Catheter Ablation for Persistent Atrial Fibrillation

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Atrial Fibrillation

- First reported by Sir William Harvey in 17th century: chaotic motion of atria in open chest animals
- First described in 1903 by Hering
Atrial Fibrillation Demographics by Age


### U.S. population

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Population with AF x 1000</th>
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Epidemiological Time Bomb

It is estimated the number of persons with Atrial Fibrillation (AF) to increase three to four-fold from 2.6 million in 2010 to epidemic proportions of 12-16 million in 2050.

- 35% of the increase being due to the increased incidence and

- 65% being due to the increased population size, and a larger proportion of elderly patients

<table>
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<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td><strong>Paroxysmal AF</strong></td>
<td>• AF that terminates spontaneously or with intervention within 7 d of onset.</td>
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<td>• Episodes may recur with variable frequency.</td>
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<td><strong>Persistent AF</strong></td>
<td>• Continuous AF that is sustained &gt;7 d.</td>
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<td><strong>Long-standing persistent AF</strong></td>
<td>Continuous AF &gt;12 months in duration.</td>
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<td><strong>Permanent AF</strong></td>
<td>• The term “permanent AF” is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm.</td>
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<td>• Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF.</td>
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<td>• Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve.</td>
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<td><strong>Nonvalvular AF</strong></td>
<td>• AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.</td>
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Therapeutic Approaches to Atrial Fibrillation

- Anticoagulation
- Antiarrhythmic suppression
- Control of ventricular response
  - Pharmacologic
  - Catheter modification/ablation of AV node
- Curative procedures
  - Catheter ablation
  - Surgery (maze)
Rhythm vs Rate control Trials

- PIAF
  - Lancet 2000
- AFFIRM
  - NEJM 2002
- RACE
  - NEJM 2002
- STAF
  - JACC 2003
- Hot CAFÉ
  - Chest 2004
Rate vs. Rhythm control

- None of the RCTs found rate control inferior in terms of mortality or quality of life.
- One study showed rate control reduced the mortality in patients without Heart Failure, in over 65s and in patients with coronary heart disease.
- Reduced rates of hospitalization and adverse events with rate control
- No difference in the rate of thromboembolic or hemorrhagic events
- Rate control is more cost effective.
What Trials Did Not Tell Us?

• Optimal management for patients with moderate or severe disabling symptoms related to atrial fibrillation

• Long-term implications of rate vs. rhythm control (mean duration of follow-up only 3.5 years), especially in younger patients.

• Outcome if better tools to maintain sinus rhythm were available
Rate vs. Rhythm Control

• With antiarrhythmic drug efficacy that is only slightly better than throwing a coin, it is not surprising that neither rate control nor rhythm control using antiarrhythmic drugs fail to impact survival.

• While one may interpret the trial findings as to the adequacy of both therapies, the opposite is more likely to be true:
  – Both strategies are inadequate, leading to arrhythmia progression and unabated mortality rates.
What Needs to be Studied

• A rate control strategy
• A rhythm control strategy with antiarrhythmic drugs
• A rhythm control strategy employing ablative therapy
Therapeutic Approaches to Atrial Fibrillation

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When did the story of ablation for AF begin ...

1998
Pulmonary Vein Spike Discharges
Initiation of AF by PV Discharges
Pulmonary Vein Isolation (PVI) is the Cornerstone of AF Ablation . . .

HRS Consensus Statement

“Ablation strategies which target the PVs and/or PV antrum are the cornerstone for most AF ablation procedures.”

Class I
Level of evidence A
Paroxysmal AF

Catheter Ablation for Paroxysmal AF

Recommendations

AF catheter ablation is useful for symptomatic paroxysmal AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm-control strategy is desired.

In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm-control strategy before therapeutic trials of antiarrhythmic drug therapy, after weighing the risks and outcomes of drug and ablation therapy.

