RHYTHM 2017

Arrhythmias & Heart Failure

New Insights & Technological Advances

March 2-3

9th Congress Edition

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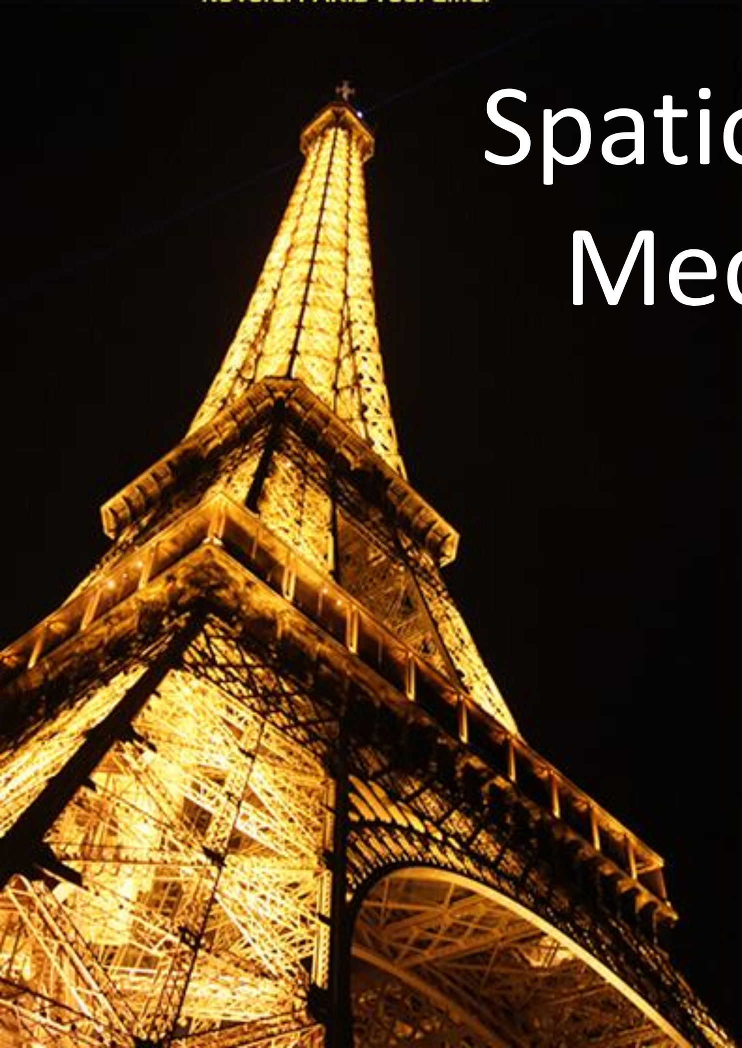

Spatio-temporal Dispersion: Mechanistic Significance

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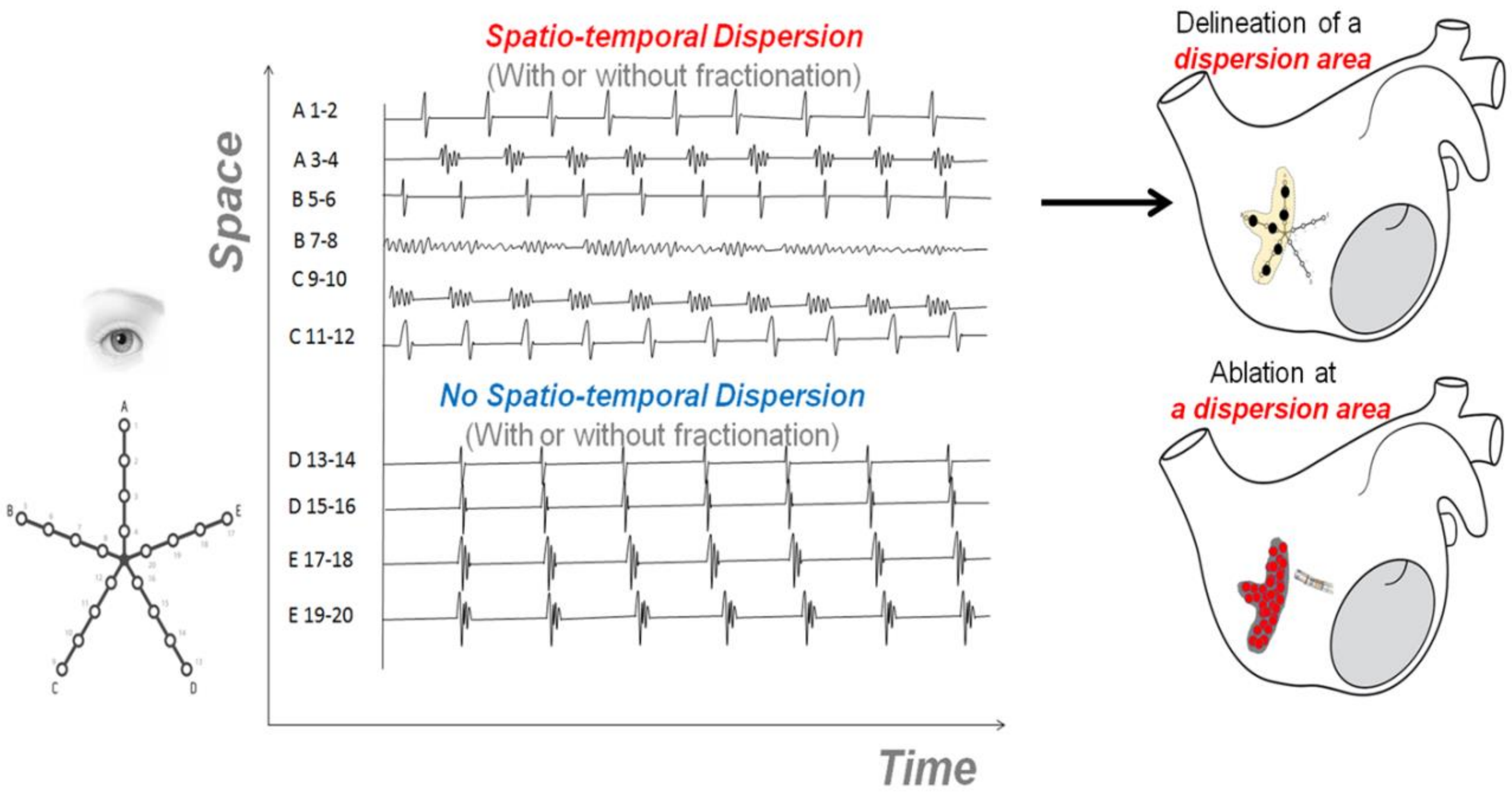
Rhythm

March 2, 2017

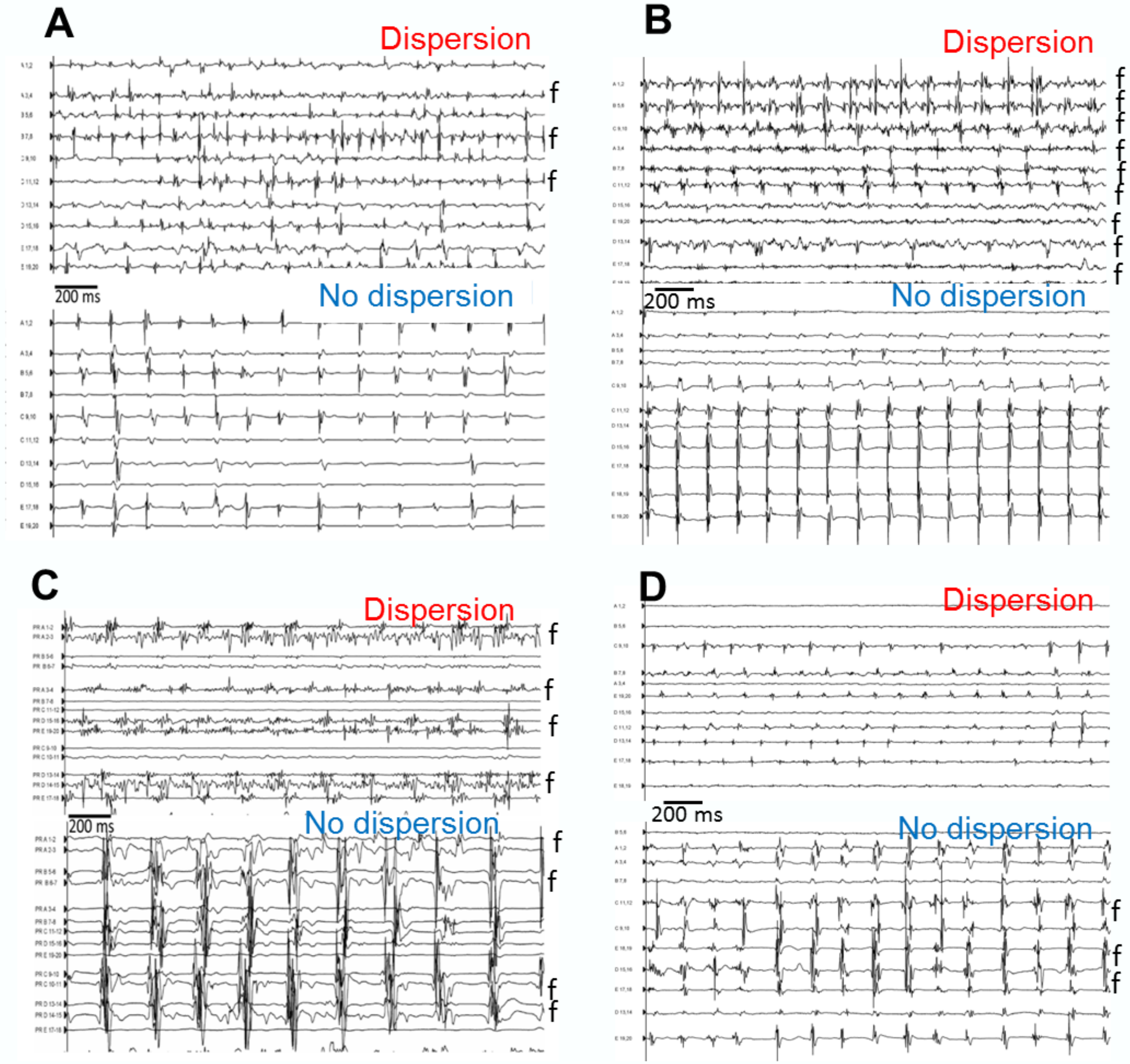
Jérôme Kalifa:

Disclosure: Co-founder Volta Medical

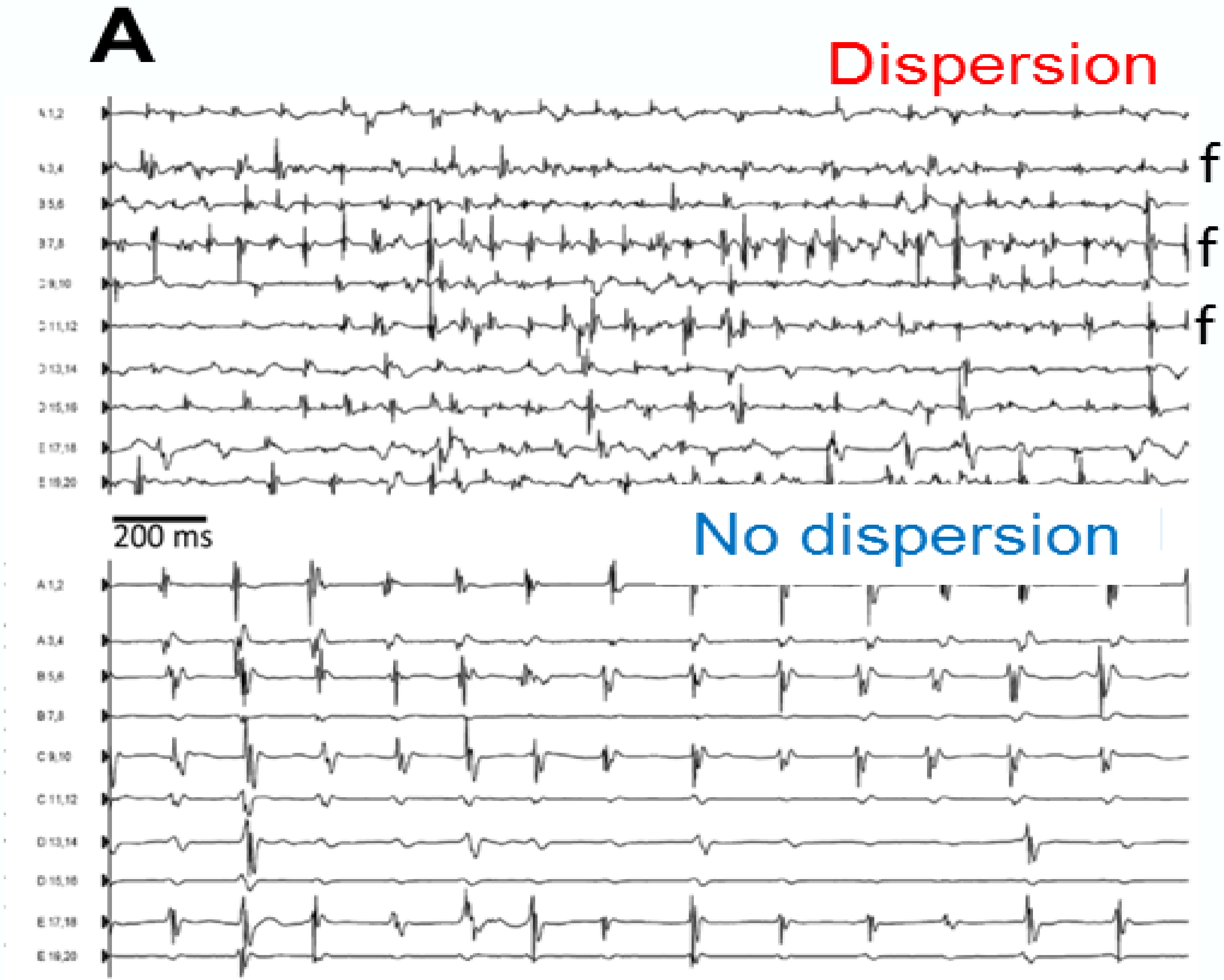
Spatio-Temporal Dispersion of Electrograms: Definition



Spatio-Temporal Dispersion of Electrograms: Examples



Spatio-Temporal Dispersion of Electrograms: Examples

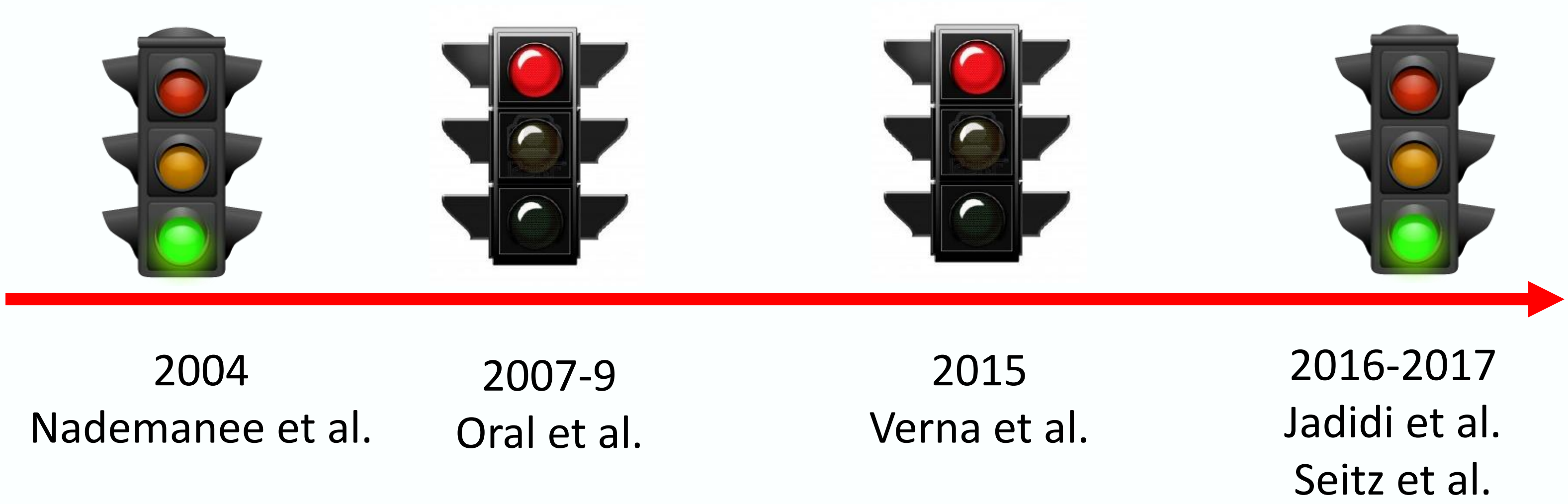


ST Dispersion

- Spatial clustering of abnormal electrograms.

- Abnormal electrograms may be fractionated or not.

CFAEs


2004
Nademanee et al.
2007-9
Oral et al.
2015
Verna et al.
2016-2017
Jadidi et al.
Seitz et al.

1. Are all CFAEs identical?
2. Do they "live" alone or together?

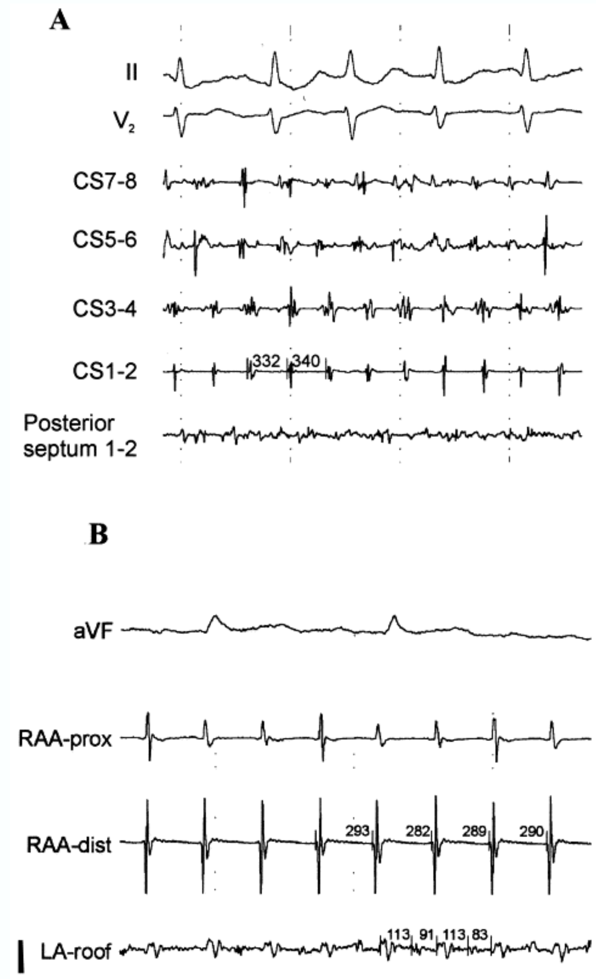
Electrogram-based ablation
Complex Fractionated Atrial Electrograms
Nademanee et al. , JACC 2004

CFAEs definition as bipolar electrograms detected by the ablation catheter:

1) Atrial electrograms that have fractionated electrograms composed of two deflections or more.

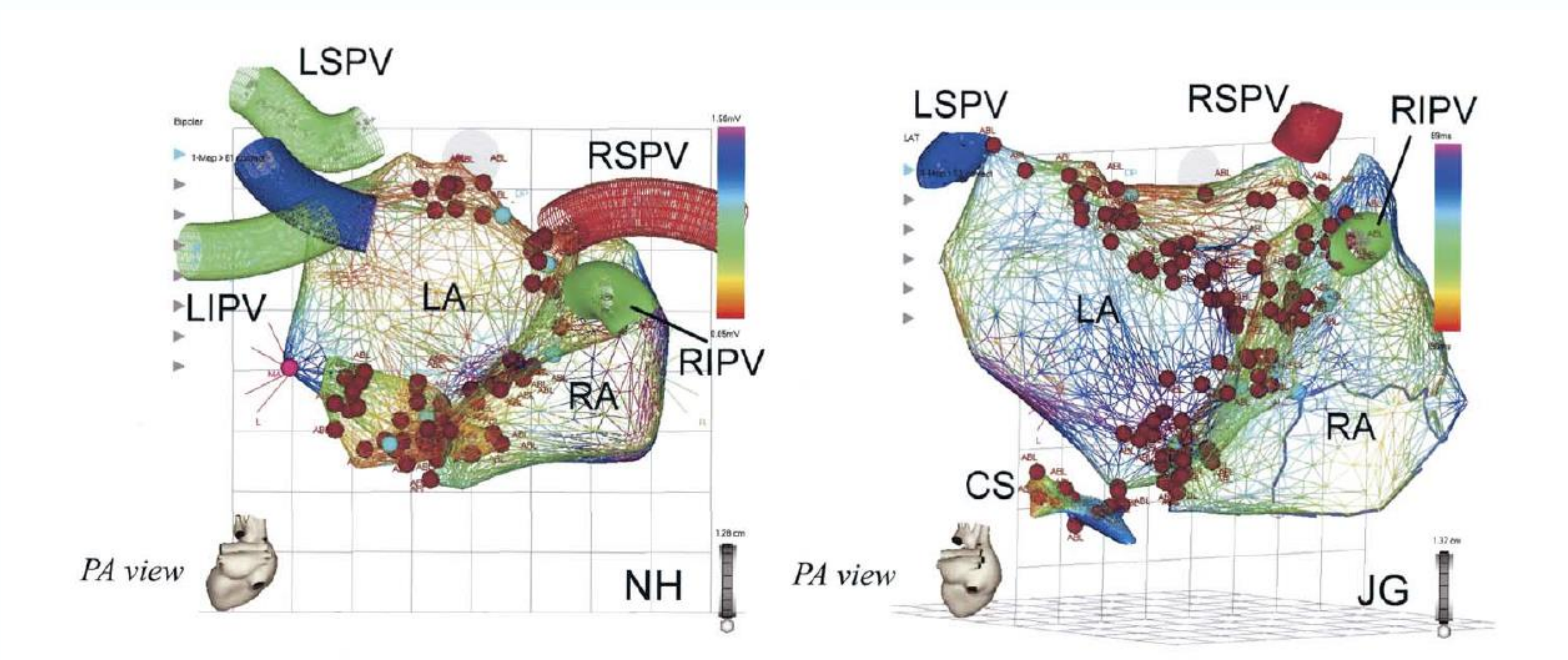
2) Perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-s recording period (Fig. A).

3) Atrial electrograms with a very short cycle length (≤120 ms) (Fig. B) averaged over a 10-s recording period.



Electrogram-based ablation
Complex Fractionated Atrial Electrograms
Nademanee et al. , JACC 2004

Prospective Study: 121 patients (92 men, 29 women; mean age, 63 ± 12), 64 of whom had persistent AF, and 57 paroxysmal AF (PAF)



Electrogram-based ablation Complex Fractionated Atrial Electrograms Nademanee et al. , JACC 2004

- Termination of AF without external cardioversion in 115 of the 121 patients (95%); 32 (28%) required concomitant ibutilide treatment.

- One-year follow-up, 110 (91%) patients were free of arrhythmia and symptoms, 92 after one ablation and 18 after two.

Electrogram-based ablation Complex Fractionated Atrial Electrograms Nademanee et al. , JACC 2004

Prospective Study: 121 patients (92 men, 29 women; mean age, 63 ± 12), 64 of whom had persistent AF, and 57 paroxysmal AF

***One** area spanning Several RA-LA regions*

***Two** areas spanning Several RA-LA regions*

***Three or more** areas spanning Several RA-LA regions*

Table 1. Classification and Regional Differences of CFAE Distributions

AF Classification	Number of Patients (Types)	Number of Patients at Various Location of CFAE Distribution
Type I AF: CFAEs localize in only one area	23 (16 PAF and 7 CAF)	10 pulmonary veins (4 RSPV; 3 LSPV; 1 LIPV and 2 both RSPV and LSPV) 8 interatrial septum 4 proximal CS 1 inferolateral aspect of the right atrium (Fig. 4)
Types II AF: CFAEs localize in two areas	43 (21 PAF and 22 CAF)	19 pulmonary veins and septum 9 septum and proximal CS 4 pulmonary veins and left posteroseptal mitral annulus 3 pulmonary vein and cavotricuspid isthmus 5 septum and mitral annulus 3 septum and the roof of the left atrium
Type III AF: CFAEs localize in ≥3 areas	55 (20 PAF and 35 CAF)	46 interatrial septum (83%) 37 pulmonary veins (67%) 34 left atrial roof (61%) 32 proximal CS and its os (59%) 13 mitral annulus (24%) 17 cavotricuspid isthmus (31%) 4 inferolateral aspect of the right atrium (7%) 2 SVC and right atrial junction (4%)

AF = atrial fibrillation; CAF = chronic atrial fibrillation; CFAE = complex fractionated atrial electrogram; CS = coronary sinus; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; PAF = paroxysmal atrial fibrillation; RSPV = right superior pulmonary vein; SVC = superior vena cava.

CFAEs: Landmark Studies

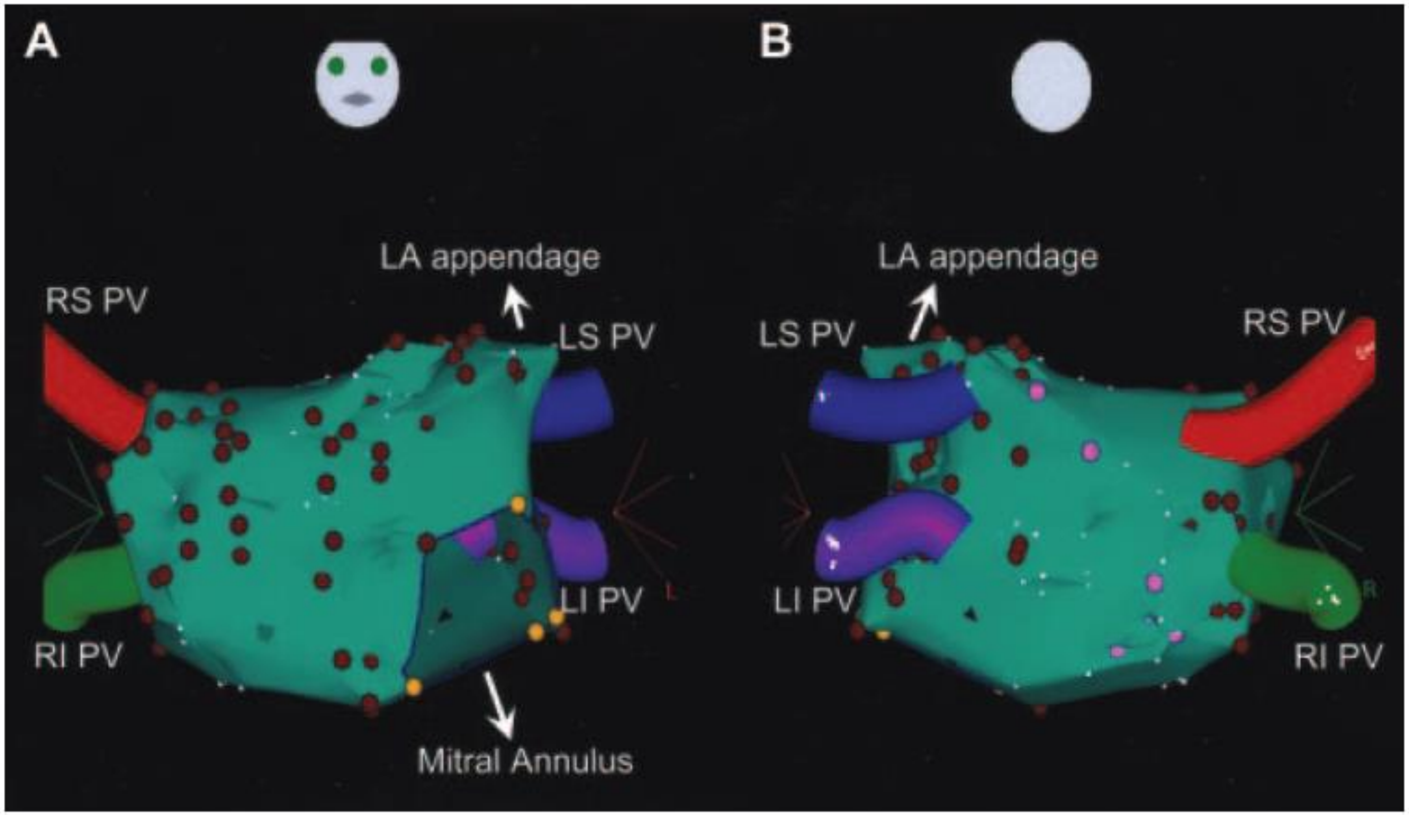
Radiofrequency Catheter Ablation of Chronic Atrial Fibrillation Guided by Complex Electrograms

Hakan Oral, MD; Aman Chugh, MD; Eric Good, DO; Alan Wimmer, MD; Sujoya Dey, MD; Nitesh Gadeela, MD; Sundar Sankaran, MD; Thomas Crawford, MD; Jean F. Sarrazin, MD; Michael Kuhne, MD; Nagib Chalfoun, MD; Darryl Wells, MD; Melissa Frederick, MD; Jackie Fortino, RN; Suzanne Benloucif-Moore, NP; Krit Jongnarangsin, MD; Frank Pelosi, Jr, MD; Frank Bogun, MD; Fred Morady, MD

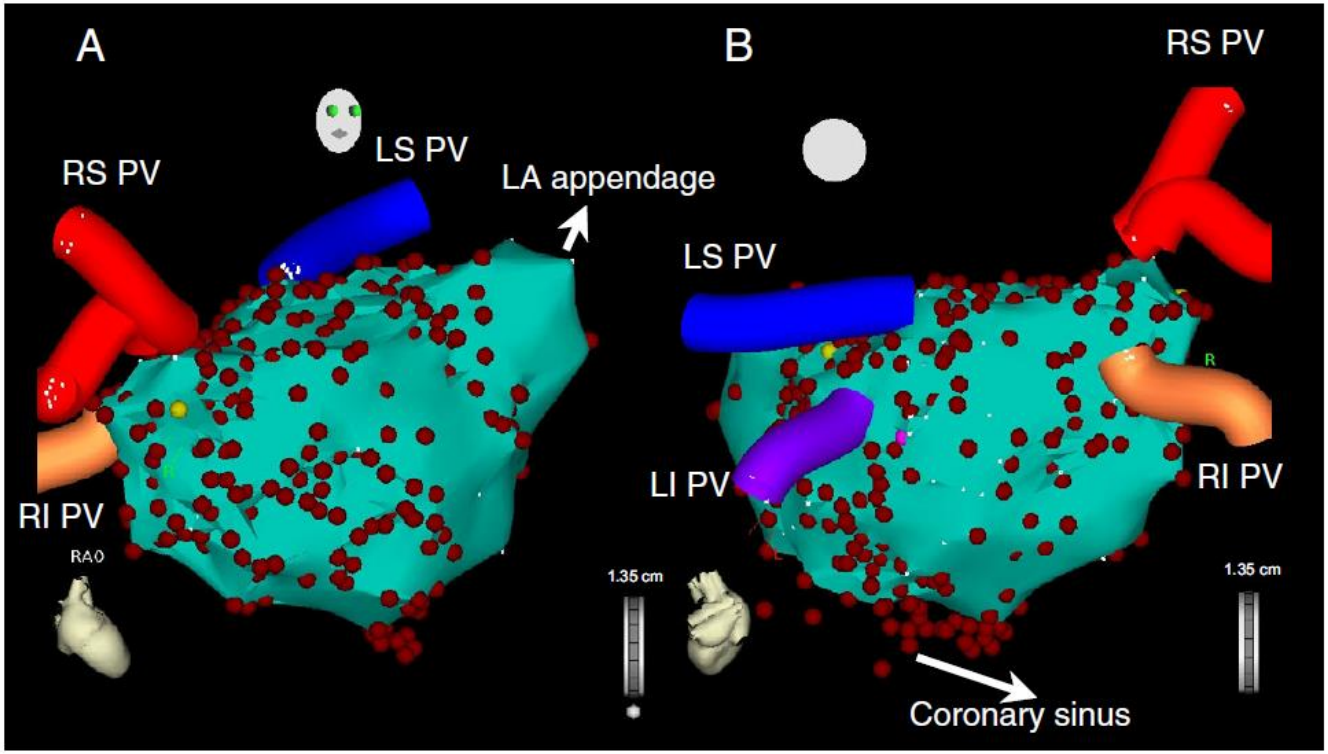
Radiofrequency ablation of left atrial and coronary sinus CFAEs resulted in maintenance of sinus rhythm in 57% of patients with chronic AF.
A second ablation procedure was necessary in 44% of patients. CFAEs in or near the PVs were commonly present during repeat ablation procedures. Macroreentrant atrial flutter occurred after ablation in ≈25% of patients, and multiple macroreentrant circuits were common in these patients.

Conversion of AF to sinus rhythm during ablation of CFAEs occurred in only a small proportion of patients and was not predictive of the long-term clinical outcome.

CFAEs-guided ablation: Oral et al. Circulation 2007



CFAEs-guided ablation: Oral et al. JACC 2009

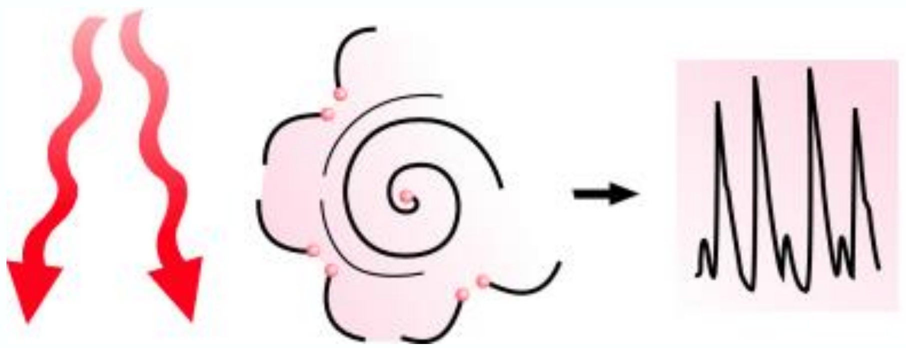


ST Dispersion

- Spatial clustering of abnormal electrograms.
- Abnormal electrograms may be fractionated or not.

CFAEs: Mechanisms

Velocity and directionality changes



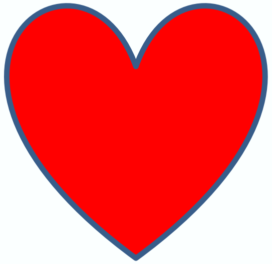
- Anatomic features
- Fibers direction changes
- Transverse conduction
- Longitudinal depressed conduction
- Conduction gating
- Interstitial fibrosis
- Ischemia
- Ion channels distribution

Velocity and directionality changes

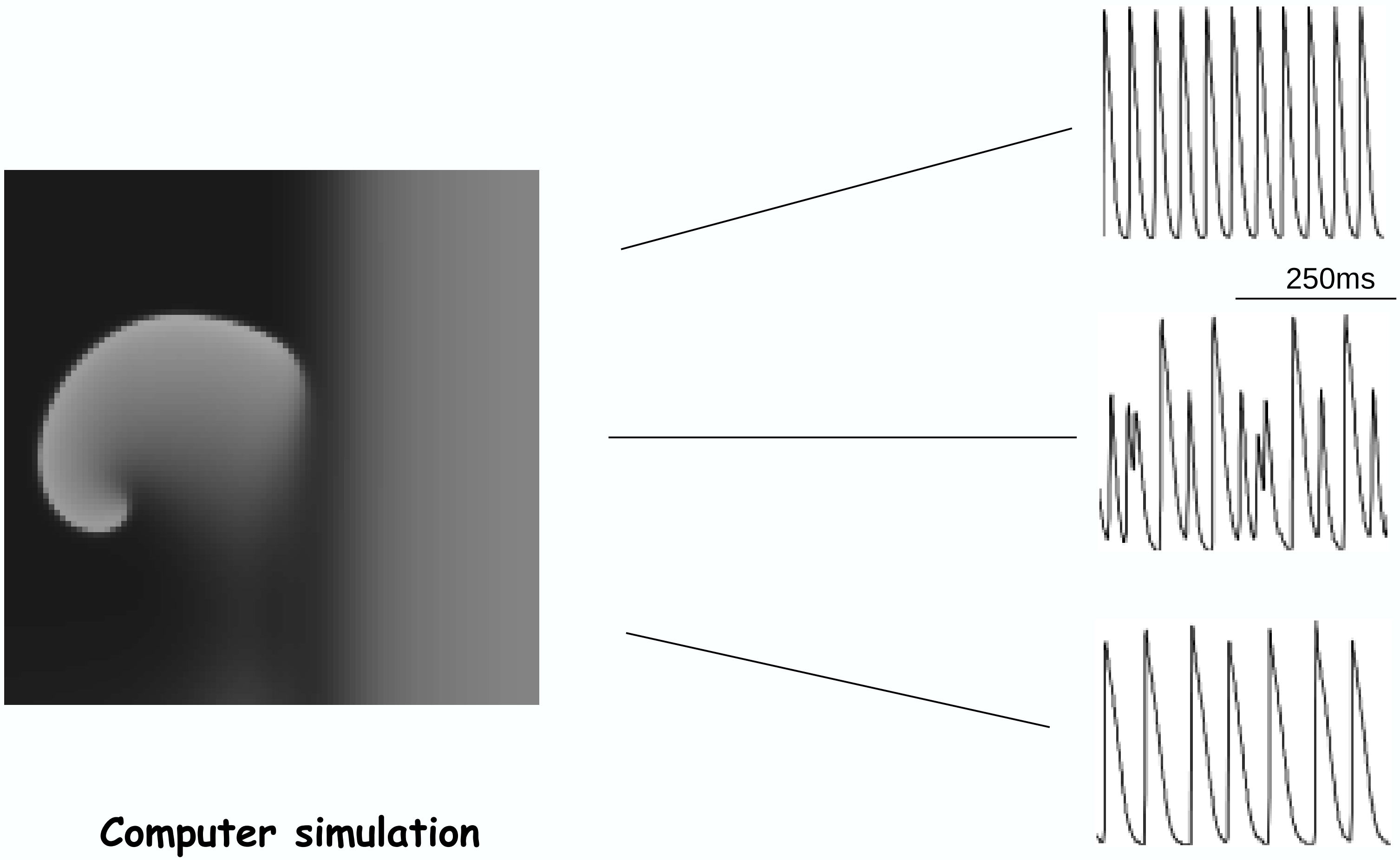
- Delays
- Blocks
- Colliding waves
- Wave breaks

Which factors may lead to the clustering of CFAEs?

What make different peoples live together in good intelligence?



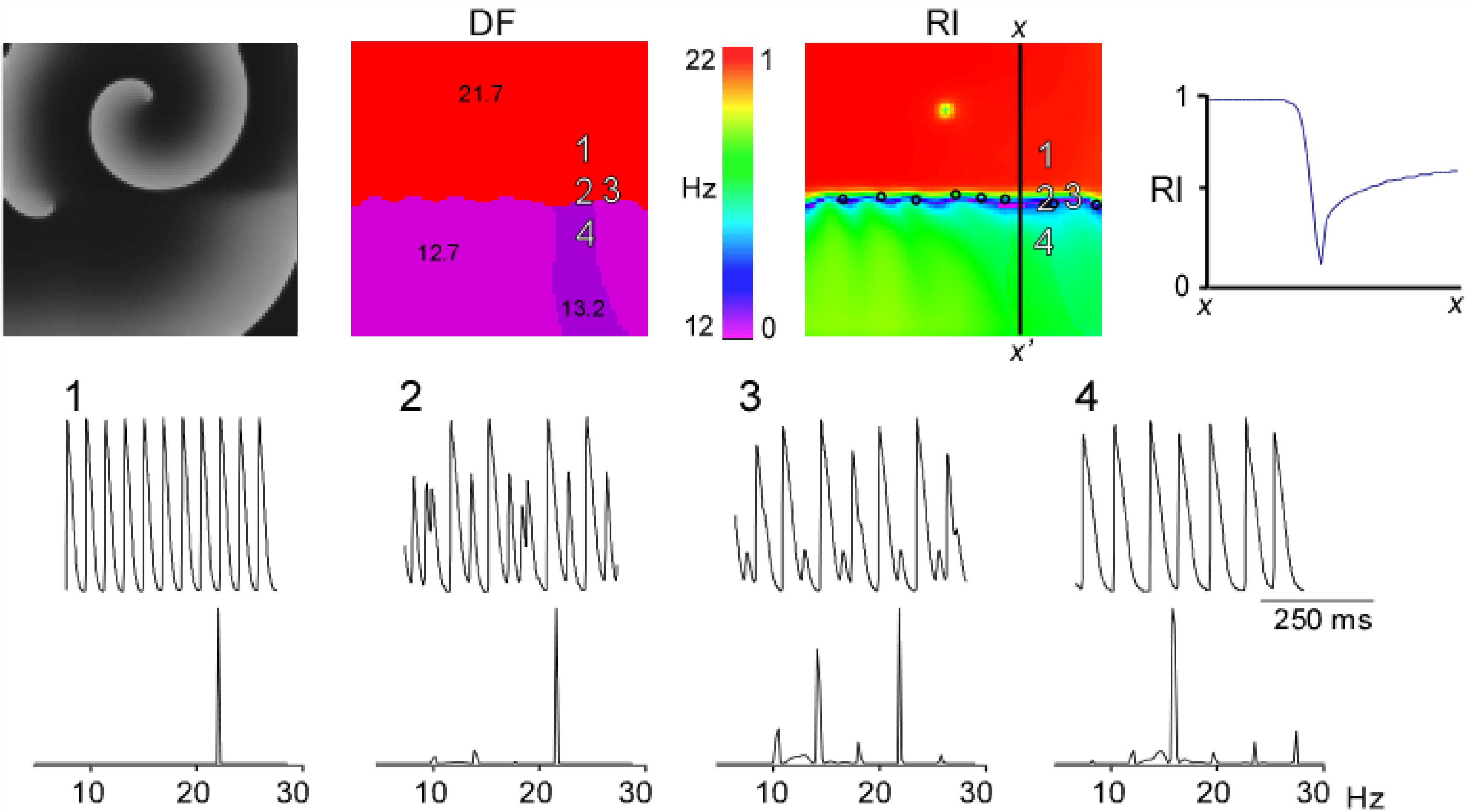
Numerical Simulation



Computer simulation
5X5-cm
human atrial cell model
(Dx = 0.1 mm, dt =0.025 msec)
Heterogeneity in IK,ACh conductance.

