nuova metodica per il trattamento della fibrilalzione atriale persistente

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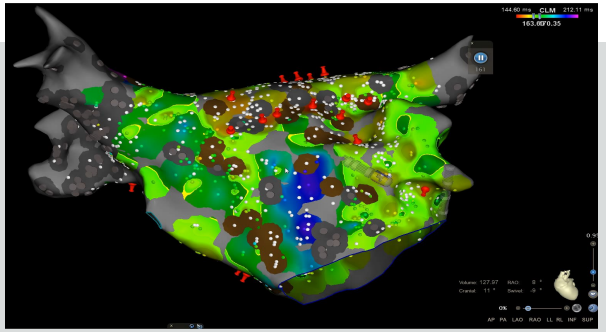
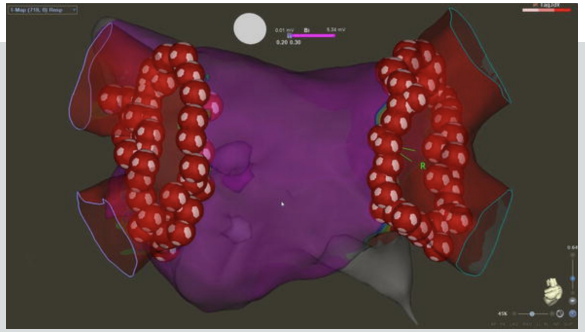




I.R.C.C.S.
POLICLINICO SAN DONATO

Atrial Fibrillation

- 5-fold increased risk of stroke [1]
- Increased risk of heart failure
- Impared QoL[3,4]
- Icreased health care costs[6]

THE CHALLENGE:

Adequate AF management aiming at reduction of stroke risk and QoL improvement [7]

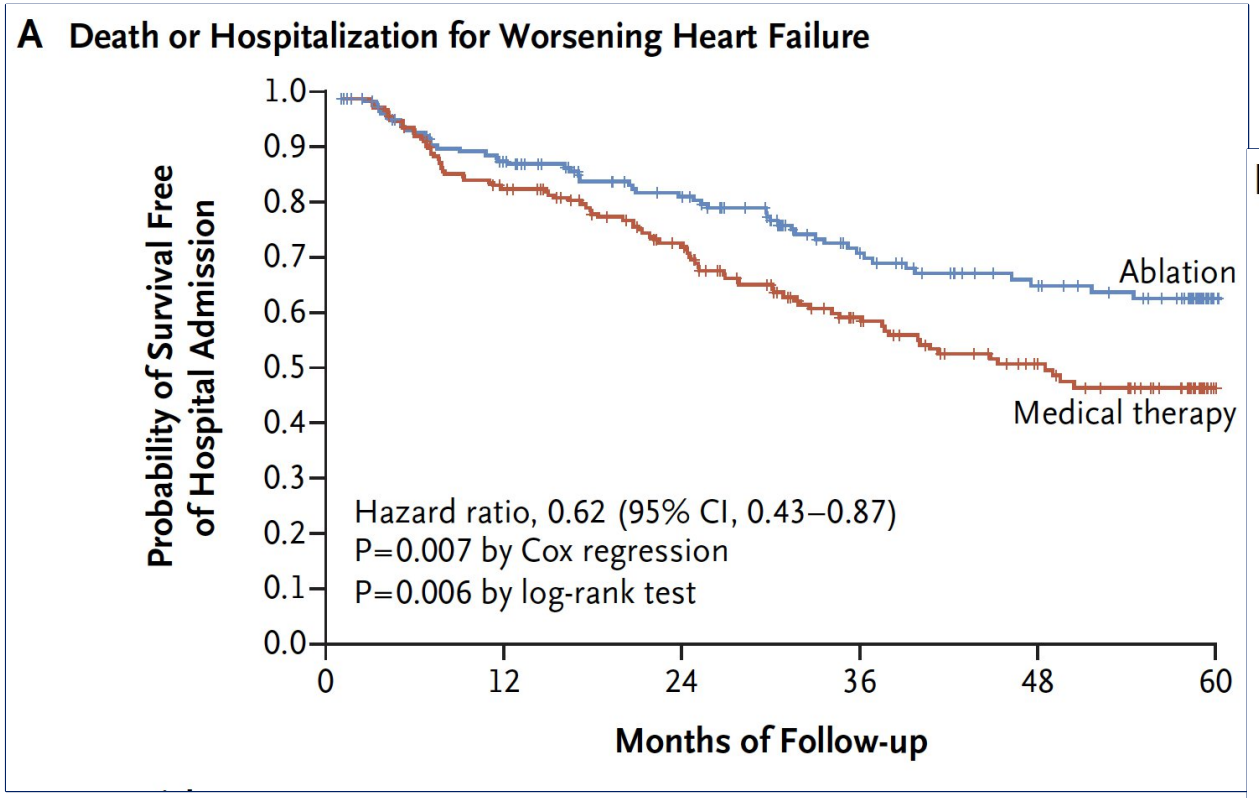
1Wolf PA, et al. Stroke. 1991;22:983-988.; 2 White PD: Heart disease. New York, NY, The McMillan Co, 1937.; 3 Singh SN, et al. J Am Coll Cardiol. 2006;48:721-730.; 4 Kang Y. Heart Lung. 2006;35:170-177.;5 Kim MH, et al. Adv.Ther. 2009;26:847-857. ; 6 Zoni-Berisso, et al. Clinical Epidemiology 2014:6 213–220.; 7 January CT, et al, J Am Coll Cardiol. 2014; 64:e1-e76.

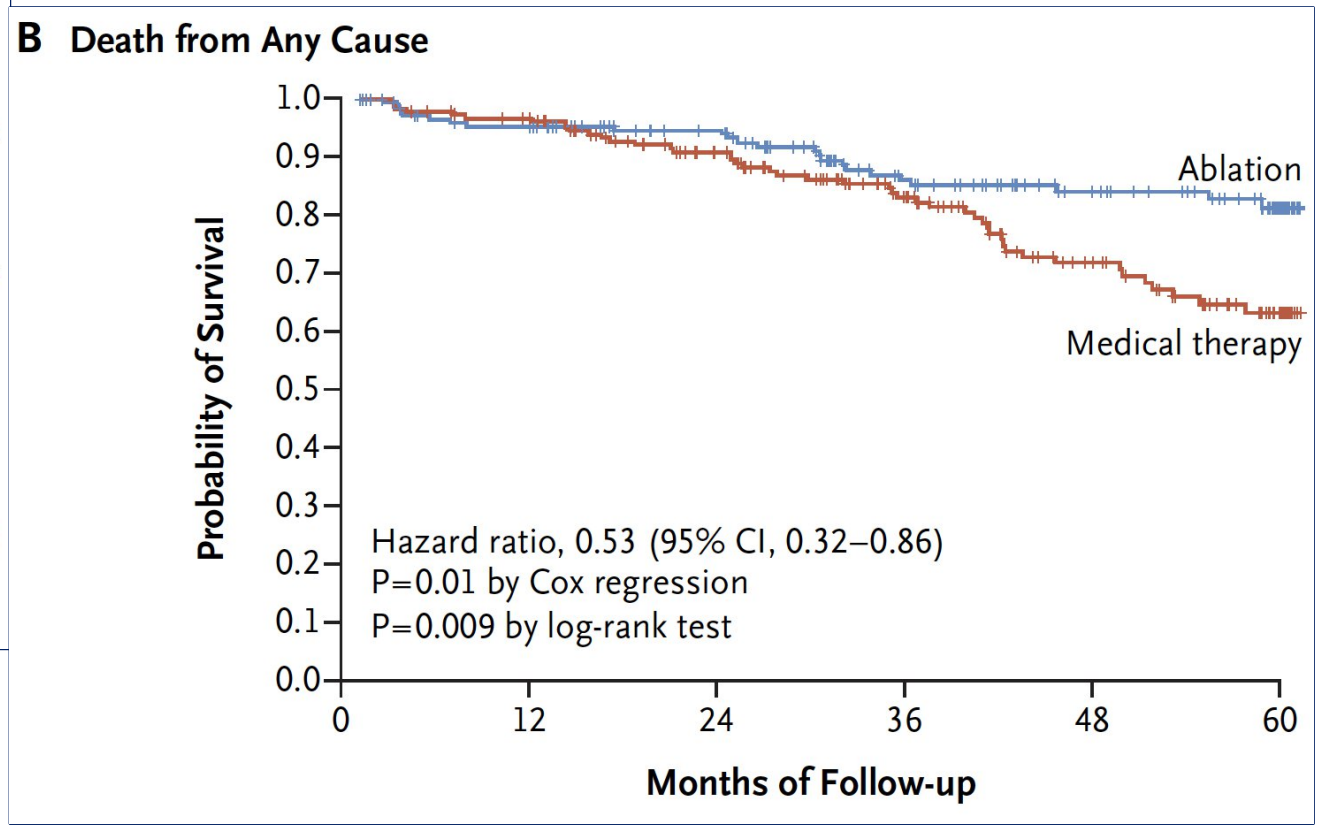
Catheter Ablation for Atrial Fibrillation with Heart Failure

Nassir F. Marrouche, M.D., Johannes Brachmann, M.D., Dietrich Andresen, M.D., Jürgen Siebels, M.D., Lucas Boersma, M.D., Luc Jordaens, M.D., Béla Merkely, M.D., Evgeny Pokushalov, M.D., Prashanthan Sanders, M.D., Jochen Proff, B.S., Heribert Schunkert, M.D., Hildegard Christ, M.D., Jürgen Vogt, M.D., and Dietmar Bänsch, M.D., for the CASTLE-AF Investigators*

- NYHA II, III, or IV
- EF < 35%
- ICD

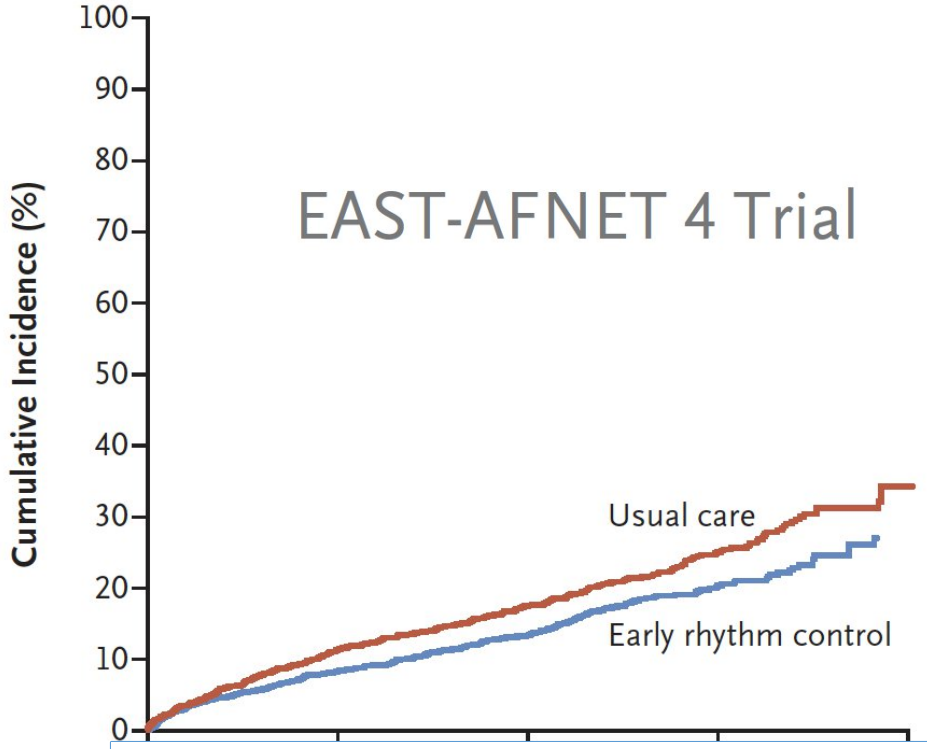
Characteristic	Treatment Type	
	Ablation (N=179)	Medical Therapy (N=184)
Type of atrial fibrillation — no. (%)		
Paroxysmal	54 (30)	64 (35)
Persistent	125 (70)	120 (65)
Long-standing persistent (duration >1 year)	51 (28)	55 (30)





Primary end point

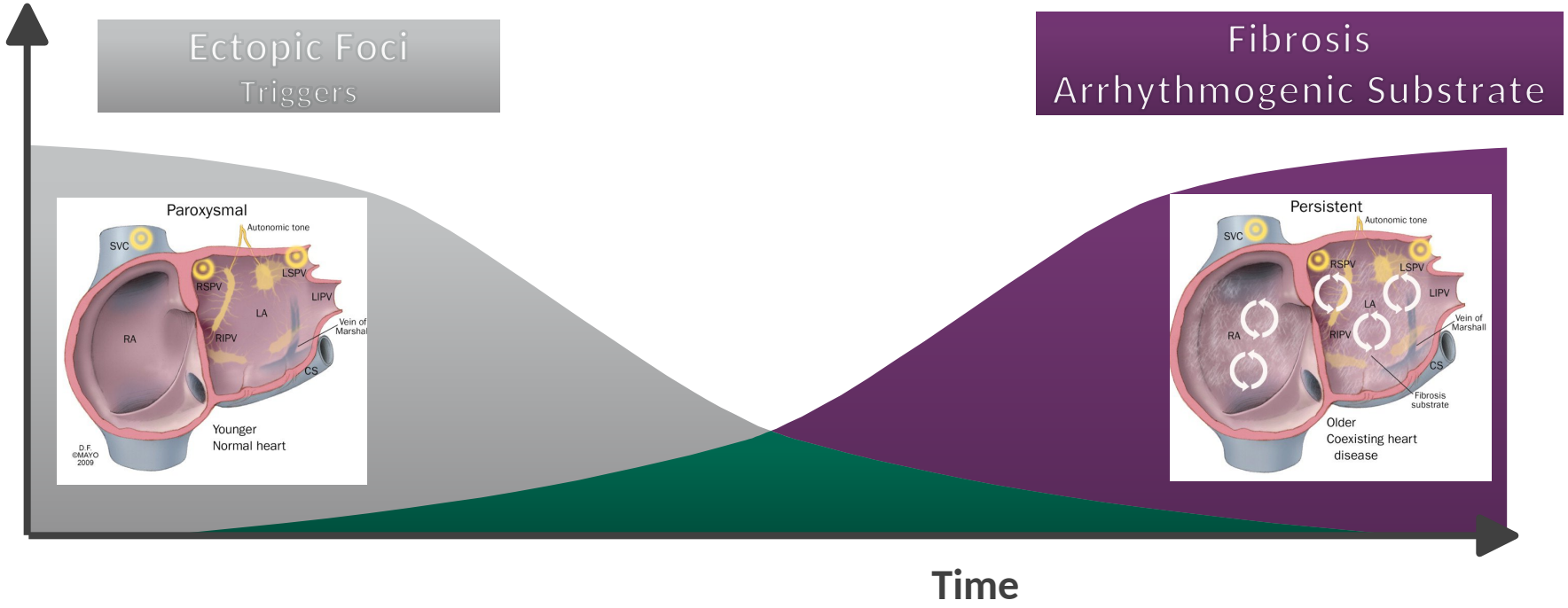
Early Rhythm-control therapy



Early rhythm-control therapy, primarily with AADs (<20% of patients had received ablation at 2-year follow-up), was associated with a lower risk of cardiovascular outcomes

Outcome	Early Rhythm Control (N=1395)	Usual Care (N=1394)
	number (percent)	
Primary composite safety outcome	231 (16.6)	223 (16.0)
Stroke	40 (2.9)	62 (4.4)
Death	138 (9.9)	164 (11.8)
Serious adverse event of special interest related to rhythm-control therapy	68 (4.9)	19 (1.4)

Atrial Fibrillation Evolution



Paroxysmal AF → **Persistent AF** → **Long-standing persistent AF**

Non-Paroxysmal AF ablation

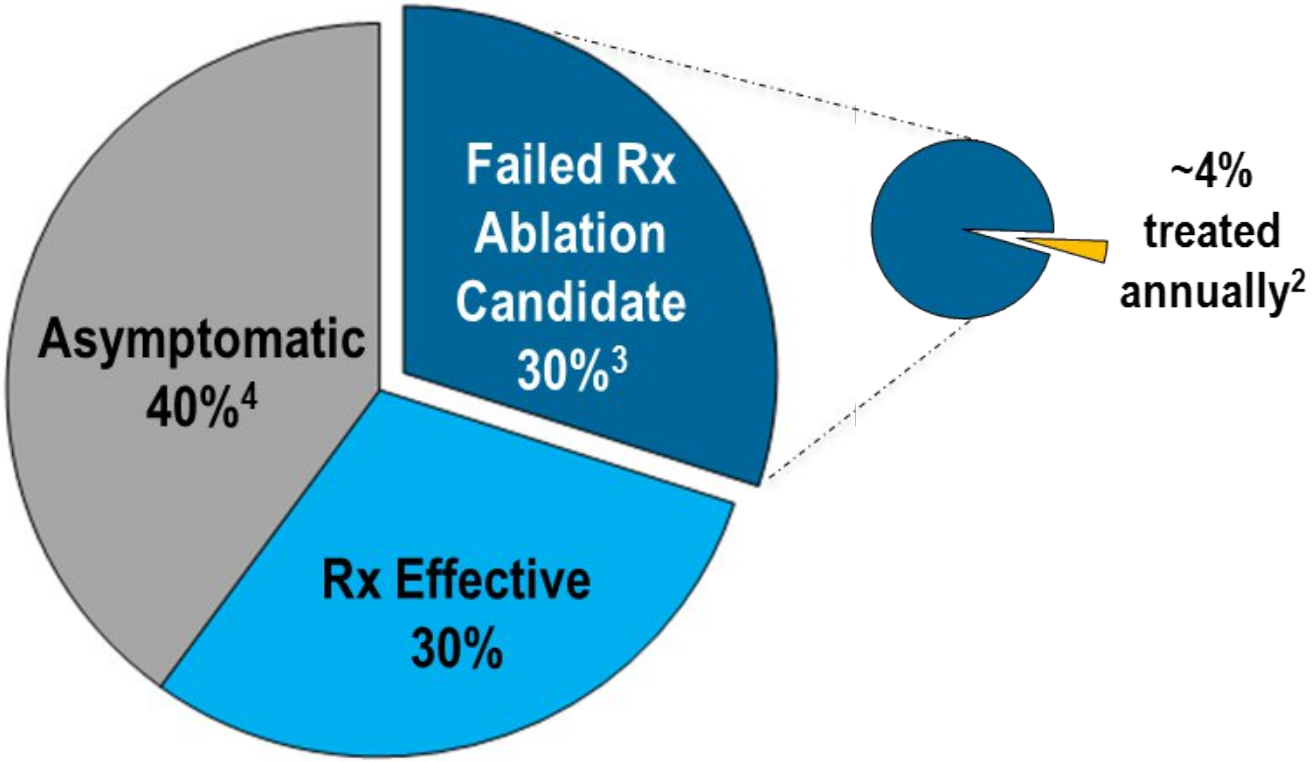
- Rates of success for persistent and long-standing persistent AF remain limited after single procedure

	After 1 procedure	After more than 1 procedure
Paroxysmal	70 % to 80%	roughly 90%
Persistent	40% to 60%	40% to 70%
Long-Standing	20% to 50%	35% to 60%

- Oral, Pappone et al. NEJM 2006
- Jones et al. JACC 2013
- Hummel et al. Heart Rhythm 2014
- Mont et al. Eur Heart J 2014
- Hunter et al. Heart Rhythm 2014
- Di Biase et al. Circulation 2016

AF IS UNDERTREATED

Global symptomatic AF prevalence >33 million



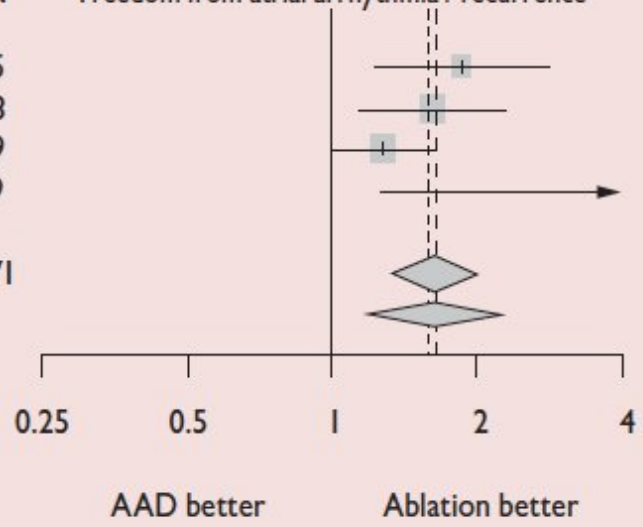
Calkins H, et al. *Heart Rhythm*, 2012

Pers-AF: fewer data available but….