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation
Different Story of Persistent AF

• At least for paroxysmal AF, PV ablation appears to be sufficient to treat most patients.
  – Single procedure success rates of approximately 70% at 1 year and long-term outcomes (3 to 5 years) of 80% with multiple procedures.

• The clinical results for PVI as a sole ablation strategy in persistent AF have been relatively disappointing.
  – Reported success rates vary from 25 to 70%. 

Matthew W. Ablation of Persistent AF: Have We Come Full Circle, or Are We Chasing Our Tails? VOL. 66, NO. 24, 2015
Ablation Strategies

- PV isolation, antral ablation
- Extra-PV triggers
- Ablation of ganglionic plexi
- Complex, fractionated atrial electrograms (CFAE) ablation
- Linear ablation
- Rotor ablation
PV Isolation by RF Ablation
RF ablation: PV Isolation during AF
RF ablation: PV Isolation during AF
RIPV Reentry
Antral ablation, RIPV slower
Antral ablation, RIPV slower
Termination of AF with termination of RIPV tachycardia
Termination of AF
Termination of AF during Ablation

- Directly to sinus or after conversion to atrial tachycardia
- Variable reports: 15-70%
- Controversial as a predictor of long term success
PV Isolation by Cryoablation
PV Isolation during Cryoablation
Antral PV Isolation

• Circumferential or antral PV isolation yields long-term sinus rhythm in only ≈24% of patients with long-standing persistent AF

Cryoablation in Persistent AF

• A study using the second-generation cryoballoon reported a 60% success rate after 1 year and a single procedure in patients with persistent AF.

• However, the majority of patients in the study (60%) presented to the laboratory in sinus rhythm.

Extra PV Sources

Shock resistant long persistent AF
PV Potentials
PV Isolation

Conversion to atrial flutter during isolation of LSPV
PV Isolation

Conversion to atrial tachycardia during isolation of LSPV
Halo in SVC, RF in RSPV
Termination
Acceleration and loss of signals in SVC
Dissociated SVC Potential
Final Sinus Rhythm
Additional Substrate Modification

• Currently, the field of persistent AF ablation has been marked by conflicting results when evaluating varied techniques of substrate modification.

• The two most common techniques for substrate modification are the creation of linear lesions in LA and focal ablation to eliminate atrial signals that show complex activity “complex fractionated electrograms”.
Linear Ablation

• Lines of ablation are commonly tried including mitral isthmus and roof lines.

• More extensive ablation may cause new, iatrogenic areas of arrhythmogenesis where tissue is incompletely ablated or linear block is not achieved.
CFAE Ablation

What are CAFÉ’s

- EGMs with CL < 120 ms
- EGMs with continuous electrical activity
- EGMs with low amplitude and more than 2 deflections
- EGMs with CL shorter than in the CS or LAA

Modified from Walid I. Saliba, M.D.
Does CAFÉ offer additional success?

• Different techniques, operators, skills, interpretations, endpoints, experiences, follow up’s in trials.

• Significance of CAFÉ: Active vs Passive role?

• Is it just more Controlled Debulking?
“The modest efficacy attained in this study despite extensive ablation of left atrial and coronary sinus CFAEs suggests either that CFAEs do not accurately identify sites that are critical to the maintenance of chronic AF or that ablation of CFAEs is not sufficient to eliminate the driving mechanisms of chronic AF in a large proportion of patients.”
Stepwise Approach

• About 10 years ago, Haïssaguerre et al published their results with a stepwise ablation approach in patients with persistent AF.

Steps

LSPV

Post CS & LA-CAFE

Post Antral Isolation

AT Ablation
Stepwise Approach

• The steps included PV isolation, electrogram-based, and linear ablation.

• The end point of the procedure was AF termination during radiofrequency ablation, that is, without antiarrhythmic drugs or cardioversion.

• AF was terminated by ablation in ≈85% of patients and after a mean follow-up of 11 months, 95% of patients were in sinus rhythm.
Cumulative Benefit

Cumulative benefit up to a limit

Number of Patients Terminating with each Step of Ablation

Progressive decrease in incremental benefit per stage after five stages of ablation beyond which further LA ablation is probably of no clinical benefit.

