Treatment of atrial fibrillation by advanced ablation technology

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Conflict of interests

- Lecture fees and congress support by:

- Medtronic, Biotronik, St. Jude Medical
Treatment of atrial fibrillation by advanced ablation technology

Prof. Ernst G. Vester
Klinik für Kardiologie
Evangelisches Krankenhaus Düsseldorf
Advanced ablation of AF

- Definitions, targets, general results
- Special approaches: „Single shot“ devices
- Fibrosis imaging
- Complex fractionated atrial electrograms (CFAE)
- Ganglionicated Plexi (GP), Fad pads
- Left atrial appendage (LAA)
- Rotors
Advanced ablation of AF

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A new classification of clinical types of atrial fibrillation as proposed by the Consensus Conference of AFNET/ European Heart Rhythm Association (from Kirchhof et al.)

<table>
<thead>
<tr>
<th>AF type</th>
<th>Clinical presentation</th>
<th>Possible pathophysiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defined types of AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual AF</td>
<td>AF in patients with inherited cardiomyopathies including hypertrophic cardiomyopathies.</td>
<td></td>
</tr>
<tr>
<td>Focally induced AF</td>
<td>Patients with repetitive atrial runs and frequent, short episodes of paroxysmal atrial tachycardia. Often highly symptomatic. Younger patients with dilated and/or thickened atrial walls (chronic AF). Atrial arrhythmia may result in atrial tachycardia and adverse clinical outcomes.</td>
<td></td>
</tr>
<tr>
<td>Postoperative AF</td>
<td>Atrial fibrillation occurring after cardiac/pulmonary surgery in patients who were in sinus rhythm before surgery and had no prior history of AF.</td>
<td>The antiarrhythmic mechanisms conveying sudden death in these patients also contribute to the occurrence of atrial fibrillation. Localization/triggers, in most cases originating from the pulmonary veins, increase AF. AF due to perioperative events is also considered to be part of this type of AF.</td>
</tr>
</tbody>
</table>

| Complex types of AF         |                       |                                             |                                             |
| Yablokov AF                 | Atrial fibrillation manifesting before 80 years in patients with mitral stenosis or patients after mitral valve surgery. | Increased left atrial pressure (stenosis) and mitral valve regurgitation (stenosis) contribute to atrial enlargement and structural atrial damage in these patients. |                                             |
| AF in the elderly           | AF which first manifests at an age ≥80 years. | Ageing of the atria (possibly including accelerated ageing): Increased fibrosis and collagenization, type of cardiomyocytes, increased atrial and myocardial stiffness contribute to this type of AF. |                                             |
| Polygenic AF                | This type of AF is defined by the presence of common gene variants which are associated with early-onset AF. | Currently unclear, possibly including shortening of the atrial action potential and/or left atrial cardiomyocytes with abnormal automaticity. |                                             |
| Unclassified AF             | AF which does not fulfill any of the other definitions. These forms of AF may be rather common, illustrating the need for a better classification. | Shortening of atrial refractoriness (e.g., tachycardia-induced atrial remodeling or enhanced parasymptomatic tone) or localized conduction disturbances due to atrial fibrosis induced by structural heart disease may contribute to this type of AF. |                                             |
Summary of the electrophysiologic substrate in posterior left atrial wall amenable to catheter ablation using the linear approach.

Huang, SKS., Wood, MA; Catheter Ablation of Cardiac Arrhythmias; Saunders Elsevier. 2006.
AF Ablation Strategies
Pioneer work: „Spontaneous initiation of AF by ectopic beats origination in the pulmonary veins“

Catheter ablation of AF should target isolation of the pulmonary veins.
MRI relationship of the pulmonary vein ostia and left atrial appendage
Electrical isolation of the PV
Electrical isolation of the PV
The Atrial Fibrillation Ablation Pilot Study: a European Survey on methodology and results of catheter ablation for atrial fibrillation conducted by the European Heart Rhythm Association

Arbelo E et al., Eur Heart J 2014
Distribution of centres and patients included in the Atrial Fibrillation Ablation Pilot by country

Arbelo E et al, EHJ, 2014
Rate of use of pharmacological treatment at discharge and at the 12-month follow-up

Arbelo E et al, EHJ, 2014
Kaplan–Meier arrhythmia-free survival curve by type of atrial fibrillation

Arbelo E et al, EHJ, 2014
The atrial fibrillation ablation - Pilot Study

72 centres in 10 European countries from Oct 2011 - May 2012

1391 1st AF ablations

Arrhythmia documentation by:
- ECG 76%
- Holter 52%
- Transtelephonic monitoring 8%
- Implanted system (Reveal) 4.5%

Over 50% of the patients become asymptomatic
21% of the patients were readmitted due to post ablation arrhythmias

Arbelo E et al, EHJ, 2014
Success rates in relationship with the type of atrial fibrillation