Freedom from recurrence of atrial fibrillation or atrial arrhythmias, comparing catheter ablation with antiarrhythmic drug therapy in patients with persistent or long-standing persistent atrial fibrillation

Study	Ablation Events	Ablation N	AAD Events	AAD N	RR	95% CI	W(fixed)	W(random)
Forleo	28	35	15	35	1.87	[1.23; 2.83]	17.5%	27.7%
Mont 2009	69	98	21	48	1.61	[1.14; 2.27]	32.8%	32.0%
Oral 2006	57	77	40	69	1.28	[1.00; 1.62]	49.1%	38.9%
Stabile 2006	13	26	0	19	20.00	[1.26; 319.89]	0.7%	1.4%
Fixed effects model		236		171	1.61	[1.34; 1.94]	100%	-
Random effects model					1.59	[1.14; 2.22]	-	100%

Heterogeneity:I-squared = 58,9%, p= 0.063



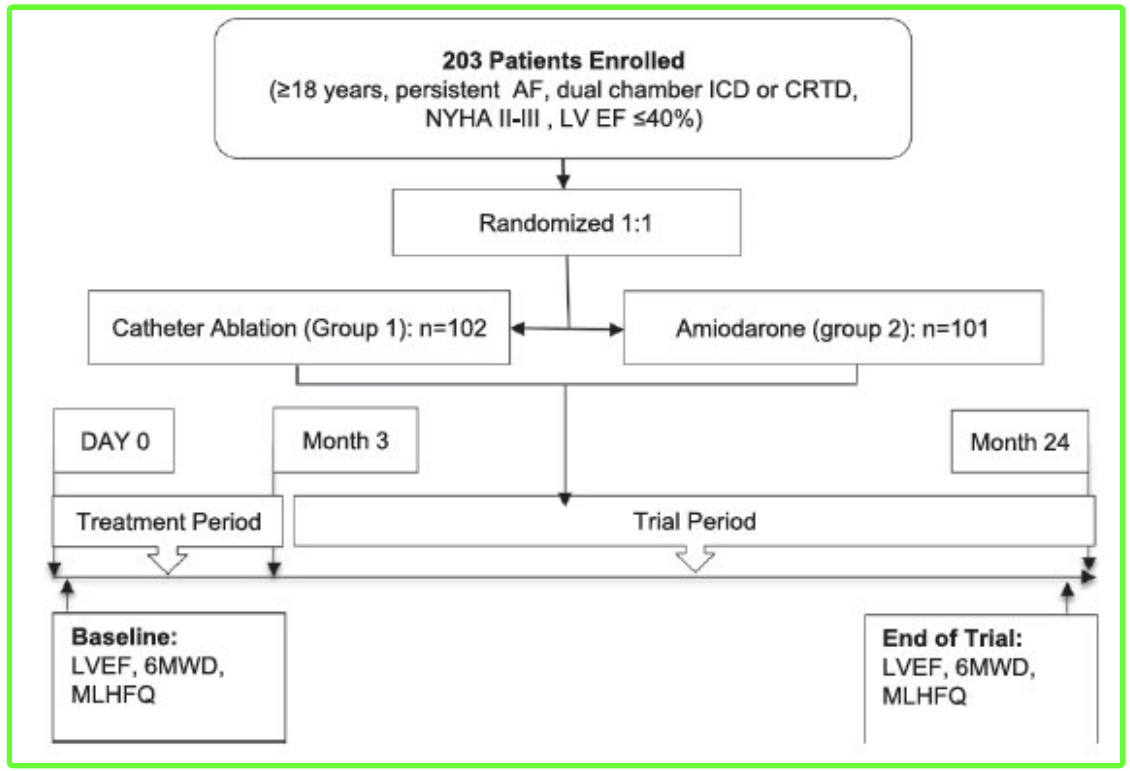
Lower recurrence rates after CA

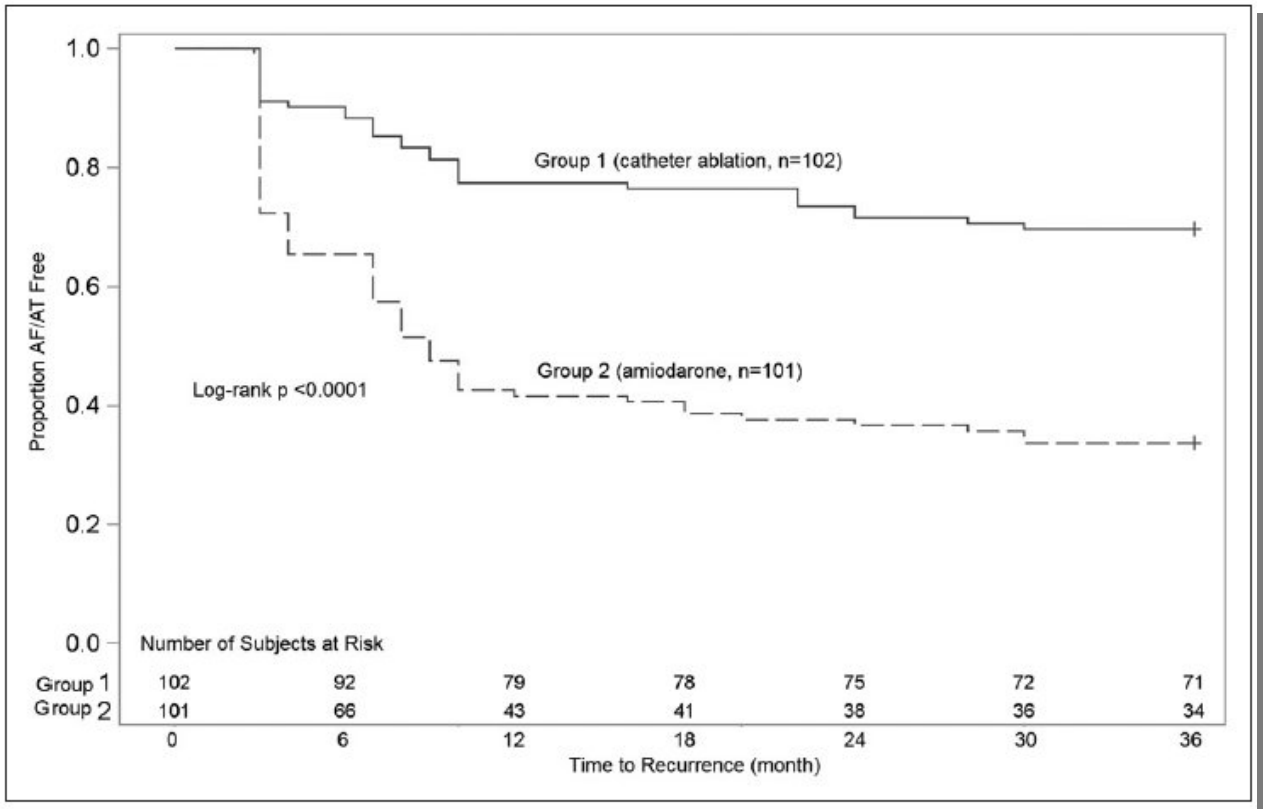
ESC Guidleines 2016

Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device

Results From the AATAC Multicenter Randomized Trial

Luigi Di Biase, MD, PhD; Prasant Mohanty, MBBS, MPH; Sanghamitra Mohanty, MD; Pasquale Santangeli, MD; Chintan Trivedi, MD, MPH; Dhanunjaya Lakkireddy, MD; Madhu Reddy, MD; Pierre Jais, MD; Sakis Themistoclakis, MD; Antonio Dello Russo, MD; Michela Casella, MD; Gemma Pelargonio, MD; Maria Lucia Narducci, MD; Robert Schweikert, MD; Petr Neuzil, MD; Javier Sanchez, MD; Rodney Horton, MD; Salwa Beheiry, RN; Richard Hongo, MD; Steven Hao, MD; Antonio Rossillo, MD; Giovanni Forleo, MD; Claudio Tondo, MD; J. David Burkhardt, MD; Michel Haissaguerre, MD; Andrea Natale, MD





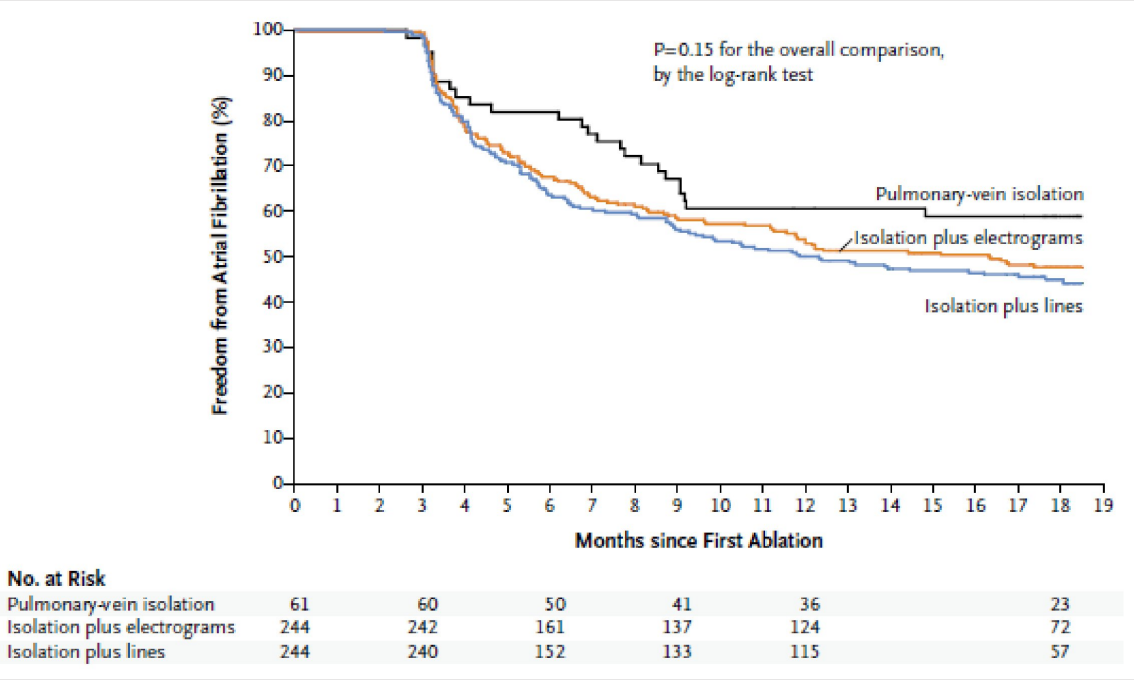
Circulation 2016

Atrial Fibrillation

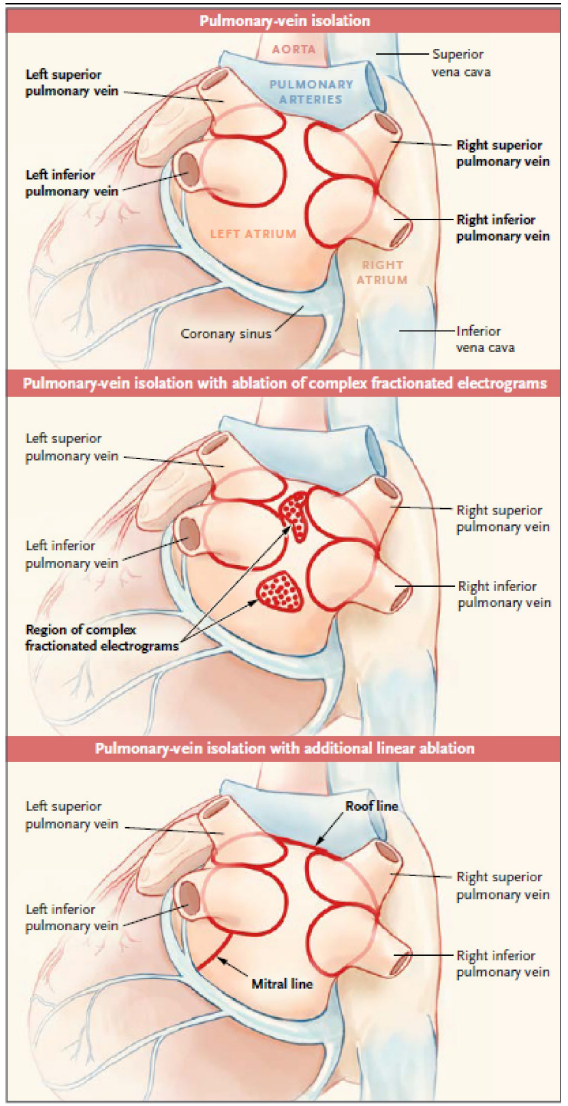
Radiofrequency Catheter Ablation

Approaches to Catheter Ablation for Persistent Atrial Fibrillation

Atul Verma, M.D., Chen-yang Jiang, M.D., Timothy R. Betts, M.D., M.B., Ch.B., Jian Chen, M.D., Isabel Deisenhofer, M.D., Roberto Mantovan, M.D., Ph.D., Laurent Macle, M.D., Carlos A. Morillo, M.D., Wilhelm Haverkamp, M.D., Ph.D., Rukshen Weerasooriya, M.D., Jean-Paul Albenque, M.D., Stefano Nardi, M.D., Endrj Menardi, M.D., Paul Novak, M.D., and Prashanthan Sanders, M.B., B.S., Ph.D., for the STAR AF II Investigators*



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



Verma A, et al. STAR AF II Trial. NEJM 2015

Atrial Fibrillation

Strategies for Catheter Ablation

Left atrial linear lesion
successful treatment o
Spectral Analysis Identifies S
Maintaining Atrial F

Prashanthan Sanders, MBBS, PhD*; Omer Bere
Ravi Vaidyanathan, BE; Li-Fern Hsu
Yoshihide Takahashi, MD; Martin Rotter, MI
Robert Ploutz-Snyder, PhD; José

Ablation of Rotor and Focal Sources Reduces Late Recurrence of Atrial Fibrillation Compared With Trigger Ablation Alone

Extended Follow-Up of the CONFIRM Trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation)

Sanjiv M. Narayan, MD, PhD,*† Tina Baykaner, MD,*† Paul Clopton, MS,† Amir Schricker, MD,*† Gautam G. Lalani, MD,*† David E. Krummen, MD,*† Kalyanam Shivkumar, MD, PhD,‡ John M. Miller, MD§

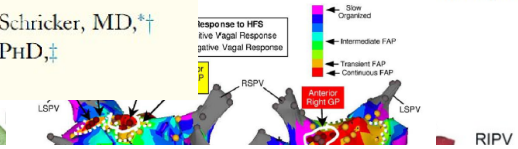
Left Anterior Oblique

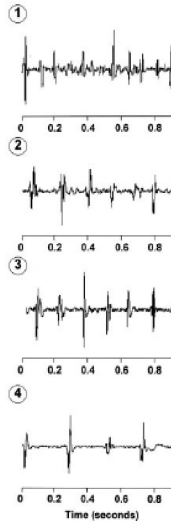
Posterior-Anterior

itonomic ganglionated plexus
rial fibrillation

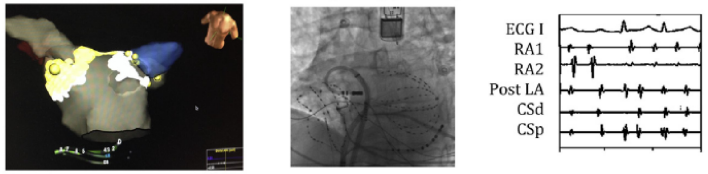
erlag, PhD, Eugene Patterson, PhD,
BM, BCh, MA, Warren M. Jackman, MD, FHRS

Medicine, University of Oklahoma Health Sciences Center,

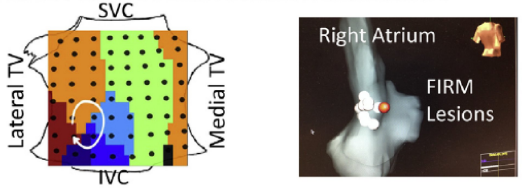




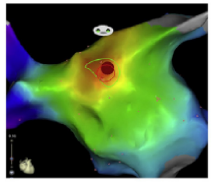
A
AF Despite WACA/Roof Line, Mapped by FIRM

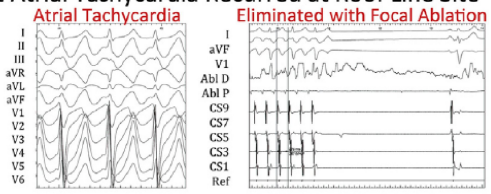


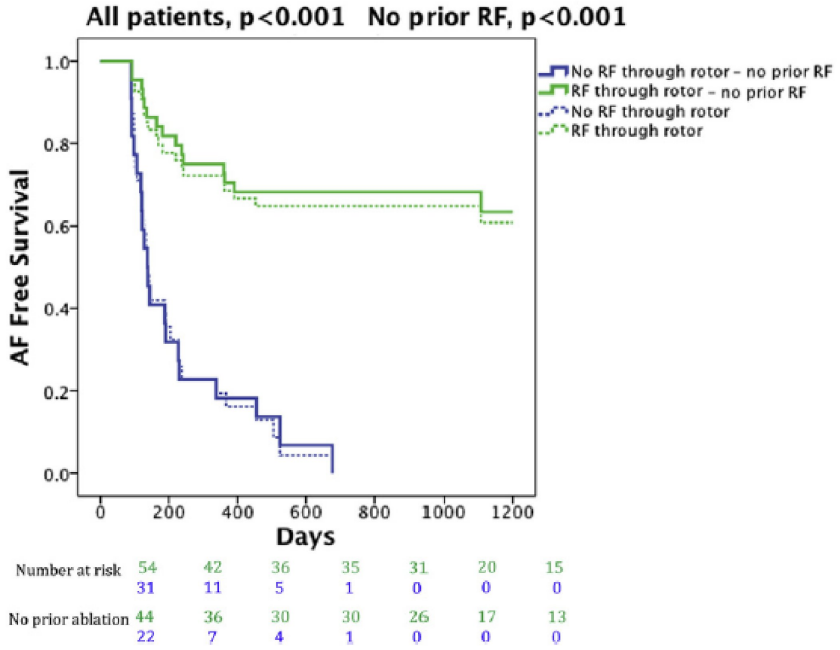
B
RA Rotor, Where FIRM Ablation Eliminates AF



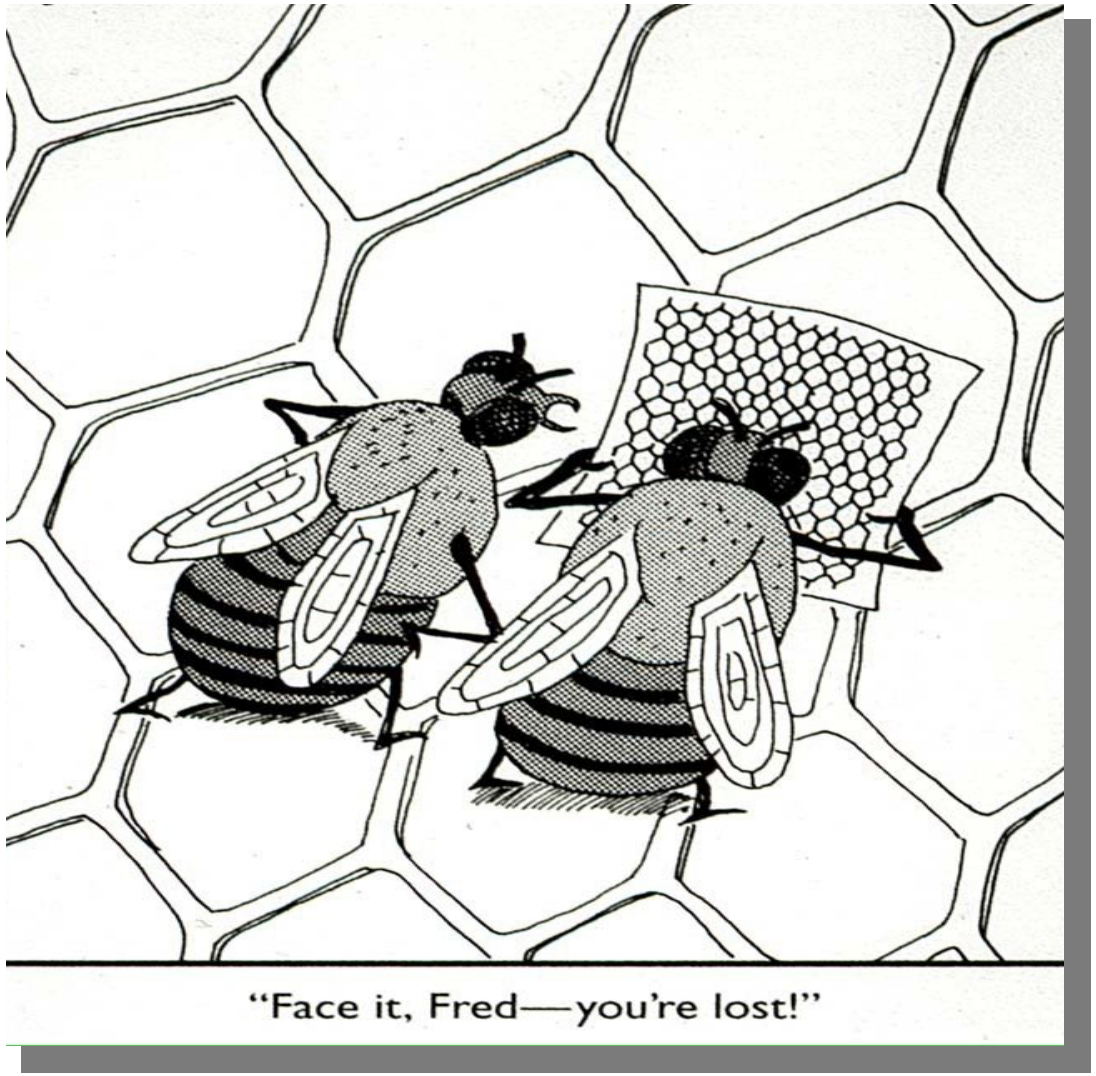
C
At 852 days, No AF but Atrial Tachycardia Recurred at Roof Line Site







- Narayan S, et al. JACC 2014



"Face it, Fred—you're lost!"