Modified from Walid I. Saliba, M.D.
5 Year Results

- Persistent AF may be terminated during RF ablation in ≈80% of patients.
- After a total of 317 procedures (median 2) and a median follow-up of almost 5 years, 65% of patients remained in sinus rhythm without antiarrhythmic drugs.
- Arrhythmia free outcomes were ≈90%, 80%, and 63% at 1, 2, and 5 years.

Long Term Results

• Despite the excellent acute and midterm results, long-term freedom from atrial arrhythmias could only be achieved in about two thirds of the patients.

• Possible factors that may help explain late recurrences include:
  – Lack of complete, transmural lesions
  – Incomplete understanding of the arrhythmia mechanisms
  – Slow drug washout (e.g. amiodarone)
Late Recurrence

• Catheter ablation is effective in eliminating triggers and drivers of AF in both paroxysmal and persistent AF, but of course does not undo the structural changes that led to AF in the first place.

• Catheter ablation also does not render the atrium immune to the pathophysiologic insults related to comorbidities such as sleep apnea, obesity, hypertension, and diabetes mellitus.
STAR AF II Trial

• The efficacy of additional linear ablation or ablation of complex fractionated atrial electrograms has recently been called into question with the publication of the STAR AF II data demonstrating no benefit, and possibly even harm, compared with PV isolation alone.

Star AF II

• The study was conducted in 48 experienced centers in 12 countries, including China.

• 589 patients with persistent AF were randomized in a 1:4:4 format to PVI alone (n=67), PVI+lines (n=259), or PVI+CFAE ablation (n=263).

• The reasoning behind uneven randomization was that the guidelines recommended more ablation in persistent AF.
STAR AF II Results

• Ablation characteristics suggested skillful ablation.
  – PVI was successful in 97% of all groups
  – CFAE were eliminated in 80%
  – Roof lines were successful in 93% and mitral isthmus lines in 75%.

• Procedure and fluoroscopy times were increased in the two PVI-plus groups.
  – 60 more minutes of procedure time
  – 10 to 12 minutes extra X-ray exposure.
STAR AF II Outcomes

• The primary outcome was reached in
  – 59% of patients in the PVI-alone group
  – 48% in the PVI+CFAE group, and
  – 44% of the PVI+lines group.

• The numerical superiority of PVI alone did not reach statistical significance (p=0.15).

• After two ablation procedures, the results were similar. 72% for PVI alone; 60% for PVI+CFAE, and 58% for PVI+lines.
STAR AF II Outcomes

P=0.15 for the overall comparison, by the log-rank test

No. at Risk

<table>
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<th>Procedure</th>
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<th>60</th>
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<td>Pulmonary-vein isolation</td>
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<tr>
<td>Isolation plus electrograms</td>
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<td>161</td>
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<td>72</td>
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<tr>
<td>Isolation plus lines</td>
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<td>240</td>
<td>152</td>
<td>133</td>
<td>115</td>
<td>57</td>
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Complications did not differ in statistical significance, but Sedation-related issues, access-site problems, and fluid overload were numerically higher in the extra-ablation groups.

Three patients suffered transient ischemic attacks or strokes and one patient died; All four were in the groups with more extensive ablation.
STAR AF II Conclusions

• The authors made two conclusions:
  – First, additional ablation beyond PVI increased procedure time but did not improve freedom from AF.
  – Second, PVI alone achieved freedom from AF in little more than half the patients, which is comparable to published success rates for ablation in patients with paroxysmal AF.

• A major criticism of STAR-AF2 is that lines were not blocked in 26% of patients.
BOCA Trial

• In BOCA, the investigators prospectively randomized 131 persistent AF patients in 1:1 fashion to PVI+lines (roof and mitral, control) or PVI+lines+CFAE.

• Conduction block was confirmed in 95% of mitral lines and 100% of roof lines and PVI.