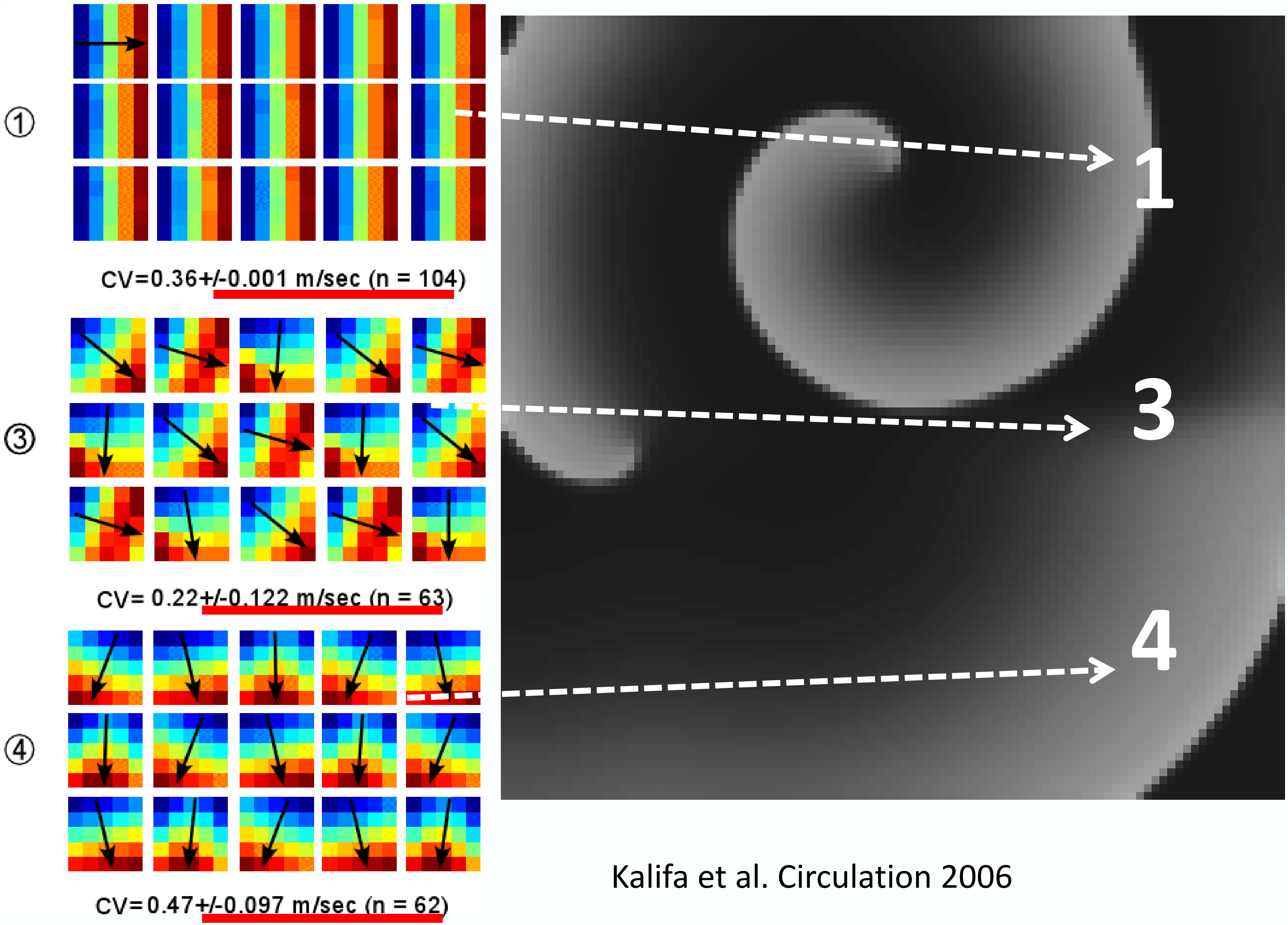
Kalifa et al. Circulation 2006

Numerical Simulation

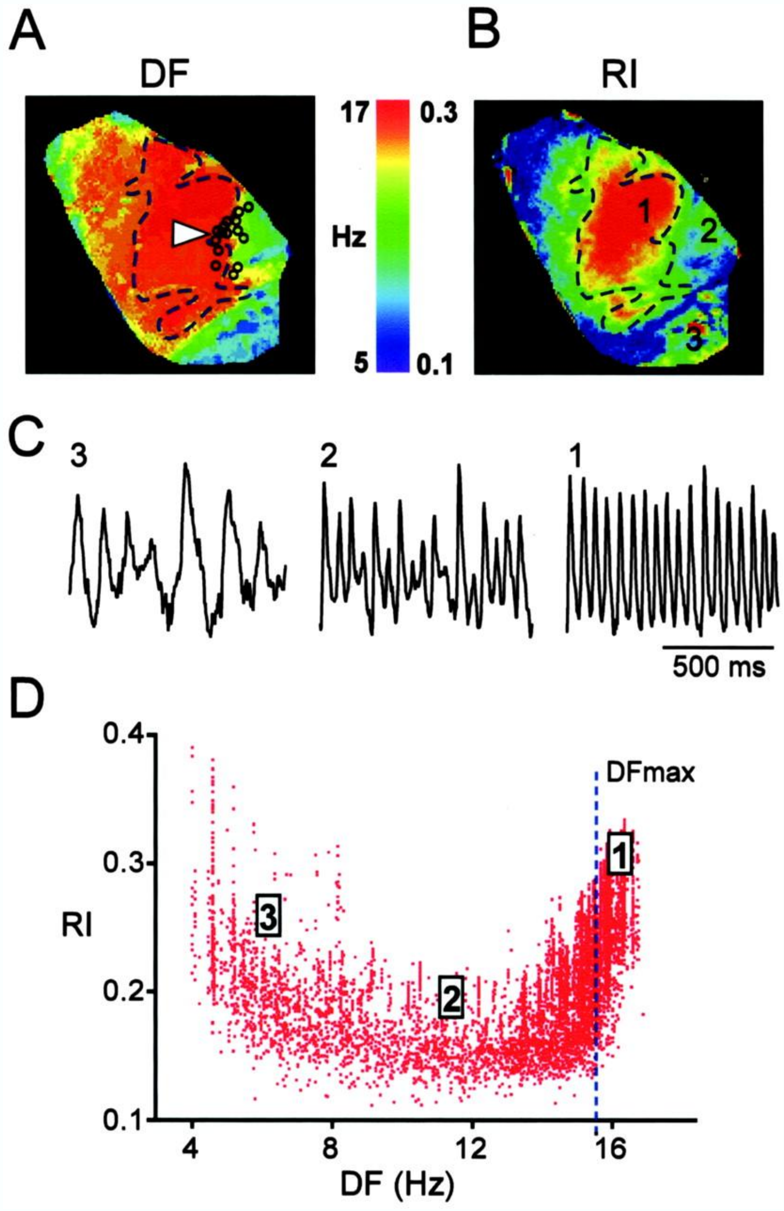


Kalifa et al. Circulation 2006

Computer simulation
Directionality analysis

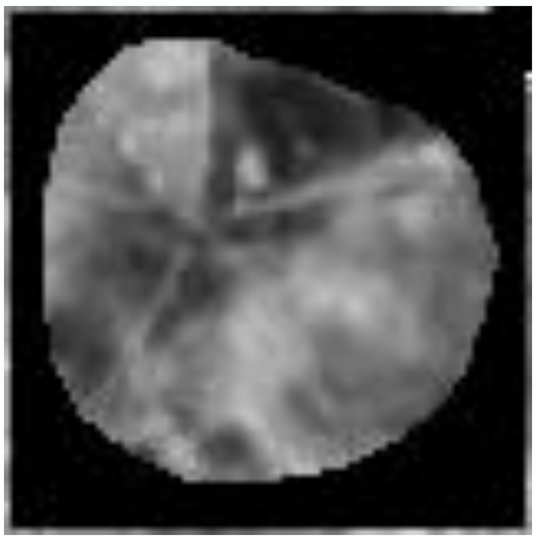


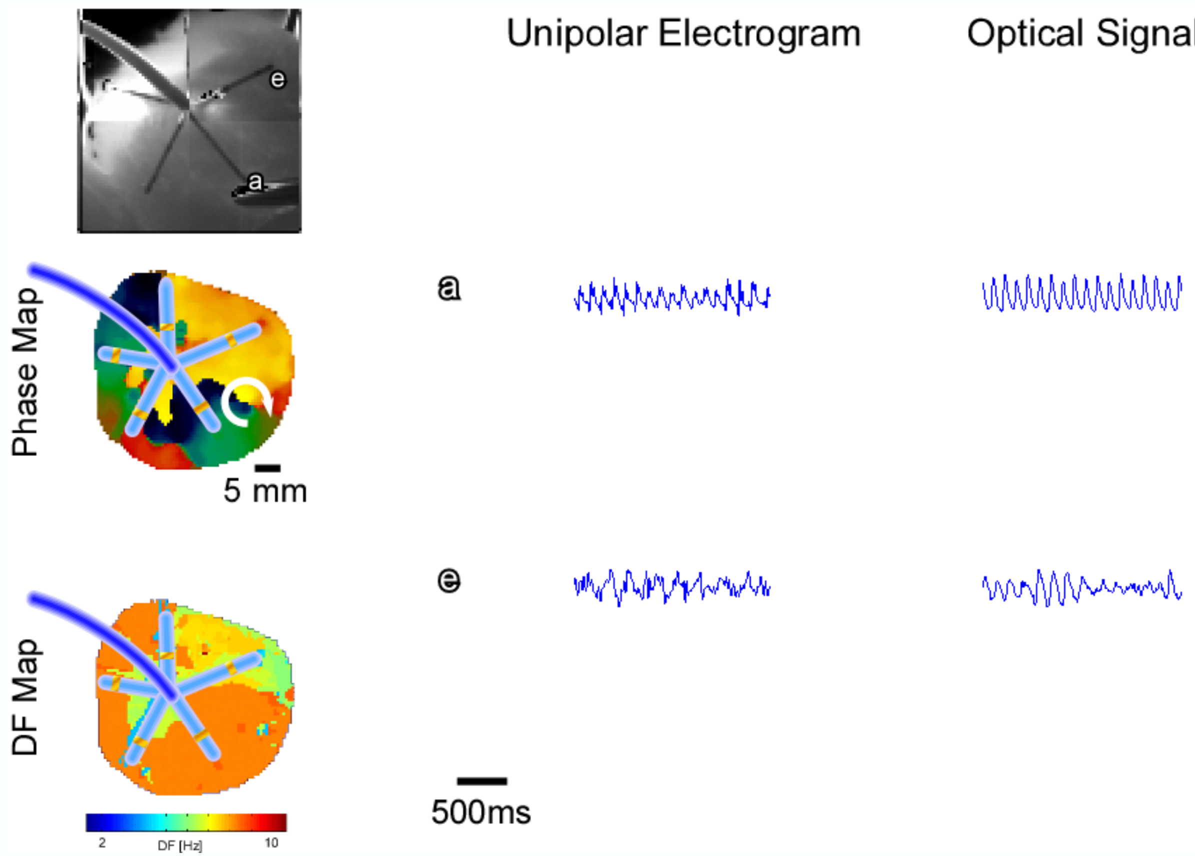
Kalifa et al. Circulation 2006



Kalifa et al. Circulation 2006

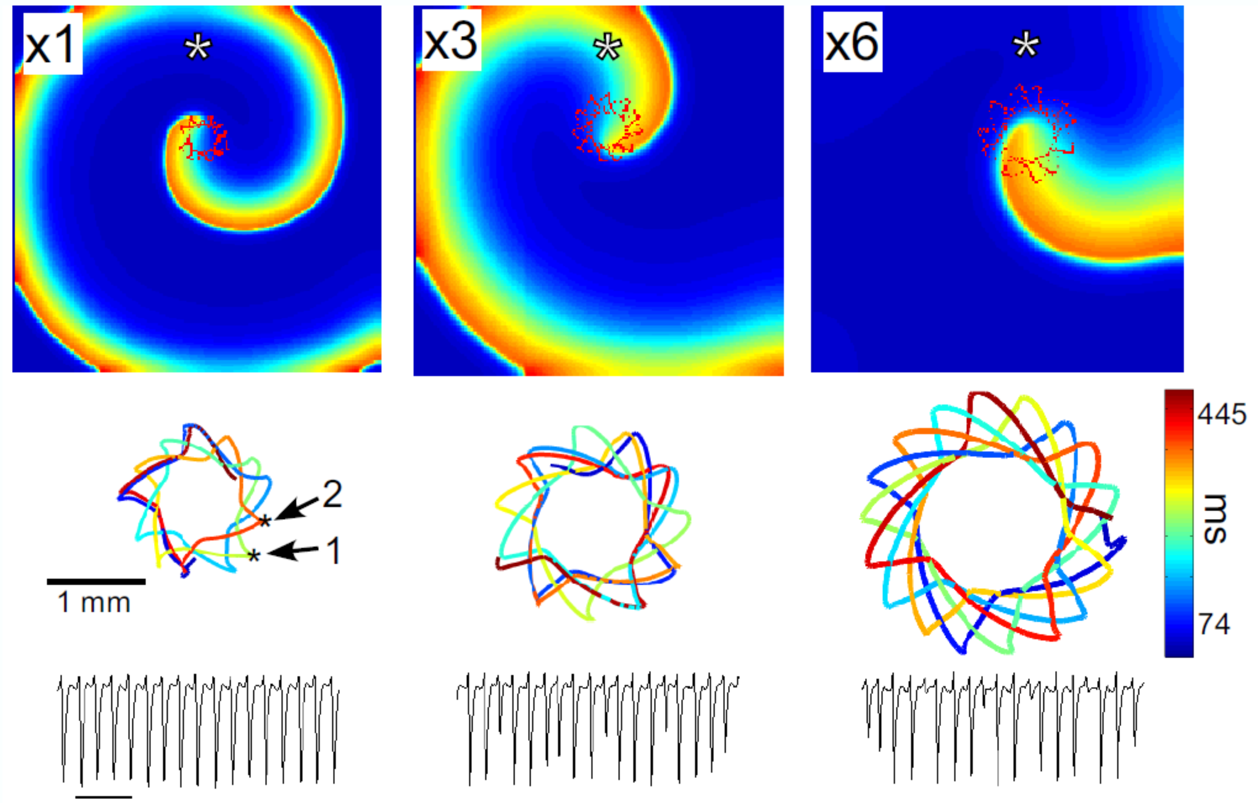
Regular and Fractionated electrograms in the vicinity of a rotor





Rotor Core Meandering

Diffusion coefficient ratio

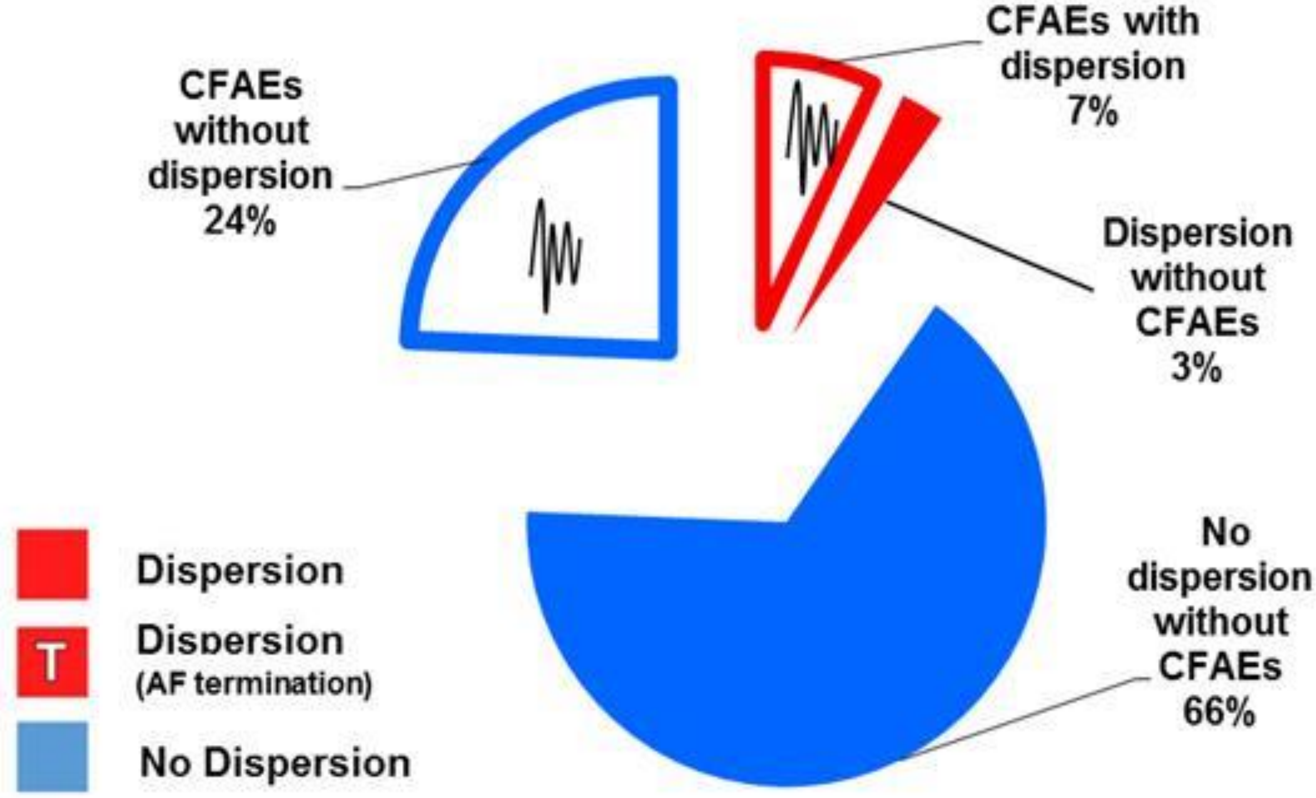


Zlochiver et al. Heart Rhythm 2008

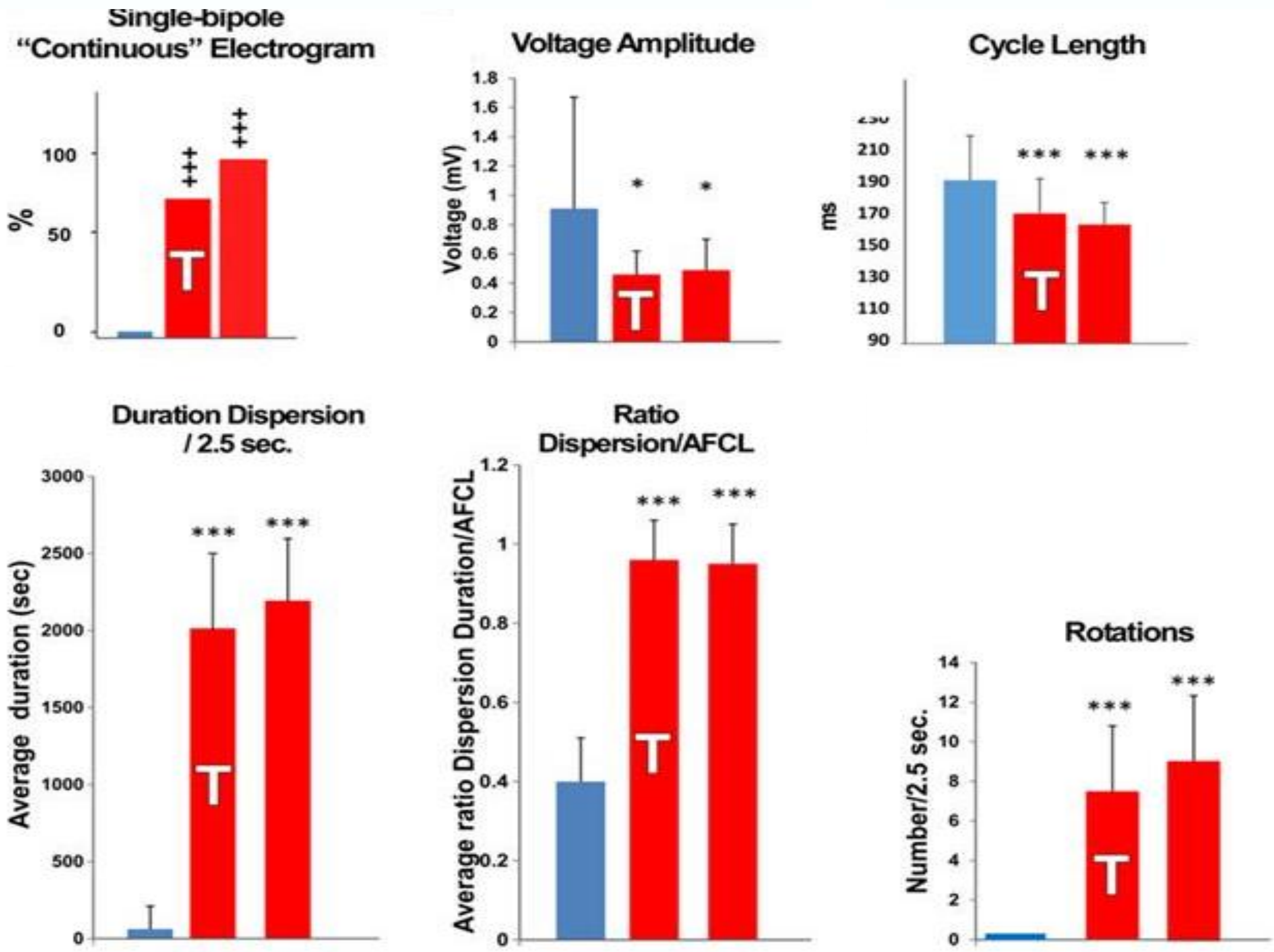
Electrogram-based Ablation
AF signal Frequency-based Ablation

Results: Multipolar Electrogram Analysis

% Dispersion area with low voltage (<0.5 mV) : 20 ± 25%



Results: Electrogram Analysis (II)

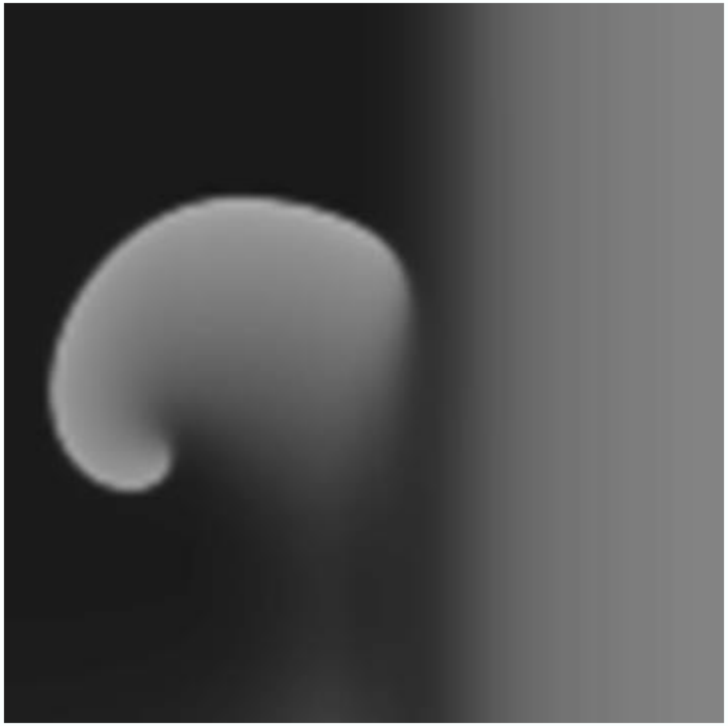


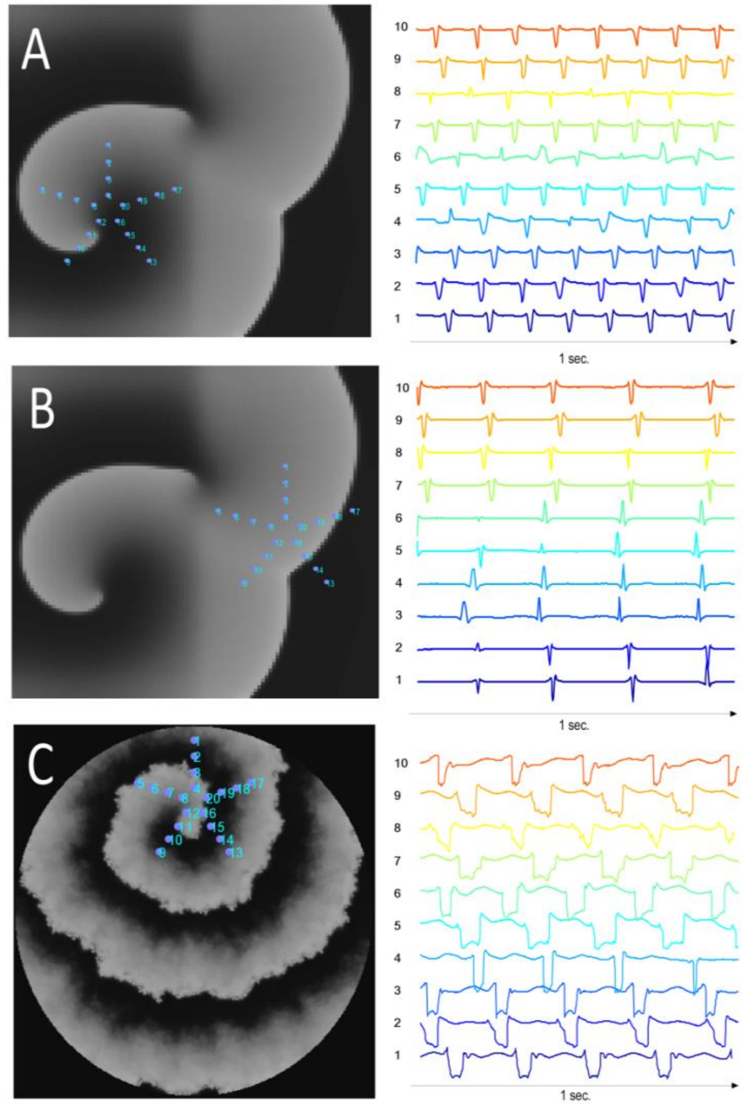
	LAA CL	Driver CL	Non driver CL	Continuous CFE in driver regions	Global voltage <0,5 mV in driver regions	Majority of AF CL In driver regions
Takayashi et al. *JACC 2008*	167 ms	166 ms*	182 ms	yes	yes	yes
Haissaguerre et al. *Circ 2014*	NA	185 ms	189 ms	yes	No (0,8 mV)	yes
Jadidi et al. *Circ ep 2016*	168 ms	NA	NA	yes	yes	yes
Seitz et al. (PAF excluded)	174 ms	165 ms*	190 ms	yes	yes	yes

*: CL significantly shorter than in non driver regions

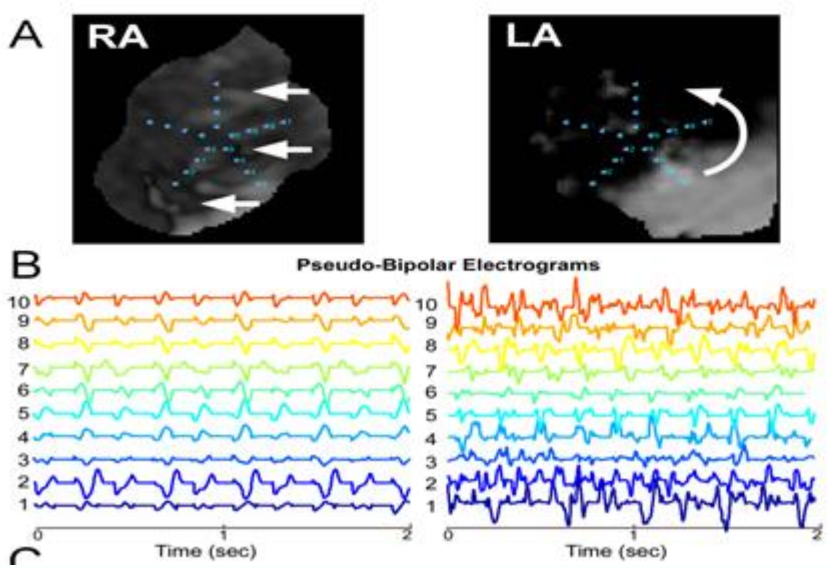
Numerical Simulations and Optical Mapping experiments

Numerical Simulations





Optical Mapping



Summary: Multipolar Electrogram Abnormalities

- Spatio-temporal dispersion of multipolar electrograms represents an ***electrical footprint of waves emanating from rapid fibrillatory sources and propagating within a heterogeneous atrial muscle.***

Conclusions

- Visually recognizable multipolar electrogram footprints may be used for the delineation and ablation of AF drivers regions
- At the mechanistic level, the relationship between frequency and fractionation needs to be further investigated.
- Particular attention will have to be paid to the relationship between frequency, fractionation and the spatial distribution of fibrosis.

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AHA

Conclusions

- Visually recognizable multipolar electrogram footprints may be used for the delineation and ablation of AF drivers regions
- These approaches will need to be evaluated in randomized studies.
- The spatial clustering of abnormal electrograms is non-random, driver-determined phenomenon.
- The relationship between frequency and spatio-temporal dispersion needs to be further investigated.
- Particular attention will have to be paid to the relationship between spatio-temporal dispersion and the spatial distribution of fibrosis.

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Benefits of Atrial Substrate Modification Guided by Electrogram Similarity and Phase Mapping Techniques to Eliminate Rotors and Focal Sources Versus Conventional Defragmentation in Persistent Atrial Fibrillation

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Ablation of AF Guided by Spatiotemporal Electrogram Dispersion Without Pulmonary Vein Isolation

A Wholly Patient-Tailored Approach

Julien Seitz, MD,[a] Clément Bars, MD,[a,b] Guillaume Théodore, MD,[c] Sylvain Beurtheret, MD,[a] Nicolas Lellouche, MD, PhD,[d] Michel Bremondy, MD,[a] Ange Ferracci, MD,[a] Jacques Faure, MD,[a] Guillaume Penaranda,[e] Masatoshi Yamazaki, MD, PhD,[f] Uma Mahesh R. Avula, MD,[f] Laurence Curel, MS,[a] Sabrina Siame,[a] Omer Berenfeld, PhD,[f] André Pisapia, MD,[a] Jérôme Kalifa, MD, PhD[f]

Questions

- **Electrogram-based Ablation of Atrial Fibrillation: Is There Still a Future?**

- **What can we hope from visual rendition approaches? The temptation of over-simplification**

- **Can we use visual appraisal of multipolar intra-cardiac electrogram during AF?**

Background

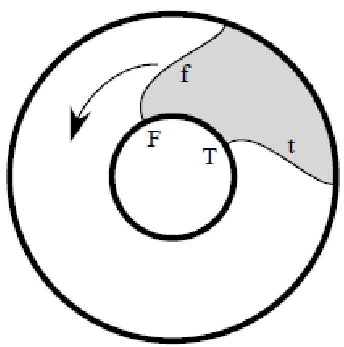
1. Rotors
2. CFAEs

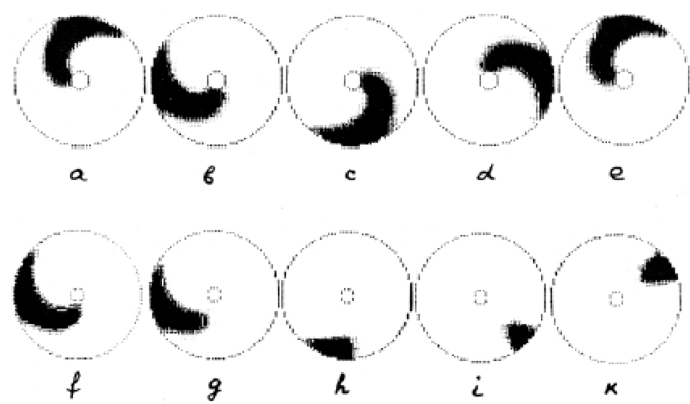
Background

1. **Rotors**
2. CFAEs

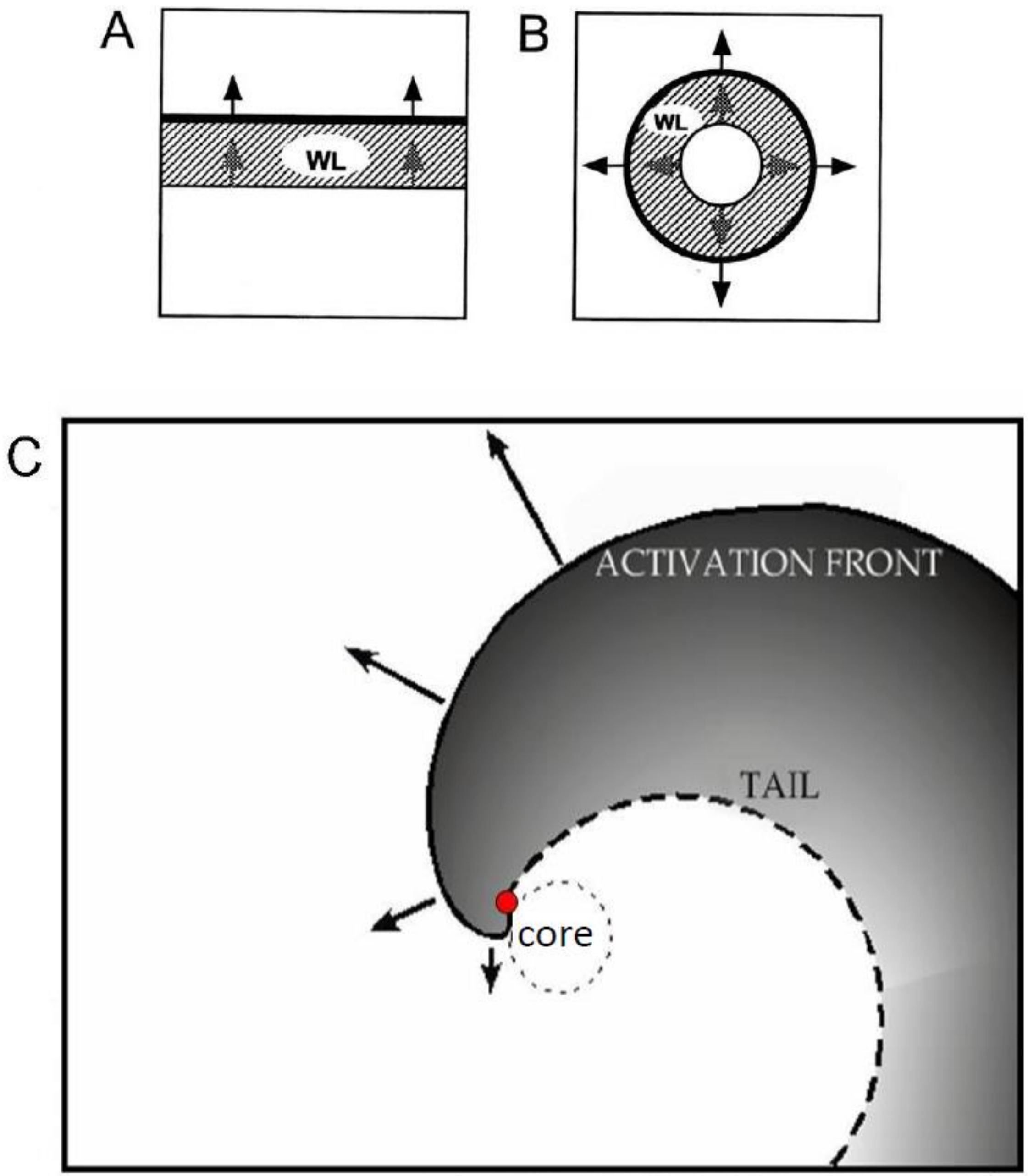
Rotors - Special Type of Reentry

Anatomical core → Functional core



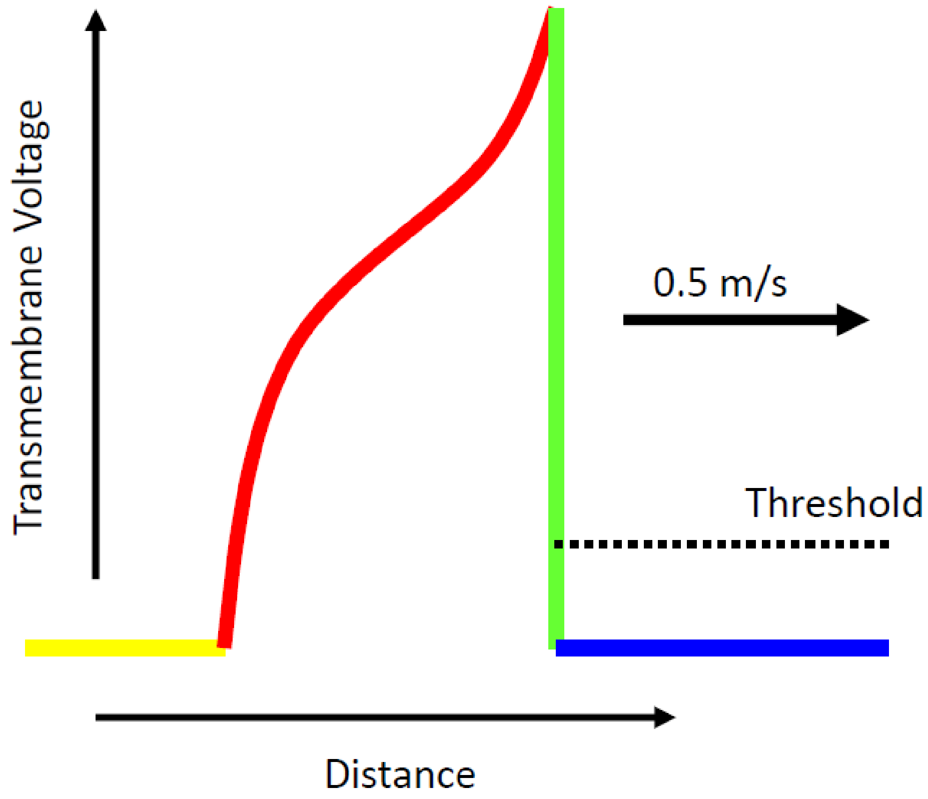


Courtesy Dr. Berenfeld

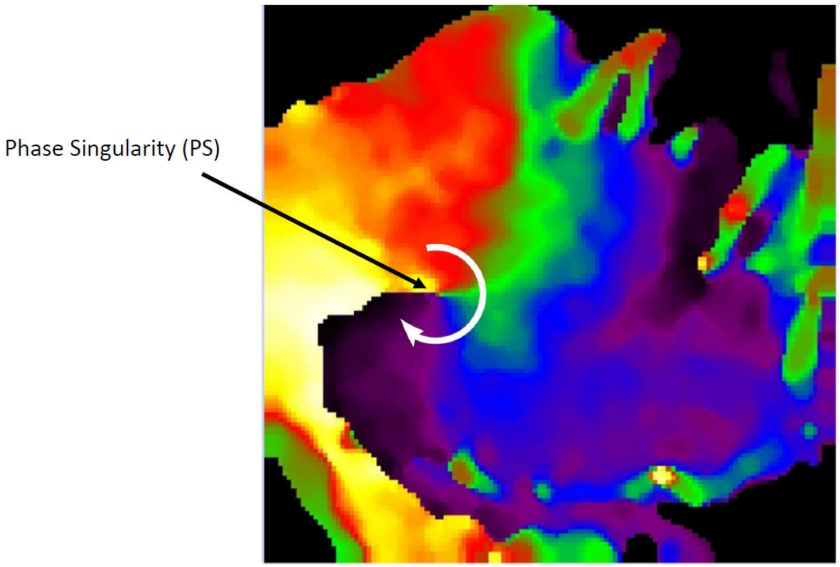


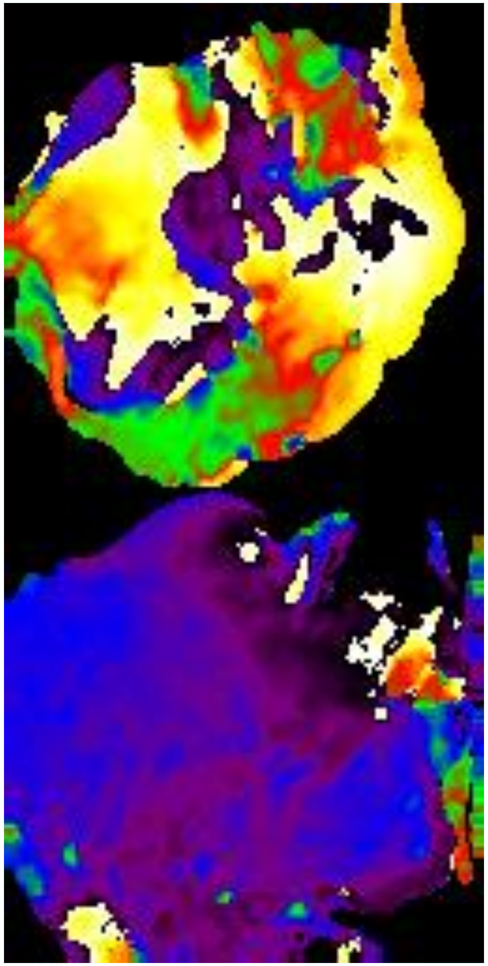
Courtesy Dr. Berenfeld

Color-coded phases of the action potential



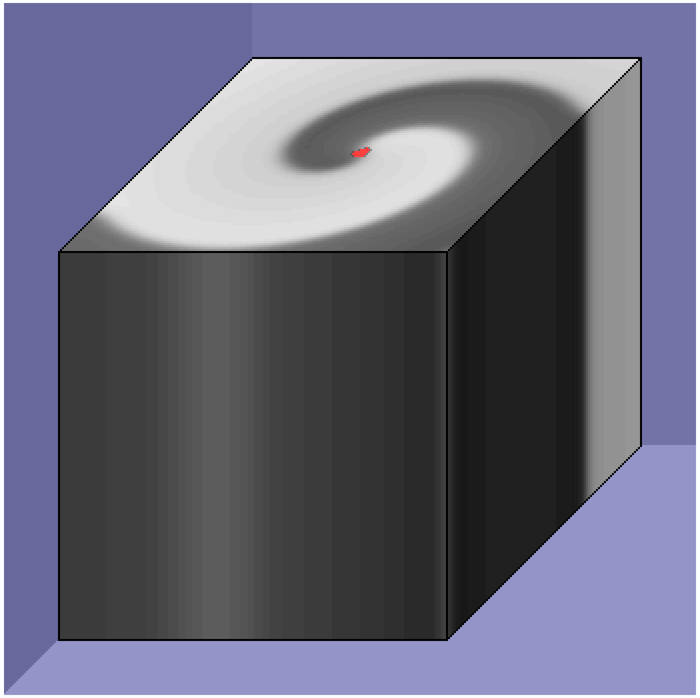
Courtesy Dr. Berenfeld

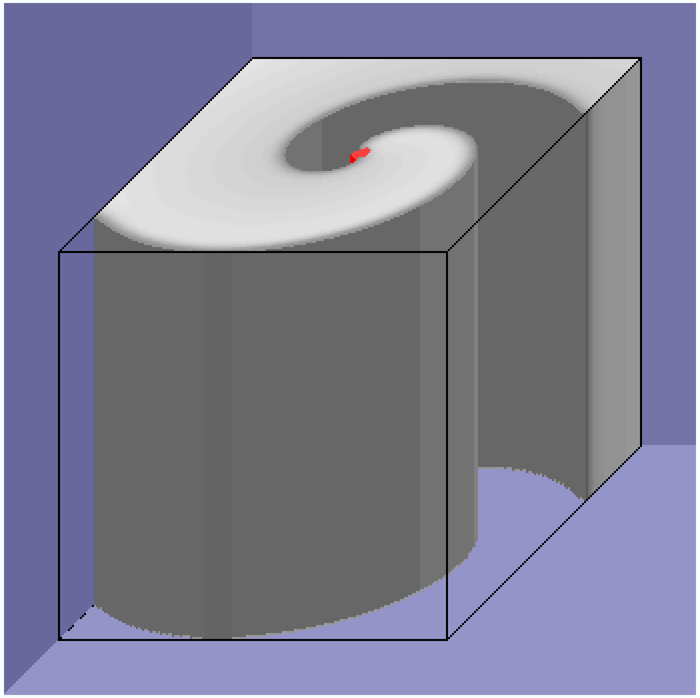

Phase Singularity (PS)

