Catheter ablation

- Unlike most other arrhythmias, atrial fibrillation is usually involving multiple different areas and multiple different circuits.
- The mechanism of the atrial fibrillation may change over time, so that paroxysmal atrial fibrillation is different than persistent atrial fibrillation.
Calkins H et al. Europace 2012;europace.eus027
Cryo Balloon isolation of Pulmonary veins

1. Access targeted vein
2. Inflate and position
3. Occlude and ablate
4. Assess PVI
Procedural Success Given as Freedom From CTF as a Function of Time

(A) Intention-to-treat primary effectiveness endpoint for freedom from chronic treatment failure (CTF) between patients treated with cryoablation and those treated with drugs. (B) Freedom from any AF between the on-treatment cryoablation and drug-treated patients. KM = Kaplan-Meier estimates; OR = odds ratio.
• New Generation Cryo balloon
• Success rate 80% with one procedure
• Procedure duration about 2 hours
• Main complication is phrenic nerve palsy: 2-6%-almost always transient, rarely last months
Arrhythmia monitoring methods and definition of procedure success (Freedom from AF Only or AF/AT/AFL) varied between studies.
Catheter Ablation: 2016 Caveats

• PAF: Fire and Ice Trial (2016): RCT noted similar outcomes with point by point RFCA or Cryoballoon PVI. Cryoballoon had less rehospitalizations and less pain post op. Yet- did not randomly compare pressure sensing RFCA or second generation cryoballoon which are current standards

• PsAF and long standing PsAF: Evolving approaches for ablation. PVI alone not sufficient as a long term result. Targeting complex fractionated sites, and dominant rotor sites improved outcomes in PsAF only marginally.

• Posterior wall isolation + PVI: ablation within or outside of atrium evolving as current standard
CONVERGENT (HYBRID) ABLATION OF AF

Rationale: posterior LA wall between pulmonary veins serves as both trigger source and substrate to initiate and maintain AF.

Technique: epicardial approach with delivery of contiguous RF lines between PVs, then PVI endocardially, possible CFAE targeted too.

Experience: emerging. > 2000 cases worldwide. Overall success: 70-80% symptomatic improvement. Documented CIED resolution of AF, after blanking period of 90 days, TBD by RMHRI.

Rocky Mountain Heart Rhythm Institute: multiple centers in Denver (RMC/TMCA/SMC) will eventually report accrued partial CIED data – estimated 2017
Convergent video
TMCA experience

• 101 cases 2014
• PAF vs PsAF
• Male:female
• Followup: > 90 days blanking
• Ppm, ILR: when available
• Symptom assessment
• Upcoming registry
TMCA AF ABLATION:
101 CASES

PAF: PsAF = 74/27
Mean age: 61
LA diameter: 4.6

Techniques of ablation:
- RFCA (23)
- CRYOBALLOON (60)
- PVI +:
  - CFAE (13)
  - HYBRID (4)

Overall: > 90 days, 80% remain in NSR symptom free (59/74 and 22/27)

1. Ablation exceeds expected 50% response to AAD
2. Ablation augments response to AAD
Catheter ablation for paroxysmal and persistent Atrial fibrillation: 2016 clinical caveats

1. Ablation exceeds expected 40% long term response to AAD
2. Ablation augments response to AAD
3. Ablation with a hybrid technique is the best available therapy for LS PsAF
4. Individualized treatment is paramount to success
5. Symptom improvement is primary goal
The FIRE AND ICE Trial

Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation

Primary Endpoint and Secondary Analyses Results
Contents

• Background of Atrial Fibrillation
• FIRE AND ICE Trial Design
• Primary Endpoint Results
• Secondary Analyses Results
Background of Atrial Fibrillation

- Atrial fibrillation (AF) is the most common arrhythmia with prevalence > 33 million
- Catheter ablation is a Class I Level A recommendation for treatment of symptomatic paroxysmal AF (PAF) refractory or intolerant to ≥1 Class I or III antiarrhythmic drug (AAD)
- Pulmonary vein isolation (PVI) is the cornerstone of AF ablation strategy

~4%² treated annually
FIRE AND ICE Trial and Design

• Compare the safety and efficacy of PVI by either:
  – **Cryoablation** (Arctic Front™ / Arctic Front Advance™ catheters) guided by fluoroscopy OR
  – **RFC ablation** (THERMOCOOL® / THERMOCOOL® SF / THERMOCOOL® SMARTTOUCH® catheters) guided by CARTO® 3D mapping system

