Ablation of persistent AF
Is it different than paroxysmal?

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Classification of Atrial Fibrillation
ACC/AHA/ESC Guidelines

First Detected

Paroxysmal (Self-terminating)

Persistent (Not self-terminating)

Permanent

Is this the right way to divide the AF population?

What we do know

AF Begets AF

HTN, OSA, Pulmonary Dz, Valve

Aging, DM, MI, Valve

Calcium Overload - Breakdown of Intracellular Structure / Mitochondria & Surface Proteins

AF Begets AF

Facilitates Further AFib

Atrial Myopathy and Intra-myocardial Fibrosis and Scarring – Conduction Slowing

Rapid Atrial Rates Result in Intracellular Calcium Overload

PV Anatomy and Cellular Physiology - Spontaneous Rapid Depolarizations.....Initiates AFib

Cycle of Change with AF

PAF onset
Is this a continuum or are PAF and PerAF different entities?

**What we have known for a long time**

**Cardioversion of PerAF**

Duration of AF is the best predictor of recurrent AF

*P = <0.02

Dittrich HC. Am J Cardiol. 1989
Is our current classification scheme appropriate?

**Clinical Classifications of Atrial Fibrillation**
Poorly Reflect Its Temporal Persistence

Insights From 1,195 Patients Continuously Monitored With Implantable Devices

**Methods**
Cardiac rhythm histograms of 1,195 patients (mean 73.0 ± 10.1 years, follow-up 3.49 ± 4.0 years) with implantable devices were noninvasively monitored in accordance with current guidelines. AF burden, measured as the proportion of time spent in AF, was obtained from the device. Additionally, we evaluated the agreement between clinical and device-derived AF classifications.

**Results**
Patients within the same clinical class were highly heterogeneous with regards to AF temporal persistence. Agreement between the clinical AF classification and the objective device-derived assessments of AF temporal persistence was poor (Cohen’s kappa: 0.12 [95% CI: 0.05 to 0.18]). Patient characteristics influenced the clinical decision to classify AF as paroxysmal or persistent. Higher ejection fraction (odds ratios 0.97 per unit and 95% CI: 0.95 to 0.98 per unit; p < 0.0001) and presence of coronary artery disease (odds ratio: 0.83 [95% CI: 0.32 to 0.88]; p = 0.04) were independently associated with a lower probability of being classified as persistent AF for the same AF burden level.

**Conclusions**
The currently used clinical AF classifications poorly reflect AF temporal persistence.

There is significant overlap in the documented AF burden between patients categorized as PAF vs PerAF.

**Charitos et al, JACC 2014**

Do PerAF and PAF have the same basic triggering mechanism?

**Single procedure efficacy of isolating all versus arrhythmogenic pulmonary veins on long-term control of atrial fibrillation:**
A prospective randomized study

103 pt (70% PAF, 30% PerAF)
Randomized to all PVI – ALL (51) vs PVI – Arrhythmogenic (52)

Distribution of arrhythmogenic PVs was the same for both PAF and PerAF
(< 2 veins in 29%, 3 veins in 40% and 4 veins in 31%)
Indicating that PAF and PerAF have the same basic PV triggering mechanism

However PerAF was a predictor of late recurrence (57% NSR @ 1 yr)

**Dixit et al, Heart rhythm 2008**
Is the substrate the same for PerAF and PAF?

**Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation**

The DECAAF Study

15 centers / 6 countries, 329 patients referred for 1st AF ablation

- PAF 168 (65%), PerAF 75 (29%), Perm / LS PerAF 17 (6%)

Pattern of AF was not a good predictor of the degree of fibrosis

Degree of fibrosis was strongly associated with AF recurrence

Marrouche et al, JAMA 2014

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**PAF vs PerAF**

**Same or different?**

- PAF patients can progress to PerAF and has similar triggers (same basic process)
- Some PAF and PerAF Pts can have similar AF burden during long term monitoring
- CMR fibrosis grading has shown significant overlap between PAF and PerAF
Not all Persistent AF is the same

Persistent Atrial Fibrillation From the Onset

A Specific Subgroup of Patients With Bialtrial Substrate Involvement and Poorer Clinical Outcome

129 Persistent AF patients from onset (PsAFonset) vs 231 PsAF patients which had transitioned from PAF

PsAF onset patients

1. A unique set of demographics:
   a. Younger;
   b. A higher proportion of men;
   c. Obese;
   d. Presence of cardiovascular disease (e.g., hypertension); and
   e. Larger LA and RA size
2. Electrophysiological properties and AF drivers:
   a. Shorter AF cycle length;
   b. Higher degree of fractionation;
   c. Lower bialtrial endocardial voltages;
   d. Increased number and widespread distribution of re-entrant AF drivers; and
   e. Less focal drivers
3. Poorer prognosis:
   a. Low acute AF termination rate; and
   b. Higher AF and AT recurrence after ablation

Lim et al, JACC clinical electrophysiology, 2016

Mean # procedures = 1.4

P<0.001

Freedom from AF/AT

Three Randomized Trials
RFA vs AA Drugs
Arranged according to Duration of AF

Callans, Circulation, 2008
PAF vs PerAF
Same or different?