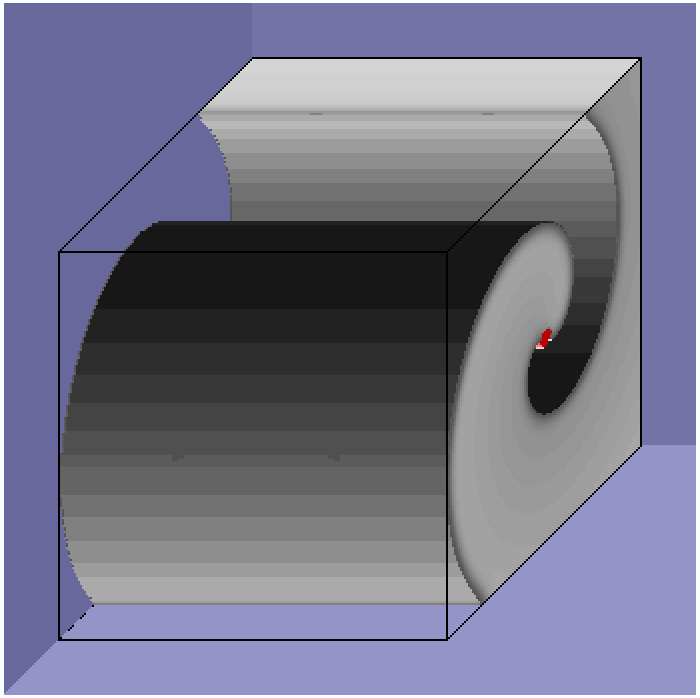


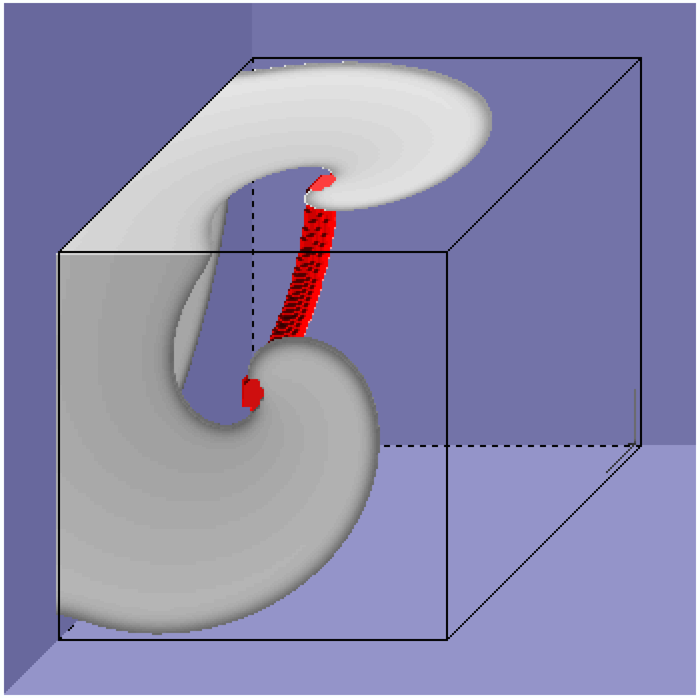
Rotors are 3D phenomena

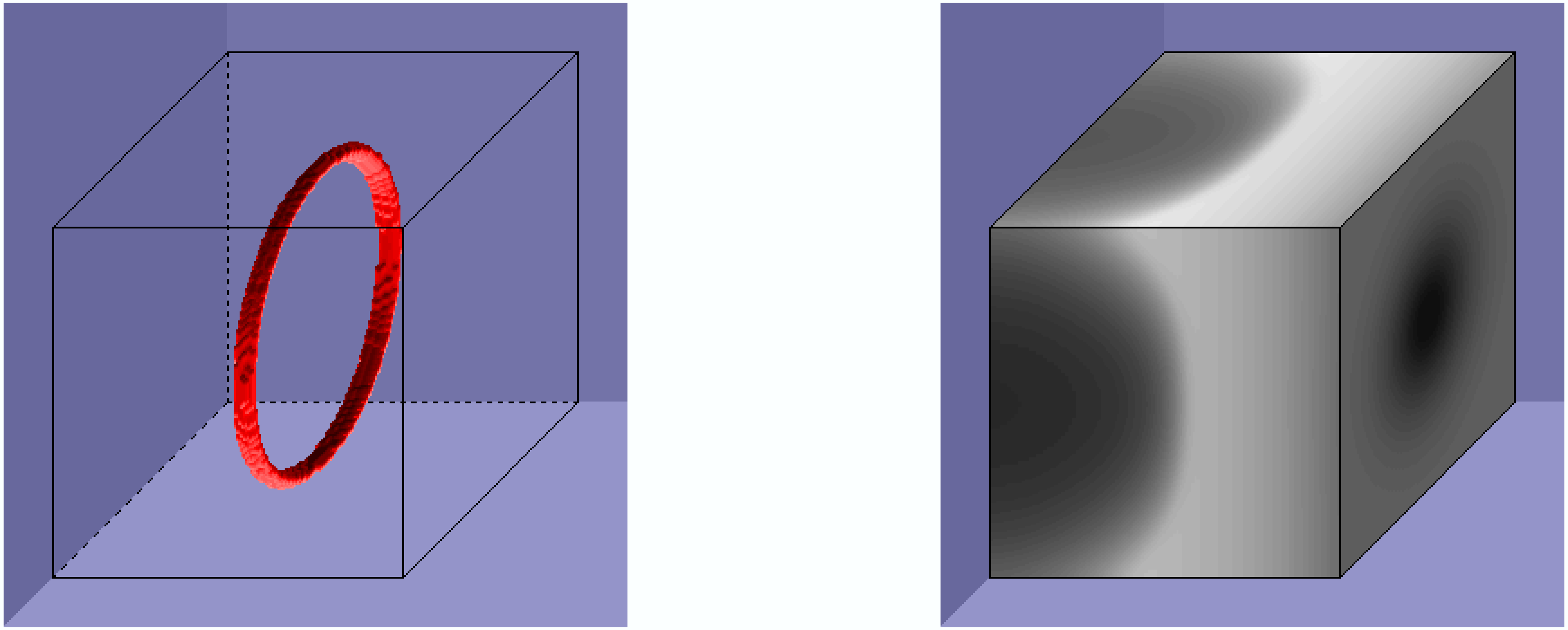
Examples: Numerical simulations and endocardial-epicardial optical mapping









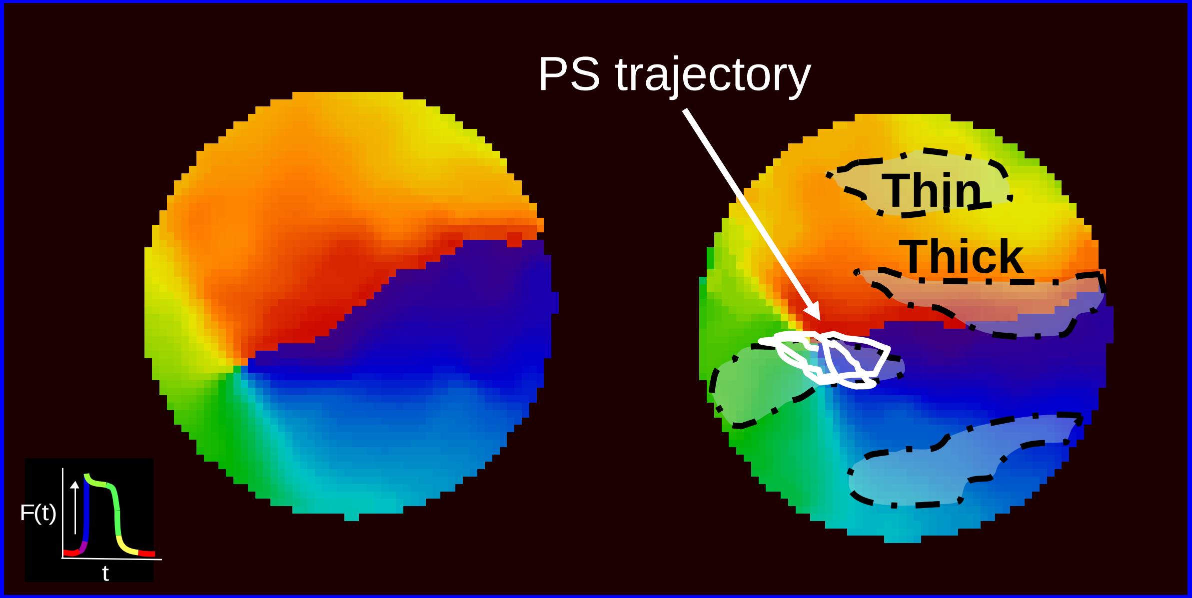


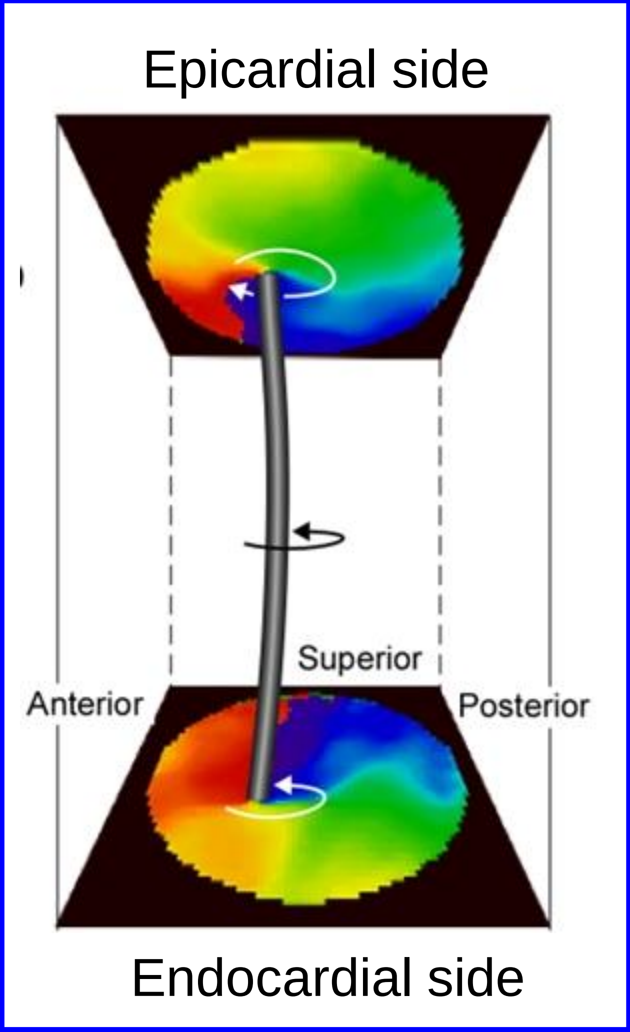
Optical Mapping

Patterns recorded:
Long-lasting Reentrant activity:
I-shaped filament SW

Epicardium

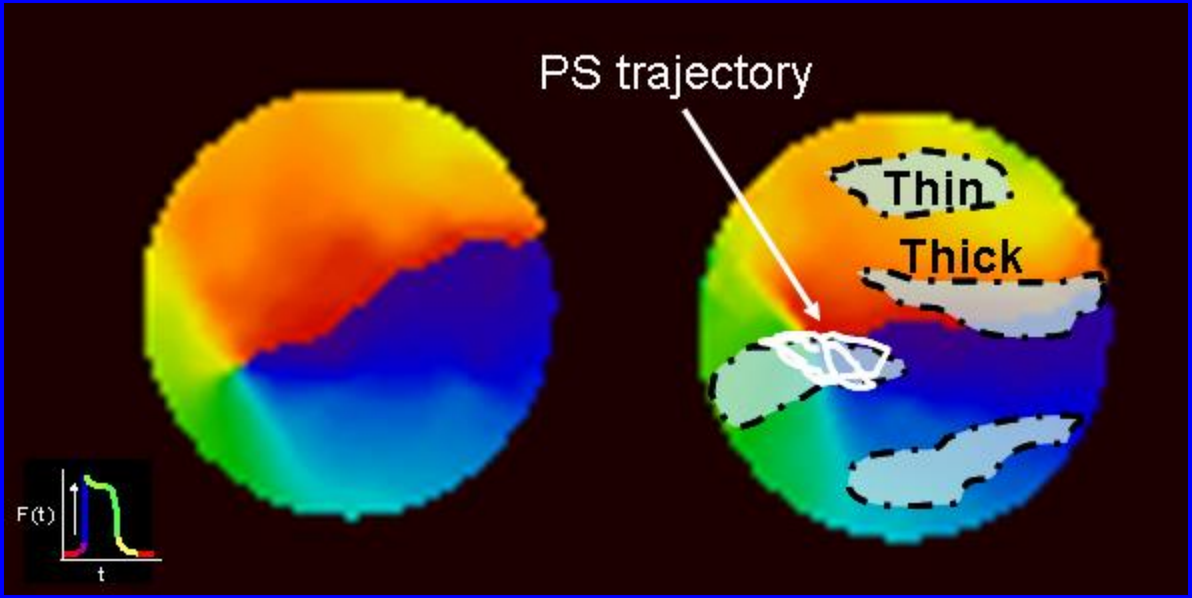
Endocardium

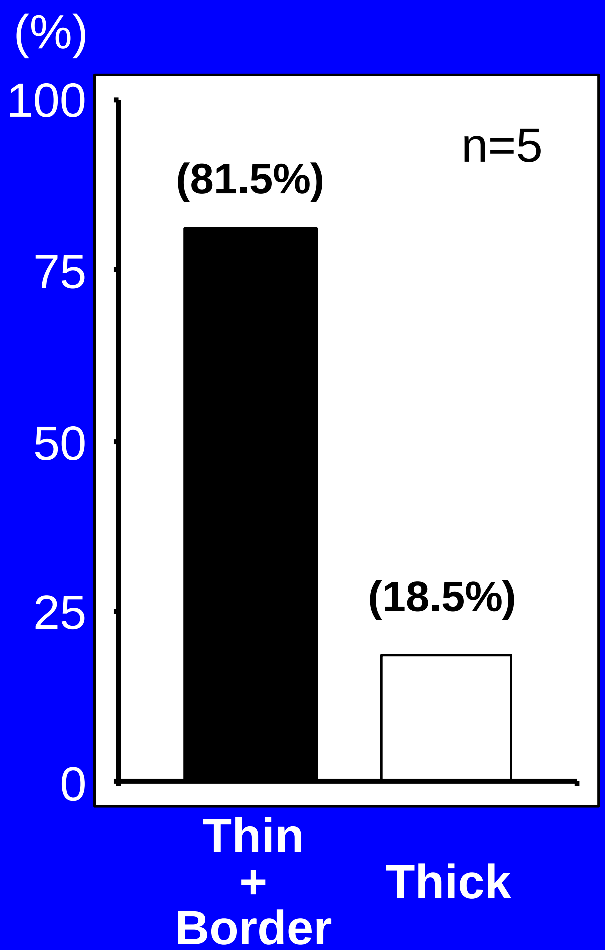




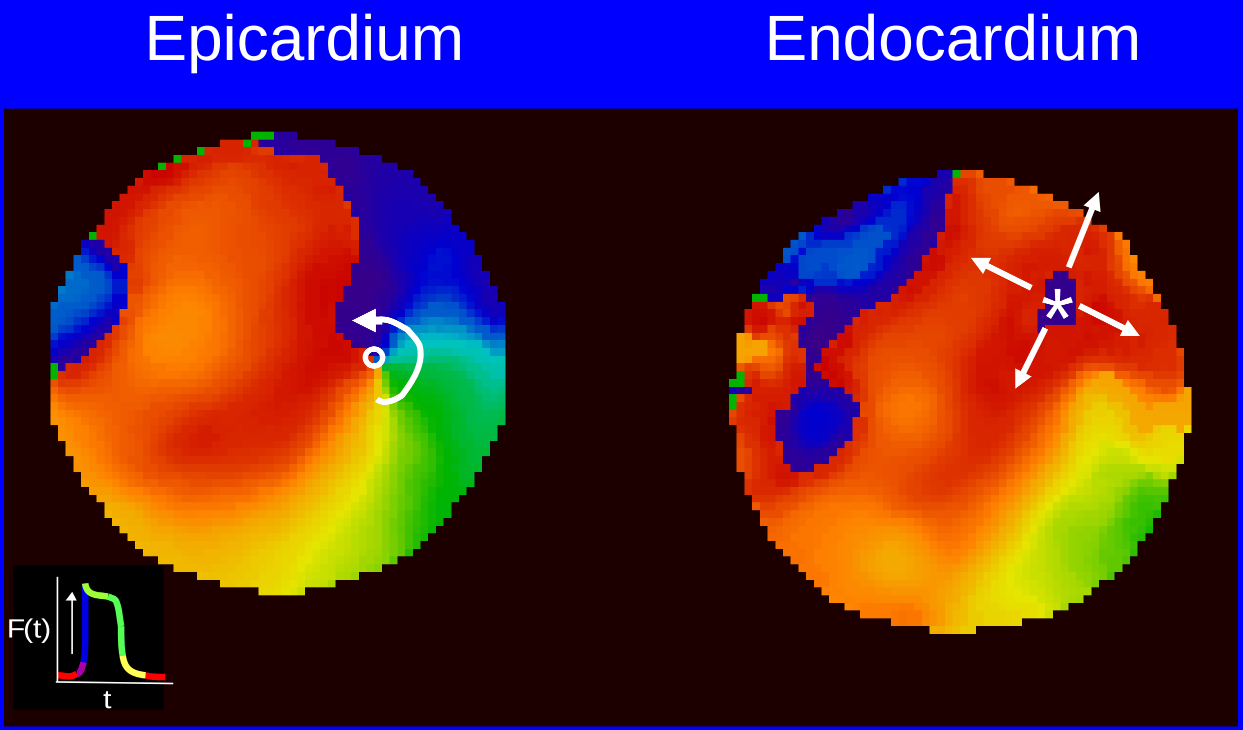
Patterns recorded:
Long-lasting Reentrant activity:
I-shaped filament SW

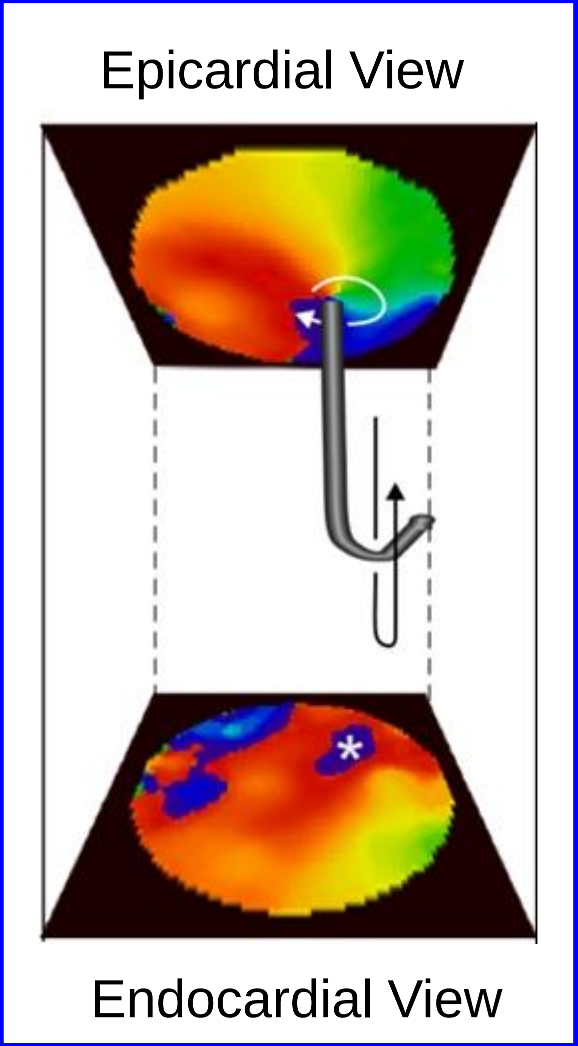
Epicardium Endocardium





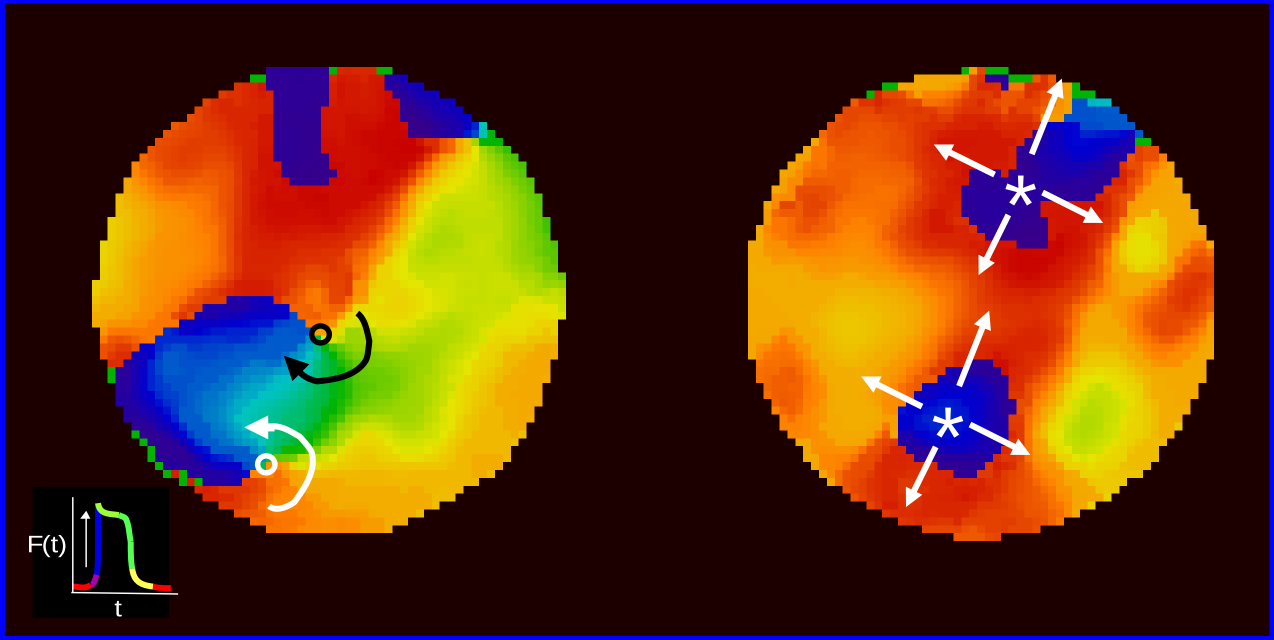
Patterns recorded:
Short-lived Reentrant activity:
L-shaped filament SW

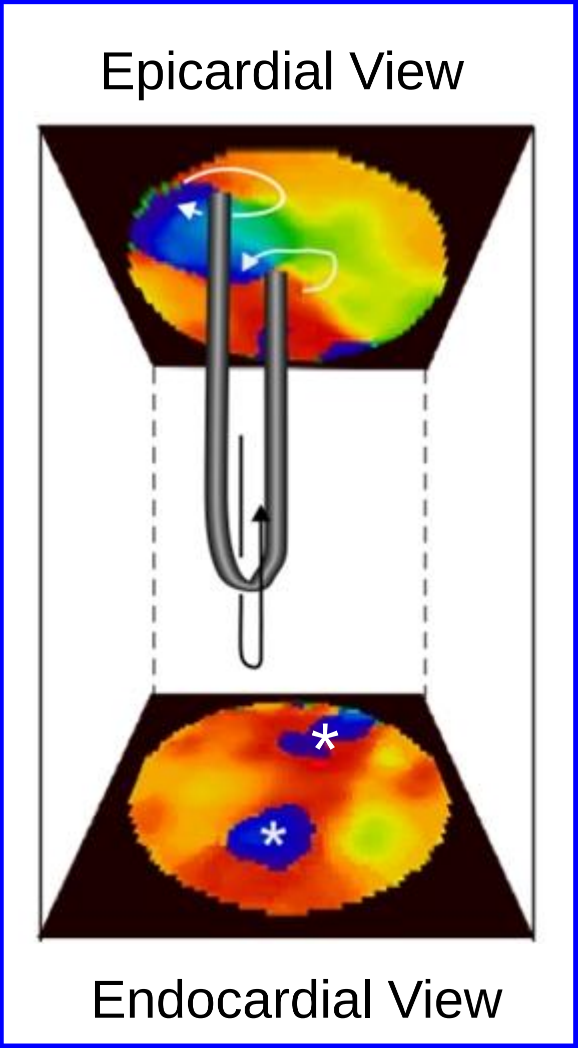




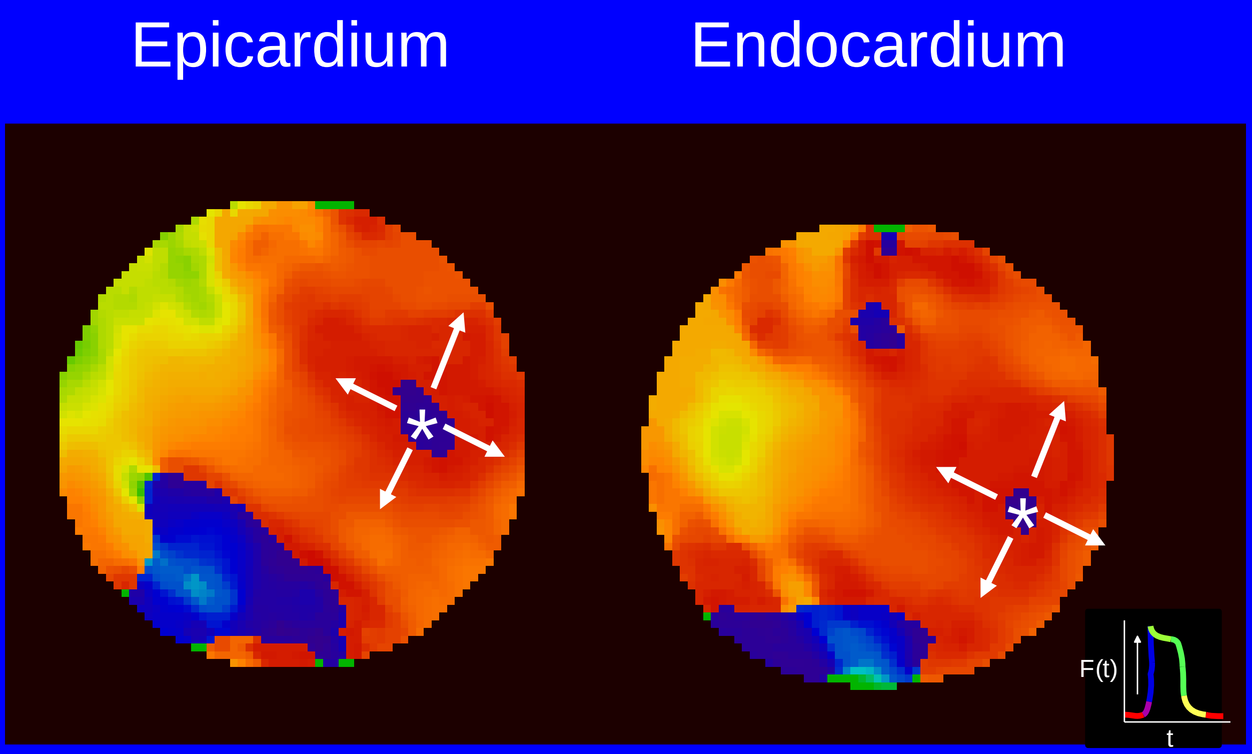
Patterns recorded:
Short-lived Reentrant activity:
U-shaped filament SW

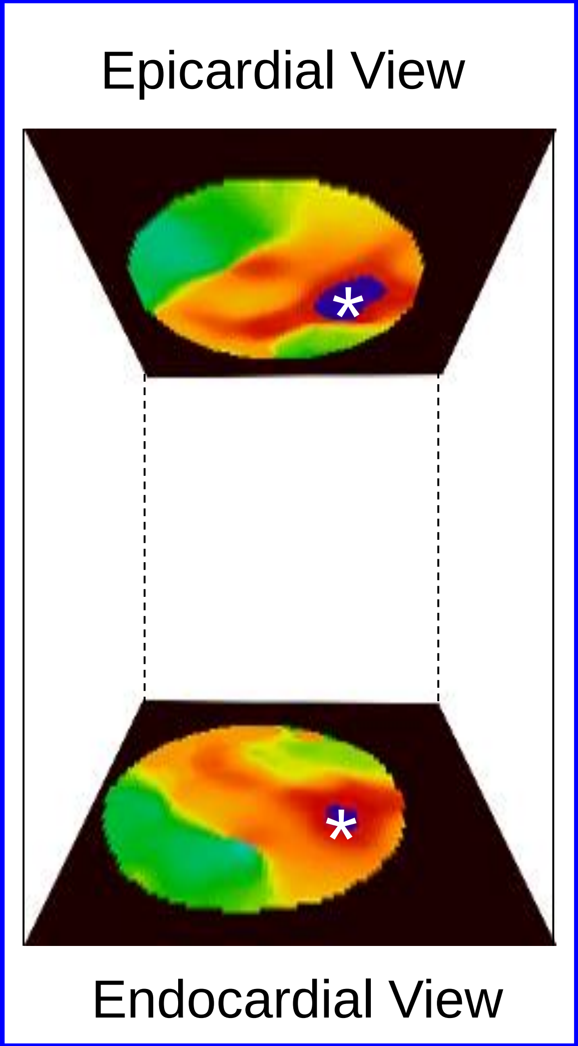
Epicardium Endocardium





Patterns recorded: Simultaneous endocardial and epicardial breakthroughs





Providencia et al.
Circ Arrhythm 2015

Meta-analysis: impact of CFAE ablation in patients with both persistent and paroxysmal AF.

13 studies were included, 9 of which were randomized controlled trials.

Among the 1415 patients (number of participants per study, 35–318), **815 underwent PV+CFAE ablation and 600 underwent PV isolation only.** CFAEs were defined by an **automated algorithm** in 6 studies and on the basis of **visual inspection** in the remaining.

CFAE ablation failed to improve outcomes in patients with paroxysmal (n=398, 28%), persistent, and long-standing persistent AF.

Only 2 of the 13 studies suggested benefit, and the remainder were neutral.

Nonrandomized studies were more likely to report a positive outcome. **There was a trend toward better outcomes in the PV+CFAE group if the patients underwent linear ablation and in patients with a longer history of AF.**

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Benefits of Atrial Substrate Modification Guided by Electrogram Similarity and Phase Mapping Techniques to Eliminate Rotors and Focal Sources Versus Conventional Defragmentation in Persistent Atrial Fibrillation

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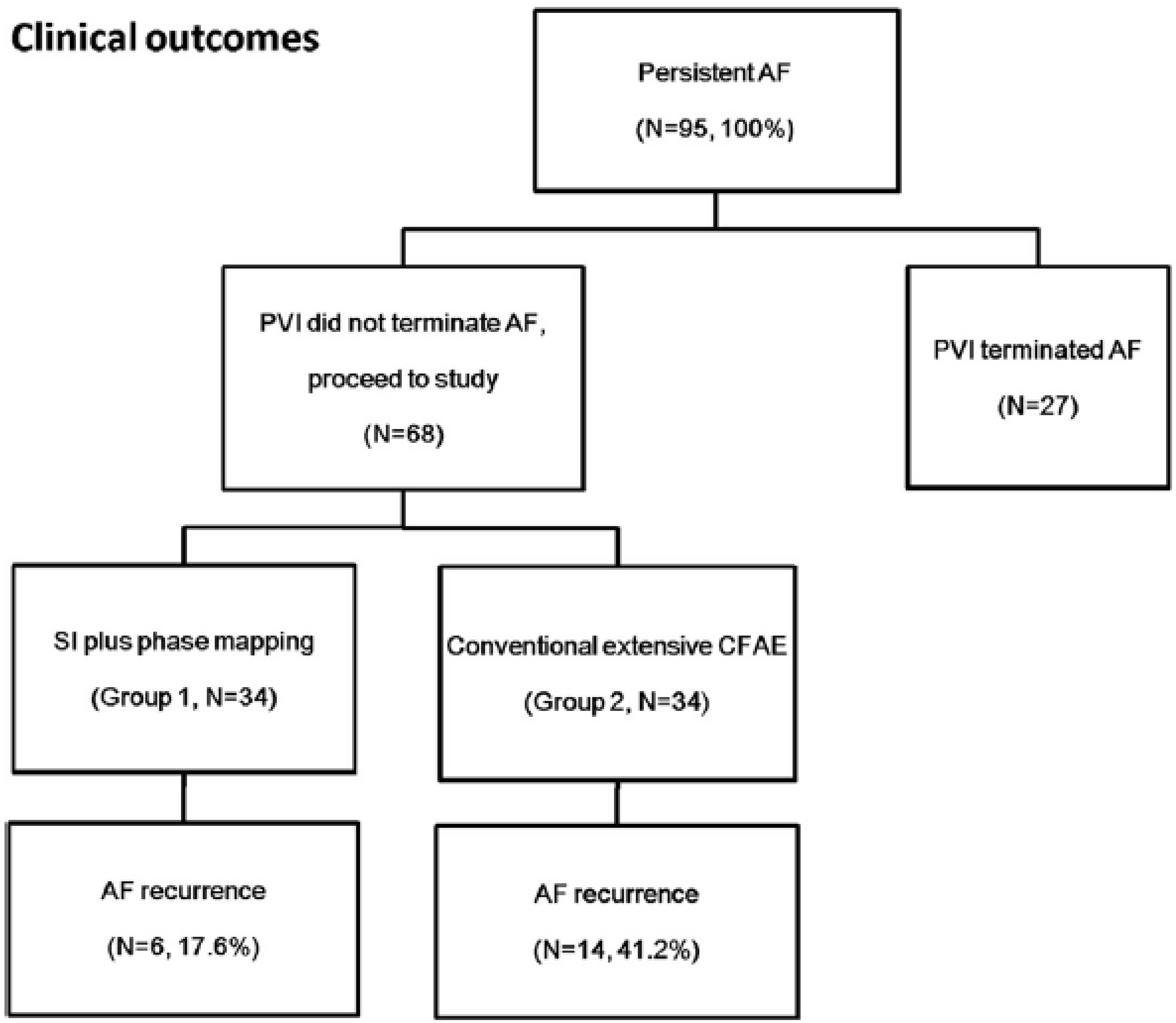
Lin et al. JACC EP 2016: Methods

Patients with persistent AF (sustained >7 days or lasting 7 days but necessitating pharmacologic or electrical cardioversion) and those with symptomatic, refractory AF, or intolerance to at least one class I or III antiarrhythmic medication were included in the study.

Randomly assigned to either the nonlinear phase mapping-guided substrate ablation (group-1) or extensive CFAE ablation (group-2). In the index procedure, only PVI and substrate ablation were performed.

FIGURE 1 Study Flowchart



Study flowchart showing the number of patients and primary ablation outcome. AF = atrial fibrillation; CFAE = complex fractionated atrial electrograms; PVI = pulmonary vein isolation; SI = similarity index.