• **Primary Efficacy Endpoint:** Time to first documented recurrence of AF>30s/AT/AFL, prescription of AAD, or re-ablation

• **Primary Safety Endpoint:** Time to first all-cause death, all-cause stroke/TIA or treatment-related serious AEs (e.g. phrenic nerve injury, atrioesophageal fistula, etc.)
### Key Inclusion Criteria
- Symptomatic PAF
- Prior AAD failure
- $\geq 18 \ & \leq 75$ years of age

### Key Exclusion Criteria
- Previous LA ablation or surgery
- PCI, MI within 3M of enrollment
- Stroke/TIA within 6M of enrollment
- LVEF $< 35$
- LA diameter $> 55$mm

<table>
<thead>
<tr>
<th>Subjects Enrolled and Randomized (1:1) to Cryoballoon Ablation or RFC Ablation</th>
<th>Day 0</th>
<th>Blanking Period</th>
<th>3M</th>
<th>6M</th>
<th>9M</th>
<th>12M</th>
<th>Every 6M Thereafter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly and Symptomatic Tele-ECG Monitoring</td>
<td></td>
<td></td>
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<tr>
<td>In-Office Visit with 24h Holter</td>
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<td>Telephone Follow-up</td>
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<tr>
<td>Quality-of-Life Questionnaire</td>
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</tbody>
</table>

Maximum follow-up duration of 33 months
FIRE AND ICE Trial and Design

- Investigators must have documented experience
  - $\geq$ 50 cases with either technology; each center had to provide at least one investigator proficient in both techniques
  - $\geq$ 10 cases before introduction of advanced-generation catheters
- Anticoagulation per guidelines/hospital standards
- PVI-only approach (CTI flutter ablation allowed, no additional lines or CFAE ablation)
- Must confirm PV isolation with a mapping catheter
  - 30-minute waiting period after last application
- Energy source crossover not permitted
- AADs discontinued after 90 day blanking period
  - Amiodarone required to be discontinued day of procedure
FIRE AND ICE Trial Methods

RFC Ablation (“FIRE”)
• Power was not to exceed
  – 40 Watts at A/I aspect
  – 30 Watts at P/S aspect
• 3D electroanatomical mapping

Cryoballoon Ablation (“ICE”)
• Max. freeze duration of 240s recommended
• Bonus freeze after isolation recommended
• Phrenic nerve pacing required

RFC Ablation of PV

Cryoballoon Ablation of PV
Primary Endpoint Results
Primary Efficacy Endpoint Met

- Cryoballoon: 64.1%
- RFC: 65.4%
Primary Efficacy by Catheter Category

Subjects Free From Primary Efficacy Event (%)

Number at Risk

<table>
<thead>
<tr>
<th>Catheter Category</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>600</th>
<th>700</th>
<th>800</th>
<th>900</th>
<th>1000</th>
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<tbody>
<tr>
<td>Arctic Front</td>
<td>90</td>
<td>83</td>
<td>58</td>
<td>42</td>
<td>36</td>
<td>32</td>
<td>30</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Arctic Front Advance</td>
<td>279</td>
<td>251</td>
<td>183</td>
<td>151</td>
<td>128</td>
<td>99</td>
<td>76</td>
<td>45</td>
<td>35</td>
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<tr>
<td>THERMOCool/THERMOCool SF</td>
<td>284</td>
<td>260</td>
<td>187</td>
<td>151</td>
<td>121</td>
<td>104</td>
<td>84</td>
<td>54</td>
<td>42</td>
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<tr>
<td>THERMOCool SMARTTouch</td>
<td>93</td>
<td>90</td>
<td>55</td>
<td>40</td>
<td>28</td>
<td>15</td>
<td>9</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Days Since Procedure
Primary Safety Endpoint Met

<table>
<thead>
<tr>
<th>Safety Event Type</th>
<th>RFC (n=376)</th>
<th>Cryoballoon (n=374)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death*</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>All-cause stroke/TIA</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Arrhythmia-related SAE</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Non-arrhythmia-related SAE</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>40</td>
</tr>
</tbody>
</table>

