Ablation of Persistent AF – What Should We do Beyond PVI?

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Disclosures

• None
Background

- PVI is the accepted base strategy for AF ablation
- PVI alone is associated with lower efficacy in persistent compared with paroxysmal AF
- Additional ablation after PVI is often performed either empirically or if AF is not terminated by PVI
- There is currently no consensus beyond PVI in patients with persistent AF
Key Questions Guiding Ablation Strategy For Persistent AF

• In whom should we do more than PV isolation?

• What should we do?

• When should we stop doing it?
Mechanisms promoting development of persistent AF

• Electrical remodeling
  – Shortening and loss of rate adaptation of atrial refractory period.

• Structural remodeling
  – Non-degenerative changes in cell size, glycogen accumulation, myolysis, connexion expression, etc.
  – Fibrosis and left atrial enlargement, due to both underlying process such as structural heart disease, and also AF itself
Acute Electrical Remodeling During AF

![Graphs showing CV and AERP changes over pacing interval](image-url)
Structural Remodeling After 4 Months of AF

<table>
<thead>
<tr>
<th>Myolysis</th>
<th>Dedifferentiation</th>
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<tbody>
<tr>
<td>SR</td>
<td>AF</td>
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<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
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<thead>
<tr>
<th>Connexins</th>
<th>Ultrastructure</th>
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<tbody>
<tr>
<td>SR</td>
<td>AF</td>
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<tr>
<td>Cx40</td>
<td></td>
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<tr>
<td>Cx43</td>
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Who Does Well With PVI Alone?

Figure 1. Diagram of the Sites of 69 Foci Triggering Atrial Fibrillation in 45 Patients.

Haisseguerre et al. NEJM 1998;339:659
Sites of Dominant Frequency

![Bar graph showing the percentage of paroxysmal and persistent tachycardia at different sites: PV-PLAW, LA, RA, CS.](Atienza_et_al_Heart_Rhythm_2009_6_33-40)
Measurement of Left to Right Frequency Gradients

Baseline

Post-PVAl
DF Gradient Predicts Good Response to PVAI

Change in DF gradient with RFA

Baseline DF gradient predicts response
Voltage Mapping to Assess LA Scar

- Areas of low voltage were associated with larger LA, lower EF, increased C-RP
- Presence of LA scar, age and persistent AF predicted recurrent AF after PVI
LA Scar by Voltage Map Predicts Failure of PVAI

Verma et et. JACC 2005;45:285-292
Assessment of Fibrosis With LGE MRI
Multicenter DECAAF Study

Higher recurrence with more extensive fibrosis
Potential Additional Targets After PVI

- Complex fractionated atrial electrograms (CFAEs)
- Linear ablation (LA roof, mitral isthmus)
- Non-PV triggers initiated with high dose isoproterenol
- Other thoracic veins (SVC, coronary sinus)
- Stepwise approach (PVI, CFAEs, roof, mitral isthmus, CS)
- Phase mapping for rotors/focal sources (FIRM)
- Autonomic inputs
Linear Lesions

• May interrupt rotors or drivers in their path
• May interrupt macroreentry driving AF
• Eliminates more atrial substrate and partially compartmentalizes the atria.
What are CFAEs?

- Relatively low voltage areas defined as:
  - 1) fractionated atrial EGMs composed of two deflections or more, and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-s recording period
  - 2) atrial EGMs with a very short cycle length (≤120 ms)

Nadamanee et al. JACC 2004;43:2044-53
Mechanisms of Unipolar EGM Fractionation

Mechanism of CFAE

- Driver
- Passive
  - Farfield, double potentials
  - Fibrillatory conduction due to remote rapid AF
  - Wavefront collision
  - Slow conduction
  - Conduction delay to slower frequency

- Difficult to distinguish driver from passive CFAEs with current techniques
To improve outcomes for persistent AF, guidelines suggest that “operators should consider more extensive ablation based on linear lesions or complex fractionated electrograms” in addition to PV isolation. Whether more extensive ablation improves outcomes is unclear.

Purpose of study was to compare the efficacy of three different AF ablation strategies in patients with persistent AF:

1. Pulmonary vein isolation (PVI) alone
2. PVI plus complex fractionated electrograms (PVI+CFE)
3. PVI plus linear ablation (PVI+Lines).

1Calkins et al. Heart Rhythm 2012;9:632
Results - Primary Outcome

Documented AF > 30 seconds after one procedure with or without AAD

Verma et al. NEJM 2015;372:1812
“There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.”

