CardioVascular Learning Network | CME

Signal Analysis in Electrophysiology

Faculty

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Faculty Disclosures

- **Dr. Baykaner:** Advisory Board/speaker—Johnson & Johsnson, Medtronic, PaceMate, Volta, iRhythm; research funding—NIH, Janssen
- **Dr. Hummel**: Consultant—Medtronic, Volta Medical, Element Science, Abbott; Research Support—Abbott, Medtronic
- **Dr. Zei**: Advisory Board—Volta Medical, Varian, Biosense Webster; Consultant—Volta Medical, Medtronic, Abbott, Biosense Webster; Research Support—Varian, Abbott, Biosense Webster

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Program Information

- This program is provided by HMP Education, an HMP Global company
- Supported by an educational grant from Volta Medical and GE Healthcare

Learning Objectives

- Enhance the understanding of signal analysis and importance of signal clarity among electrophysiologists, cardiologists, and other healthcare professionals
- Highlight the importance of quality ECGs in EP recording, that they are the basis of the algorithm
- Demonstrate the practical application of AI and ML in analyzing ECGs
- Provide an overview of major clinical trials that are applicable to this topic

ECG = electrocardiogram; EP = electrophysiology; AI = artificial intelligence; ML = machine learning.

Importance of Signal Analysis and ECGs

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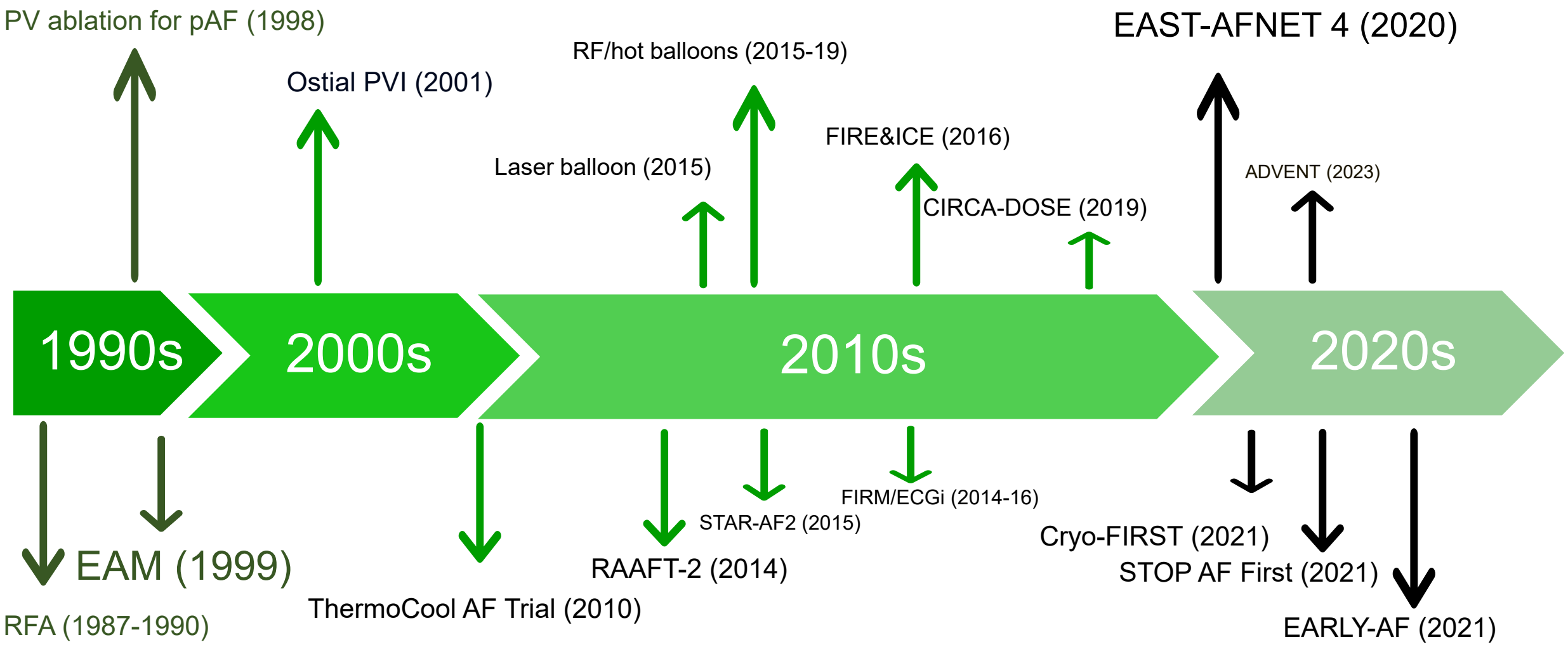
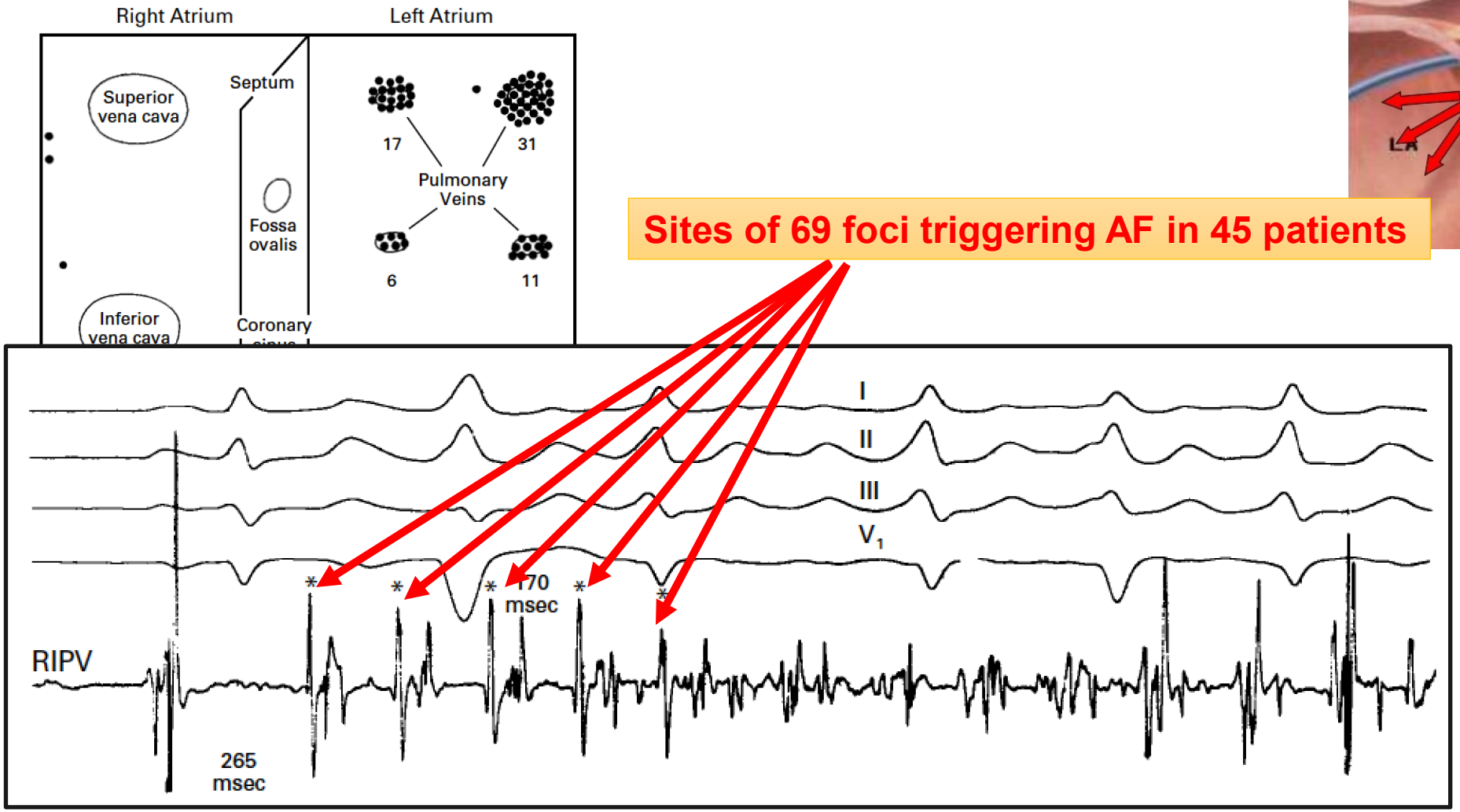
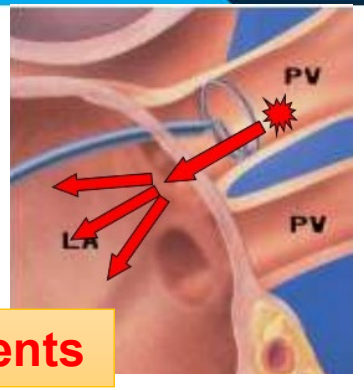
Background: Analysis of Atrial Signals for Treatment of AF



AF = atrial fibrillation; PV = pulmonary vein; pAF = paroxysmal atrial fibrillation; PVI = pulmonary vein isolation; RFA = radiofrequency ablation; EAM = electroanatomic mapping; FIRM = focal impulse and rotor modulation; ECGi = electrocardiographic imaging.

Signal Annotation in AF: Early Days



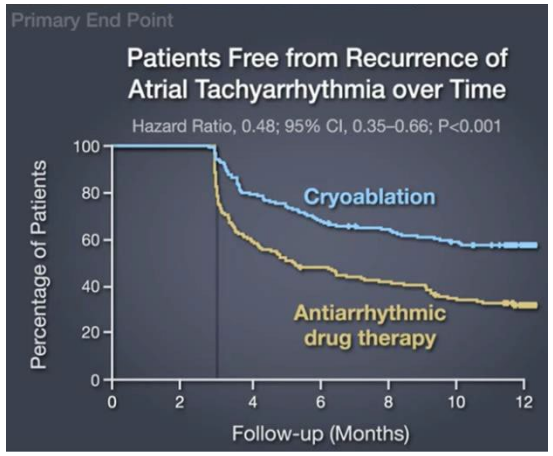


Sites of 69 foci triggering AF in 45 patients

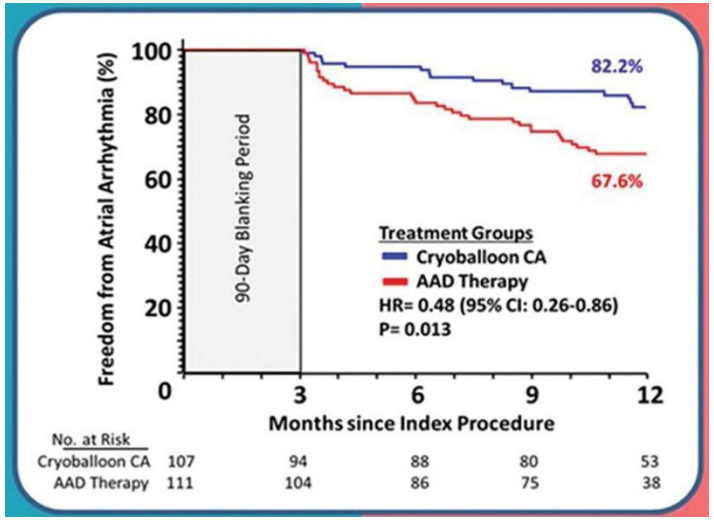
Haïssaguerre M, et al. *N Engl J Med.* 1998;339(10):659-666. Kuck KH, et al. *N Engl J Med.* 2016;374(23):2235-2245.

Eliminating Sites with Early Signals "Initiating" AF in the PVs—ie, AF Triggers

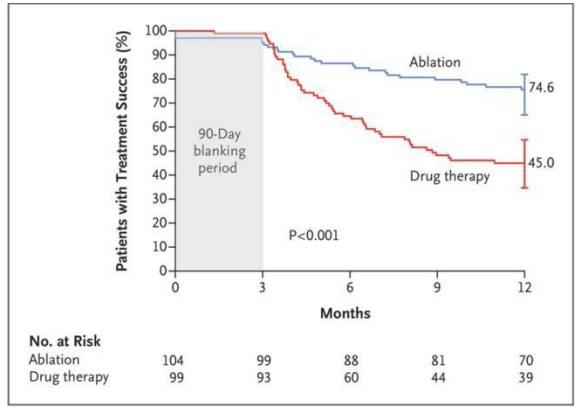
EARLY-AF



CRYO-FIRST

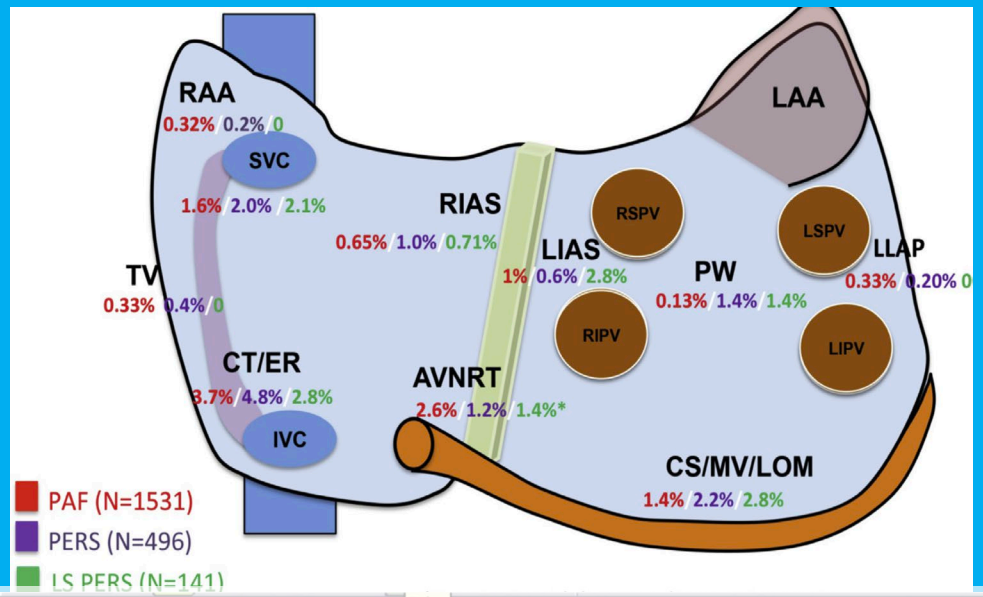


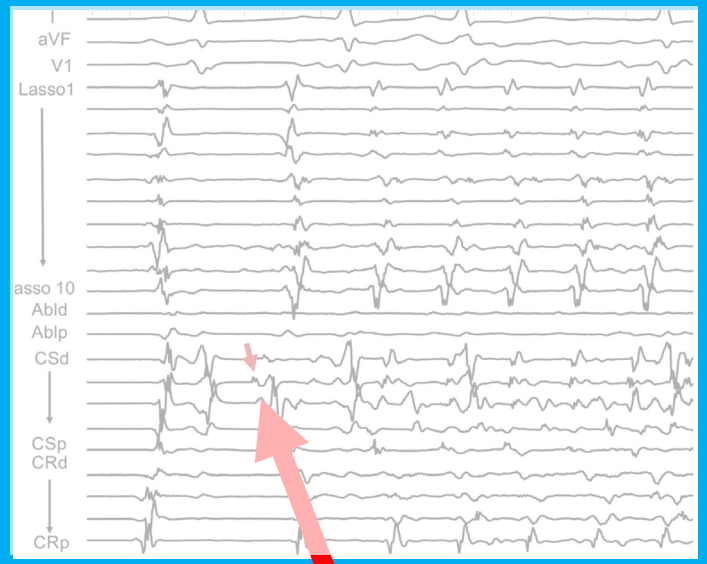
STOP AF-FIRST

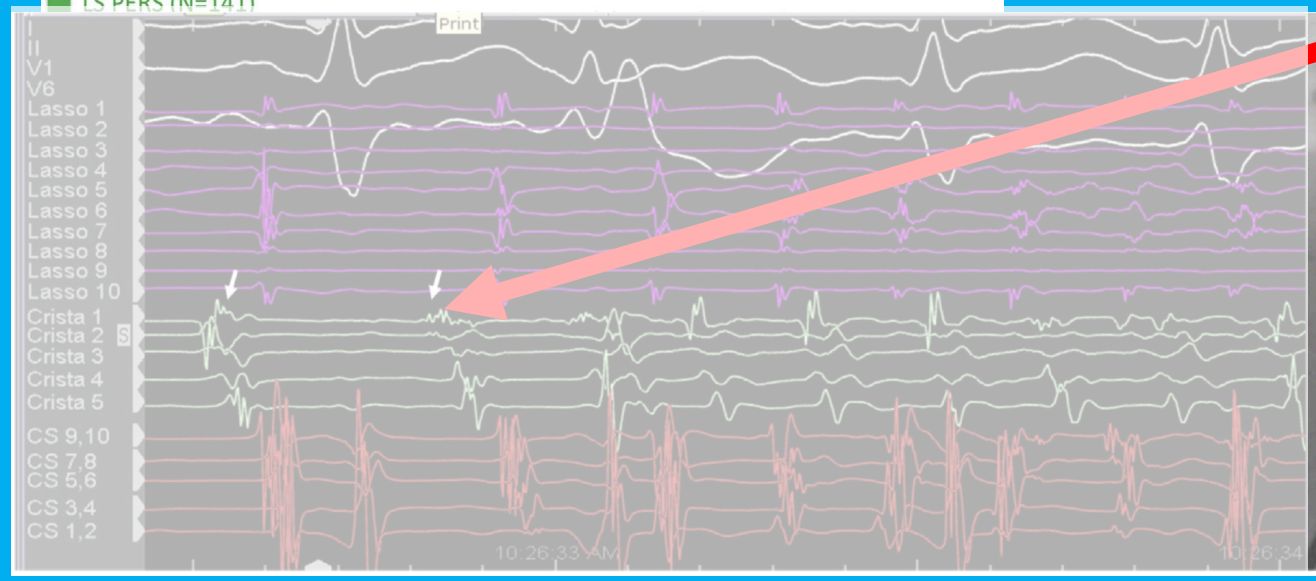


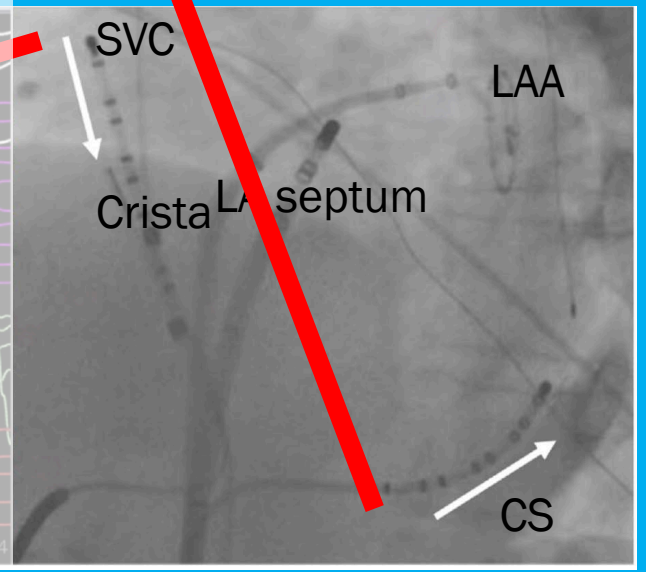
Andrade JG, et al. *N Engl J Med*. 2021;384(4):305-315. Kuniss M, et al. *Europace*. 2021;23(7):1033-1041. Wazni OM, et al. *N Engl J Med*. 2021;384(4):316-324.

Demonstration of Early AF Signals From Non-PV Location—ie, Extra PV Triggers







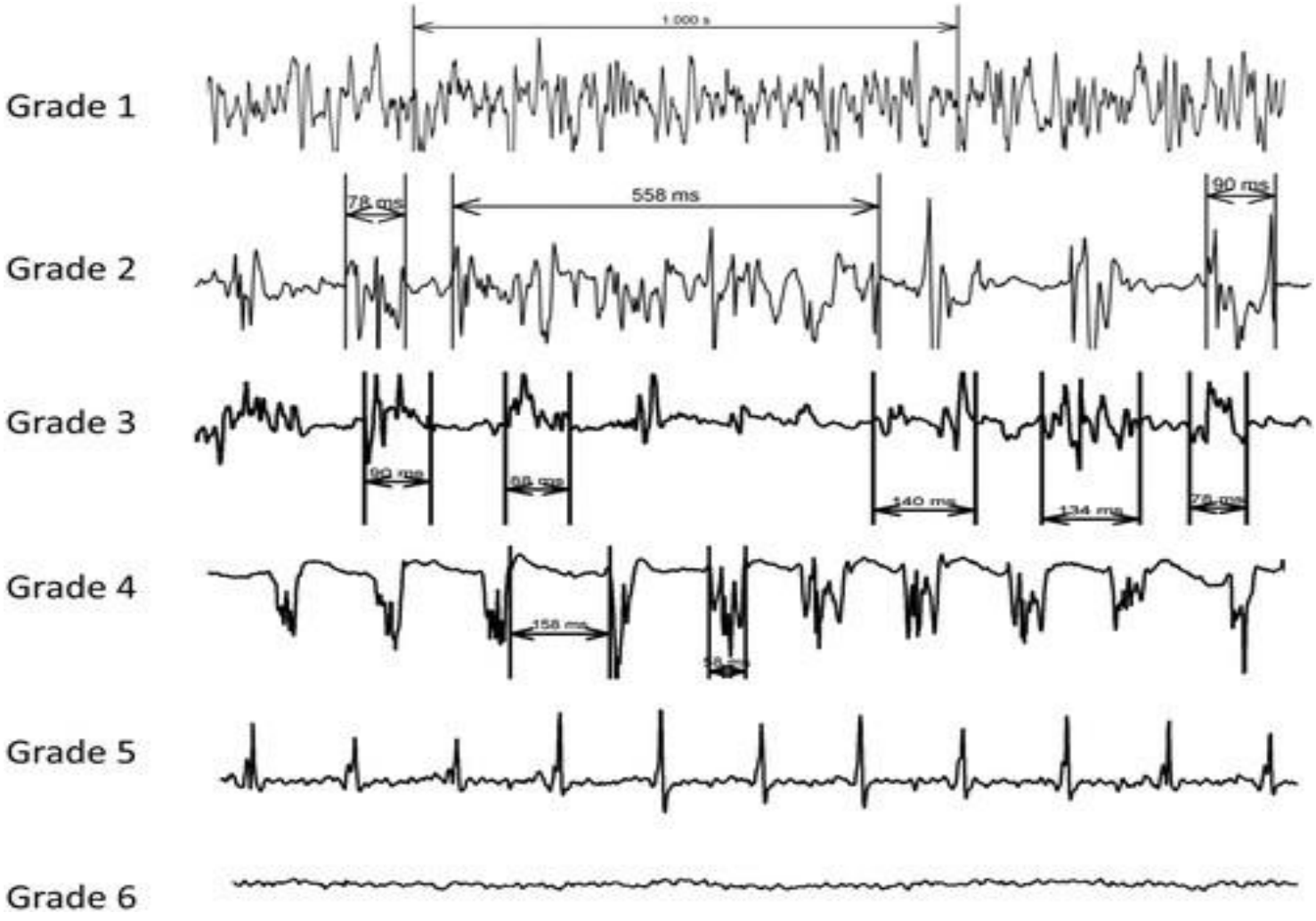


TV = tricuspid valve; L/RAA = left/right atrial appendage; SVC = superior vena cava; IVC = inferior vena cava; CT = crista terminalis; ER = eustacian ridge; L/RIAS = left/right interatrial septum; AVNRT = atrioventricular nodal reentrant tachycardia; L/RSPV = left/right superior pulmonary vein; L/RIPV = left/right inferior pulmonary vein; PW = posterior wall; CS = coronary sinus; MV = mitral valve; LOM = ligament of Marshall; LLAP = left lateral accessory pathway; PERS = persistent atrial fibrillation; LS PERS = long-standing persistent atrial fibrillation.

Santangeli P, et al. *Heart Rhythm*. 2017;(7):1087-1096.

Signal quality is important to assess if the signal is “early.”

Complex Appearing Signals in AF



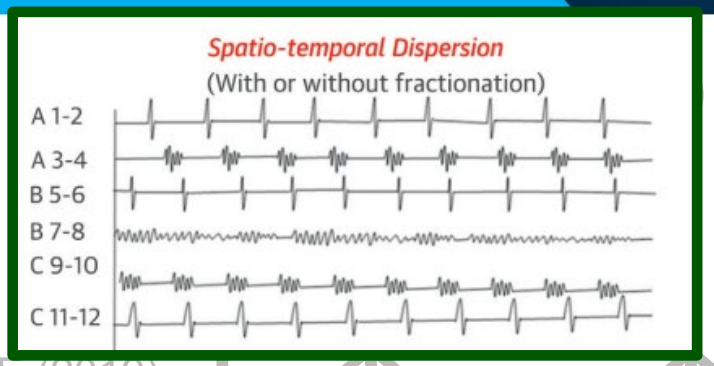
Roten L, et al. *Curr Cardiol Rev.* 2012;(4):327-346.

Targeting of Complex Appearing Signals for AF

K. Nademanee, J. McKenzie, E. Kosar, M. Schwab, B. Sunsaneewitayakul, T. Vasavakul, C. Khunnawat, T. Ngarmukos

A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate

J Am Coll Cardiol, 43 (2004), pp. 2044-2053



RF/hot balloons (2015-19)

2001)

Oral, et al. (Circ, 2007)
Deisenhofer, et al. + (JCE, 2007)

FIRE&ICE (2016)

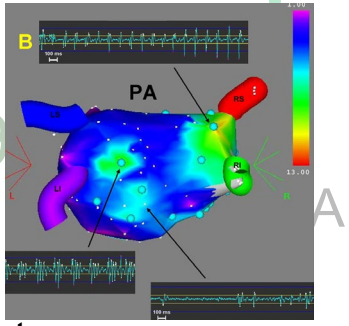
Laser balloon (2015)

CIRCA-DOSE (2019)

Seitz, Kalifa, et al. (2017)

1990s | 2000s | 2010s | 2020s

CFAE integration to EAM (2007)



EAM (1999

RFA (1987-1990)

AF Trial (2010)

RAAFT-2 (2014)

STAR-AF2 (2015)

FIRM/ECG (2014-16)

Verma, et al. (NEJM, 2015)

Cryo-FIRST (2021)

STOP AF First (2021)

EARLY-AF (2021)

CFAE = complex fractionated electrograms.

Nademanee K, et al. *J Am Coll Cardiol.* 2004;43(11):2044-2053. Oral H, et al. *Circulation.* 2007;115(20):2606-2612. Schmitt C, et al. *J Cardiovasc Electrophysiol.* 2007;18(10):1039-1046. Verma, A et al. *N Engl J Med.* 2015;372(19):1812-1822. Seitz J, et al. *J Am Coll Cardiol.* 2017;69(3):303-321.

Signal quality is important to assess if the signal is “complex” vs “simple.”