<table>
<thead>
<tr>
<th>Type AF</th>
<th>No. countries</th>
<th>No. centres</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal</td>
<td>10</td>
<td>70</td>
<td>871</td>
</tr>
<tr>
<td>Persistent</td>
<td>10</td>
<td>61</td>
<td>265</td>
</tr>
<tr>
<td>Long-lasting persistent</td>
<td>10</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>Overall</td>
<td>10</td>
<td>70</td>
<td>1226</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type AF</th>
<th>Success without antiarrhythmic drugs (AADs)(^a)</th>
<th>Success with antiarrhythmic drugs (AADs)(^a)</th>
<th>Overall success(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Median (IQR) between countries</td>
<td>n (%)</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>381 (43.7)</td>
<td>42.0 (39.4–51.9)</td>
<td>256 (29.4)</td>
</tr>
<tr>
<td>Persistent</td>
<td>80 (30.2)</td>
<td>27.0 (17.9–47.1)</td>
<td>99 (37.4)</td>
</tr>
<tr>
<td>Long-lasting persistent</td>
<td>33 (36.7)</td>
<td>42.9 (31.6–50.0)</td>
<td>18 (20.0)</td>
</tr>
<tr>
<td>Overall</td>
<td>494 (40.3)</td>
<td>41.1 (28.6–50.0)</td>
<td>373 (30.4)</td>
</tr>
</tbody>
</table>

Arbelo E et al, EHJ, 2014
Advanced ablation of AF

- Definitions, targets, general results
- **Special approaches: „Single shot“ devices**
- Fibrosis imaging
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PVAC-Catheter
1st Generation
„Lasso“-Map and RF-Ablation

„all in one device“

1st edition: 10-polar circular catheter for mapping and ablation using duty-cycled and alternating (unipolar and bipolar) energy
ICE: PVAC in RIPV
LA/PV-Signals on PVAC – before ablation
LA/PV-Signals on PVAC – after 1st ablation
LA/PV-Signals on PVAC – final result - entry block
LA/PV-Signals on PVAC – exit block
Duty-cycled multi-electrode radiofrequency vs. conventional irrigated point-by-point radiofrequency ablation for recurrent atrial fibrillation: comparative 3-year data

De Greef et al, Europace 2014
Kaplan-Meier plot representing the time to documented recurrence during the 3 years follow-up period

At 3 years, single-procedure success off-drugs in PVAC-guided ablation was comparable to conventional PVI (65% vs. 55%, P ¼ NS).
### PVAC vs. point by point RF ablation in AF

<table>
<thead>
<tr>
<th>Technique</th>
<th>Patients (N)</th>
<th>Success %</th>
<th>FU duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Para-surgical atrial flutter (PAF)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buxo et al.</td>
<td>PVAC</td>
<td>11</td>
<td>70</td>
</tr>
<tr>
<td>Kuchar et al.</td>
<td>PVAC</td>
<td>19</td>
<td>73</td>
</tr>
<tr>
<td>Becker et al.</td>
<td>PVAC</td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td>Chow et al.</td>
<td>PVAC</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Tong et al.</td>
<td>PVAC</td>
<td>27</td>
<td>48</td>
</tr>
<tr>
<td><strong>Para-surgical atrial fibrillation (PAF) AF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross et al.</td>
<td>PVAC</td>
<td>20</td>
<td>55</td>
</tr>
<tr>
<td>Tong et al.</td>
<td>PVAC/PVs/Ps/MAA/MMAAC</td>
<td>12</td>
<td>63</td>
</tr>
<tr>
<td><strong>PAF + PAF AF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bierman et al.</td>
<td>PVAC</td>
<td>40</td>
<td>65</td>
</tr>
</tbody>
</table>

**PVAC vs. point by point comparison**

- **Point by point**
  - Average success: 59.5%

- **PVAC**
  - Average success: 67.5%

De Greef et al. Europace 2014
5 year Follow-Up with PVAC vs. Irrigated RF

Single Procedure Success off Drugs

80% paroxysmal

Safety Profile

*Statistically significant

<table>
<thead>
<tr>
<th></th>
<th>PVAC</th>
<th>Irrigated RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Complications</td>
<td>1.30%</td>
<td>4.80%</td>
</tr>
</tbody>
</table>

Procedure Time

*Statistically significant

<table>
<thead>
<tr>
<th></th>
<th>PVAC</th>
<th>Irrigated RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minutes</td>
<td>134</td>
<td>178</td>
</tr>
</tbody>
</table>

Ablation characteristics:

<table>
<thead>
<tr>
<th></th>
<th>cPVI group</th>
<th>MER group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure duration (min)</td>
<td>177.7 (± 48.7)</td>
<td>133.9 (± 38.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ablation time (min)</td>
<td>45.3 (± 30.3)</td>
<td>32.6 (± 12.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
<td>29.7 (± 12.3)</td>
<td>31.9 (± 12.3)</td>
<td>0.064</td>
</tr>
</tbody>
</table>

Data are presented as means ± their SD. P-value between cPVI and MER group: Student’s t-test. cPVI: conventional point-by-point pulmonary vein isolation; MER: multi-electrode catheter pulmonary vein isolation.

Advanced duty-cycled multielectrode RF ablation: Benefits of “Gold”

- What Benefits Does Gold Offer?