• Single procedure AF control is better for PAF (70-80%) than PerAF (40-50%)
• PerAF is more heterogenous group than PAF (Short term vs Long standing PerAF vs PerAF from onset)
• Bottom line – the pattern of AF is important but doesn’t tell the whole story

EP Physician vs Persistent AF
No difference in outcomes between PAF and Per / LS PerAF
Indicates that the LAA and RA may be important for ablating PerAF

The question is how to find that spot in everyone
Atrial Fibrillation Ablation
Evolution of a Moving Target
Can’t we just throw technology at the problem?

Is it a mapping issue, lesion set issue, energy source issue ...?

Strategies for Ablation of PerAF

1. PVI (WACA) alone (Like what we do for PAF)
2. PVI + Additional Trigger Mapping
3. PVI + CFAE (or CFAE alone)
4. PVI + linear lesions
   - Roof, Mitral Isthmus, Box lesion set, LAA isolation
5. Stepwise approach / Frequency gradients
   - AF termination endpoint
**Pulmonary Vein Antral Isolation and Nonpulmonary Vein Trigger Ablation without Additional Substrate Modification for Treating Longstanding Persistent Atrial Fibrillation**

**PV Ablation for Persistent Atrial Fibrillation.** Introduction: Effectiveness of antral pulmonary vein isolation (PVAI) and ablation of non-PV triggers (non-PVTAs) in controlling longstanding persistent atrial fibrillation (AF) has not been reported. We sought to describe clinical outcomes with this ablation strategy in patients (pts) followed for at least 1 year.

**Methods:** Two hundred pts underwent PVAI for longstanding persistent AF and were followed for recurrence. Thirty-three pts with <1-year follow-up and 37 pts with additional RF atrial ablation were excluded, leaving 130 pts for analysis.

**Results:** All 130 pts (108 men, mean LA 4.7 ± 0.6 cm, mean AF duration of 38 ± 44 months) underwent PVAI with entrance/exit block. In addition, 24 pts (15 pts during the initial procedure and 9 additional pts at repeat ablations) had 40 non-PVTAs, including 3 with AVNRT. During follow-up, atrial flutter (AFL) was noted in 7 (5%) pts. The AF-free survival after single procedure without antiarrhythmic drugs (AAD) was 38%. Repeat AF or AFL ablation was performed in 37 pts (28%) with PV reconnection uniformly identified (3.7 ± 0.5 veins/pt). During mean follow-up of 41.1 ± 23.8 months (range 12–103 months), 85/130 pts (65%) were in sinus rhythm with 65 pts (50%) off AAD, 20 pts (15%) on AAD. Additionally, 9 pts (7%) have had rare episodes of AF such that 72% of pts have had good long-term clinical outcome. Of the 36 pts with recurrent AF, 20 pts have not had a repeat procedure.

**Conclusions:** PVAI with non-PVTA for longstanding persistent AF provides good long-term AF control in over 70% of patients with infrequent (5%) AFL. AAD therapy and repeat PVAI may be required for this optimal outcome. (J Cardiovasc Electrophysiol, Vol. 23, pp. 806–813, August 2012)

**Note: Only 15/130 (11%) had non-PVTAs identified**

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**Is PerAF a Bialtrial Disease?**

**Randomized Evaluation of Right Atrial Ablation After Left Atrial Ablation of Complex Fractionated Atrial Electrograms for Long-Lasting Persistent Atrial Fibrillation**

**What is a CFAE?**

CFAE = CL < 120ms, CL < AF CL in CS, fractionated egms or CEA

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Lin et al, JCE 2012

Oral et al, 2008
Randomized Evaluation of Right Atrial Ablation After Left Atrial Ablation of Complex Fractionated Atrial Electrograms for Long-Lasting Persistent Atrial Fibrillation