Limitations in Current Atrial Fibrillation Treatment

- Incomplete understanding regarding arrhythmogenic mechanism
- Different mechanisms in paroxysmal and persistent AF remain unknown
- Absence of real-time three-dimensional AF substrate mapping, current AF ablation therapy remains an anatomical approach NOT a mechanism targeted therapy
- **Current standard of care – One treatment for ALL, not patient-specific (PVI)!!!!!!**

ESC European Society of Cardiology
Europace (2019) 21, 1193–1202
doi:10.1093/europace/euz123

Non-paroxysmal atrial fibrillation mapping: characterization of the electrophysiological substrate using a novel integrated mapping technique

Giuseppe Ciconte[1], Gabriele Vicedomini[1], Wenwen Li[2], Jan O. Mangual[2], Luke McSpadden[2], Kyungmoo Ryu[2], Massimo Saviano[1], Raffaele Vitale[1], Manuel Conti[1], Žarko Calović[1], Vincenzo Santinelli[1], and Carlo Pappone [1]*

- Consecutive 83 pts with non-PAF (Pers and LSPers)
- All undergoing blinded high-density AF mapping (dedicated CL EnSite software and 20 poles circular mapping catheter)
- RFCA with standard lesion set (mCPVA): PVI, mitral line and posterior box isolation
- High density AF mapping repeated if AF persisted after ablation

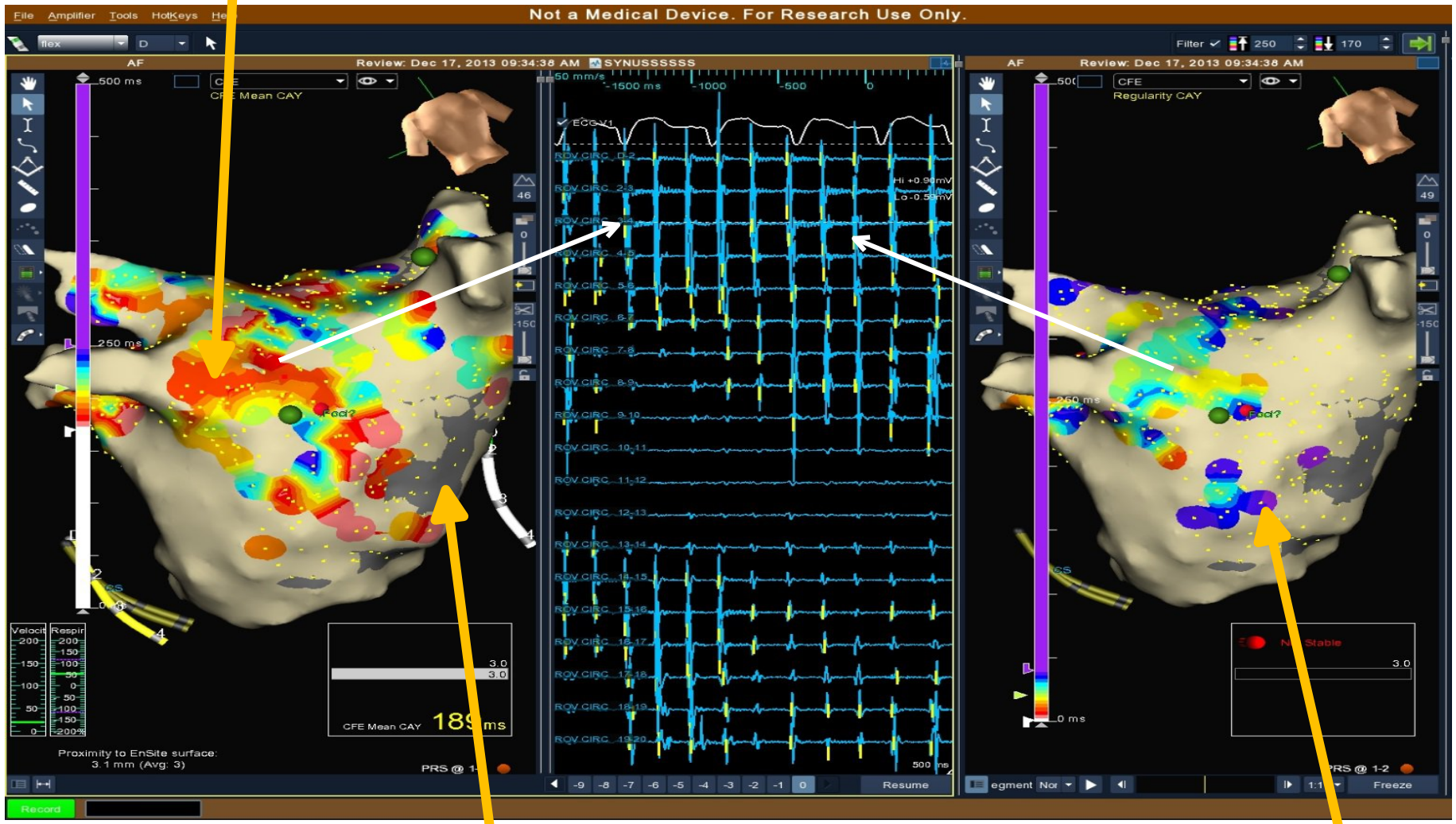
Ciconte G, ….. Pappone C. Europace 20

Cycle Lenght Mapping

Fastest

Mean CL (150~250 ms)

Stdev of CL (1~40 ms)



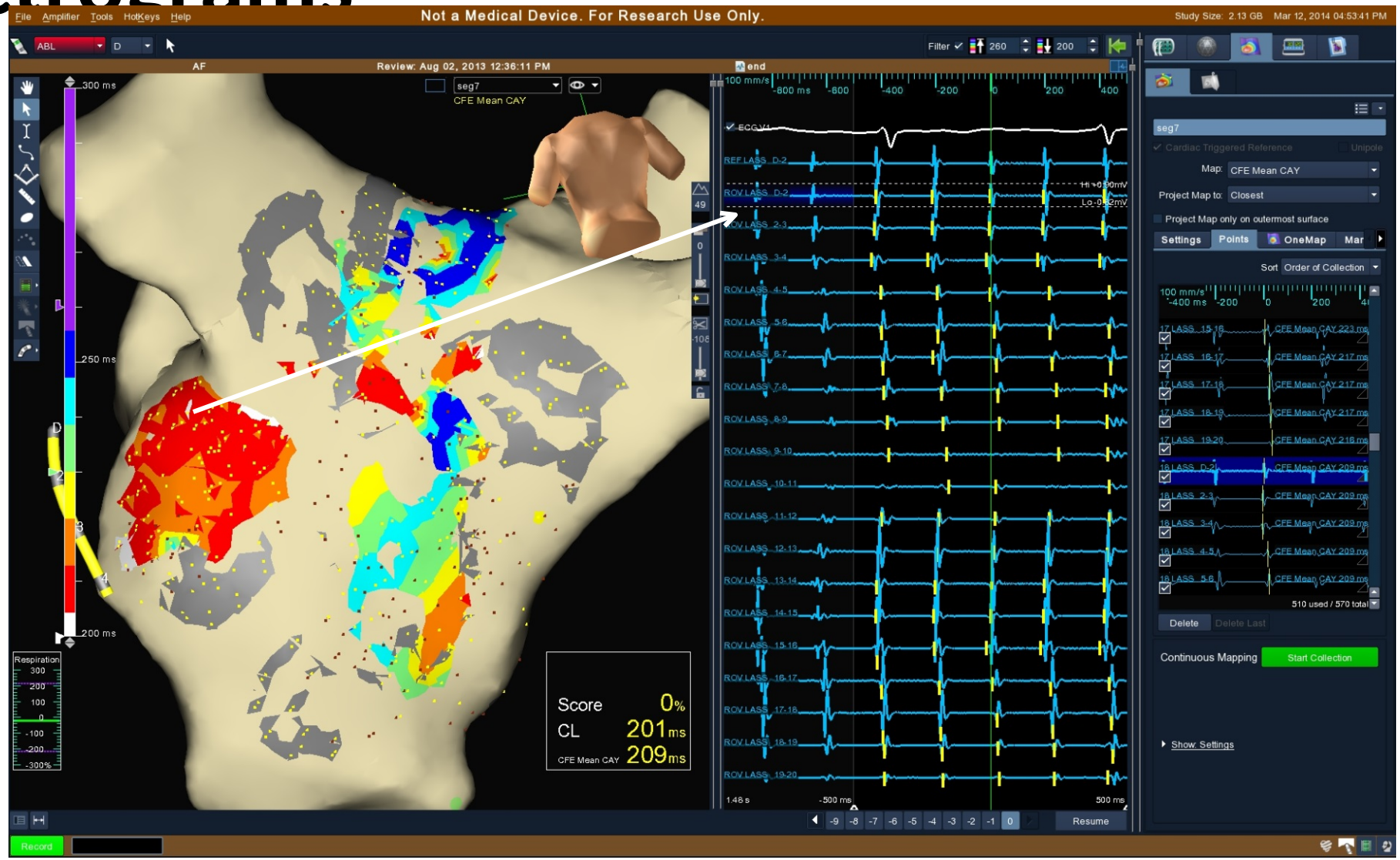
Scar areas

Slowest

Repetitive-regular EGMs show mean CL <250 ms and a SD of CL range 0-30 ms.
Slower activities (>250 ms) were not considered in this analysis to exclude potential bystander areas

The software allows to adjust this cut-off, according to each patient specific characteristics.

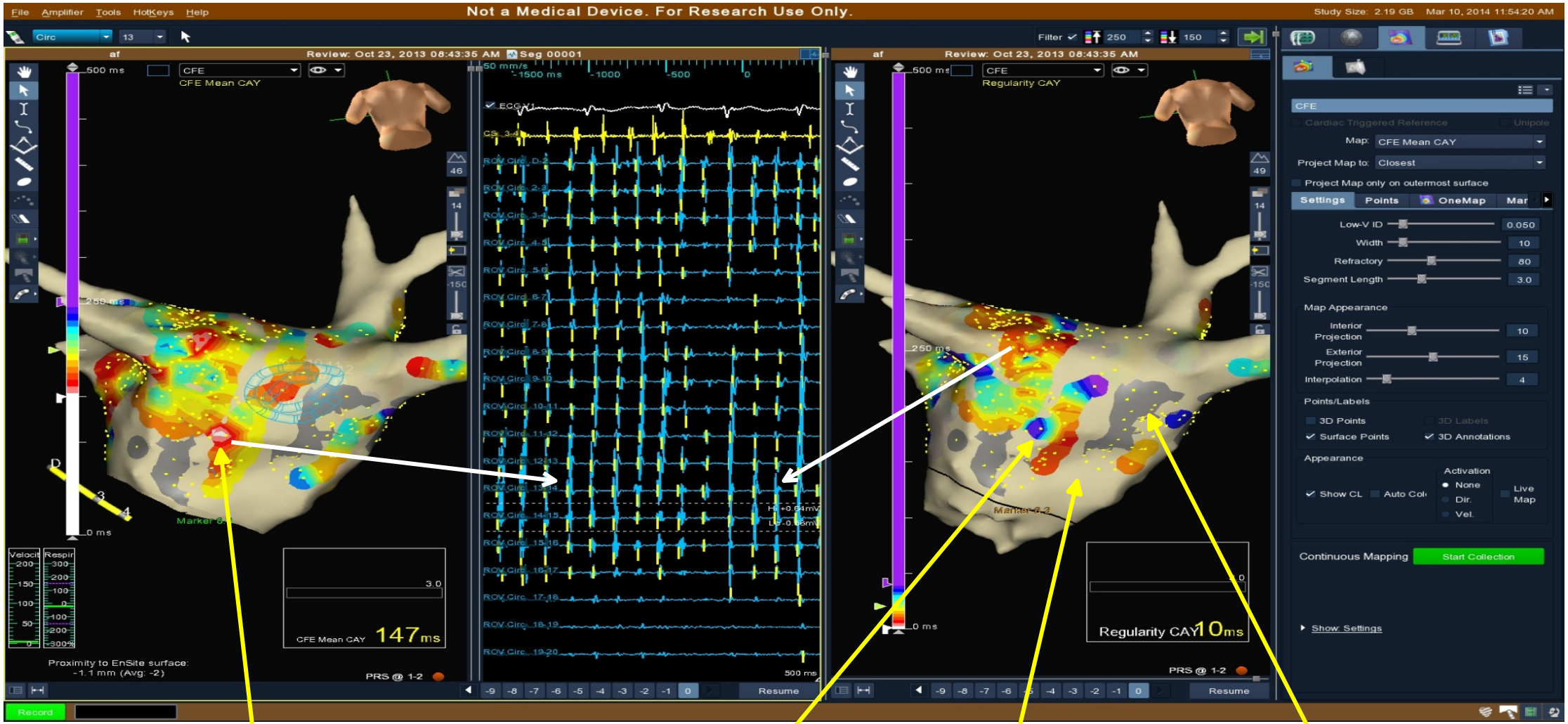
Regular CL map and Example of Electrograms



Software algorithm

Mean CL
(150~250 ms)

Stdev of CL
(1~40 ms)



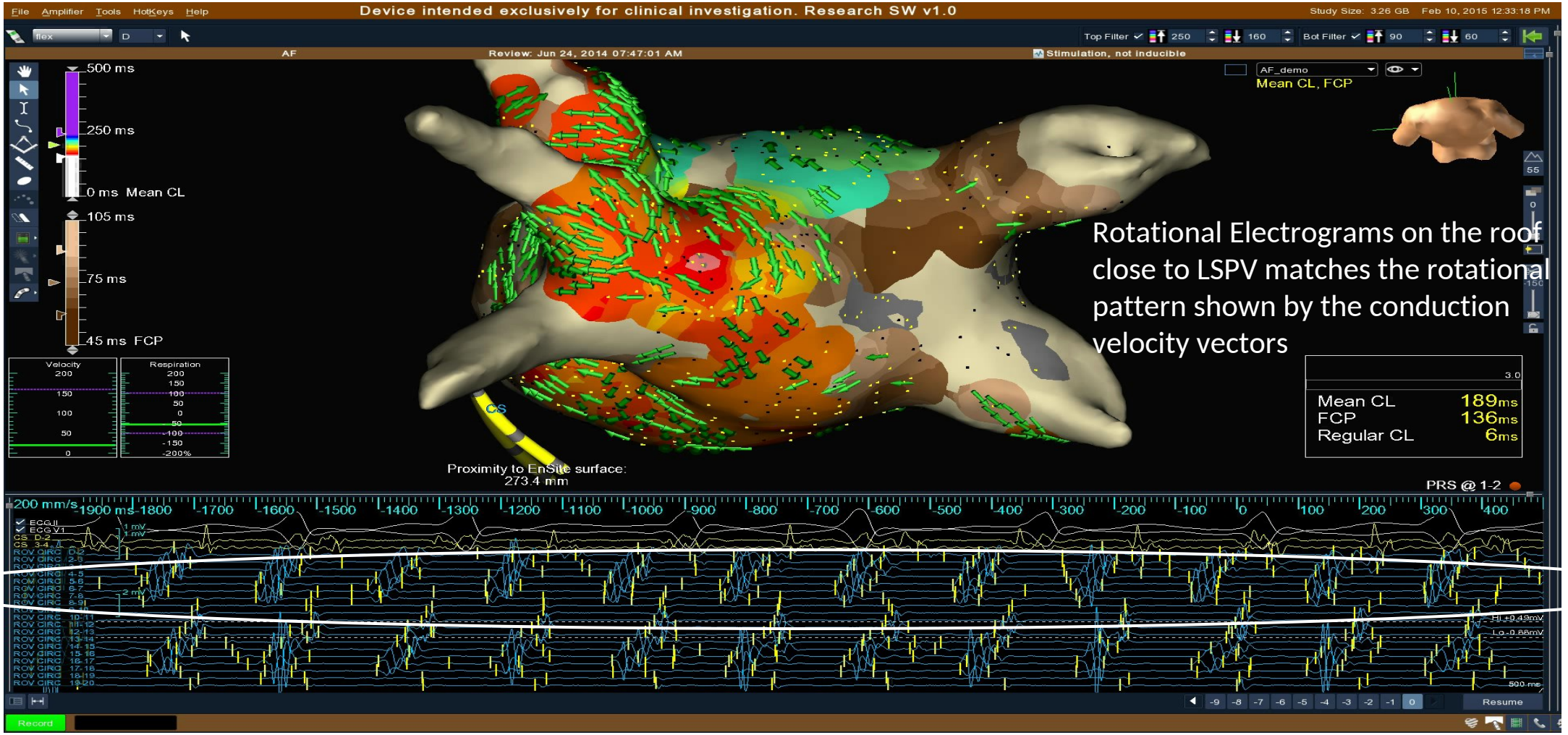
Fastest driver

Slowest driver

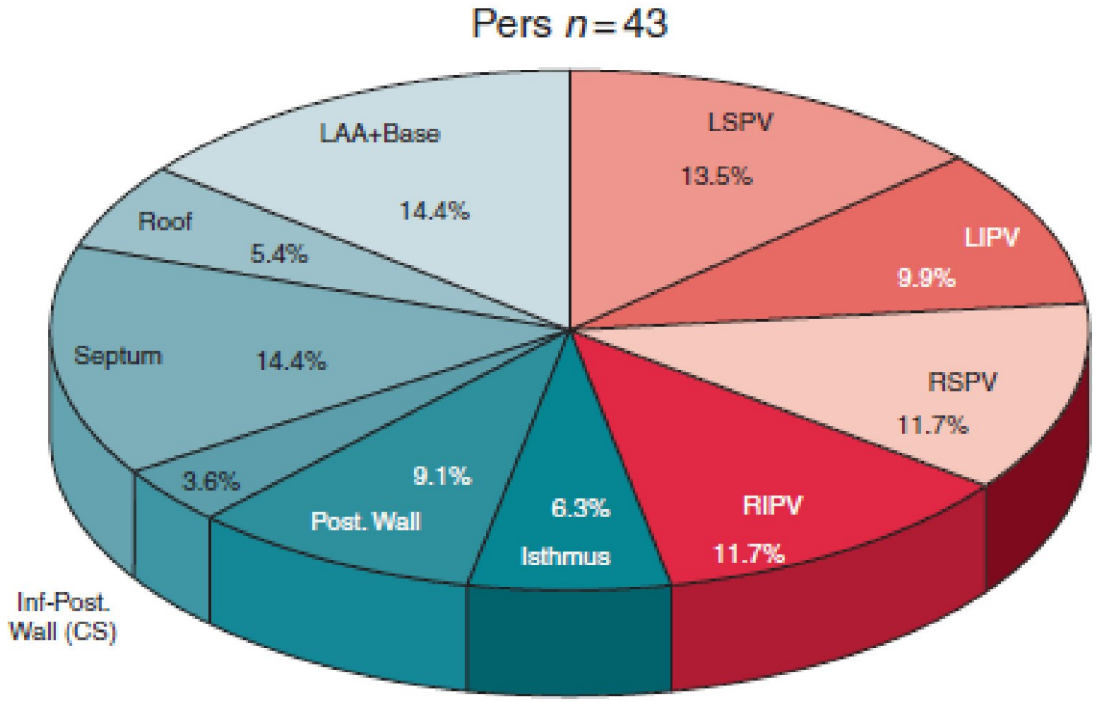
Fragmented

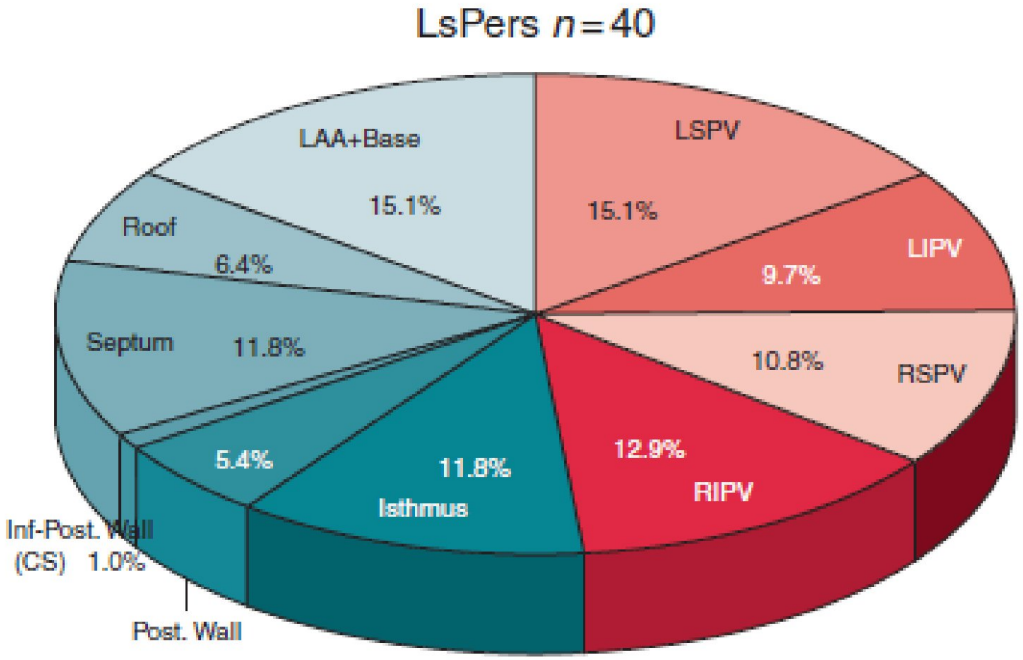
SCAR Areas

AF Integrated Substrate Map: Roof Rotor Detailed Dynamic View



AF SOURCES distribution

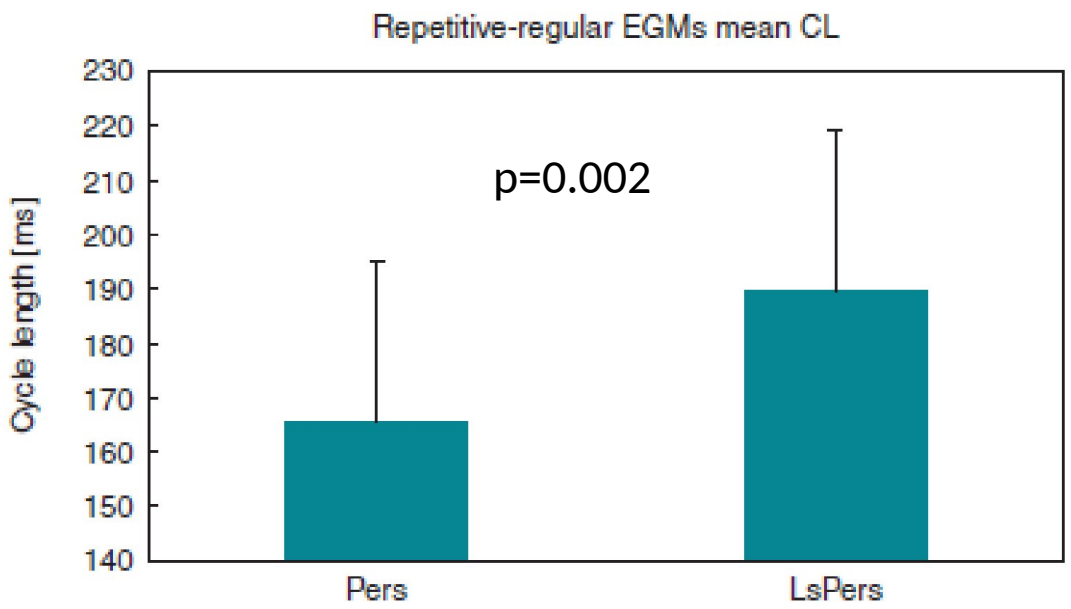


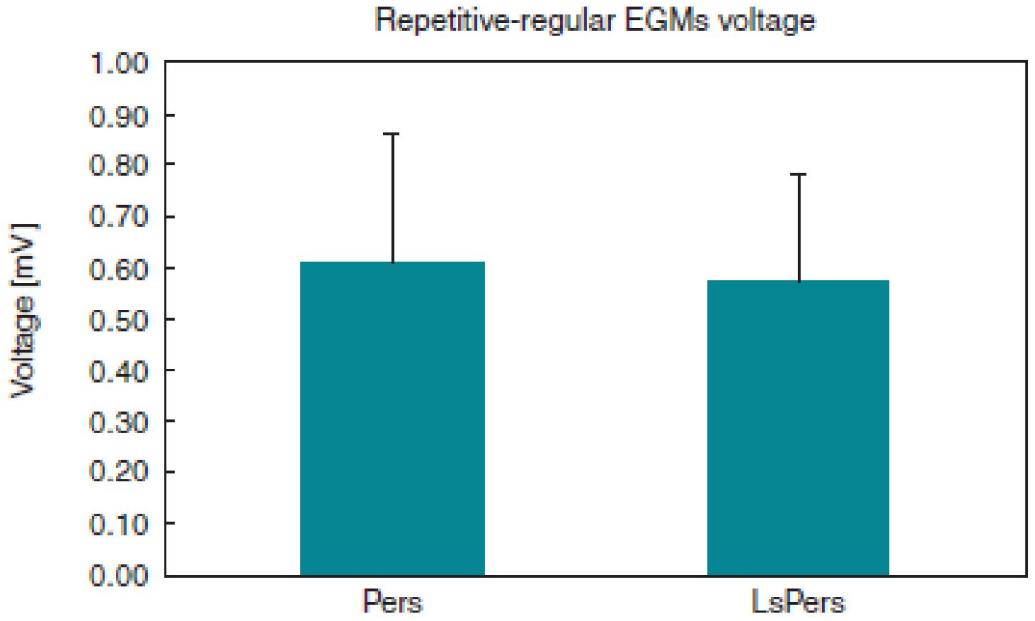


- Regions with RepReg-EGMs were 376.
- 174/376 (46%) were identified in the PVs antrum
- 202/376 (54%) in non-PV regions.
- Integrated substrate map showed that 75% Rep-Reg regions were surrounded by fragmented activities.

Ciconte G, ….. Pappone C. Europace

AF SOURCES characteristichs





- PersAF patients showed faster RepReg EGM regions as compared to LSPersAF.