  - Thermal conductivity
    - Platinum = 71.6 W/m°C
    - Gold = 317 W/m°C
  - Precise temperature control across the electrode*
  - Ability to drive more power, if desired*
  - Create deeper lesions, if desired*

Create more consistent lesions independent of cardiac flow conditions
Contact Assessment using Temperature and Power

- **Low Power**
  - Power: <3W
  - Temp: 60°C

- **Good Contact**
  - Power: >3W
  - Temp: 50-65°C

- **No Contact**
  - Power: 9W (Max)
  - Temp: <50°C

Blood Flow

- **Excess Contact**
- **Good Contact**
- **Poor Contact**
Contact Assessment - During ablation

**GENius**
Temperature Only

**GENius with ContactIQ**
Temperature and Power

- **Green Bar** = 55 - 65° C
- **Blue Bar** = < 55° C
- **Green Bar** = 50 - 65° C + Power ≥ 3W
- **Yellow Bar/Black Box** = 50 - 65° C + Power < 3W
- **Yellow Bar/White Box** = < 50° C
Effective contact seconds

PVAC GOLD shows that greater than 30 seconds of Effective Contact is highly predictive of transmural lesions in a preclinical model.
Dresden experience – PVAC Gold® - 227 patients
ACE rates using various technologies

Caution: Clinical results across studies/protocols may not be comparable.
All studies included used 1.5T MRI scanner and used a consistent lesion definition as per Gaita/Herrera-Siklódy (DWI + ADC + FLAIR)
„balloon based technique“
Cryoablation (Cryocath)
Advances in Cryo technology
Optimal balloon positioning with CBG1 and CBG2

(A and B) Occlusion of LSPV with a CB, demonstrated by PV angiography. Illustration of the ideal freezing zone of CBG1 (blue area) and CBG2 (red area, includes the blue area).

Straube et al., Europace, 2014
Pre- and postablation images recorded with the 3-dimensional electroanatomic mapping system

The scale on the NavX voltage map was set from 0.2 to 1.2 mV. The purple region represents voltage 41.2 mV, and the gray region represents voltage 0.2 mV. A: A preablation voltage map demonstrating the posterior left atrial (LA) and 4 pulmonary veins. B: A postablation voltage map demonstrating cryoballoon lesion demarcation on the posterior LA wall.

Koenigsberg DN et al, HeartRhythm, 2015
REPRODUCIBLE OUTCOME DATA WITH THE CRYOBALLOON IN PAROXYSMAL AF AT 1 YEAR

Di Giovanni, JCE 2014; Fürnkranz, JICE 2014; Aytemir, Europace 2014; Metzner, Circ AEP 2014; Chierchia, Europace 2014; Kumar, JICE 2014; Jourda, Europace 2014

G2: 91% of veins isolated at 3.4 months post-ablation (68/75 veins in 21 pat.)

Reddy, JCE 2015
2ND GEN. CB: PAROXYSMAL VS. PERSISTENT AF
FREEDOM FROM AF/AT: SINGLE CB PROCEDURE SUCCESS

n=560 pts., 63.5 yrs., 45% pers. AF, LA 43 vs. 47 mm p<0.01, LA volume 120 vs. 149 ml p<0.01

recurrence: ≥ 30sec AF/AT and/or symptoms after blanking period
FU at 3, 6, 9, 12 months, thereafter every 6 months (incl. holter)

AAD

Dorwarth, Straube, Hoffmann, DGK 4/2015

2nd Gen CB → high rate of freedom from AF/AT also in pers. AF
Second-generation cryoballoon ablation for paroxysmal atrial fibrillation: 1-year follow-up
Chiercha GB et al., 2014

Inclusion: 42 patients
30 male (71 %) mean age 57.9 ± 21.1 years
12 female (29%)

Treatment (all patients) with the large 28 mm CB-A; total 168 PV’s were depicted on pre-procedural CT scan and 100% isolated with CB only (=100%).

Freedom from AF off-antiarrhythmic drug treatment after a single procedure (mean 11.6 ± 2 months follow up) 78%
if the blanking period was considering (3 months) 83%

Most frequent complication: phrenic nerve palsy (PNP) in 19 % of individuals

Chierchia GB et al, Europace, 2014
Advanced ablation of AF

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- Special approaches: „Single shot“ devices
- **Fibrosis imaging**
- Complex fractionated atrial electrograms (CFAE)
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- Rotors
Pre-Ablation Fibrosis/Structural Remodeling Based Staging

AF Phenotype and Degree of Fibrosis

Histological Basis for LA Wall Fibrosis

Evaluation of pulmonary vein encirclement with ablation scar
Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation

The DECAAF Study

Cumulative Incidence of Arrhythmia Recurrence Without Covariate Adjustment Through Day 475 After the Blanking Period

Personalized treatment of atrial fibrillation

LGE-MRI to stage patients with Atrial Fibrillation
Utah Classification

- Utah I
  - Ablation
- Utah II
  - Ablation
- Utah III
  - Localized Stress
  - Ablation
- Utah IV
  - Diffuse Stress
  - Medical management
  - Medical management
DECAAF – Subanalyse
DECAAF – Subanalyse
DECAAFL – Subanalyse
DECAAF – Subanalyse

Efficiency of DE-MRI-Guided Fibrosis Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation (DECAAF II)

The University of Utah
DECAAF II

Figure 1: DECAAF II Study Overview
DECAAF II

Group 1

Group 2
Personalized therapy of atrial fibrillation

Advanced ablation of AF

- Definitions, targets, general results
- Special approaches: „Single shot“ devices
- Fibrosis imaging
- **Complex fractionated atrial electrograms (CFAE)**
- **Ganglionated Plexi (GP), Fad pads**
- Left atrial appendage (LAA)
- Rotors
Catheter Ablation of Longstanding Persistent Atrial Fibrillation – Are We on the Right Path? –