*Unrelated to treatment/device
## Key Treatment-Related Serious Adverse Events

<table>
<thead>
<tr>
<th>Event (N, %)</th>
<th>RFC (n=376)</th>
<th>Cryoballoon (n=374)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groin Site Complication*</td>
<td>16 (4.3%)</td>
<td>7 (1.9%)</td>
</tr>
<tr>
<td>Atrial Flutter/Atrial Tachycardia**</td>
<td>10 (2.7%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Phrenic Nerve Injury unresolved at discharge</td>
<td>0 (0%)</td>
<td>10 (2.7%)***</td>
</tr>
<tr>
<td>Unresolved at 3 months</td>
<td>0 (0%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Unresolved at &gt; 12 months</td>
<td>0 (0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Cardiac Tamponade/Pericardial Effusion</td>
<td>5 (1.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>2 (0.5%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Atrial Septal Defect</td>
<td>1 (0.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Esophageal Ulcer</td>
<td>0 (0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>0 (0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Atrioesophageal Fistula</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pulmonary Vein Stenosis</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Procedural Characteristics

Shorter, More Consistent* Procedure Times with the Cryoballoon

<table>
<thead>
<tr>
<th>Time Measurement (minutes)</th>
<th>RFC (n=376)</th>
<th>Cryoballoon (n=374)</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure Time***</td>
<td>140.9 ± 54.9</td>
<td>124.4 ± 39.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LA Dwell Time***</td>
<td>108.6 ± 44.9</td>
<td>92.3 ± 31.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fluoroscopy Time</td>
<td>16.6 ± 17.8</td>
<td>21.7 ± 13.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Secondary Analyses Results
Secondary Analysis Background

Secondary parameter analysis important in a comprehensive clinically meaningful evaluation

Secondary analyses included:\n- All-cause hospitalization
- Cardiovascular hospitalization* (including AF hospitalization†)
- Repeat ablation
- Direct current cardioversion (DC Cardioversion)
Freedom From All-Cause Hospitalization

21% Fewer All-Cause Hospitalizations in the Cryoballoon Group vs Radiofrequency Group

Event Free Survival

Log-Rank p-value = 0.01

Modified ITT Analysis

**Cryo**: 210 events in 122 subjects (122/374; 32.6%)

**RFC**: 267 events in 156 subjects (156/376; 41.5%)
Freedom From Cardiovascular Hospitalization

34% Fewer CV Hospitalizations in the Cryoballoon Group vs Radiofrequency Group

**Event Free Survival**

- Cryoballoon: 139 events in 89 subjects (89/374; 23.8%)
- RFC: 203 events in 135 subjects (135/376; 35.9%)

**Modified ITT Analysis**

- **Cryo:** 139 events in 89 subjects (89/374; 23.8%)
- **RFC:** 203 events in 135 subjects (135/376; 35.9%)
Freedom From Repeat Ablation

33% Fewer Repeat Ablations in the Cryoballoon Group vs Radiofrequency Group

Event Free Survival

Log-Rank p-value = 0.03

Modified ITT Analysis

Cryo: 49 events in 44 subjects (44/374; 11.8%)

RFC: 70 events in 66 subjects (66/376; 17.6%)
Freedom From DC Cardioversion

50% Fewer DC Cardioversions in the Cryoballoon Group vs Radiofrequency Group

**Event Free Survival**

- **CRYOBALLOON**: 13 events in 12 subjects (12/374; 3.2%)
- **RFC**: 28 events in 24 subjects (24/376; 6.4%)

**Total Events**

- **CRYOBALLOON**
- **RFC**

**Modified ITT Analysis**

- **Cryo**: 13 events in 12 subjects (12/374; 3.2%)
- **RFC**: 28 events in 24 subjects (24/376; 6.4%)
FIRE AND ICE Study Conclusions

• Primary Endpoints: PVI by cryoballoon ablation was found to be non-inferior to PVI by RFC ablation in terms of efficacy and safety, but had shorter and more consistent procedure times\(^1\)

• Subjects treated with cryoballoon compared to RFC had significantly fewer:\(^2\)
  – Cardiovascular hospitalizations (including AF hospitalizations)
  – Repeat ablations
  – All-cause hospitalizations
  – Direct current cardioversions
Thank You For Your Time