Fall in Korea

Electrophysiological Observation from Atrial Fibrillation Ablation Studies

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Executive advisor for KHRS foreign development

President of C&S Charitable Foundation

Financial disclosure

- Consultant and lecturer for Abbott medical
- Consultant and lecturer for Johnson and Johnson medical

Introduction: History of arrhythmia

- Chinese pulse theory laid the foundation for the study of arrhythmias and clinical electrophysiology in the 5th century BC.
- The most significant breakthrough in the identification and treatment of cardiac arrhythmias first occurred in 20th century.
- Clinical significance including SCD of cardiac rhythm disturbances has favored these advances.
- In the last four decades, our knowledge of electrophysiology and pharmacology has increased exponentially, especially percutaneous interventional arrhythmia therapy
- This presentation will address lessons learned from the catheter based arrhythmia therapy focusing atrial fibrillation.

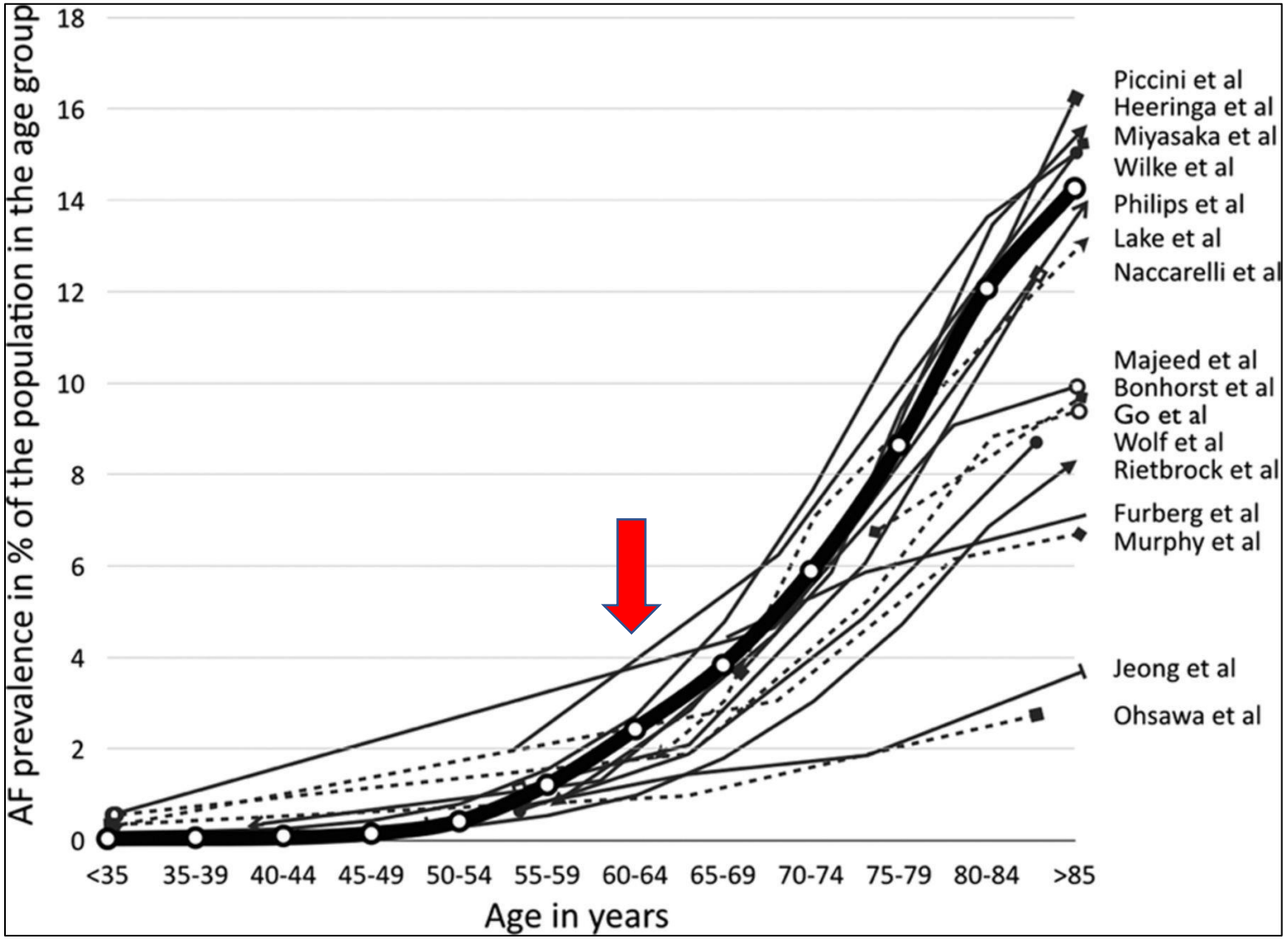
Topics presentation

- Epidemiology of atrial fibrillation
- Risk factors that directly influence progression of atrial fibrillation
- Atrial fibrillation ablation developments
- Currently practiced ablations modalities
- Future directions

Atrial fibrillation Epidemiology

- Atrial fibrillation (AF) is the most common sustained tachyarrhythmia currently affects world wide 1% to 2% of the general population.
- Aging is one of the strongest determinant of AF occurrence
- Prevalence of AF is increasing due longer longevity and projected to increase from ≈9 million to 12 to15 million for the United States population alone by 2050

Atrial fibrillation Epidemiology : prevalence



Modified from Andrade et al.(*CircRes*.2014;114:1453-1468.)