Analysis

- Conventional: Dominant Frequency (FFT) and interval analysis (NavX, fractionation index= short intervals <60 ms)

- Non-linear: Phase analysis, Similarity Index, Curve, Divergence and Rotor Index

Wave Directionality Analysis

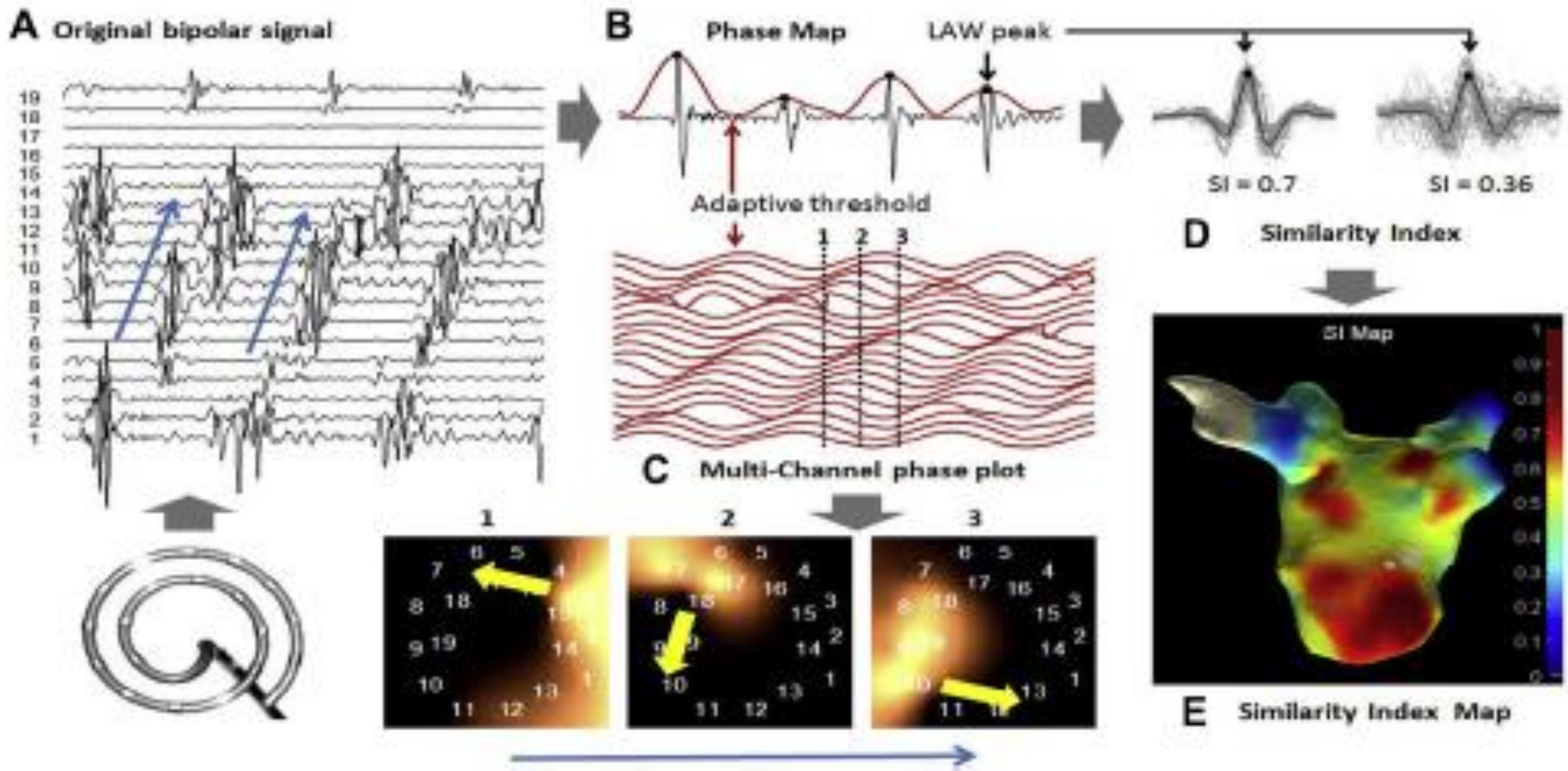
- **Signal decomposition** (finite number of oscillations modes within a given signal)
- **Hilbert Transform**: assumes angular displacement values for each time series value. Helps with distinguishing between wavefront and wavetail. Defines four propagation types—including rotor, focal point, traveling wave, and random fraction.
- The real-time phase mapping was subsequently used to confirm the propagation types and **characterize the averaged wave propagation** by several quantifiable parameters - the curl (curvature forces), the divergence, and the rotor identification index (RI) derived from the SI **vector field**.

Quantification

- **The electrogram similarity index (SI)** offers a quantitative way to measure how frequently and consistently the wave from the sources travels between two electrodes, even under highly fractionated regions. ***How much patterns of propagation exhibit spatio-temporal periodic patterns?***
- The **curl** indicated whether a vector field is **rotational**, whereas the **divergence** represented whether a vector field **spreads out** from a source or converges toward a sink. The RI was mathematically defined as the product of the divergence and curl as given by
- $\mathbf{RI} = (\boldsymbol{Div} > \mathbf{0}) \times \boldsymbol{Div} \times \boldsymbol{Curl}$

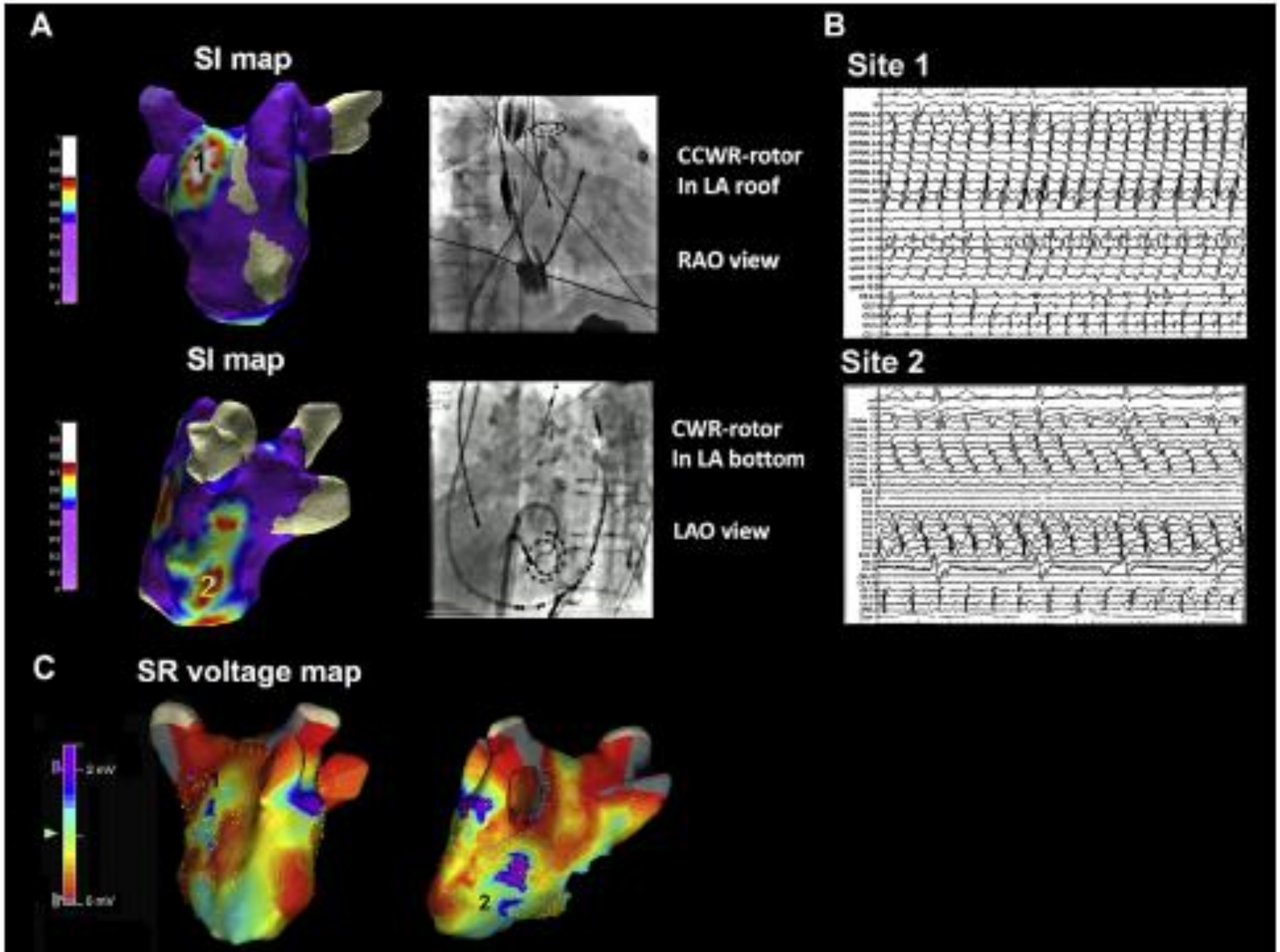
A higher RI indicates that the wave propagation is rotating around the center of a rotor and spreading outward to the rotor's periphery. The propagation "Rotor, focal sources, traveling wave, and random fractionated can be distinguished."

FIGURE 3 Illustration SI Mapping/Phase Mapping



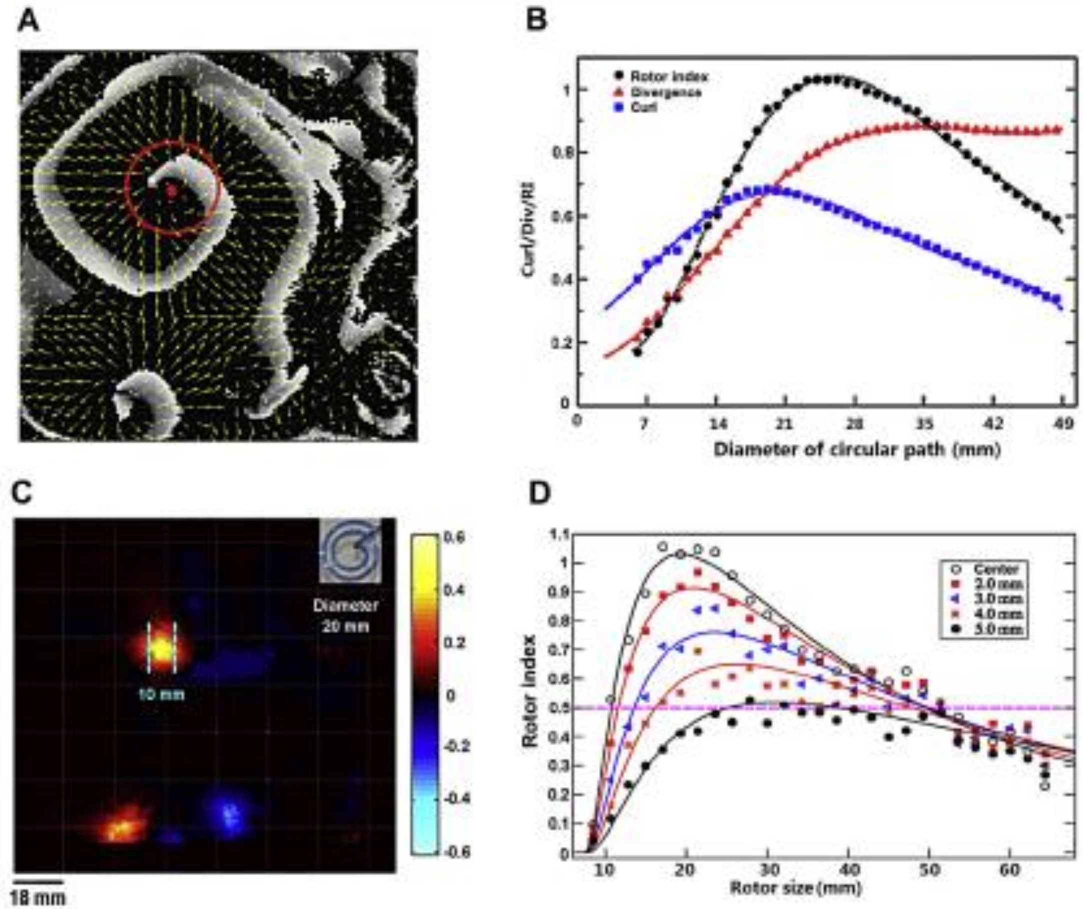
The bipolar fibrillation electrograms (A) was first band-pass filtered (10 to 300 Hz) for preprocessing. The associated envelope of the filtered signal was subsequently obtained by the order-statistic filter, which could effectively attenuate noise and far-field contamination to highlight the local activation wave (LAW) (B). Multiple electrode catheter facilitates characterization of wavefront propagation by real-time phase mapping derived from the reconstructed envelop function (C). Similarity index was quantified based on the temporal and spatial consistency of morphological repetitiveness of LAW (D). Rotors were identified in the high SI region with aids of real-time 3D display of the similarity index/phase mapping (E). AF = atrial fibrillation; CFAE = complex fractionated atrial electrograms; PVI = pulmonary vein isolation; SI = similarity index. Also see Online Video 3.

FIGURE 2 Similarity Index Mapping, Fluoroscopy, and Intracardiac Recordings in Persistent AF



Examples of SI mapping **(A)**, fluoroscopy **(middle)**, and intracardiac mapping **(B)** in a patient with persistent AF, with 2 rotors in the LA. **(C)** Bipolar voltage during SR. Rotors were located at the boundaries of the low-voltage zone. CWR = clockwise; CCWR = counterclockwise; LA = left atrium; LAO = left anterior oblique view; RAO = right anterior oblique view; SR = sinus rhythm; other abbreviations as in Figure 1. Also see Online Video 2.

FIGURE 4 Quantifying Rotors in the High-Similarity Electrogram Region

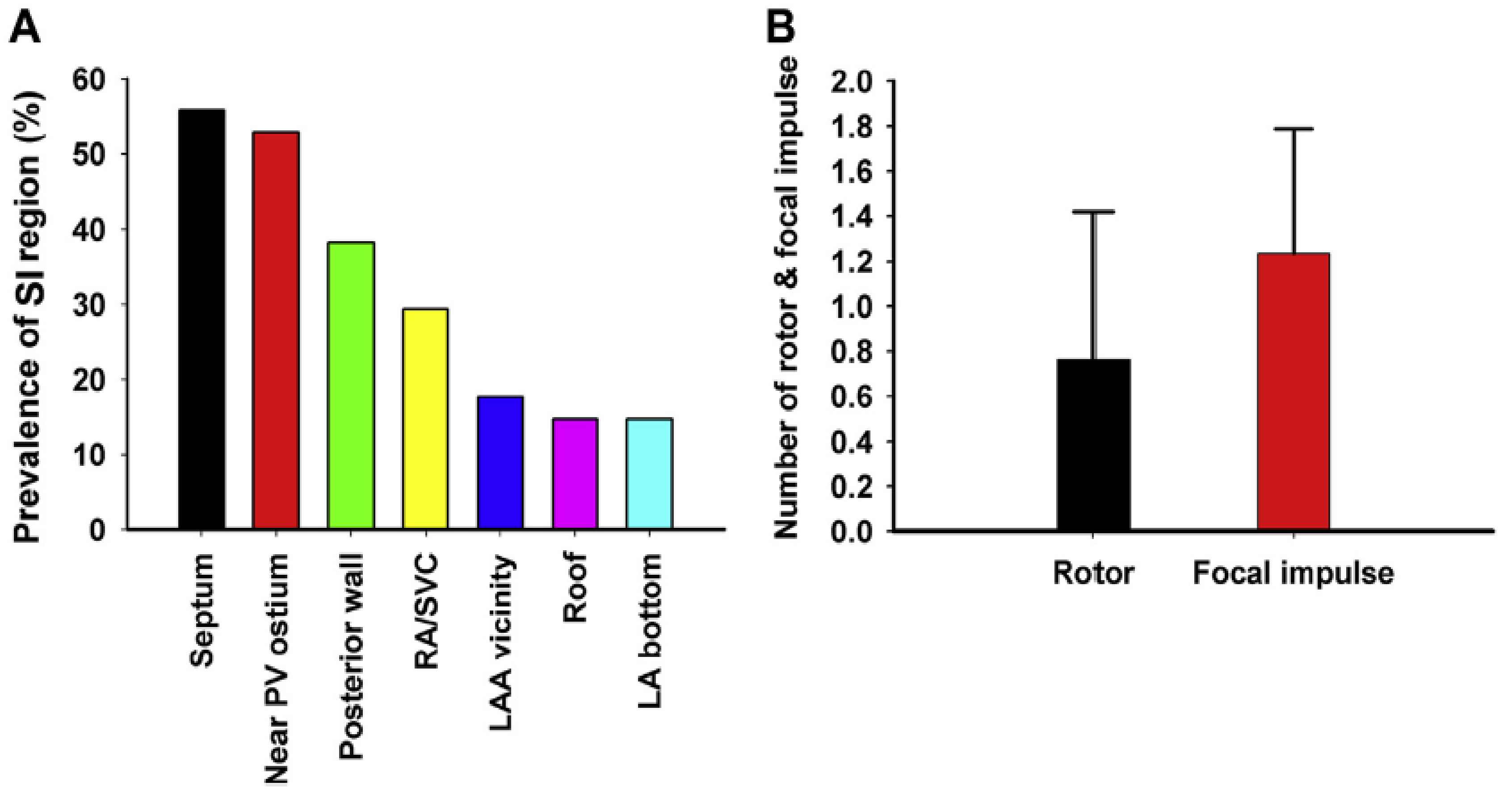


The vector field **(A)**, showing averaged waveform propagation, was used to quantify the rotors in the high-similarity electrogram region. The quantifying physical parameters were the divergence (**[B]** Div) and curvature force (**[B]** Curl). The rotor identification index (**[B]** RI) was mathematically defined as the product of the divergence and curl. The curl, divergence, and maximum RI values **(B)** were dependent on the integrating path radius and distance to the rotor center. The regional distribution of the RI was integrated into an automatic algorithm to define the rotors in a demonstrative model **(C)**. The relationships among the RI, rotor size, and the distance between the attached site and rotor center (deviations) are shown. By attaching a double-spiral catheter to the simulated substrates, 5 different curves show the functions of RI for different sizes of rotors when positioning the catheter at the sites deviated from the center of the rotor (deviations of 0 **[circle]** to 5.0 mm **[solid circle]**) **(D)**. According to **D**, a rotor with a deviation toward the center could be detected only if its size was 1.3 to 2 times larger than the diameter of the catheter (i.e., ≈26 to 40 mm) with an RI value of 0.5. In contrast, if the catheter was on the center of the rotor, we could detect a rotor dimension ranging from 0.5 to 2.5 times the diameter of the catheter dimension (i.e., ≈10 to 50 mm) with an RI value of 0.5. Also see Online Video 1.

Results

	Group-1 PVI+SI/Phase Map (n = 34)	Group-2 PVI+CFAE (n = 34)	p Value
Procedure and Outcomes			
Ablation lesion (excluding PVI)	86 ± 38	128 ± 63	0.01
Ablation time, min	97 ± 33	141 ± 47	0.01
Procedure time, min	134 ± 48.5	154 ± 41.1	0.12
Complication resulting from procedure	1 (3%)	0 (0%)	> 0.99
AF recurrences	6 (17.6%)	14 (41.2%)	0.03
Recurrence of LA AT or AFL	6 (17.6%)	3 (8.8%)	0.28

FIGURE 5 Prevalence of SI Region Distribution and Average Number of SIs

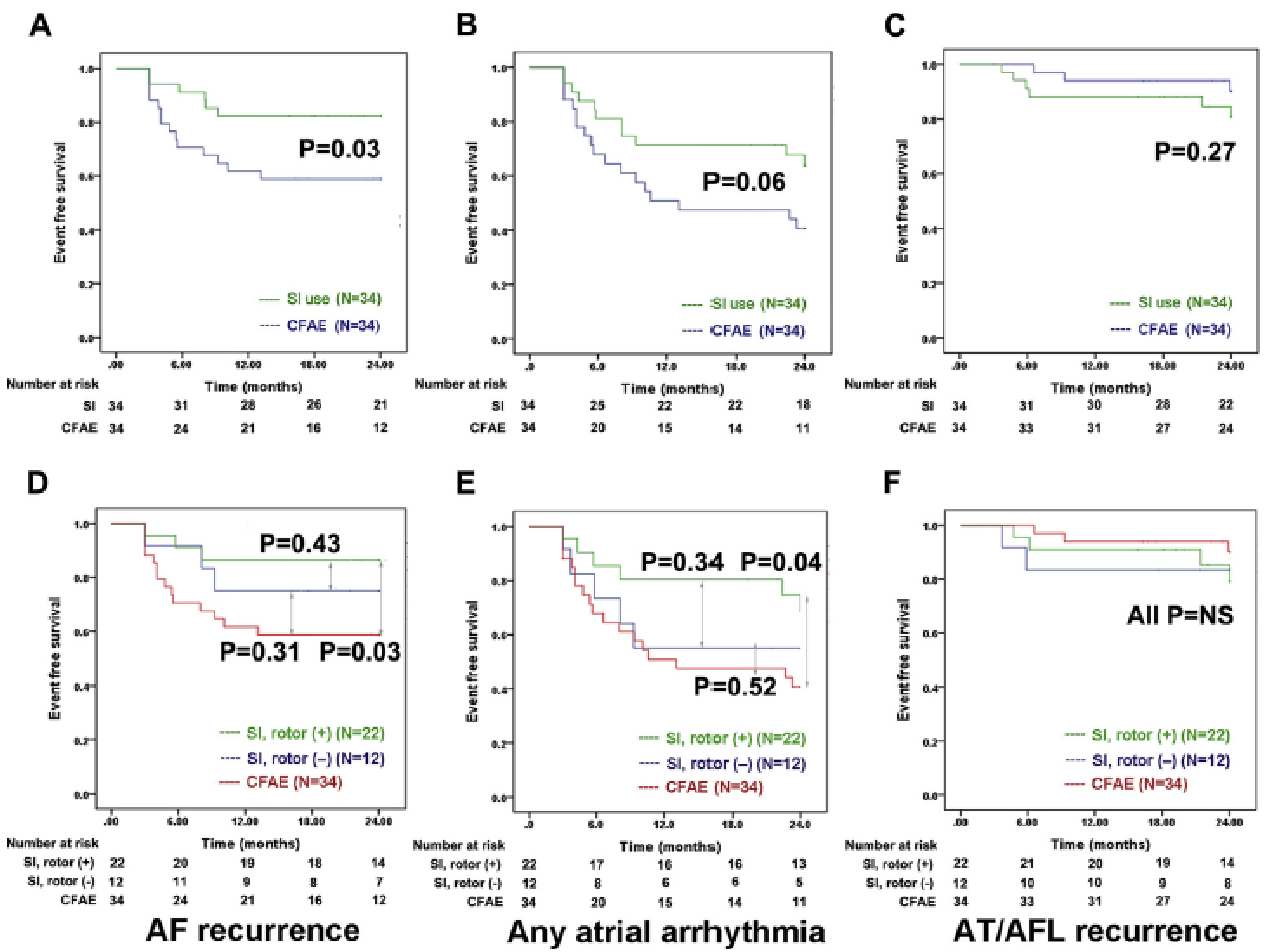


(A) Prevalence of SI region distribution and **(B)** average number of SIs and rotor or focal impulses of each patient. LAA = left atrial appendage; PV = pulmonary vein; SVC = superior vena cava.

Results: Procedural termination

- Termination rate was higher in group-1 than in group-2 (23 [68%] vs. 9 [27%], respectively; p ¼ 0.001).
- In group-1 patients, the termination rate was higher in the patients in whom more rotors were identified (100%, 67%, and 50%, with 2, 1, and 0 rotors, respectively; p ¼ 0.06).
- Overall, 32 patients (47%) had procedural AF termination (23 patients from group-1 [68% of 34] and 9 patients from group-2 [27% of 34]; p ¼ 0.001) to SR (n ¼ 29 [91%]).

FIGURE 6 Kaplan-Meier Survival Curves After the Index Ablation Procedure



Kaplan-Meier survival curves are shown after the index ablation procedure for AF recurrence **(A, D)**, all types of atrial arrhythmias **(B, E)**, and AT or AFL **(C, F)**. AFL = atrial flutter; AT = atrial tachycardia; other abbreviations as in Figure 1.

Conclusions

- Results suggest that procedural termination is more likely to occur when AF sources have been localized and targeted.

- Were the AF termination observed a byproduct of the previously completed PV isolation?

- Non-linear renditions analysis — especially the ones designed for quantifying sources—may largely underestimate the number and extent of AF driver regions.

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Ablation of AF Guided by Spatiotemporal Electrogram Dispersion Without Pulmonary Vein Isolation

A Wholly Patient-Tailored Approach

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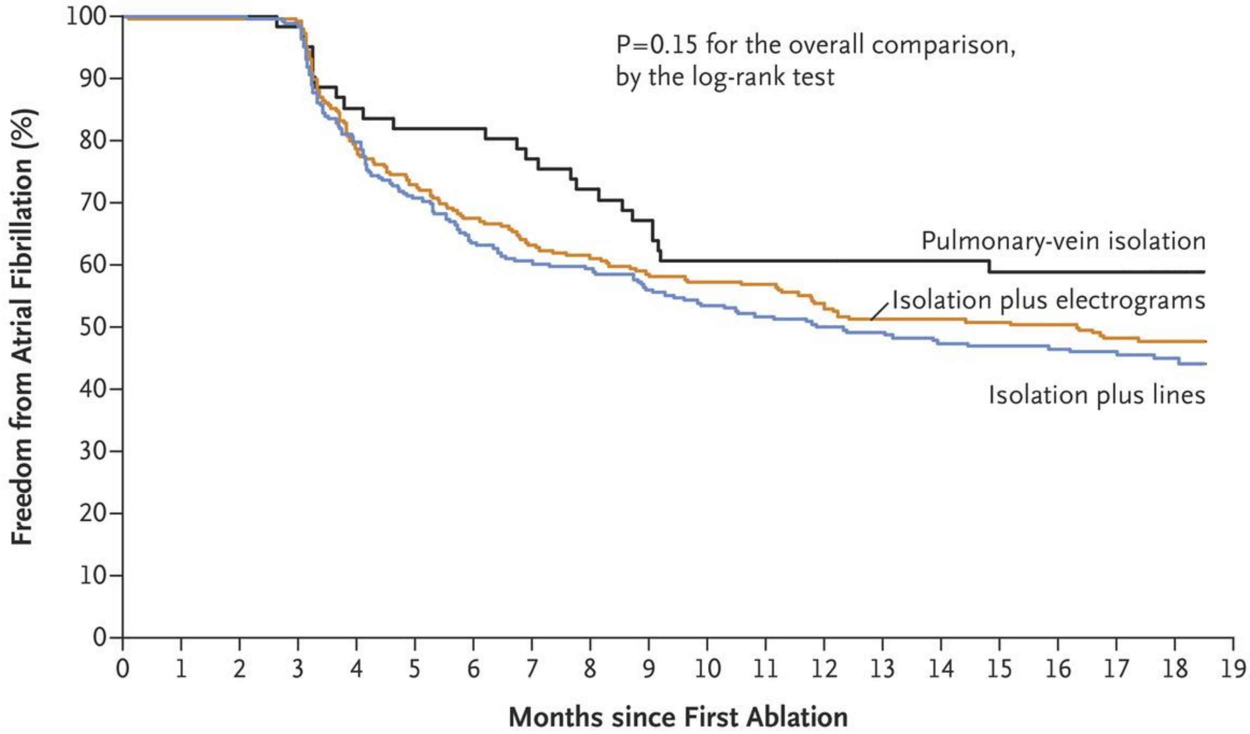
STAR-AF 2
Verma et al. NEJM 2015

Randomized study:
Patients with symptomatic persistent atrial fibrillation (i.e., a sustained episode lasting more than 7 days) refractory to at least one antiarrhythmic agent, and were undergoing ablation for the first time
Patients were randomly assigned in a 1:4:4 ratio to one of the following three strategies:
Pulmonary-vein isolation alone (67 patients)
Pulmonary-vein isolation plus ablation of complex fractionated electrograms (263 patients)
Pulmonary-vein isolation plus linear ablation across the roof of the left atrium and in the mitral valve isthmus (259 patients)

18 months of follow-up with rigorous monitoring

Primary outcome: Freedom from AF after a single procedure.

STAR-AF 2



No. at Risk

Pulmonary-vein isolation	61	60	50	41	36	23
Isolation plus electrograms	244	242	161	137	124	72
Isolation plus lines	244	240	152	133	115	57

STAR-AF 2

- **No reduction** in the rate of recurrent atrial fibrillation when either linear ablation or ablation of complex fractionated electrograms was performed in addition to ablation with pulmonary-vein isolation.

- **Findings are not in accordance with the current guideline recommendation** that patients with persistent atrial fibrillation who undergo pulmonary-vein isolation should have additional substrate ablation to improve outcome.

STAR-AF 2

The **termination of atrial fibrillation**, the end point of ablation with complex fractionated electrograms, was achieved in **only 45% of participants.**

An automated software program was used to detect complex fractionated electrograms.

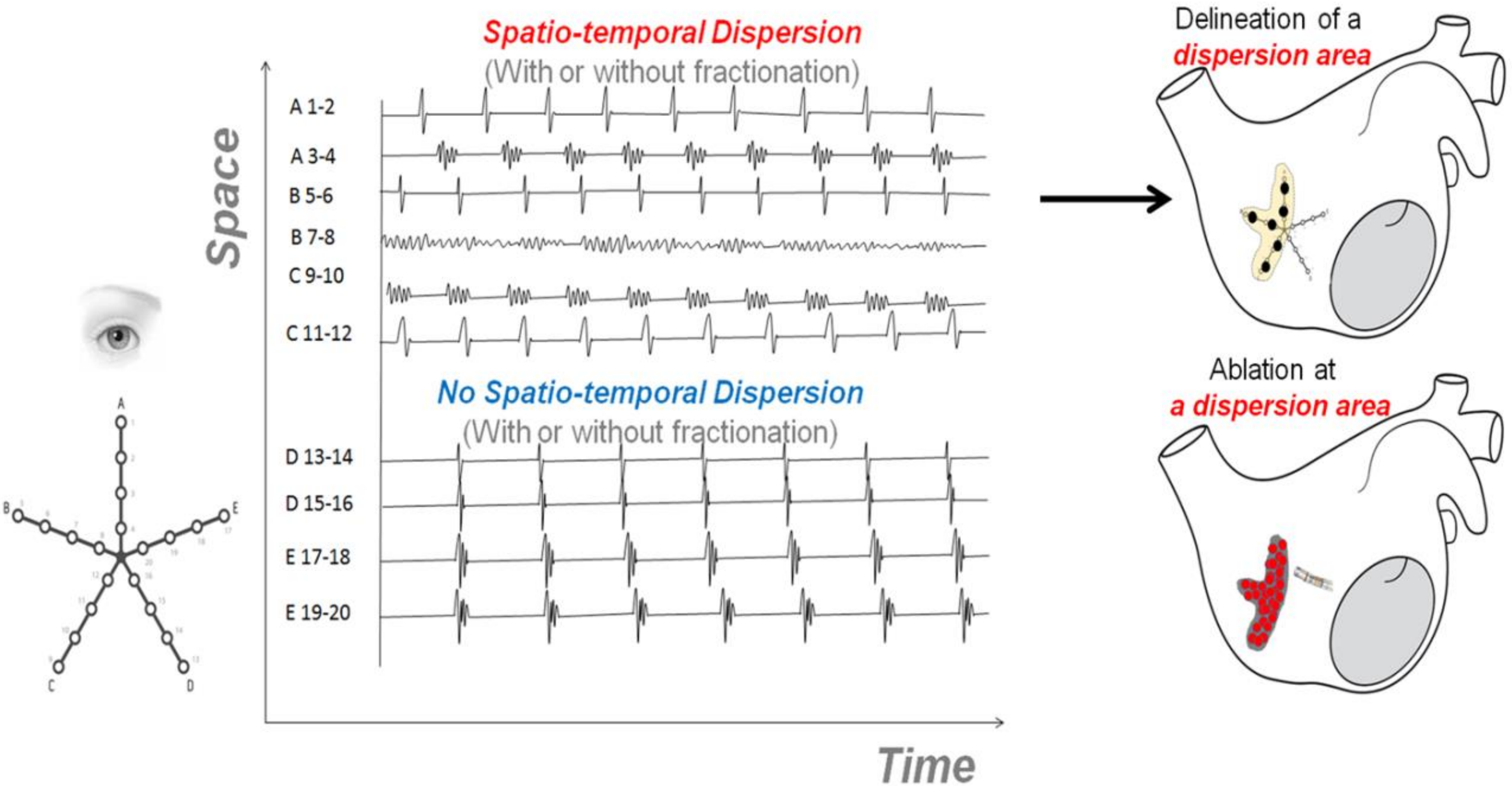
Background

- ***Multipolar electrogram abnormalities have been described in patients in AF.*** *Jadidi, Arentz et al.2016; Ganesan, Ghoraani et al. 2015*

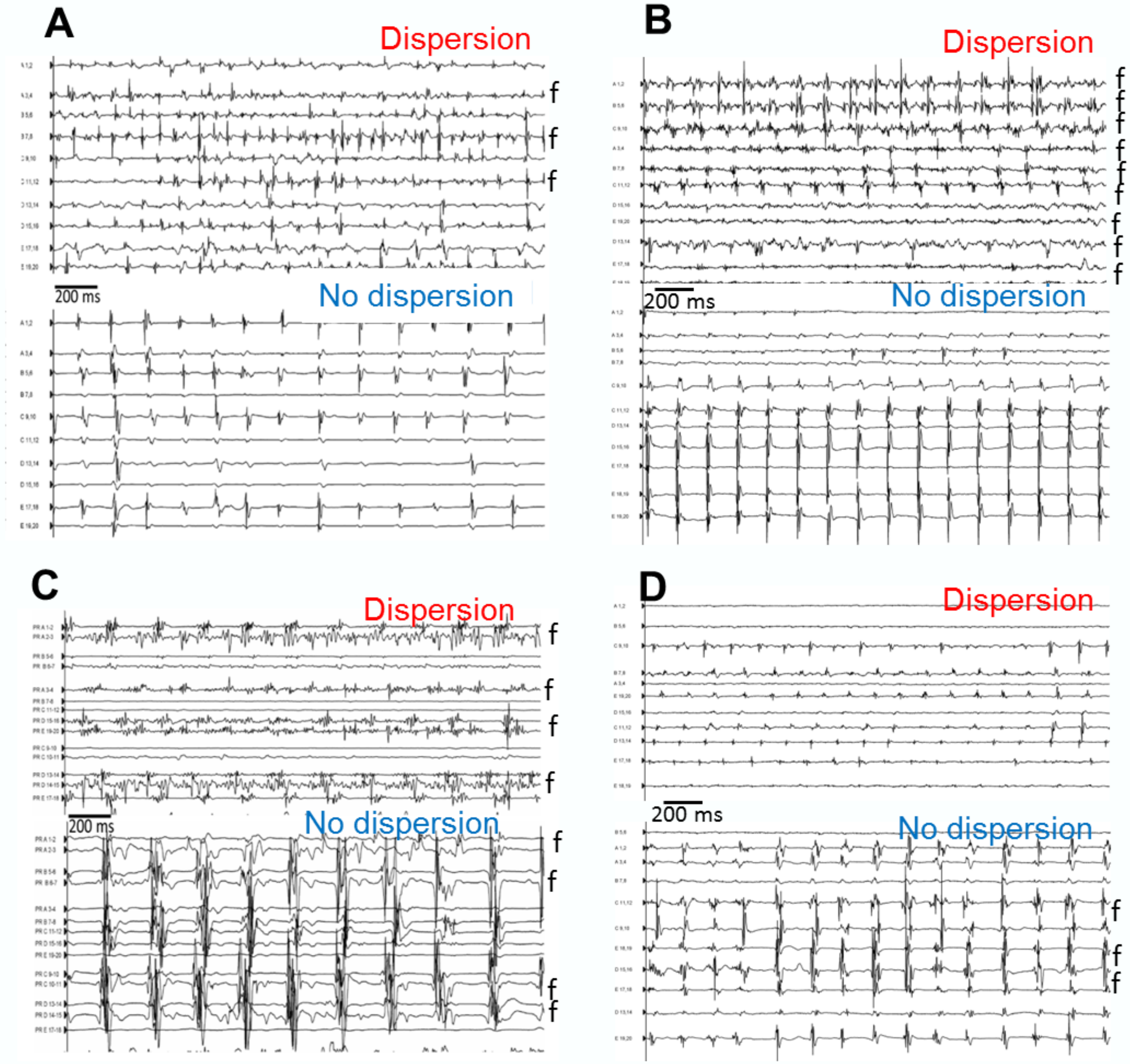
Objectives

- Multipolar electrogram abnormality: the spatio-temporal dispersion of multipolar electrograms. ***Rostock et al., Heart Rhythm 2006; Takahashi et al. JACC 2008***
- Determine whether STD morphologies may enable the identification of AF drivers regions.
- Demonstrate that STD regions are effective target sites for ablation of any type of AF.