Mapping During Fibrillation: 1959-1990s

American Heart Journal
Volume 58, Issue 1, July 1959, Pages 59-70

Atrial Fibrillation as a Self-Sustaining Arrhythmia Independent of Focal Discharge

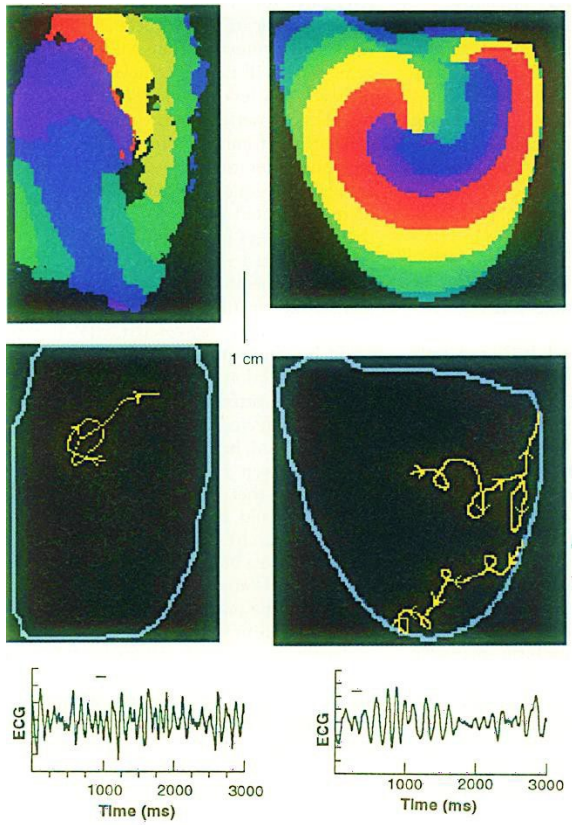
G. K. Moe, M.D., and J. A. Abildskov, M.D., Syracuse, N. Y.

"We may further conclude that **true fibrillation may be self-sustained and independent of whatever initiating agency**, provided the atria are large enough (as the adult human atria probably are)…"

Mechanisms of Cardiac Fibrillation

By R. A. Gray, J. Jalife, A. V. Panfilov, W. T. Baxter, C. Cabo, J. M. Davidenko, A. M. Pertsov, A. V. Panfilov, P. Hogeweg, A. T. Winfree
+ See all authors and affiliations

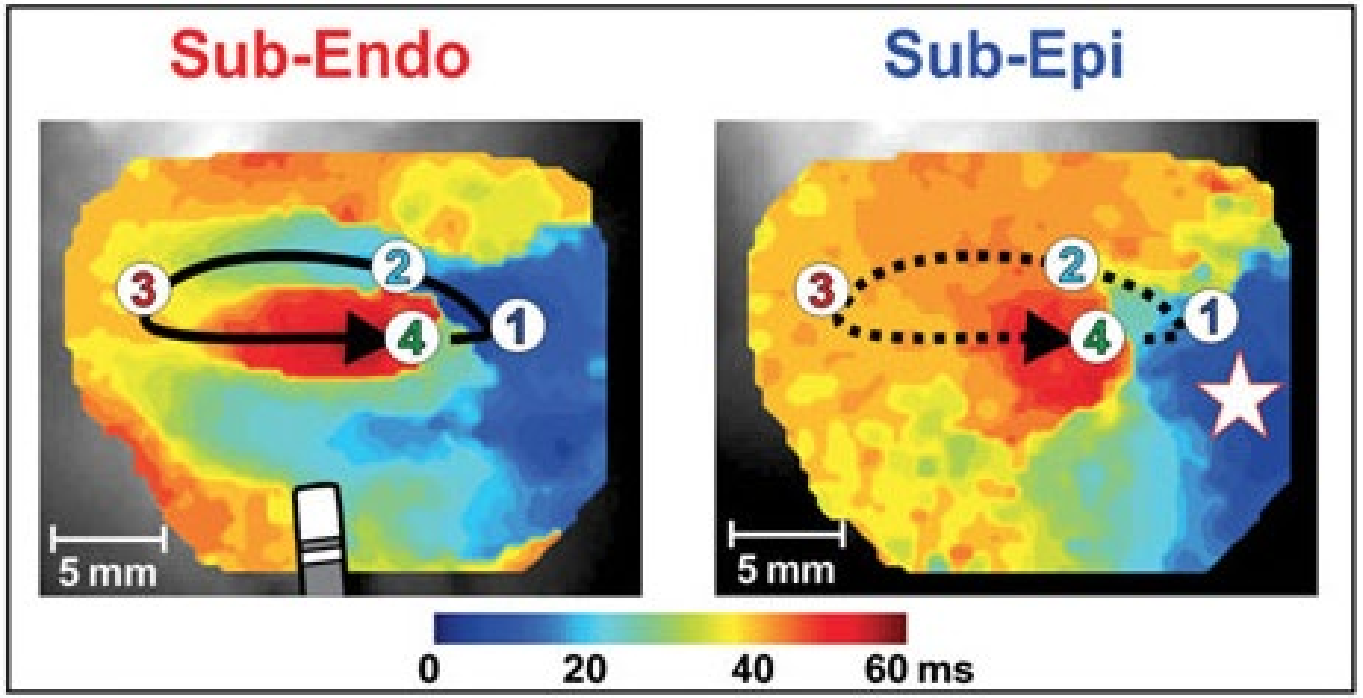
Science 17 Nov 1995:
Vol. 270, Issue 5239, pp. 1222
DOI: 10.1126/science.270.5239.1222



"…In 3 episodes of fibrillation, video of transmembrane potential demonstrated **single rapidly moving rotor** associated with **turbulent activity** as recorded by an **electrogram.**"

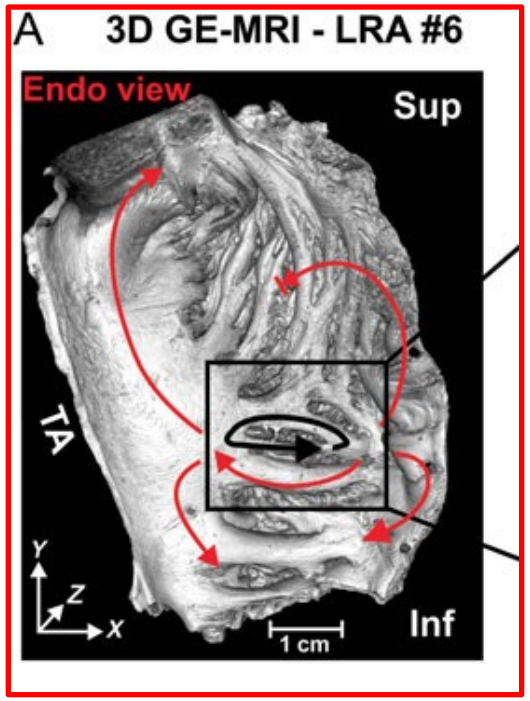
Moe GK, et al. *Am Heart J.* 1959;58(1):59-70. Gray RA, et al. *Science.* 1995;270(5239):1222-1223.

Mapping during Fibrillation: 2000s

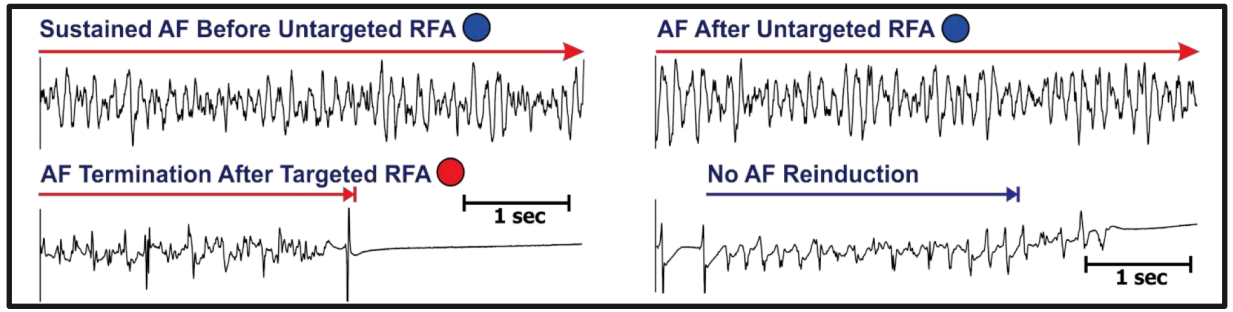


Stable endocardial foci, related to fibers, <u>micro-fibrosis</u> on 9T MRI)

Transient foci, variable on epicardium

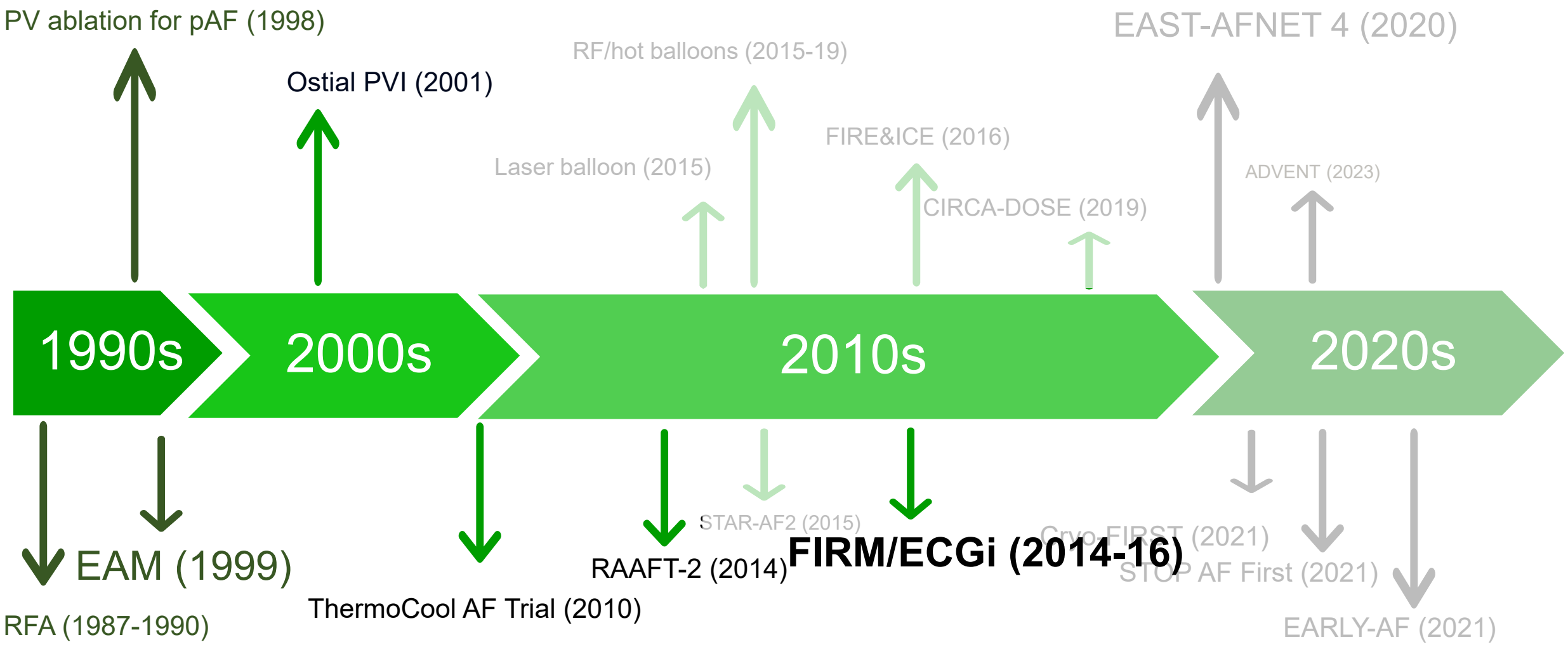


Endocardial ablation terminates AF



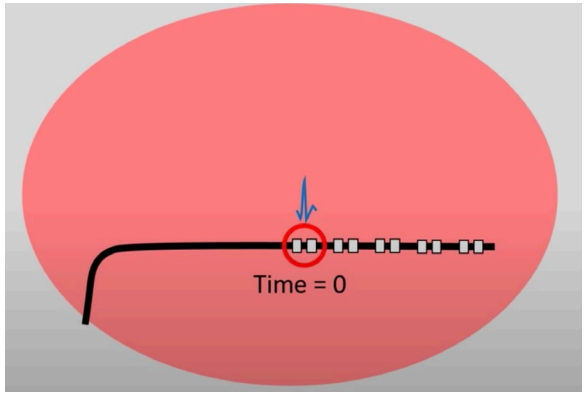
GE-MRI = gradient echo magnetic resonance imaging; LRA = left radial approach.
Fedorov, et al. *Eur Heart J.* 2015;36(35):2390-2401.

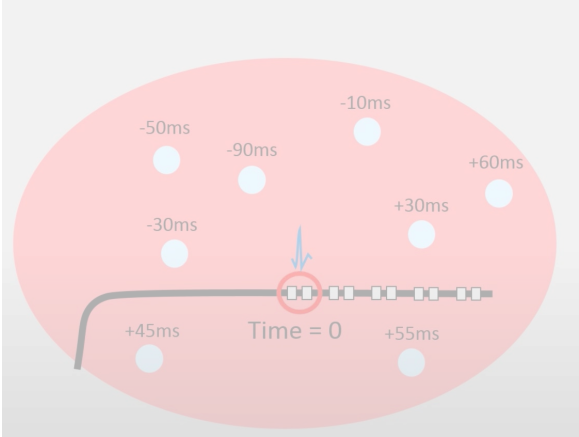
Mapping of Atrial Fibrillation

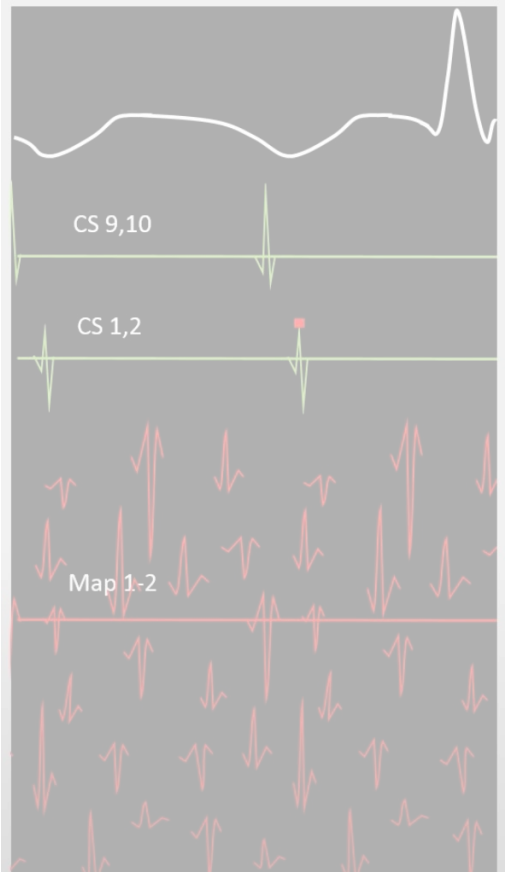


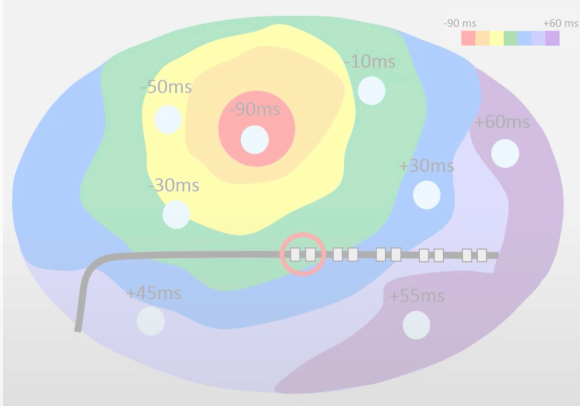
Mapping AF: Basics

Activation mapping basics:





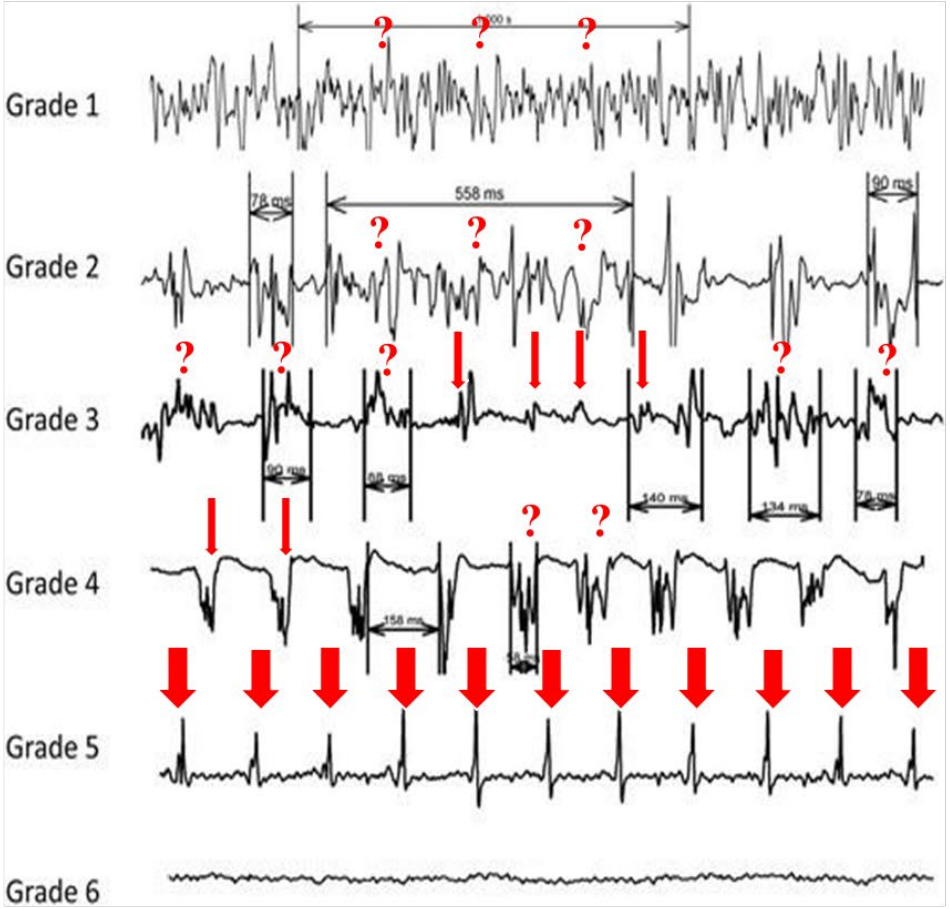




Cooper J. March 16, 2019. Accessed October 11, 2024. https://www.youtube.com/watch?v=CoRDSVjHQVU.

Challenges with Mapping AF

Complex signals make it difficult to determine local activation times.

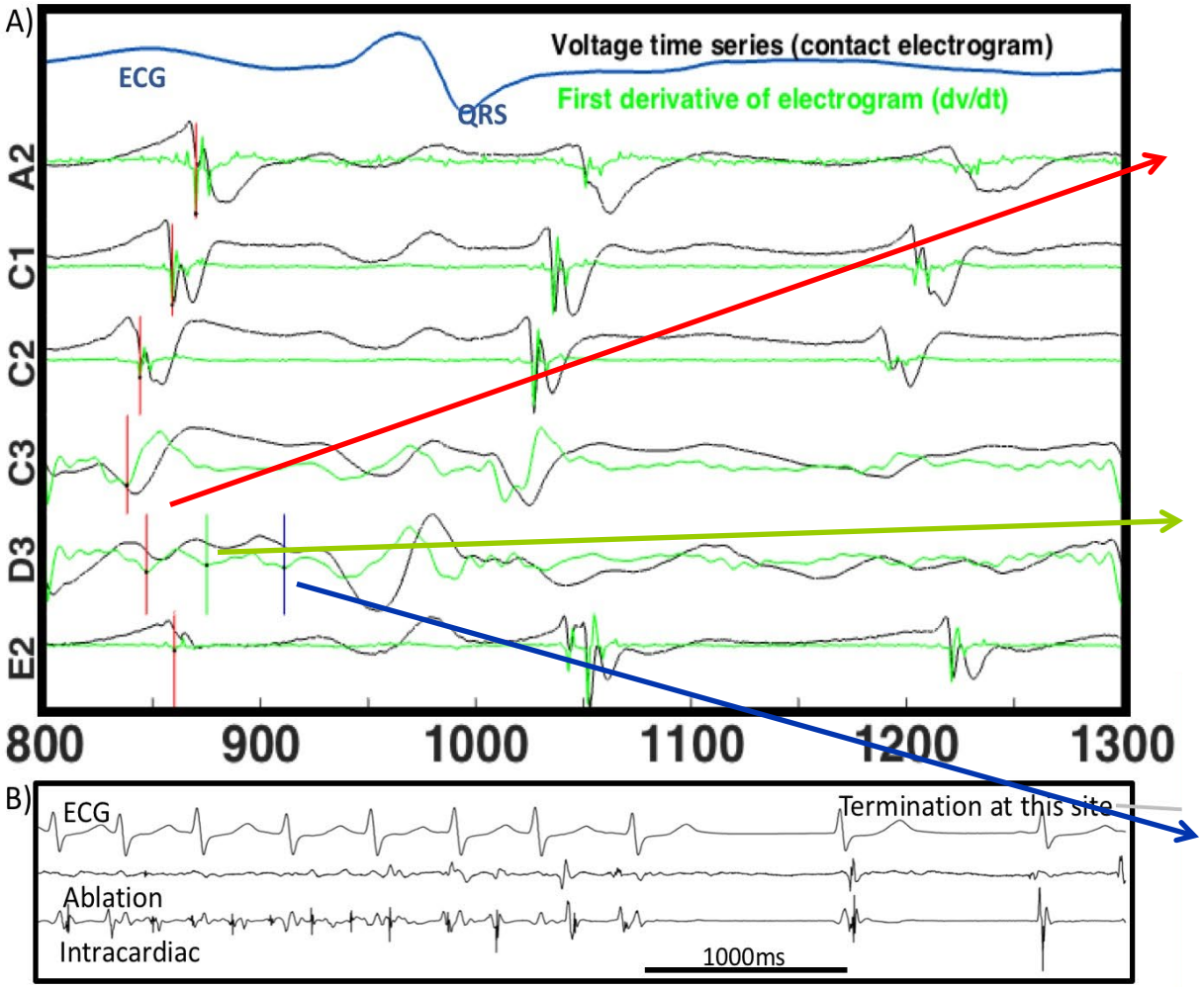


Reasons for fractionated bipolar electrograms: multidirectional wavefronts i.e., far-field, functional conduction blocks, scar etc.

Grade	Electrogram Criteria
1	Uninterrupted fractionated activity
	Fractionated activity (defined as continuous deflections without pause at the isoelectric line for ≥70 ms) occupying ≥70% of sample, and at least 1 uninterrupted episode of fractionated activity lasting ≥1 second
2	Interrupted fractionated activity
	Fractionated activity occupying ≥70% of sample
3	Intermittent fractionated activity
	Fractionated activity occupying 30–70% of sample
4	Complex electrograms
	Discrete electrograms (<70 ms) and complex (≥5 direction changes), with any fractionated activity occupying <30% of sample (otherwise grade 3)
5	Normal electrogram
	Discrete electrograms (<70 ms) and simple (≤4 direction changes)
6	Scar
	No discernible deflections

Hunter RJ, et al. *Circ Arrhythm Electrophysiol.* 2011;4(5):622-629.

Mapping AF: Problems with Unipolar Signals

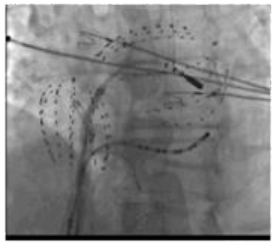


Zaman JAB, et al. *Circ Arrhythm Electrophysiol*. 2018;11(1):e005258.

Approaches to Mapping AF

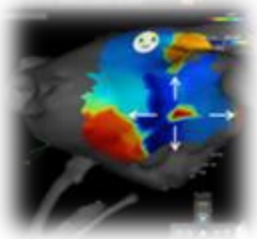
Panaromic Contact Mapping

- FIRM
- Ablamap®



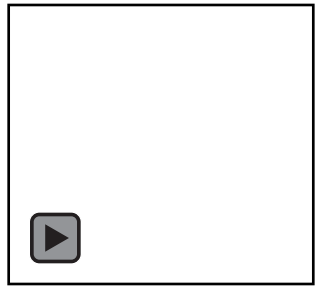
Sequential Contact Mapping

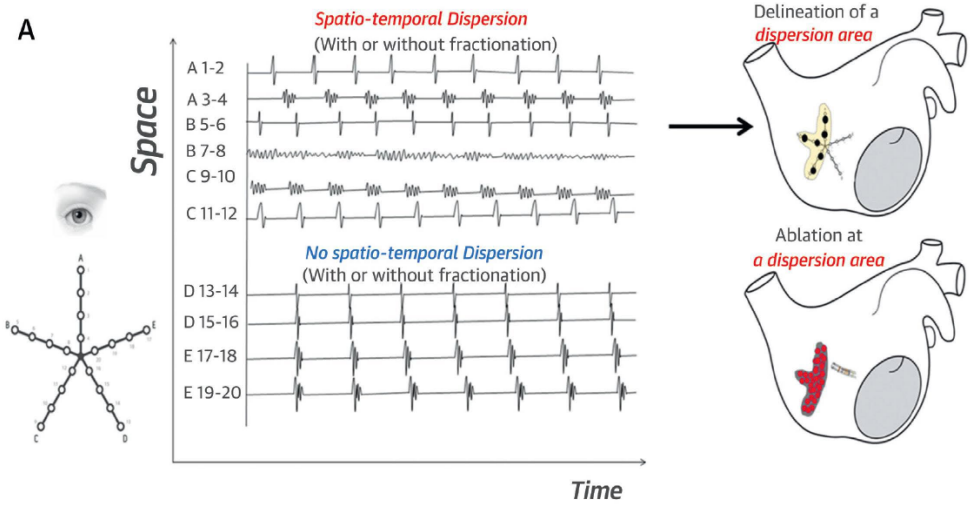
- CARTOFINDER™
- AF-Xplorer™ (EGM dispersion)
- STAR
- RADAR



Non-Contact Mapping

- AcQMap®
- ECGi





EGM = electrogram; STAR = stochastic trajectory analysis of ranked signals; RADAR = Real-Time Electrogram Analysis for Drivers of Atrial Fibrillation.

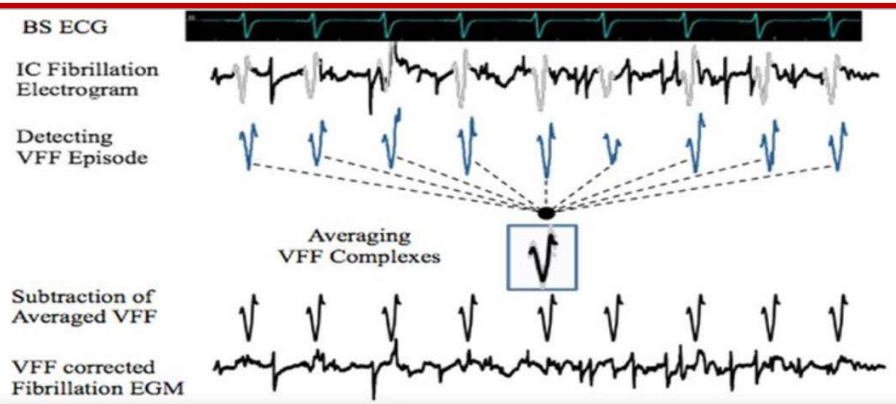
Seitz J, et al. *J Am Coll Cardiol*. 2017;69(3):303-321.