Wong KCK, et al. No benefit of complex fractionated atrial electrogram ablation in addition to circumferential pulmonary vein ablation and linear ablation: benefit of complex ablation study. Circ Arrhythm Electrophysiol. 2015;8:1316–1324.
BOCA Results

• Patients in the CFAE arm had no advantage over the control arm
  – Similar single (46.2% versus 56.9%,) and multiprocedure (78% versus 80%) freedom at 12 m.
  – More atrial flutters and longer procedural and ablation times.

![Graph showing freedom from AF/AT after first ablation procedure](image)
CHASE-AF Trial

- Patients with persistent AF after PVI.
- To compare:
  - PVI
  and
  - A stepwise approach (full defrag) consisting of PVI, ablation of CFAE, and additional linear ablation lines

CHASE-AF Population

- 205 patients with de novo ablation for persistent AF
- Prospectively randomized to either PVI alone (n = 78) or full defrag (n = 75)
  - 52 patients not randomized due to AF termination with the original PVI.
- The primary endpoint was recurrence of any atrial arrhythmias after a blanking period of 3 months.
CHASE-AF Outcomes

- 241 ablations were performed (mean: 1.59 in the PVI-alone group, 1.55 in the full-defrag group).

- With the stepwise approach, termination of AF occurred in 45 (60%) patients.

- Arrhythmia-free survival did not differ whether patients underwent single or multiple procedures (p = 0.468).
CHASE-AF Outcomes

- The stepwise approach (full defrag) did not appear to provide additional benefit over PVI alone in these patients.
Based on these studies a stepwise approach aimed at AF termination does not seem to provide additional benefit over PVI alone in patients with persistent AF.

It is associated with significantly longer procedural and fluoroscopic duration as well as radiofrequency application time.
Why is more ablation worse?

- More Ablation: Potential for more atrial Flutter
- More ablation: Compromise LA mechanical function
- More ablation: Interatrial / intra-atrial dyssynchrony
- More ablation: More fluoroscopy / More potential complications
“Less-is-More" Message

• These trials show that non-targeted debulking of atrial tissue, based on early assumptions that AF is a random process, fails to improve patient outcomes.

• The overwhelming message that less is more for AF ablation makes us think twice about which AF mechanisms are ablated by current lesion targeting.
Why Line and Café Not Effective

- If AF is caused by disordered wavelets that self-sustain, as hypothesized by Moe from computer models, then lines and additional lesions should reduce the tissue available for these wavelets and should thus improve outcomes.
Fundamental AF Mechanisms

• AF may be driven by 2 fundamental mechanisms:
  – Preferred regional mechanisms (sources) driving disorganized waves or
  – Disorganized wavelets that self-sustain, that is, without preferred regional sources, such as the multiple-wavelet or endo-epi dissociation hypotheses.
Fundamental AF Mechanisms

• AF may be driven by 2 fundamental mechanisms:
  – Disorganized wavelets that self-sustain, that is, without preferred regional sources, such as the multiple-wavelet or endo-epi dissociation hypotheses.
  
  or

  – Preferred regional mechanisms (sources) driving disorganized waves
AF Mechanisms

- Current data emphasize the need to better understand persistent AF mechanisms rather than designing empirical ablation lesion sets which do not take into account the varied and individual underlying mechanisms in different AF populations.
A Bi-atrial Disease?

• Studies increasingly show that persistent AF is a bi-atrial disease, with a third of sources occurring in the right atrium on endocardial or epicardial mapping.

• Ablation lines intersected only 40% to 60% of sources, and such patients had substantially higher success than those in whom sources were missed.

Rotors

• High-resolution optical mapping in animal models suggest the presence of *spiral wave re-entry* sustaining fibrillation of both the ventricles and the atria.

• Multiple groups have attempted to demonstrate such spiral waves and rotors by high-density epicardial mapping in human AF.