Ciconte G, ….. Pappone C. Europace

AF SOURCES characteristichs

Table 2 Electrophysiological substrate clinical characteristics

	Overall ($n = 83$)	PersAF ($n = 43$)	LsPersAF ($n = 40$)	P-value
Baseline electrophysiological substrate characteristics				
Mean CV (m/s)	0.38 ± 0.10	0.37 ± 0.11	0.39 ± 0.09	0.37
Mean voltage (mV)	0.59 ± 0.22	0.64 ± 0.24	0.55 ± 0.21	0.08
Mean RR-EGM CL (ms)	180 ± 31	166 ± 29	190 ± 29	<0.001[a]
Mean fragmented EGM CL (ms)	88 ± 25	85 ± 24	90 ± 26	0.36
Surface area (%) of substrate				
RR-EGMs (%)	20 ± 10	21 ± 11	19 ± 10	0.39
Fragmented EGMs (%)	23 ± 17	15 ± 14	27 ± 17	<0.001[a]
Voltage <0.05 mV area (%)	14 ± 12	12 ± 9	17 ± 13	0.04[a]

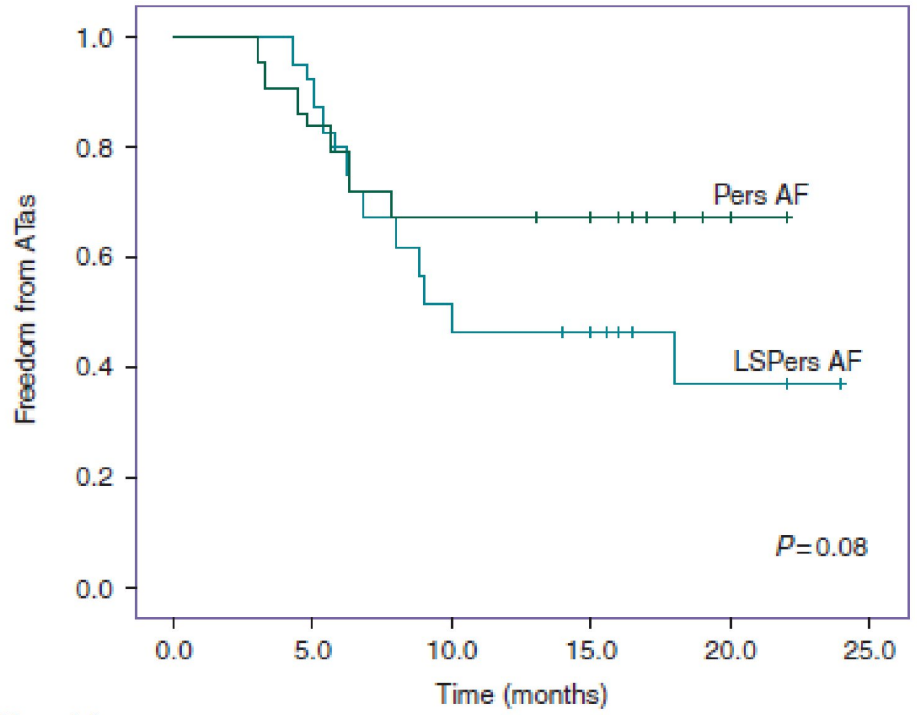
PersAF patients had faster mean RepReg-EGMs, while LSPersAF showed a larger surface area exhibiting fragmentation

Ciconte G, ….. Pappone C. Europace

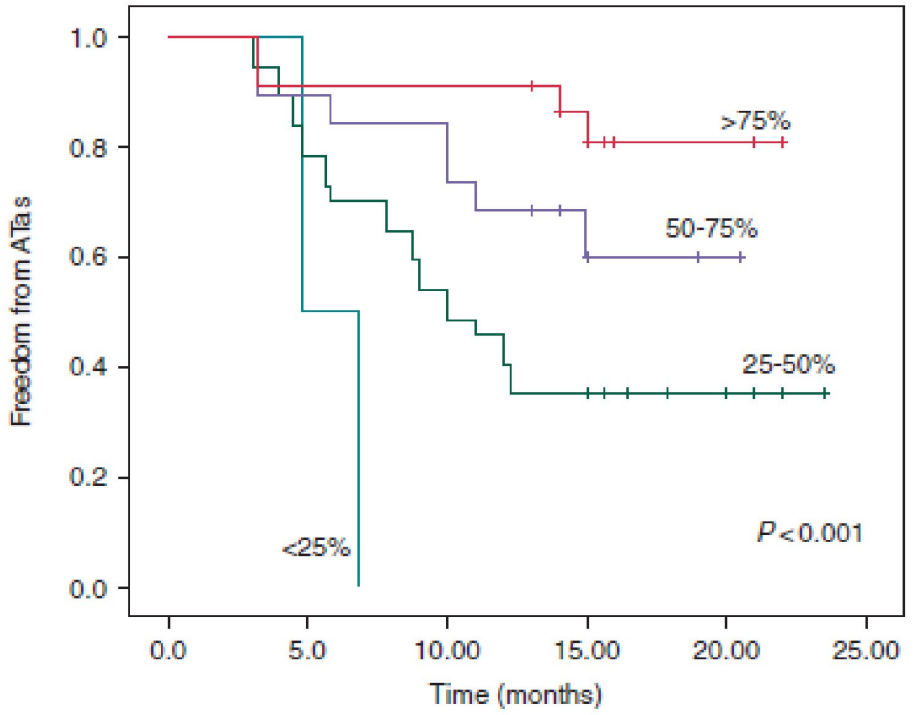
Atrial fibrillation termination by CPVA

- Radiofrequency catheter ablation terminated AF in 33 patients: 19 in PersAF group (19/33, 58%), 14 in LSPersAF group (14/33, 42%; P= 0.50).
- Atrial fibrillation termination occurred during ablation in regions exhibiting RR-EGMs in 31/33 cases (94%).
- Patients converting to SR during ablation had more RR-EGMs ablated than those remaining in AF (4.00 ± 2.06 vs. 2.81 ± 1.45; P =0.003).
- Patients experiencing SR conversion during ablation showed a 63% AF freedom, although not significantly different as compared to those who did not (21/33, 63% vs. 23/50 46%, P=0.12).

CLINICAL OUTCOME



N. at risk						
Pers AF	43	36	29	24	6	0
LSPers AF	40	35	18	16	4	0



N. at risk						
Q1: <25% RR EGMs	4	2	2	0	0	0
Q2: 25-50% RR EGMs	37	29	18	10	6	0
Q3: 50-75% RR EGMs	19	17	14	4	2	0
Q4: >75% RR EGMs	23	21	21	9	2	0

At the latest follow-up, arrhythmia freedom was higher among patients receiving ablation >75% of Rep-Reg sites (Q4 82.6%, Q3 63.1%, Q2 35.1%, and Q1 0%; P< 0.001).

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Circulation:
Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

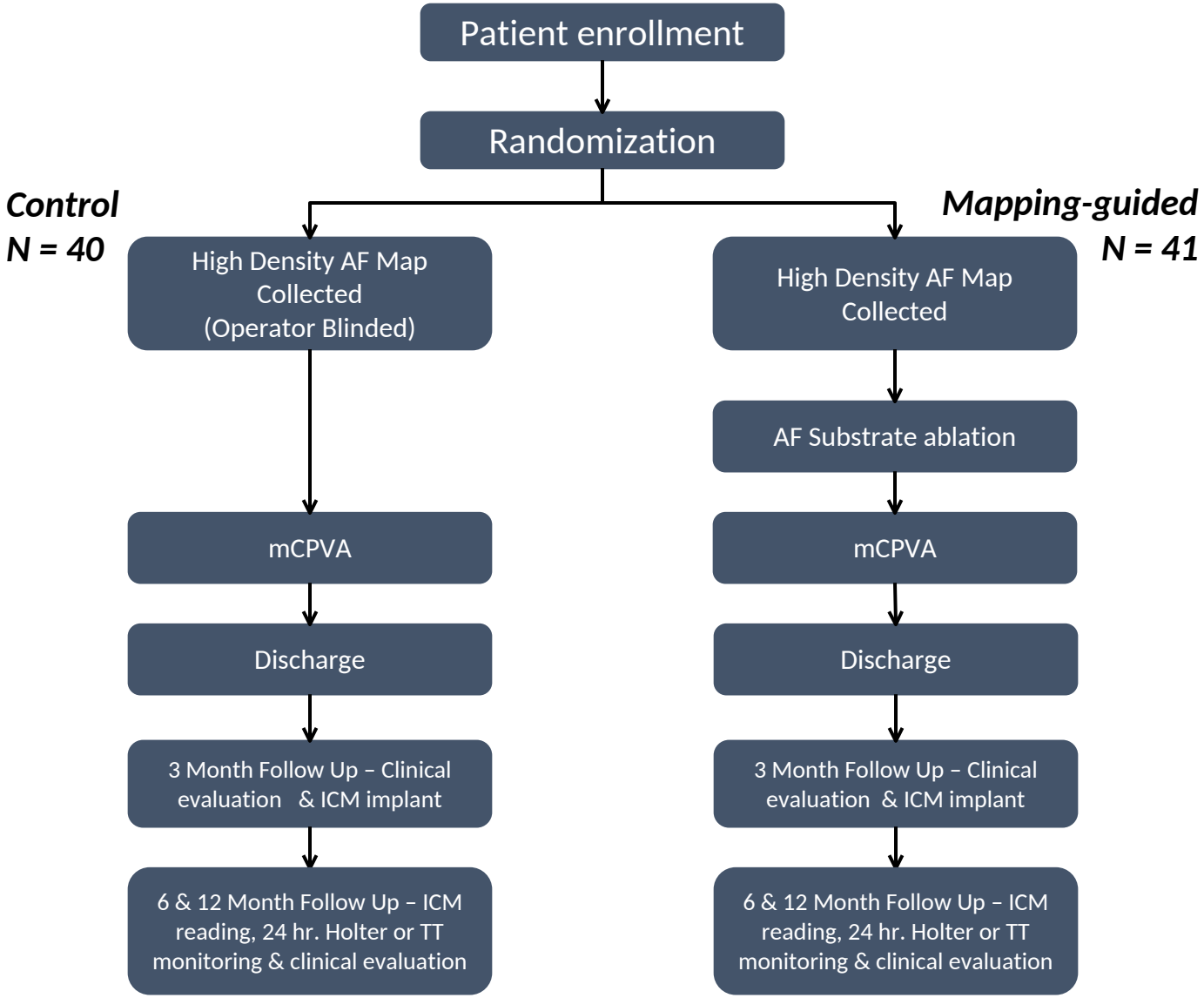
Clinical Outcome of Electrophysiologically Guided Ablation for Nonparoxysmal Atrial Fibrillation Using a Novel Real-Time 3-Dimensional Mapping Technique

Results From a Prospective Randomized Trial

Clinical Trial Registration:

URL: https://www.clinicaltrials.gov. Unique identifier NCT02571218

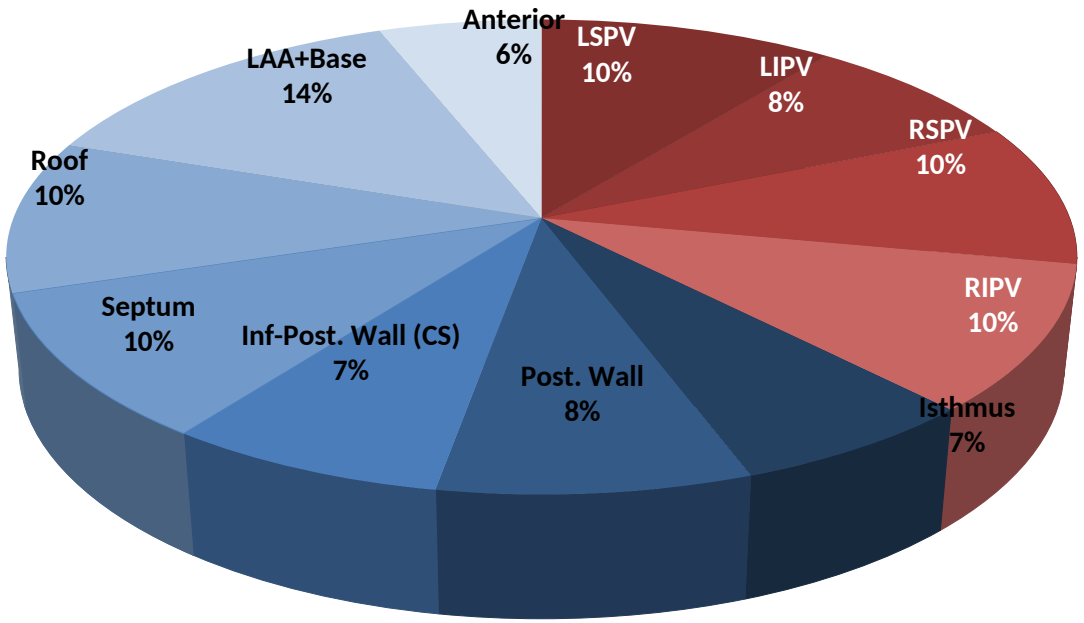
METHODS



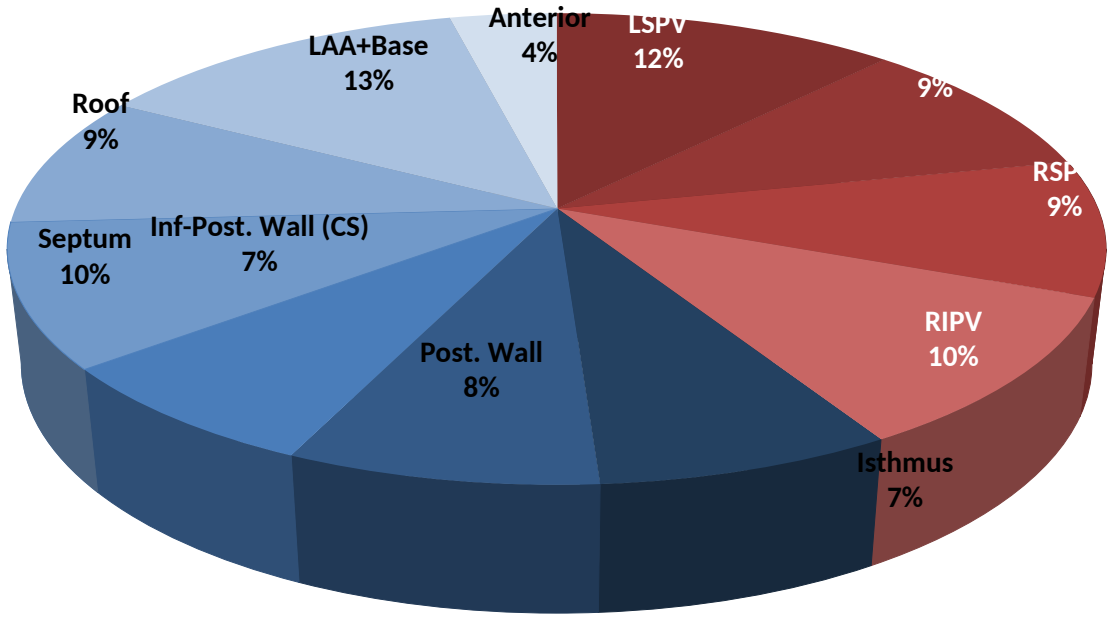
Study workflow

Anatomical distribution of AF drivers

Control group



Mapping-guided group



There were 247 fast/regular sites identified in the Control group and 232 in the substrate arm (p=0.11), 38% and 41% of which located in the PVs in the control and substrate arm, respectively.

Circ Arrhythmia Electrophysiol 2018

ACUTE PROCEDURAL OUTCOME

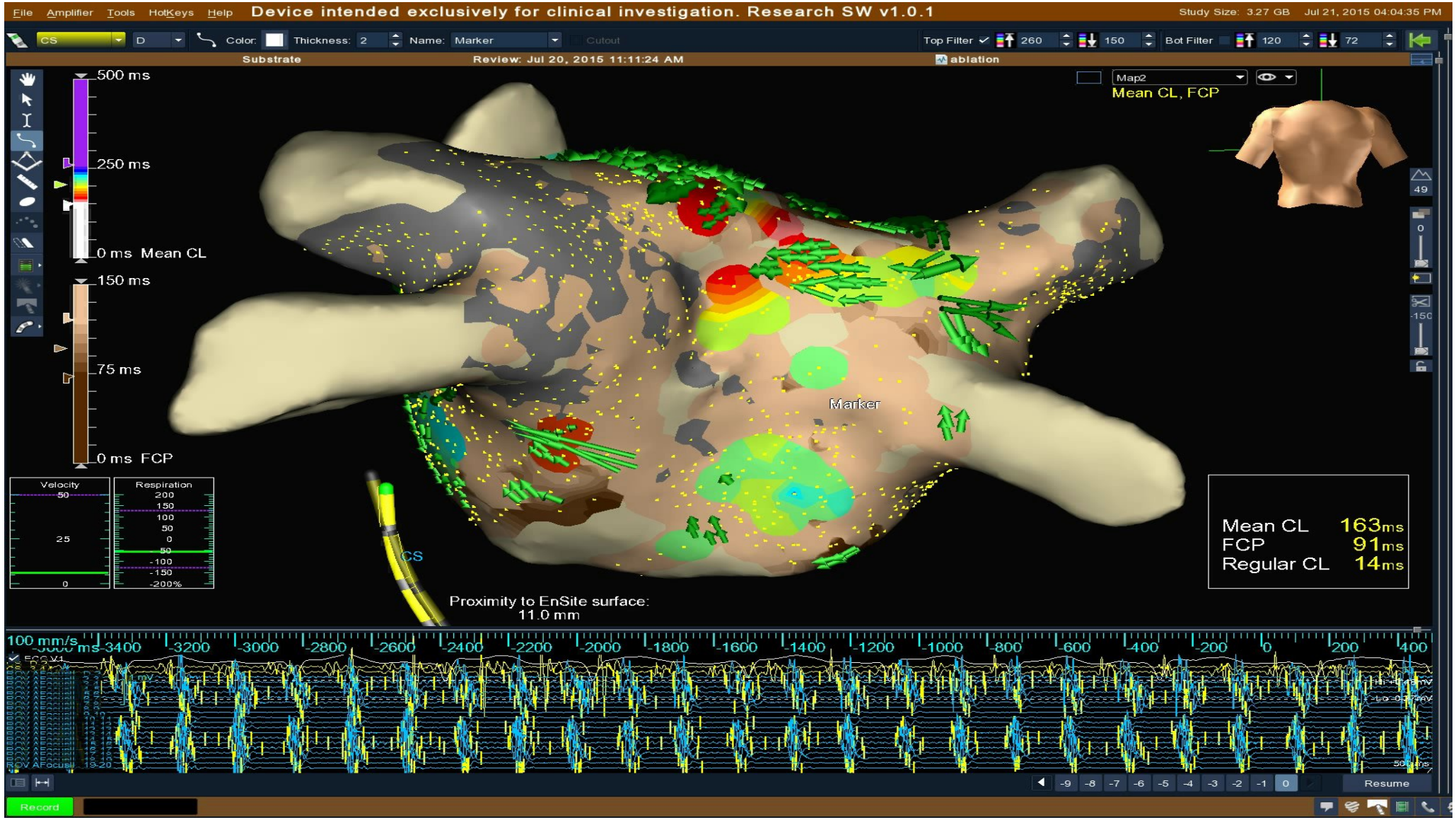
	Control group (N=40)	Mapping group (N=41)	P-value
AF termination	**12 (30%)**	**25 (61%)**	**0.007**
Cardioversion	**28 (70%)**	**16 (39%)**	**0.007**
AF re-inducible by pacing	**8/26 (31%)**	**3/33 (9%)**	**0.05**
Procedure time [min]	**125 ± 25**	**141 ± 29**	**0.02**
Mapping time [min]	23.1 ± 7.8	25.2 ± 8.0	0.46
RRa RF time [min]	NA	17.7 ± 9.8	NA
Complete RF time	33.0 ± 10.9	35.4 ± 13.3	0.38

- Mapping-guided ablation resulted in intraprocedural arrhythmia termination in 25 patients (25/41, 61%), whereas the remaining 16 (39%) experienced a significant AFCL prolongation.
- In Control group, 12/40 (30%) individuals converted to sinus rhythm during ablation, whereas in the remaining 28 pts showed AFCL prolongation (188.6±45.6 versus 213.5±56.2 ms; $p<0.001$).