Mapping Technique	AF Type Mapped	Number of Ablation Targets	Atrial Location	Source Characterisation	Acute Termination Percentage	Freedom from AF at 12 Months, with/ without PVI
Panoramic Contact Mapping						
FIRM (RhythmView)[10,62,63]	Paroxysmal, persistent and long standing persistent	3–5	LA 70%	Stable rotations 76%, rces 24%[10]	56% (60% to sinus)[10] RA in 22%[62] In meta-analyses 27–53% (sinus or AT)	Meta-analysis: 72.5%[7] Persistent AF RCT: 77.7% (FIRM + PVI subgroup)[25]
Electrographic flow mapping (Ablacon)[35,36]	Persistent AF	4–6	RA 30% PV 40%	al 51%, focal 49%	100% RA in 10%	Pending
Sequential Contact Mapping						
CARTOFINDER (Biosense Webster)[37,38,42]	Persistent and long standing persistent	1–3	LA 63% RA 27% Non-PV 79%[64]	Rotational activity 70%, focal activations 30–100%[38,42]	63% (58% to AT)[42] 15% (all sinus)[64]	71%[38] 70%[64]
Spatiotemporal dispersion (Volta Medical)[43]	Persistent AF	4–		of micro-	95% (85% to AT)	85% without PVI (1.4 procedures, at 18 months)
STAR[45]	Persistent AF	2–3 (p	LA 95% RA 5%	Early sites of activation	29% (75% to AT)	80% (AT/AF at 18 months)
RADAR (CardioNXT) [46]	Persistent AF Longstanding AF	3.9 ± 1.3 (LA) 2.5 ± 1.4 (RA)	Inconsistent RA mapping	Rotational (73%) and focal sites	55%	74% AF freedom at 13 months (on/off drugs)
Non-contact Mapping						
Charge/dipole density (Acutus)[48,65]	Persistent AF	2–3	RA not mapped LA anterior 70%	Localised irregular activity Localised rotational ivity	50–60%	73%[65]
Body surface, ECGI (CardioInsight, EP Solutions)[13,51,66]	Persistent and long standing persistent	3–	RA 30% LPV/LAA 82%[13] LA 53% RA 27% Septum 20%[51]	s 80% Focal breakthrough 20%[13]	80% (66% to AT)[13] 64% (79% to AT) (PVs 37%, LA 35%, RA in 28%)[51]	85%[13] 78%[51]

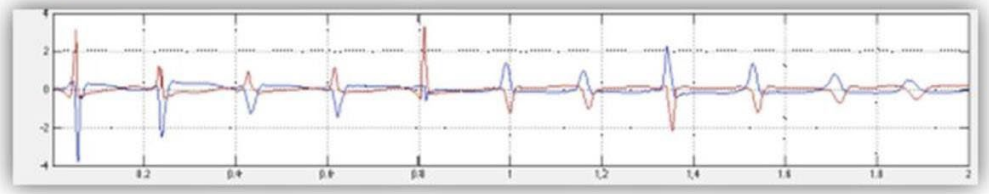
Zaman JAB, et al. *Arrhythm Electrophysiol Rev*. 2022:11:e08.

CARTOFINDER

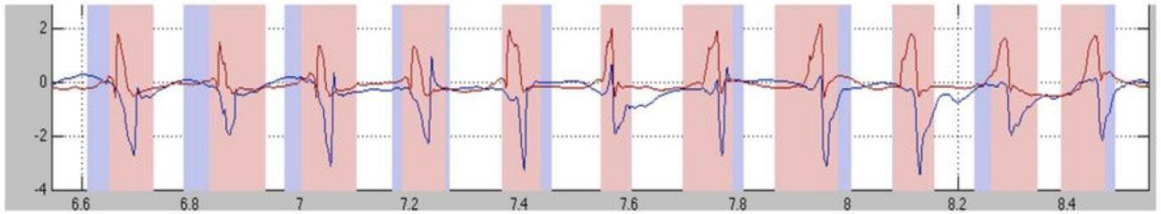
Subtraction of far-field ventricular signal



Calculate bipolar electrogram for each BC electrode

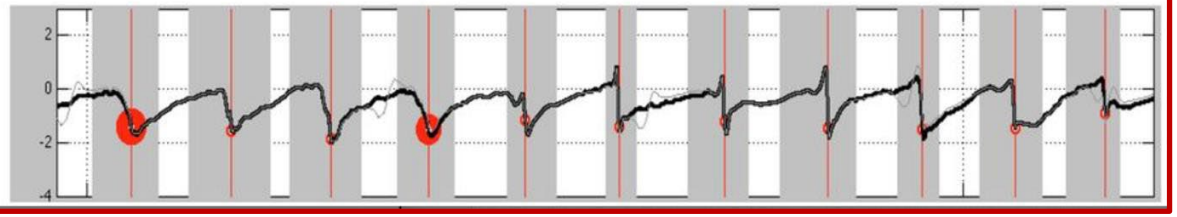


Determine bipolar electrogram windows



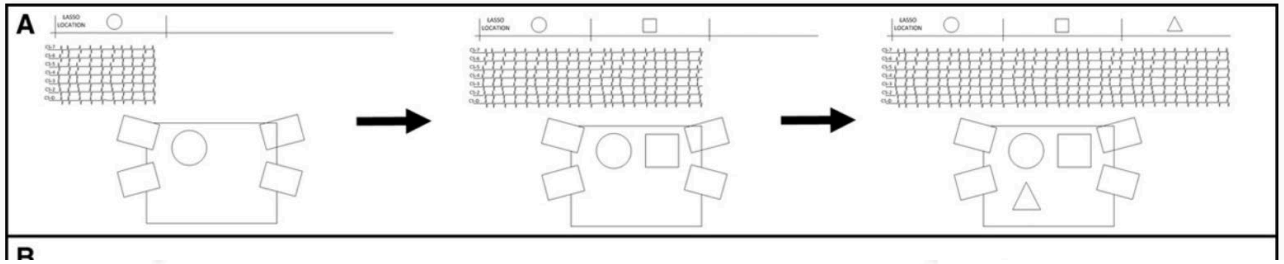
Apply bipolar windowing on unipolar signals

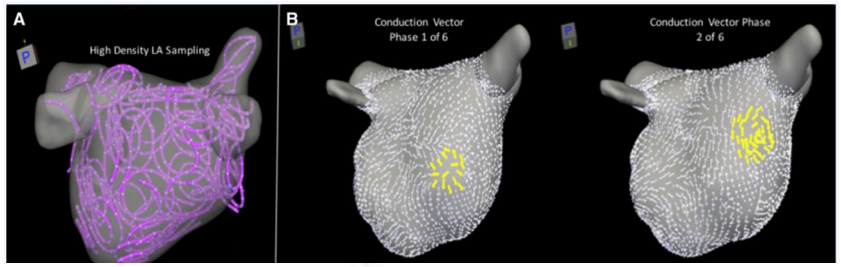
Performing a wavelet analysis to identify annotations

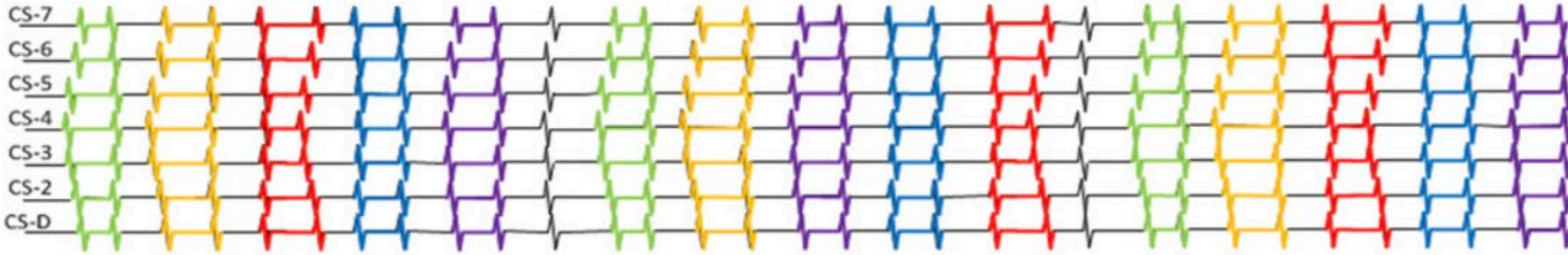


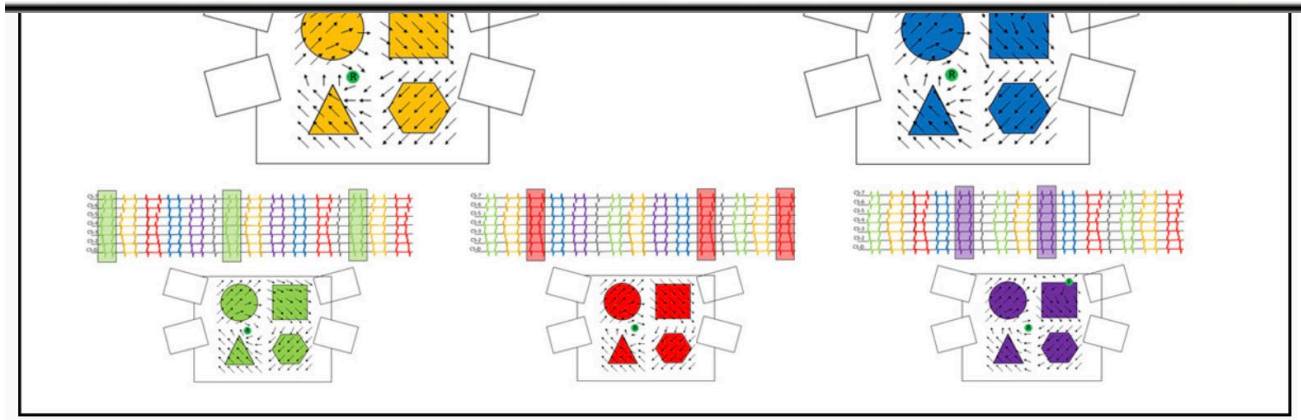
Daoud EG, et al. *JACC Clin Electrophysiol*. 2017;3(3):207-216.

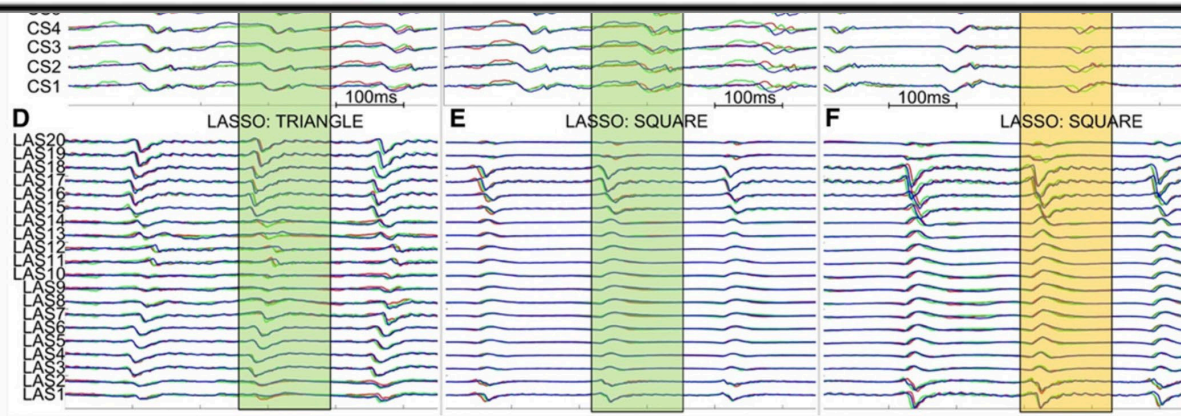
RADAR











Choudry S, et al. *Circ Arrhythm Electrophysiol.* 2020;13(1):e007825.

RADAR

RADAR: High Resolution Mapping and Ablation of Persistent and Longstanding Persistent AF

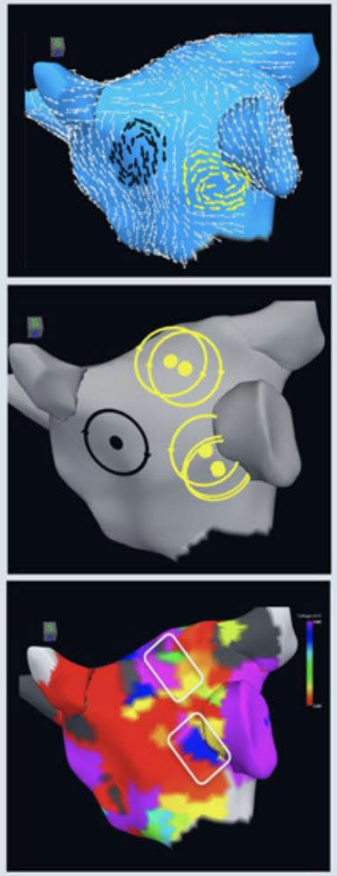
High Resolution **Conduction Vector** Maps During AF

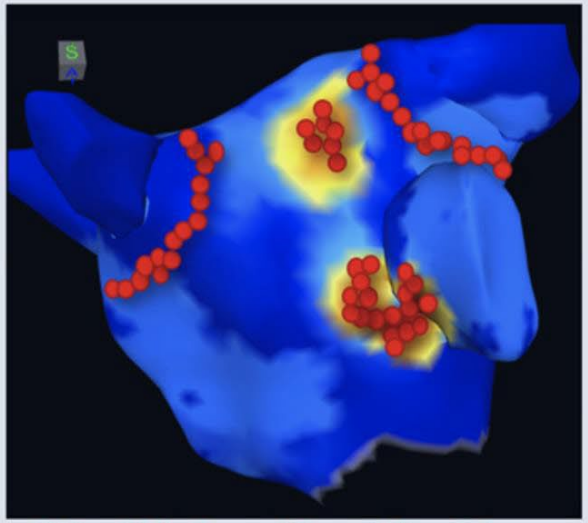
↓

Repetitive Driver Regions Highlighted

↓

Voltage Maps Highlighting Transitions from Low to High Voltage





PVI + Ablation of Repetitive Drivers In Voltage Transition Zones

64 pts across U.S. centers

- LA size: 5.4 ± 1 cm
- BMI: 31.7 ± 6 kg/m^2
- 13.4 ± 35 months of continuous AF
- Failed Prior Ablations in 41%

OUTCOMES

13 Month Follow-Up

74%

Single procedure AF-Free On or Off AADs

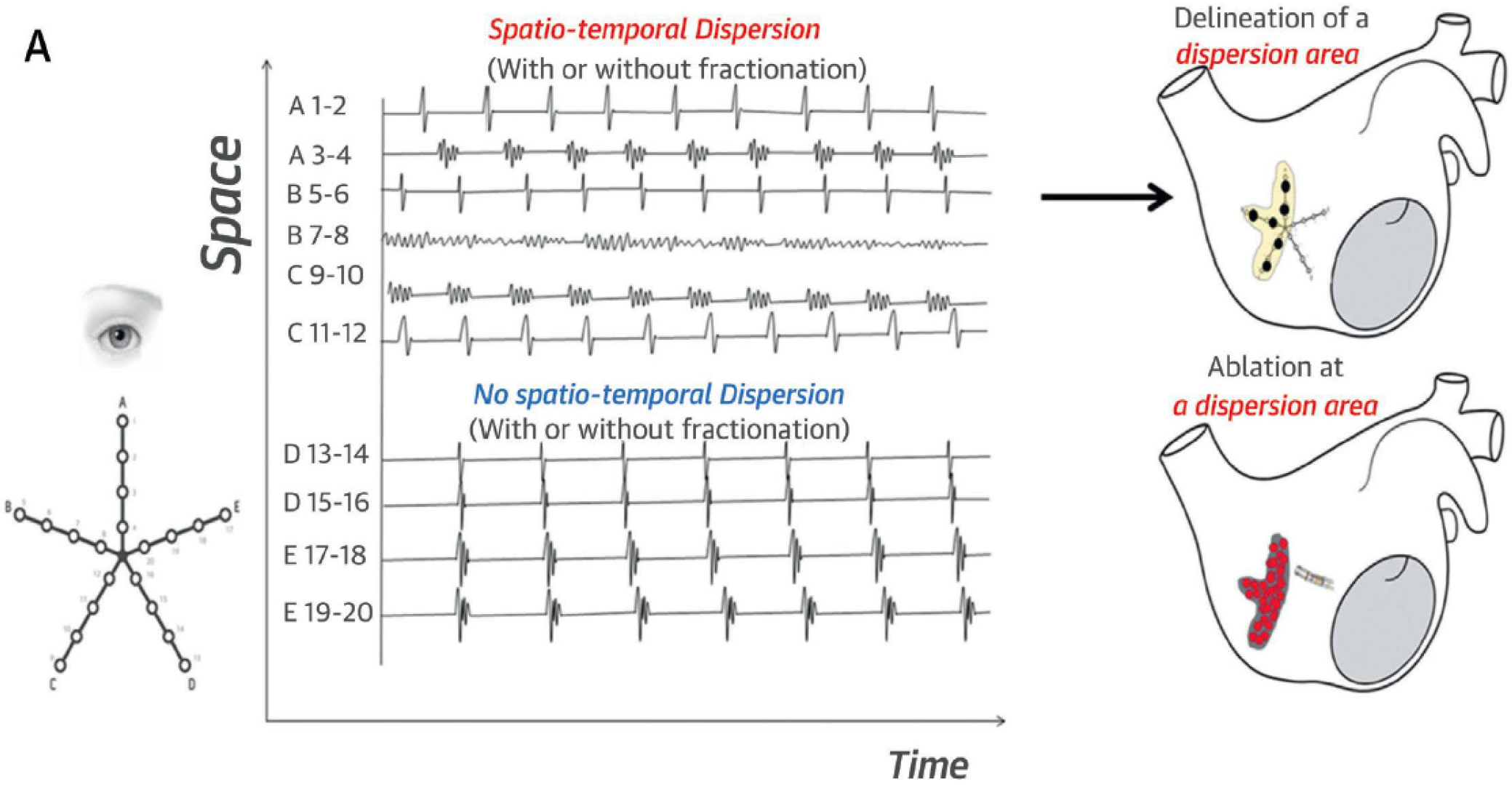
Patients who achieved acute termination of AF during the ablation procedure had:

- **82% Freedom From AF**
- **74% Freedom from AF/AT/AFL**

AADs = anti-arrhythmic drugs; AT = atrial tachycardia; AFL = atrial flutter.

Choudry S, et al. *Circ Arrhythm Electrophysiol.* 2020;13(1):e007825.

EGM Dispersion



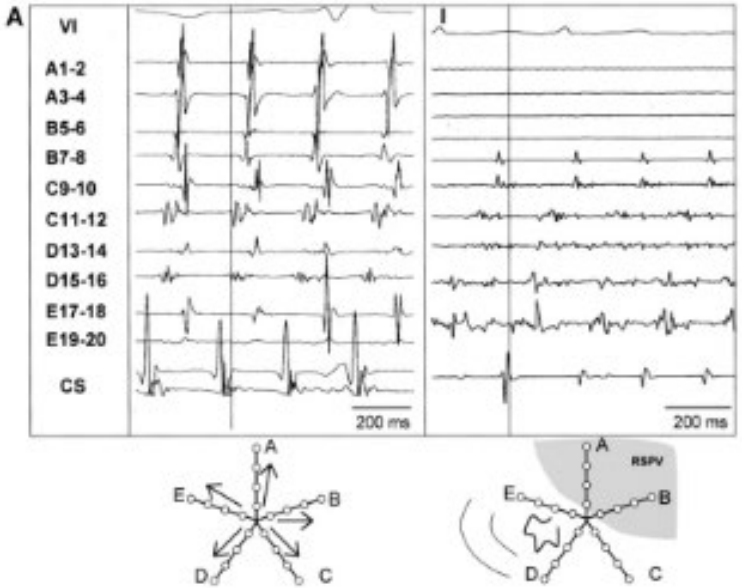
Haïssaguerre M, et al. *Circulation.* 2006;113(5):616-625. Kalifa J, et al. *Circulation*. 2006;113(5):626-633. Narayan SM, et al. *Heart Rhythm*. 2011;8(2):244-253. Seitz J, et al. *J Am Coll Cardiol*. 2017;69(3):303-321.

Spatio-Temporal Dispersion of EGMs: Mechanistic Meaning?

ARRHYTHMIA/ELECTROPHYSIOLOGY

Localized Sources Maintaining Atrial Fibrillation Organized by Prior Ablation

Michel Haïssaguerre, MD, Mélèze Hocini, MD, Prashanthan Sanders, MBBS, PhD, Yoshihide Takahashi, MD, Martin Rotter, MD, Frederic Sacher, MD, Thomas Rostock, MD, Li-Fern Hsu, MBBS, Anders Jonsson, MD, Mark D. O'Neill, MBChB, DPhil, Pierre Bordachar, MD, Sylvain Reuter, MD, Raymond Roudaut, MD, Jacques Clémenty, MD, and Pierre Jaïs, MD

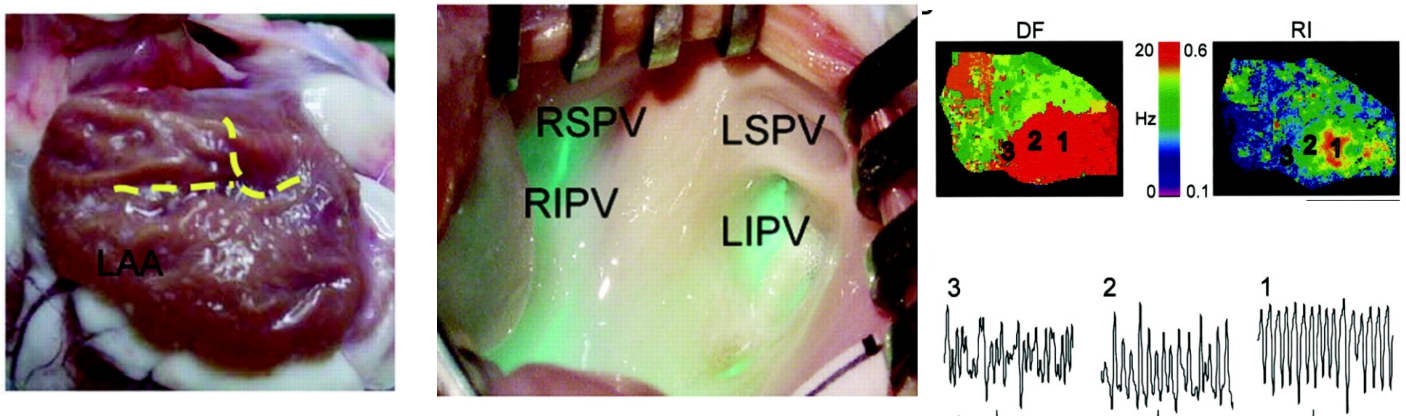


ARRHYTHMIA/ELECTROPHYSIOLOGY

Mechanisms of Wave Fractionation at Boundaries of High-Frequency Excitation in the Posterior Left Atrium of the Isolated Sheep Heart During Atrial Fibrillation

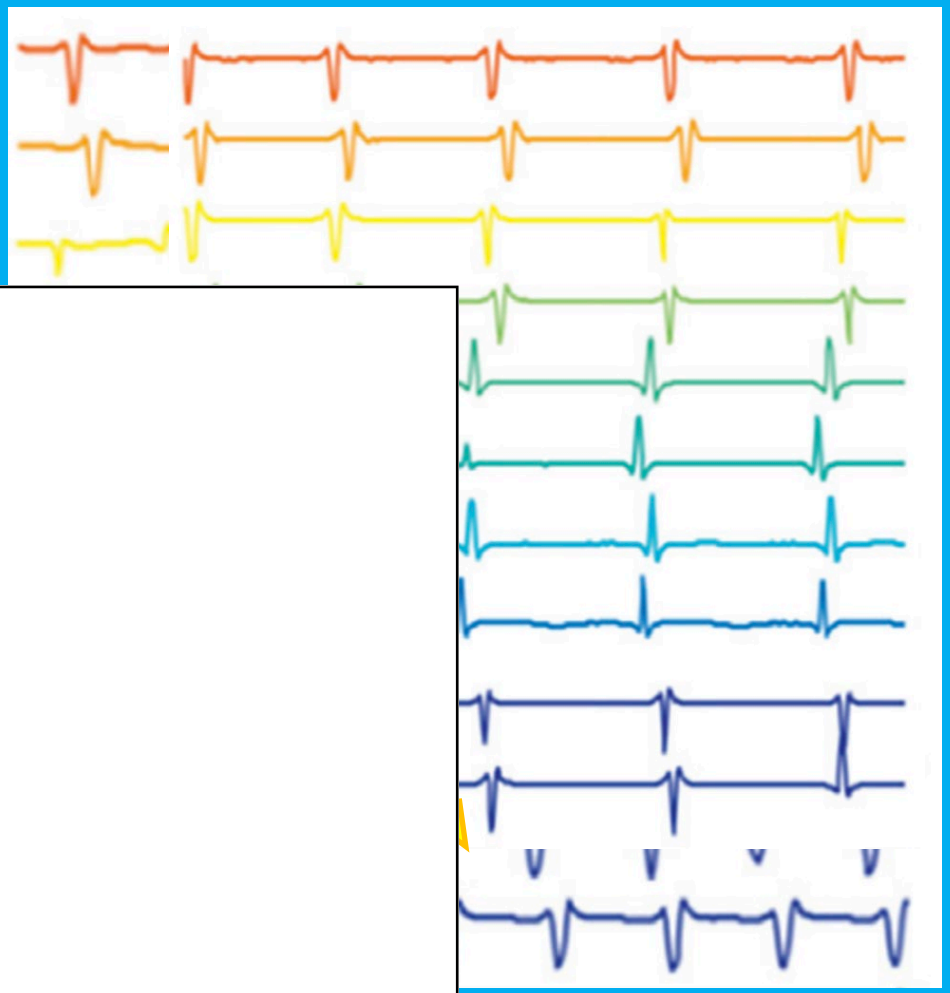
Jérôme Kalifa, MD, Kazuhiko Tanaka, MD, Alexey V. Zaitsev, PhD, Mark Warren, PhD, Ravi Vaidyanathan, MS, David Auerbach, MS, Sandeep Pandit, PhD, Karen L. Vikstrom, PhD, Robert Ploutz-Snyder, PhD, Arkadzi Talkachou, MS, Felipe Atienza, MD, PhD, Gérard Guiraudon, MD, José Jalife, MD, and Omer Berenfeld, PhD

"…Sites consistent with localized AF "drivers" in optically mapped sheep AF also **lie adjacent to fractionated electrograms**"



Haïssaguerre M, et al. *Circulation.* 2006;113(5):616-625. Kalifa J, et al. *Circulation*. 2006;113(5):626-633. Narayan SM, et al. *Heart Rhythm*. 2011;8(2):244-253. Seitz J, et al. *J Am Coll Cardiol*. 2017;69(3):303-321.