• Although transient rotational activity centered on a core of high-frequency activity consistent with rotors has been described, there are no reports of sustained spiral wave re-entry in human persistent AF demonstrated through such methods.

Focal Impulse and Rotor Modulation (FIRM)

• The initial study of 92 patients with paroxysmal or persistent AF reported localized rotors or focal impulses in 97% of patients, with a mean of 2.1±1.0 focal sources per patient.

• Catheter ablation specifically targeted at the location of these AF sources achieved the primary end point of AF termination or sustained AF slowing in 86%, with AF termination in 56% after 4.3±6.3 minutes of ablation.

CONFIRM Trial

• Over a median of 9 months after a single procedure, freedom from AF was achieved in 82% after FIRM-guided ablation compared with 45% after a conventional PVI–based ablation strategy.

Rotor Ablation

- Subsequent multicenter registry study from 10 centers recruiting 78 patients, of which 62% had persistent AF and 9% had longstanding persistent AF, provided independent support for these findings.

- The authors reported a similar number of focal sources distributed widely throughout the atria, with 88% freedom from AF after the index procedure at >1-year follow-up.

FIRM Technique

• A limitation of the FIRM technique, well acknowledged by Narayan et al, is the dependence on a basket catheter that may not adequately adapt to individual variation in atrial geometry to provide optimal atrial coverage.

• There are also limitations inherent in the representation of a complex 3D structure as a 2D rectangular grid of regularly spaced electrodes that assumes an ideal spherical fit of the basket catheter.
Not CONFIRMed

- Other groups have not confirmed the results of ‘CONFIRM’.

- In one study of 24 patients (50% paroxysmal and 58% in sinus rhythm at the time of the procedure), they report that FIRM guided mapping was able to identify $2.3 \pm 0.9$ focal sources per patient with a left atrial dominance, similar to the original data.

Contradictory Results

• However, they reported AF termination in only 1 of the 24 participants, with 50% achieving the primary end point, when atrial arrhythmia organization and cycle length slowing were included in its definition.

• The majority of cases of acute procedural success were achieved in patients with induced AF and that cardioversion was required in all participants presenting to the laboratory in AF.

The Shortcomings of FIRM

• In this study and in others using FIRM mapping, the lack of distinguishing electrogram features at the putative site of focal drivers such as rotors is a striking finding.

• Electrograms at FIRM-identified ablation sites were not found to differ in dominant frequency or Shannon entropy values compared with the atrial regions that did not harbor focal AF drivers.

AF begets AF

• Studies suggest that AF by itself is a key causative factor in the progression of atrial remodeling in humans, independent of other known factors including hypertension, obesity, and diabetes.

• Like in cancer, the later the intervention, the worst the outcome and a higher number of non-PV triggers is generally found.

The Window of Opportunity

• The concept that AF promotes AF via electrophysiological and structural remodeling was described nearly 20 years ago.

• Paroxysmal AF is associated with significant left atrial remodeling, especially in patients with AF burden >10%.

• Progression of paroxysmal AF is more common with medical therapy than with ablative therapy.

Natural History of AF

Paroxysmal
Self-terminating AF episodes
Sinus can be restored electrically or chemically
Atrial remodeling
- Refractory period decreases
- Conduction velocity decreases
Favors arrhythmia
Trigger initiation
Substrate maintenance
Ablation of triggers

Persistent
Sinus cannot be maintained electrically or chemically
Atrial remodeling
- Refractory period decreases
- Conduction velocity decreases
Favors arrhythmia
Trigger initiation
Substrate maintenance
Modification of substrate
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Modified from Walid I. Saliba, M.D.
Catheter Ablation for Persistent AF

Recommendations

AF catheter ablation is reasonable for some patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication.

AF catheter ablation may be considered before initiation of antiarrhythmic drug therapy with a class I or III antiarrhythmic medication for symptomatic persistent AF when a rhythm-control strategy is desired.

AF catheter ablation may be considered for symptomatic long-standing (>12 months) persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm-control strategy is desired.

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