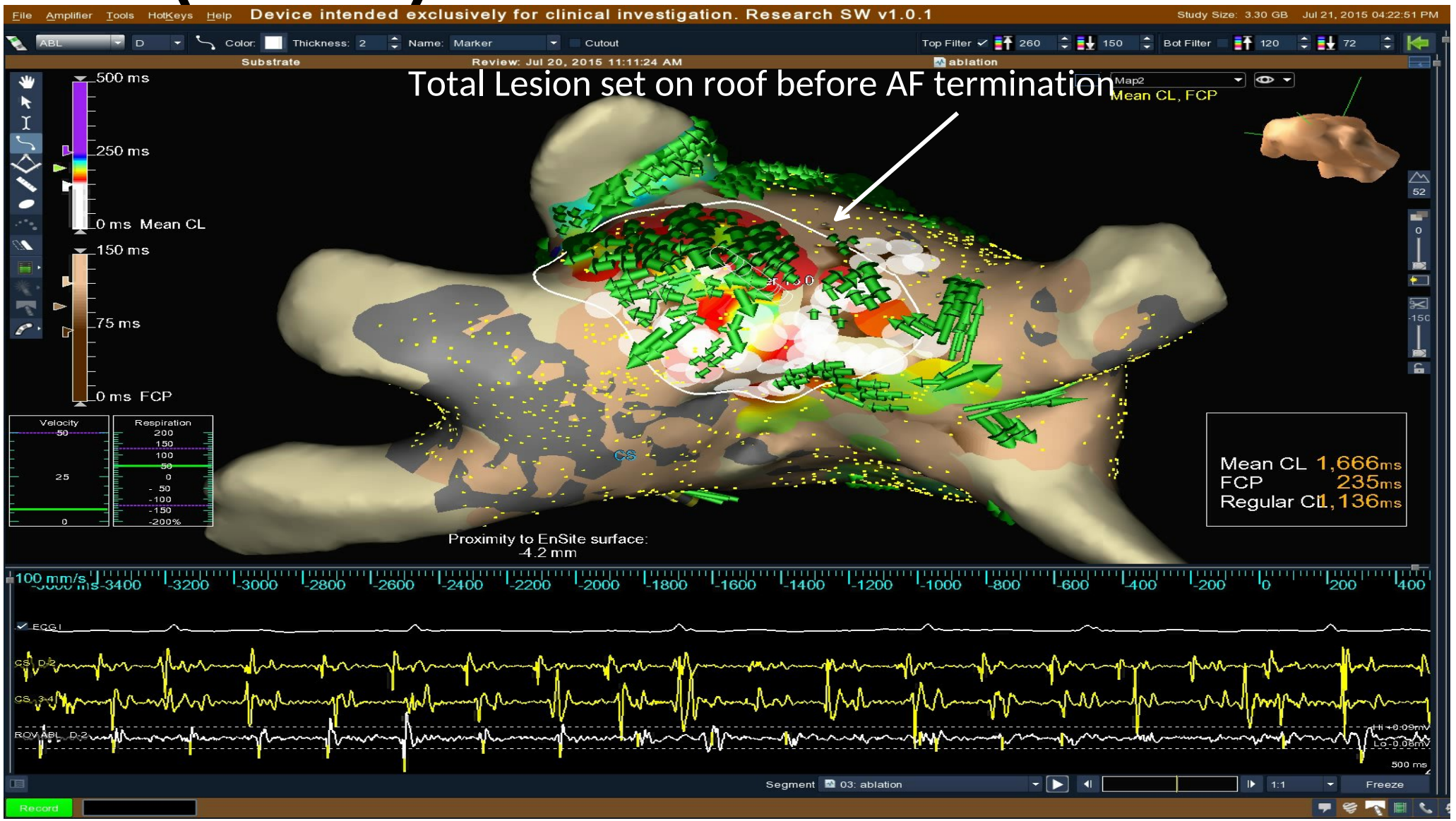
Example of Driver Ablation

- 75 yo female
- 1st time ablation
- LV EF 55%
- LA area 31.3 cm^2

Driver map (movie)



Sinus rhythm after 3.5 minutes of substrate ablation (movie)



RESULTS

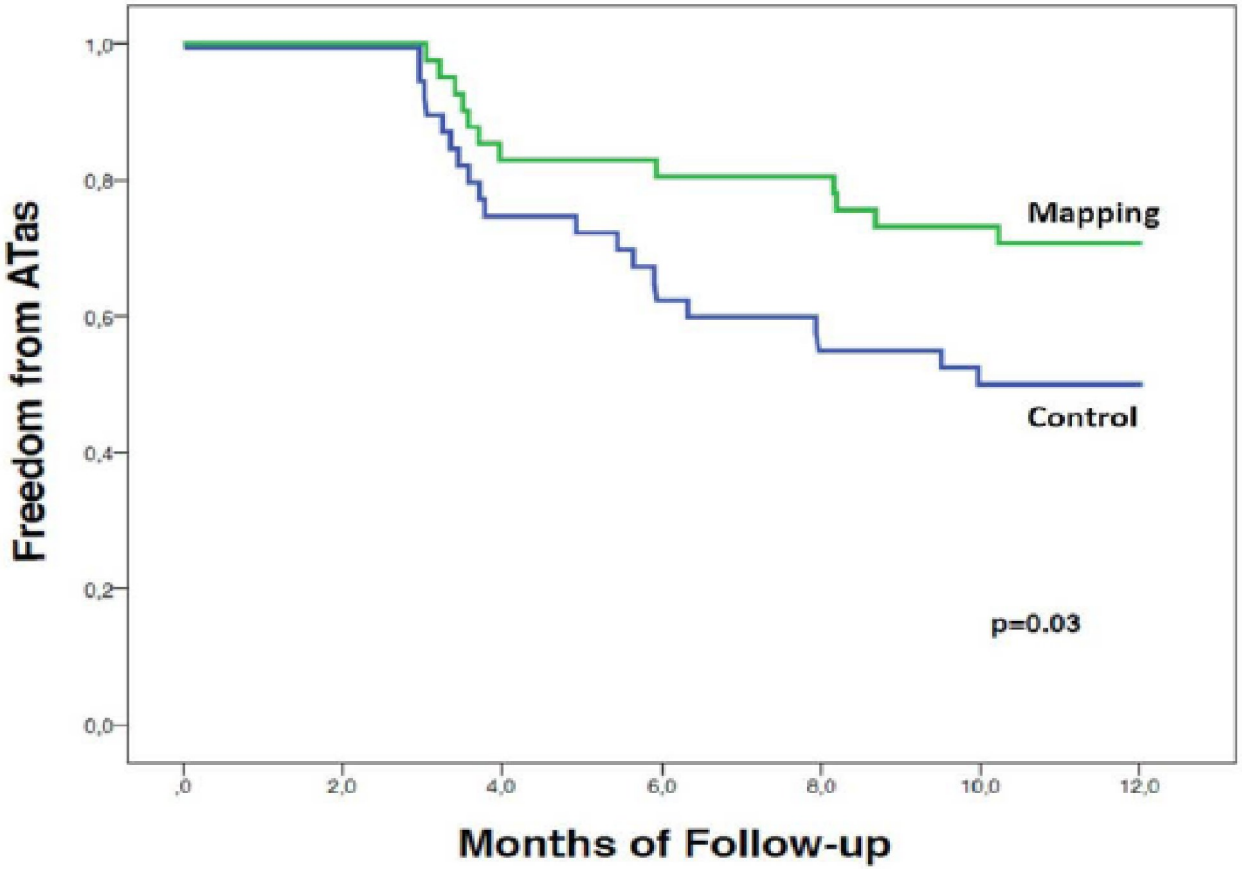
-AF Freedom rate at 12-month follow-up

- At 6 and 12 month follow up patients were monitored for symptomatic AF episodes by ICM, 24-hr Holter, TT recordings or clinical evaluation

  - Table 3. Distribution of subject monitoring method

Subject monitoring method	Control arm (N=40)	Substrate arm (N=41)
ICM	**29 (73%)**	**28 (68%)**
24-hr Holter	**5 (13%)**	**2 (5%)**
Transtelephonic monitoring	**1 (3%)**	**0 (0%)**
Clinical evaluation	**5 (13%)**	**11 (27%)**

1-year CLINICAL OUTCOME

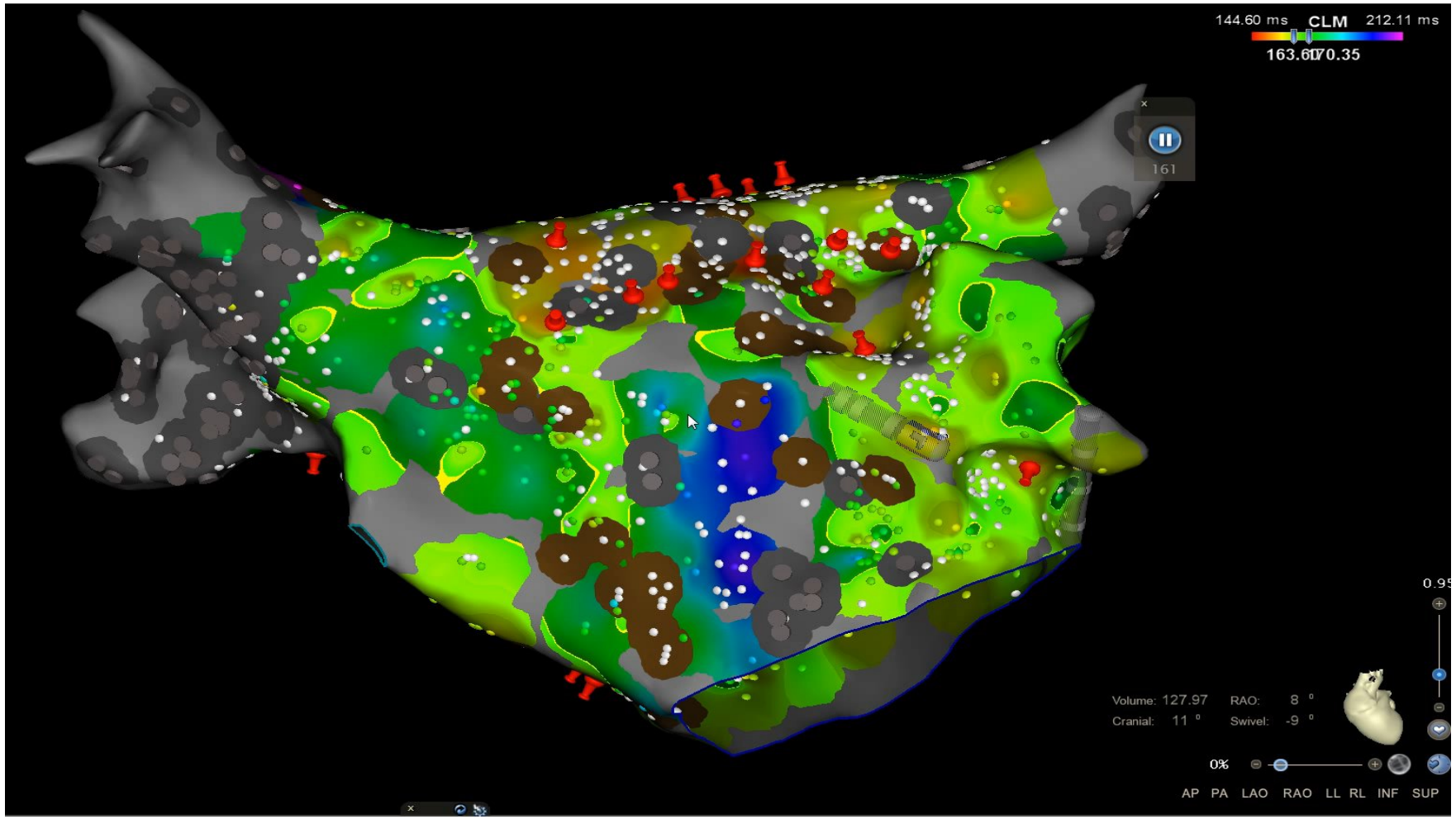


N° at risk							
Mapping	41	41	36	34	34	31	30
Control	40	40	30	25	23	22	21

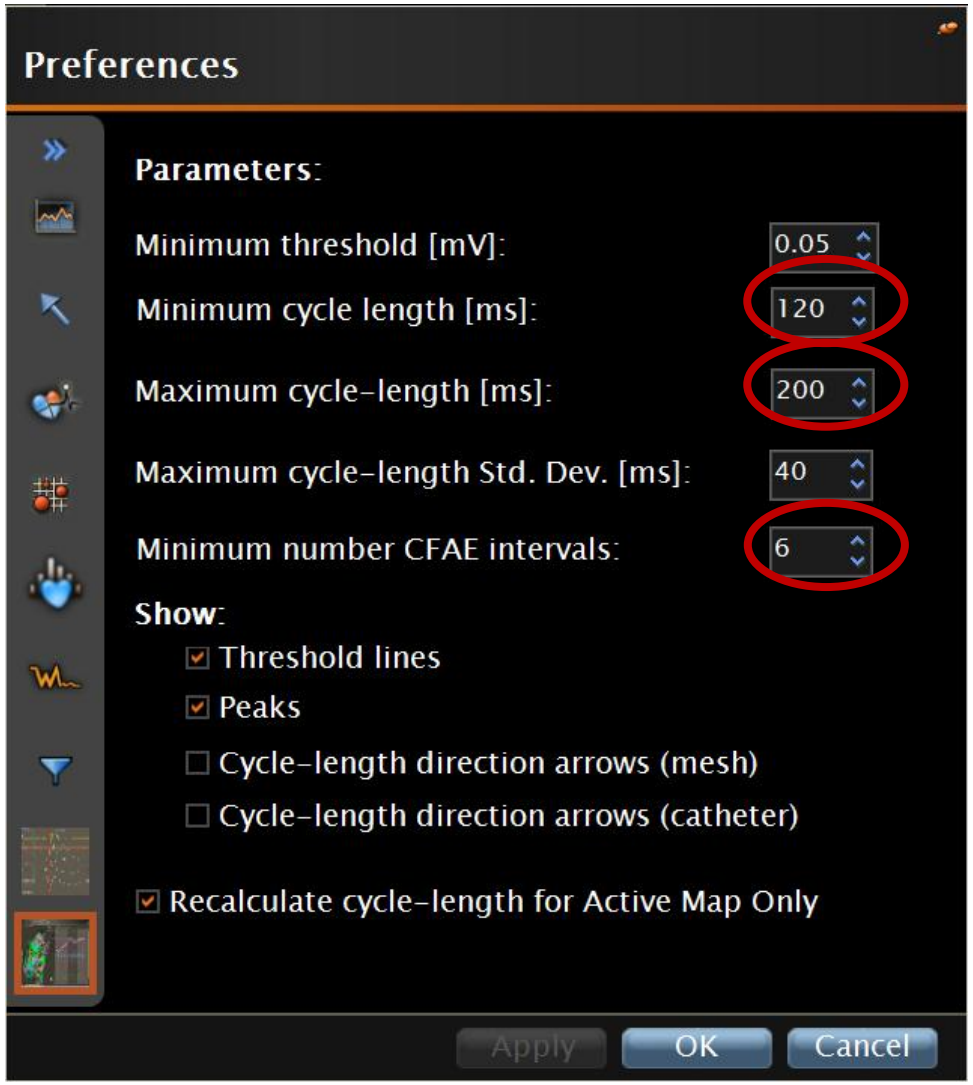
- All 81 patients completed the 1-year follow-up.
- Among 81 patients, 57 (70.3%) received an ICM (72% in control versus 68% in mapping group; p=0.80), whereas the
- remaining 24 subjects (29.6%) received event transtelephonic and 24-hour ECG Holter monitors.

Cycle Length Mapping

Long standing Persistent AF Cases



Cycle Length Mapping - SETTINGS



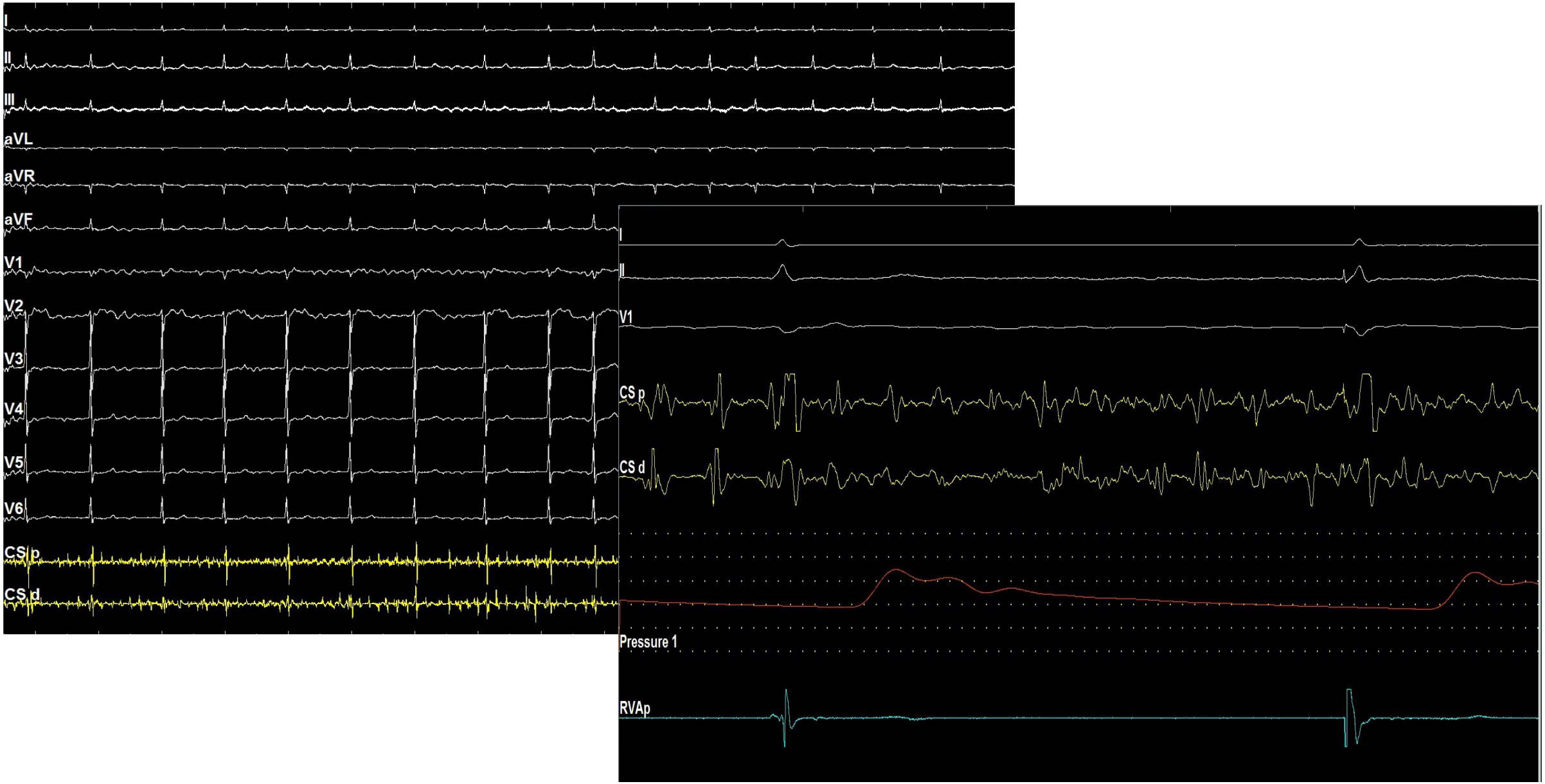
- Initial Standard Preferences, to be changed in relation with the specific clinical case

METHODS

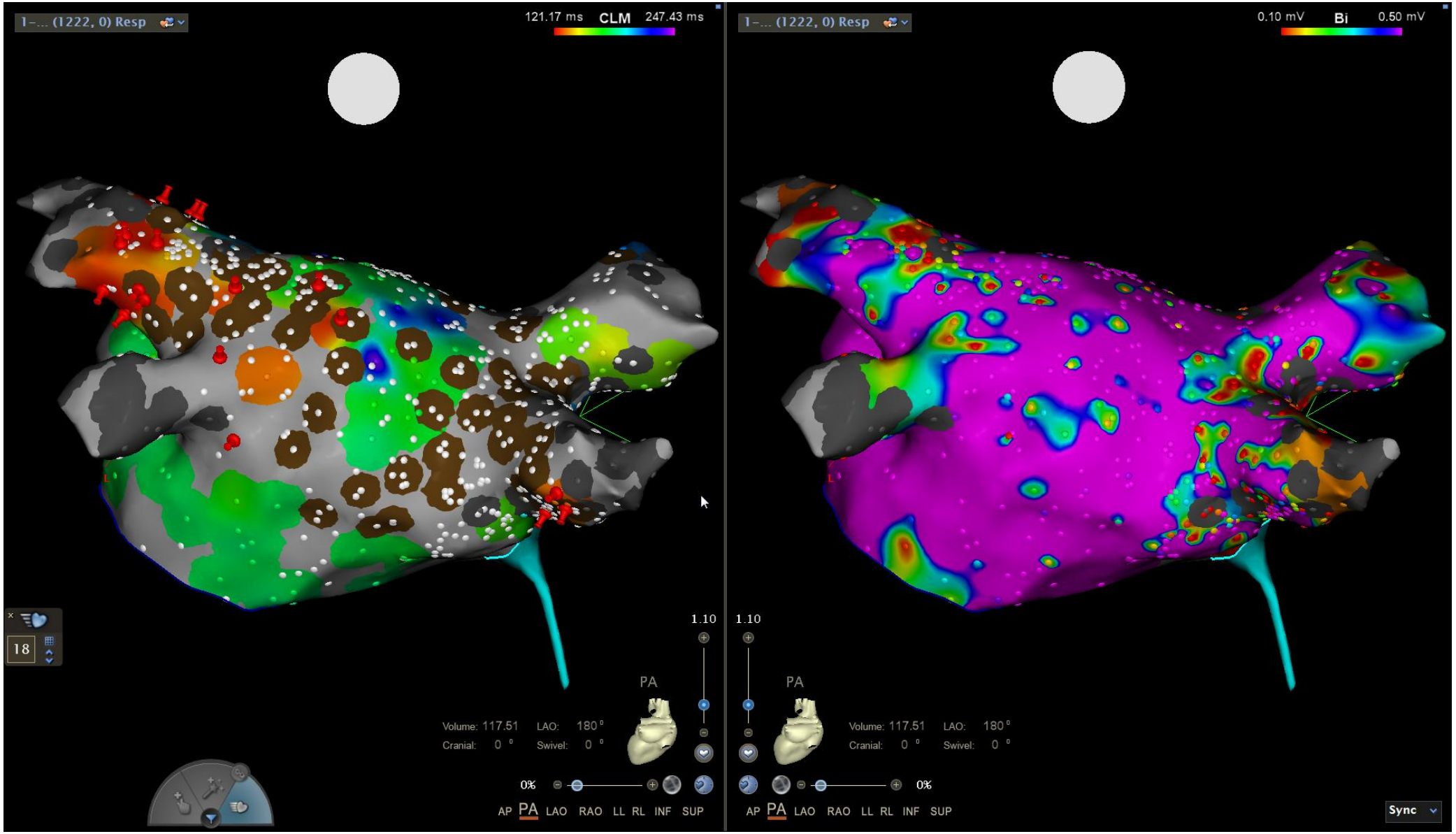
- LA Anatomical recontruction with PentaRay® Catheter
- Manual Mapping, acquiring points after 3-5 seconds of stability
- Automatically identification of triggering targets (shortest medium cycle lenghts points)
- **Targeting the ablation using propagation tool and focusing on first 2 milliseconds**
- Identify fragmented areas and Scar Areas

PATIENT HISTORY – Case 2

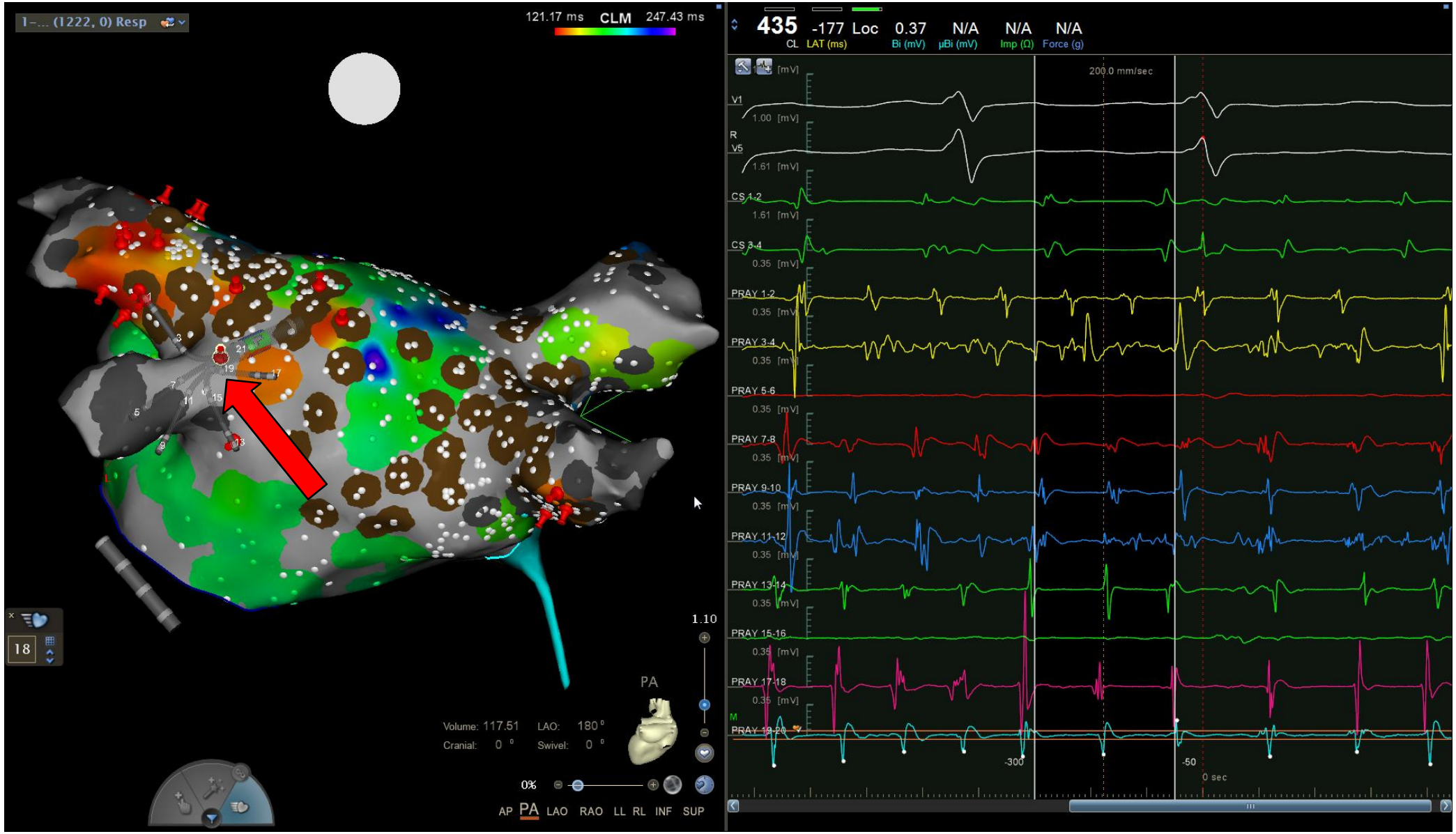
- 65 years old, Female
- Persistent AF since 4 years
- Resistent to external cardioversion and multiple AADs trials (class I and III)
- Dilated LA (125 ml),
- EF 45% in CAD treated with previous CABG