Spatio-Temporal Dispersion of EGMs

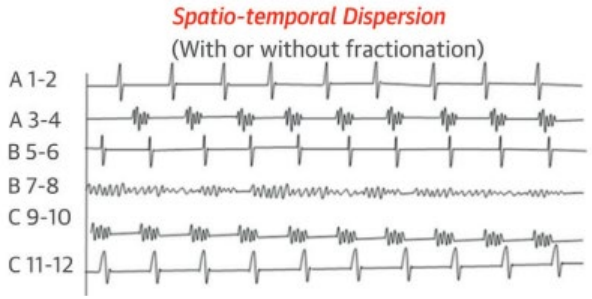


Haïssaguerre M, et al. *Circulation*. 2006;113(5):616-625. Kalifa J, et al. *Circulation*. 2006;113(5):626-633. Narayan SM, et al. *Heart Rhythm*. 2011;8(2):244-253. Seitz J, et al. *J Am Coll Cardiol*. 2017;69(3):303-321.

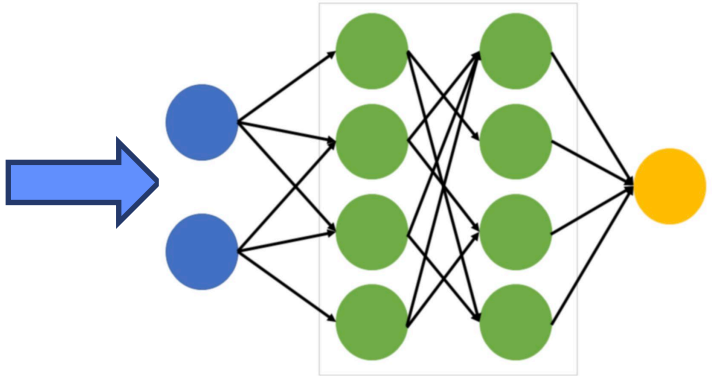
Signal quality is important to be able to annotate onset/peak of a signal which is key to most mapping algorithms.

Are signals important for advanced models?

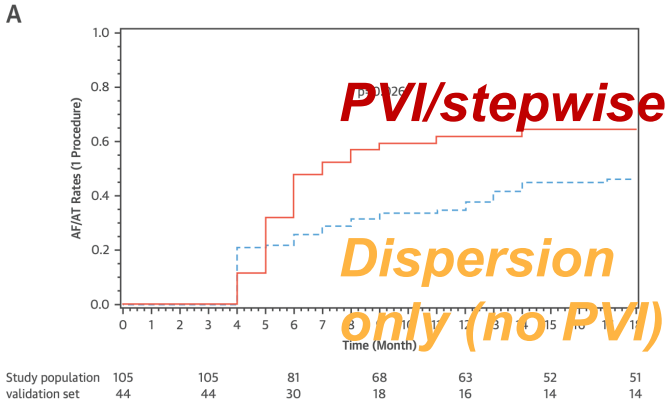
Machine Learning Model to Annotate EGMs with Dispersion

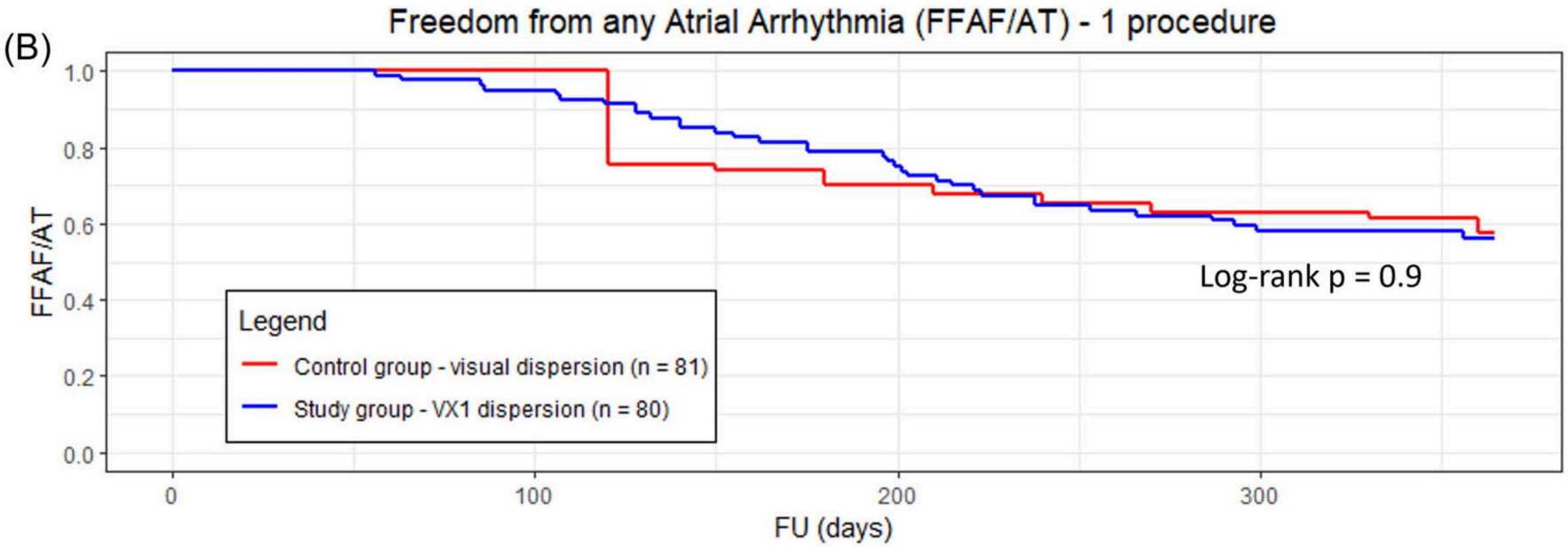


Raw EGMs
EGM features



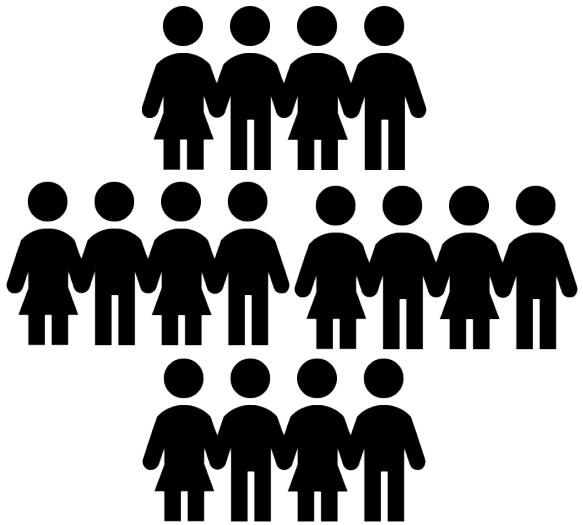
Output labels:
Dispersion
No dispersion





Seitz J, et al. *J Am Coll Cardiol*. 2017;69(3):303-321. Seitz J, et al. *J Cardiovasc Electrophysiol*. 2022;33(11):2250-2260.

ML Predictive Models by Cardiac Signals to Predict Responders to Catheter Ablation of AF

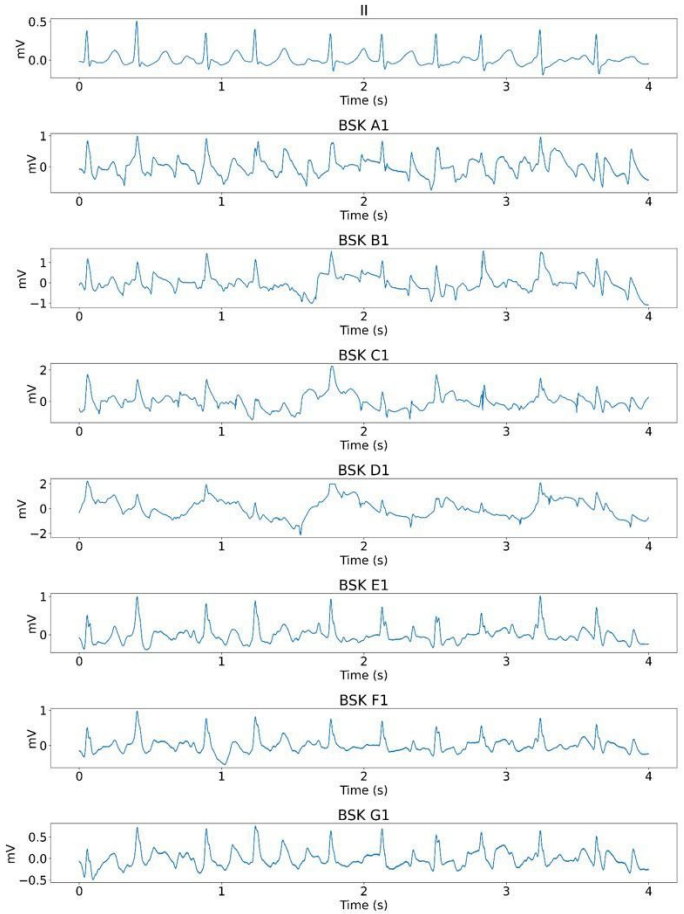


N=156 patients who underwent catheter ablation in 2015-2017

Catheter ablation

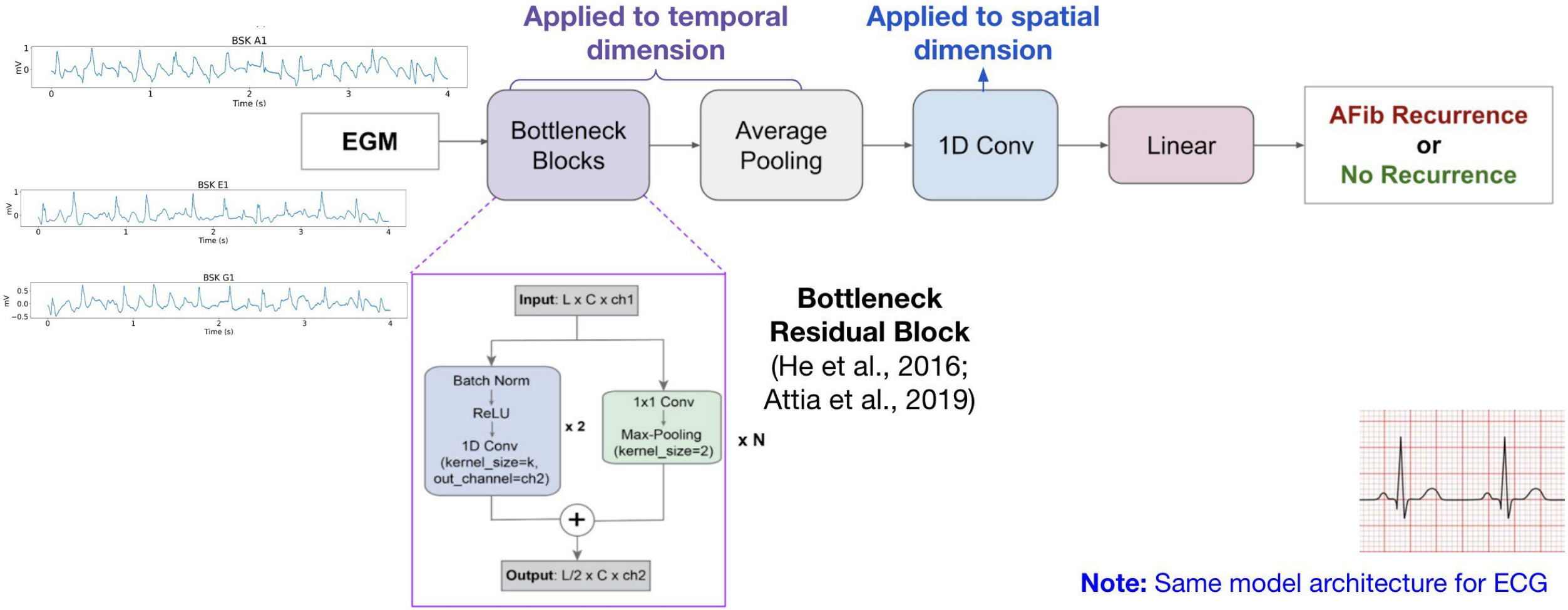
12-lead ECG in sinus and panoramic **unipolar EGMs in AF** available for analysis

Stratified, patient-wise 10-fold cross-validation



Tang S, et al. *Circ Arrhythm Electrophysiol.* 2022;15(8):e010850.

ML Model Architecture for EGM and ECG Analysis

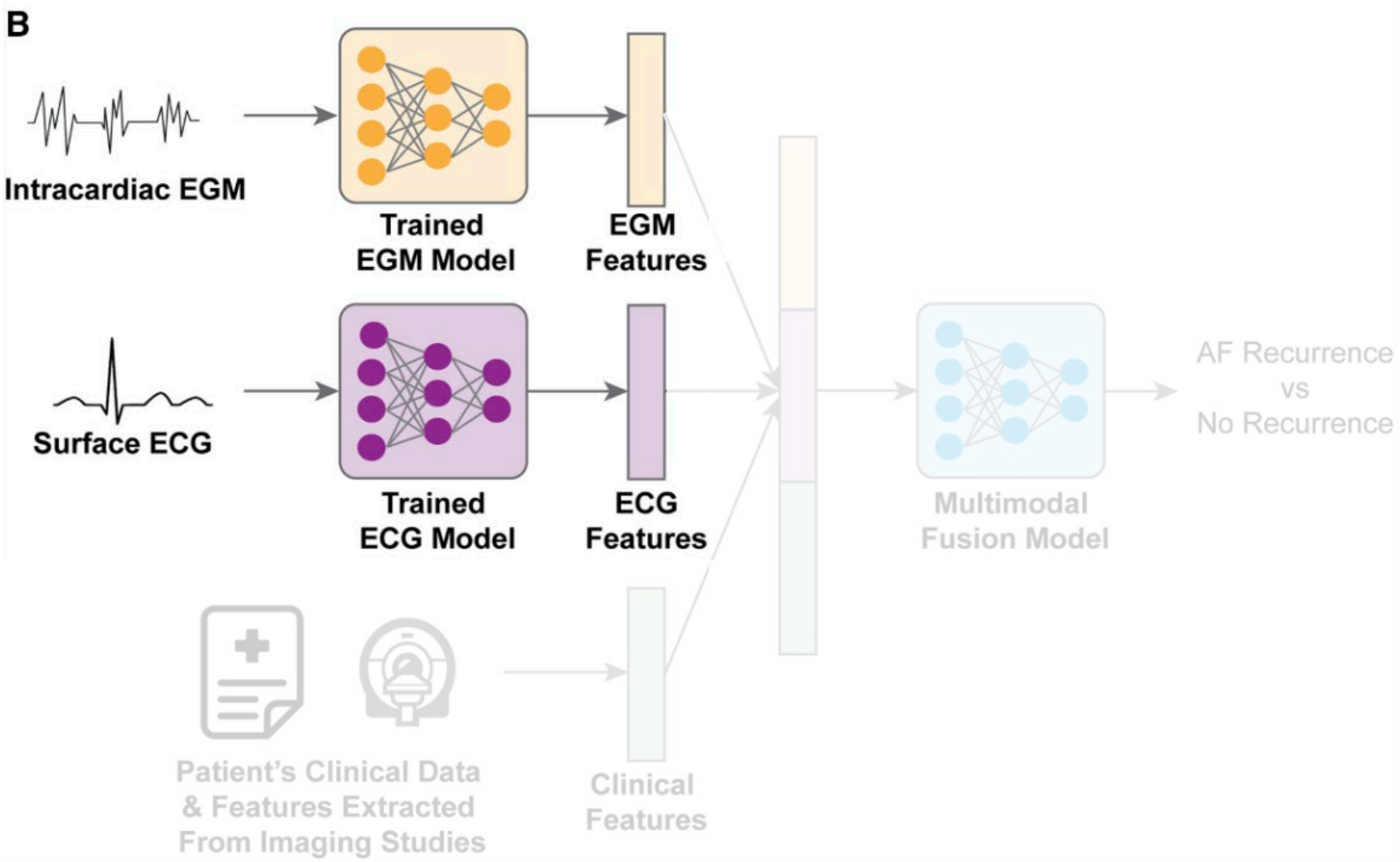


Bottleneck Residual Block
(He et al., 2016; Attia et al., 2019)

Note: Same model architecture for ECG

Tang S, et al. *Circ Arrhythm Electrophysiol.* 2022;15(8):e010850.

ML Model Architecture for EGM and ECG Analysis



Tang S, et al. *Circ Arrhythm Electrophysiol.* 2022;15(8):e010850.

Results of the One-Year AF Recurrence Prediction

11.7 points improvement in AUROC

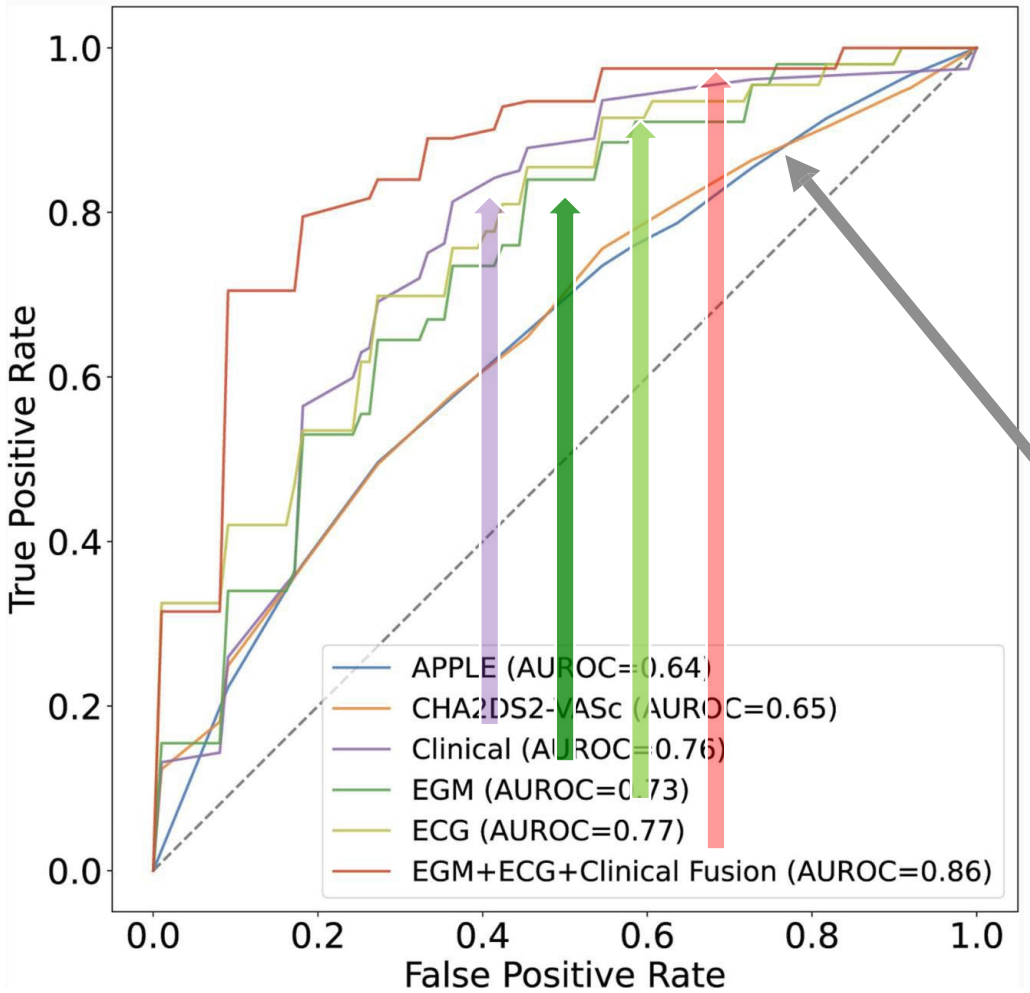
	AUROC	Sensitivity	Specificity	Accuracy	F1-Score
APPLE	0.64 ± 0.13	**0.92 ± 0.14**	0.35 ± 0.33	0.50 ± 0.21	0.53 ± 0.11
CHA2DS2-VASc	0.65 ± 0.13	0.91 ± 0.16	0.43 ± 0.36	0.56 ± 0.23	0.57 ± 0.12
CNN (EGM)	0.73 ± 0.11	0.89 ± 0.12	0.63 ± 0.13	0.70 ± 0.10	0.63 ± 0.09
CNN (ECG)	0.77 ± 0.12	0.81 ± 0.18	0.77 ± 0.18	0.78 ± 0.11	0.68 ± 0.11
Fusion of EGM, ECG & Clinical Data	**0.86 ± 0.08**	0.87 ± 0.20	**0.87 ± 0.12**	**0.87 ± 0.08**	**0.78 ± 0.11**

9.2 points improvement in AUROC

AUROC = area under the receiver operating characteristic curve; APPLE = age > 65 years, persistent AF, impaired estimated glomerular filtration rate (eGFR) (< 60 ml/min/1.73 m2), left atrial (LA) diameter ≥ 43 mm, ejection fraction (EF) < 50%; CNN = convolutional neural network; CHA2DS2-VASc = congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or TIA or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category.

Tang S, et al. *Circ Arrhythm Electrophysiol.* 2022;15(8):e010850.

Receiver Operating Characteristics (ROC) Curves of the Clinical Feature-Based Models, Signal-Based Models, and the Fusion Model



Existing clinical scores:
CHADS2Va2sc
APPLE

Tang S, et al. *Circ Arrhythm Electrophysiol.* 2022;15(8):e010850.

Summary

- AF treatment, whether based on mapping of PACs that trigger AF, mapping of complexity of the electrograms, or mapping of fibrillatory conduction patterns during AF, is highly dependent on the quality and clarity of the signals recorded
- Signals (surface/intracardiac) are relevant to advanced signal processing models using machine learning

PAC = premature atrial contraction.

Thank You!

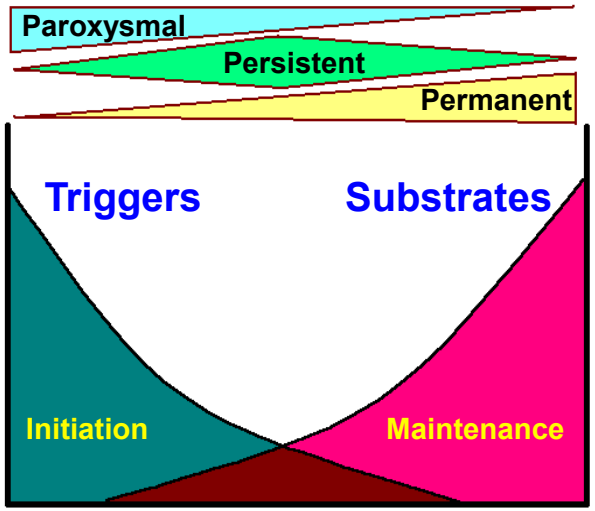
tina4@stanford.edu

@TinaBaykaner

Practical Application of Artificial Intelligence and Machine Learning in Cardiac Electrophysiology

John D. Hummel, MD, FHRS, FACC
Professor of Internal Medicine
Ohio State University
Columbus, Ohio

Spectrum of AF



AF begets AF

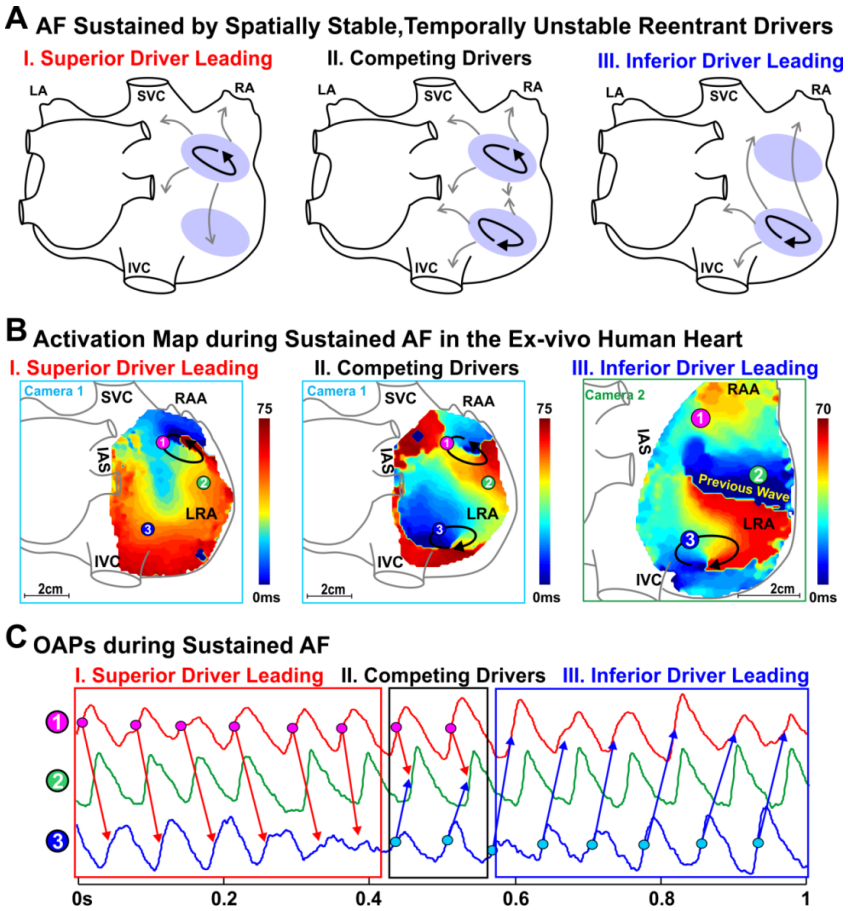
- ***Electrical* remodeling**
  - ↓Atrial ERP, ↑spatial heterogeneity of ERP, ↓normal ERP rate adaptation
  - Slow conduction
    - Modulation of Na channels, gap junctions (connexins), altered tissue structure
- ***Structural* remodeling**
  - Macro-atrial dilation
  - Micro-atrial fibrosis

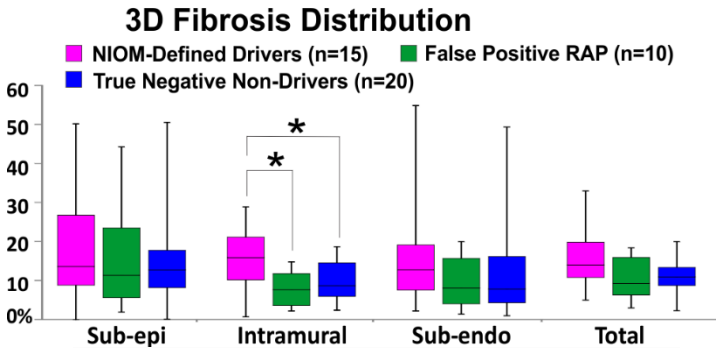
- Unmet challenge in AF ablation
  - Accurately identifying extra-PV drivers, eliminating them
    - Contrasting literature on usefulness of mapping systems for extra-PV drivers
    - Higher percentage of non-PV drivers in redo AF ablation and persistent AF compared to de novo PAF

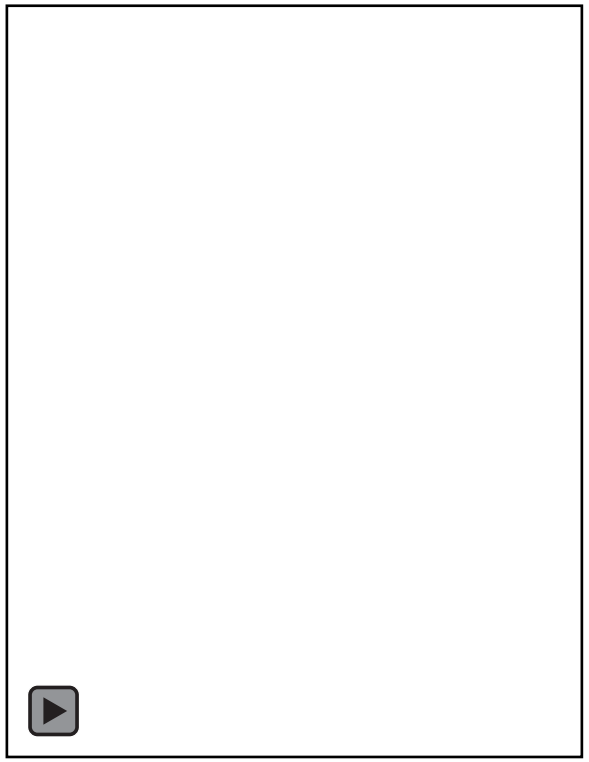
ERP = effective refractory period.
Kumar S, et al. *Prog Biphys Mol Biol*. 2012;110(2-3):278-294.