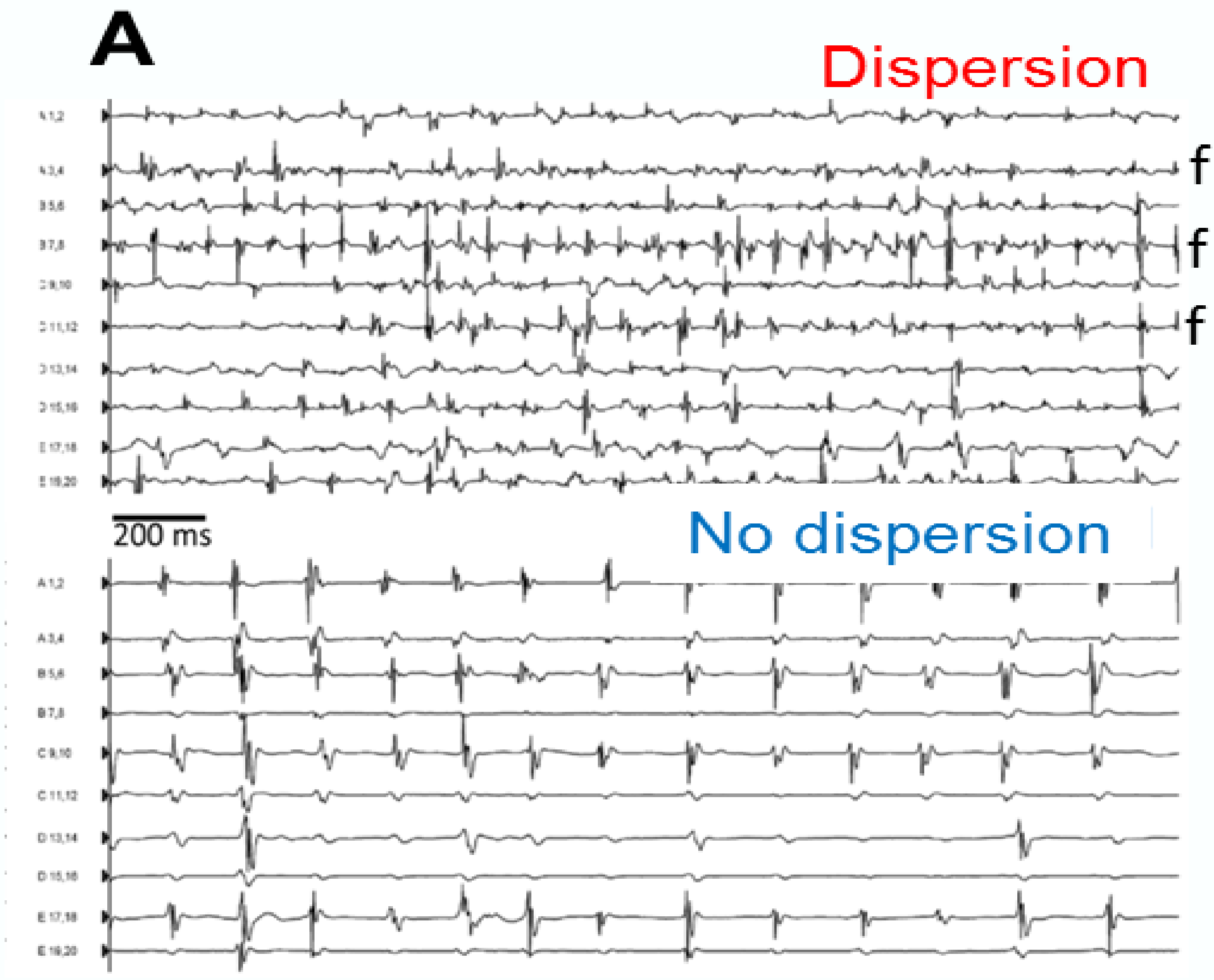
Spatio-Temporal Dispersion of Electrograms: Definition



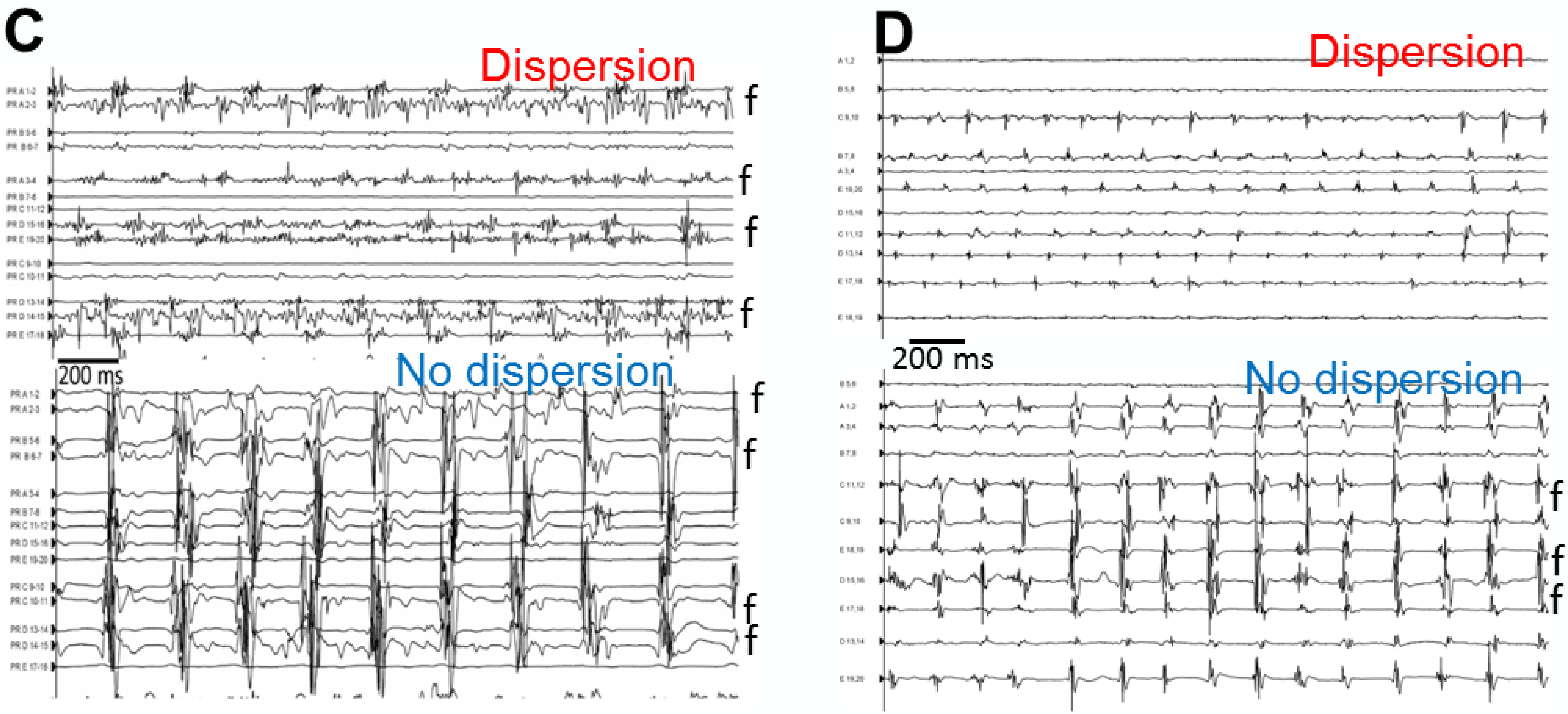
Spatio-Temporal Dispersion of Electrograms: Examples



Spatio-Temporal Dispersion of Electrograms: Examples



Spatio-Temporal Dispersion of Electrograms: Examples



Clinical Study

- **Prospective enrollment of 105 patients** in 3 centers for AF ablation : paroxysmal AF (n=24), persistent AF (n=51), long-standing persistent AF (n=30)
- **Validation set:** 47 controls PVI/Stepwise
- **AF sequential mapping in both atria** with the 20-pole catheter PentaRay.
- **Tagging and ablation** of regions harboring **spatio temporal dispersion**
- **No isolation** of pulmonary veins
- **Ablation endpoints :** AF termination acutely, and freedom from AF after one year follow-up and a single procedure.
- ***Analysis of intra-cardiac electrograms in dispersion and non-dispersion regions.***

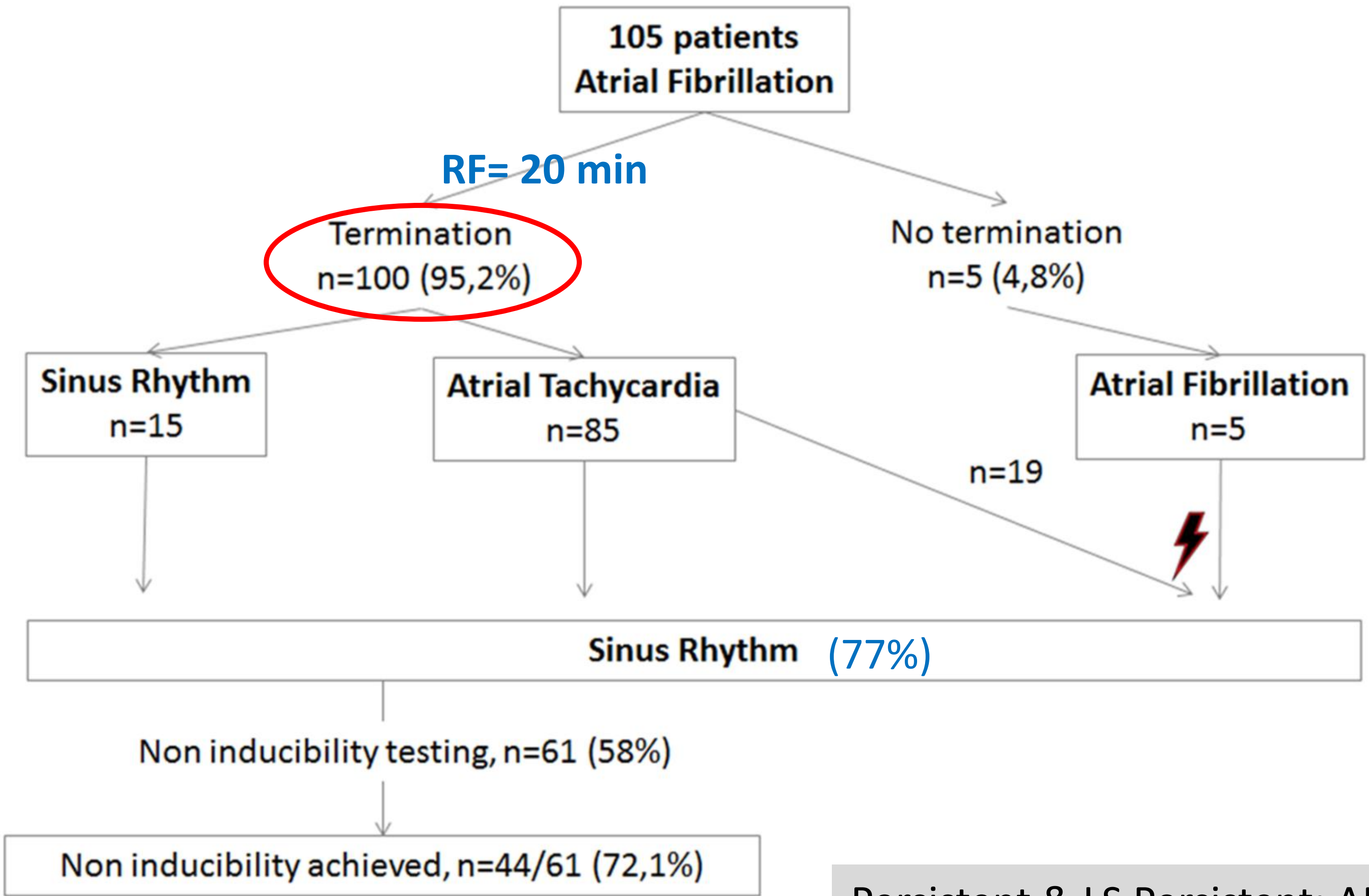
Numerical simulations and optical mapping experiments

- ***Automated mapping fractionation maps***: CARTO setting "SCI 30-40"(16) : 30 and 40 ms as lower and upper limits, respectively.
- ***Quantification of spatio-temporal dispersion in numerical simulations*** (2D, Nattel, Courtemanche, normal and fibrotic conditions) ***and optical mapping experiments*** **after** ***generation of pseudo multipolar recordings in rotor and bystander regions.***

Clinical Results

	Study population (n=105)	Validation set (n=47)	p
Age (years), mean ± SD	63 ±11	58±11	0.0046
Male, n (%)	80 (76.2%)	35 (74%)	0.8191
AF type			
Paroxysmal AF, n (%)	24 (22.8%)	9 (19,2%)	0,6
Non-paroxysmal AF, n (%)	81 (77,2%) LS-Pers. = 30	38(80,8%)	0,6
Maximum sustained AF duration (months), mean + SD	12.2 ± 20 Pers+LS pers=14 ±21 LS pers=33 ±27	19.4±31.6	0.2457
Structural heart disease, n(%)	38 (36%)	14 (35%)	0.4665
Hypertension, %	48(45,7%)	20 (42,5%)	0.5217
Diabetes, %	13(12.4%)	5(10,6%)	0,5995
LA diameter (mm),mean ± SD	45,6± 7,6	42,4±12,4	0,09
LVEF (%), median mean ± SD	52 ± 11	54 ± 12	0,2082
Amiodarone before ablation, %	32%	NA	
Spontaneous AF at the beginning of procedure (persistent and longstanding persistent AF only), n	65 (80,2% of the non PAF)	NA	
Prior AF ablation	0	0	
LAA CL (ms)	182[164-203] non PAF: 174[157-200]	NA	

Procedural outcome



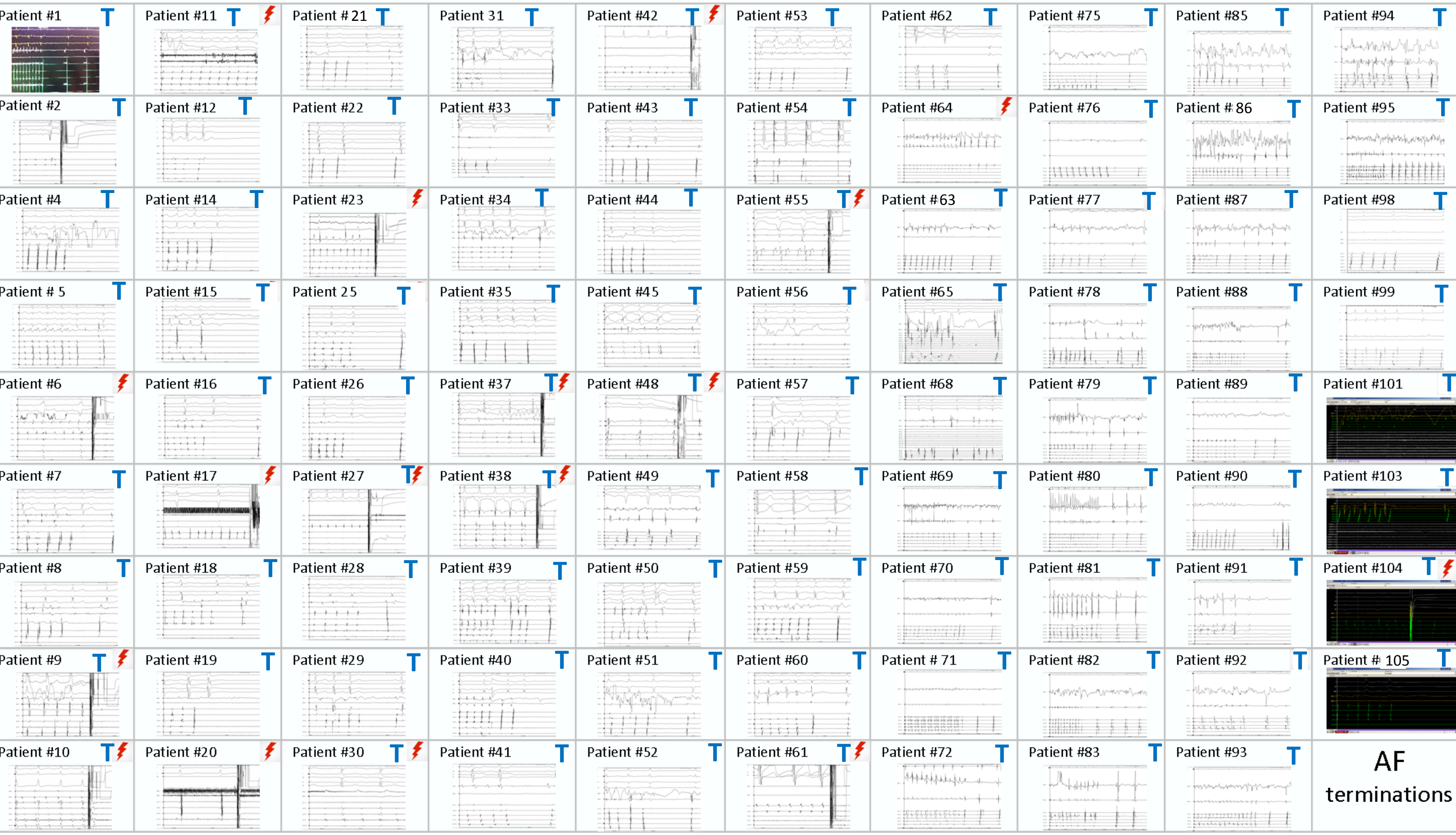
RF time = 49±21 minutes

Non extensive ablation: Ablated surface= 17±10% LA and 10±5 % biatrial area

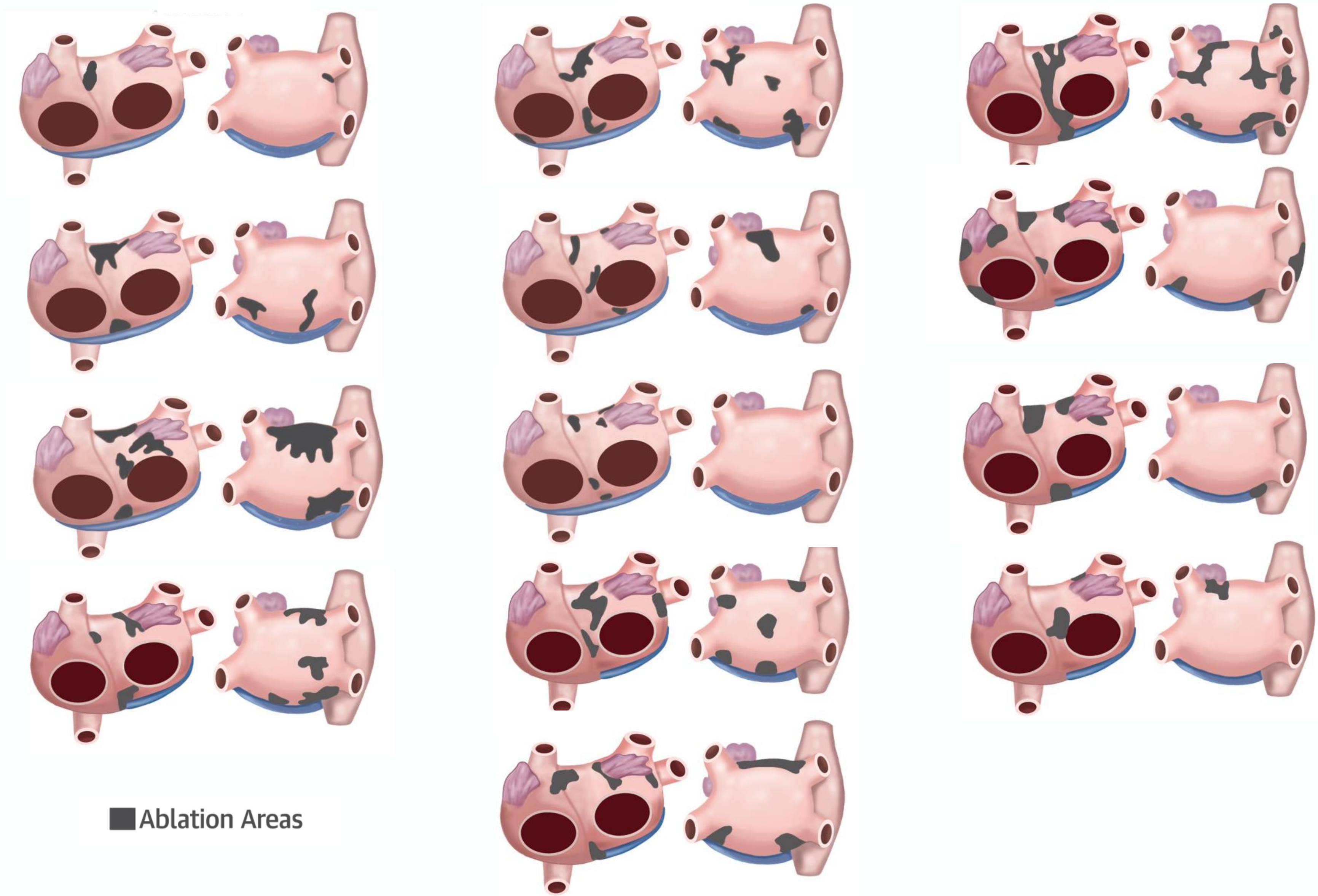
Persistent & LS Persistent: AF termination = 95% & SR conversion = 72%

LS persistent: AF termination = 90%, SR conversion = 53%

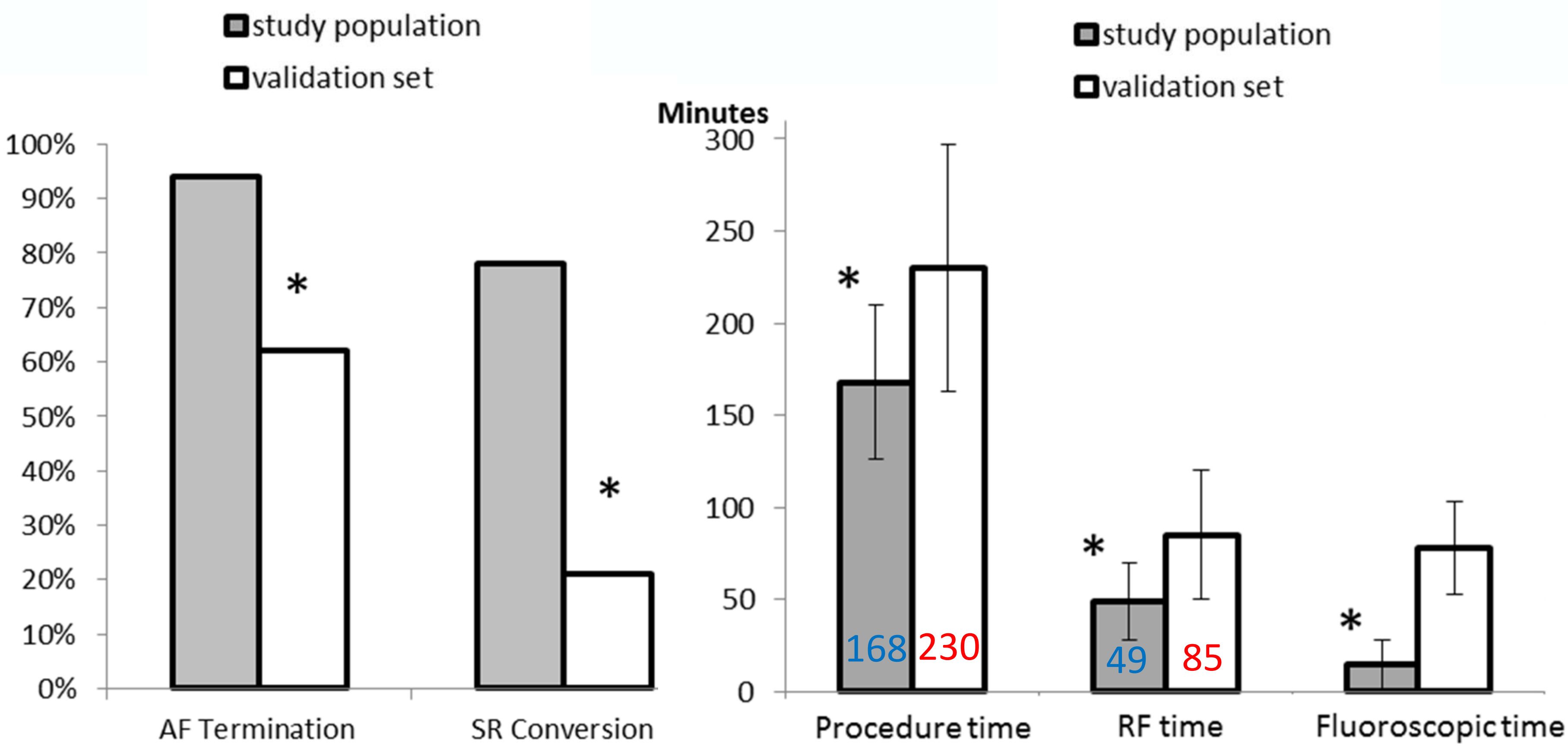
AF terminations (T)



Distribution of AF drivers is patient-dependent



Results


study population
validation set
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
*
*
AF Termination
SR Conversion
study population
validation set
Minutes
300
250
200
150
100
50
0
*
*
*
168
230
49
85
Procedure time
RF time
Fluoroscopic time

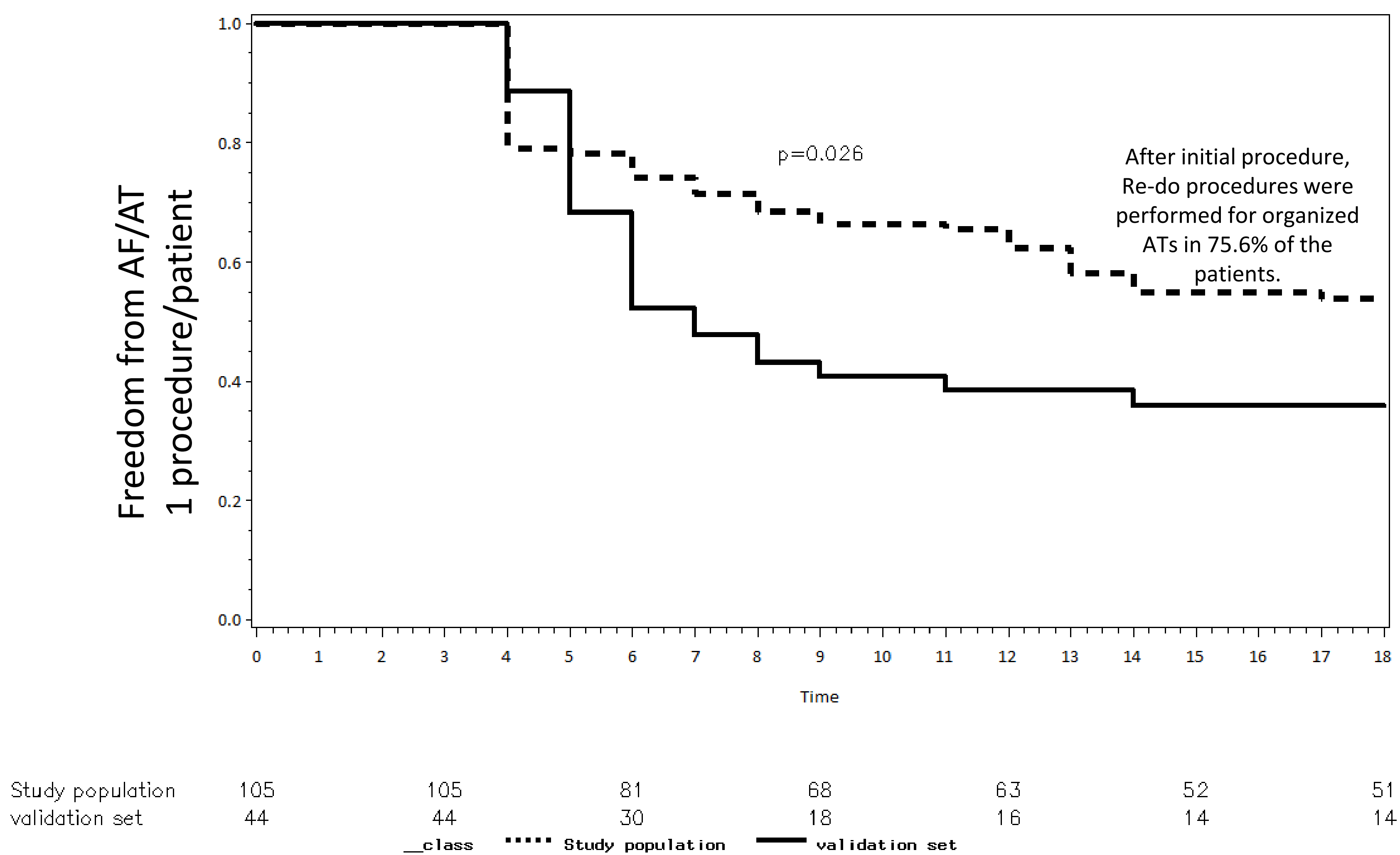
18-month follow-up

Completed in 91% of the patients:
follow-up visits and 24-hour Holter ,
7days holter-monitor/ PM-ICD memories in 20 pts

Seitz, Bars, Theodore, Pisapia, Kalifa et al. JACC (In press)

18 month-FU: 55% free from AF/AT after 1 procedure

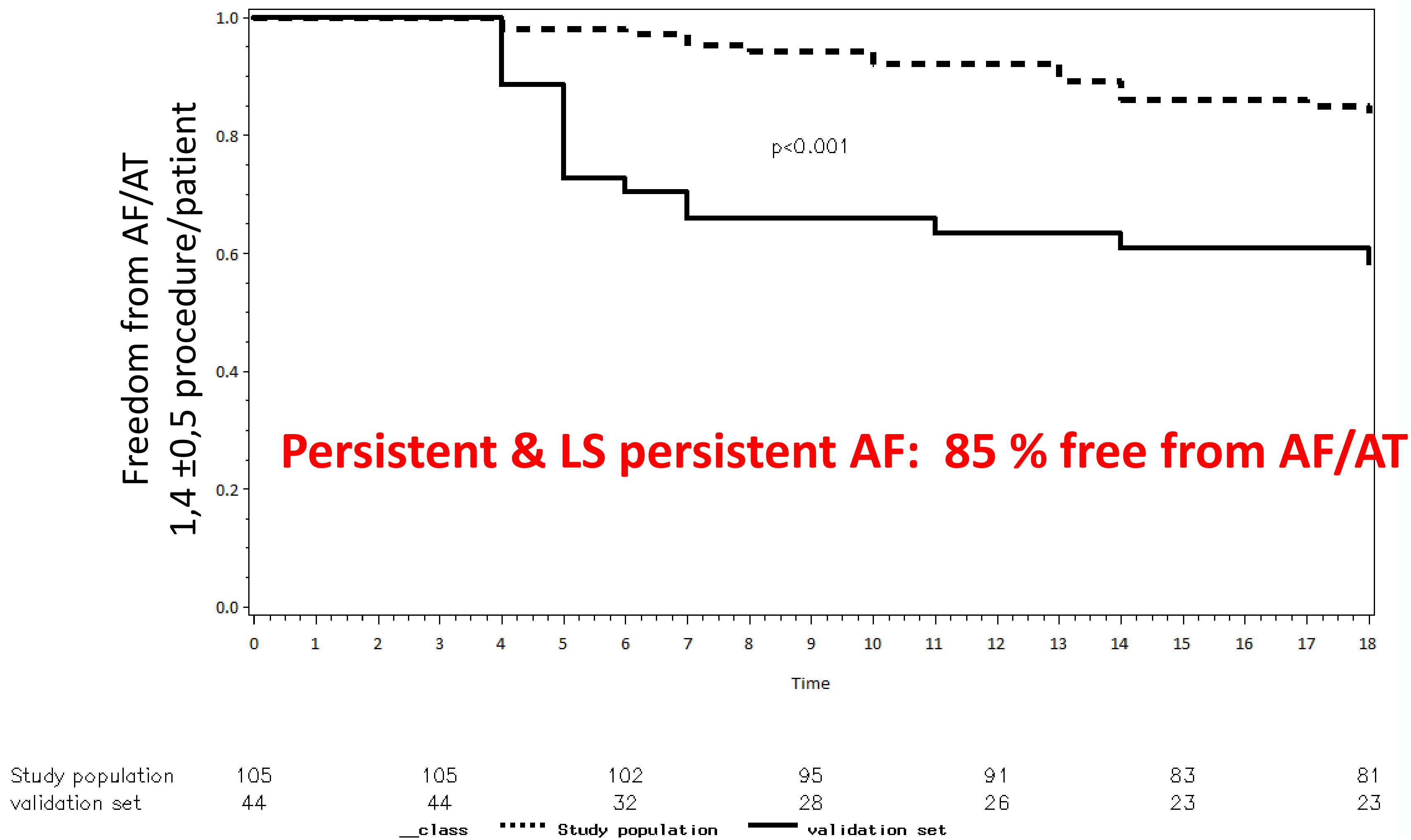
with or without AA drugs



Seitz, Bars, Theodore, Pisapia, Kalifa et al. JACC (In press)

18-month FU: 85% free from AF/AT after 1,4 procedure/patient

with or without AA drugs



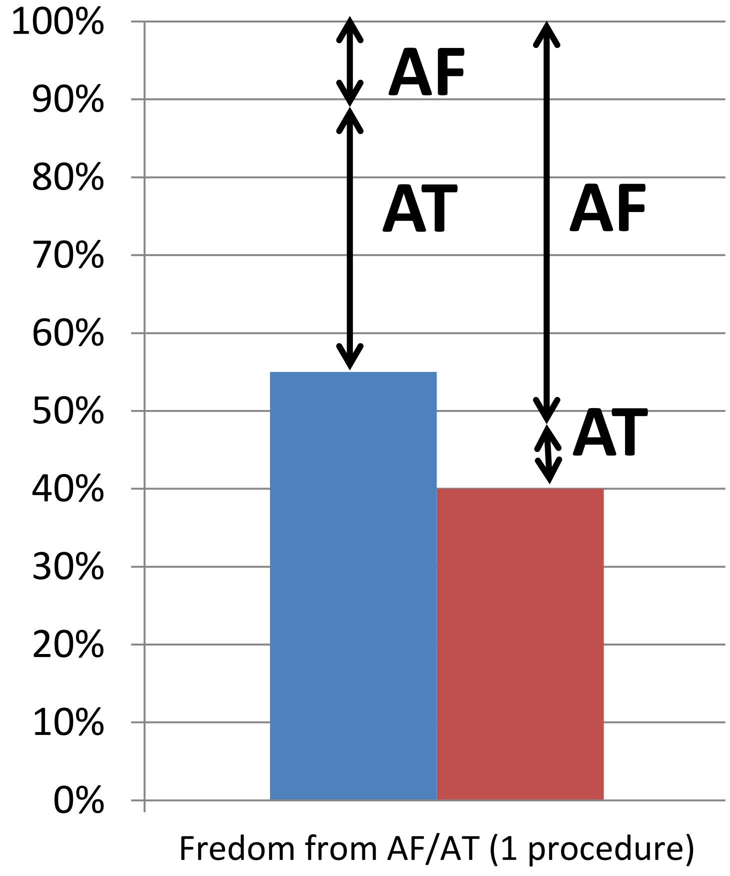
Seitz, Bars, Theodore, Pisapia, Kalifa et al. JACC (In press)

AA drugs before ablation

	AA drugs before ablation	Pts presenting in SR	Prior AF ablation
Rostock et al. Circ ep 2008	41%	0%	0%
O'Neill et al, EHJ 2009	25%	0%	0%
Narayan et al. JACC 2012	0%	30%	42%
Haissaguerre et al. Circ 2014	43%	25%	20,3% (PVI)
Verma et al. (STAR AF2, PVI grp) NEJM 2015	0%	NA	0%
Jadidi et al. Circ ep 2016	NA	31%	22% (PVI)
Seitz et al. (present study)	32%	38% (non PAF=20%)	0%

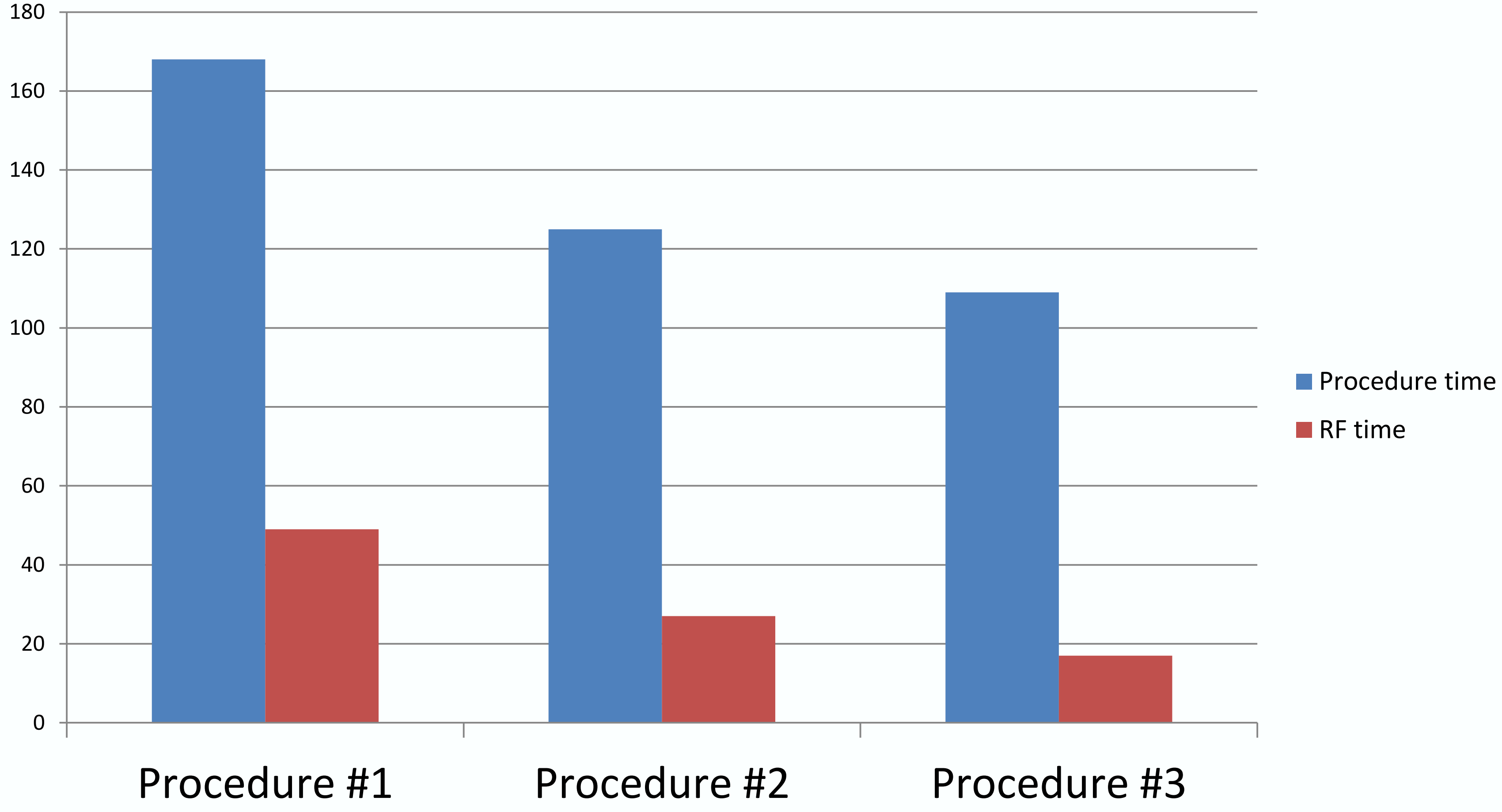
Atrial fibrillation
&
Atrial tachycardias….

Substrate HD vs STAR AF2*



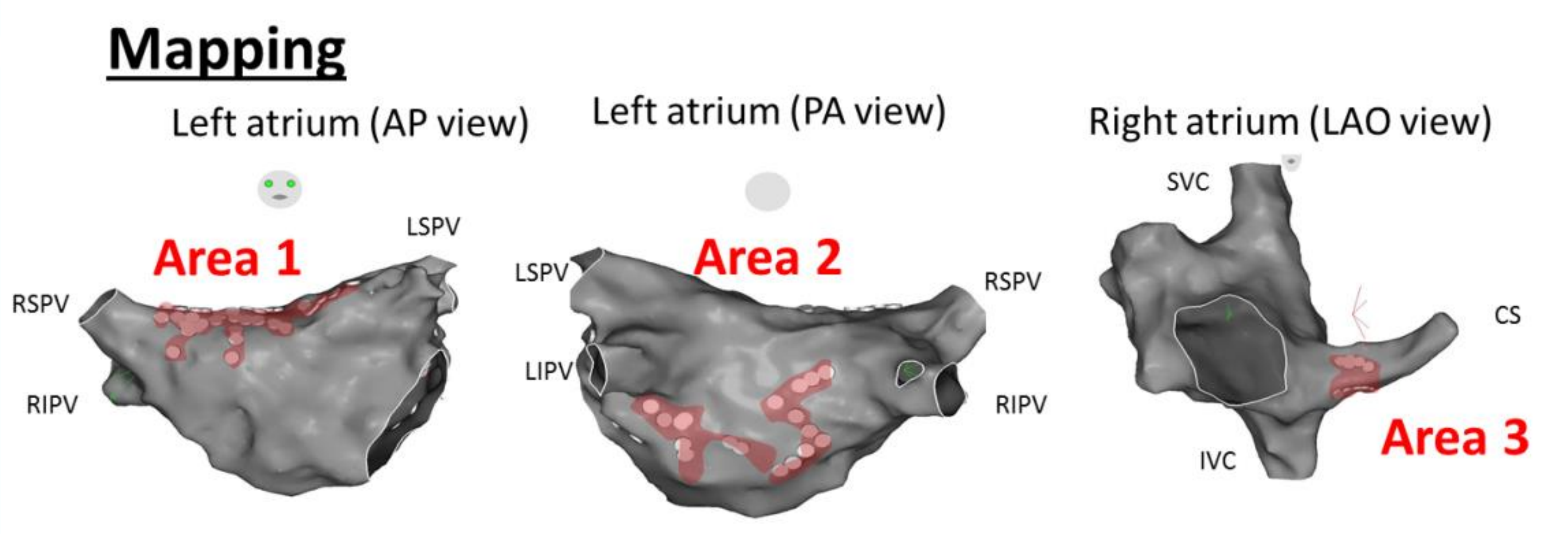
* average results of 3 groups (PVI, PVI+cfe, PVI+lines)

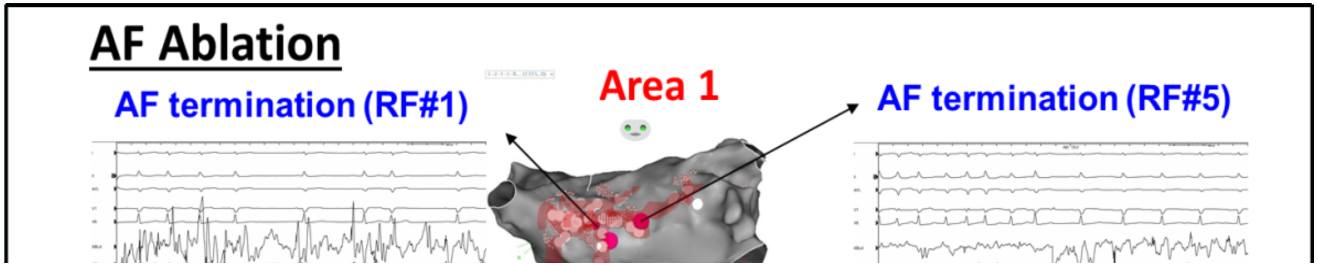
Procedure and RF time: Index and redos



Seitz, Bars, Theodore, Pisapia, Kalifa et al. JACC (In press)

AT and its relationship with the index AF driver locations





Analysis in 21 patients:

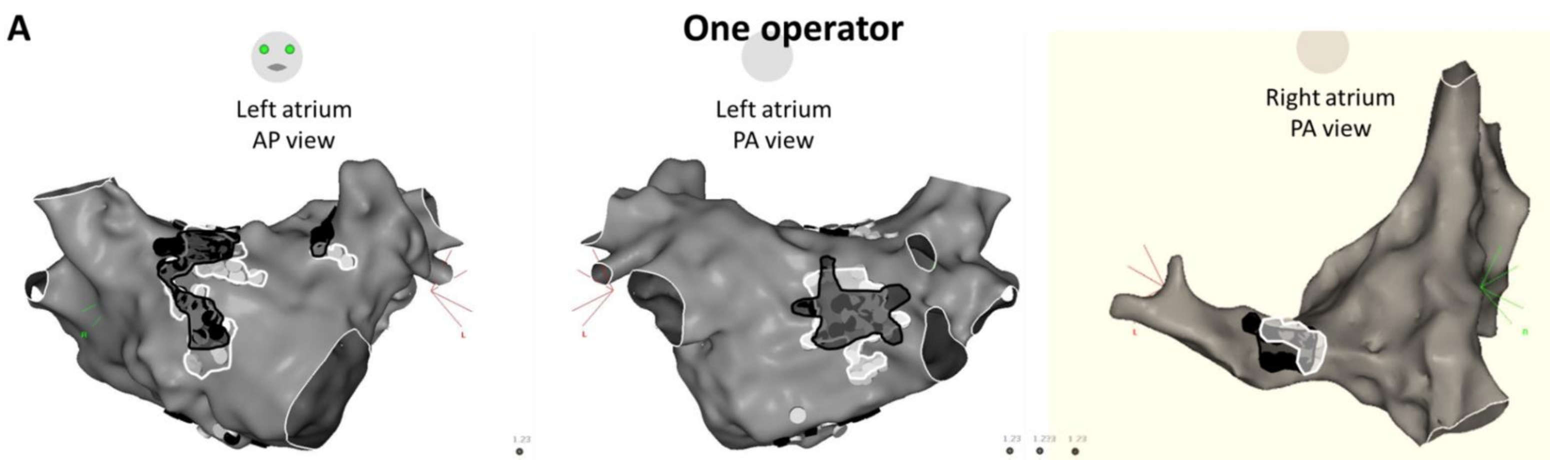
44 ATs, 22 macroreentries & 22 localized AT (88,6% from non-ablated regions).