Known Risk factors for Afib (estimated lifetime risk, 22%–26%)

Non-treatable condition

Treatable condition

Partially-Treatable condition

Table 1. AF Risk Factors

Risk Factor	Estimated Increased Risk	Comments
Established		
Age	≈2	Per decade
Male sex	1.5	
Hypertension	1.2–1.5	BP >140/90 mm Hg
Valvular heart disease	1.8–3.4	
LV systolic dysfunction	4.5–5.9	
Obesity	1.39–2.35	
Alcohol consumption	1.34–1.46	Heavy alcohol use (≥36 g/d)
Emerging		
Prehypertension	1.28	Systolic BP 130–139 mm Hg vs <120 mm Hg
Increased pulse pressure	1.26	Per 20-mm Hg increment
Obstructive sleep apnea	2.8–5.6	
Physical activity	2.87	Cumulative lifetime practice >1500 h
Diastolic dysfunction	3.33–5.26	
Familial and genetic	1.85	AF in ≥1 parent
Hypertrophic cardiomyopathy	4–6	
Congenital heart disease	N/A	
Potential		
Coronary artery disease	N/A	Data inconclusive
Chronic kidney disease	1.3–3.2	Graded risk
Inflammation	1.47–1.77	Independent predictive value unclear
Pericardial fat	1.28–5.30	Risk related to thickness and volume of pericardial fat
Tobacco use	1.51–2.05	

AF indicates atrial fibrillation; BP, blood pressure; LV, left ventricular; and N/A, not available.