CFAE-Guided Ablation

Comparison of anatomical approach (A) vs. CFAE-guided linear ablation (B)

Kim Young-Hoon; Circ J 2012; 76: 1299 – 1306.
LA electrophysiological targets in persistent AF:

Complex fractionated atrial electrograms (CFAE)

CFAE ablation

Long-standing and permanent AF

Exit block of the box lesion

Kumagai, K; Circ J 2011; 75:2350-2311.
Inverse Relationship Between Fractionated Electrograms and Atrial Fibrosis in Persistent Atrial Fibrillation

Detection, Segmentation, and 3-Dimensional Reconstruction of Atrial DE (Delayed Enhancement)

A) High-resolution (1.25 1.25 2.5 mm) delayed enhancement (DE) magnetic resonance imaging.

(B) Segmentation of the left atrial wall between the inner (red) and outer (green) markers.

(C) Regions of DE are depicted in yellow.

(D) Voxel intensity histogram analysis of left atrial wall identifies DE as voxel intensities >4 SD than the mean in-plane voxel intensity.

(E) Three-dimensional (3D) reconstruction of left atrial blood pool and DE areas. Dense DE regions are measured using the red marker in E with corresponding red arrows in C, and patchy DE regions are measured using the green marker in E with corresponding green arrows in C. ao = descending aorta.

Relationship of Atrial DE to Continuous CFAE Sites

Shorter AFCL is associated with increased amount of DE.

Conclusions

• However, **19% of CFAE occur within or around dense DE sites.**

• These findings may be of clinical importance for choosing the ablation strategy in patients with persistent AF.

• **The region of slow conduction (with fractionated or rapid activity)** within or around the areas of atrial fibrosis may be a promising ablation target in patients with persistent AF.

• Alternatively, novel global biatrial mapping systems are currently in the clinical evaluation phase and will allow for a more mechanistically oriented ablation strategy in persistent AF that targets the patient-specific AF sources and drivers.

The Effect of Fat Pad Modification during Ablation of Atrial Fibrillation: Late Gadolinium Enhancement MRI Analysis

Definition of GP Areas

Merging LA, Scar, and FP Image
1) Patient without recurrence (34 pts)  

- FP area: 25.3 ± 1.9 mm²  
- Scar area: 45.8 ± 1.6 mm²  
- Ablated FP area: 5.4 ± 1.3 mm²  

2) Patient with recurrence (26 pts)  

- FP area: 27.4 ± 1.8 mm²  
- Scar area: 65.9 ± 6.3 mm²  
- Ablated FP area: 4.3 ± 1.5 mm²  

Ph < 0.05
Optimal Method and Outcomes of Catheter Ablation of Persistent AF: The STAR AF 2 Trial

presented at ESC 2014 Barcelona

Atul Verma, Jiang Chen-yang, Tim Betts, John Radcliffe, Jian Chen, Isabel Deisenhofer, Roberto Mantovan, Laurent Macle, Carlos Morillo, Prashanthan Sanders on behalf of the STAR AF 2 Investigators

ClinicalTrials.gov NCT01203748

The STAR AF 2 trial was funded by St Jude Medical Inc.
Methods

- Roof line
- Pulmonary veins
- Encircling lesions around pulmonary veins
- Posterior mitral line
- Anterior view of left atrium
- Left posterior view of left atrium

Automated algorithm displays complex electrogram areas in red/white.
Complex fractionated electrograms (CFE) are atrial electrical signals with very rapid or continuous deflections as shown in both panels.

Areas of CFE (red/white) are targeted for ablation (brown dots).
Primary Outcome

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

p=0.15
## Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>PVI</th>
<th>PVI+CFE</th>
<th>PVI+LINES</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from AF after 1 procedure</td>
<td>59 %</td>
<td>48 %</td>
<td>44 %</td>
<td>0.15</td>
</tr>
<tr>
<td>Freedom from AF/AFL/AT after 1 procedure</td>
<td>49 %</td>
<td>41 %</td>
<td>37 %</td>
<td>0.15</td>
</tr>
<tr>
<td>Freedom from AF after 2 procedures</td>
<td>72 %</td>
<td>60 %</td>
<td>58 %</td>
<td>0.18</td>
</tr>
<tr>
<td>Freedom from AF/AFL/AT after 2 procedures</td>
<td>60 %</td>
<td>50 %</td>
<td>48 %</td>
<td>0.24</td>
</tr>
<tr>
<td>Percentage of patients still on AAD at 18 mo</td>
<td>11 %</td>
<td>12 %</td>
<td>12 %</td>
<td>0.35</td>
</tr>
</tbody>
</table>

* AAD = antiarrhythmic drugs
## Complications

<table>
<thead>
<tr>
<th>Category</th>
<th>PVI (n=64)</th>
<th>PVI+CFE (n=254)</th>
<th>PVI+Lines (n=250)</th>
<th>Total (n=568)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access site hematoma</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Access site arteriovenous fistula or pseudoaneurysm</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Sedation related complication</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Skin burn</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Transient ischemic attack or Stroke</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Atrial esophageal fistula - procedural death</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Percentage:
- Access site hematoma: 5%
- Access site arteriovenous fistula or pseudoaneurysm: 6%
- Pericarditis: 3%
- Fluid overload: 4%
- Sedation related complication: 8%
- Skin burn: 1%
- Cardiac tamponade: 3%
- Transient ischemic attack or Stroke: 3%
- Atrial esophageal fistula - procedural death: 6%
Conclusions