I
II
III
aVL
aVR
aVF
V1
V2
V3
V4
V5
V6
CS p
CS d
I
II
V1
CS p
CS d
Pressure 1
RVAp

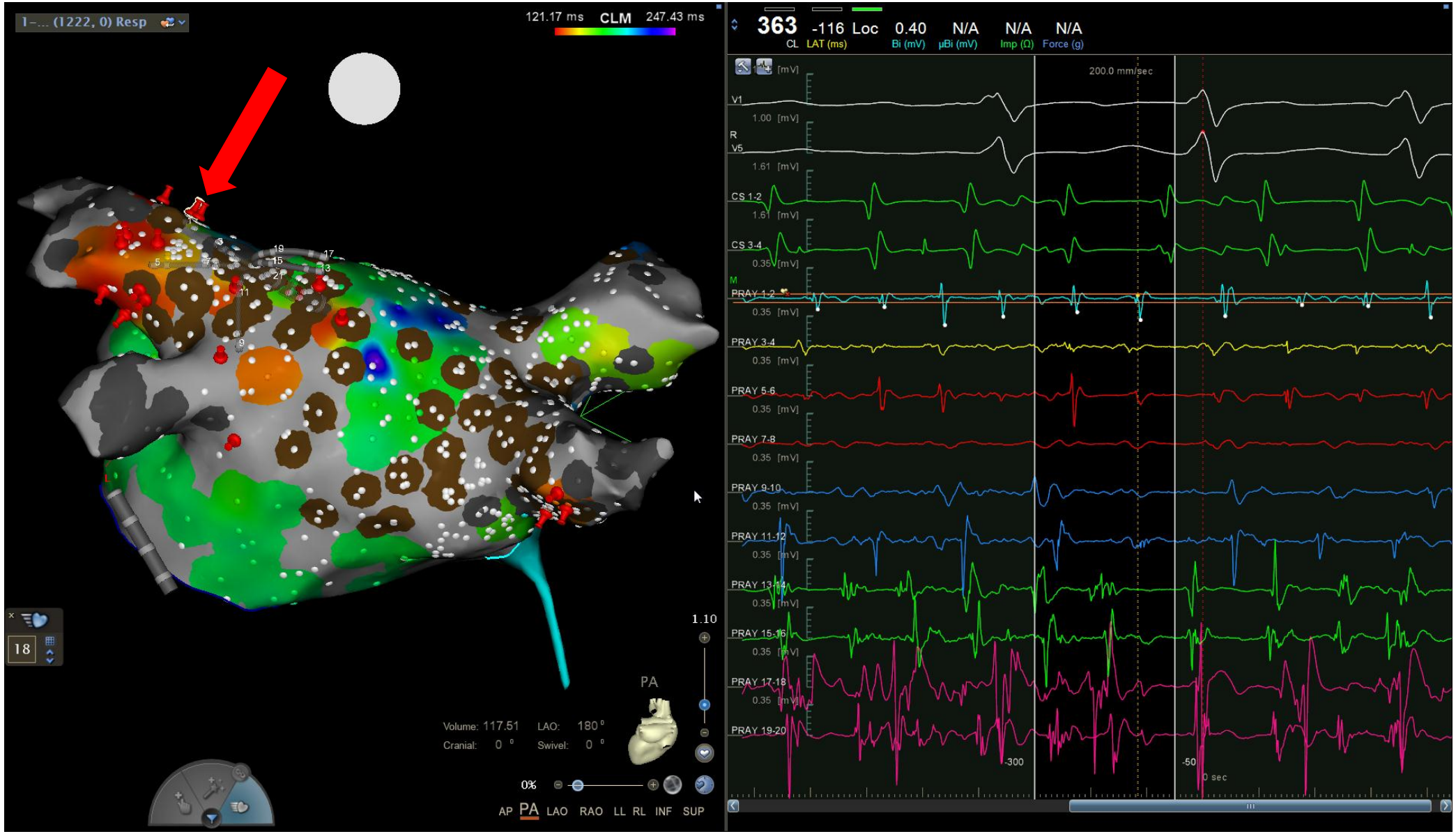
CLM vs BIP


1 –... (1222, 0) Resp
121.17 ms
CLM
247.43 ms
1.10
PA
Volume: 117.51
LAO: 180°
Cranial: 0°
Swivel: 0°
0%
AP PA LAO RAO LL RL INF SUP
1 –... (1222, 0) Resp
0.10 mV
Bi
0.50 mV
1.10
PA
Volume: 117.51
LAO: 180°
Cranial: 0°
Swivel: 0°
0%
AP PA LAO RAO LL RL INF SUP
Sync