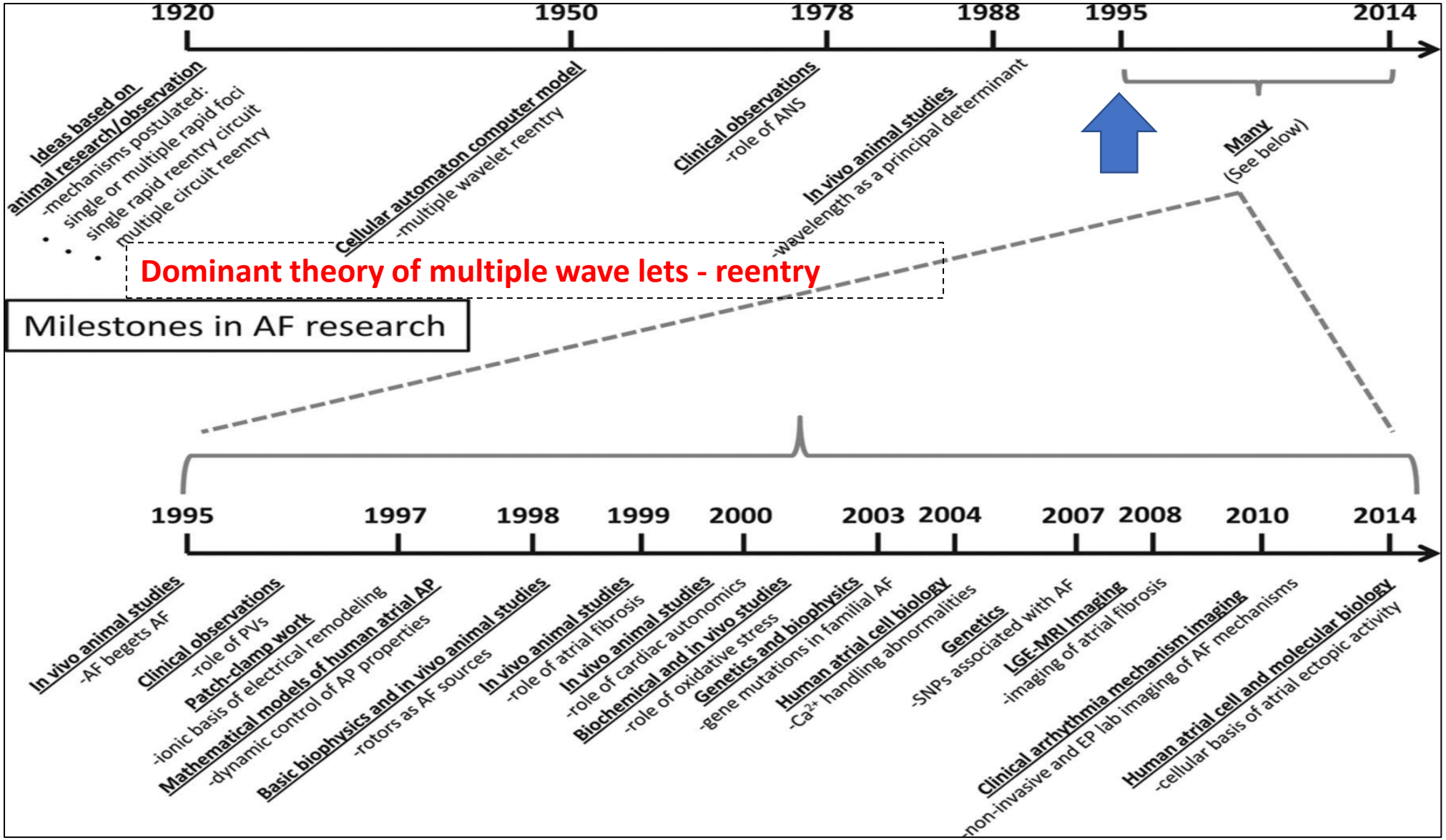
US

East Asia

Professor G. Moe Atrial Fibrillation Multiple Wavelets hypothesis, 1959

- Both circus movement and ectopic focus mechanisms have been produced experimentally, it is unrealistic to propose that only one of these mechanisms can exist in patients.
- The term “atrial fibrillation” is applied both clinically and experimentally to tachycardias so rapid that uniform atrial excitation does not occur.
- Irregular atrial activity it becomes difficult to prove which of several possible mechanisms exists. **It is conceivable that a circus movement could generate multiple wavelets**

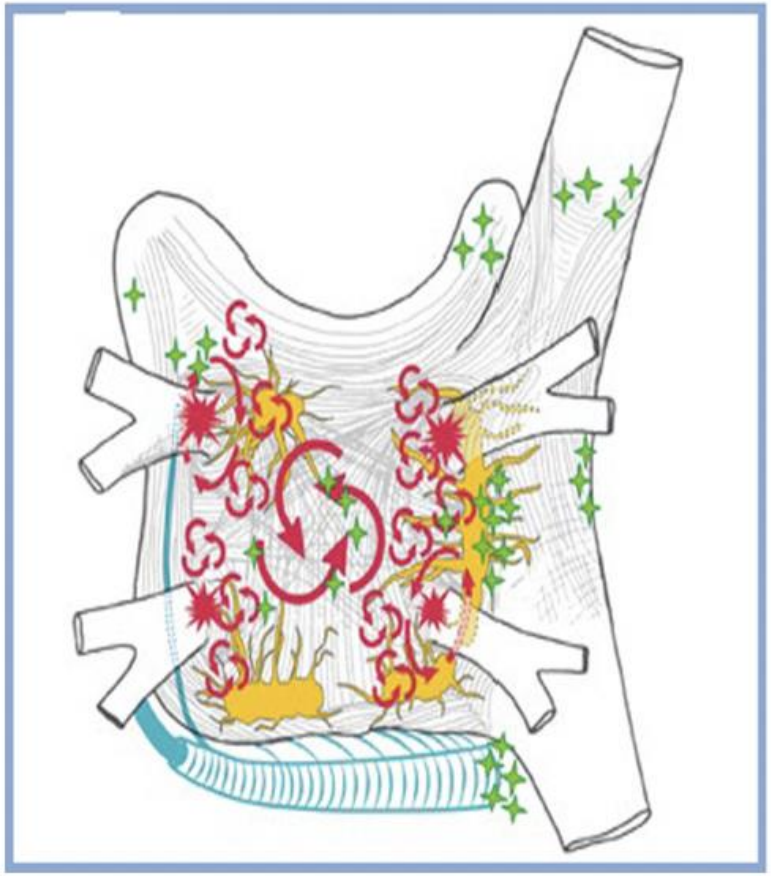
Schematic representation of the history of atrial fibrillation (AF) research