- Largest randomized trial to examine outcomes of catheter ablation in persistent AF
- Additional CFE or Lines ablation increased procedural time (may increase risk)
- No benefit in AF reduction when additional substrate ablation (CFE or Lines) was performed on top of PVI
- PVI alone achieved freedom from recurrence in about 50% of patients – comparable to published success rates from randomized, multicenter trials in paroxysmal AF
Documented AF > 30 seconds after one procedure with or without AAD
Advanced ablation of AF

• Definitions, targets, general results
• Special approaches: „Single shot“ devices
• Fibrosis imaging
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Neues vom ESC London 2015

- BELIEF-Trial:

  - Verbessert die empirische LAA Isolation zusätzlich zur komplexen linksatrialen Ablation die Langzeit-Prognose bei Pat. mit lang persistierendem AF?
  - Multicenter, randomisiert

De Biase et al
Left Atrial Appendage: An Underrecognized Trigger Site of Atrial Fibrillation


**Methods**

- This was a randomized, parallel-group study assessing whether empirical electrical isolation of the LAA in addition to a standard ablation with an extended PV antrum, could improve the freedom from atrial arrhythmia in LSP AF patients.

- **Power Calculation:** The study had 80% power to detect at least 20% difference in success rate (50% to 70%) at 12 month follow-up (using log-rank test), with two-sided Type I error of 0.05.

- 173 patients were enrolled and randomly assigned (1:1 ratio) to:
  - Extensive ablation plus *Empirical Electrical LAA isolation* (group 1, n=85)
  - Extended PV antrum and non PV triggers ablation (group 2, n=88)

- Patients ≥18 years of age, with LSP AF refractory to antiarrhythmic drugs were included in the study.
173 Patients Enrolled
(>18 years, long-standing persistent AF refractory to antiarrhythmic drugs)

Randomized 1:1

- Standard Ablation = Empirical LAA isolation (Group 1): n = 85
- Standard Ablation alone (Group 2): n = 88

Follow-up After Index Procedure

Ablation Success Assessed at 12 Month

62 Patients underwent a second procedure (27 group 1 and 35 group 2). LAA isolation was performed in all patients during repeat ablation

Follow-up after radio

Outcome Assessed at 24 month
At the 12 month follow-up, 48 (56%) in group 1 and 25 (28%) in group 2 were recurrence-free on AAD after a single procedure. (Log-rank p=0.001, unadjusted HR 1.92 [1.3 to 2.9]).
The cumulative success after multiple procedures was 65 (76%) in group 1 and 49 (56%) in group 2.

ALL THE PATIENTS UNDERWENT LAA ISOLATION
(Log-rank p = 0.003, unadjusted HR 2.24 [95% CI 1.3-3.8])
Relative contribution of different ablation targets in the AF disease continuum

- PV Triggers
- Non-PV Triggers
- Other Non-PV Triggers

Substrate?

- LAA

Paroxysmal  Persistent  Long-standing persistent
CONCLUSIONS

The results of this randomized study show that both after a single and redo procedures in patients with long standing persistent AF, the **EMPIRICAL ELECTRICAL ISOLATION** of the LAA improve the long-term freedom from atrial arrhythmias without increasing complications.

Future studies examining the physiopathology of these findings are necessary.
AF ablation: Mapping and Imaging

- The substrate
- Intracardial signals
- Point by point vs circular mapping
- 3D imaging
- Lines
- Ganglionated Plexi (GP)
- Complex fractionated atrial electrograms (CFAE)
- Left atrial appendage (LAA)
- Pad pads
  - Magnetic robotic ablation
- Rotors
- Technical improvements and safety
Remote-controlled magnetic pulmonary vein isolation using a new three-dimensional non-fluoroscopic navigation system: A single-centre prospective study

Remote magnetic navigation system
Carto 3 system features
Carto 3 system features
Remote magnetic with open-irrigated catheter vs. manual navigation for ablation of atrial fibrillation: a systematic review and meta-analysis

Remote magnetic navigation vs. MCN; outcome: atrial tachyarrhythmia recurrence

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>RMN Events</th>
<th>Total</th>
<th>MCN Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
<th>Odds ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arya 2011</td>
<td>29</td>
<td>70</td>
<td>96</td>
<td>286</td>
<td>38.1%</td>
<td>1.40 [0.82, 2.39]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choi MS 2011</td>
<td>4</td>
<td>41</td>
<td>5</td>
<td>70</td>
<td>5.8%</td>
<td>1.41 [0.36, 5.56]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luthje 2011</td>
<td>50</td>
<td>107</td>
<td>24</td>
<td>54</td>
<td>25.2%</td>
<td>1.10 [0.57, 2.12]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miyazaki 2010</td>
<td>9</td>
<td>30</td>
<td>17</td>
<td>44</td>
<td>11.1%</td>
<td>0.68 [0.25, 1.83]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natale 2011</td>
<td>8</td>
<td>43</td>
<td>8</td>
<td>44</td>
<td>9.3%</td>
<td>1.03 [0.35, 3.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorgente 2010</td>
<td>15</td>
<td>35</td>
<td>10</td>
<td>29</td>
<td>10.5%</td>
<td>1.43 [0.52, 3.94]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>326</td>
<td></td>
<td>527</td>
<td></td>
<td>100.0%</td>
<td>1.18 [0.85, 1.65]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 115 (RMN) vs. 160 (MCN)