Importantly, 17/22 (77,3%) localized ATs arose from dispersion regions that were not previously ablated

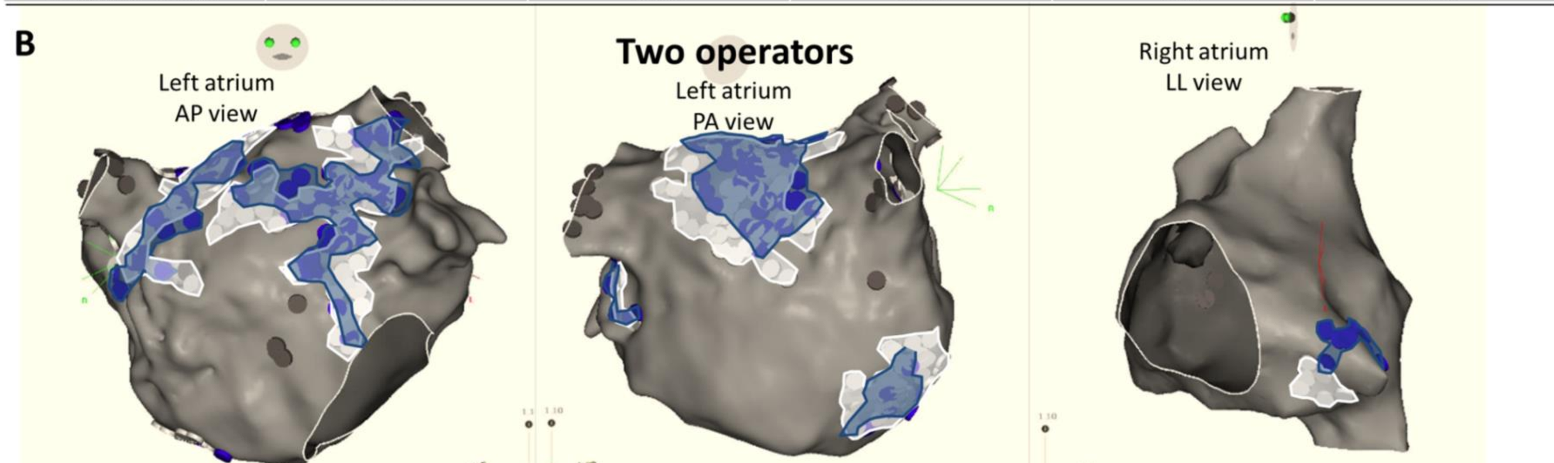
The 2 ATs located in dispersion regions that had not been ablated

Stability over time- Inter-operator reproducibility of mapping

Mapping #2 25 minutes after mapping #1



N=13 patients	Mapping 1	Mapping2	Match mapping 1 & 2	Mismatch mapping 1	Mismatch mapping 2
Involved areas	5,6±0,9	5,3±1	5,2±0,9	0,4±0,6	0,07±0,3
Mapping surface (cm2)	30±12	28±12	26±13	4±3	2±2
% biatrial surface	14±8	13±9	12±9	2±1	1±1



N=7 patients	operator 1	operator 2	Match operator 1 & 2	Mismatch operator 1	Mismatch operator 2
Involved areas	6±0,8	6,3±0,7	6±0,8	0	0,3±0,5
Mapping surface (cm2)	32±11	29±8	23±7	12±3	7±4
% biatrial surface	11±4	10±3	8±2	4±1	2±1

Clinical Results

Acute ablation results:

- AF termination in **100/105 patients (95.2%)**
- **The location and extent of active AF regions** are highly patient-dependent
- We observed **larger active AF regions** and **the need for longer procedure/radiofrequency times to terminate AF in patients with long-standing persistent AF** vs. both paroxysmal and persistent AF patients ($p<0.005$)

After 18 months follow-up:

- **87% and 91% of the patients were free from AF** respectively after a single procedure and after 1.4 ±0.6 procedures (no statistical difference between AF groups).
- **55% and 88% of patients were free from any arrhythmia (AF/AT)** respectively after a single procedure and after1.4 ±0.6 procedures

Results: : localization and extent of dispersion regions

Regions	Dispersion Areas (% of patients)
Left pulmonary veins and left appendage	79%
Right pulmonary veins and posterior interatrial groove	78%
Inferior and posterior left atrium	73%
Upper half of right atrium and appendage	42%
Lower half of right atrium	31%
Anterior left atrium and roof	77%
Anterior interatrial groove	77%

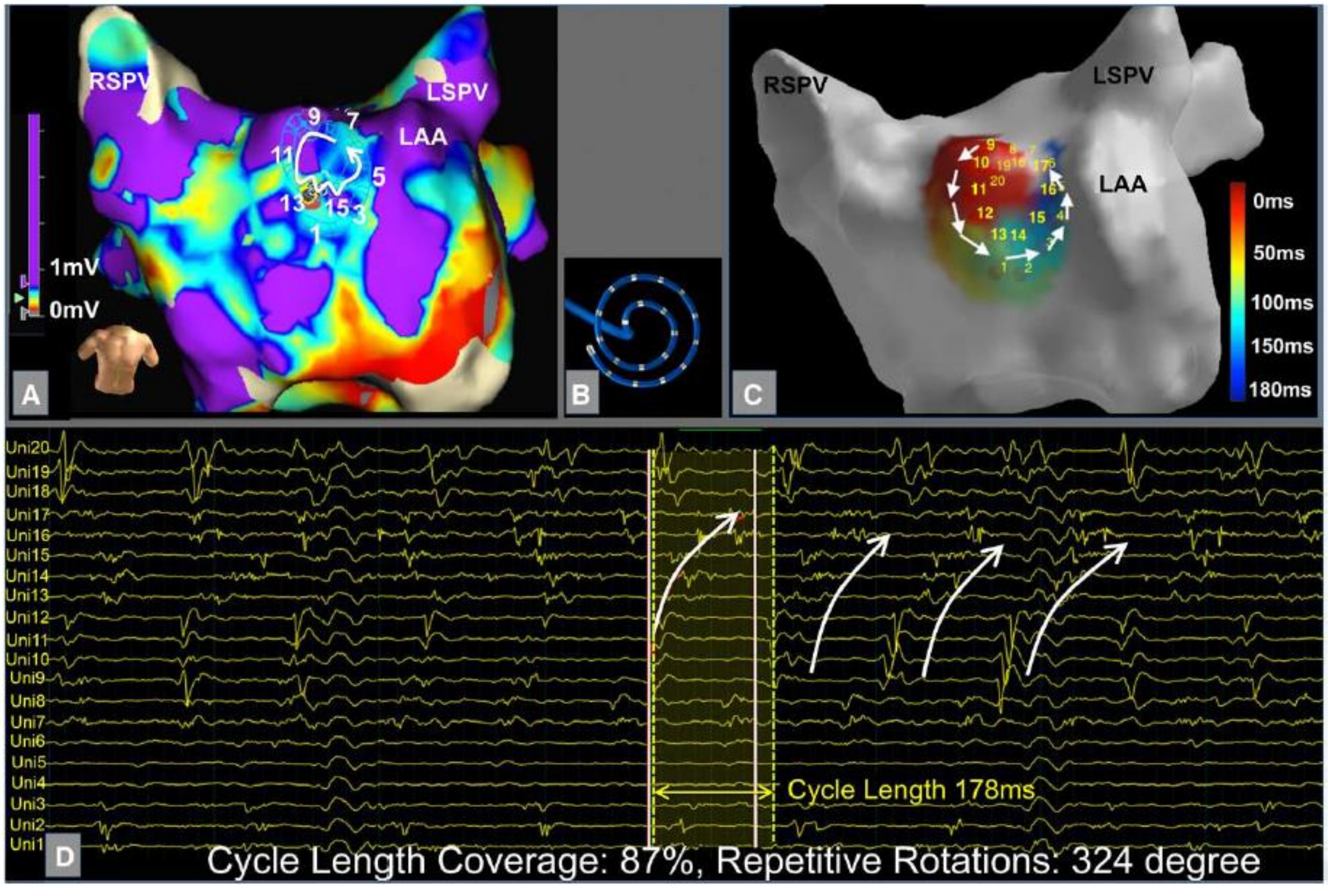
Results: : localization and extent of dispersion regions

AF type	Total active regions area (cm2)	Mean active region area (cm2)	Number of active regions	Total biatrial ablated area (cm2)	Biatrial ablated area/biatrial area (%)	Procedure time to terminate AF (min)	RF time to terminate AF (min)
Paroxysmal (n=24)	18,6±10	4,4±1,9	4,5±1,7	24,6±12,1	6,1±2,6	30[8-67,5]	9[5,5-23]
Persistent (n=51)	17,3±9	3,8±1,5	4,6±1,2	20,9±7	5,2±1,5	32,5[19-66,5]	17[13-34]
Long standing Persistent (n=30)	**40,8±11,8***	**6,2±1,8***	**5,8±1,2***	**55,2±17,3***	**12,5±5,8***	63[47-102]	36[23,5-50]
All patients (n=105)	22,5±13,5	4,9±3,6	4,7±1,5	31,1±18,8	7,5±4,6	46[21-72]	20[10-37,5]

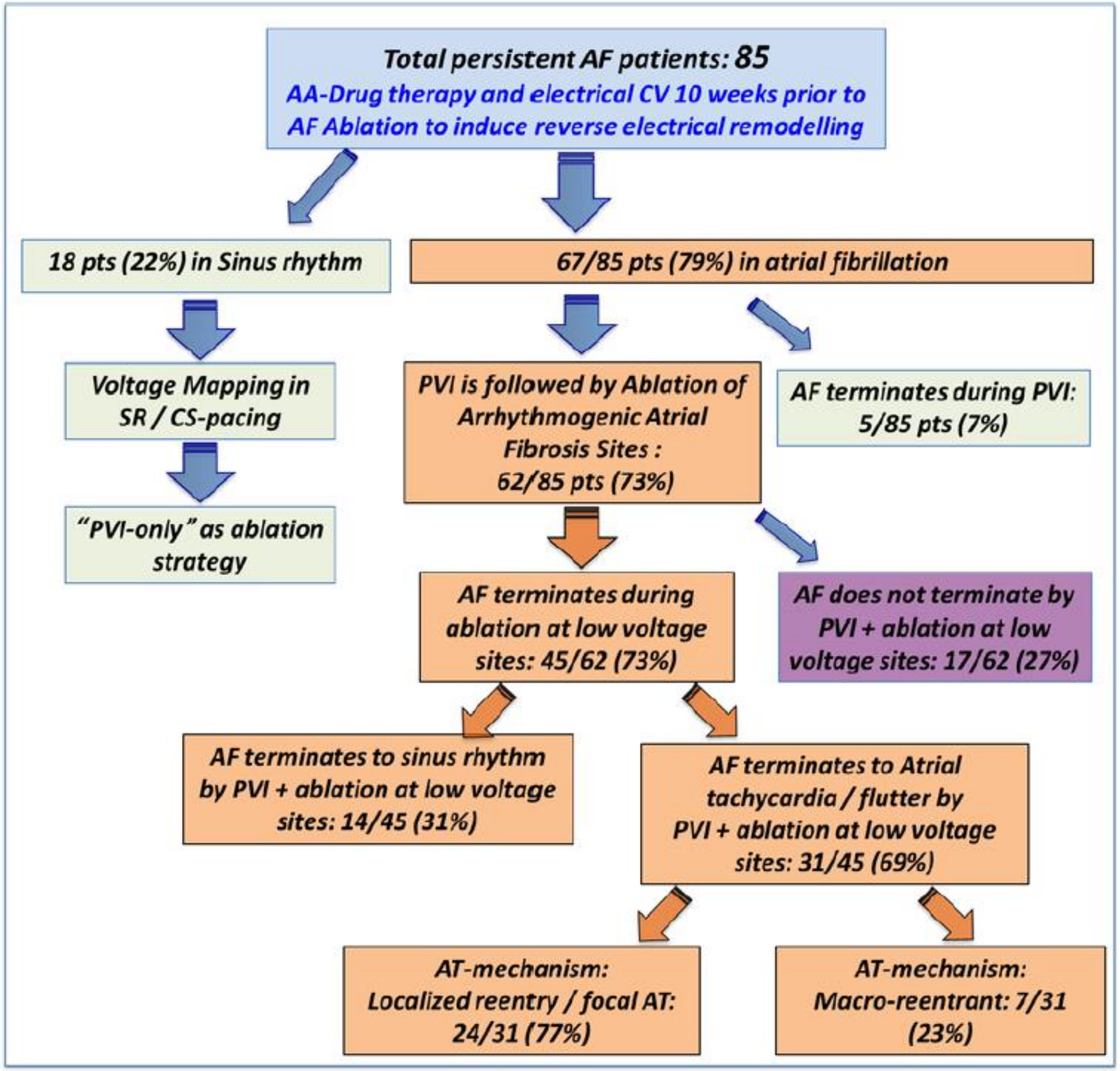
Location of active regions	Left PV area	Right PV area	Inferior & posterior LA area	Upper half RA	Lower half RA	Anterior LA and roof area	Anterior inter-atrial groove area
% of patients	79%	78%	73%	42%	31%	77%	77%

Signal Analysis

Jadidi et al. Circ Arrh. 2016



Jadidi et al. Circ Arrh. 2016



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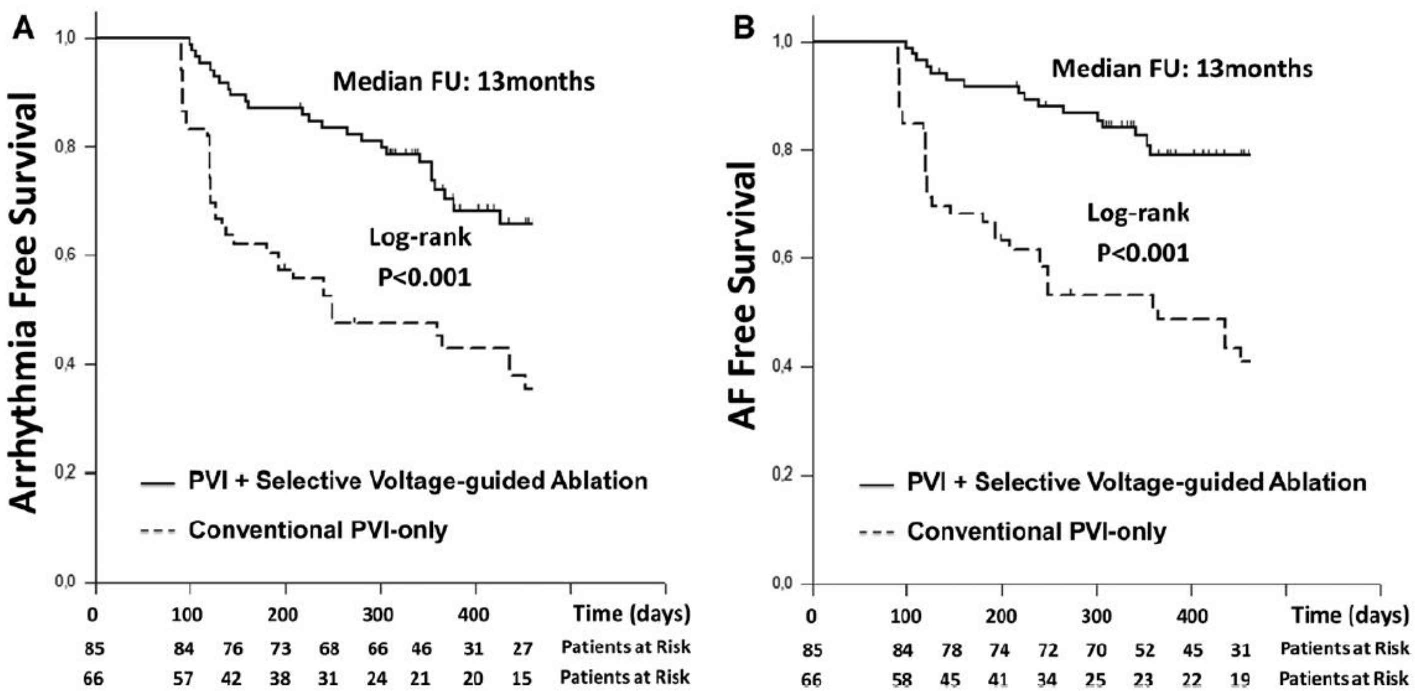


Summary: Multipolar Electrogram Abnormalities

- Spatio-temporal dispersion of multipolar electrograms represents an ***electrical footprint of waves emanating from rapid fibrillatory rotors and propagating within a heterogeneous atrial muscle.***
- Multipolar electrode sequential mapping of spatio-temporal dispersion ***represents a discreet and patient-tailored approach to efficiently map and ablate active AF regions in patients with all types of AF.***

Conclusions

- Electrogram-based ablation strategies based upon multipolar electrogram morphologies are distinct from single electrode based, CFAEs map-based, or driver visual rendition-based approaches.
- Visually recognizable multipolar electrogram footprints may be used for the delineation and ablation of AF drivers regions
- These approaches will need to be evaluated in randomized studies.
- At the mechanistic level, the relationship between frequency and fractionation needs to be further investigated.
- Particular attention will have to be paid to the relationship between frequency, fractionation and the spatial distribution of fibrosis.

Acknowledgments

Julien Seitz, Clément Bars , Guillaume Théodore, Sylvain Beurtheret, Nicolas Lellouche, Michel Bremondy, Ange Ferracci , Jacques Faure, Guillaume Penaranda, Masatoshi Yamazaki, Uma Mahesh R. Avula, Laurence Curel, Omer Berenfeld, André Pisapia, José Jalife

CVC directors

NIH, AHA

BACK UP

	LAA CL	Driver CL	Non driver CL	Continuous CFE in driver regions	Global voltage <0,5 mV in driver regions	Majority of AF CL In driver regions
Takayashi et al. *JACC 2008*	167 ms	166 ms*	182 ms	yes	yes	yes
Haissaguerre et al. *Circ 2014*	NA	185 ms	189 ms	yes	No (0,8 mV)	yes
Jadidi et al. *Circ ep 2016*	168 ms	NA	NA	yes	yes	yes
Seitz et al. (PAF excluded)	174 ms	165 ms*	190 ms	yes	yes	yes

*: CL significantly shorter than in non driver regions

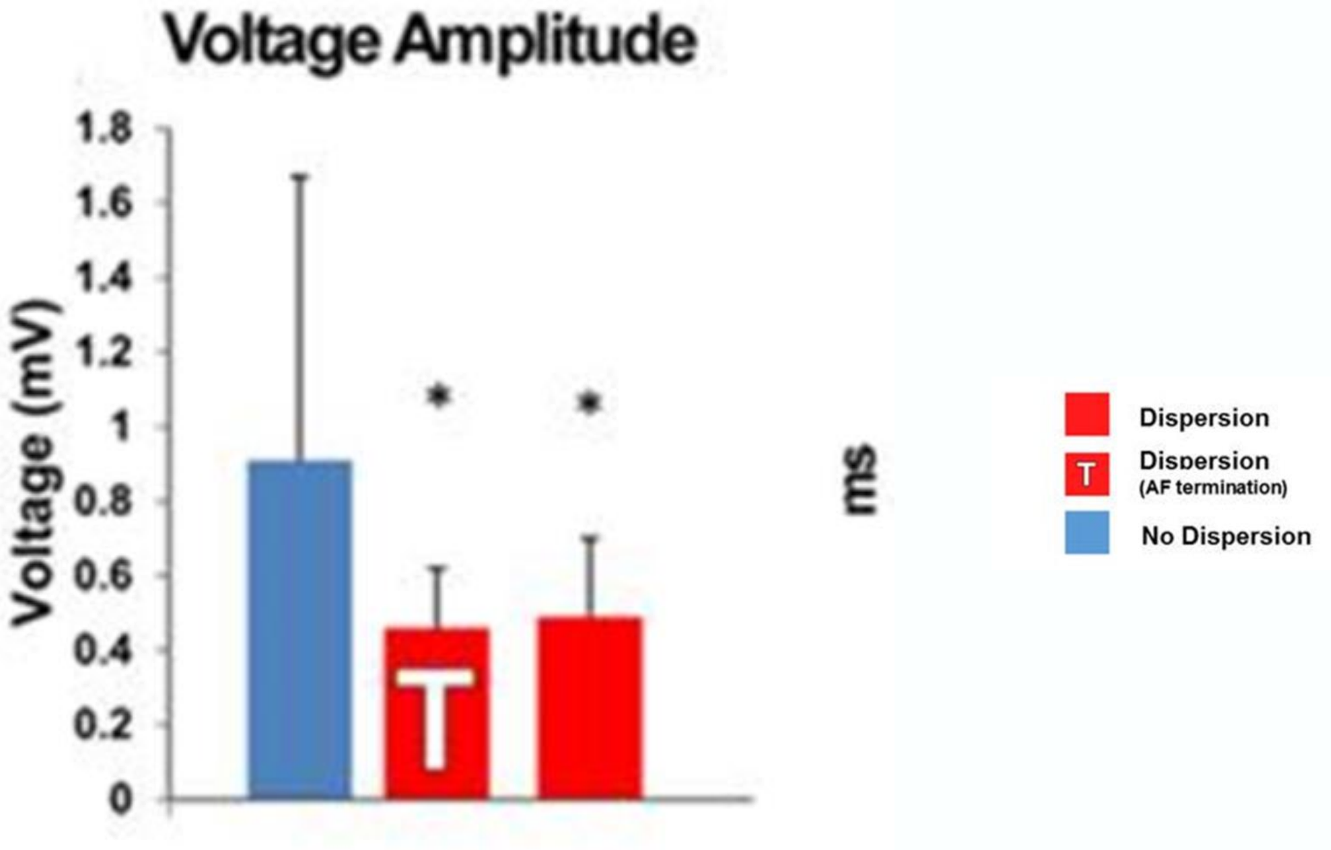
AA drugs before ablation

	AA drugs before ablation	Pts presenting in SR	Prior AF ablation
Rostock et al. Circ ep 2008	41%	0%	0%
O'Neill et al, EHJ 2009	25%	0%	0%
Narayan et al. JACC 2012	0%	30%	42%
Haissaguerre et al. Circ 2014	43%	25%	20,3% (PVI)
Verma et al. (STAR AF2, PVI grp) NEJM 2015	0%	NA	0%
Jadidi et al. Circ ep 2016	NA	31%	22% (PVI)
Seitz et al. (present study)	32%	38% (non PAF=20%)	0%

Regions	Dispersion Areas (% of patients)
Left pulmonary veins and left appendage	**79%**
Right pulmonary veins and posterior interatrial groove	**78%**
Inferior and posterior left atrium	**73%**
Upper half of right atrium and appendage	**42%**
Lower half of right atrium	**31%**
Anterior left atrium and roof	**77%**
Anterior interatrial groove	**77%**

	AA drugs before ablation	Pts presenting in SR	Prior AF ablation	Sustained AF duration (months)	Long-standing persistent	Paroxysmal	LA diameter	structural Heart disease	AF termination	LAA CL
Rostock et al. Circ ep 2008	41%	0%	0%	median: 12 (range:3-264)	NR	0%	50 ±7 mm	64%	77%	155 ms
O'Neill et al, EHJ 2009	25%	0%	0%	21.8+33.2, median: 12 (range:1-240)	54%	0%	47 ± 9 mm	48%	85%	151+21 ms
Narayan et al. JACC 2012	0%	30%	42%	NR	NR	19%	43 ± 6 mm	NR (>28%)	56%	NR
Haissaguerre et al. Circ 2014	43%	25%	20,3% (PVI)	NR	20%	0%	48 ± 7 mm	61%	80%	NR (local driver CL ~185 ms)
Verma et al. (STAR AF2, PVI grp) NEJM 2015	0%	NR	0%	NR (78% > 6 months)	NR	0%	44 ± 6 mm	NR (>7,5%)	8%	NR
Jadidi et al. Circ ep 2016	NR	31%	22% (PVI)	NR	0%	0%	44 ± 5 mm	14%	73%	168±27 ms
Seitz et al. (present study)	32%	38% (non PAF=20%)	0%	12.2 ± 20	29%	22,80%	45,6 ± 7,6 mm	36%	95%	182[164-203] ms, non pAF=174[157-200]

Global lower voltage in dipersion regions

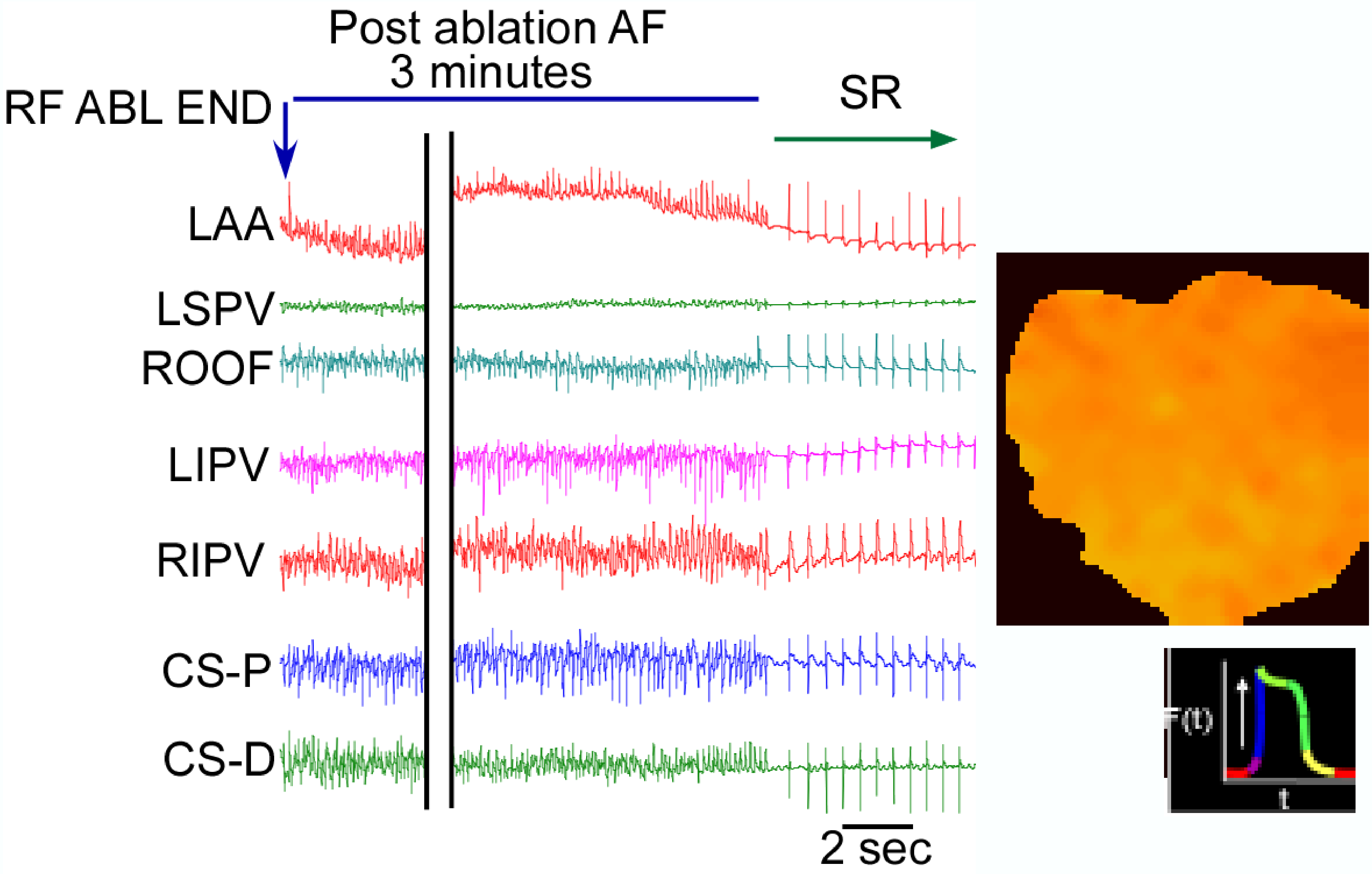


Dispersion and Low voltage maps

- Biatrial Voltage maps (<0,5 mv) compared to dispersion maps in 43 patients:

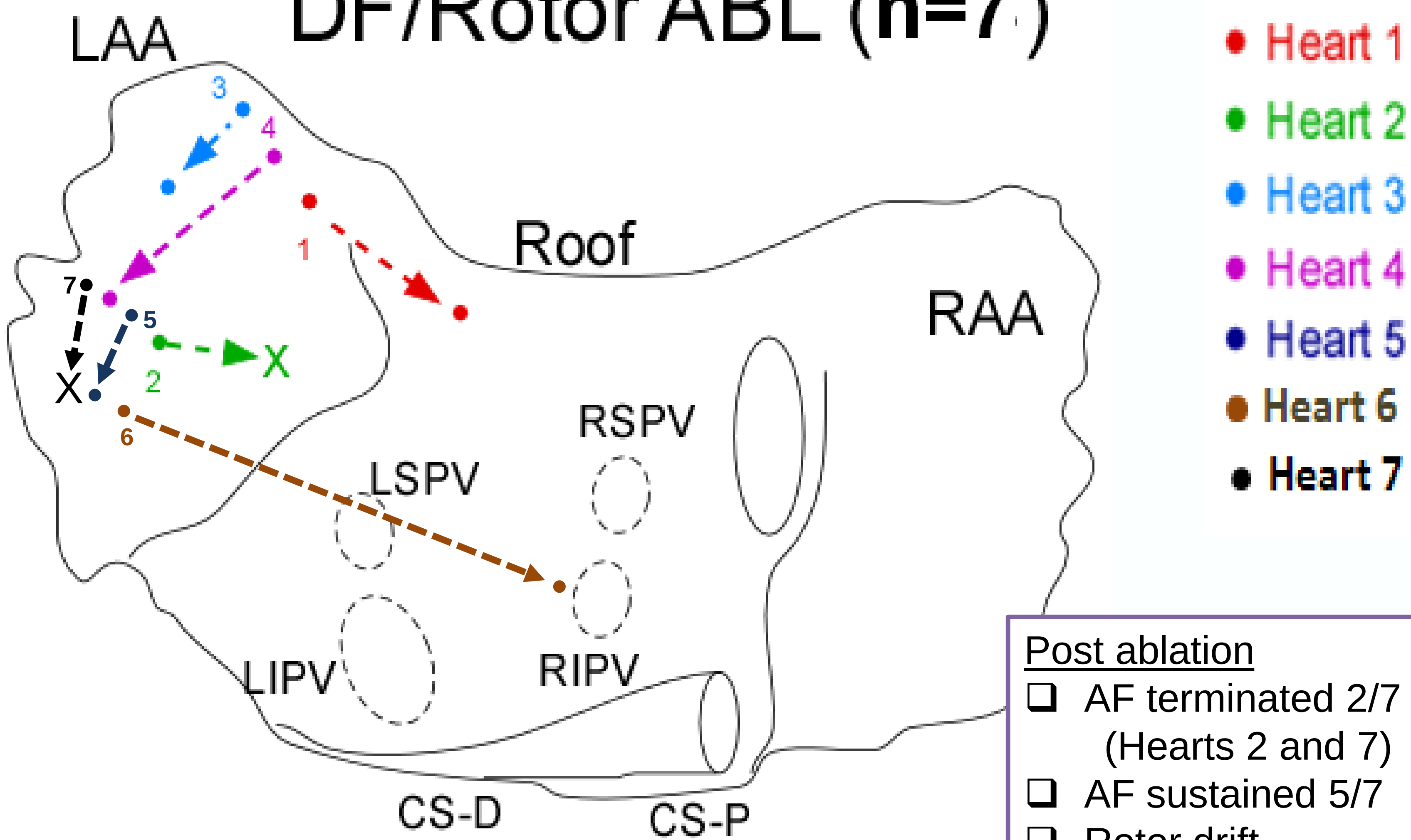
- low voltage regions = 92,6 +/- 83,4 cm2
- Dispersion regions = 22,5 +/- 13,5 cm2
- 21 % of the dispersion regions exhibited low voltage
- 3,8% of the low voltage area exhibited dispersion

DFmax/rotor ablation – AF termination



5-15W, 30-60 sec/ablation point

DF/Rotor ABL (n=7)

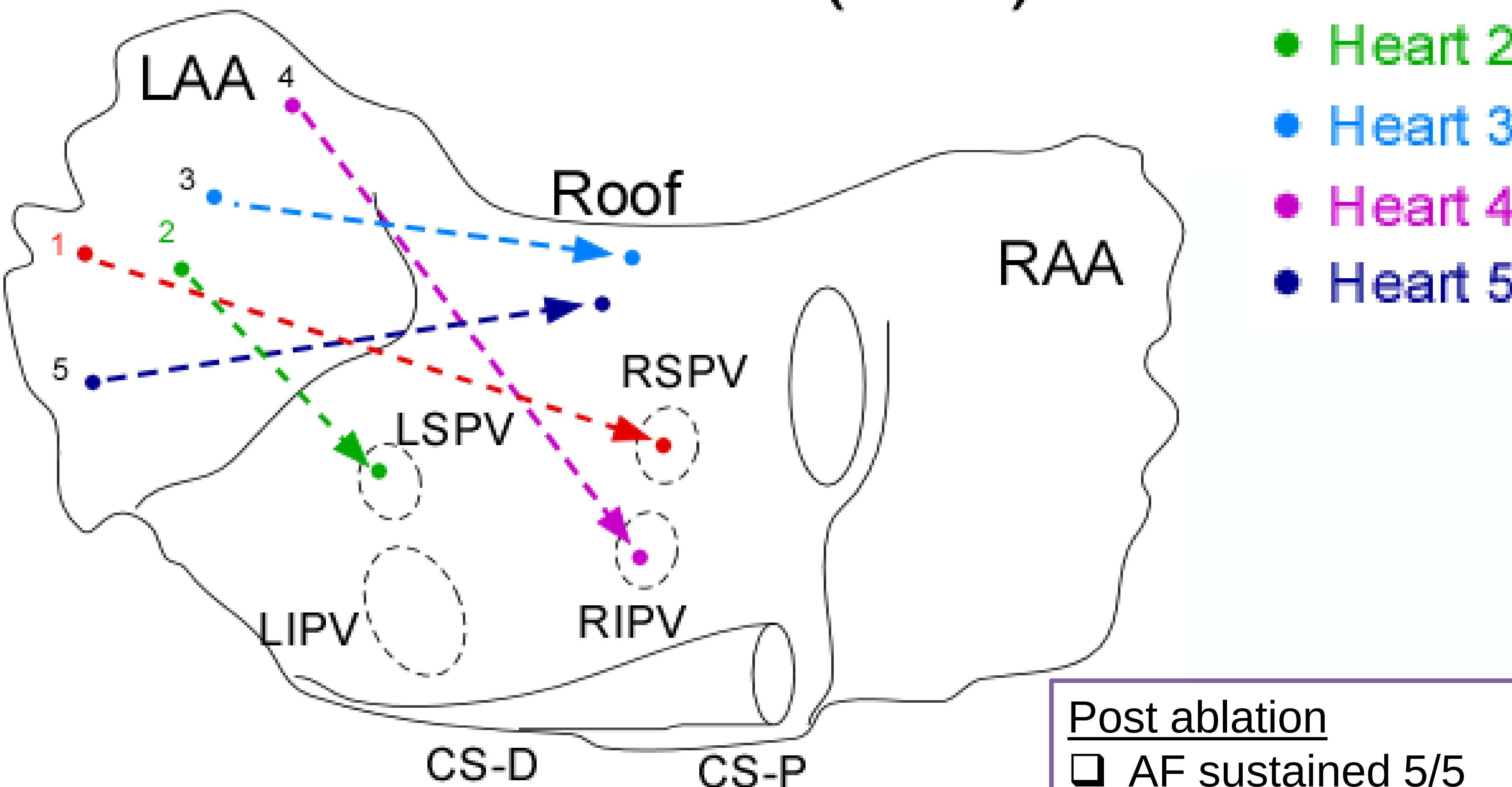


Post ablation

- AF terminated 2/7 (Hearts 2 and 7)
- AF sustained 5/7
- Rotor drift
  - LAA to Roof: 1/7
  - LAA to PVs: 1/7
  - Within LAA: 5/7

Rotor meandering

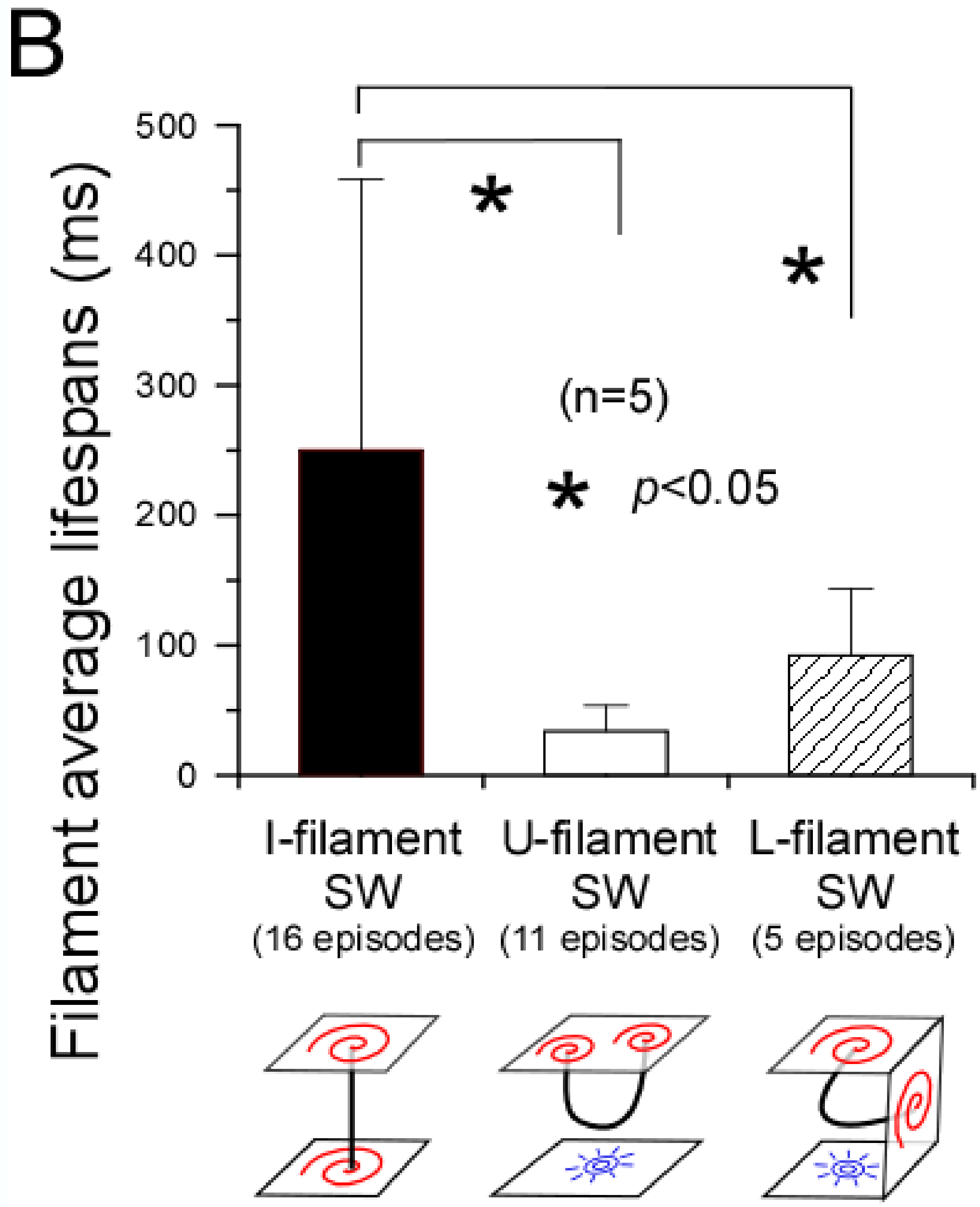
HWD ABL (n=5)



<u>Post ablation</u>

- ❑ AF sustained 5/5
- ❑ Rotor drift
  - LAA to Roof: 2/5
  - LAA to PVs: 3/5

Figure 5


B
Filament average lifespans (ms)
500
400
300
200
100
0
*
*
(n=5)
* p<0.05
I-filament
SW
(16 episodes)
U-filament
SW
(11 episodes)
L-filament
SW
(5 episodes)

On-Target DFmax/Rotor ablation

- DFmax decreases significantly
- AF may or may not terminate
- If AF does not terminate, the electrical source remains in a nearby region

Nearly-Missed HWD/CFAEs ablation

- Frequency unchanged
- AF does not terminate
- Electrical sources move to the PVs.