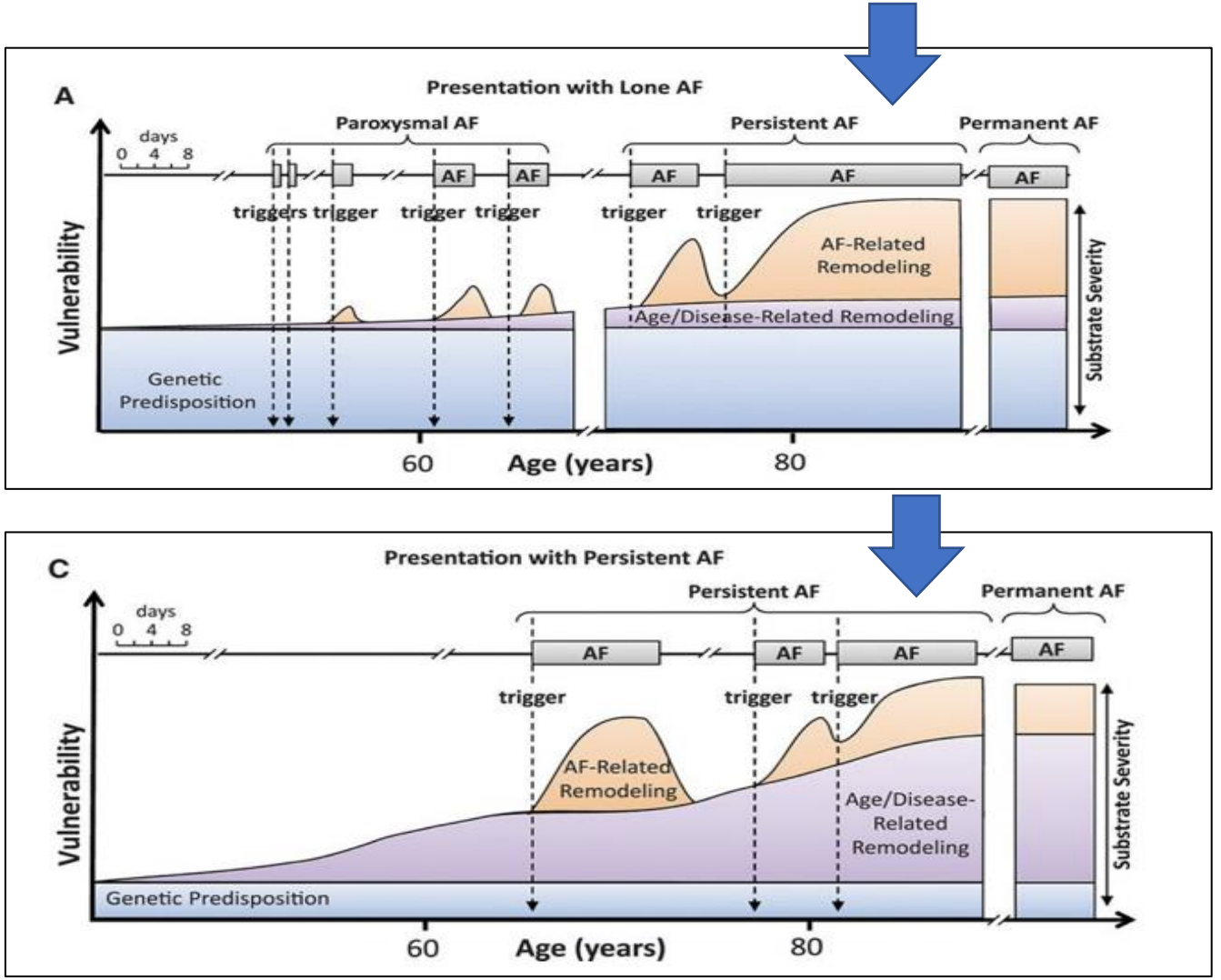
Nishida et al **(*Circ Res*. 2014;114:1447-1452.)**

Less trigger and less PV dependent persistent forms of Afib

Multiple wavelets schematic



Modified from Goldberger et al. Circ Arrhythmia and EP. 2024: 17: 8, e012939



Modified from Heijiman et al. (*Circ Res*. 2014;114:1483-1499.)

Chronic stage of A fib

Multiple wavelets and reentry A fib based non-medical therapies

1) catheter based DC shock ablation of AV junction to control rapid V rate
2) cardiac surgery to cerate linear ablation to eliminate reentry “MAZE”
3) **catheter based “MAZE” linear ablation in A fib pts in EP lab**

Surgical ablations:
AT, AVNRT
(cryo),WPW and VT

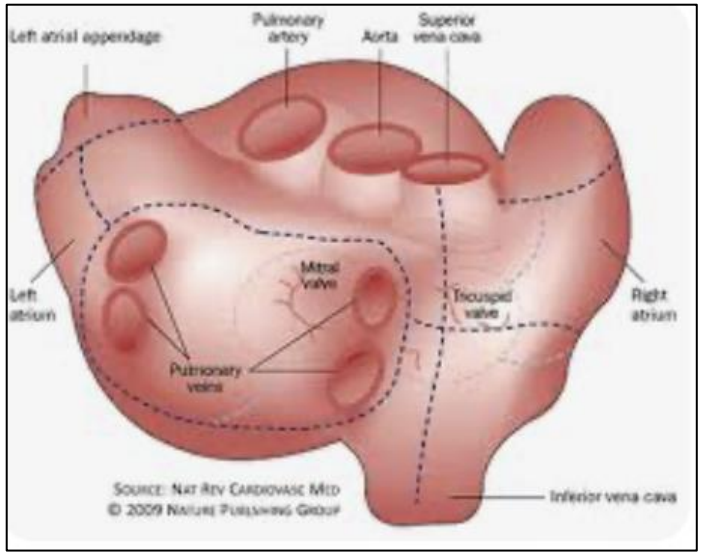
Cox J
MAZE surgery to “cure: atrial fibrillation

1971 — 1979 — 1982 — 1987 — 1994

Wellens
EP prog. St
Study and
Mapping

Scheinman and Gallager
AV junction
Ablation for rate control with
PM implant

John Swartz: Catheter based MAZE feasibility study: successfully performed catheter based MAZE in chronic A fib pts to convert sinus rhythm.
Opened door for EP labs to explore catheter based A fib ablation