Heterogeneity: $\chi^2 = 0.00$, df = 5 ($P = 0.86$); $I^2 = 0$

Test for overall effect: $Z = 1.00$ ($P = 0.32$)

Remote magnetic navigation and MCN; outcome: PVI

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>RMN Events</th>
<th>RMN Total</th>
<th>MCN Events</th>
<th>MCN Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arya 2011</td>
<td>61</td>
<td>70</td>
<td>285</td>
<td>286</td>
<td>16.3%</td>
<td>0.02 [0.00, 0.19]</td>
<td></td>
</tr>
<tr>
<td>Choi MS 2011</td>
<td>34</td>
<td>41</td>
<td>63</td>
<td>70</td>
<td>23.4%</td>
<td>0.54 [0.17, 1.67]</td>
<td></td>
</tr>
<tr>
<td>Luthje 2011</td>
<td>96</td>
<td>107</td>
<td>47</td>
<td>54</td>
<td>24.3%</td>
<td>1.30 [0.47, 3.57]</td>
<td></td>
</tr>
<tr>
<td>Miyazaki 2010</td>
<td>26</td>
<td>30</td>
<td>44</td>
<td>44</td>
<td>11.4%</td>
<td>0.07 [0.00, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Solheim 2011</td>
<td>10</td>
<td>23</td>
<td>22</td>
<td>65</td>
<td>24.6%</td>
<td>1.50 [0.57, 3.97]</td>
<td></td>
</tr>
<tr>
<td>Sorgente 2010</td>
<td>35</td>
<td>35</td>
<td>29</td>
<td>29</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>306</strong></td>
<td><strong>490</strong></td>
<td><strong>548</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>0.41 [0.11, 1.47]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>262</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 1.51; \chi^2 = 17.36, df = 4 (P = 0.002); I^2 = 77%$
Test for overall effect: $Z = 1.37 (P = 0.17)$
Remote magnetic navigation vs. MCN; outcome: major complications

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>RMN Events</th>
<th>Total</th>
<th>MCN Events</th>
<th>Total</th>
<th>Weight</th>
<th>Peto odds ratio Peto fixed, 95% CI</th>
<th>Peto odds ratio Peto fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arya 2011</td>
<td>1</td>
<td>70</td>
<td>11</td>
<td>286</td>
<td>29.4%</td>
<td>0.48 [0.11, 2.03]</td>
<td></td>
</tr>
<tr>
<td>Choi MS 2011</td>
<td>0</td>
<td>41</td>
<td>9</td>
<td>70</td>
<td>30.0%</td>
<td>0.18 [0.04, 0.74]</td>
<td></td>
</tr>
<tr>
<td>Luthje 2011</td>
<td>5</td>
<td>107</td>
<td>1</td>
<td>54</td>
<td>20.0%</td>
<td>2.18 [0.39, 12.22]</td>
<td></td>
</tr>
<tr>
<td>Miyazaki 2010</td>
<td>0</td>
<td>30</td>
<td>1</td>
<td>44</td>
<td>3.7%</td>
<td>0.19 [0.00, 10.08]</td>
<td></td>
</tr>
<tr>
<td>Natale 2011</td>
<td>0</td>
<td>43</td>
<td>0</td>
<td>44</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solheim 2011</td>
<td>0</td>
<td>23</td>
<td>0</td>
<td>65</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soriente 2010</td>
<td>1</td>
<td>35</td>
<td>4</td>
<td>29</td>
<td>17.9%</td>
<td>0.22 [0.04, 1.38]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>349</td>
<td>592</td>
<td>100.0%</td>
<td></td>
<td>0.41 [0.19, 0.88]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 5.54$, df = 4 ($P = 0.24$); $I^2 = 28\%$

Test for overall effect: $Z = 2.28$ ($P = 0.02$)

AF ablation: Mapping and Imaging

- The substrate
- Intracardial signals
- Point by point vs circular mapping
- 3D imaging
- Lines
- Ganglionated Plexi (GP)
- Complex fractionated atrial electrograms (CFAE)
- Left atrial appendage (LAA)
- Fad pads
- Magnetic robotic ablation
- **Rotors**
- Technical improvements and safety
Advanced ablation of AF

- Definitions, targets, general results
- Special approaches: „Single shot“ devices
- Fibrosis imaging
- Complex fractionated atrial electrograms (CFAE)
- Ganglionated Plexi (GP), Fad pads
- Left atrial appendage (LAA)
- Rotors
The FIRM principle: Focal Impulse and Rotor Modification

Computational Mapping of “Electrical Rotor” During Atrial Fibrillation

Conclusions

Localized Sources Often Sustain Human Atrial Fibrillation

- Direct evidence from Optically Mapped Sheep atria $^{1,2}$
- Indirect Evidence from Canine atria $^{3}$

Until 2011, Human AF:
- Little or no prior evidence for rotors

CONFIRM (2011): AF rotors/sources typically sustain human AF
Focal Impulse and Rotor Modulation (FIRM) – Multicenter Validation