-Donald Rumsfeld
Lessons From STAR-AF 2

• We need to better identify the patients with persistent AF who do well with PVI only
  – 60% of patients in PVI only group were free of AF after single procedure

• We need to get better at making complete linear lesions
  – Roof line complete in 93%; mitral isthmus line in 75%

• We need to get better at identifying important from unimportant CFAEs
Identification of Rotors and Focal Sources (FIRM)
CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) Trial

- 92 pts with paroxysmal or persistent (72%) AF
- Randomized (1:2) to FIRM-guided vs FIRM-blinded ablation
- Conventional group: wide area PVAI (+roof line in persistents)
- FIRM-guided ablation achieved termination in 20/36 and slowing in additional 11
- 24% of sites in RA
- Single procedure efficacy 82 vs 45% at 273 days
Current Endpoints of Ablation For Persistents

- Termination of AF
- Slowing of CL, DF
- Elimination of all CFAEs
- Completion of lesion set
Stepwise Approach in Bordeaux for Longstanding Persistents

- 60 patients with persistent AF for mean of 17 months
- 87% terminated to SR
- Single procedure success 62% at 11 months
- 88% success with multiple procedures
Restoration of Sinus Rhythm Prior to Ablation

- 40 patients with longstanding persistent AF (>1yr), restore SR 1 month, compared with matched control
- Less ablation performed in SR group, 47 vs 97 min
- 38/40 in SR group terminated during RFA vs 31/40 in control

Heart Rhythm 2012;9:1025–1030
## Characteristics of Procedure

<table>
<thead>
<tr>
<th>Table 2 Characteristics of the first procedure</th>
<th>SR group (n = 40)</th>
<th>Control group (n = 40)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Amiodarone within the preceding 3 mo, n (%)</td>
<td>17 (42.5)</td>
<td>19 (47.5)</td>
<td>.59</td>
</tr>
<tr>
<td>Atrial fibrillation cycle length (ms), mean ± SD</td>
<td>183 ± 32</td>
<td>166 ± 20</td>
<td>.06</td>
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<tr>
<td>Procedural duration (min), mean ± SD</td>
<td>199.8 ± 69.8</td>
<td>283.5 ± 72.3</td>
<td>***</td>
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<tr>
<td>Fluoroscopy time (min), mean ± SD</td>
<td>51.0 ± 24.9</td>
<td>96.3 ± 32.1</td>
<td>***</td>
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<tr>
<td>Radiofrequency duration (min), mean ± SD</td>
<td>47.5 ± 18.9</td>
<td>97.0 ± 30.6</td>
<td>***</td>
</tr>
<tr>
<td>Left line, n (%)</td>
<td>17 (42.5)</td>
<td>33 (82.5)</td>
<td>***</td>
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<tr>
<td>Roof line, n (%)</td>
<td>14 (35.0)</td>
<td>33 (82.5)</td>
<td>***</td>
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<tr>
<td>Mitral line, n (%)</td>
<td>7 (17.5)</td>
<td>30 (75.0)</td>
<td>***</td>
</tr>
<tr>
<td>CFAE ablation, n (%)</td>
<td>16 (40.0)</td>
<td>35 (87.5)</td>
<td>***</td>
</tr>
<tr>
<td>Ablation in the coronary sinus, n (%)</td>
<td>5 (12.5)</td>
<td>28 (70.0)</td>
<td>***</td>
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<tr>
<td>Termination of AF by ablation, n (%)</td>
<td>38 (95.0)</td>
<td>31 (77.5)</td>
<td>*</td>
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</table>
Termination as Endpoint

- AF may persist due to combination of underlying stable drivers, electrical remodeling, and structural remodeling.
- Termination of persistent AF likely implies sufficient modification of substrate and elimination of drivers.
- AF may persist after removal of these drivers, however, due to potentially reversible remodeling.
- Thus if ablation always proceeds until termination of AF, unnecessary ablation is likely performed in many.
Conclusions

- Patients with significant fibrosis outside the PV antrum, enlarged left atrium, longstanding AF, and underlying structural heart disease are likely to require ablation beyond PVI to achieve long-term freedom from AF.

- On the other hand, many patients with persistent AF without these characteristics who have activation gradients from the PV antrum to the rest of the atria may do well with PVI alone. Not all of these patients’ AF will terminate with PVI.
Conclusions

• Optimal lesion set for given patient is still unclear but should probably be tailored to underlying substrate
• Improved techniques to identify mechanisms of AF in individual patients are needed
• While termination of AF generally portends a favorable prognosis, if ablation is always carried out until termination, excessive lesions are likely created in many
• Improved endpoints that recognize elimination of stable drivers in the face of ongoing AF are needed.