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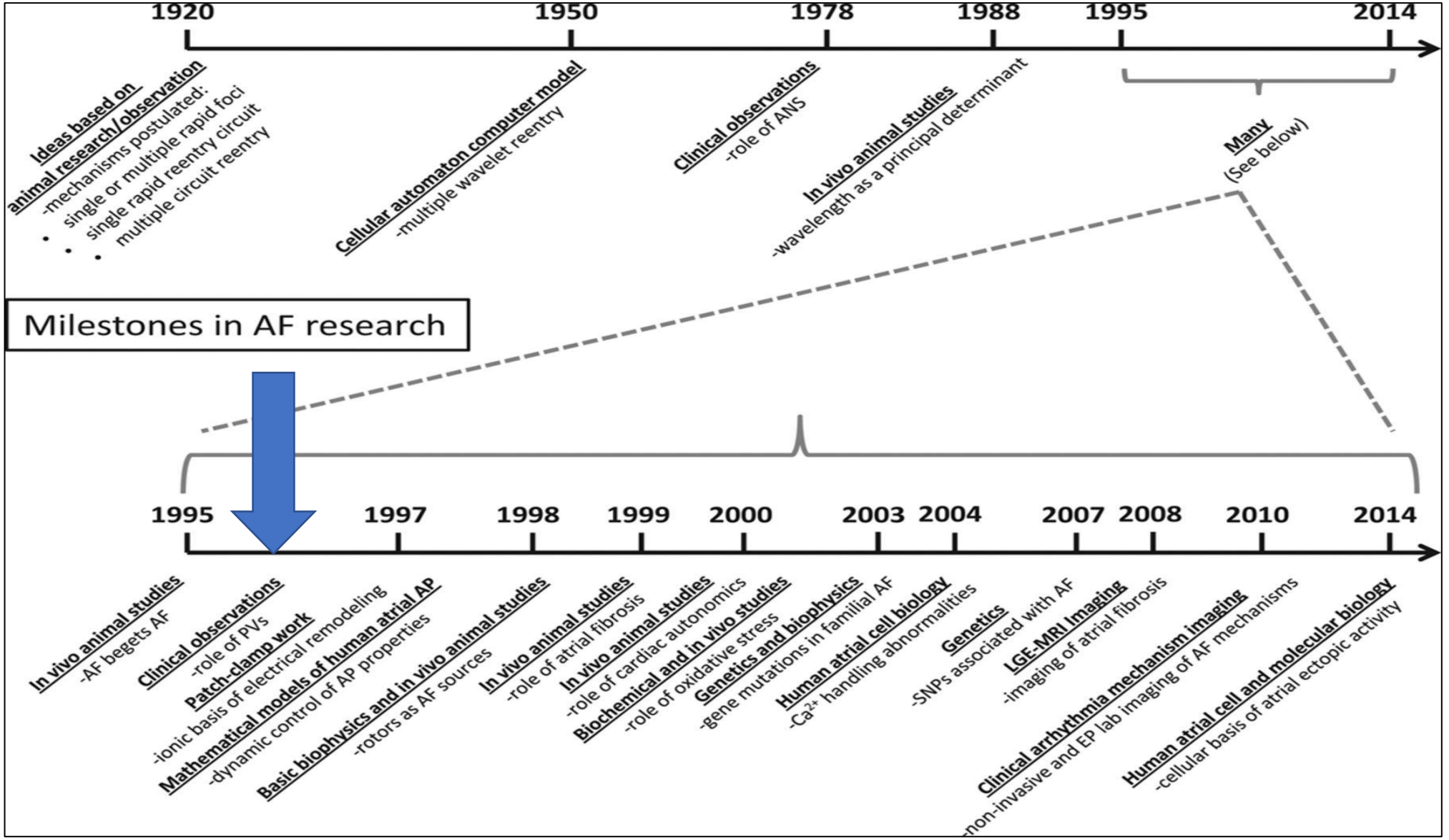