LA / CS CFAEs

LA RFA for AF = 85
AF terminated = 19
Sinus rhythm = 14 (74%)
Repeat ablation = 5 (26%)
AF persisted after LA RFA = 66 (randomized)
Sinus rhythm = 17 (89%)
No further RFA = 33
RA RFA = 33
Sinus rhythm without antiarrhythmics at 17±6 months = 8 (24%)
Sinus rhythm without antiarrhythmics at 17±6 months = 10 (30%)

Termination of AF during LA CFAE ablation is a good prognostic sign
RA CFAE ablation did not provide additional benefit

Triggers vs Substrate

Randomized Ablation Strategies for the Treatment of Persistent Atrial Fibrillation

RASTA Study
156 patients randomized to 3 different RFA arms, 1 yr F/U
Mean AF duration = 47 ± 50 mths

Arm 1 = 55 pts
PVI + Identified Non-PV triggers

Arm 2 = 50 pts
PVI + emperic Non-PV trigger Sites

Arm 3 = 51 pts
PVI + LA CFAEs Automated CFAE algorithm
**Conclusion:** Triggers are more important than substrate or CFAEs are the wrong substrate to target

### Randomized Ablation Strategies for the Treatment of Persistent Atrial Fibrillation

<table>
<thead>
<tr>
<th>Procedure Efficacy at 1 year After Single Ablation</th>
<th>Overall Procedure Efficacy With ≥ 1 Ablation</th>
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<td><img src="image1.png" alt="Graph A" /></td>
<td><img src="image2.png" alt="Graph B" /></td>
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**Dixit et al, 2012**

### Stepwise AF Ablation

**Ablation to termination**

1. **STEP 1:** Lesion-guided pulmonary vein isolation
2. **STEP 2:** Roof line ablation
3. **STEP 3:** Ablation of CS region and complex LA activities
4. **STEP 4:** Mitral isthmus ablation

**Average case time > 4 hours, low termination rate to NSR**

**O’Neill et al, J Interventional Card Electrophysiology, 2006**
Approaches to Catheter Ablation for Persistent Atrial Fibrillation

**Methods**

We randomly assigned 500 patients with persistent atrial fibrillation in a 1:2:2 ratio to ablation with pulmonary-vein isolation alone (87 patients), pulmonary-vein isolation plus ablation of electrograms showing complex fractionated activity (363 patients), or pulmonary-vein isolation plus additional linear ablation across the left atrial roof and mitral valve isthmus (29 patients). The duration of follow-up was 18 months. The primary end point was freedom from any documented recurrence of atrial fibrillation lasting longer than 30 seconds after a single ablation procedure.

**Results**

Procedure time was significantly shorter for pulmonary-vein isolation alone than for the two other procedures (p<0.001). After 18 months, 93% of patients assigned to pulmonary-vein isolation alone were free from recurrent atrial fibrillation, as compared with 49% of patients assigned to pulmonary-vein isolation plus complex electrogram ablation and 46% of patients assigned to pulmonary-vein isolation plus linear ablation (p<0.05). There were also no significant differences among the three groups for the secondary end points, including freedom from atrial fibrillation after two ablation procedures and freedom from any atrial arrhythmia. Complications included tamponade (three patients), stroke or transient ischemic attack (three patients), and atroventricular block (one patient).

**Conclusions**

Among patients with persistent atrial fibrillation, we found no reduction in the rate of recurrent atrial fibrillation when either linear ablation or ablation of complex fractionated electrograms was performed in addition to pulmonary-vein isolation.
What’s “New” for Persistent AF Ablation

1. Risk Factor Modification
2. New energy sources (Cryo-balloon)
3. Substrate Ablation (Fibrosis – CMR vs Egm)
4. Rotor Mapping (Endocardial vs Epicardial)

Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation

The ARREST-AF Cohort Study

Methods: 281 consecutive patients undergoing AF ablation. 149 with a body mass index >27 kg/m² and ≥1 cardiac risk factor were offered risk factor management (RFM) according to American Heart Association/American College of Cardiology guidelines. After AF ablation, all 61 patients who opted for RFM and 88 control subjects were assessed every 3 to 6 months by clinic review and 7-day Holter monitoring. Changes in the Atrial Fibrillation Severity Scale scores were determined.

Results: There were no differences in baseline characteristics, number of procedures, or follow-up duration between the groups (p = NS). RFM resulted in greater reductions in weight (p = 0.002) and blood pressure (p = 0.006), and better glycemic control (p = 0.001) and lipid profiles (p = 0.01). At follow-up, AF frequency, duration, symptoms, and symptom severity decreased more in the RFM group compared with the control group (p < 0.001). Single-procedure drug-unassisted arrhythmia-free survival was greater in RFM patients compared with control subjects (p < 0.001). Multiple-procedure arrhythmia-free survival was markedly better in RFM patients compared with control subjects (p < 0.001), with 16% and 42.4%, respectively, using antiarrhythmic drugs (p = 0.004). On multivariate analysis, type of AF (p < 0.001) and RFM (hazard ratio 4.8 [95% confidence interval: 2.04 to 11.4]; p < 0.001) were independent predictors of arrhythmia-free survival.