Spatially Stable but Temporally Competing Reentrant Drivers During Sustained AF

Panoramic Optical Mapping with Four High-Resolution CMOS Cameras (40,000 pixels, 0.3-1 mm^2)



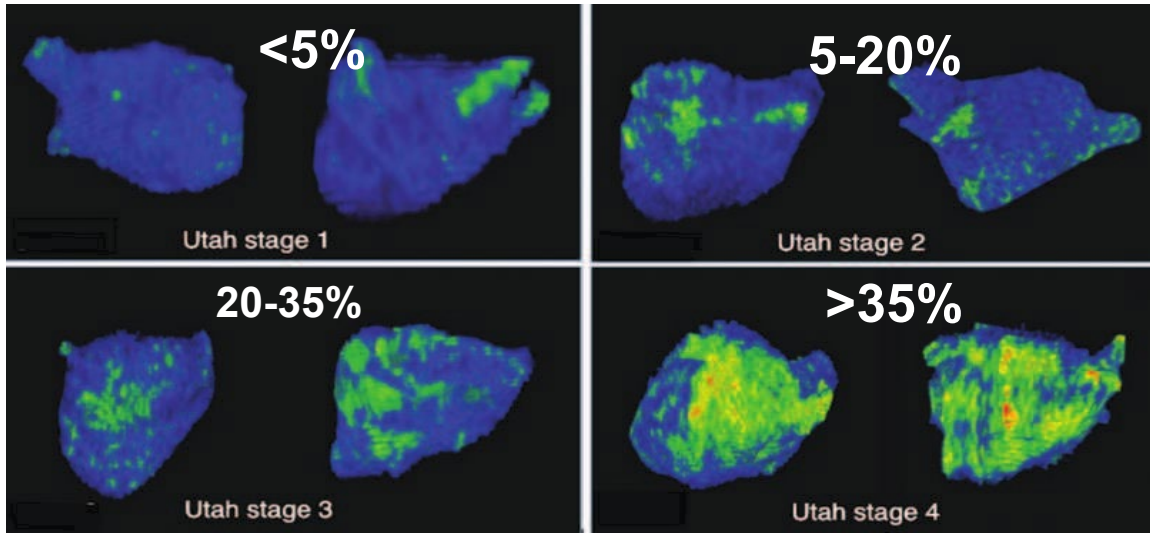


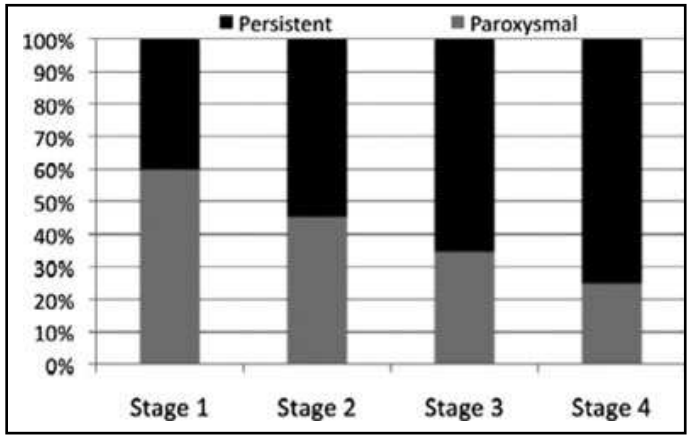


CMOS = complementary metal oxide semiconductor; OAP = optical action potential; NIOM = near-infrared optical mapping; RAP = right atrial pressure; CE-MRI = contrast-enhanced MRI.

Modified from: Li N, et al. *Circulation.* 2016;134(6):486-498. Hansen BJ, et al. *JACC Clin Electrophysiol*. 2018;4(12):1501-1515.

Atrial Fibrosis and AF Phenotype Delayed Enhancement MRI

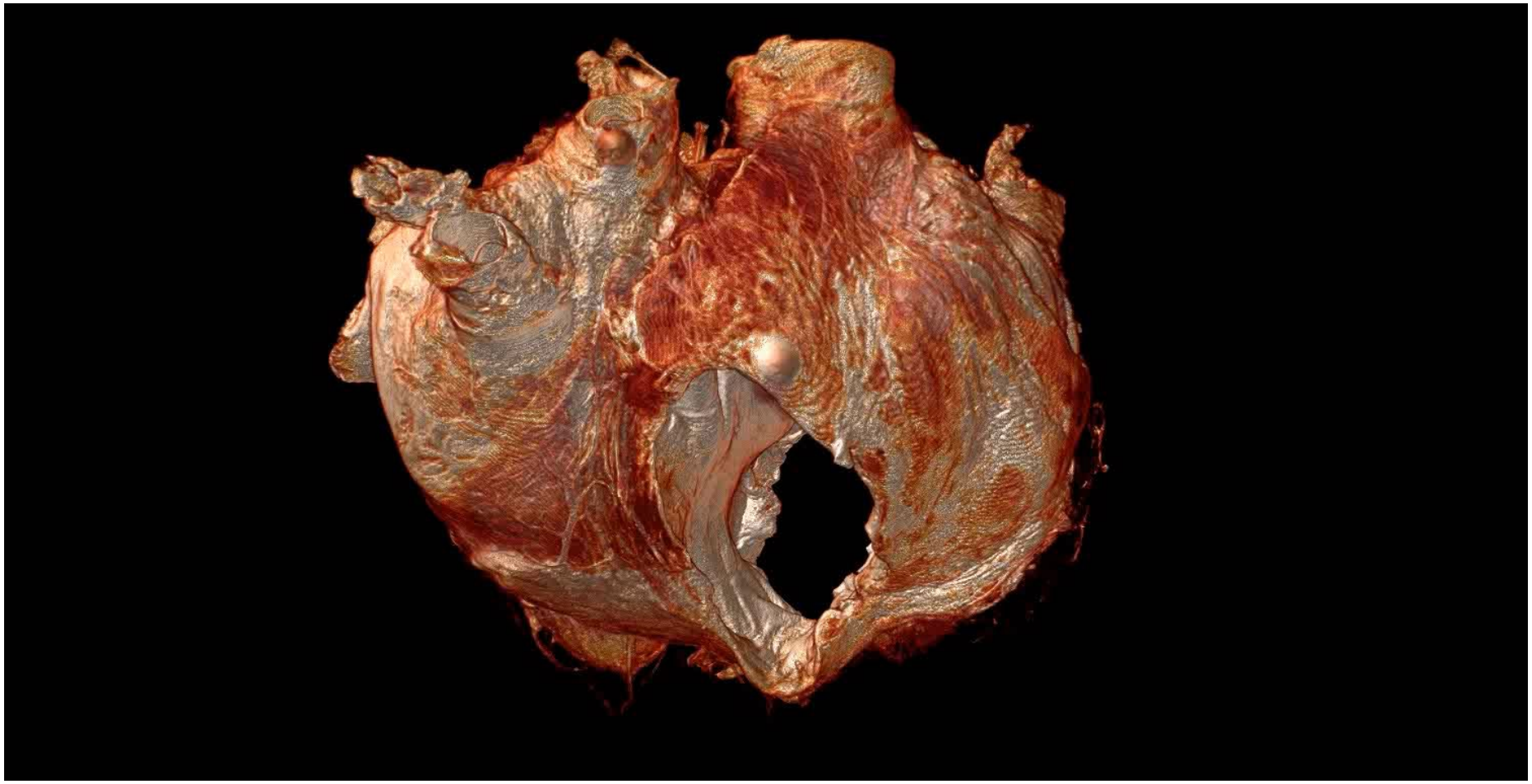




Utah LA Fibrosis Stage

Akoum N, et al. *J Cardiovasc Electrophysiol*. 2011;22(1):16-20.

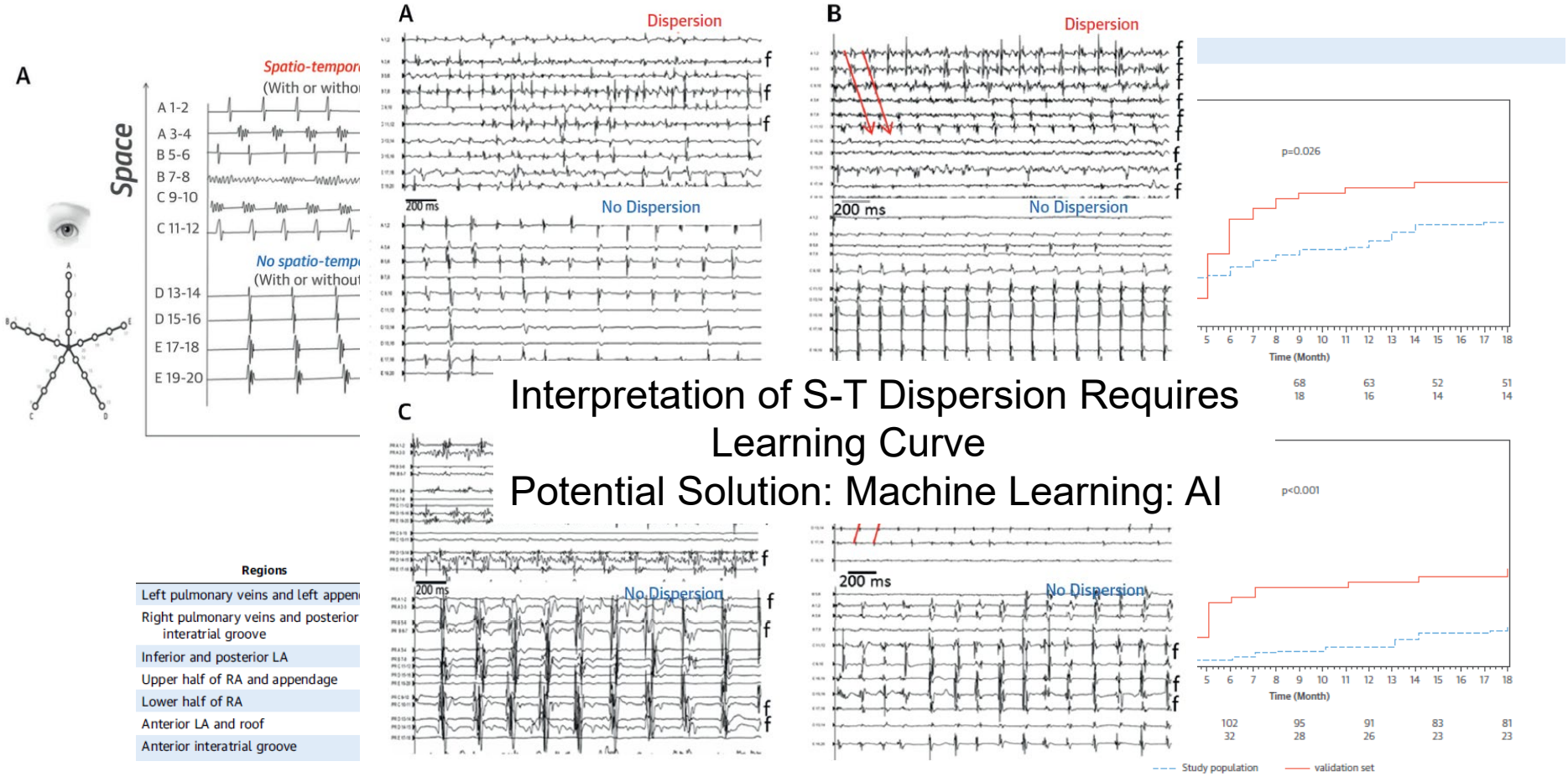
Unused Donor Hearts → Ex-Vivo Physiologic Studies—3D Structural Complexity of Diseased Human Atria: Web of Discontinuous Fibrotically-Insulated Myobundle Tunnels



Ex-Vivo Contrast-Enhanced MRI (180mm^3)

Courtesy Fedorov V, Department of Physiology and Cell Biology, The Ohio State University.

Spatio-Temporal Dispersion Mapping and Ablation Appears Beneficial



Interpretation of S-T Dispersion Requires Learning Curve

Potential Solution: Machine Learning: AI

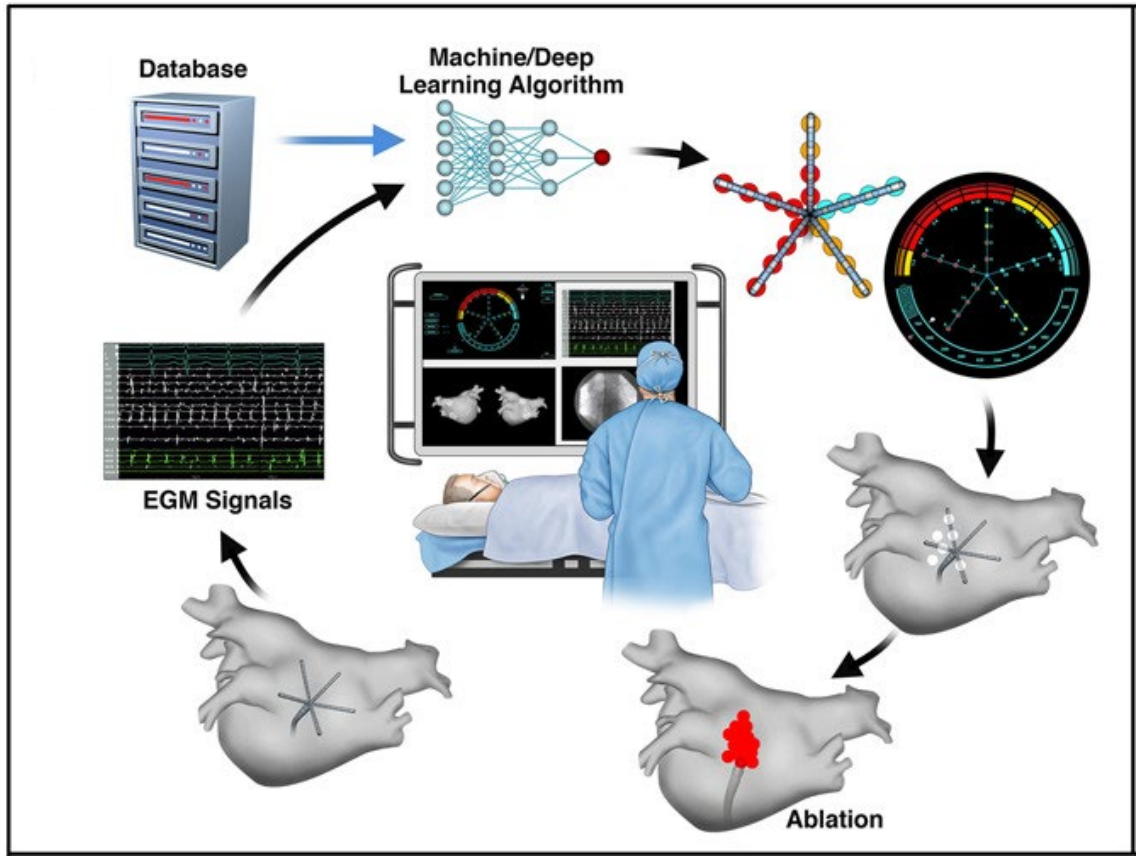
S-T = spatio-temporal.

Seitz J, et al. *J Am Coll Cardiol*. 2017;69(3):303-321.

Employment of Machine Learning/ Artificial Intelligence to Identify STD

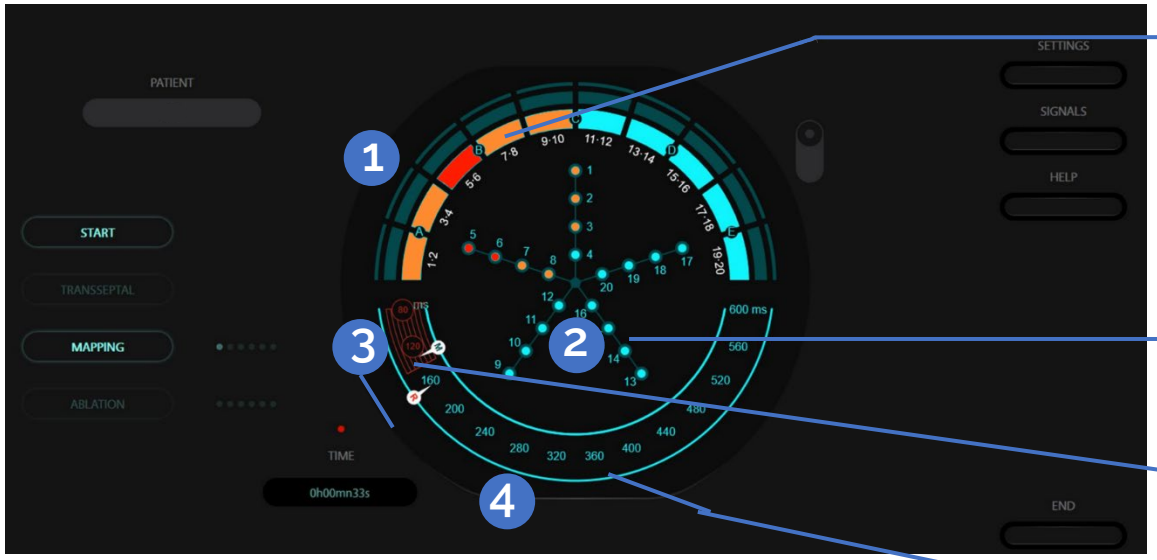
AI decision support system

- Data collection and enrichment for curated EP lab data
- Physician-validated machine learning



STD = spatio-temporal dispersion.
Seitz J, et al. *J Cardiovasc Electrophysiol.* 2022;33(11):2250-2260.