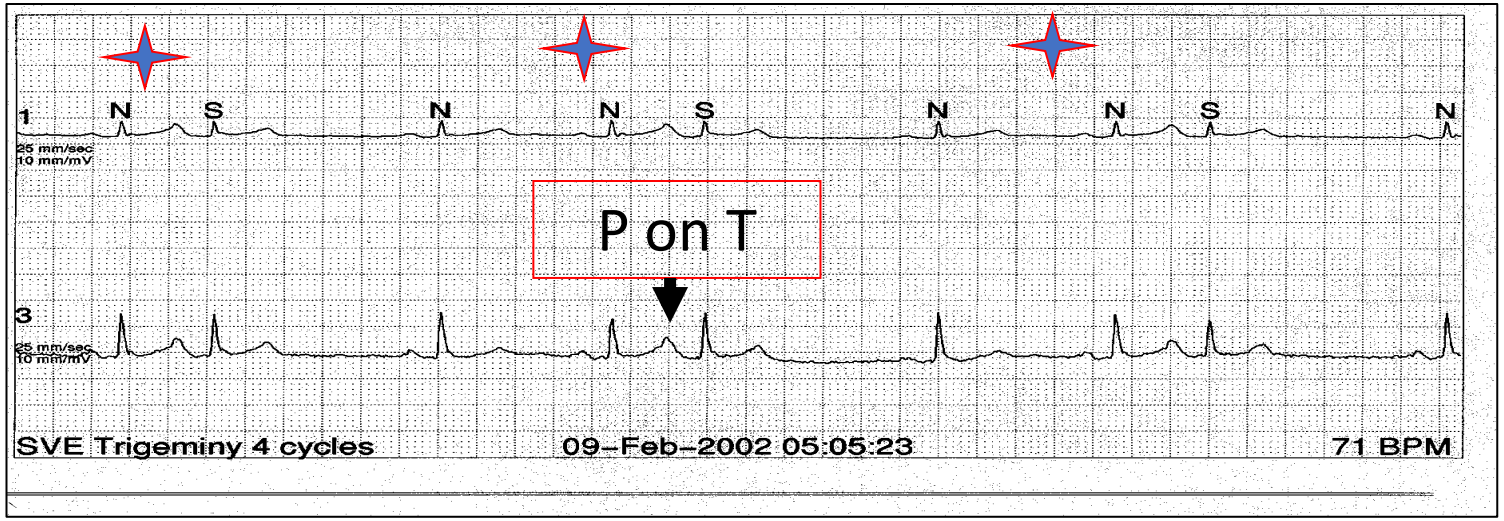
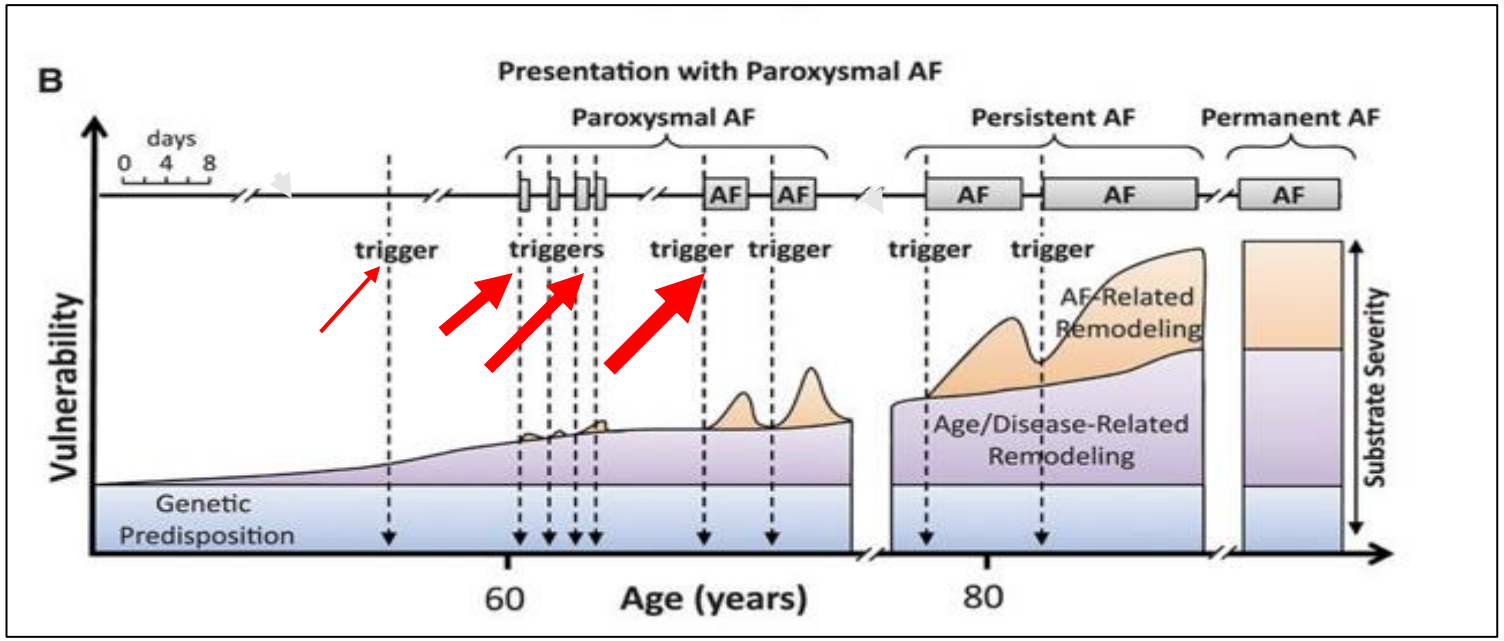