The FIRM principle: Focal Impulse and Rotor Modification

Computational Mapping of “Electrical Rotor” During Atrial Acute Termination of AF to Sinus Rhythm By FIRM Ablation Fibrillation Conclusions

CONFIRM Trial
FIRM-Ablation = „Focal Impulse and Rotor Modulation“

N = 92 Pat./107 Ablationen, parox. + persist. (72%) VHF, „FIRM“ + PVI vs. PVI allein: Rotoren in 97% der Fälle, 2,1±1,0 Rotoren. 273 d FU, überwiegend mit ILR

Narayan et al, JACC 2012
Clinical Outcomes: The CONFIRM Trial

Study Size: 92 patients (mostly Persistent)

1-Year Single procedure results:

- **44.9%** for the control arm (PVI only)
- **82.4%** of FIRM-guided cases were free of AF vs.
- Superior results also achieved in high-risk patients (sleep apnea, heart failure, metabolic syndrome, etc.)

3-Year results:

- **77.8%** of FIRM-guided cases were free of AF after a median of 1 procedure
- Superior results in high-risk patients were also maintained

Narayan SM et al; J Am Coll Cardiol; DOI 10.1016., 2014
Rotors Are Vital to Sustaining AF – On Treatment analysis of CONFIRM

Key Points/Key Findings:
- Rotors were critical to success
- Each patient had an average of 2.3 rotors
- Locations more widely distributed in Persistent AF
- > 50% were outside of PVI ablation zones

Narayan et al., On-Treatment Analysis of CONFIRM. J Am Coll Cardiol. 2013
**Multi-Center Validation Study**

Study Size: 78 patients (mostly Persistent AF)

**Purpose:**
- Determine if the CONFIRM Trial results can be replicated by 10 independent centers

1-Year Single procedure results:
- **80.5%** of FIRM-guided cases were free of AF
- **87.5%** of patients with no prior ablation were free from AF
- Rotor distributions similar to the CONFIRM trial

Summary of Clinical Outcomes

Comparison CFAE- and Rotor Ablation

By the courtesy of Sonia Ammar, Deutsches Herzzentrum München

- CT Scan with the 252 electrodes vest
- AF ‘windows’ (over several minutes) are analyzed to identify consistent drivers (bedside or in the EP lab)
- Drivers are defined as local reentrant circuits (≥1.5 rotations) or focal breakthroughs (> 2 that appear at the same spatial location per window)

ecVUE & ecSYNC are not yet cleared or approved for use by the FDA
A: Sites of AF drivers:
1) Inferior LA and CS
2) Right PVs and septum
3) Left PVs
4) Cavotricuspidal isthmus
5) RAA.

B: Total CFAE area: 325.8 cm$^2$ (79% of total mapped area).

→ AF terminated to a perimitral reentry during ablation in the RAA (yellow asterix).
A: Sites of AF drivers:
1) Left PVs and LAA
2) lateral RA
3) Inferior LA and CS
4) Cavotricuspidal isthmus
5) Right PVs and septum.

B: Total CFAE area: 182cm² (54% of mapped area).

→ AF terminated to a peritricuspid reentry during ablation in the inferior LA (yellow asterix).
## Results: procedural data

<table>
<thead>
<tr>
<th>AF termination</th>
<th>N= 16 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF termination with drivers ablation only</td>
<td>11/16 (70%)</td>
</tr>
<tr>
<td>AF termination with drivers ablation + PVI</td>
<td>12/16 (75%)</td>
</tr>
</tbody>
</table>
Results: drivers locations

<table>
<thead>
<tr>
<th>Driver locations, N= 63</th>
<th>N= 16 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nbr of drivers/patient</td>
<td>4±1 /patient</td>
</tr>
<tr>
<td>Inferior left atrium, coronary sinus</td>
<td>15/16</td>
</tr>
<tr>
<td>Right atrium</td>
<td>15/16</td>
</tr>
<tr>
<td>Right PVs and septum</td>
<td>14/16</td>
</tr>
<tr>
<td>Lefts PVs</td>
<td>12/16</td>
</tr>
<tr>
<td>Left atrial appendage</td>
<td>9/16</td>
</tr>
<tr>
<td>Driver regions with &gt;75% CFAE</td>
<td>49/63 (78%)</td>
</tr>
<tr>
<td>Driver regions with 50% CFAE</td>
<td>7/63 (11%)</td>
</tr>
<tr>
<td>Driver regions with &lt;25% CFAE</td>
<td>7/63 (11%)</td>
</tr>
</tbody>
</table>
Ongoing and Future Clinical Studies
Current/Ongoing & Future Studies

• **Company Sponsored**
  - **REAFFIRM**
    - Purpose: Evaluate the long-term effectiveness of FIRM + PVI versus PVI alone for de novo PerAF procedures
    - Design: Randomized controlled multicenter trial; 200 patients from ~25 centers throughout Europe (with some in the U.S.)
    - Status: Currently enrolling
  - **FIRM-Only for Paroxysmal AF**
    - Purpose: Evaluate the long-term effectiveness of FIRM-only ablation versus PVI for the treatment of paroxysmal AF
    - Design: Randomized controlled multicenter trial; ~200 patients from multiple centers (primarily Germany)
    - Status: planned initial enrollment in 2015
  - **Health Economics**
    - Various studies evaluating the cost effectiveness and economic benefits of FIRM-guided ablation