Color-Coded User Interface for Real-Time Regions of Interest Identification

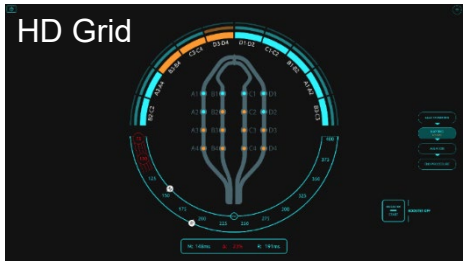


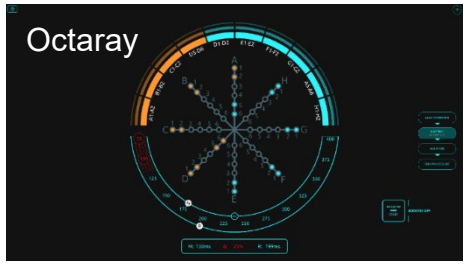
1 Dispersion location

2 Mapping catheter

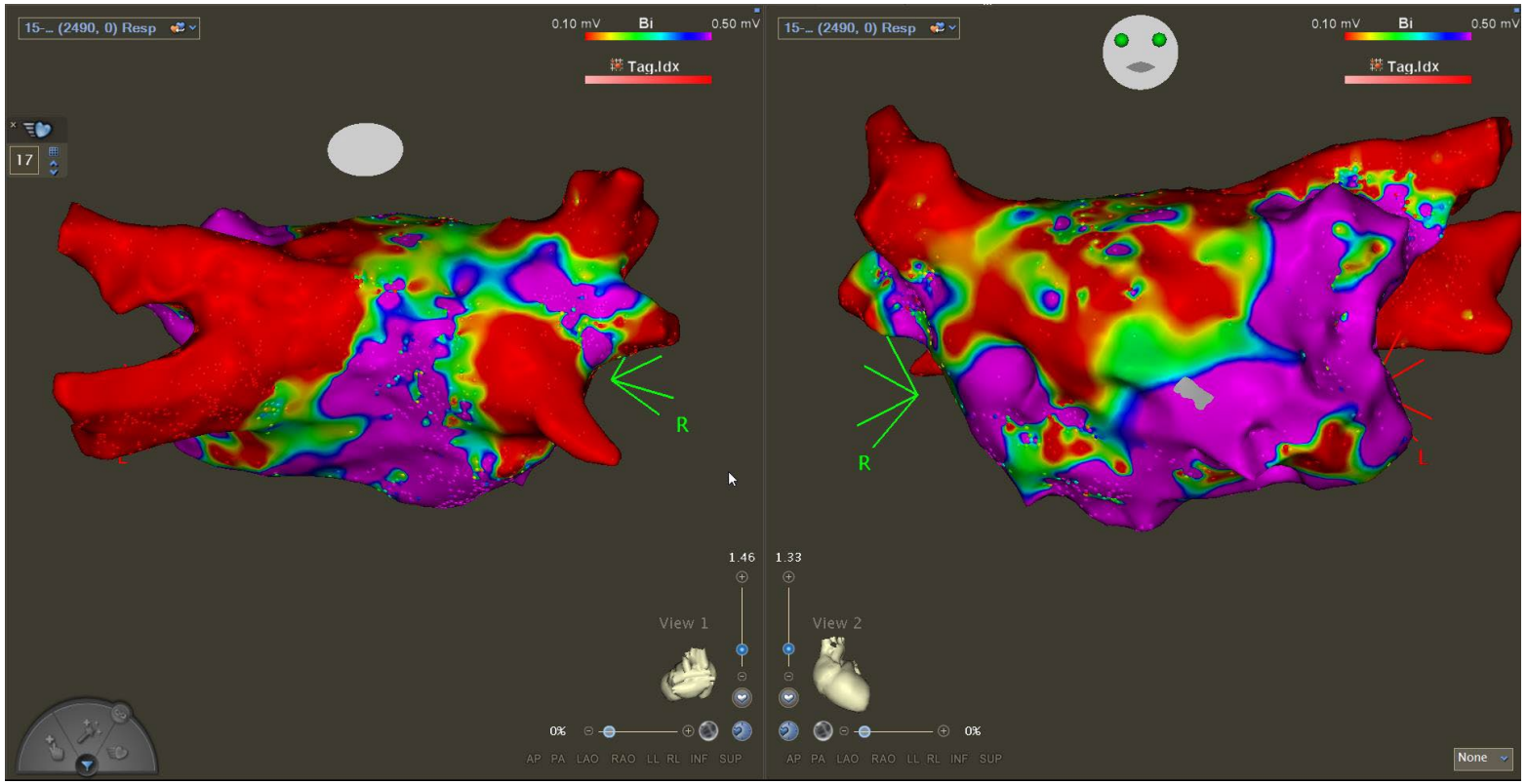
3 Mapping cycle length

4 Reference cycle length





Case Study

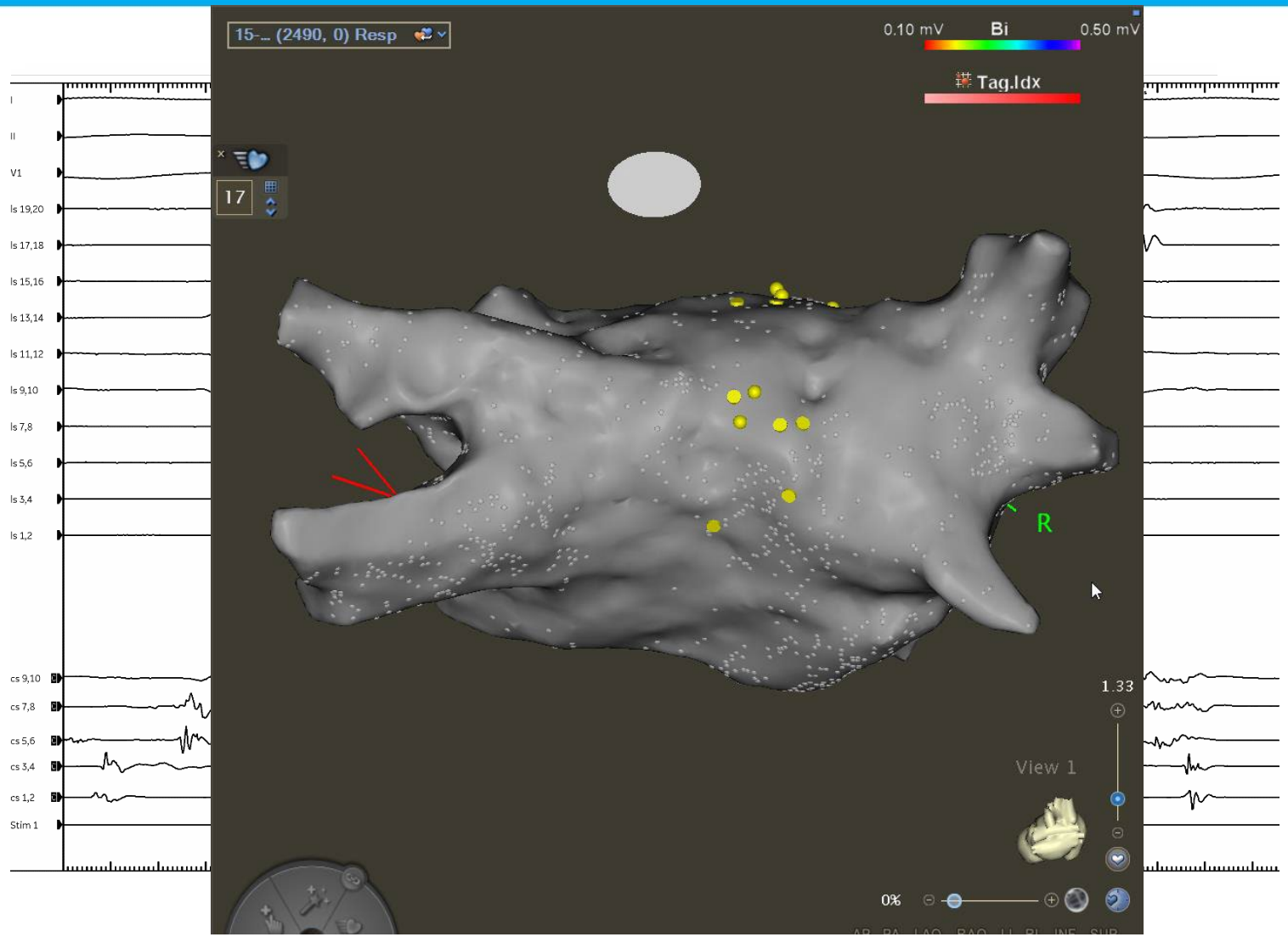


72 yo woman with recurrent persistent AF s/p PVI

History of RV hypertrophic cardiomyopathy

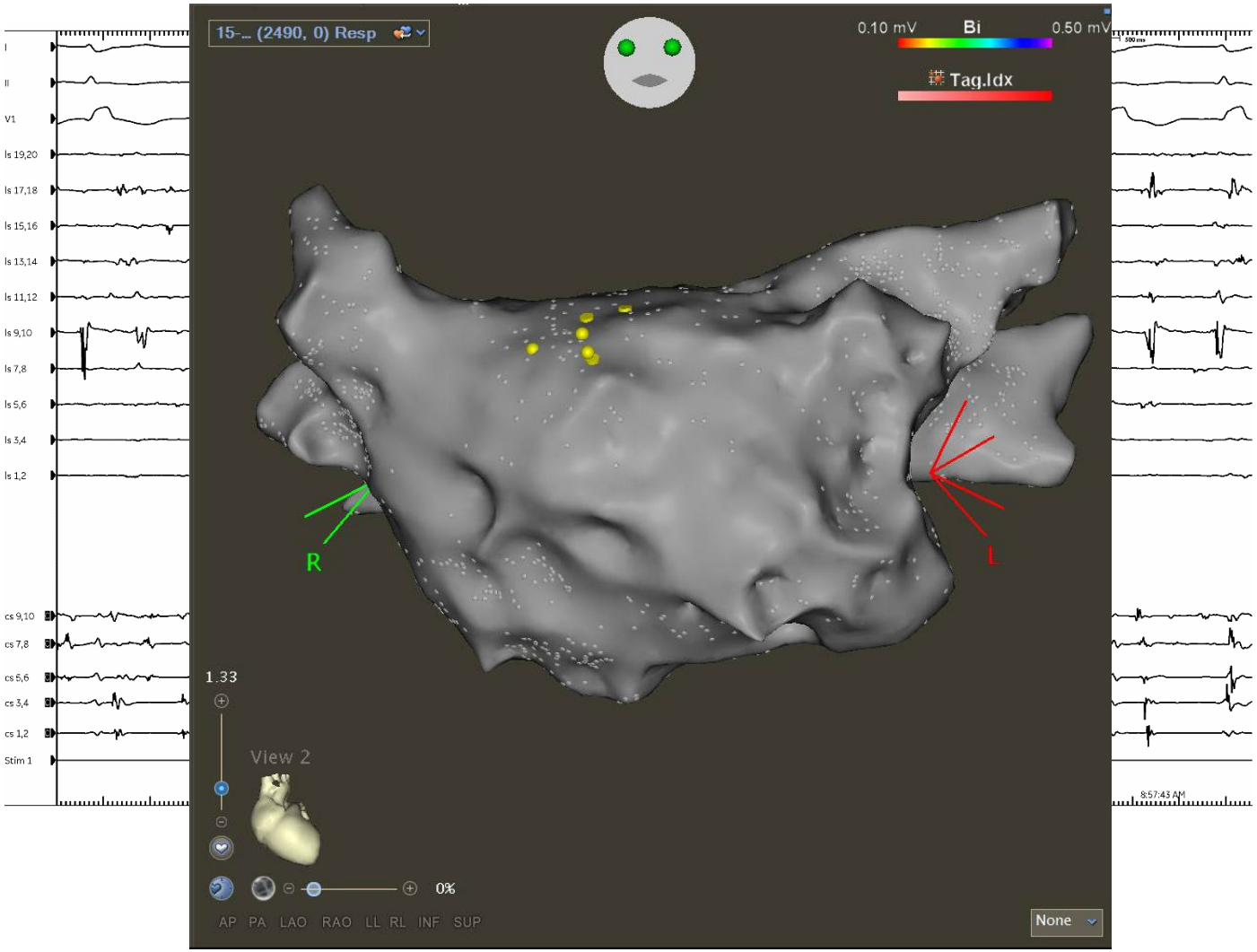
s/p = status post; RV = right ventricular.

Case Study: Posterior Wall STD Mapping



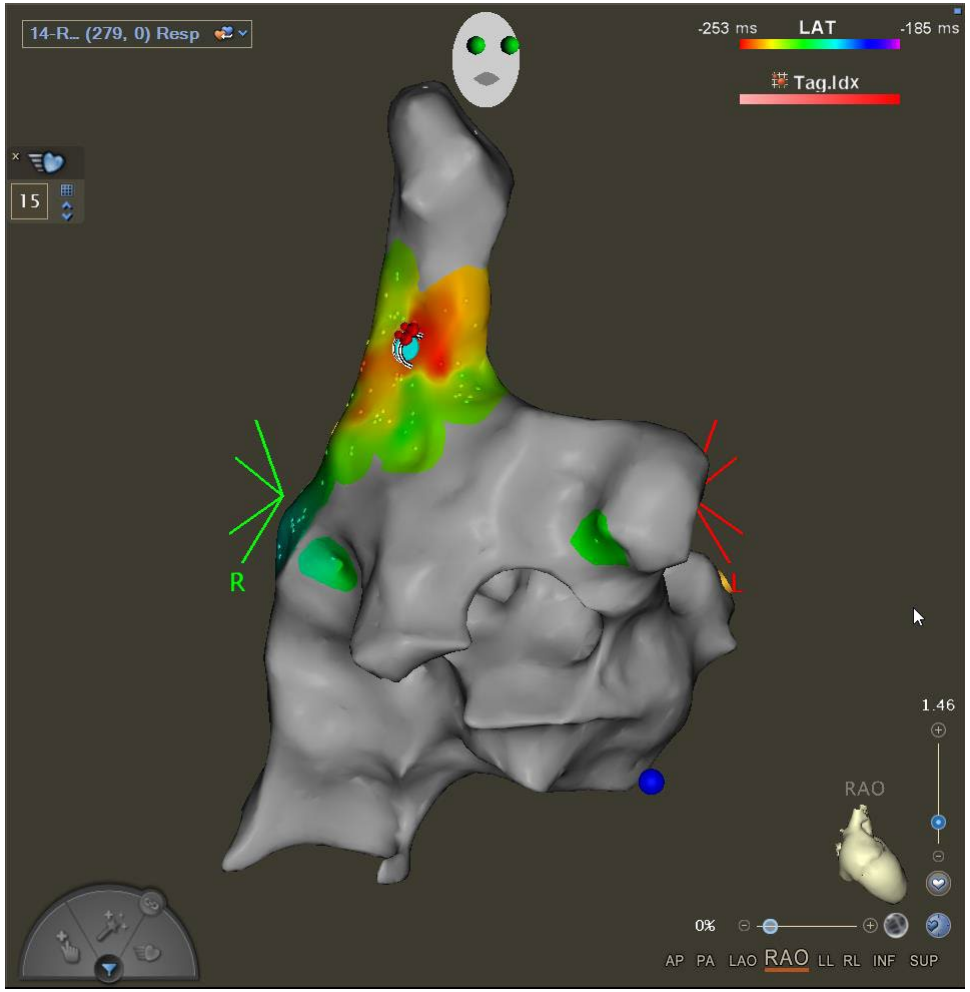
Varying degrees of dispersion

Case Study: Anterior Wall Dispersion



Variable dispersion on the anterior wall

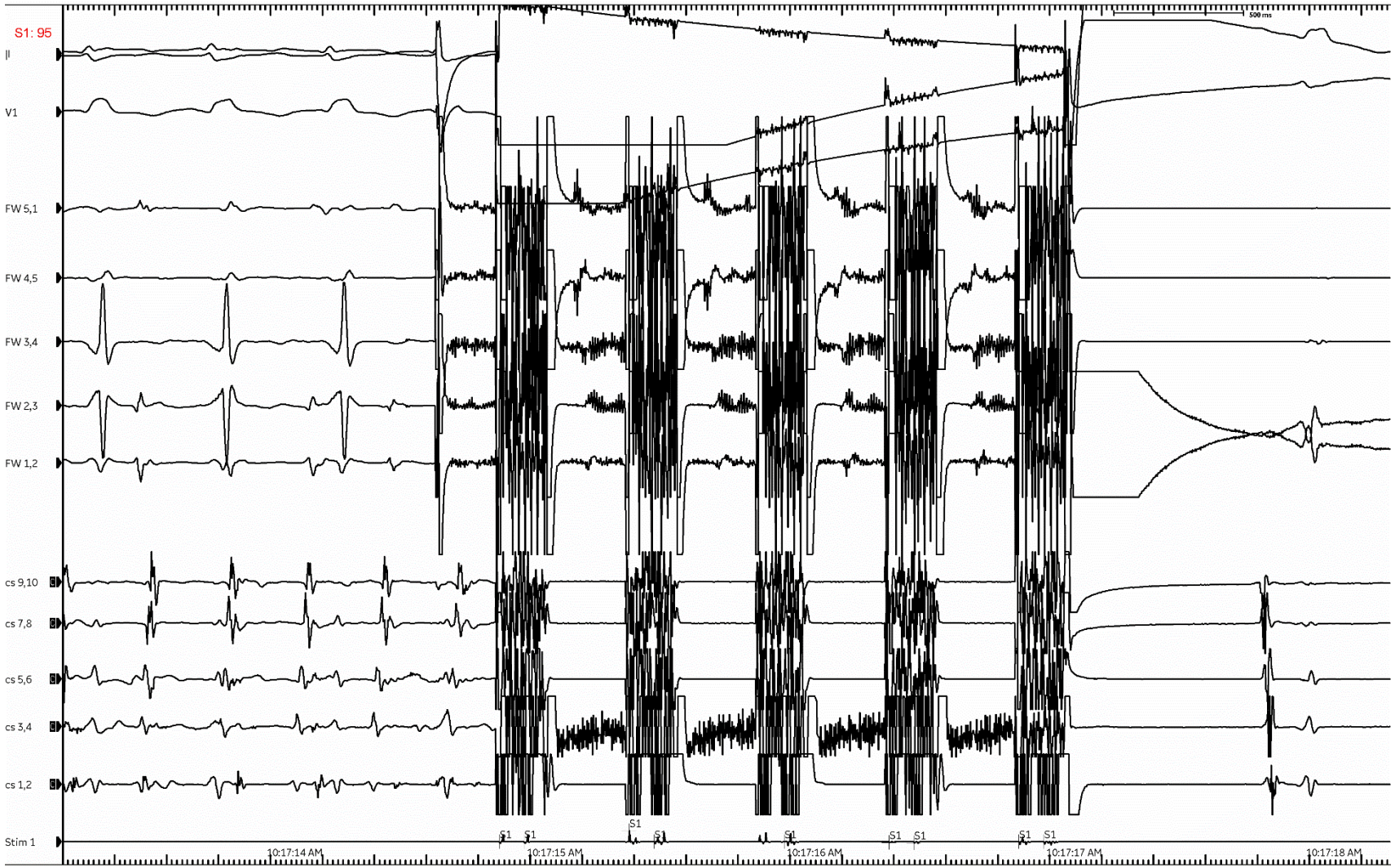
Case Study: RA Mapping



Delineation of sinus and AV node locations

RA = right atrial; AV = atrioventricular.

Case Study: RA Dispersion Mapping



Stable significant dispersion

Conclusions

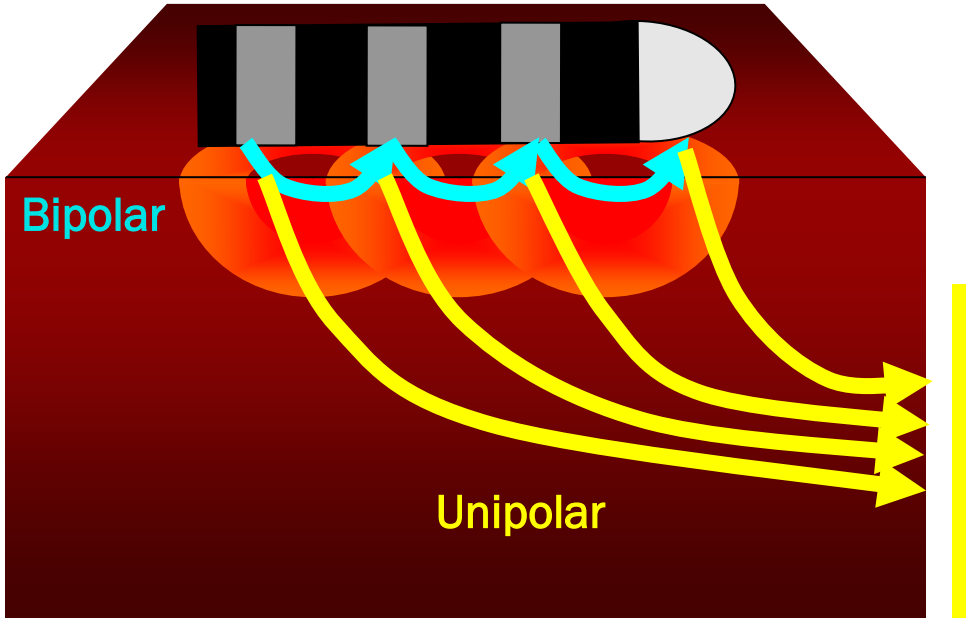
- Regions outside PVs sustain AF
- Spatio-temporal dispersion mapping can identify sources
- AI/ML-driven software streamlines identification of degrees of dispersion to quickly allow prioritization of ablation sites

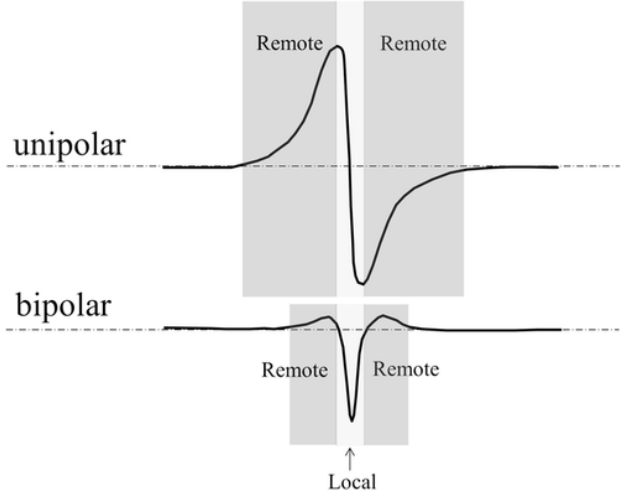
Complex Electrogram-Based Ablation in Atrial Fibrillation: Clinical Data

Paul C. Zei, MD, PhD
Electrophysiologist, Mass General Brigham
Associate Professor of Medicine
Harvard Medical School
Cambridge, Massachusetts

Baseline Assumptions

- Electrophysiology is still fundamentally based on cardiac electrophysiologic mechanisms
- Practically, this means recording myocardial electrophysiologic signals with recording electrodes placed in direct contact with the endocardial (or epicardial) surface of the myocardium of interest
- We can record signals in a “bipolar” or “unipolar” configuration
- Multiple closely-spaced high-resolution electrode catheters are the standard and enable complex temporal and spatial analysis





De Bakker JM. *Pacing Clin Electrophysiol.* 2019;42(12):1503-1516.

Limitations of Electrogram Signals

- Electrograms are recorded in the context of cardiac anatomy; understanding the local anatomy is critical
- 3-dimensional endo- to epi-cardial differences in electrograms are hard/impossible to discern with current technologies and techniques
- The human eye can recognize relatively simple timing and electrogram characteristics, but much of the information content is likely indiscernible to humans

Ground Rules for This Presentation

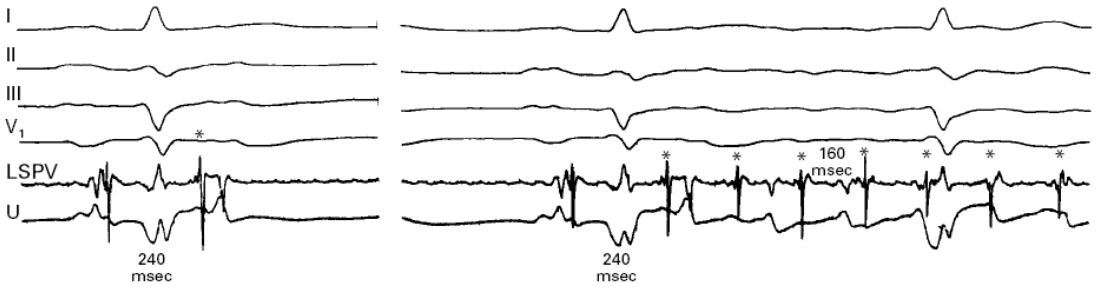
- Will not discuss basic electrograms data (out of scope)
- We will focus on application to AF ablation
- In the interest of time, the highlights of clinical data will be presented

Signal evaluation in AF mapping/ablation was important from the start!

SPONTANEOUS INITIATION OF ATRIAL FIBRILLATION BY ECTOPIC BEATS ORIGINATING IN THE PULMONARY VEINS

SPONTANEOUS INITIATION OF ATRIAL FIBRILLATION BY ECTOPIC BEATS ORIGINATING IN THE PULMONARY VEINS

MICHEL HAÏSSAGUERRE, M.D., PIERRE JAÏS, M.D., DIPEN C. SHAH, M.D., ATSUSHI TAKAHASHI, M.D., MÉLÈZE HOCINI, M.D., GILLES QUINIOU, M.D., STÉPHANE GARRIGUE, M.D., ALAIN LE MOUROUX, M.D., PHILIPPE LE MÉTAYER, M.D., AND JACQUES CLÉMENTY, M.D.

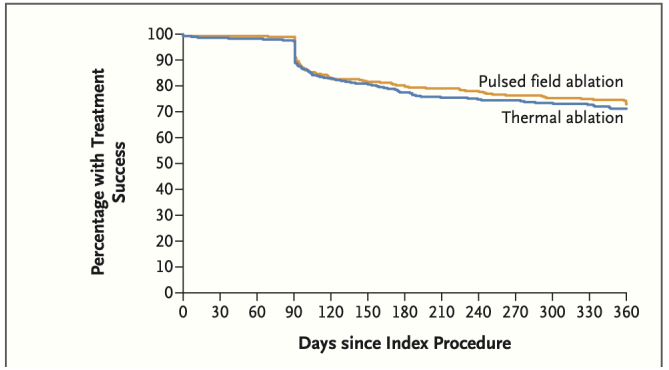


Haïssaguerre M, et al. *N Engl J Med*. 1998;339(10):659-666.

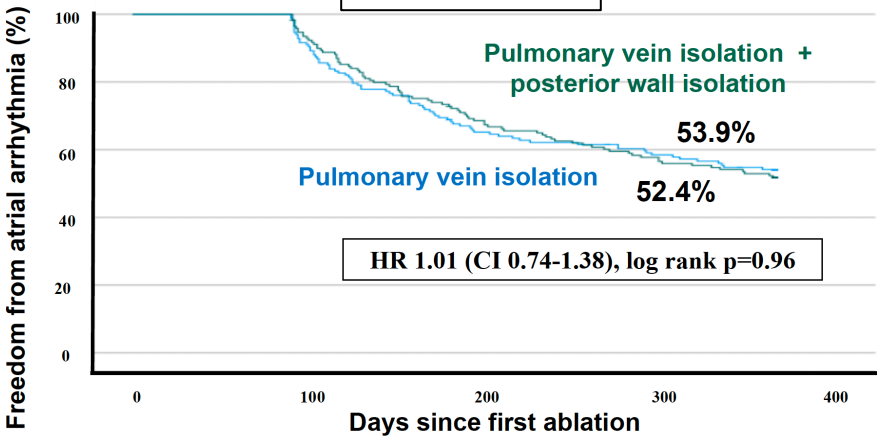
Why Examine Complex Signals during AF Ablation?

Because we can and should do better, especially for persistent AF ablation

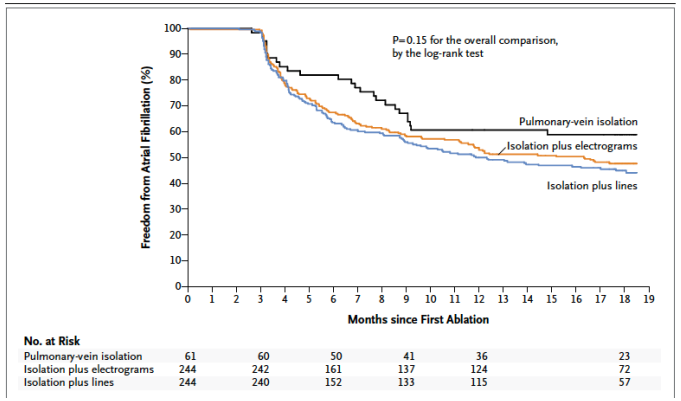
ADVENT (n=611 ablated)



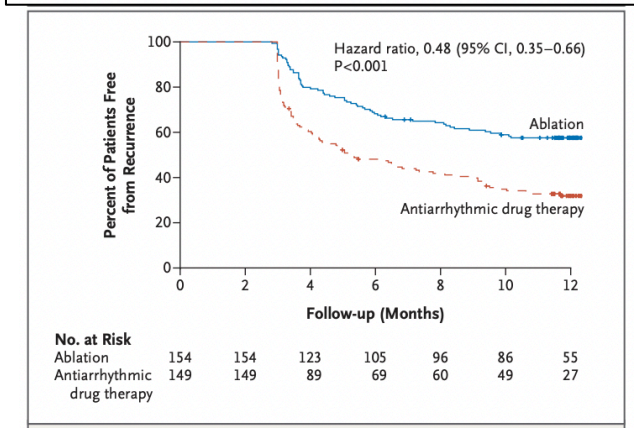
CAPLA



STAR-AF II

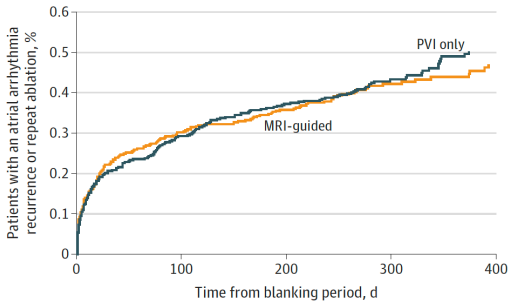


EARLY-AF (n=154 ablated)

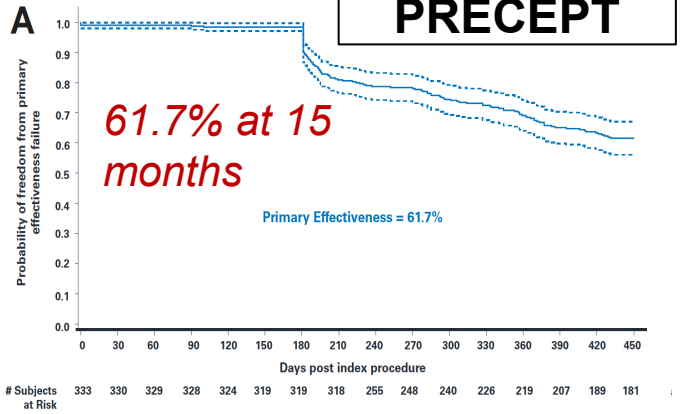


DECAAF II

Figure 2. Primary Composite of Atrial Arrhythmia Recurrence or Repeat Ablation



PRECEPT



Persistent AF

Reddy VY, et al. *N Engl J Med*. 2023;389(18):1660-1671. Jaroonpipatkul S, et al. Presented at: 15th APHRS Scientific Session. November 18-20, 2022. Singapore. Abstract OP-269-1-YIA. Verma A, et al. *N Engl J Med*. 2015;372(19):1812-1822. Andrade JG, et al. *N Engl J Med*. 2021;384(4):305-315. Marrouche NF, et al. *J Cardiovasc Electrophysiol*. 2021;32(4):916-924. Mansour M, et al. *JACC Clin Electrophysiol*. 2020;6(8):958-969.

Key “Categories” of Complex Atrial Signals

- Complex fractionated atrial electrograms (CFAE)
- Frequency domain analysis
- Rotors
- Spatio-temporal dispersion

Complex Fractionated Atrial Electrograms

Electrophysiology

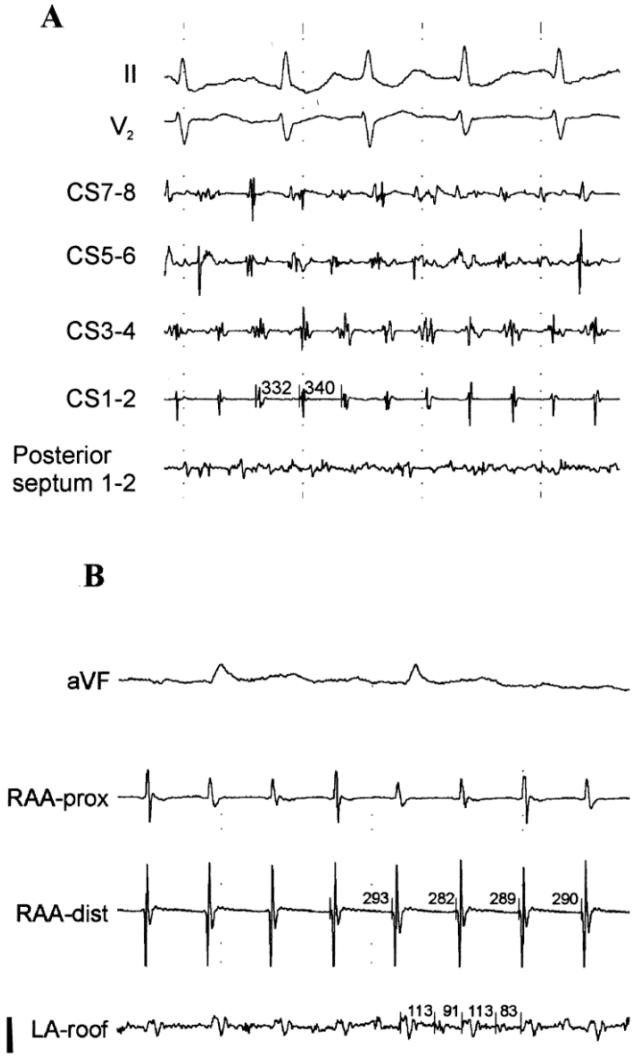
A New Approach for Catheter Ablation of Atrial Fibrillation: Mapping of the Electrophysiologic Substrate

Koonlawee Nademanee, MD, FACC,* John McKenzie, MD,* Erol Kosar, MD,* Mark Schwab, MD,* Buncha Sunsaneewitayakul, MD,† Thaveekiat Vasavakul, MD,* Chotikorn Khunnawat, MD,* Tachapong Ngarmukos, MD‡

Inglewood, California; and Bangkok, Thailand

CFAEs definition

1. Atrial electrograms that have fractionated electrograms composed of two deflections or more, and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-second recording period
2. Atrial electrograms with a very short cycle length (120 ms) averaged over a 10-second recording period



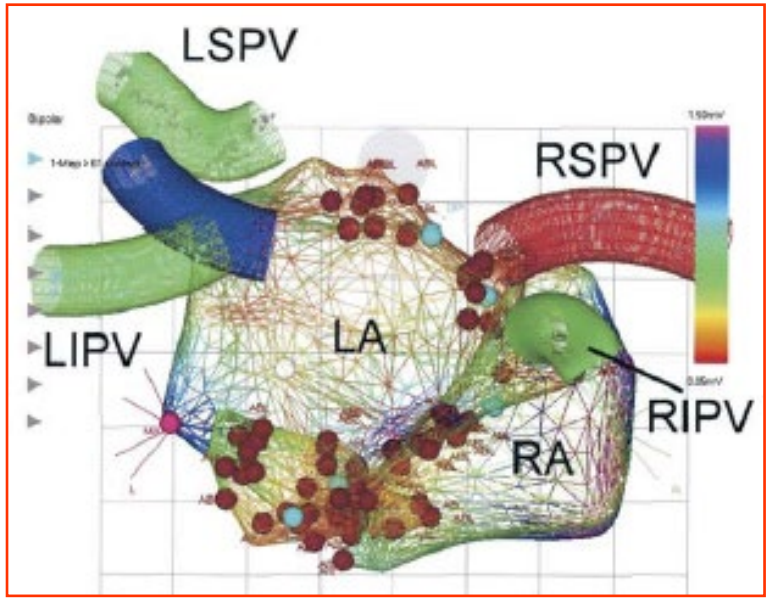
Nademanee K, et al. *J Am Coll Cardiol.* 2004;43(11):2044-2053.