Modified from Nishida et al (***Circ Res*. 2014;114:1447-1452.**)

Early Stage of Atrial fibrillation

Atrial Premature was the source of Paroxysmal Afib (70-75 % pts from Pulmonary Veins)

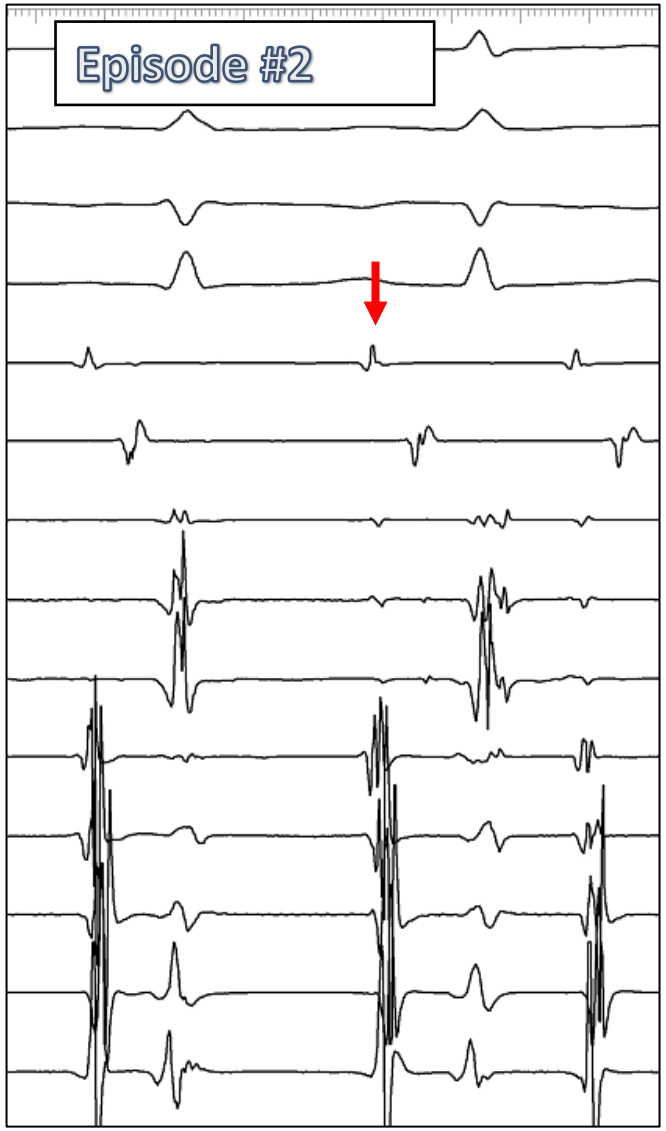




Modified from Heijiman et al. (*Circ Res*. 2014;114:1483-1499.)

Reproducible Re-initiation of focal trigger A fib episodes

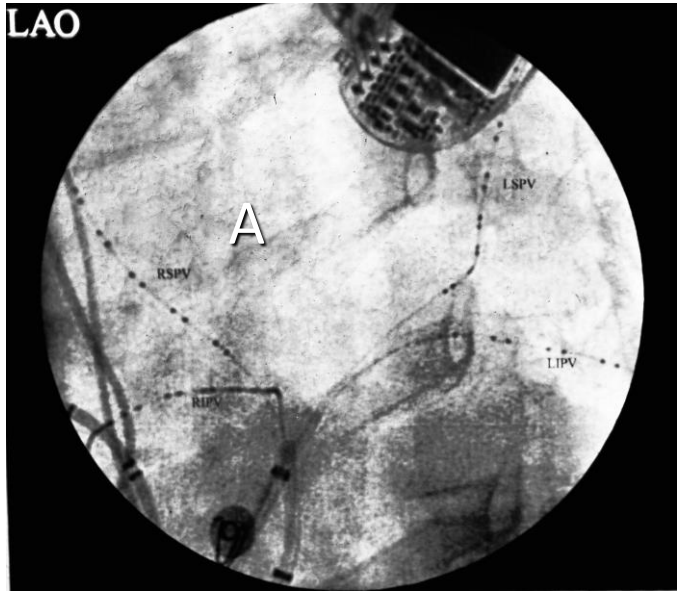
(same intracardiac activation patterns after intra cardiac cardioversions)