Disclosures

Volta Medical, Share Holder, Co-Founder

Electrogram-based ablation of atrial fibrillation

- (i) Background
- (ii) Complex Fractionated Atrial Electrograms (CFAEs)
- (iii) CFAEs Landmark Studies
- (iv) Frequency-based Ablation Studies
- (v) Visual Rendition of AF Drivers
- (vi) Multipolar-Electrogram Criteria
- (vii) Conclusions

Epidemiology of AF

Most common sustained cardiac arrhythmia[1]

Currently affects 5.1 million Americans[2]

Prevalence expected to increase to 12.1 million by 2050 (15.9 million if increase in incidence continues)[2]

Preferentially affects men and the elderly[1,2]

Lifetime risk of developing AF: ~1 in 4 for adults ≥40 years of age[3]

1. Lloyd-Jones D, et al. [published online ahead of print December 17, 2009]. *Circulation*. doi:10.1161/CIRCULATIONAHA.109.192667.
2. Miyasaka Y, et al. *Circulation*. 2006;114(2):119-125.
3. Lloyd-Jones DM, et al. *Circulation*. 2004;110(9):1042-1046.

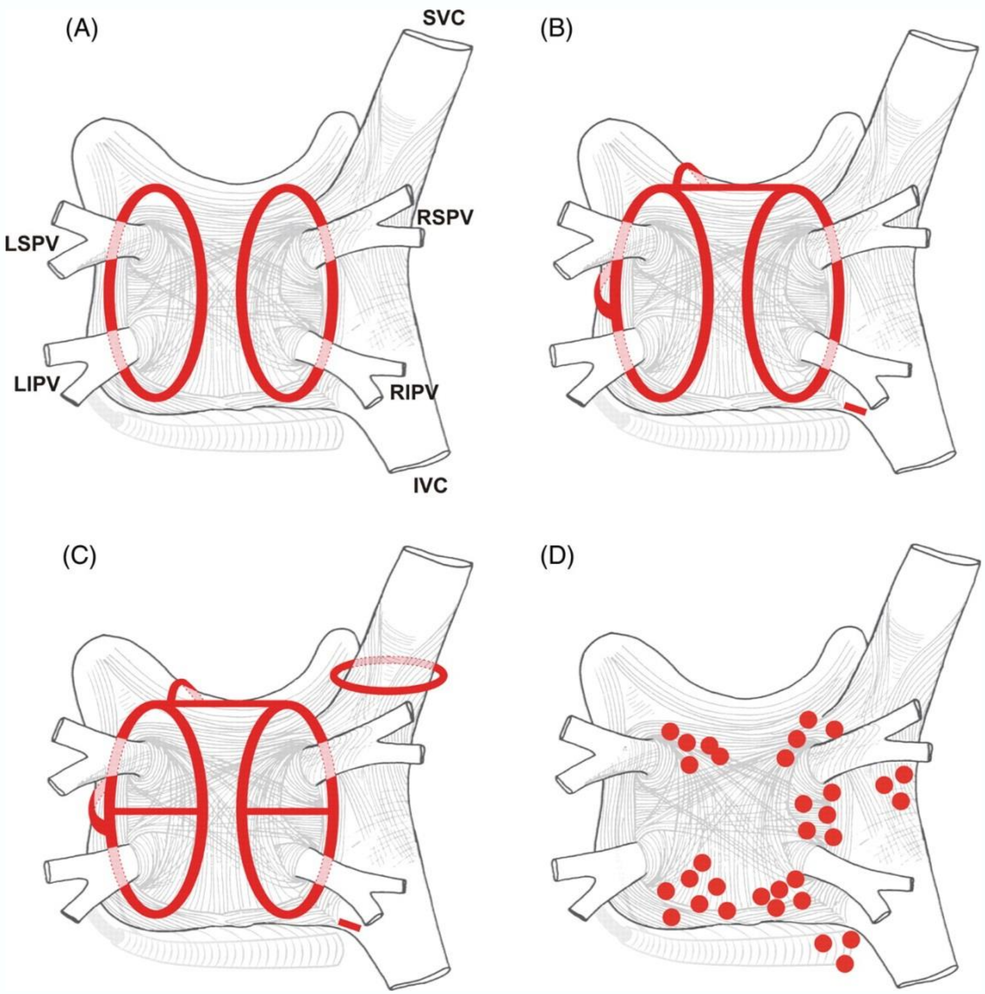
Catheter Ablation for Atrial Fibrillation

TABLE 2: CONSENSUS INDICATIONS FOR CATHETER AND SURGICAL ABLATION of AF

	CLASS	LEVEL
INDICATIONS FOR CATHETER ABLATION of AF		
Symptomatic AF refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication		
Paroxysmal: Catheter ablation is recommended*	I	A
Persistent: Catheter ablation is reasonable	IIa	B
Longstanding Persistent: Catheter ablation may be considered	IIb	B
Symptomatic AF prior to initiation of antiarrhythmic drug therapy with a Class 1 or 3 antiarrhythmic agent		
Paroxysmal: Catheter ablation is reasonable	IIa	B
Persistent: Catheter ablation may be considered	IIb	C
Longstanding Persistent: Catheter ablation may be considered	IIb	C

Calkins et al. 2012

Lesions Sets



PV isolation

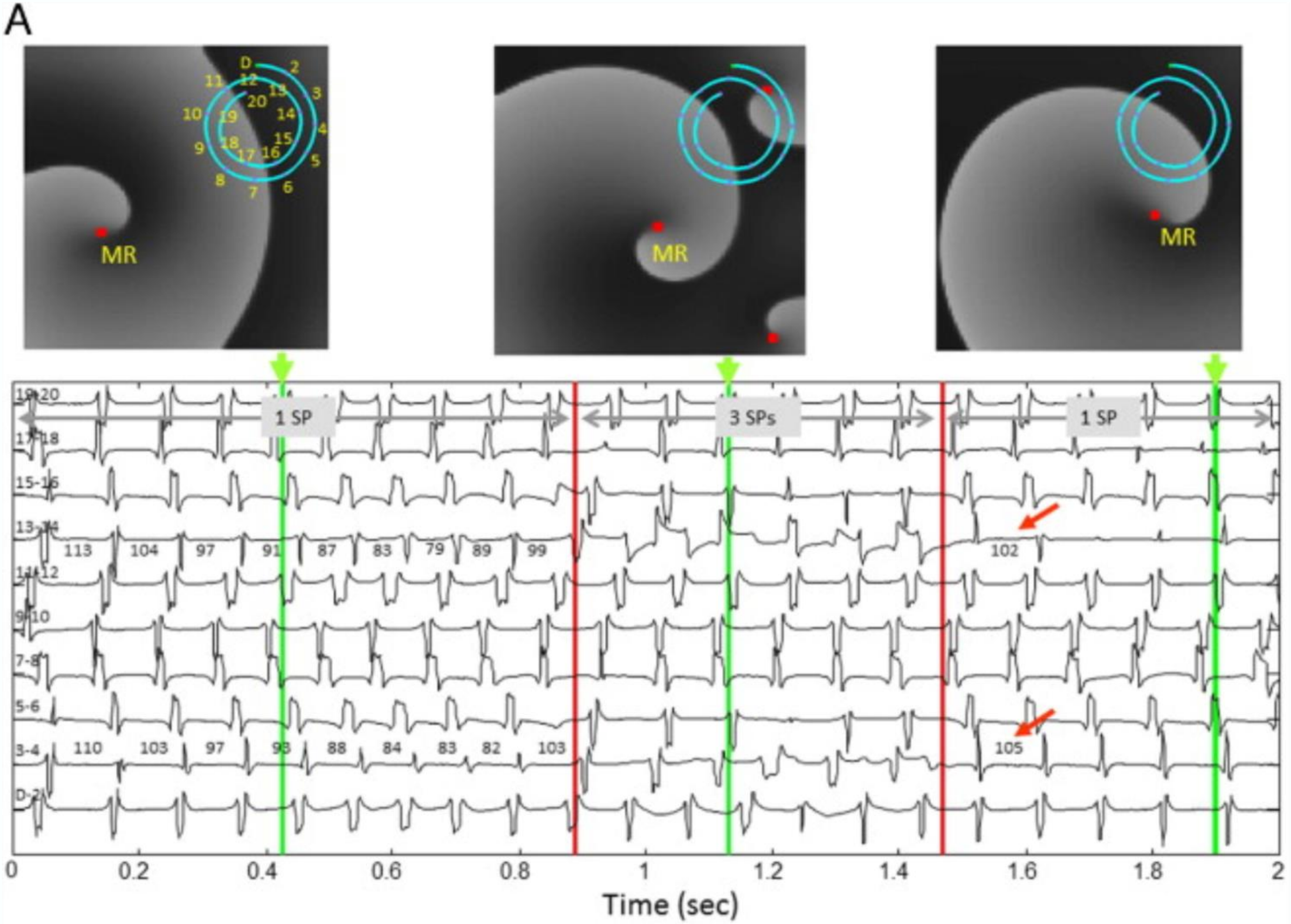
Lines

Electrogram-based ablation

Guidelines suggest that **"operators should consider more extensive ablation based on linear lesions or complex fractionated electrograms"** for ablation of persistent atrial fibrillation.

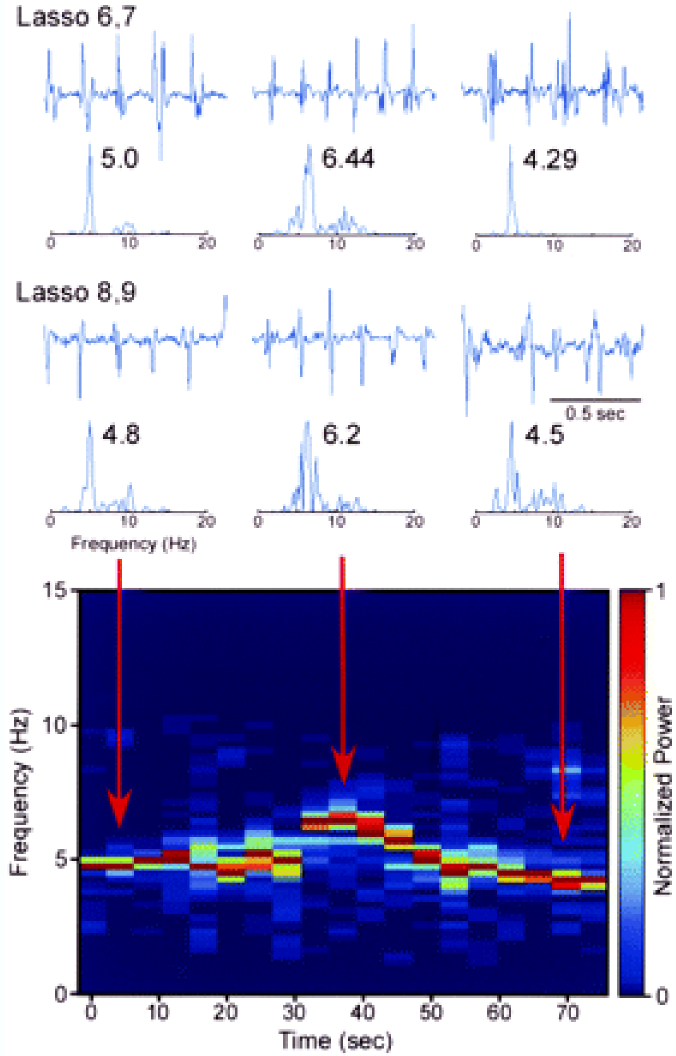
Calkins et al. Europace , Heart Rhythm 2007, 2012

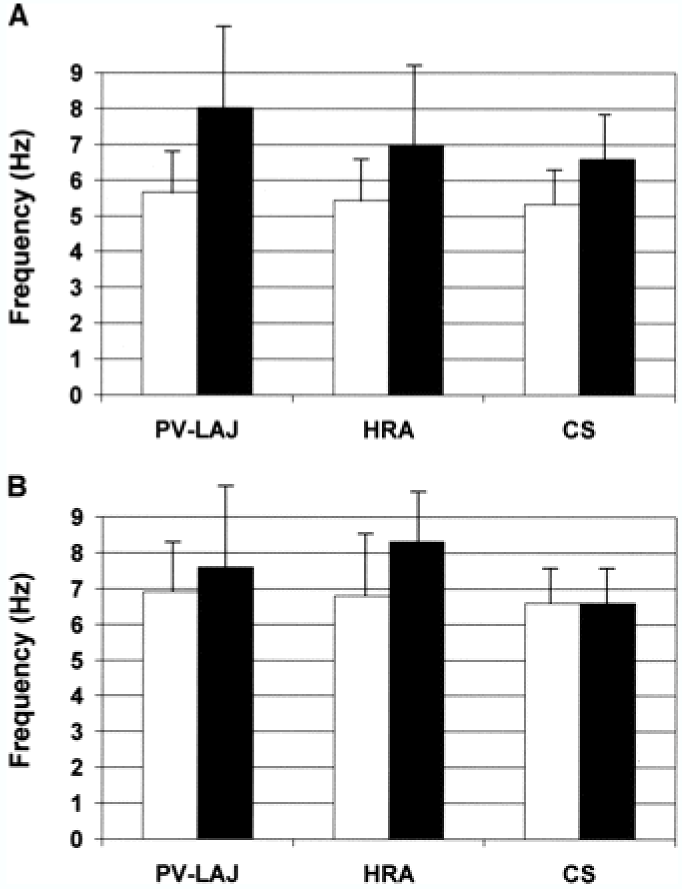
Rotor Drift



Atienza et al. JACC 2011

Reentry



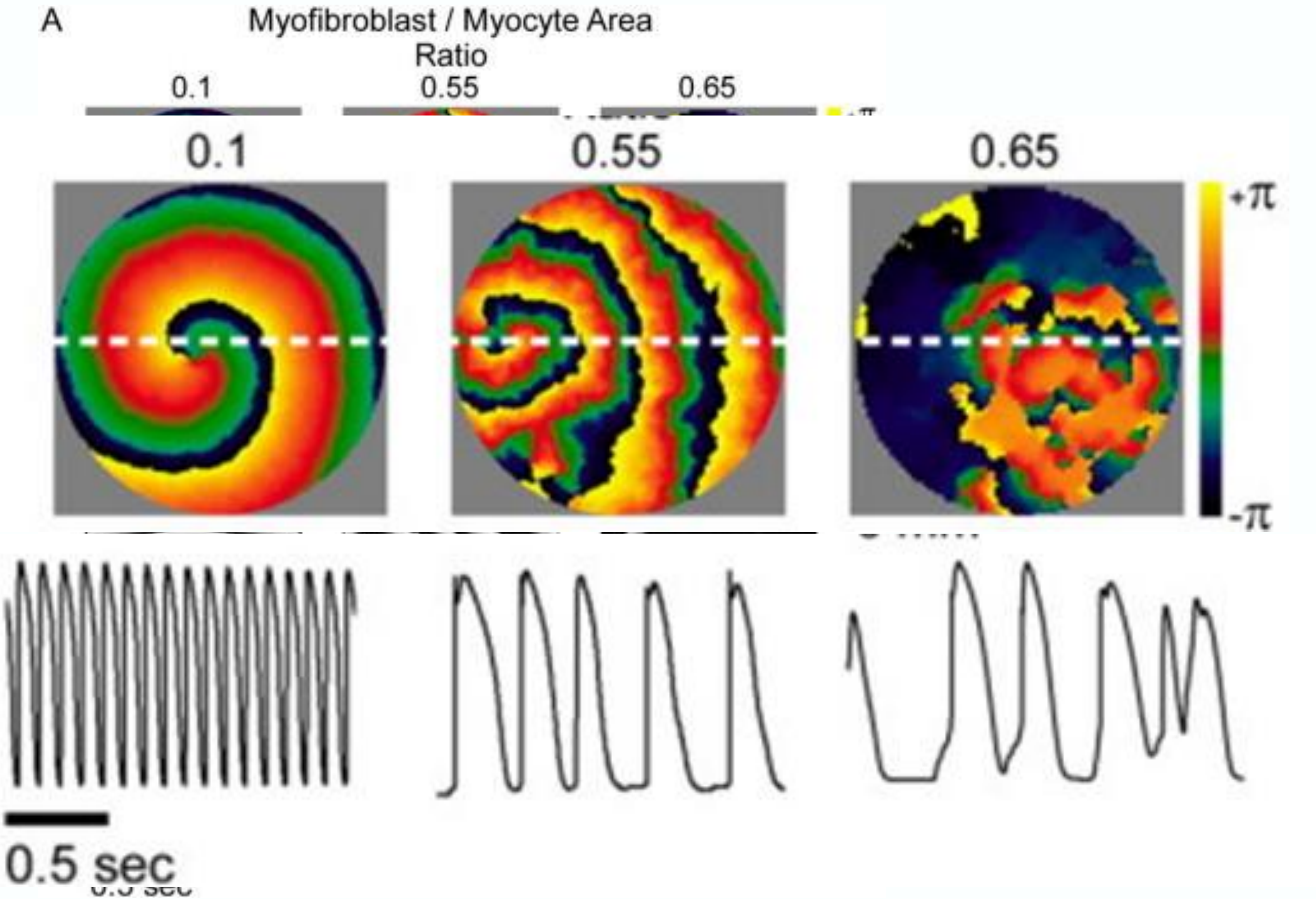


Atienza et al. Circulation 2006

Besides boundaries between frequency domains, what other rotor features may cause fractionation?

What is the relationship between CFAEs and Rotors?

- Waves emanating from high frequency rotors experience wavebreak and beat-to-beat variations in velocity and directionality result in fractionated electrograms
- Rotor meandering
- Rotor drift



Zlochiver et al. Biophysical Journal 2008

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Electrogram Fractionation-Guided Ablation in the Left Atrium Decreases the Frequency of Activation in the Pulmonary Veins and Leads to Atrial Fibrillation Termination

Pulmonary Vein Modulation Rather Than Isolation

Julien Seitz, MD,[a] Clement Bars, MD,[a,b] Ange Ferracci, MD,[a] Alexandre Maluski, MD,[a] Guillaume Penaranda, MD,[c] Guillaume Theodore, MD,[d] Jacques Faure, MD,[a] Michel Bremondy, MD,[a] Laurence Curel, MS,[a] Sylvain Beurtheret, MD,[a] Uma M.R. Avula, MD,[e] Jerome Kalifa, MD, PhD,[e] Andre Pisapia, MD[a]

ABSTRACT

OBJECTIVES This study sought to evaluate the impact of a complex fractionated atrial electrogram (CFAE)-guided ablation strategy on atrial fibrillation (AF) dynamics in patients with persistent AF.

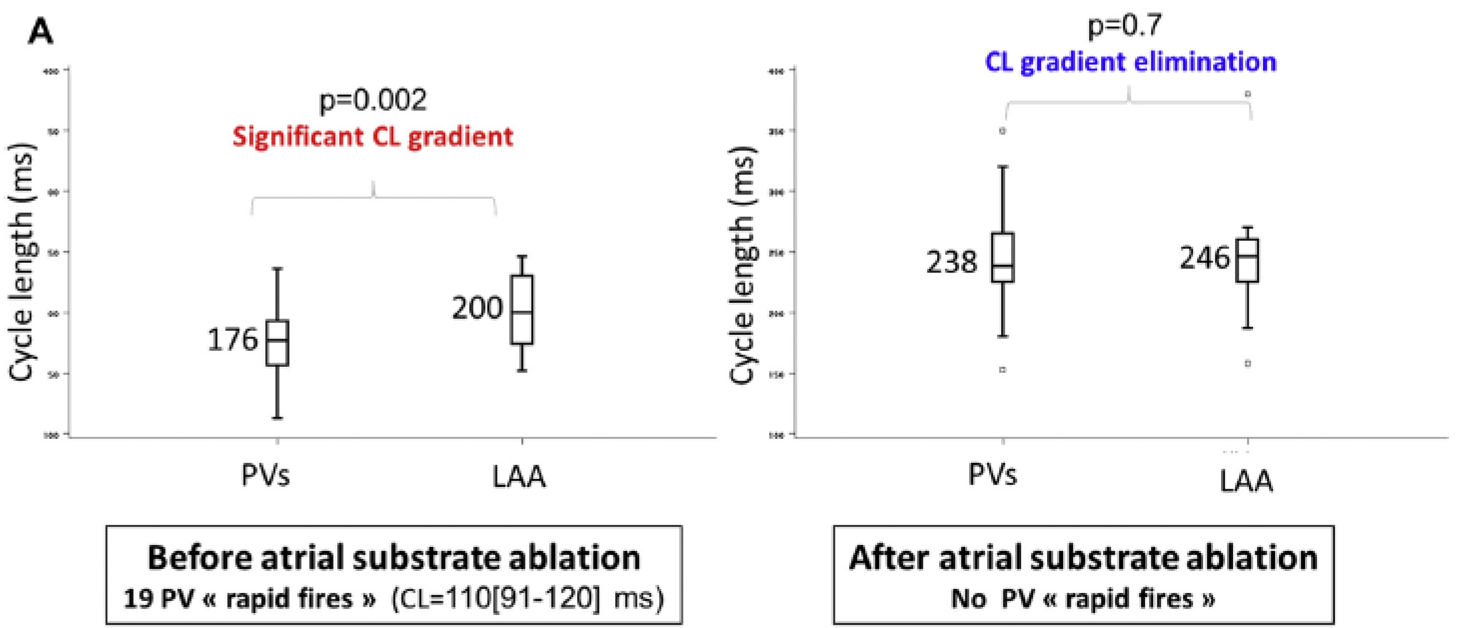
BACKGROUND It is still unclear whether complete pulmonary vein isolation (PVI) is required or if the ablation of well-delineated pulmonary vein (PV) subregions could achieve similar outcomes in persistent AF.

METHODS CFAE-guided ablations were performed in 76 patients (65.2 ± 10 years of age) with persistent AF. In 47 patients, we measured mean PVs and left atrial appendage (LAA) cycle length (CL) values (PV-CL and LAA-CL), before ablation and before AF termination. We defined "active" PVs as PV-CL ≤ LAA-CL, "rapid fires" as PV-CL ≤80% of LAA-CL, and "PV-LAA CL gradient" as a significant CL difference between the 2 regions.

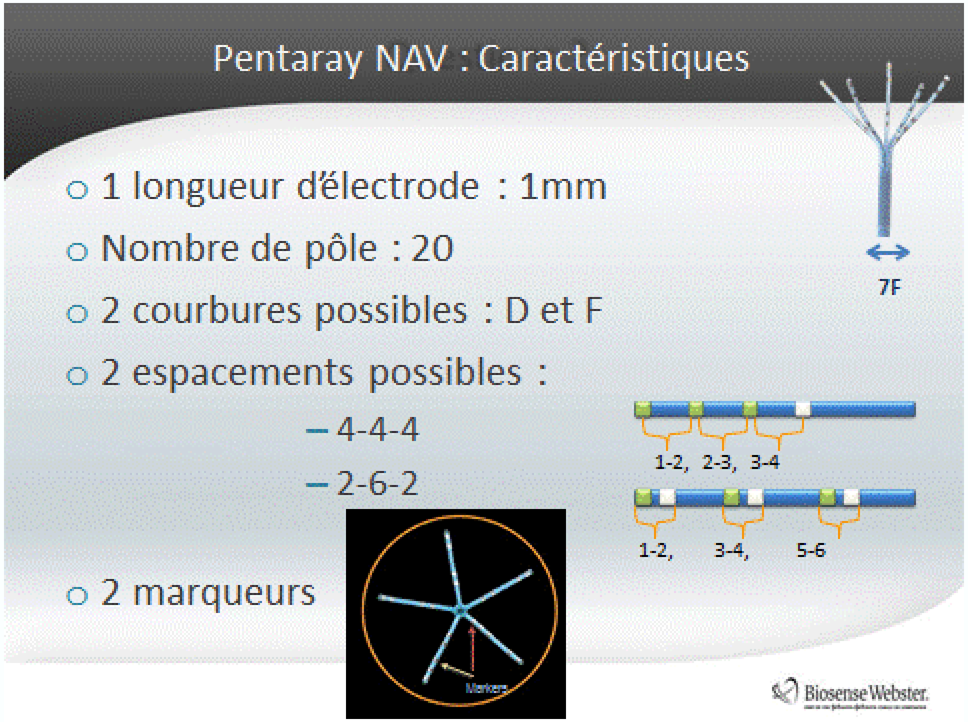
RESULTS AF termination (sinus rhythm [SR] or atrial tachycardia [AT] conversion) occurred in 92% and SR conversion in 75%. The radiofrequency time for AF termination and total radiofrequency time were 26 ± 25 min and 61.1 ± 21.6 min, respectively. Thirty of 47 patients had active PV (with 19 PV "rapid fires"). Ablation significantly increased median CL, both at PVs and LAA from 188 ms (interquartile range [IQR]: 161 to 210 ms) to 227.5 ms (IQR: 200 to 256 ms) ($p < 0.0001$) and from 197 ms (IQR: 168 to 220 ms) to 224 ms (IQR: 193 to 250 ms) ($p < 0001$), respectively. After ablation, PV-LAA CL gradients were withdrawn and all PV "rapid fires" were extinguished (without PVI). After 17.2 ± 10 months of follow-up and 1.61 ± 0.75 procedures, 86.3% and 73% of the patients were free from AF and from any arrhythmia (AF/AT), respectively.

CONCLUSIONS CFAE-guided ablation leads to a large decrease in PV frequency of activation, preceding AF termination. A PV modulation approach, rather than complete PVI, may be preferable for persistent AF.
(J Am Coll Cardiol EP 2016;2:732–42) © 2016 by the American College of Cardiology Foundation.

FIGURE 2 Atrial and PV CL Evolution Before and During Substrate Ablation

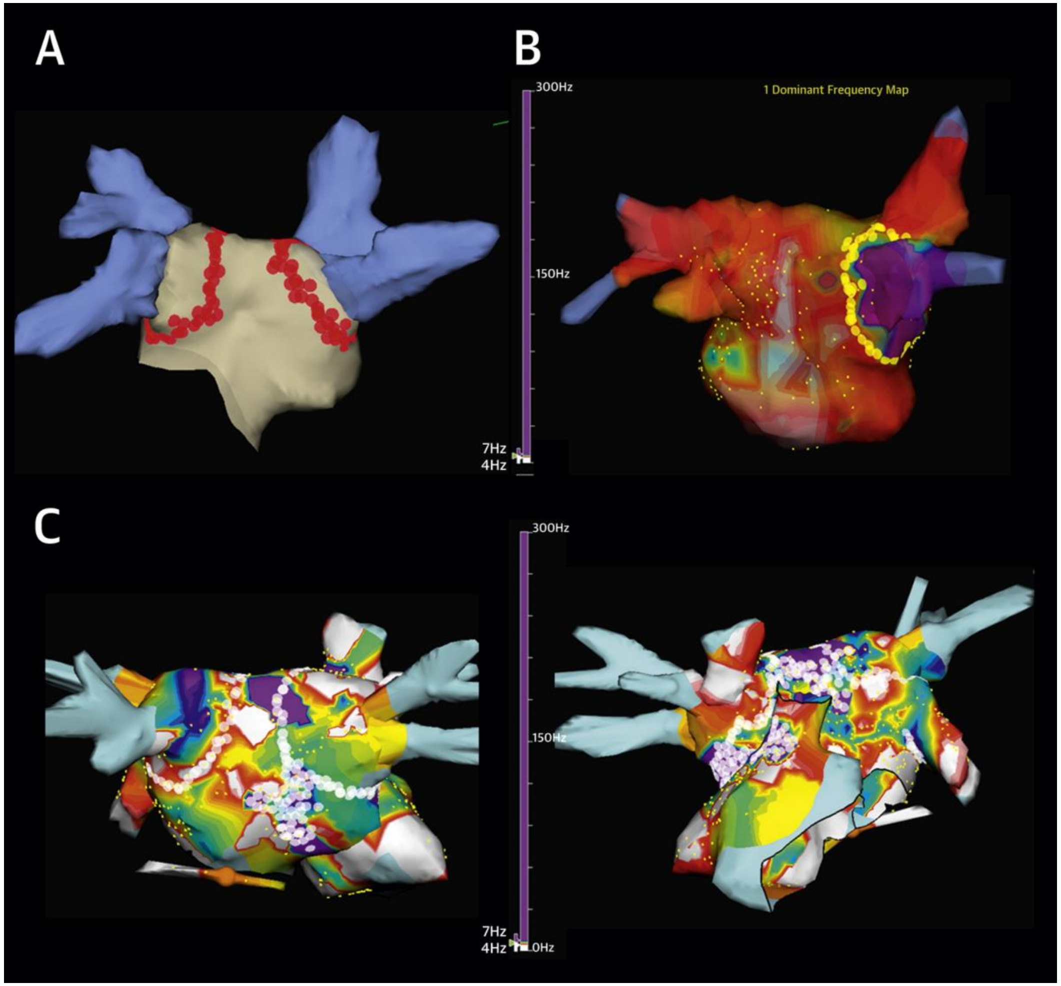


Biosense Webster Pentarray Catheter Specifications



Fanny:
Donc la distance entre l'electrode 1 et l'electrode 4 est de 13 mm.
La branche entière fait 16 mm.

Dominant Frequency-based ablation



Atienza et al. JACC 2014

Dominant Frequency-based ablation

Prospective, multicenter, single-blinded study of 232 patients (age 53 10 years, 186 males) randomized those with paroxysmal AF (n= 115) to CPVI or HFSA-only (noninferiority design) and those with persistent AF (n= 117) to CPVI or a combined ablation approach (CPVI + HFSA, superiority design).

The primary endpoint was freedom from AF at 6 months post-first ablation procedure. Secondary endpoints included freedom from atrial tachyarrhythmias (AT) at 6 and 12 months, periprocedural complications, overall adverse events, and quality of life.

Atienza et al. JACC 2014

Dominant Frequency-based ablation

A high-density dominant frequency (DF) LA map was created by sequentially moving the ablation and/or circular mapping catheter throughout the entire left atrium.

Sites with high-frequency (HF) atrial electrograms were identified by an automated algorithm designed to calculate the DF and depict local atrial activation frequency on the 3-dimensional LA shell .

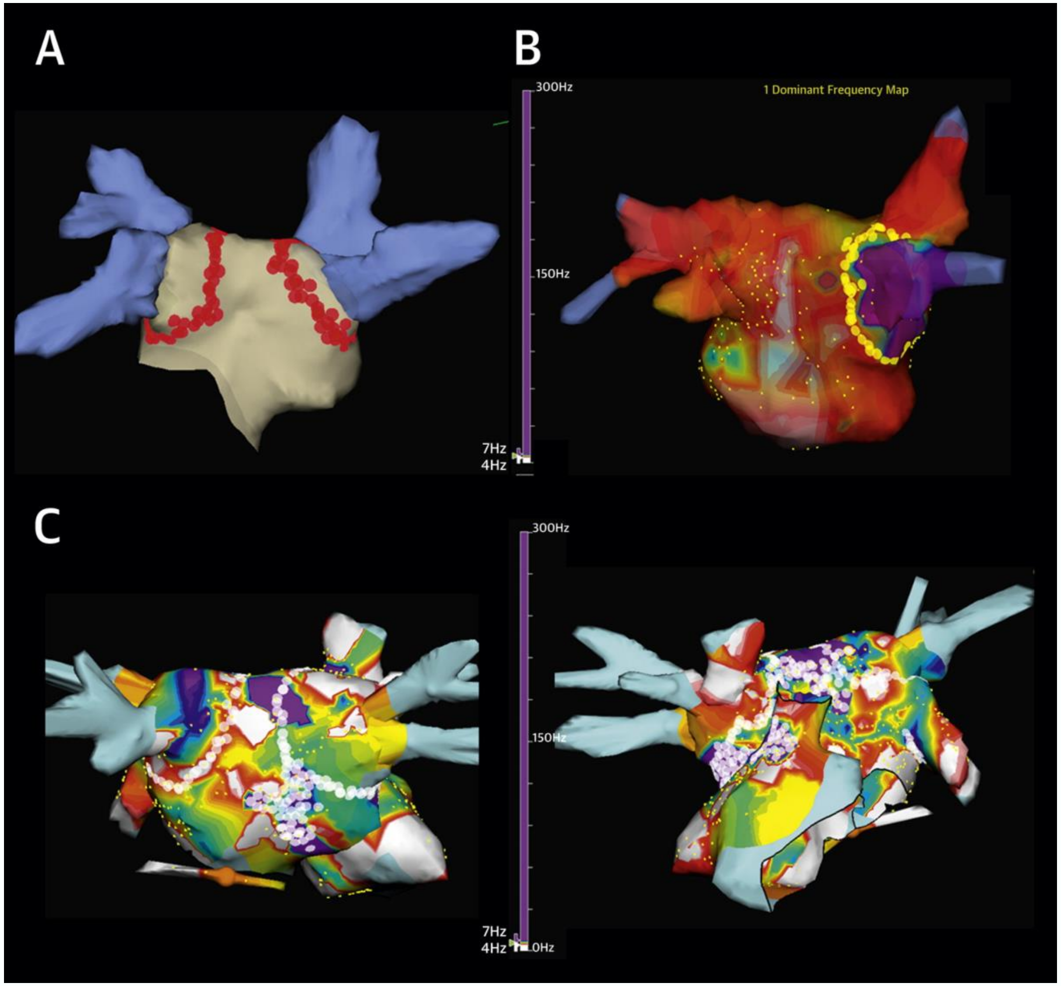
HFS were targeted until ablation endpoints were reached: 1) elimination of all HFS or conversion to SR; and 2) noninducibility of AF post-ablation. If AF did not terminate after LA HFSA, DF maps from the right atrium (RA) and coronary sinus (CS) were obtained and HFS were targeted at the operator’s discretion. A maximum of 3 to 4 HFS per chamber were targeted for ablation (4 sites in LA and 3 sites in RA and CS).

Ablation of HF sites located at a PV antrum was performed by creating a circumferential set of lesions around the ostium of the responsible vein until PV isolation was obtained.

HF sites located elsewhere in the atria were targeted for ablation until local potentials were completely abated through creation of a coin-like circumferential set of lesions

Atienza et al. JACC 2014

Dominant Frequency-based ablation



Atienza et al. JACC 2014

Dominant Frequency-based ablation

In paroxysmal AF, **HFSA** failed to achieve non-inferiority at 6 months after a single procedure but, after redo procedures, **was non-inferior to CPVI at 12 months for freedom from AF and AF/AT.** Serious adverse events were significantly reduced in the HFSA group versus CPVI patients (p = 0.02).

In persistent AF, there were no significant differences between treatment groups for primary and secondary endpoints, but CPVI + HFSA trended toward more serious adverse events.

Atienza et al. JACC 2014

Dominant Frequency-based ablation

TABLE 2 Procedural Characteristics

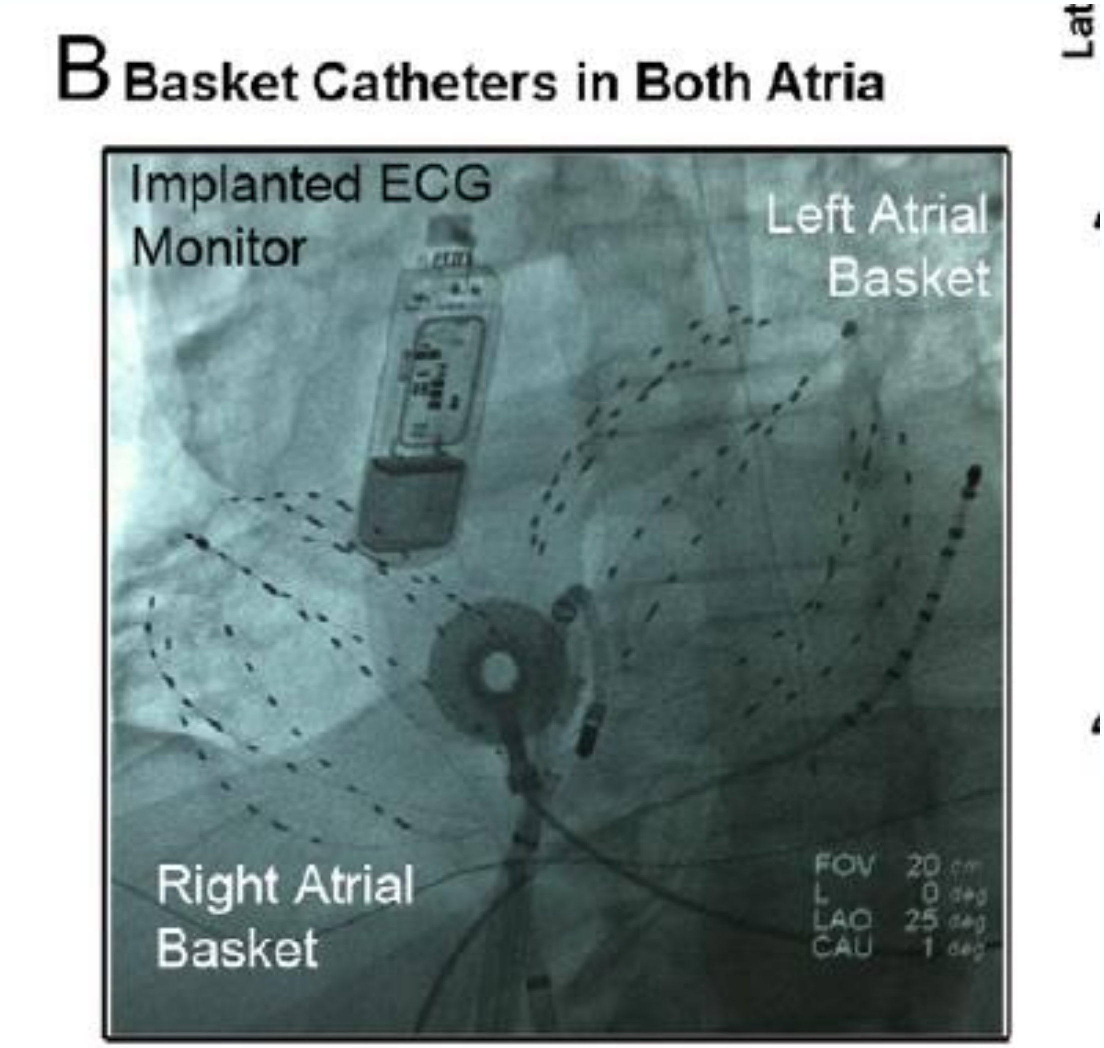
	Paroxysmal AF			Persistent AF		
	CPVI (n = 58)	HFSA (n = 55)	p Value	CPVI (n = 58)	CPVI + HFSA (n = 59)	p Value
Induced AF	46 (81)	49 (89)	0.26	11 (19)	11 (19)	0.61
Mean AF cycle length, ms	172 ± 35	176 ± 33	0.55	171 ± 33	169 ± 33	0.79
DF mapping time, min	NA	31 ± 16	NA	NA	28 ± 17	NA
RF time, min	36 (24.7-47.1)	29 (20-39)	0.01	37 (29.7-50.0)	43 (31-53)	0.10
Fluoroscopy time, min	60 (45.8-79.3)	59 (40-81)	0.66	66 (47-78.3)	67 (50-83)	0.43
Total procedure time, min	215 ± 66	228 ± 65	0.31	202 ± 58	239 ± 61	0.001
HFS	NA	3 (2-4)	NA	NA	3 (2-5)	NA
Ablated HFS	NA	2.87 (2-3)	NA	NA	3 (2.00-4.25)	NA
Total number nonablated HFS	NA	18	NA	NA	26	NA
Isolated pulmonary veins	3.79 ± 0.50	2.22 ± 1.10	<0.001	3.93 ± 0.45	3.88 ± 0.45	0.56
Patients with additional ablation lines	3	0	NA	11	22	0.03
Patients converting to SR during ablation	16 (28)	25 (45)	<0.05	3 (5)	7 (12)	0.19
Patients converting to AT during ablation	6 (10)	7 (13)	0.69	12 (21)	20 (34)	0.11
Patients with redo procedures	17 (29)	13 (24)	0.5	13 (22)	16 (27)	0.56
Ablated HFS during redo procedure	NA	3 (1.75-3.00)	NA	NA	3 (1.5-5.0)	NA
Isolated pulmonary veins during redo procedure	3.59 ± 1.00	2.46 ± 0.96	0.004	2.92 ± 1.40	3.31 ± 0.79	0.36

Values are n (%), mean ± SD, or median (interquartile range).
AT = atrial tachyarrhythmias; DF = dominant frequency; RF = radiofrequency; SR = sinus rhythm; other abbreviations as in Table 1.