CFAE—Complex Fractionated Atrial Electrograms

- N=121 patients (57 PAF, 64 persistent)
- CFAEs identified during AF targeted with ablation
- Ablation catheter bipolar signals!
- PVI not necessarily performed

Results

- CFAE locations tended towards PVs, LA roof, CS, inferolateral RA, septum
- SVC, posterior wall locations were rare
- 95% of patients had intraprocedural AF termination with ablation
- 76% one-year freedom from AF (q3mo Holter/event monitor)
- Results have not been reproduced; as a result, this strategy has not been widely adopted



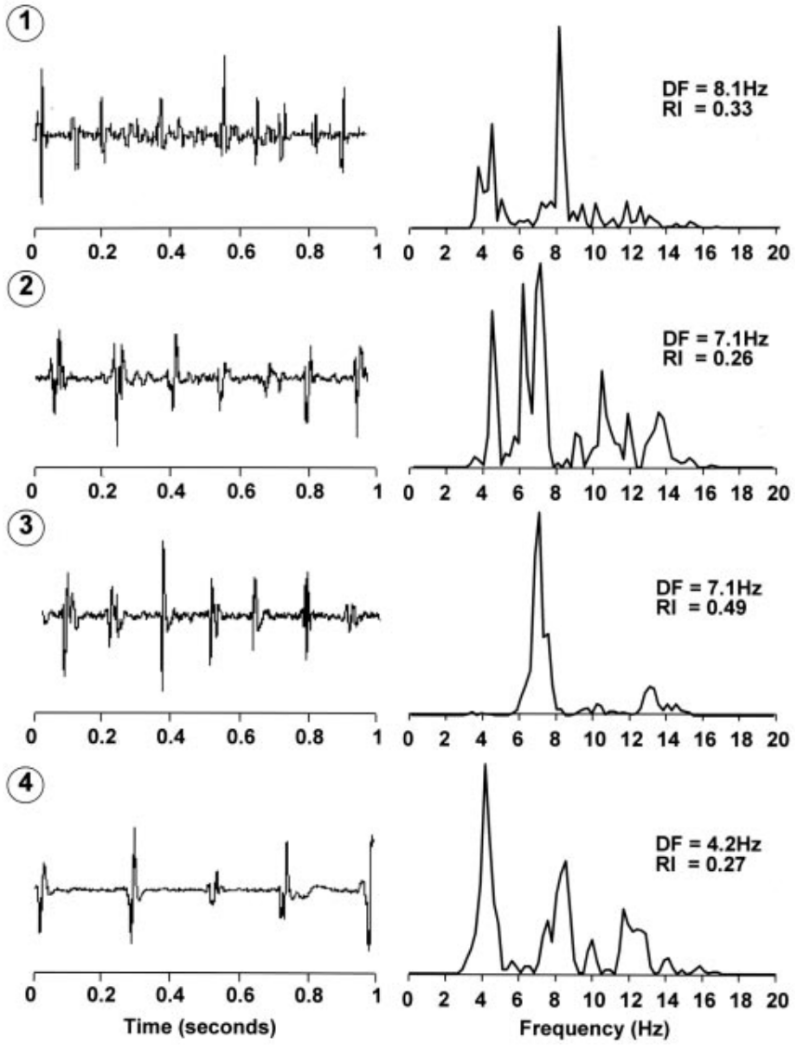
Nademanee K, et al. *J Am Coll Cardiol.* 2004;43(11):2044-2053.

Frequency Domain Analysis

Spectral Analysis Identifies Sites of High-Frequency Activity Maintaining Atrial Fibrillation in Humans

Prashanthan Sanders, MBBS, PhD*; Omer Berenfeld, PhD*; Mélèze Hocini, MD; Pierre Jaïs, MD; Ravi Vaidyanathan, BE; Li-Fern Hsu, MBBS; Stéphane Garrigue, MD, PhD; Yoshihide Takahashi, MD; Martin Rotter, MD; Fréderic Sacher, MD; Christophe Scavée, MD; Robert Ploutz-Snyder, PhD; José Jalife, MD; Michel Haïssaguerre, MD

- Definition: recorded electrograms processed through a Fourier transformation to examine frequency content
- Areas of higher frequency dominant signals were targeted with ablation (dominant frequency)



Sanders P, et al. *Circulation.* 2005;112(6):789-797.

Frequency Domain Analysis

- 32 patients (19 PAF, 13 persistent AF)
- Acute outcomes only
- Ablation strategy: PVI, mitral line, CTI
- Electrograms throughout the RA and LA recorded, but DF site analysis blinded to ablating operator, adjudicated post-ablation
- 17/19 patients with PAF had termination with ablation at a DF site, 0/13 patients with persistent AF

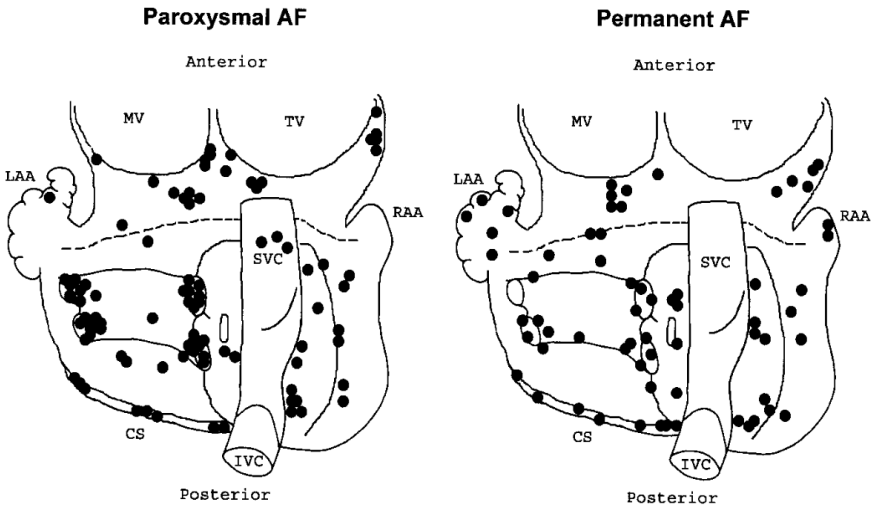


Figure 5. Schematic of all DF sites in patients with paroxysmal (left) and permanent (right) AF. Greater clustering of these sites at PV and ostial LA in patients with paroxysmal AF is seen.

CTI = cavotricuspid isthmus; DF = dominant frequency.
Sanders P, et al. *Circulation.* 2005;112(6):789-797.

Rotors

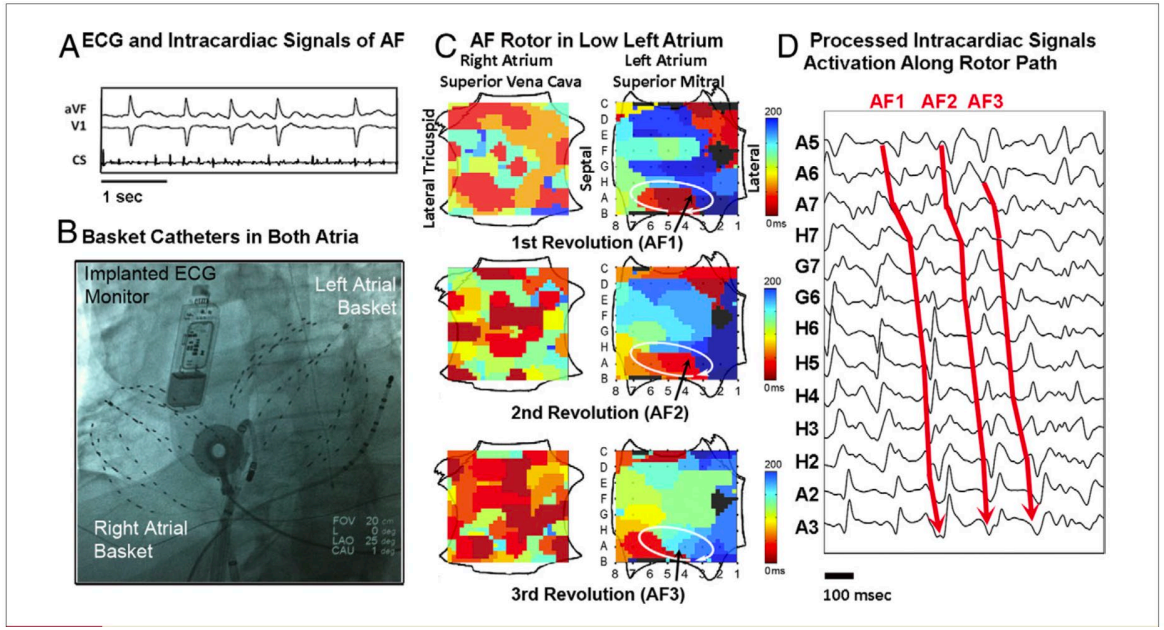
EXPEDITED PUBLICATIONS

Treatment of Atrial Fibrillation by the Ablation of Localized Sources

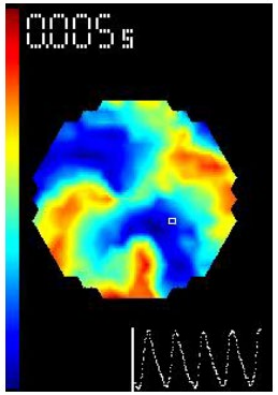
CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) Trial

Sanjiv M. Narayan, MD, PHD,*† David E. Krummen, MD,*† Kalyanam Shivkumar, MD, PHD,‡ Paul Clopton, MS,† Wouter-Jan Rappel, PHD,§ John M. Miller, MD‖

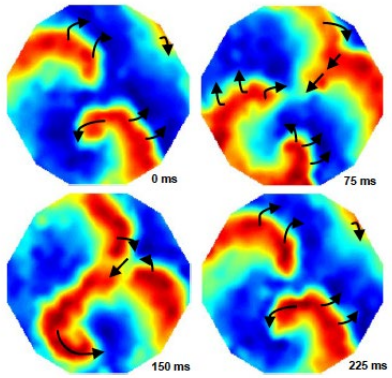
San Diego and Los Angeles, California; and Indianapolis, Indiana



Spiral wave: another variant of functional reentry



↑wavelength → reentry extinction



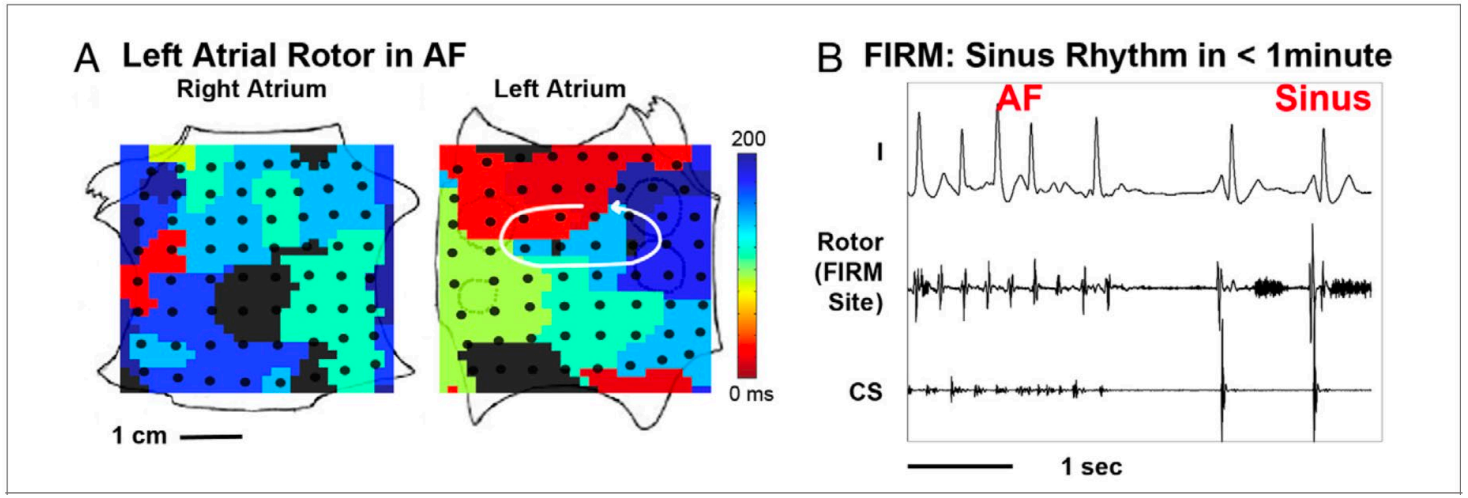
"Spiral wave":
- Circuit is as small as it can be
- Continuously excit*able* center

- Rotational activity ("rotors"): results of functional reentry
- Multiple wavelet theory
- Does targeting rotor sites impact AF recurrence?

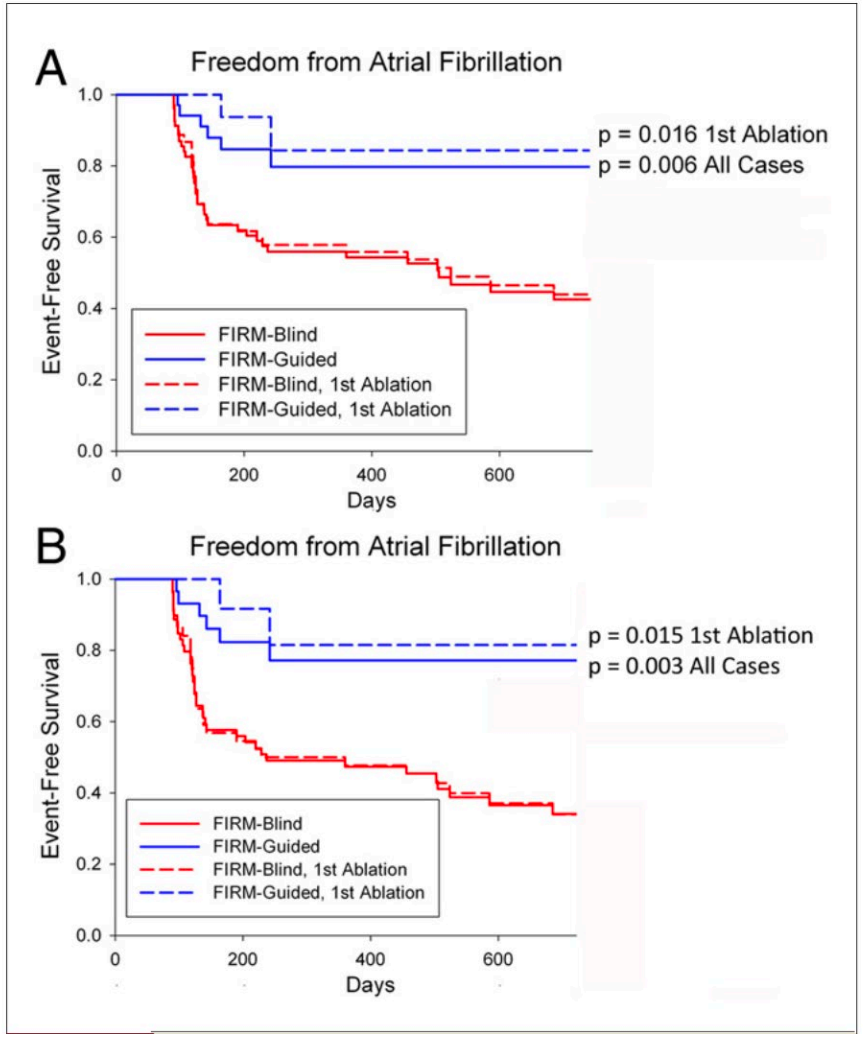
Jalife J. *Annu Rev Physiol.* 2000;62:25-50. Narayan SM, et al. *J Am Coll Cardiol*. 2012;60(7):628-636.

Rotors

- 92 patients randomized 1:2 FIRM (rotor mapping) + PVI vs PVI alone
- At 2-year follow-up, FIRM-guided ablation with significantly higher freedom from AF



Acute termination of AF to sinus rhythm by FIRM ablation



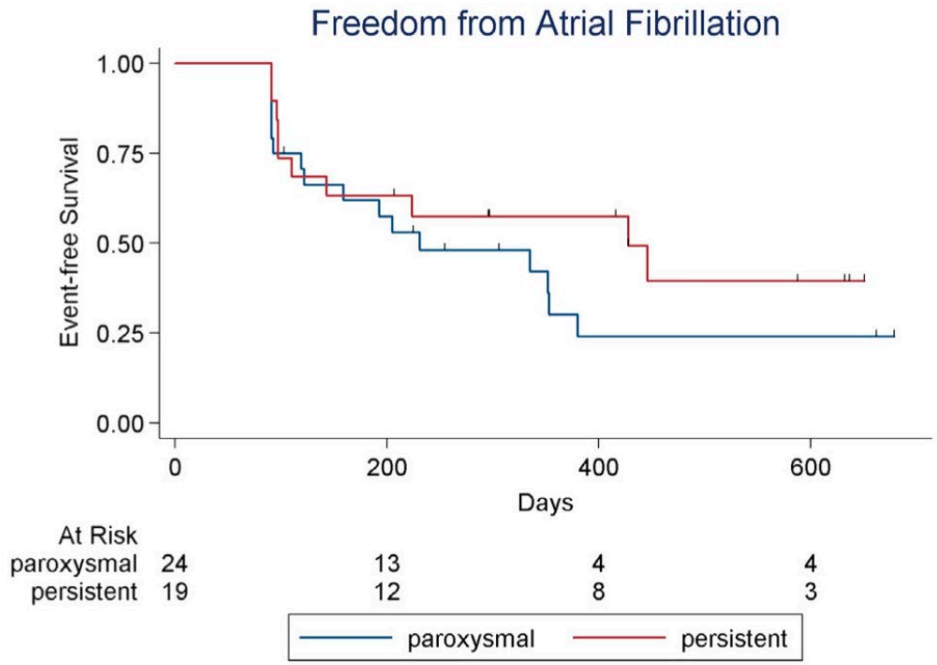
Termination of AF with rotor targeted along LA roof

Narayan SM, et al. *J Am Coll Cardiol*. 2012;60(7):628-636.

Rotors

Subsequent data showed no benefit of rotor-based ablation beyond PVI

- Double-center study (N=43), 2-year data
- Prospective, non-randomized
- Both PAF and persistent AF outcomes poor



Acute and early outcomes of focal impulse and rotor modulation (FIRM)-guided rotors-only ablation in patients with nonparoxysmal atrial fibrillation

Carola Gianni, MD,[*†] Sanghamitra Mohanty, MD, MS, FHRS,[*] Luigi Di Biase, MD, PhD, FHRS,[*‡§‖] Tamara Metz, RN, BSN,[*] Chintan Trivedi, MD,[*] Yalçın Gökoğlan, MD,[*¶] Mahmut F. Güneş, MD,[*] Rong Bai, MD, FHRS,[*] Amin Al-Ahmad, MD, CCDS, FHRS,[*] J. David Burkhardt, MD, FHRS,[*] G. Joseph Gallinghouse, MD, FHRS,[*] Rodney P. Horton, MD, FHRS,[*§] Patrick M. Hranitzky, MD, FHRS,[*] Javier E. Sanchez, MD,[*] Phillipp Halbfaß, MD,[#] Patrick Müller, MD,[#**] Anja Schade, MD,[#] Thomas Deneke, MD, PhD, FHRS,[#**] Gery F. Tomassoni, MD, FHRS,[††] Andrea Natale, MD, FHRS[*‡§‡‡§§‖‖¶¶##]

- Single-center study (N=29), 20 patients with persistent AF, 9 patients with LSPAF
- 6-month freedom from AF = 17%

LSPAF = long-standing persistent atrial fibrillation.

Buch E, et al. *Heart Rhythm*. 2016;13(3):636-641. Gianni C, et al. *Heart Rhythm*. 2016;13(4):830-835.

Spatio-Temporal Dispersion

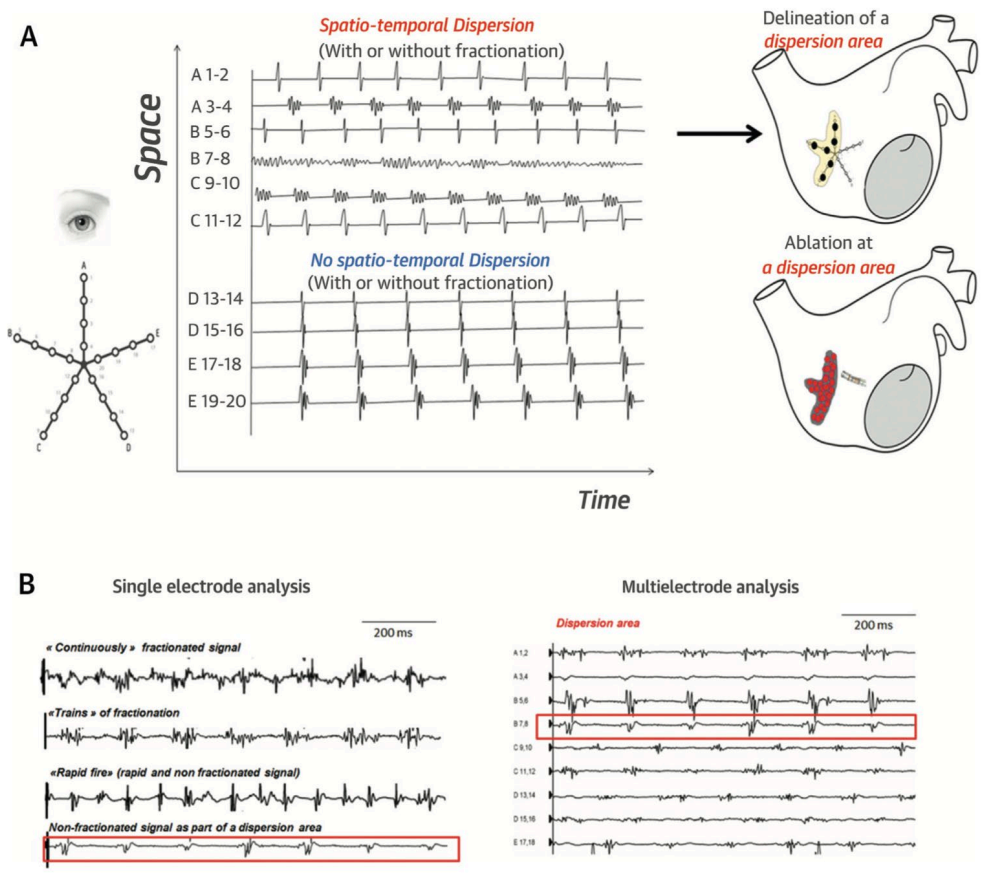
AF Ablation Guided by Spatiotemporal Electrogram Dispersion Without Pulmonary Vein Isolation

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]

"The hypothesis underlying this study is that electrograms recorded simultaneously by a multipolar catheter displaying both a spatial and temporal dispersion (dispersion areas) are indicative of AF drivers, regardless of whether or not these electrograms are fractionated."