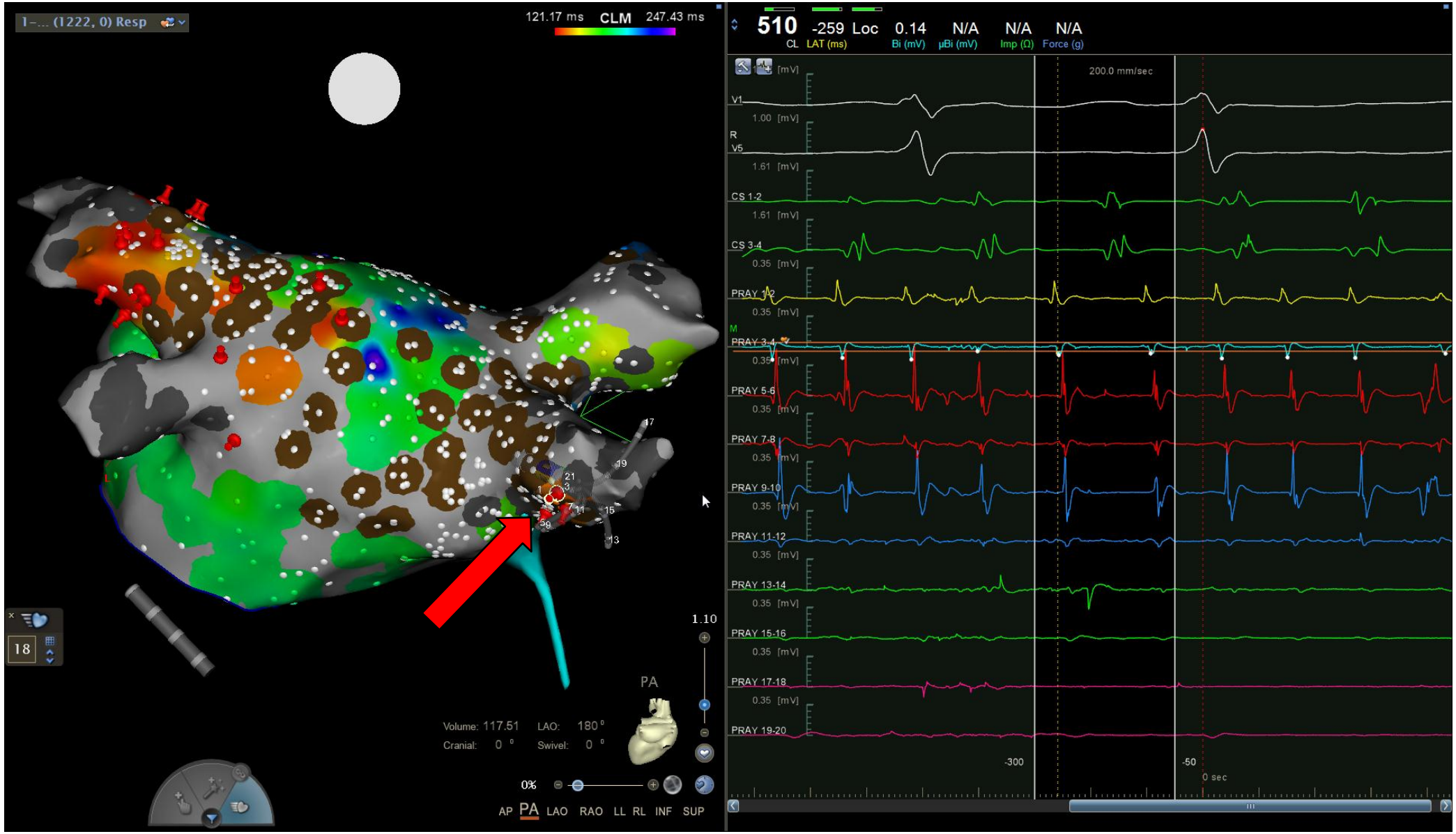
CLM – Driver, LIPV



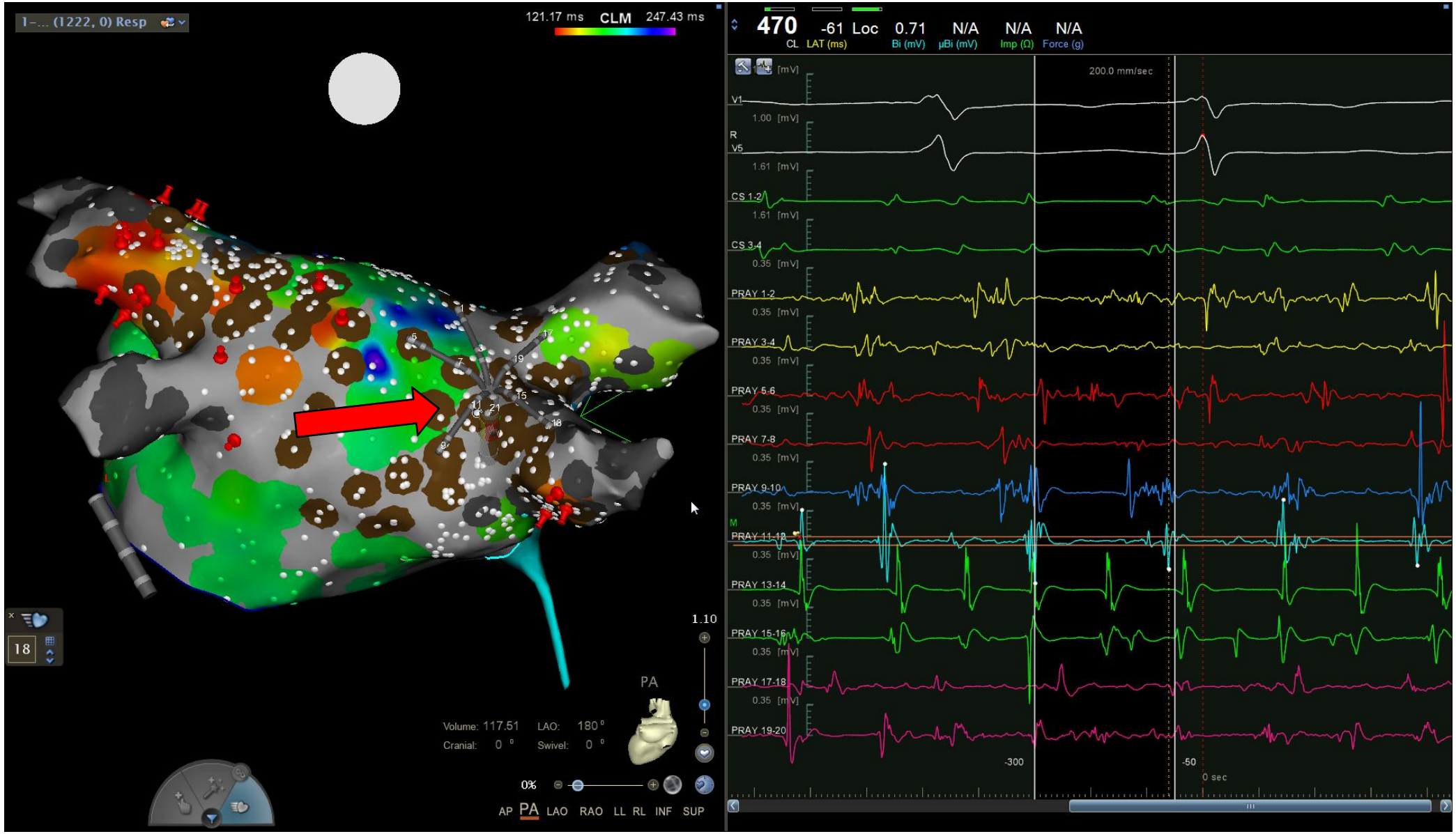
CLM – Driver, LSPV



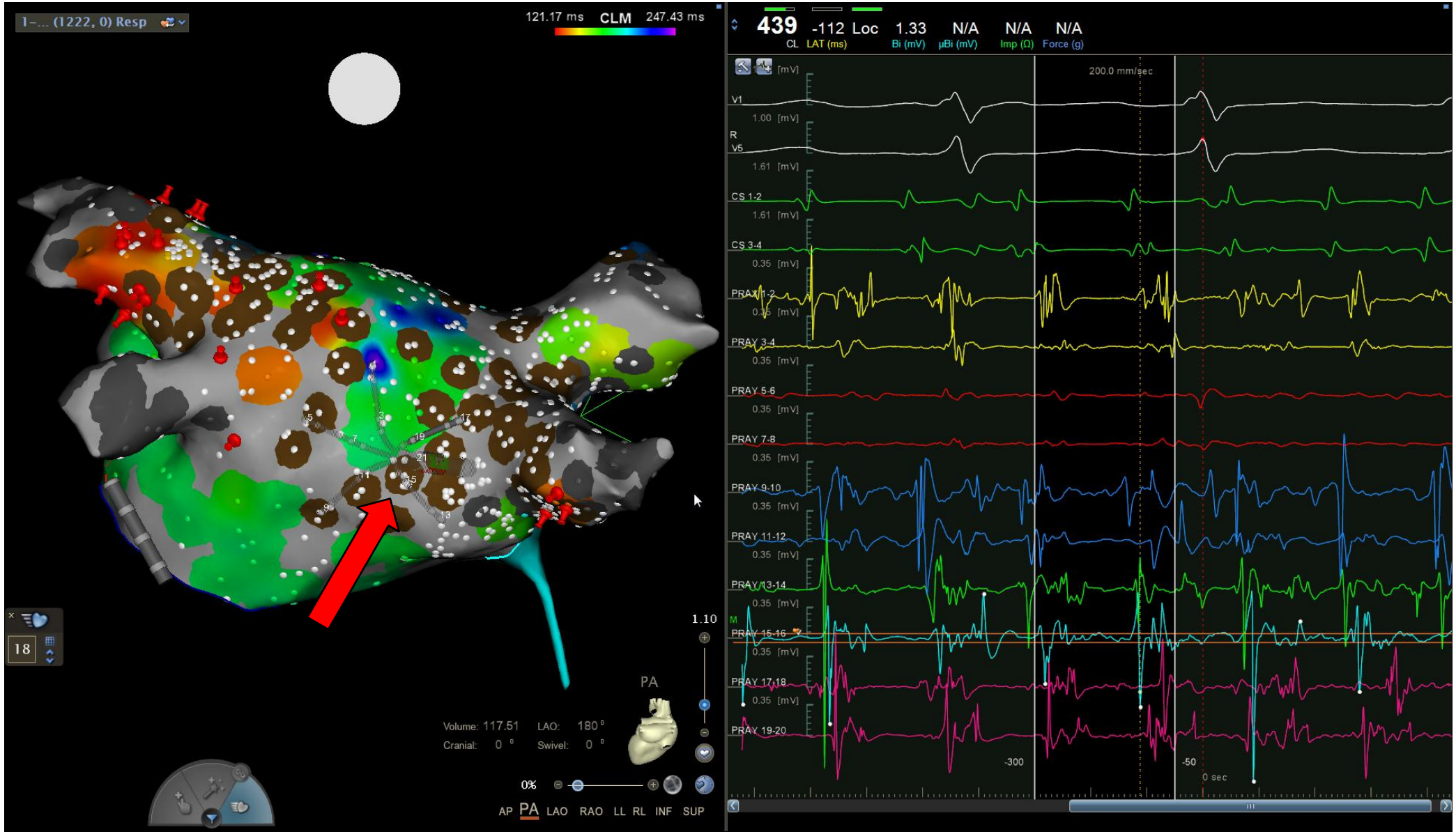
CLM – Driver, RIPV



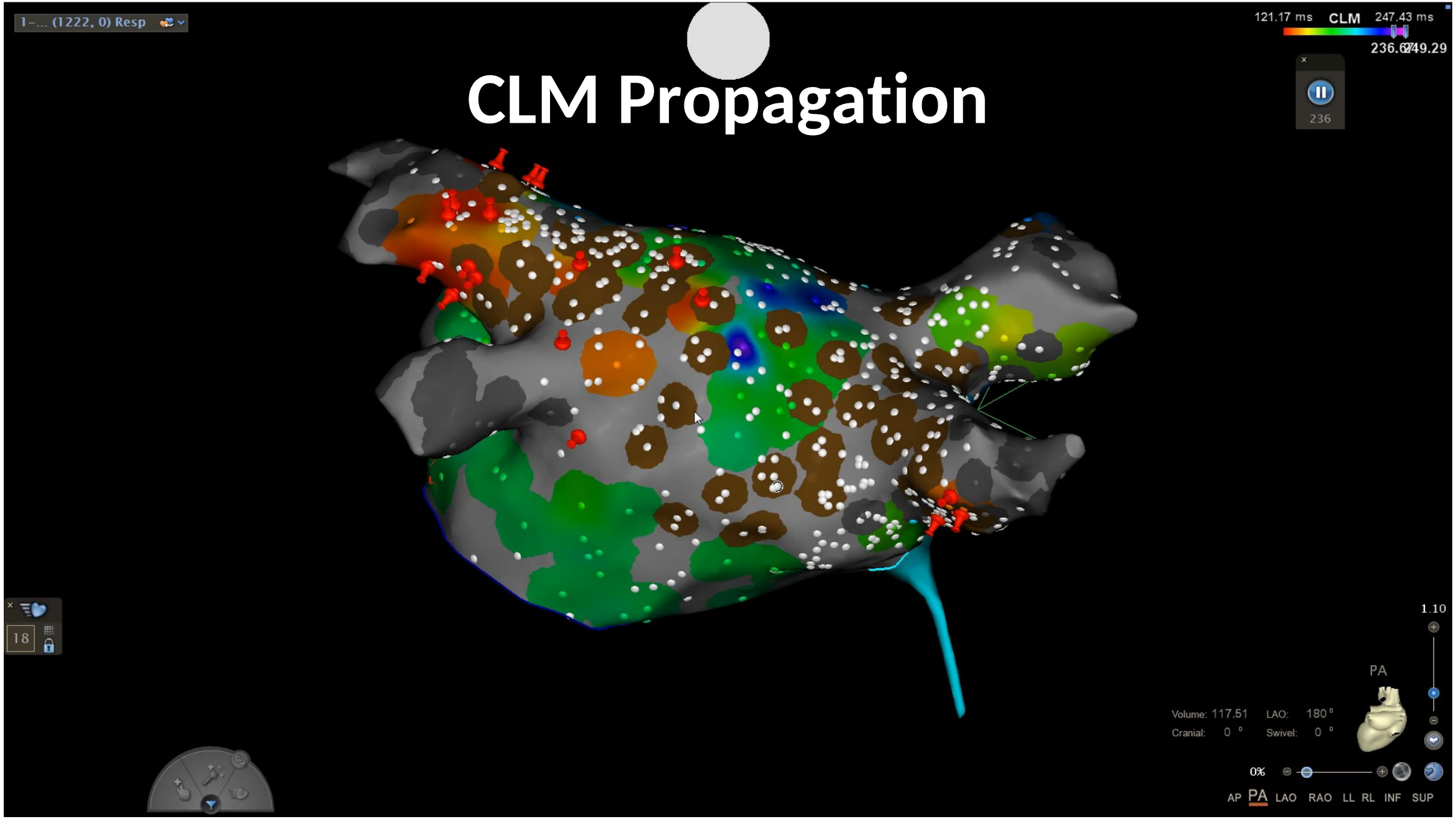
CLM – Fragmented Area 1



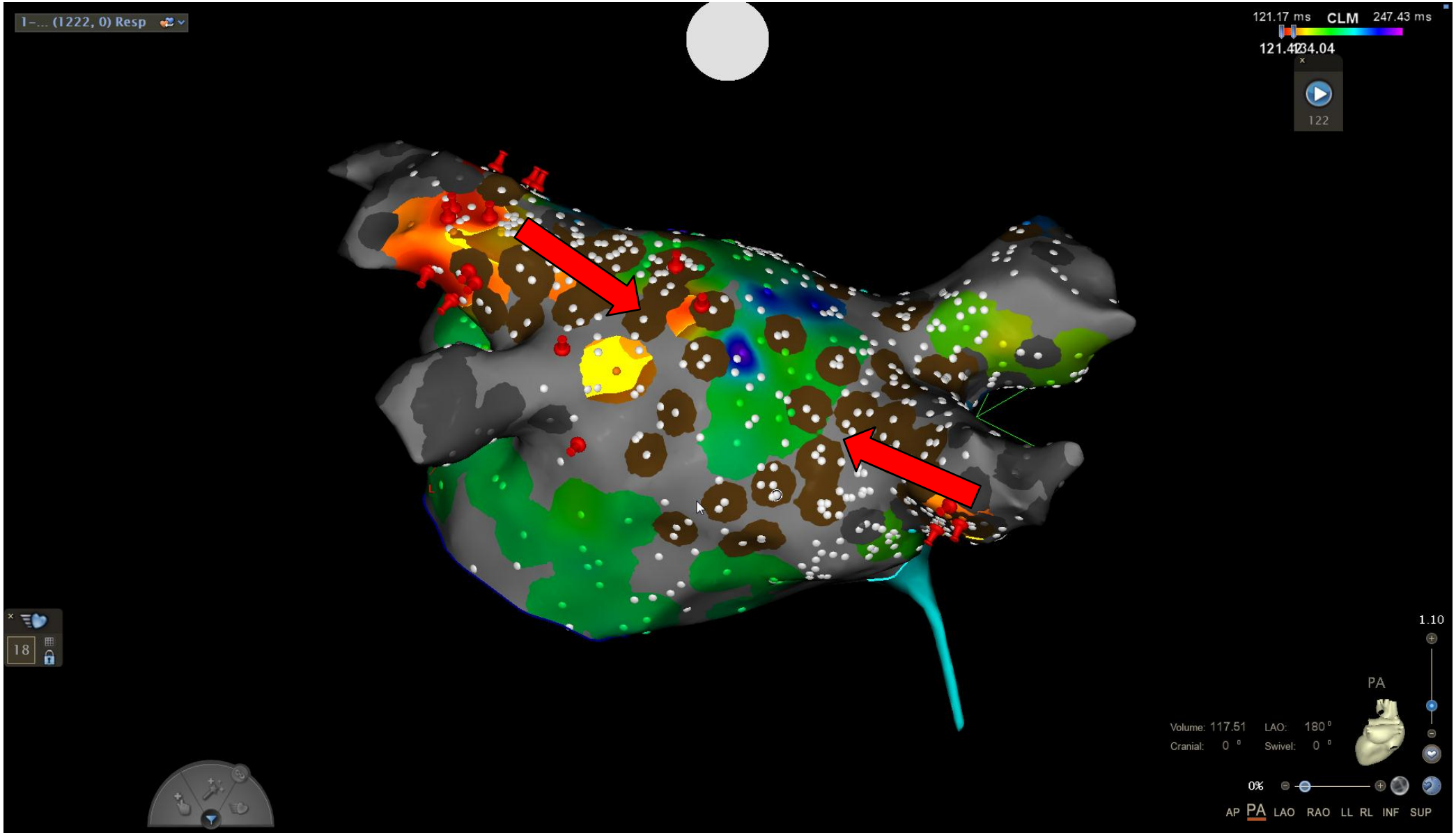
CLM – Fragmented Area 2



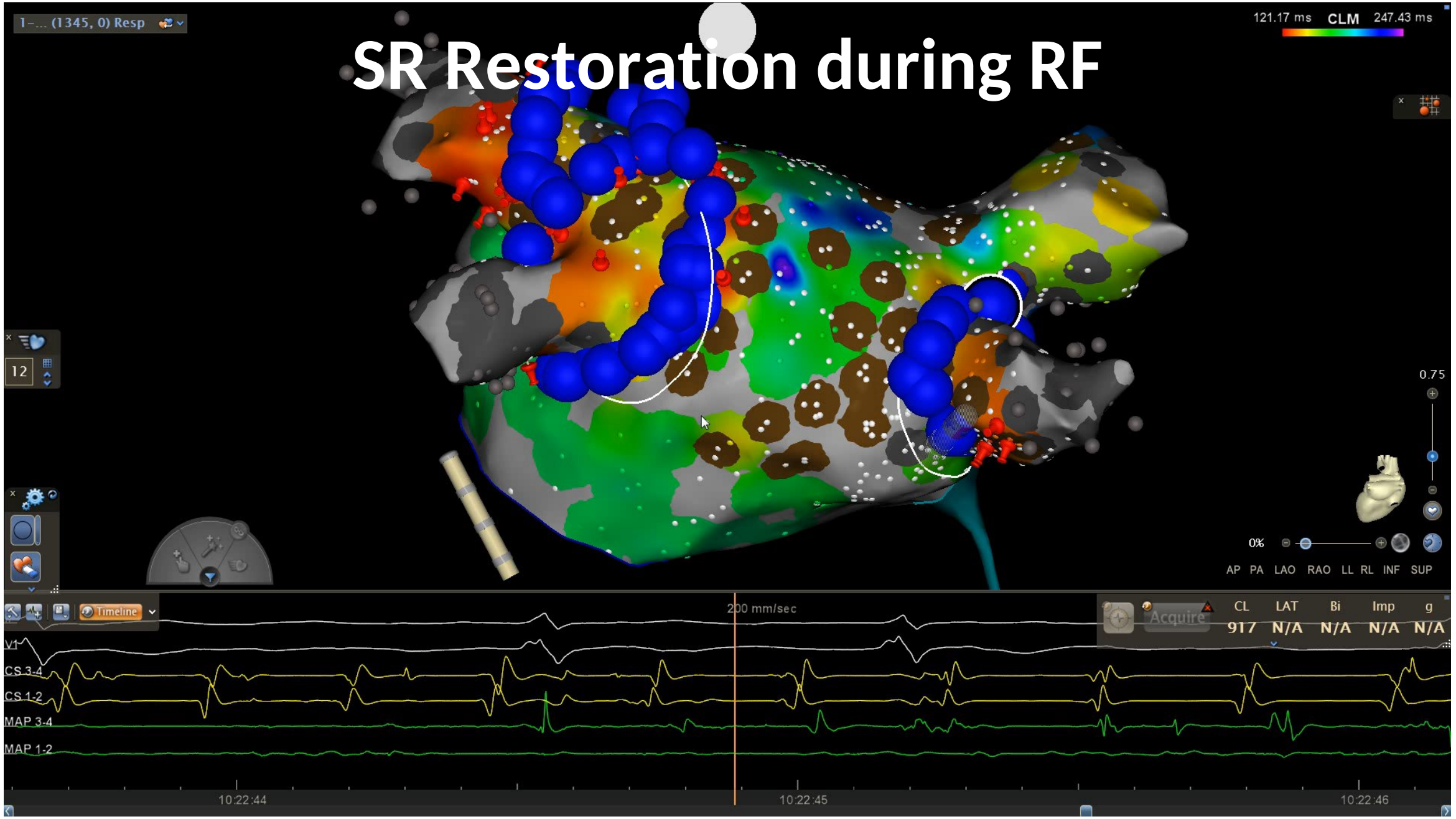
CLM Propagation



Ablation Target



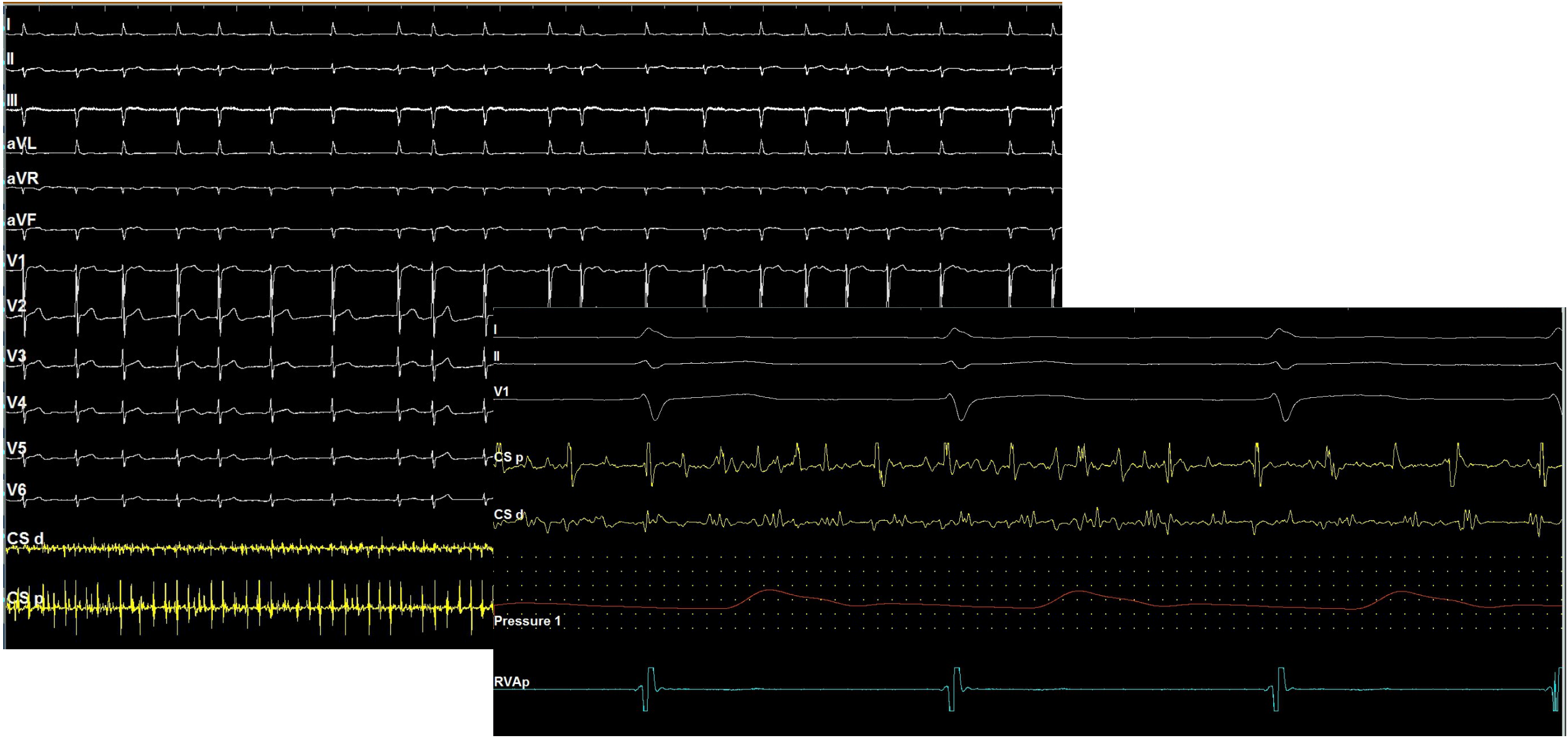
SR Restoration during RF



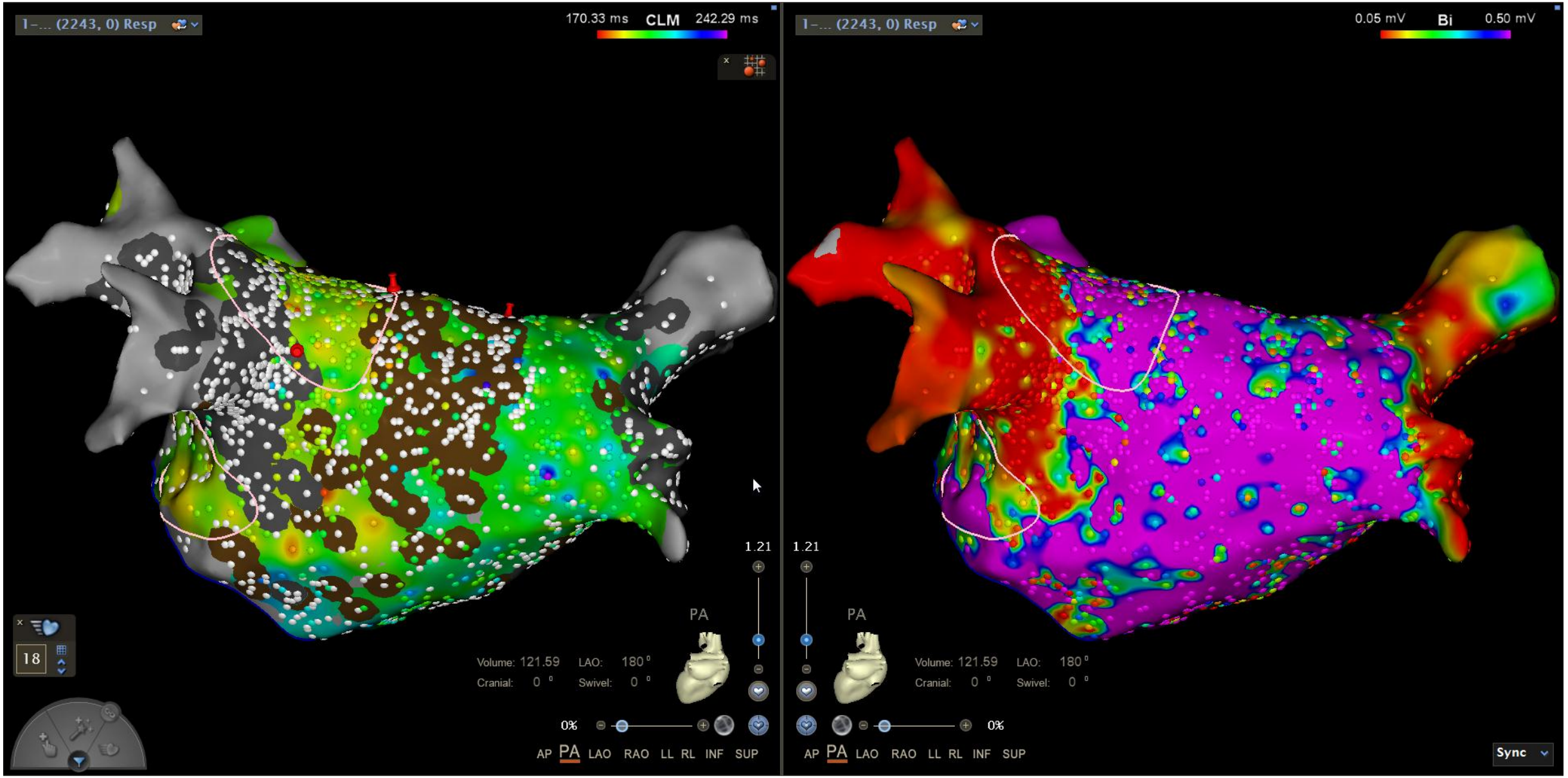
PATIENT HISTORY

- 63 years old, Male
- Long-standing Persistent AF since 3 years
- April 2018 first RF Ablation Procedure
- Recurrences in fup resistent to electrical cardioversion
- LA 115 ml, EF 56%

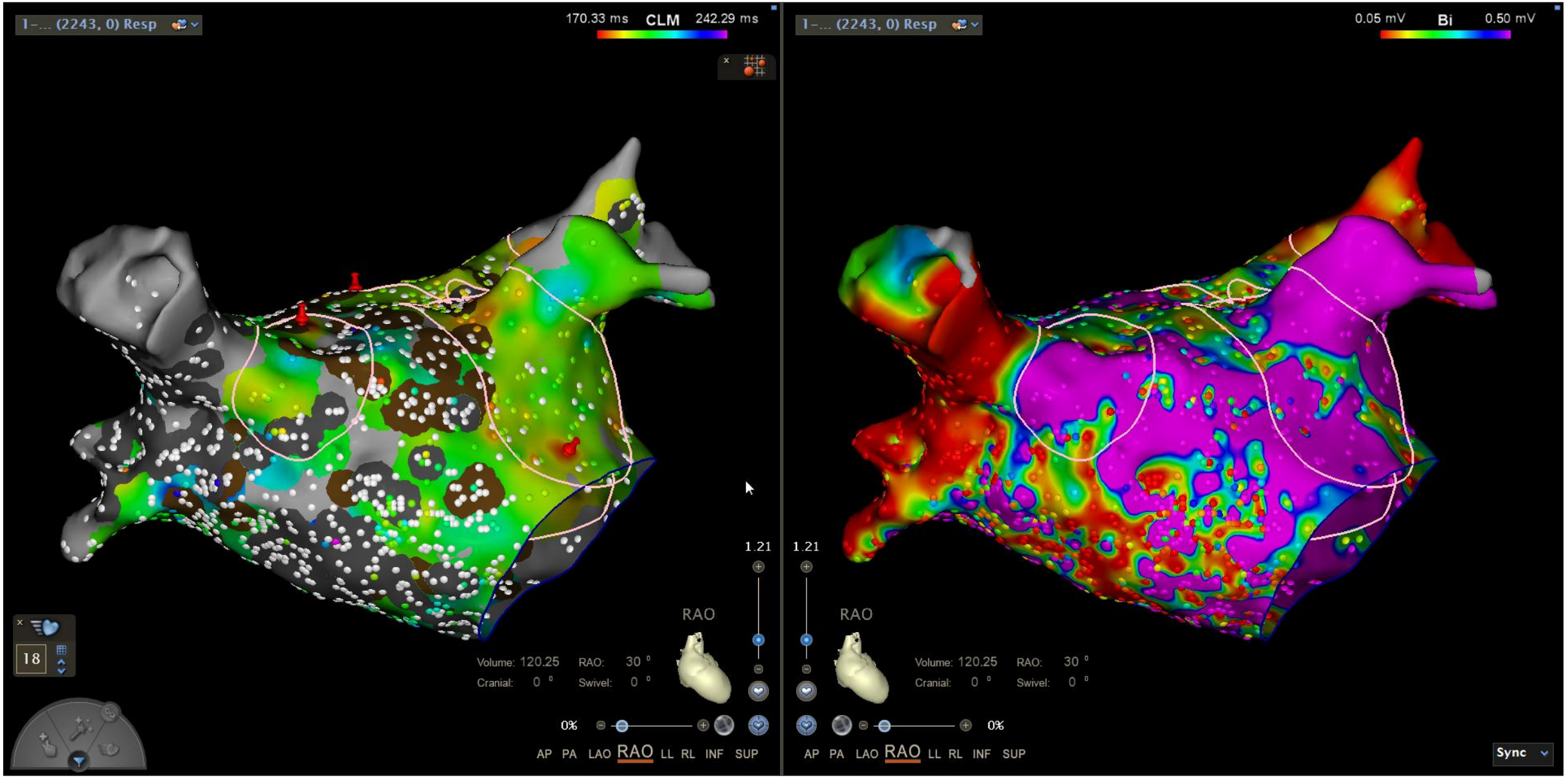
Mapping Data:
Area = 135,2 cm2
Volume = 128,2 cc
Acquired Points = 2243


I
II
III
aVL
aVR
aVF
V1
V2
V3
V4
V5
V6
CS d
CS p
I
II
V1
CS p
CS d
Pressure 1
RVAp

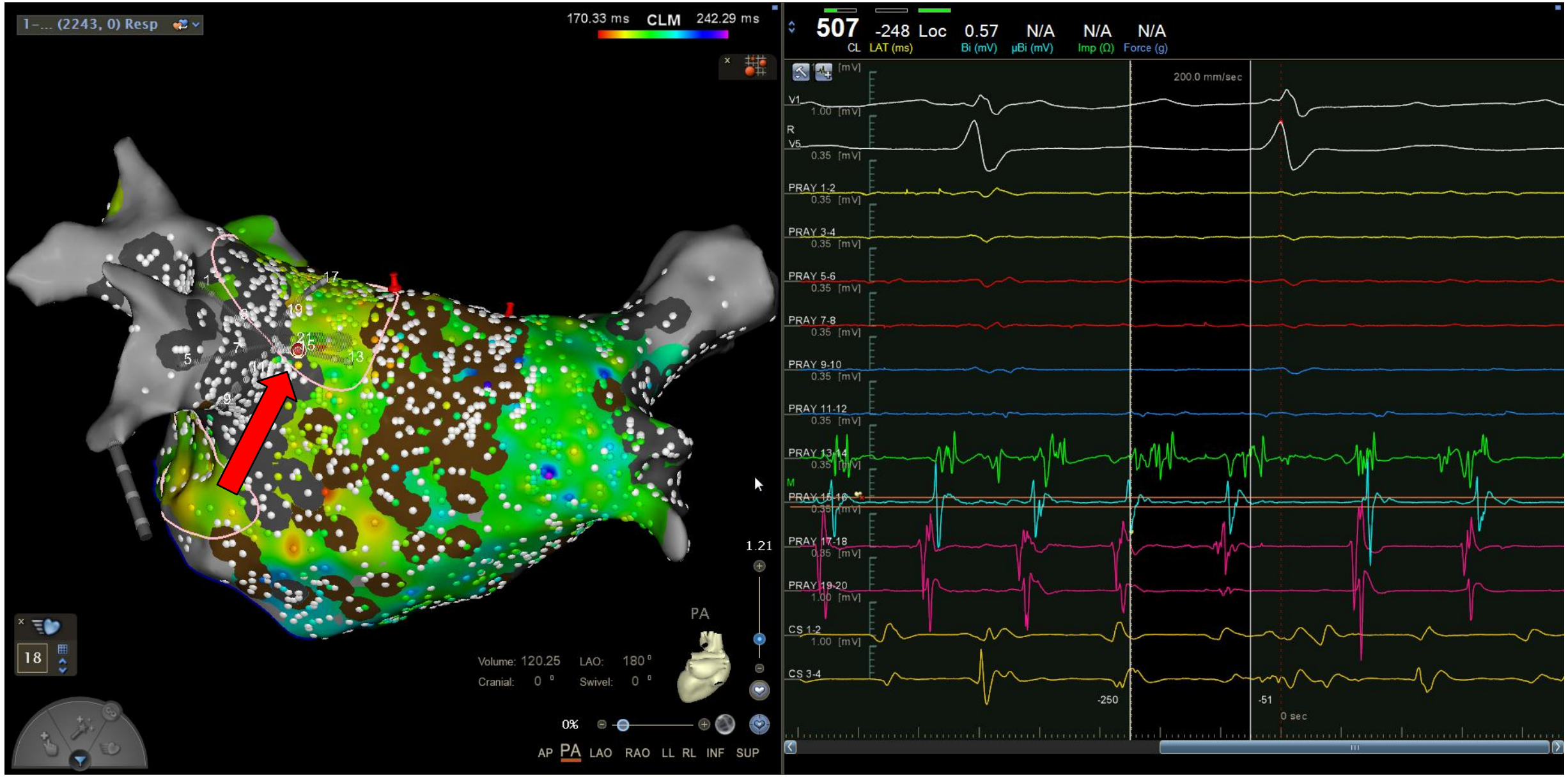
CLM vs BIP


1–... (2243, 0) Resp
170.33 ms
CLM
242.29 ms
1.21
PA
Volume: 121.59
LAO: 180°
Cranial: 0°
Swivel: 0°
0%
AP PA LAO RAO LL RL INF SUP
1–... (2243, 0) Resp
0.05 mV
Bi
0.50 mV
1.21
PA
Volume: 121.59
LAO: 180°
Cranial: 0°
Swivel: 0°
0%
AP PA LAO RAO LL RL INF SUP
Sync