Conclusions: Aggressive RFM improved the long-term success of AF ablation. This study underscores the importance of therapy directed at the primary promoters of the AF substrate to facilitate rhythm control strategies. (J Am Coll Cardiol 2014;64:2222-31) © 2014 by the American College of Cardiology Foundation.

Weight loss, CPAP, HTN and DM Rx!
Pathak et al 2014
Inclusion – symptomatic drug refractory PerAF for 1st AF ablation
Exclusion – AF > 1 yr, LA > 6 cm, significant valve dz, CHF, prior ablation
Results – 157 pt ablated with CB technology and F/U for 1 yr
PVI successful in 100%
LA procedure time = 112 ± 30 min
3 complications (2 phrenic nerve, 1 effusion)
NSR @ 1yr in 82% (17% on AARx), 68% NSR off AARx

Conclusion – In Short term PerAF
PVI with CB is a reasonable approach

Substrate Mapping (voltage vs CMR)

Box Isolation of Fibrotic Areas (BIFA): A Patient-Tailored Substrate Modification Approach for Ablation of Atrial Fibrillation

Conclusions: In approximately 40% of pts with nonparoxysmal AF, no substantial LVA were identified, and PVI alone showed high success rate. In pts with paroxysmal AF despite durable PVI and in approximately 60% of pts with nonparoxysmal AF, individually localized LVA were identified and could be targeted successfully with the BIFA strategy.

LA Electro-anatomic Voltage mapping
Normal Voltage > 1.5 mV
Low Voltage Areas (LVA) < 0.5 mV
RFA strategy – PVI alone if no LVA
PVI + BIFA of LVAs
LVAs – Anterosept 40%, Posterior – 30%

Kottkamp et al JCE 2016
Topera / FIRM - Endocardial Rotor Mapping

Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: A multicenter experience

METHODS All FIRM-guided ablation procedures (n = 62) at UCLA Medical Center and Virginia Commonwealth University Medical Center performed between January 2012 and October 2013 were included for analysis. During AF, FIRM software constructed phase maps from unipolar atrial electrograms to identify putative AF sources. These sites were targeted for ablation, along with pulmonary vein isolation in 77% of patients.

RESULTS AF was paroxysmal in 56%, and 67% had prior AF ablation. All patients had rotors identified (mean of 3.6 ± 1.2 per patient, 77% in LA). Prespecified acute procedural endpoint was achieved in 67% of patients (n = 20); AF termination in 4, organization in 7, >10% slowing of AF cycle length in 9. Acute complications occurred in 8 patients (9.1%). At 18 ± 7 months of follow-up, 37% were free from documented recurrent AF after a 3-month blanking period; 21% were free from documented atrial tachyarrhythmias and 80% from AF documented during stress. Multivariate analysis did not reveal any significant predictors of AF recurrence, including pattern of AF, acute procedural success, or prior failed ablation.

CONCLUSION Long-term clinical results after FIRM ablation in this cohort of patients showed poor efficacy, different from previously published studies. Randomized studies are needed to evaluate the efficacy and clinical utility of this ablation approach for treating AF.

Is Topera / FIRM the Wrong Technology or Wrong Concept

Baskets fit poorly in both RA and LA, often > 50% of basket EGMs aren’t useable

Endocardial recordings may be inadequate for rotor localization

Buch et al, Heart Rhythm 2016

Body Surface Rotor Mapping

Non-invasive epicardial driver area localization

CT Guided Surface Mapping

70% LA / 30% RA
80% reentry
20% focal

Figure 2: Significance of Number of Driver Regions

Arrhythmia and Electrophysiology Review 2015
Ablation Outcomes
Driver ablation alone terminated 75% of PerAF

Short term PerAF / progressed from PAF = Standard WACA PVI (RFA or Cryo-Balloon)
Intermediate term PerAF (< 1 yr) without significant fibrosis / right atrial pathology = WACA PVI and RFA of easily identifiable triggers
Long standing persistent AF or PerAF from onset with significant fibrosis / right atrial pathology = More extensive ablation with WACA PVI + additional lesions vs Consider surgical LA / RA approach
“One of the first duties of the physician is to educate the masses not to take medicine.”

Sir William Osler
(1849-1919)