FIGURE 1 Spatiotemporal Dispersion of Multipolar Electrograms

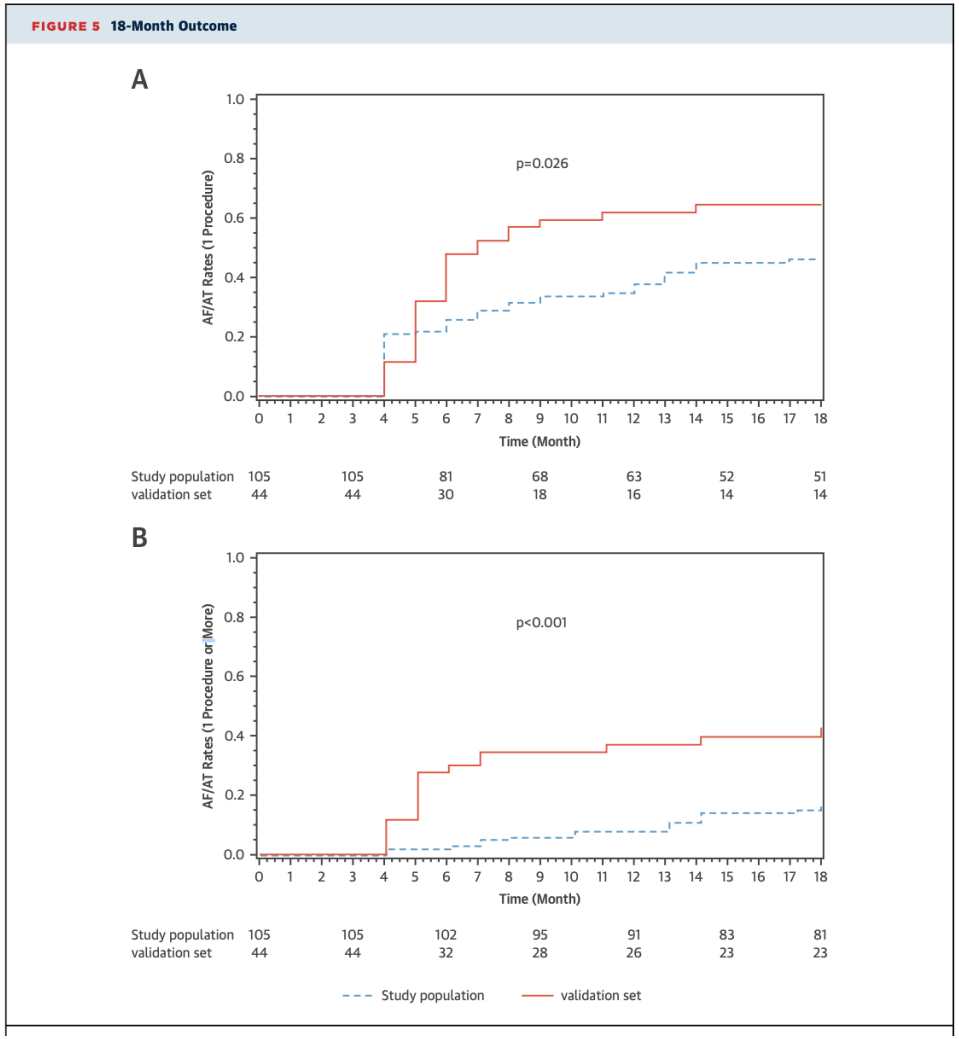


(A) Dispersion areas are defined and delineated via a mapping approach. **(B)** Single-bipole signals from dispersion regions were differentiated by fractionated or nonfractionated electrogram morphologies; nonfractionated (>120 ms) electrograms may be 1 or several of the electrograms within a dispersion region. Collectively, the bipolar electrograms span most of the atrial fibrillation (AF) cycle length recorded in the region.

Seitz J, et al. *J Am Coll Cardiol*. 2017;69(3):303-321.

Spatio-Temporal Dispersion

- N=105 patients prospectively enrolled, both PAF and persistent AF
- Prospective, non-randomized
- PVI + STD sites ablated
- Up to 3 years follow-up
- Significant reduction in AF recurrence



Seitz J, et al. *J Am Coll Cardiol*. 2017;69(3):303-321.

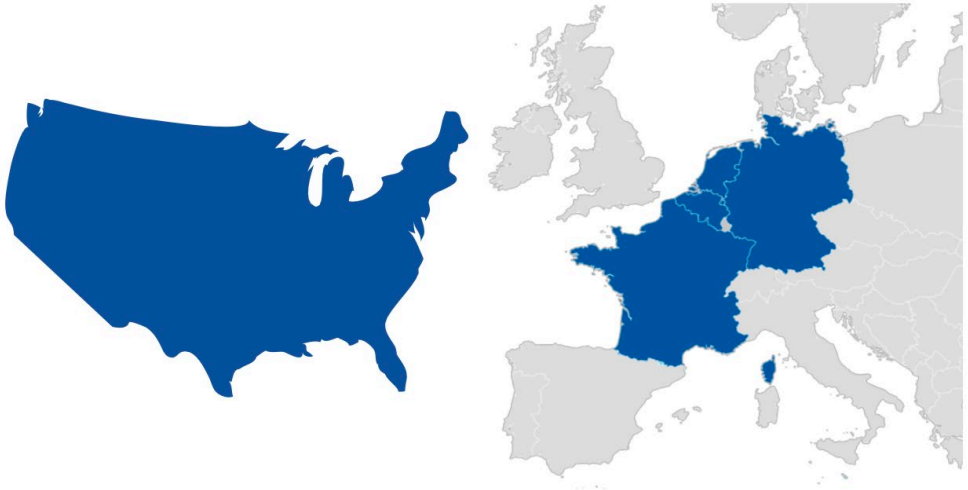
Spatio-Temporal Dispersion: Recent Developments

Spatio-temporal dispersion assisted by AI-directed ablation

- Initial AI model utilized manually identified sites of STD
- With additional data input, ablation sites that tended to organize or terminate AF were determined

HRS 2024 LBCT: TAILORED-AF at a Glance

- 374 patients
- 51 investigators
- 26 sites (8 US, 18 EU)
- 5 countries

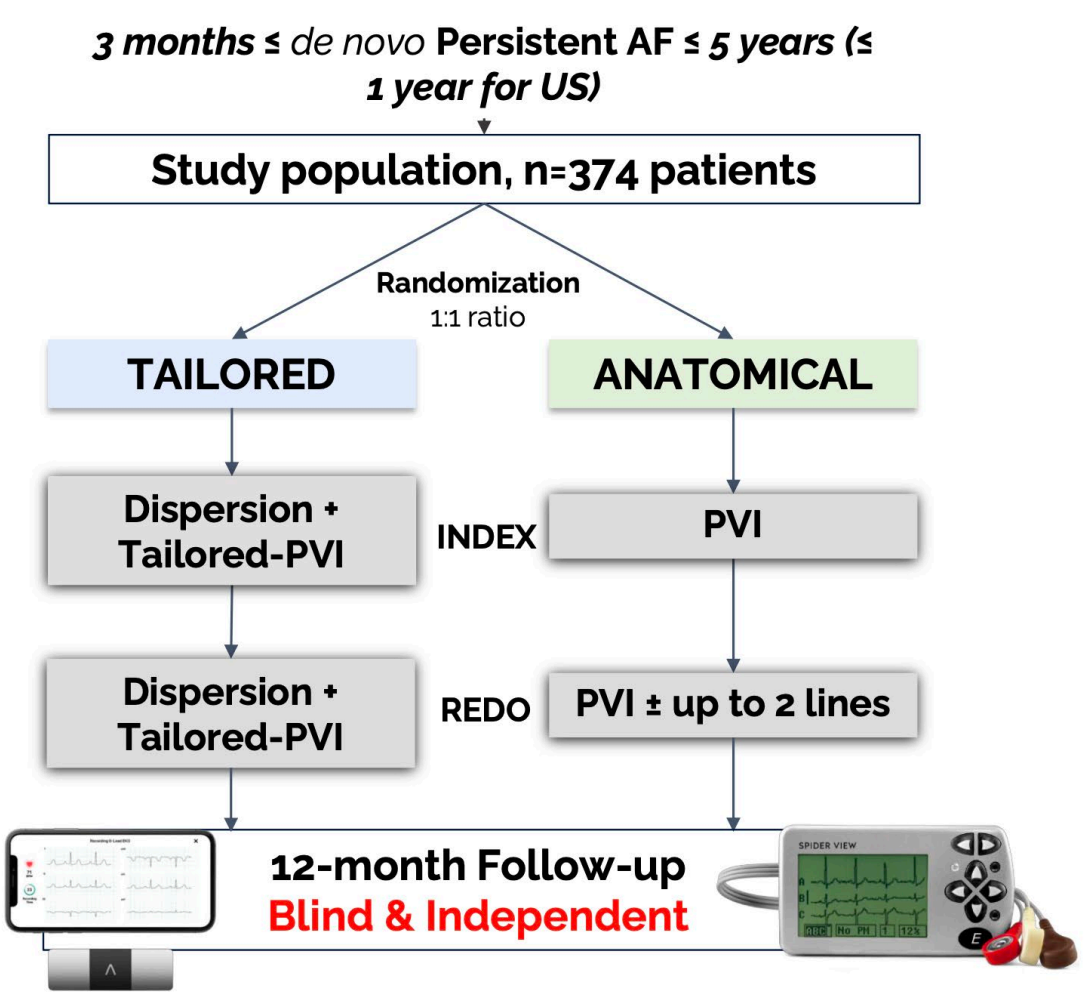


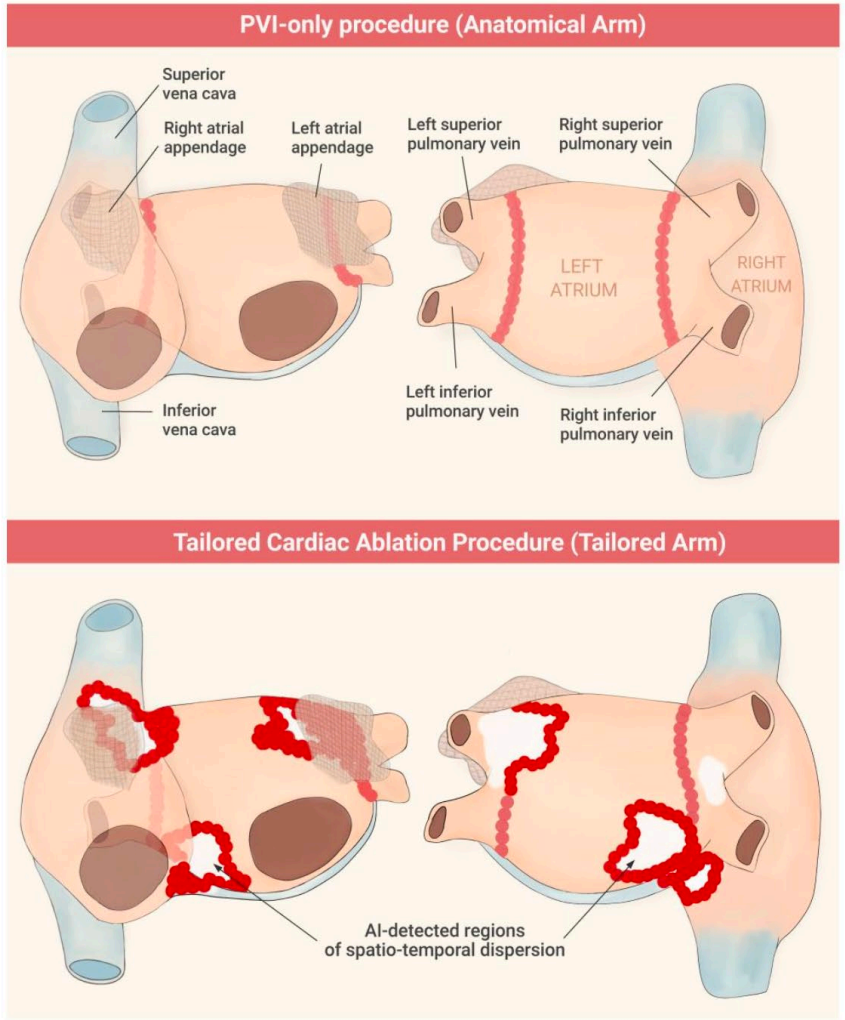
- US and EU global randomized controlled trial (FDA IDE trial)
  - Tailored ablation of AI-detected spatio-temporal dispersion + PVI

    vs
  - PVI alone for the treatment of persistent AF
- Stringent 12-month follow-up
  - Minimum of 3 office visits with ≥ 24-hour Holter-ECG at 3, 6, and 12-month
  - 6-lead Kardia: weekly + symptoms (17,000+ ECG transmissions = 83% compliance/patient)
- Blinded and independent ECG core lab

National Library of Medicine. February 12, 2021. Accessed October 9, 2024. https://clinicaltrials.gov/study/NCT04702451. Deisenhofer I, et al. Presented at: Heart Rhythm Society (HRS) Annual Meeting; May 16-19, 2024; Boston, Massachusetts. Abstract LB-469805-01.

HRS 2024 LBCT: TAILORED-AF Study Design

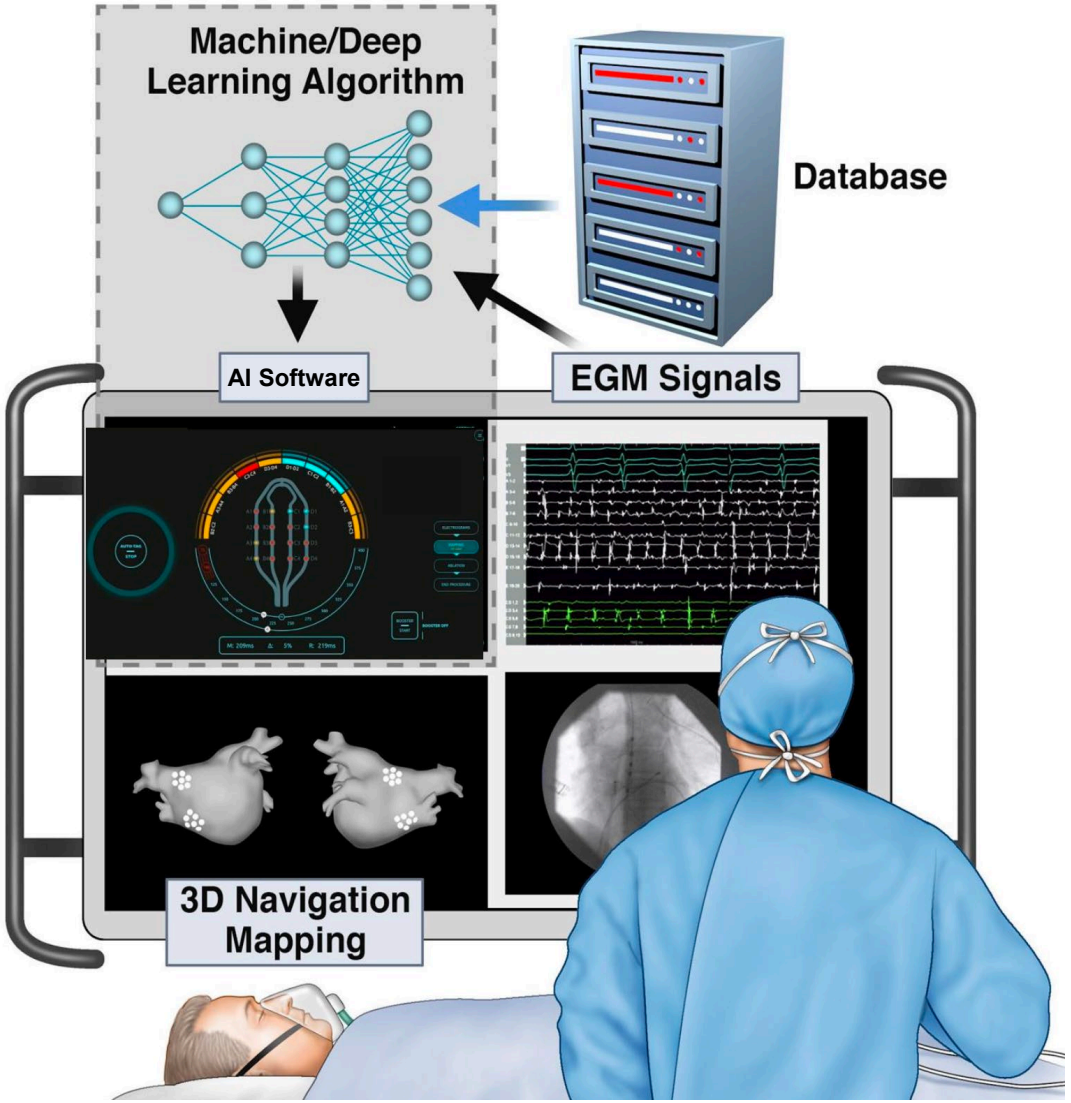




Deisenhofer I, et al. Presented at: Heart Rhythm Society (HRS) Annual Meeting; May 16-19, 2024; Boston, Massachusetts. Abstract LB-469805-01.

HRS 2024 LBCT: TAILORED-AF Workflow

- Local EGM recording with HD multi-electrode mapping catheter
- AI-driven analysis using EGM dispersion
  → Spatio-temporal dispersion
- Color-coded interface
  → Tagging in 3D map
- (Bi-atrial) ablation of dispersion areas
  – AF termination/regularization
  – Elimination of all dispersion areas



Seitz J, et al. *J Cardiovasc Electrophysiol.* 2022;33(11):2250-2260.
Deisenhofer I, et al. Presented at: Heart Rhythm Society (HRS) Annual Meeting; May 16-19, 2024; Boston, Massachusetts. Abstract LB-469805-01.

HRS 2024 LBCT: TAILORED-AF Endpoints

Primary endpoint

- **Freedom from documented AF ±AADs, at 12 months, after a single index ablation procedure**

Secondary endpoints

- **Freedom** from any documented **atrial arrhythmia (AF/AT), ±AADs**, at **12 months**, after a **single index ablation procedure**
- **Freedom** from any documented **atrial arrhythmia (AF/AT), ±AADs**, at **12 months**, after **one or two ablation procedures**

Safety endpoint

- **Safety composite endpoint at 12 months**: death, cerebrovascular event, or serious treatment-related adverse event

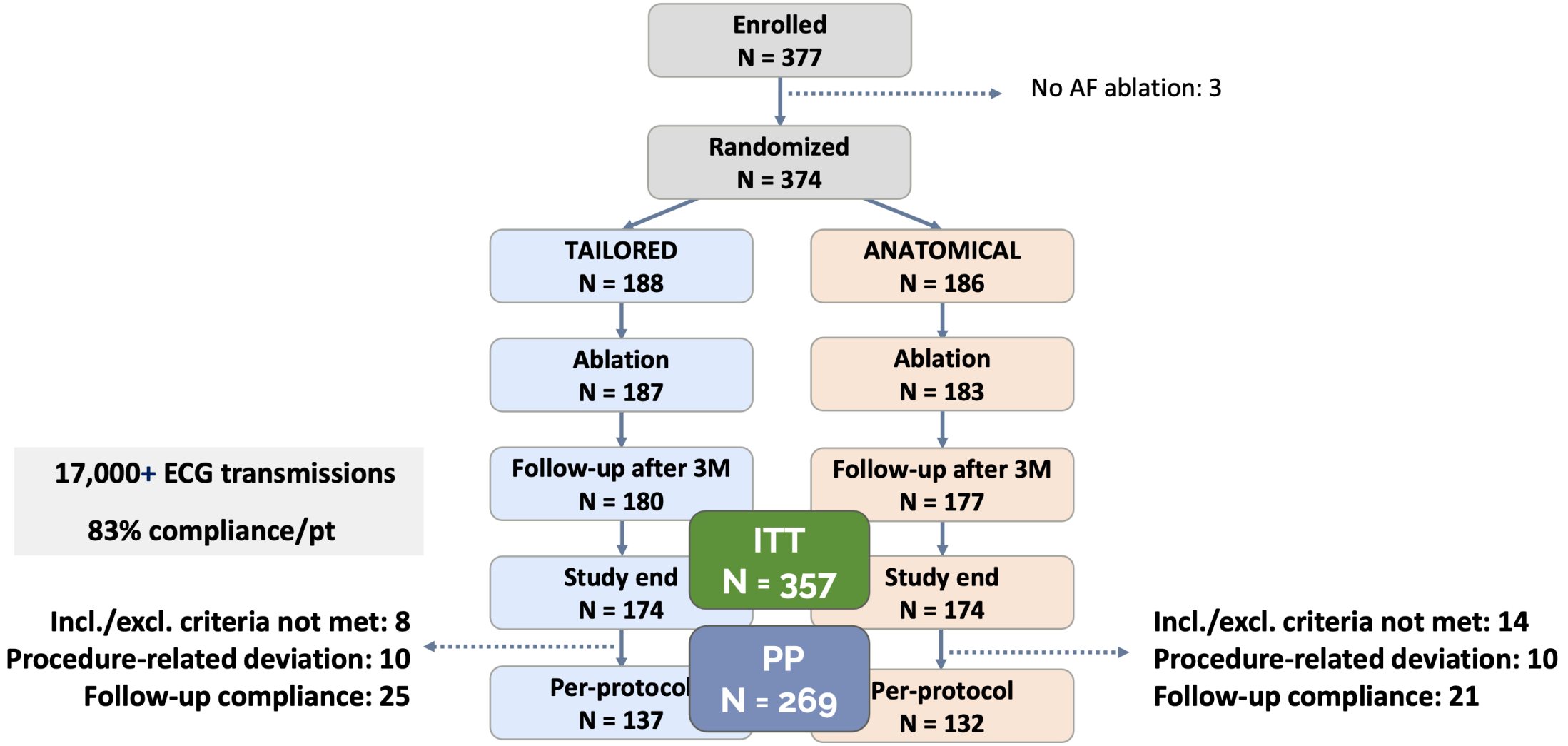
Pre-specified subgroups

- **Subjects with AF maximum sustained duration ≥ 6 months**
- Subjects presenting with spontaneous AF at procedure onset

AF/AT = atrial fibrillation/atrial tachycardia; AAD = antiarrhythmic drug.

Deisenhofer I, et al. Presented at: Heart Rhythm Society (HRS) Annual Meeting; May 16-19, 2024; Boston, Massachusetts. Abstract LB-469805-01.

HRS 2024 LBCT: TAILORED-AF Patient Flow Diagram



Deisenhofer I, et al. Presented at: Heart Rhythm Society (HRS) Annual Meeting; May 16-19, 2024; Boston, Massachusetts. Abstract LB-469805-01.

HRS 2024 LBCT: TAILORED-AF Results: Procedural Characteristics

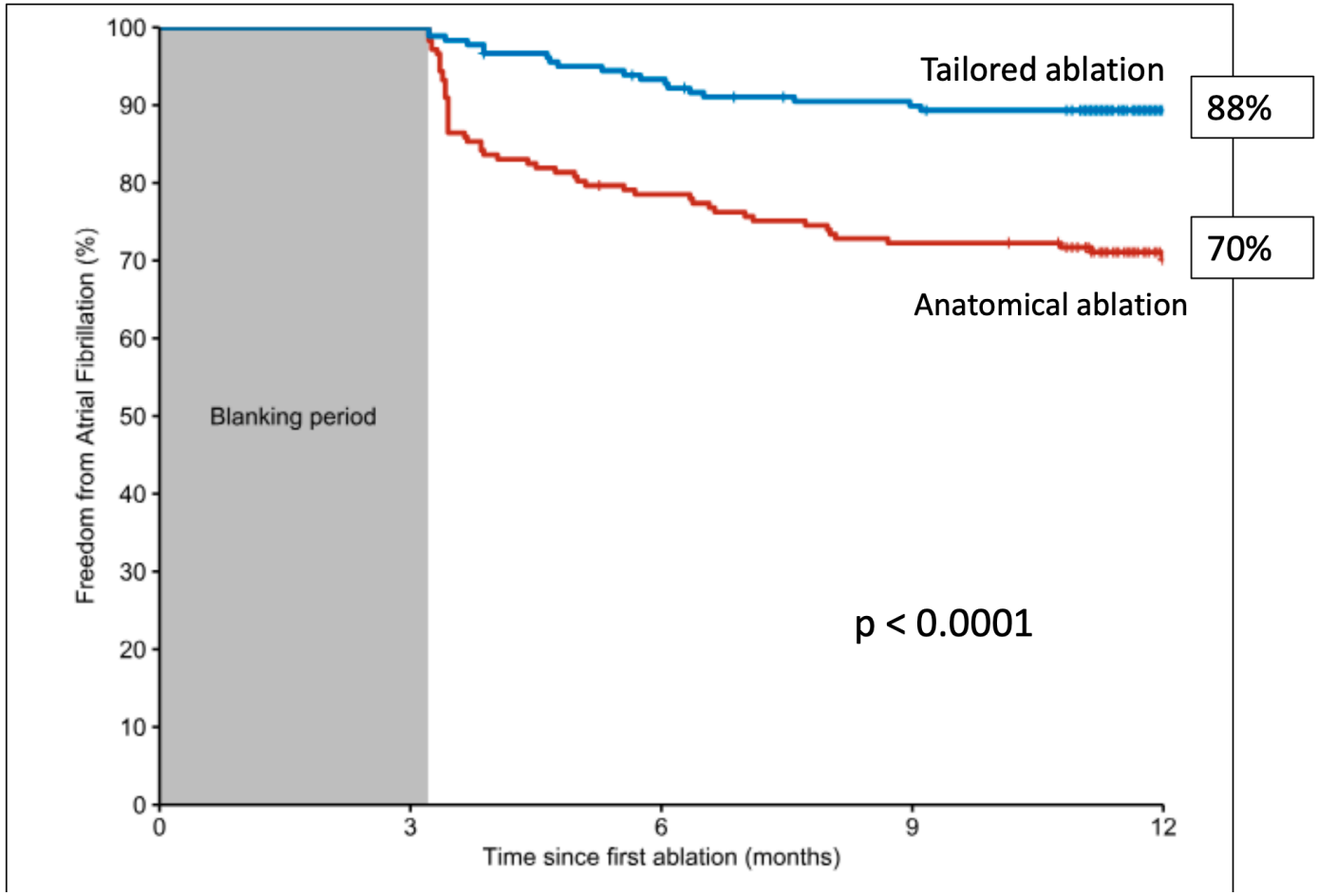
Characteristic	Tailored (N=187)	Anatomical (N=183)	*p*-value
Procedure time (min)	**178 ± 60**	**92 ± 36**	**P < 0.001**
3D nav ± AI mapping	**31 ± 22**	**10 ± 5**	**P < 0.001**
Additional Mapping Time (e.g. for AT)	**17 ± 15**	**n.a.**	**n.a.**
Fluoroscopy time (min)	9 ± 10	5 ± 4	P < 0.001
Total RF time (min)	42 ± 17	20 ± 11	P < 0.001
Acute atrial fibrillation termination by ablation – no. (%)	**122/186 (66)**	**26/169 (15)**	**P < 0.001**
Acute sinus rhythm conversion by ablation – no. (%)	100/187 (53)	23/172 (13)	P < 0.001

Deisenhofer I, et al. Presented at: Heart Rhythm Society (HRS) Annual Meeting; May 16-19, 2024; Boston, Massachusetts. Abstract LB-469805-01.

HRS 2024 LBCT: TAILORED-AF Primary Endpoint

Freedom from AF after 1 procedure, on/off AADs, at 12 months

ITT population



ITT = intention to treat.

Deisenhofer I, et al. Presented at: Heart Rhythm Society (HRS) Annual Meeting; May 16-19, 2024; Boston, Massachusetts. Abstract LB-469805-01.

Further Data Pending: Spatio-Temporal Dispersion-Guided Ablation

- RESTART study
- US-based, prospective single-arm study
- 95 patients for repeat ablation, with durable PVI found at time of second ablation enrolled
- Targeted ablation of STD sites during EPS

EPS = electrophysiology study.
Seitz J, et al. *J Am Coll Cardiol*. 2017;69(3):303-321.

Conclusions

- For EP, including specifically AF procedures, understanding and evaluation of complex electrograms is promising for improving outcomes in ablation for AF
- Various definitions of targets of interest have been evaluated over the years
- Most recently, studies targeting regions demonstrating spatio-temporal dispersion demonstrated improved freedom from AF

Thank You—Brigham and Women's Hospital Cardiac Arrhythmia Service

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Future

- More data! Beyond single institution small data sets
- Further detail—can we find more granular and actionable trends in the ablation lesion data?
- Validation—does a resultant alteration of ablation approach indeed result in improved FPI, improved lesion formation, improved clinical outcomes?
- Mapping data—can we predict/determine best ablation strategies to achieve optimal clinical outcomes?
- We are only getting started—much more to come on this!

FPI = first pass isolation.

Thank you!

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