• **Investigator Initiated**
  - **PRECISE** (long-term outcomes of FIRM-only ablation for paroxysmal AF)
  - Early Recurrence of Atrial Fibrillation (ERAF) with FIRM-guided ablation + PVI compared to PVI alone
  - Long-term clinical outcomes of FIRM + PVI with and without acute termination
  - Correlation of rotors identified by RhythmView with optically mapped rotors (in the same human heart)
  - Various other small clinical outcome studies
Reaffirm-Studie

Randomized Evaluation of Atrial Fibrillation Treatment with Focal Impulse and Rotor Modulation Guided Procedures
PI: Johannes Brachmann Coburg
Reaffirm-Study-Design

Assess the safety and effectiveness of FIRM procedures followed by conventional ablation including PVI versus a standard PVI procedure for the treatment of persistent atrial fibrillation

- 200 subjects
- Prospective
- 1:1 randomization (eCRF)
- Open-label
- International, multicenter

PI: Johannes Brachmann
Endpoints

- Primary safety endpoints
  - Acute success: Freedom from SAE related to procedure within 10 days post-procedure
  - Long-term success: Freedom from cumulative SAE related to the procedure within 1 year of index procedure
Endpoints

• Primary effectiveness endpoints
  – Long-term success
  1. Single procedure freedom from AF/AT recurrence at 3 months, and
  2. Single procedure freedom from AF/AT recurrence from 3 – 12 Months after the index procedure
Ablation of Rotor and Focal Sources Reduces Late Recurrence of Atrial Fibrillation Compared With Trigger Ablation Alone
Extended Follow-Up of the CONFIRM Trial
(Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation)

The FIRM principle: Focal Impulse and Rotor Modification

Cumulative Freedom From Primary Endpoint
Conclusions

• FIRM-guided ablation is more durable than conventional trigger-based ablation in preventing 3-year AF recurrence.

• Future studies should investigate how ablation of patient-specific AF-sustaining rotors and focal sources alters the natural history of arrhythmia recurrence.
Effectiveness and safety of simultaneous hybrid thoracoscopic and endocardial catheter ablation of lone atrial fibrillation

Pison L et al., AnnCardiothoracSurg, 2014
Success rate off antiarrhythmic drugs (Off-ADD)
Single-procedure success rate
Results

No death or conversion to cardiopulmonary bypass occurred. No patient demonstrated paralysis of the phrenic nerve. Overall, the incidence of perioperative complications was 8% (n=6). At the end of follow-up, sixty-eight patients (87%) were in sinus rhythm (SR) with no episode of AF, atrial flutter or atrial tachycardia lasting longer than 30 seconds and off antiarrhythmic drugs (ADD). Among patients with longstanding persistent AF, 15 (100%) were in SR and off AAD. Success rates were 82% (n=28) in persistent and 76% (n=22) in paroxysmal AF (P=0.08). No patient died and no thromboembolic/bleeding events or procedure-related complications occurred during the follow-up.
Prevalence, Characteristics, Mapping, and Catheter Ablation of Potential Rotors in Nonparoxysmal Atrial Fibrillation

Lin YJ et al., CircArrhythmElectrophysiol, 2013
Illustration of the substratemapping after the pulmonary vein isolation (PVI)
Catheter ablation results of the pulmonary vein isolation (PVI) and substrate mapping.

1. AF patients who received ablation (n=53)
   - PVI termination (n=16)
   - PVI did not terminate AF (n=37)
     - Substrate mapping
       - With rotor (n=8)
       - Without rotor (n=29)
         - Termination (n=8)
         - Termination (n=7)
         - No termination (n=22)

Lin YJ et al., CircArrhythmElectrophysiol, 2013
The complex fractionated atrial electrograms (CFAEs) in 1 persistent patient with atrial fibrillation after pulmonary vein isolation
Freedom of atrial arrhythmia

Kaplan–Meier curves demonstrating the freedom of atrial arrhythmia recurrence after a single (A) and multiple procedures (B). AF indicates atrial fibrillation; and PVI, pulmonary vein isolation.

Lin YJ et al., CircArrhythmElectrophysiol, 2013
Advanced ablation of AF

Conclusions

• The overall success of AF ablation is unsatisfactory and amounts to 65% for paroxysmal and 40% for persistent forms

• „Make it as simply as possible“ is the purpose of single shot devices like PVAC or Cryo reaching 65 and 80% resp. with advanced technology

• Fibrosis MRI shows a clear correlation between degree of fibrosis and outcome; if isolation of scar areas by ablation improves outcome is still unclear

• The same is true for CFAE and GP/FD ablation
Advanced ablation of AF

Conclusions

• Rotors have been shown to maintain AF (mechanism not completely understood) and can now be visualized by computational mapping using baskets/electrode vests; their abolition seems to improve results, but data still have to be reconfirmed.

• **Facit:** PV isolation remains the cornerstone of AF ablation and should be gained first by simple and safe techniques (single shot) or conv. RF ablation.

• Complex techniques (s. above) have not demonstrated a clear benefit over PVI, but can be used additionally in an individualized, exploratory approach.
Thanks for your attention and greets from Düsseldorf!