Atienza et al. JACC 2014

Electrogram-based Ablation AF Drivers Visual Rendition

CONFIRM, JACC 2012



Phase analysis

Rotor visualization

CONFIRM, JACC 2012

Table 2 Acute Results in All Cases or Those With Sustained AF During Their Procedure

Characteristic	Conventional Ablation	FIRM-Guided Ablation	p Value
Cases with intraprocedural sustained AF	65/71 (92%)	36/36 (100%)	0.10
Subjects with AF sources	63/65 (97%)	35/36 (97%)	1.00
Acute endpoint achieved	13/65 (20%)	31/36 (86%)	<0.001
AF termination endpoint	6/65 (9%)	20/36 (56%)	<0.001
Ablation time, min, at primary source	—	2.5 (1.0–3.1)	
To sinus rhythm/atrial tachycardia	3/3	16/4	0.29
AF slowing (CL prolongation) endpoint	7/65 (11%)	11/36 (31%)	0.01
Extent of AF CL prolongation, ms	28 ± 8 (18 ± 6%)	33 ± 12 (19 ± 8%)	0.38
Ablation time for acute endpoint, min	31.8 (22.1–71.5)	18.5 (7.9–24.5)	<0.001
Total procedural ablation (all cases), min	52.1 ± 17.8	57.8 ± 22.8	0.16
Complications, all cases	6 (8%)	2 (6%)	0.72
Cardiac tamponade	2	1	
Groin bleed requiring transfusion	3	1	
Vascular injury requiring surgical repair	0	0	
Permanent diaphragmatic paralysis	0	0	
Symptomatic pulmonary vein stenosis	1*	0	
Stroke/TIA	0	0	
Atrioesophageal fistula	0	0	
Death	0	0	

Values are n/N (%), mean ± SD, median (interquartile range), n (%), or n. *Required stent.
CL = cycle length; other abbreviations as in Table 1.

CONFIRM, JACC 2012

Localized rotors or focal impulses were detected in 98 (97%) of 101 cases with sustained AF, each **exhibiting 2.1 (±1) sources.**

The acute endpoint (AF termination or consistent slowing) was achieved in **86% of FIRMguided cases versus 20% of FIRM-blinded cases (p 0.001).**

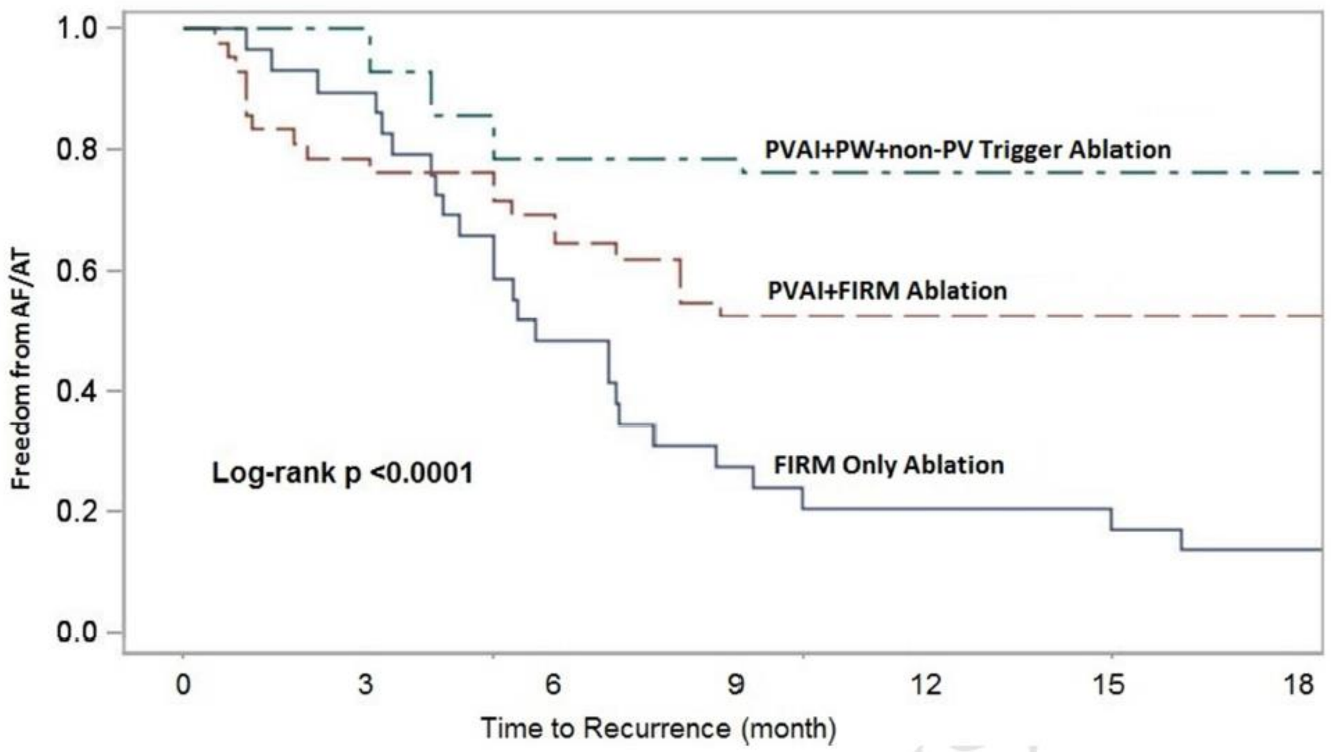
FIRM ablation alone at the primary source terminated AF in a median 2.5 min (interquartile range: 1.0 to 3.1 min). Total ablation time did not differ between groups (57.8 22.8 min vs. 52.1 17.8 min, p 0.16).

During a median 273 days (interquartile range: 132 to 681 days) after a single procedure, FIRM-guided cases had higher freedom from AF (82.4% vs. 44.9%; p 0.001) after a single procedure than FIRM-blinded cases with rigorous, often implanted, electrocardiography monitoring.

OASIS, JACC 2016

Methods: Non-paroxysmal AF patients undergoing first ablation were randomized (1:1:1) to FIRM only (group 1), FIRM+ PVAI (group 2) or PVAI+ posterior wall (PW) +non-PV trigger ablation (group 3). Freedom from atrial tachycardia (AT)/AF was the primary endpoint. Secondary endpoint included acute procedural success, defined as AF termination or ≥10% slowing or organization into AT.

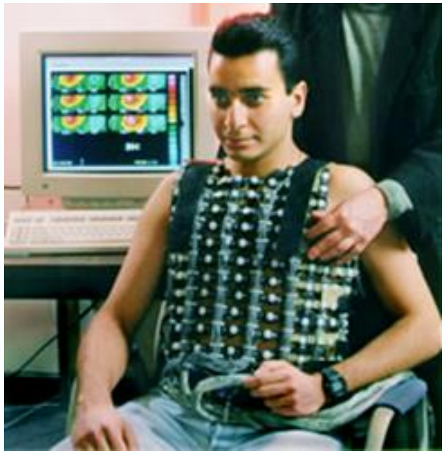
OASIS, JACC 2016



Acute procedural success after targeting the FIRM-identified rotors was achieved in a small number of patients; 41% and 26% in group 1 and 2 respectively

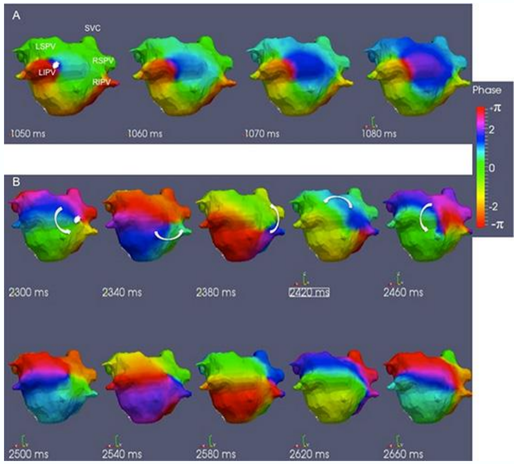
ECGi Approach, Circulation 2014

- 252-electrode mapping vest: noninvasive recording of unipolar surface torso potentials (ECVue, Cardioinsight Technologies).



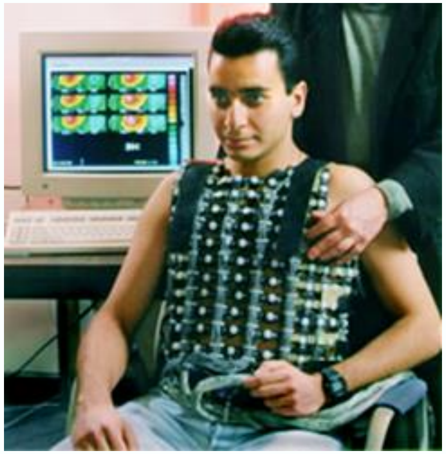
- Biatrial inverse-reconstructed potentials are calculated according to measurements obtained from thoracic computed tomography scan 3-dimensional images of individual biatrial geometries.

- Electrograms are acquired in AF during long ventricular pauses, spontaneous or provoked with diltiazem.



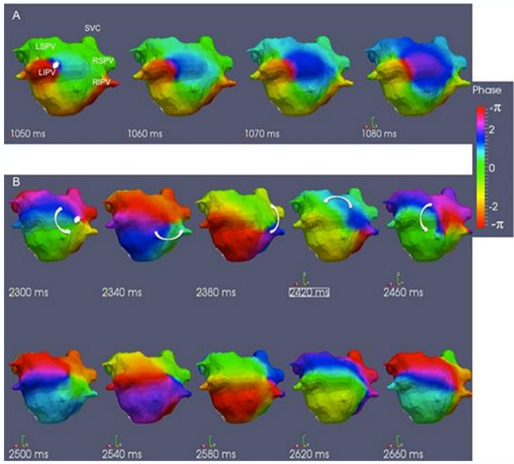
ECGi Approach, Circulation 2014

Phase maps and activation sequences are displayed on individualized ***atrial geometries*** divided into ***7 domains***,



Fibrillation driver density maps. Ablation was conducted sequentially in regions harboring the largest driver density before it was done in other regions, following a decreasing order of arrhythmogenic density.

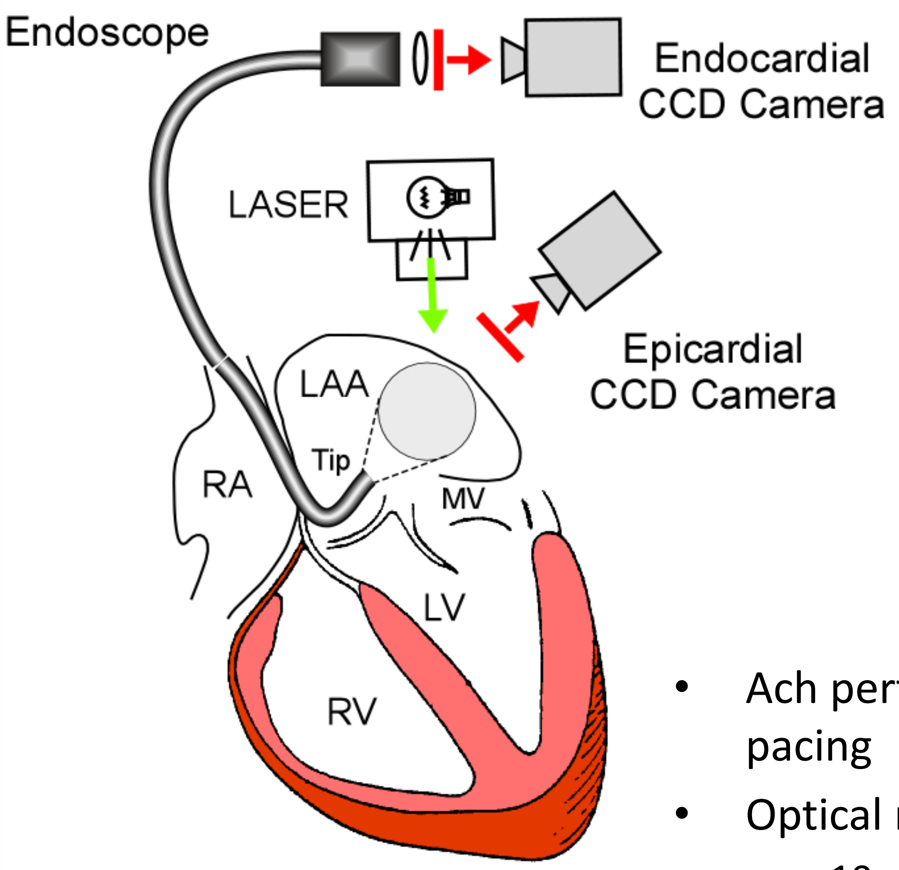
PsAF is maintained by drivers mostly located in the PV–left atrium regions, but with continued AF maintenance, as in LPsAF patients, AF sources are found beyond the PV region. The number of targeted driver regions increased with the duration of continuous AF: 2 in patients presenting in sinus rhythm, 3 in AF lasting 1 to 3 months, 4 in AF lasting 4 to 6 months, and 6 in AF lasting longer.

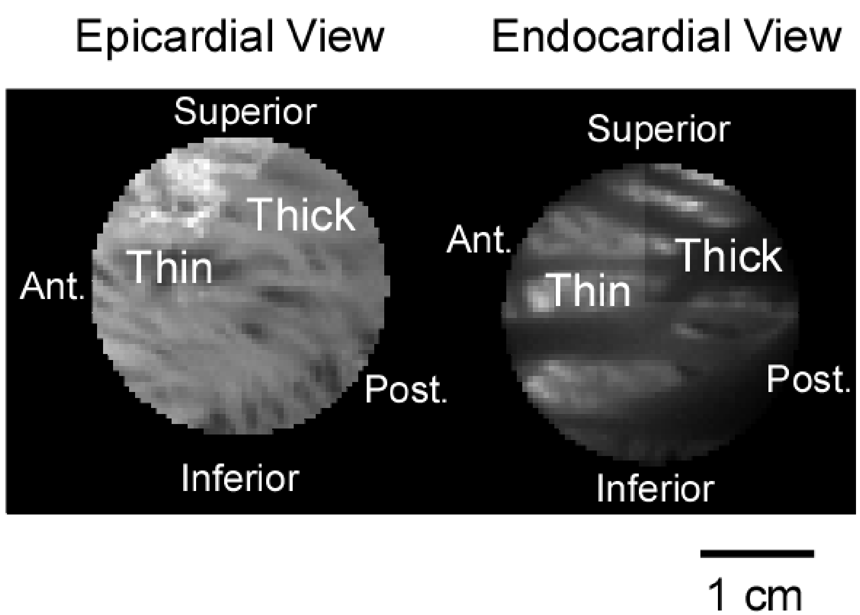


Driver ablation alone terminated **75% and 15% of persistent and long-lasting AF, respectively. At 12 months, 85% patients with AF termination were free from AF, similar to the control population (87%,);** ***P*****=not significant.**

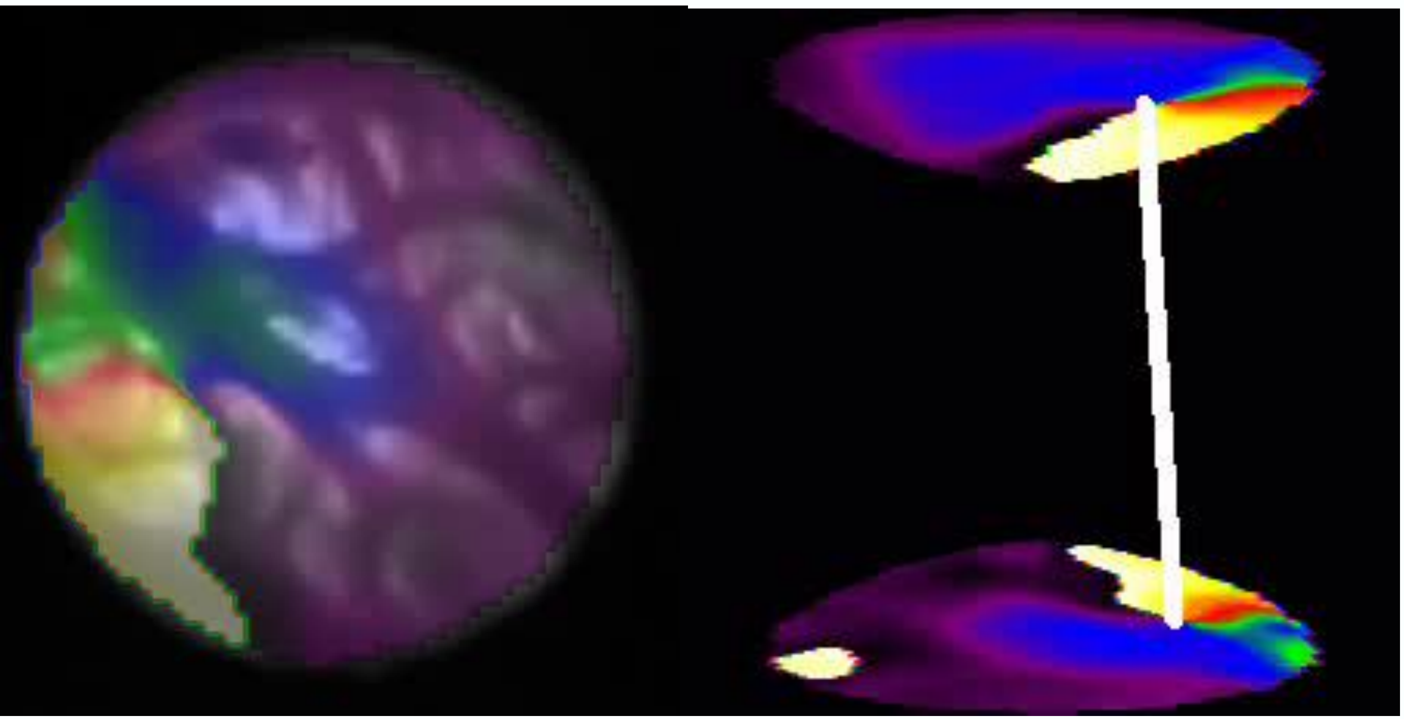
Methods- Optical imaging

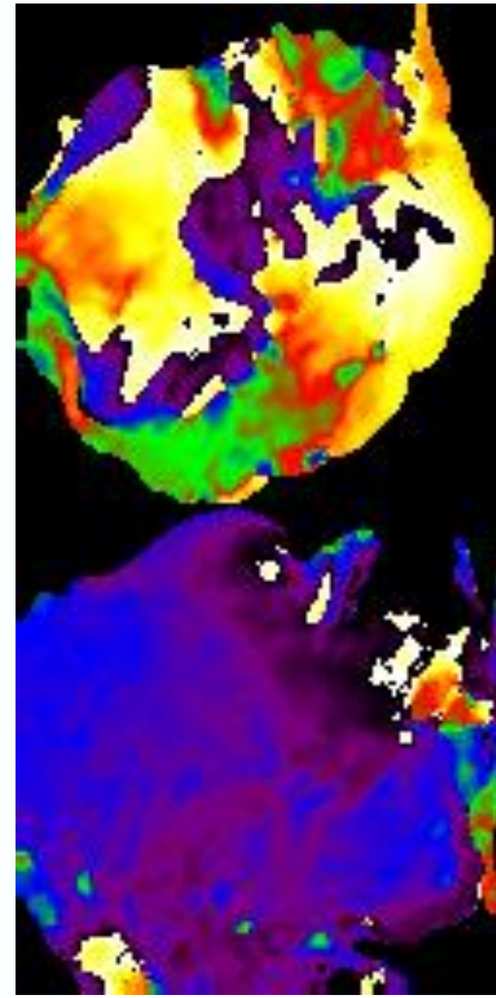
LAA view



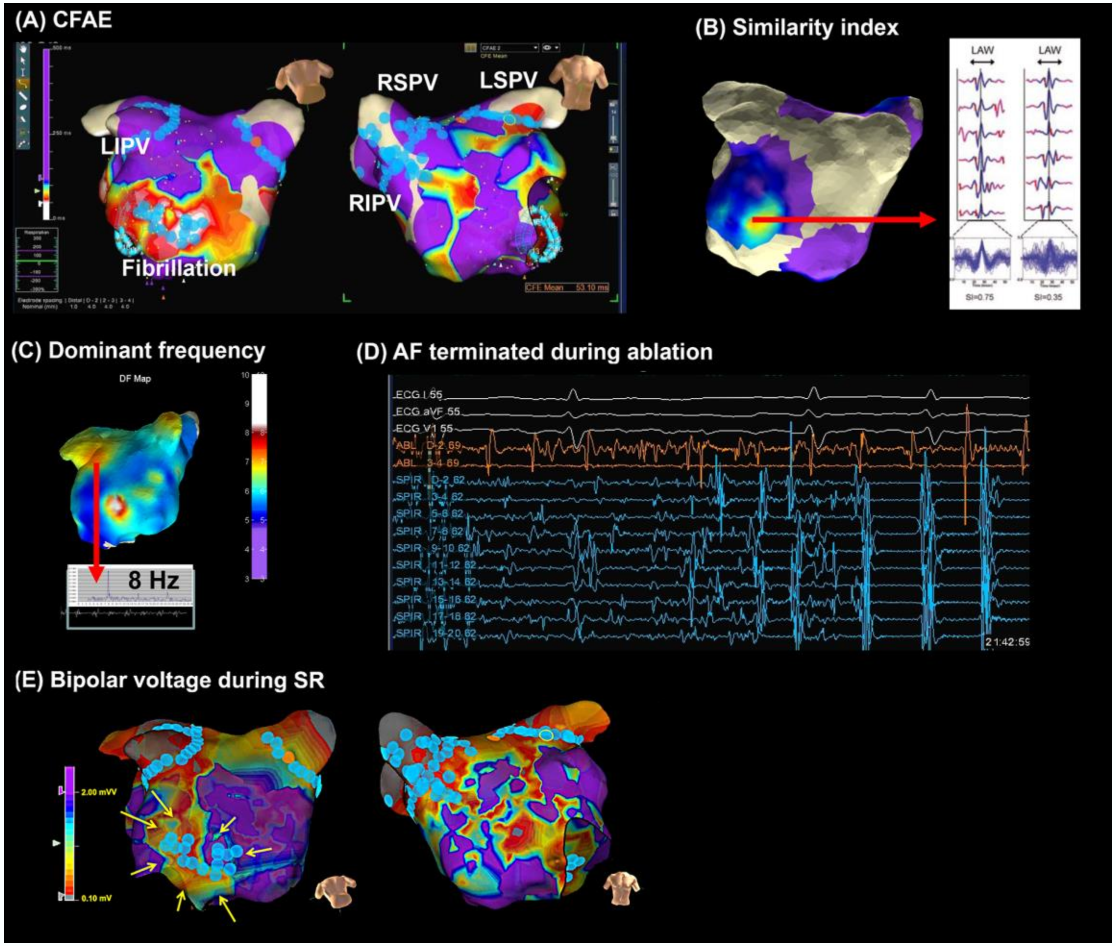


- Ach perfused (0.05-0.2µM) and AF induced by burst pacing
- Optical mapping
  - 10 µM blebbistatin
  - 10 mg/mL Di-4-ANEPPS
  - Optical movies 500-1000 frames/sec, 5-second, 80x80 pixels

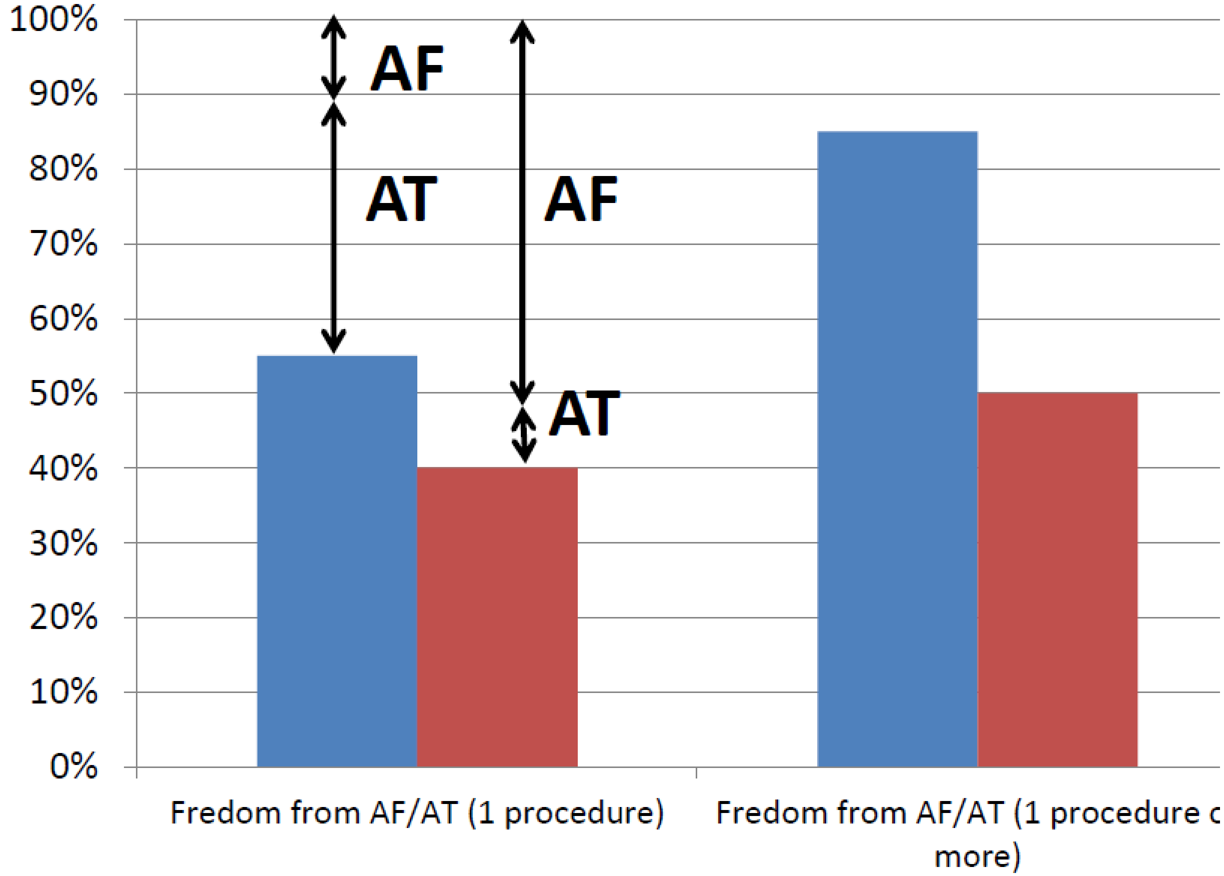




Non-linear (III)

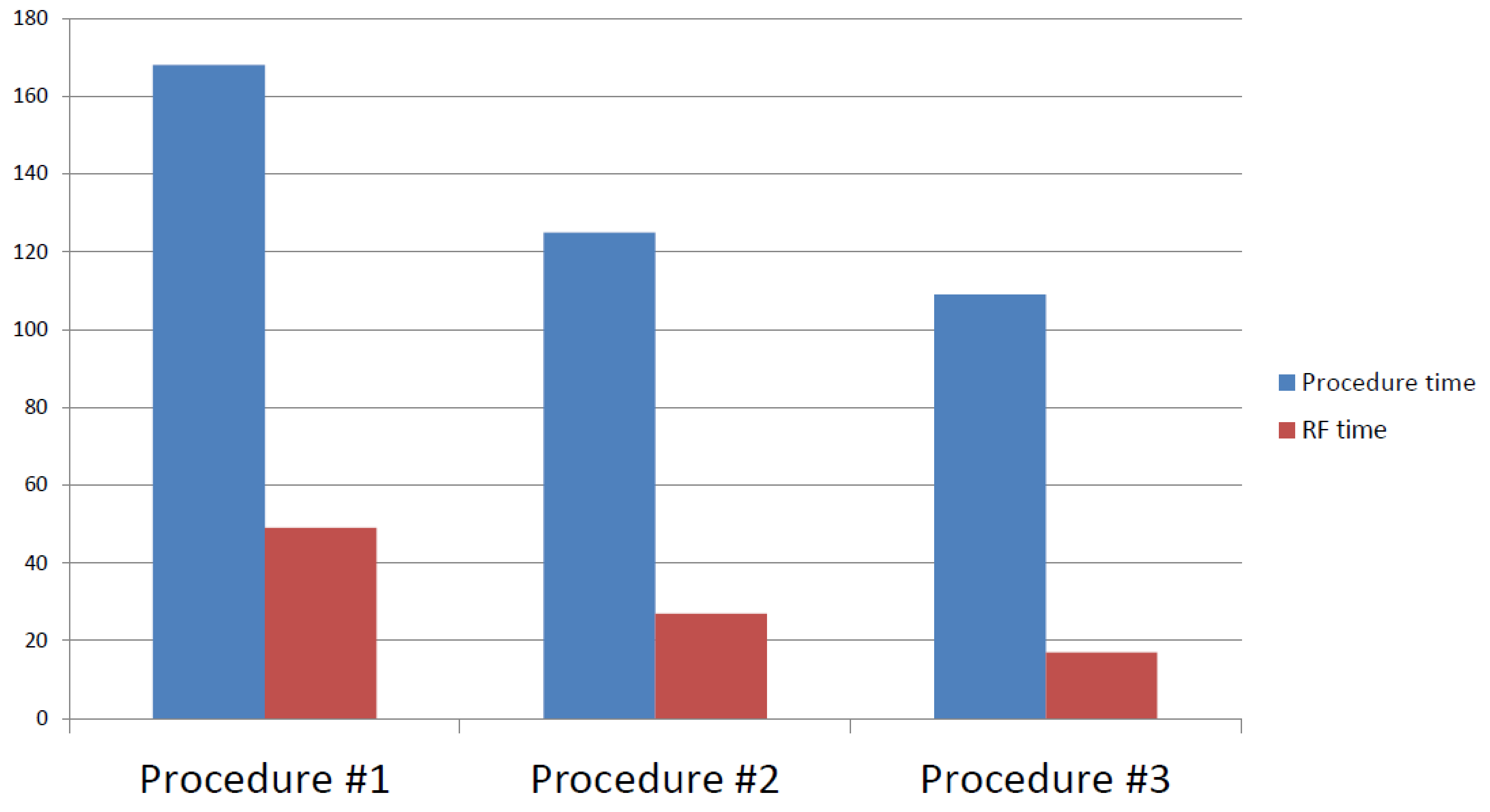


Substrate HD vs STAR AF2*



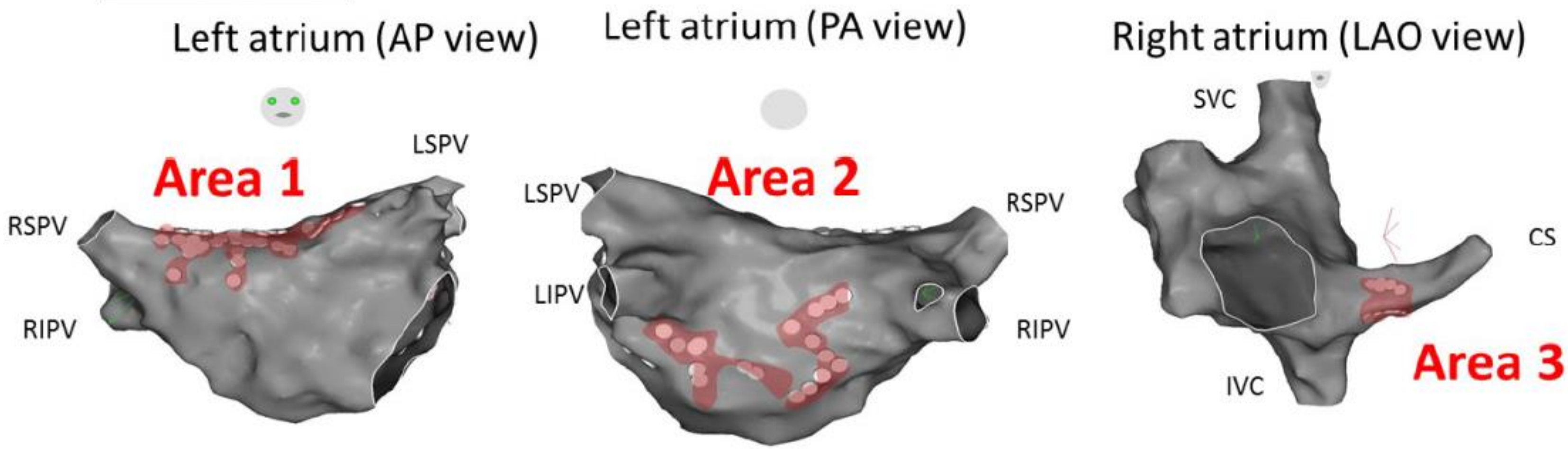
* average results of the comparable 3 groups (PVI, PVI+cfe, PVI+lines)

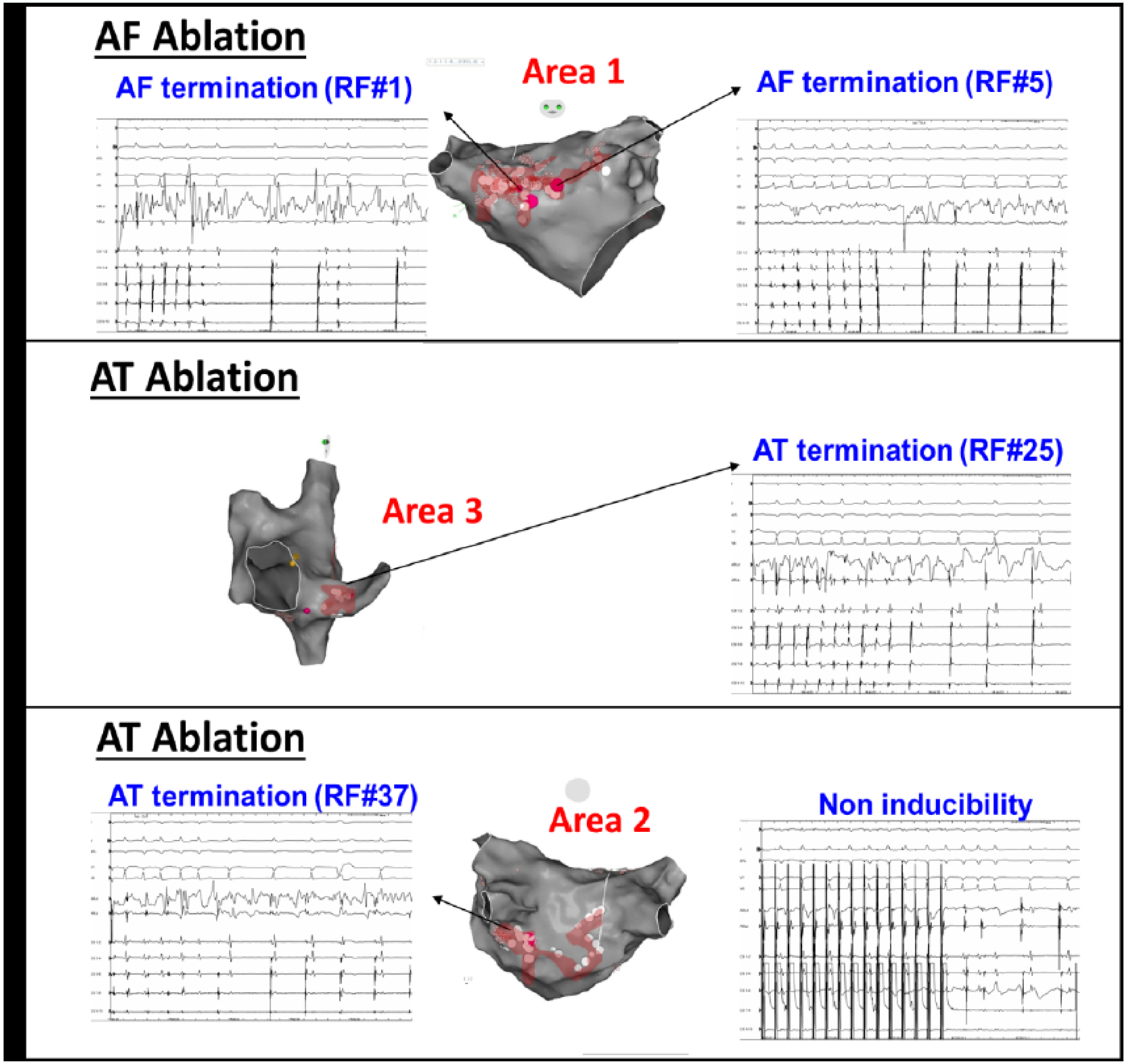
ATs are much easier to ablate than AF



Mechanism of AT and its relationship with the original AF

Mapping





The 2 ATs were located in dipersion areas non already ablated

Analysis in 21 patients:
44 ATs, 22 macroreentries & 22 localized AT (88,6% in non- ablated areas).

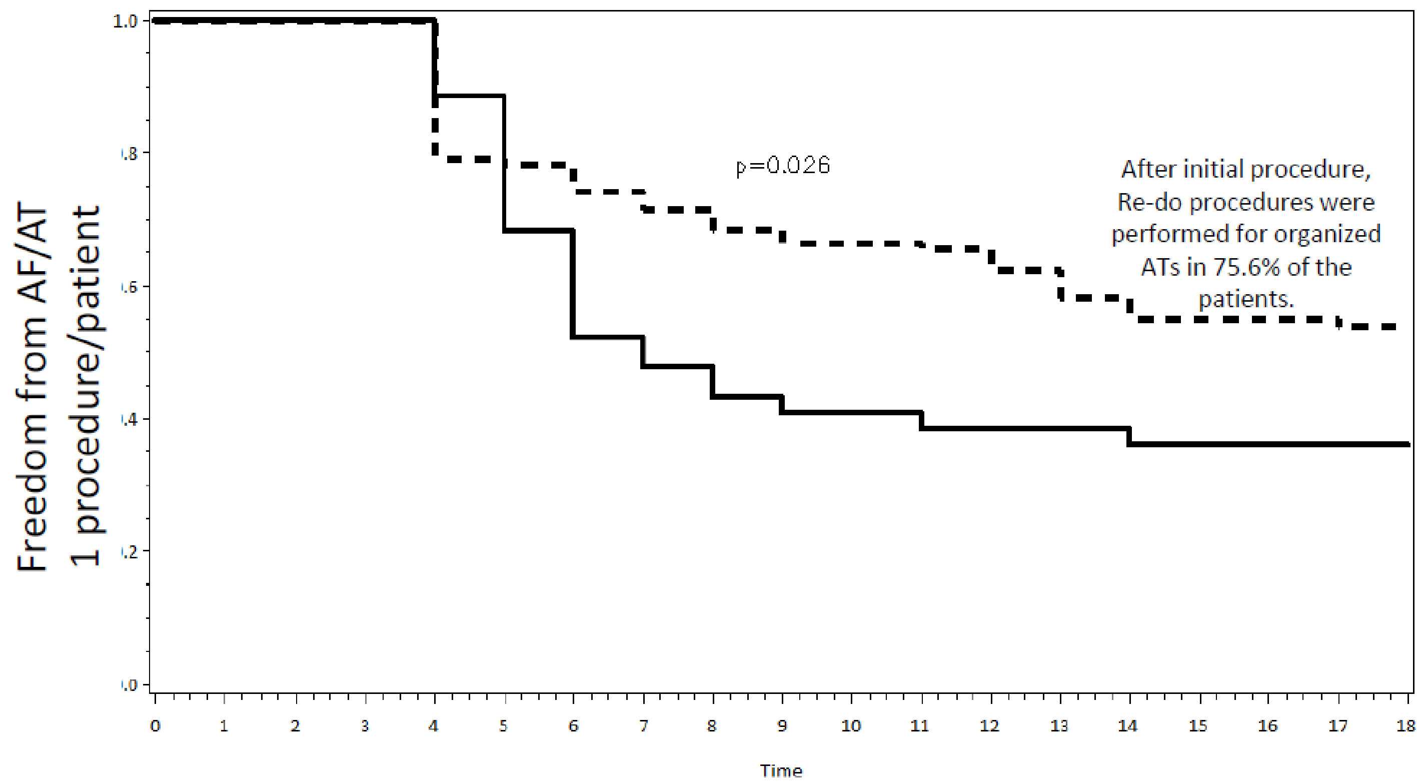
Importantly 17/22 (77,3%) localized ATs arose from dispersion regions that were not previously ablated!

18-month Follow-up

Completed in 91% of the patients: follow-up visits and 24-hour Holter , 7days holter-monitor/ PM-ICD memories in 20 pts

18 month-FU: 55% free from AF/AT after 1 procedure

with or without AA drugs



Study population	105	105	81	68	63	52	51
validation set	44	44	30	18	16	14	14

__class ▪▪▪▪ Study population ▬▬ validation set

18 month-FU: 85% free from AF/AT after 1,4 procedure/patient

with or without AA drugs