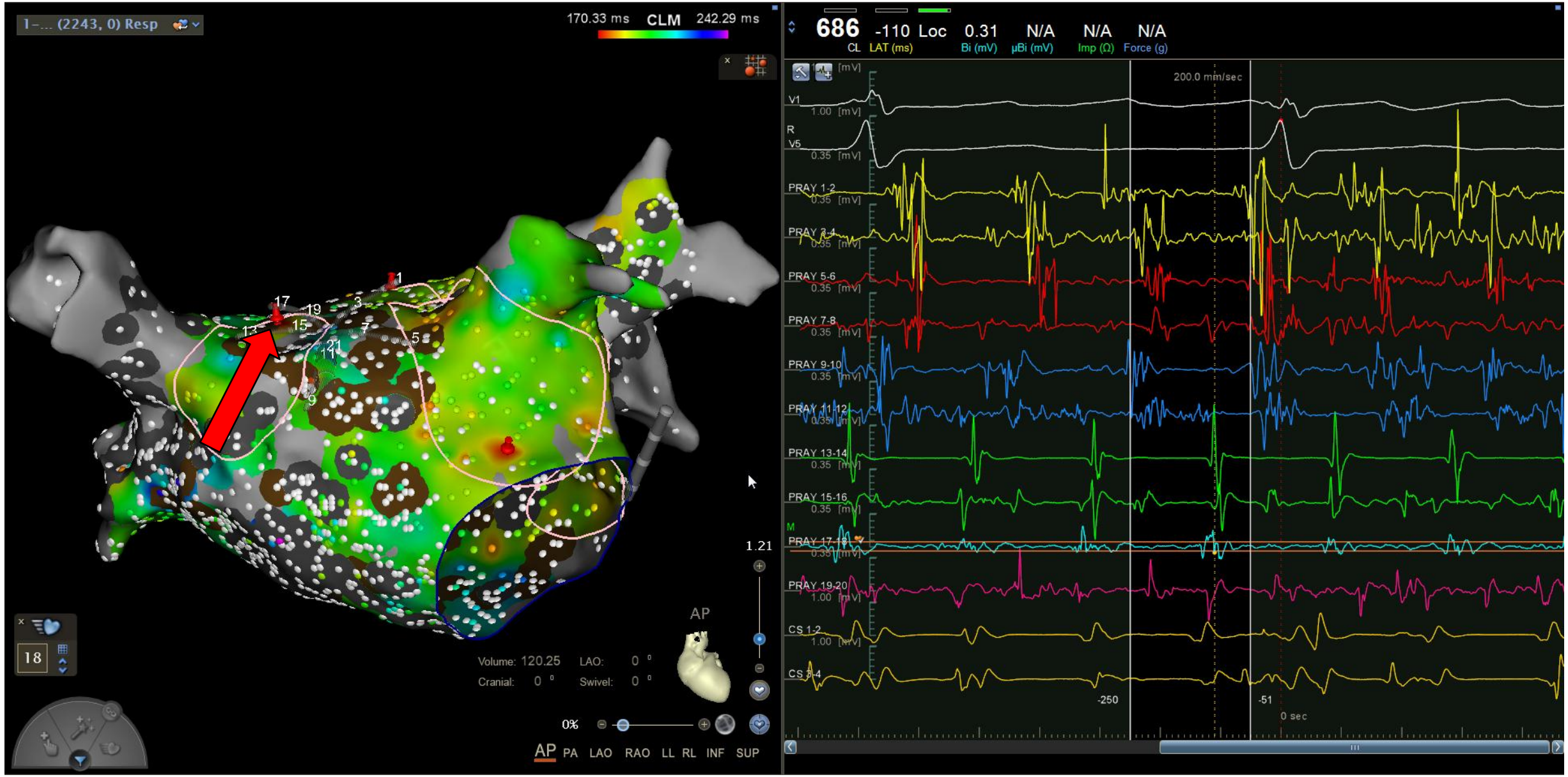
CLM vs BIP


1–... (2243, 0) Resp
170.33 ms
CLM
242.29 ms
1.21
RAO
Volume: 120.25
RAO: 30 °
Cranial: 0 °
Swivel: 0 °
0%
AP PA LAO RAO LL RL INF SUP
1–... (2243, 0) Resp
0.05 mV
Bi
0.50 mV
1.21
RAO
Volume: 120.25
RAO: 30 °
Cranial: 0 °
Swivel: 0 °
0%
AP PA LAO RAO LL RL INF SUP
Sync

CLM –Target, LIPV



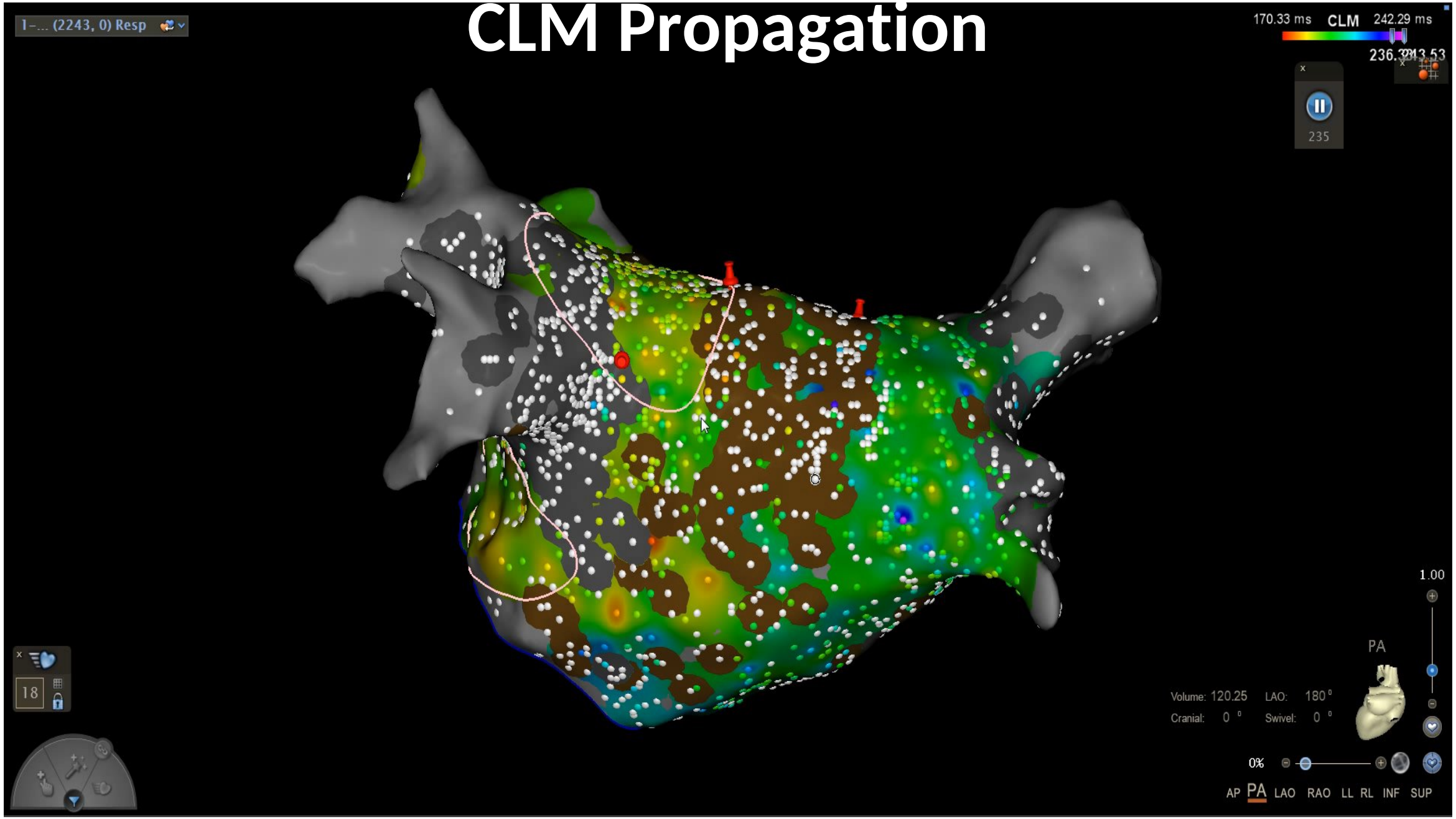
CLM –Target, Roof



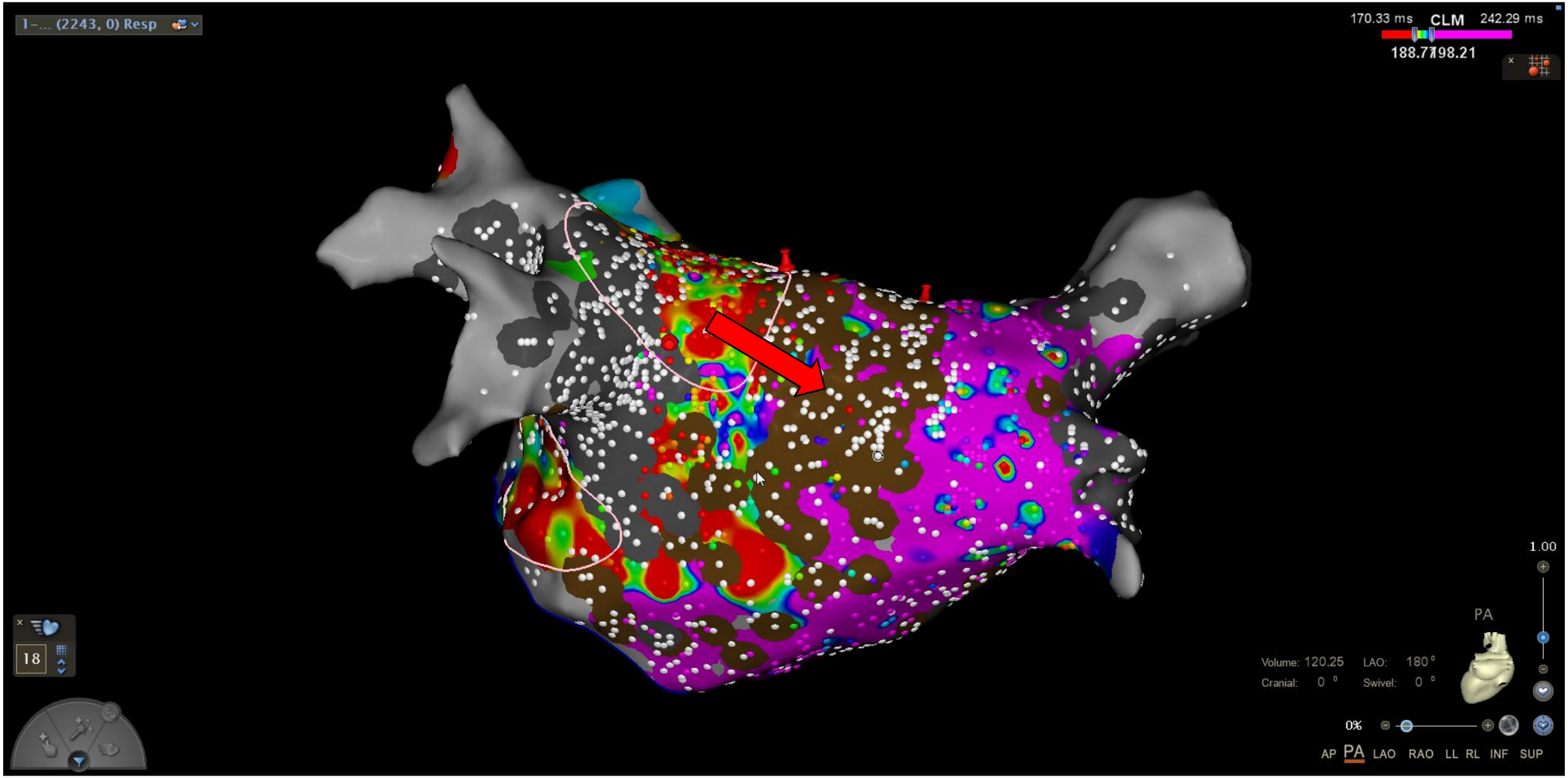
CLM – Fragmented Area 1

CLM – Fragmented Area 2

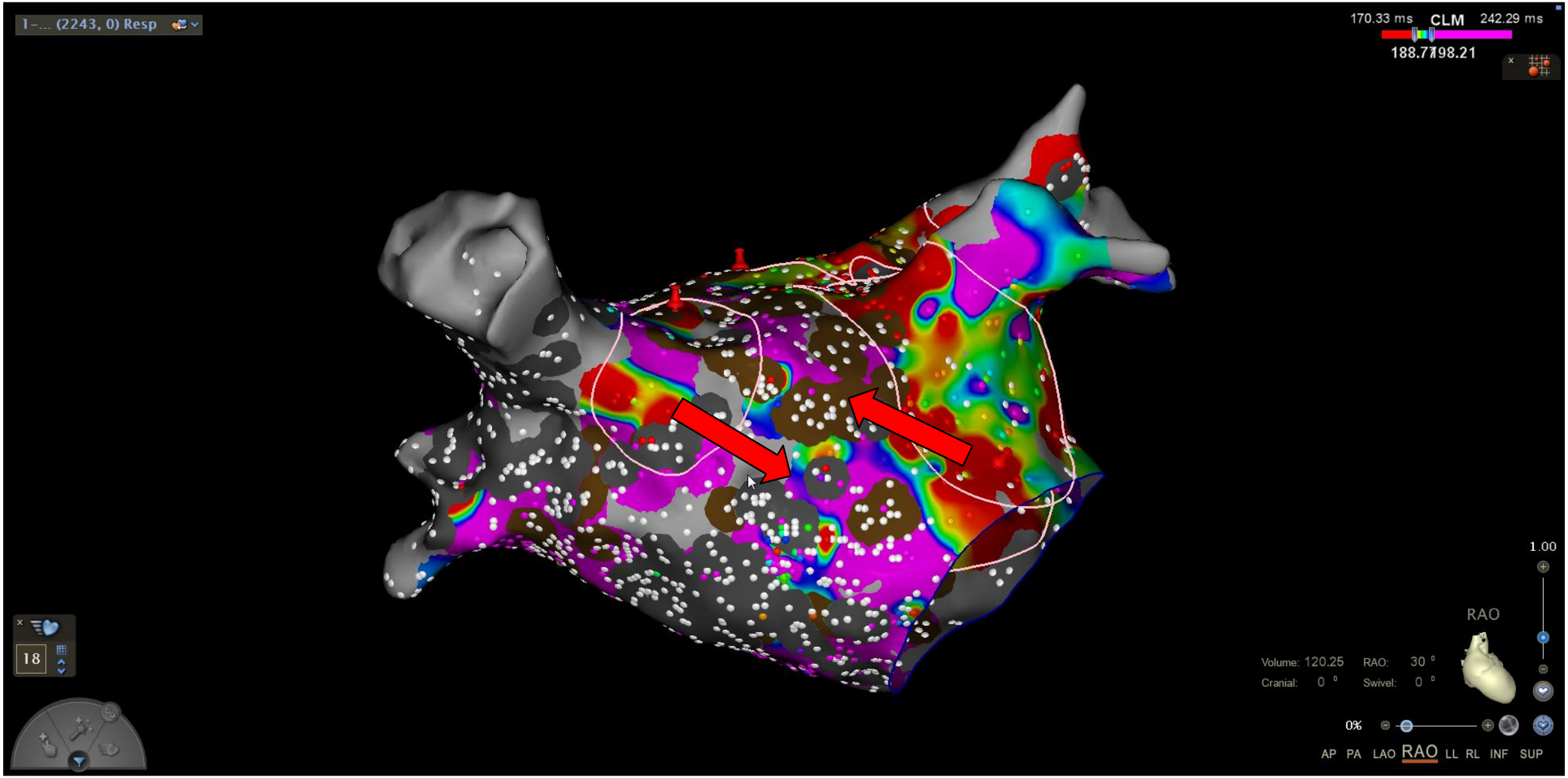
CLM Propagation



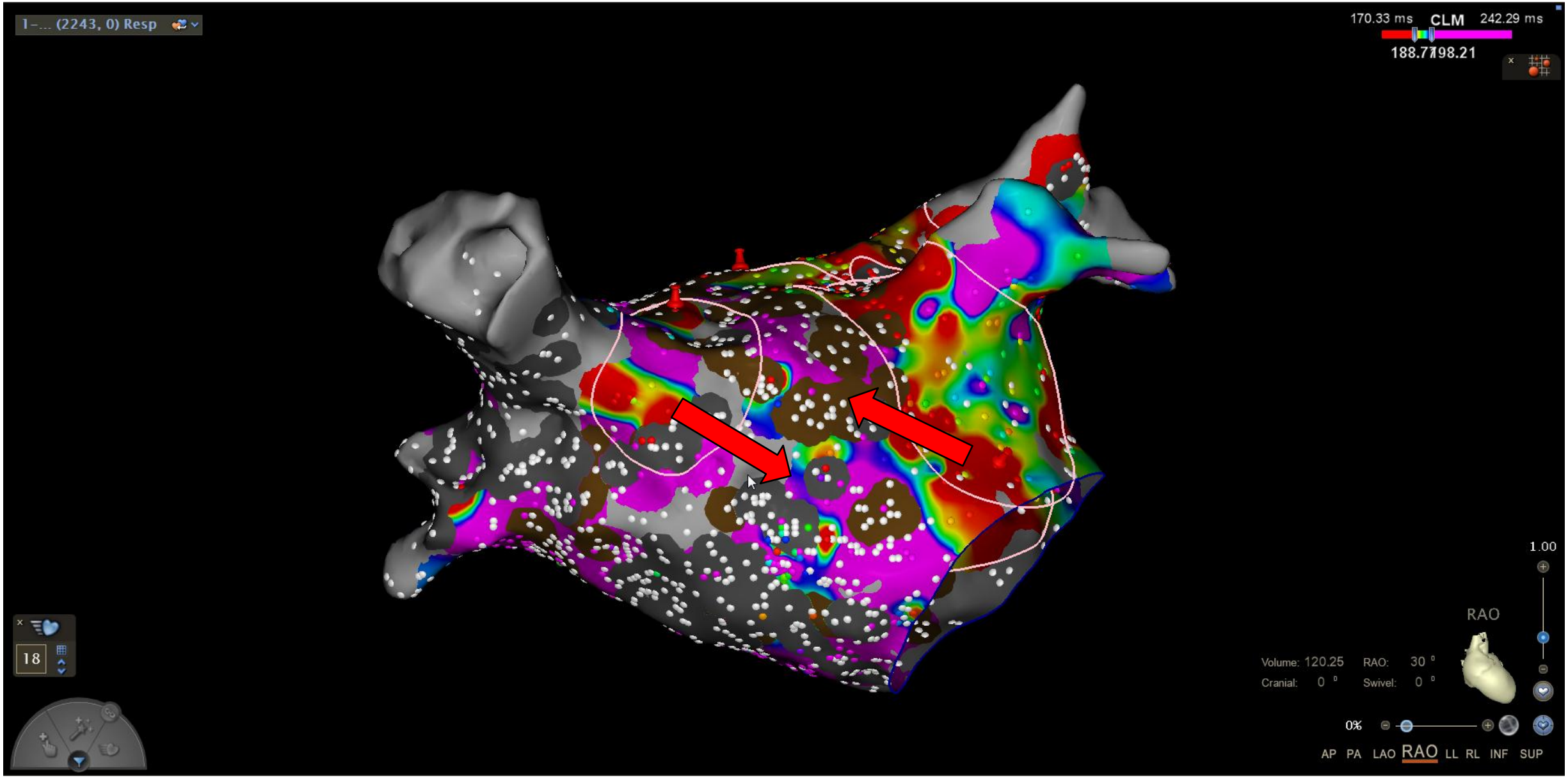
Ablation Targeting 1

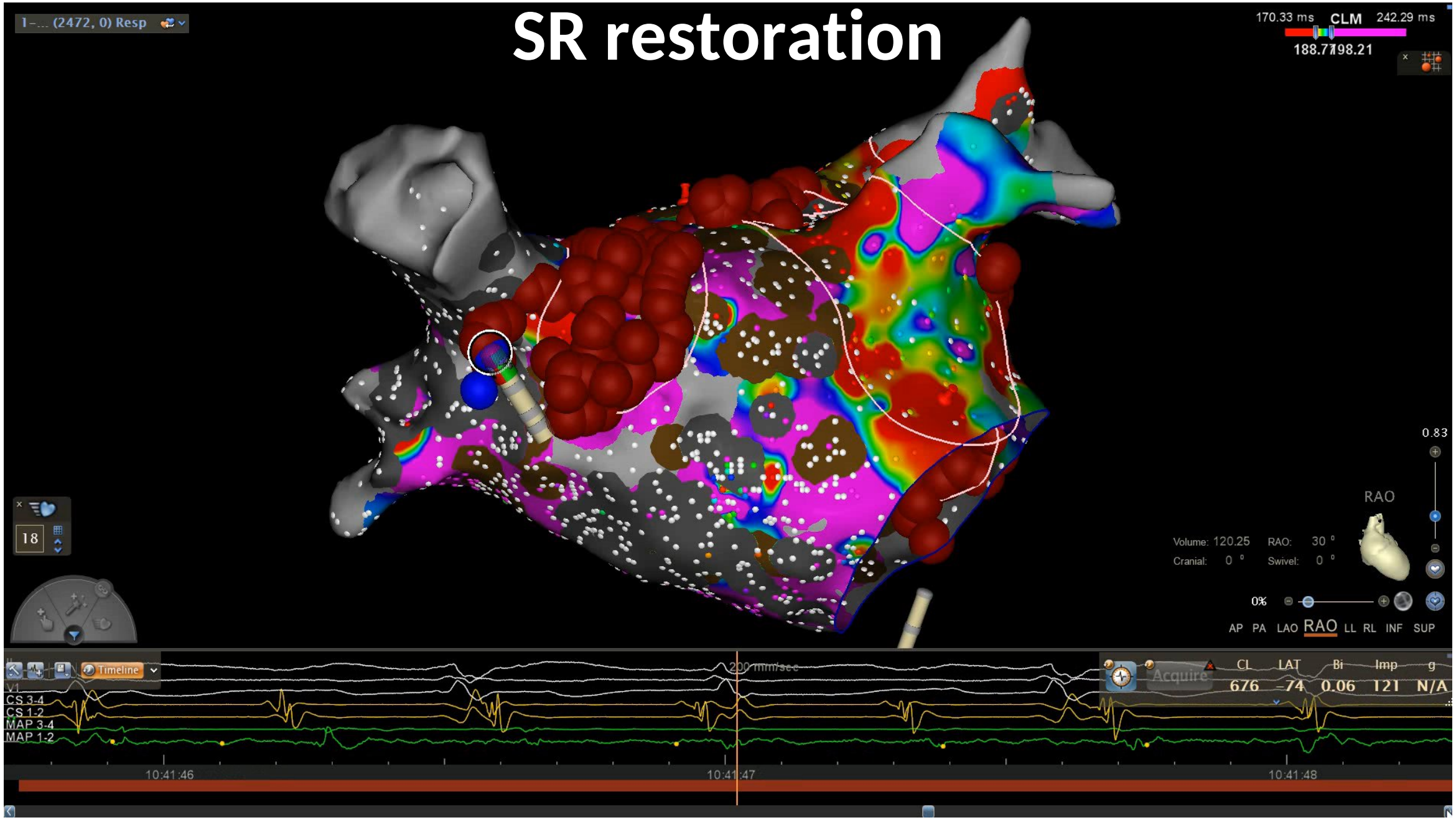


Ablation Targeting 2



Ablation Targeting 2




SR restoration
1-... (2472, 0) Resp
170.33 ms
CLM
242.29 ms
188.77
198.21
0.83
RAO
Volume: 120.25
RAO: 30 °
Cranial: 0 °
Swivel: 0 °
0%
AP PA LAO RAO LL RL INF SUP
18
Timeline
200 mm/sec
CS 3-4
CS 1-2
MAP 3-4
MAP 1-2
Acquire
CL LAT Bi Imp g
676 -74 0.06 121 N/A
10:41:46
10:41:47
10:41:48

CONCLUSIONS

- This novel AF mapping approach allows identification and characterization of multiple substrates, including fast and regular drivers, wave fronts with consistent propagation directions, fractionated activities, and low-voltage areas in real time
- The Integrated Substrate Map might facilitate identification of patient-specific features of AF and might help understand the underlying mechanisms
- AF Ablation treatment might be tailored according to the underlying mechanism in each patient
- Single or multiple mechanisms can be identified and the burden of the lesions might be reduced or increased according to the complexity of the Substrate and Dynamic mechanisms
- Future prospective studies will further clarify the role of AF substrate mapping