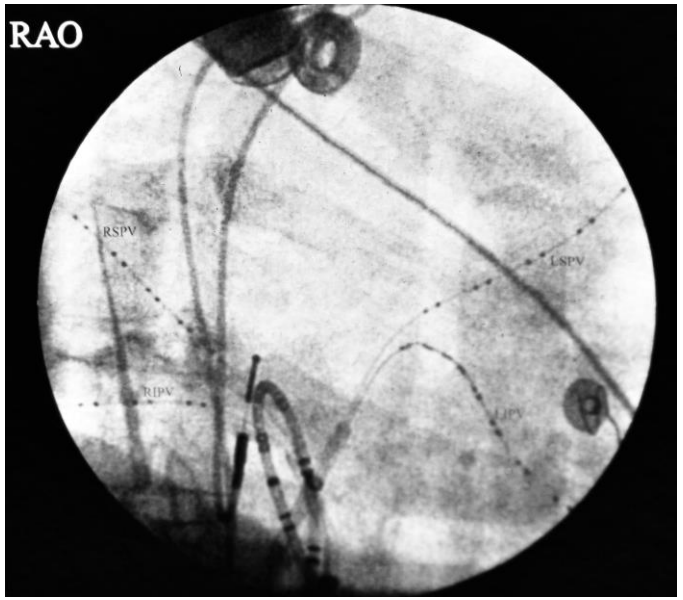


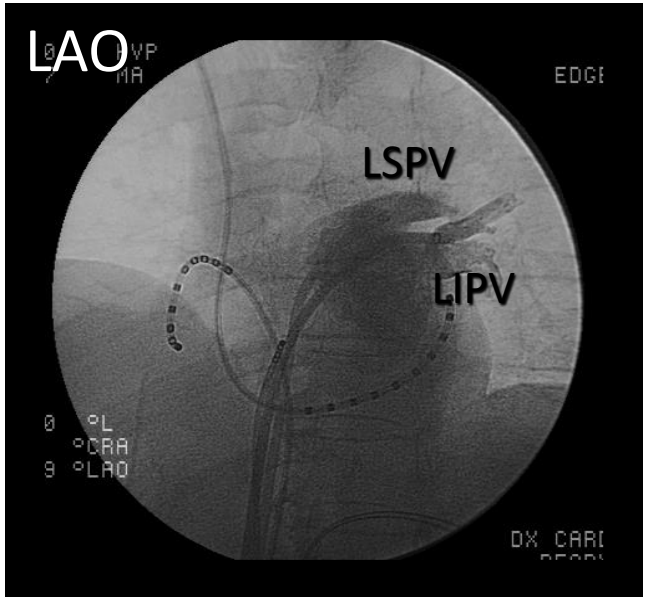
3/1996

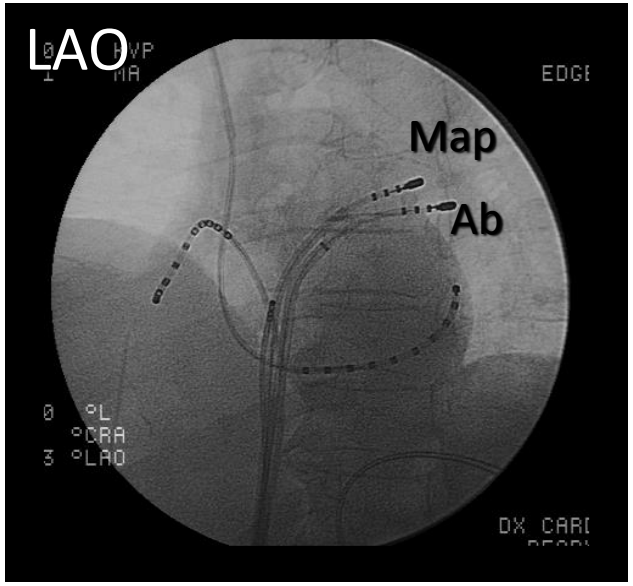
Focal Premature PV trigger mapping for A fib
Focal Ablation (Early Stage of Afib ablations)

7/1995



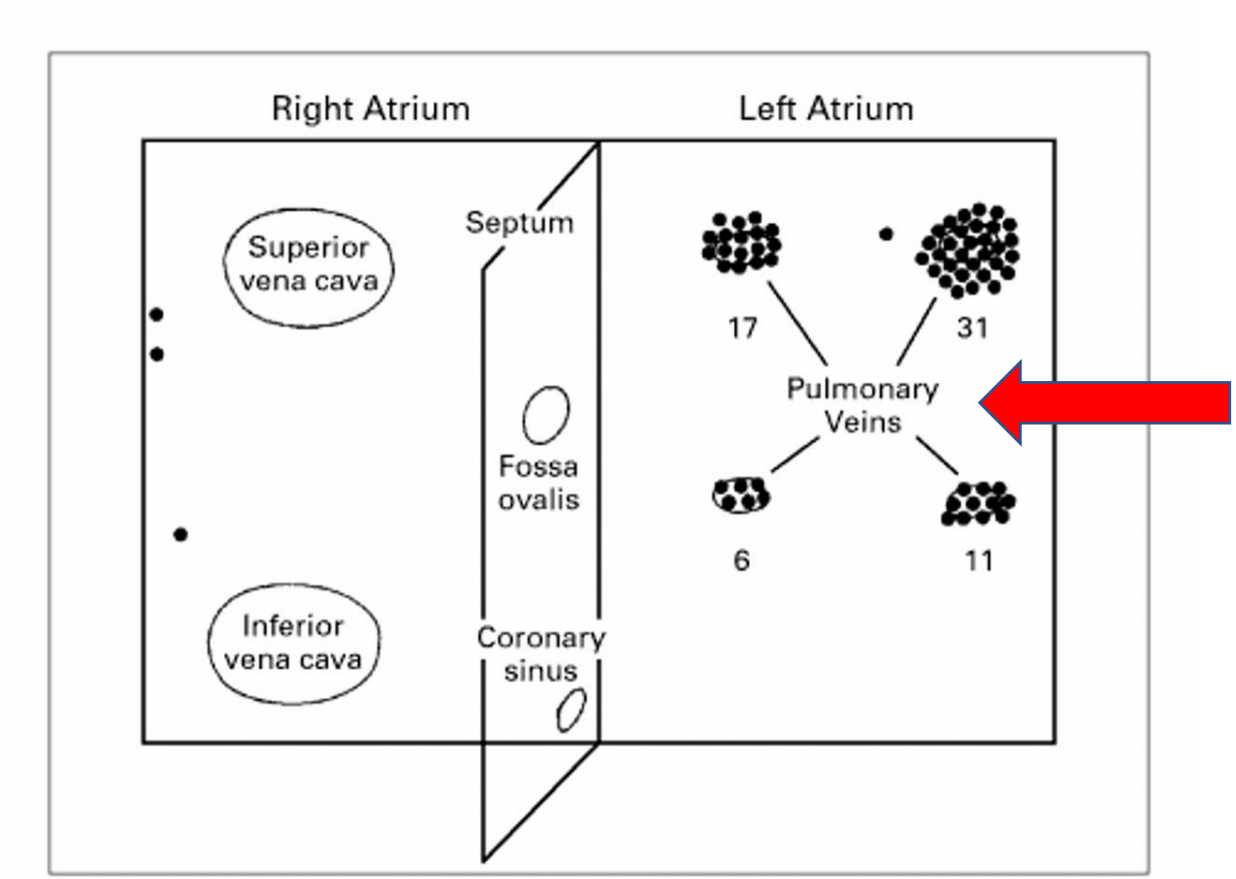






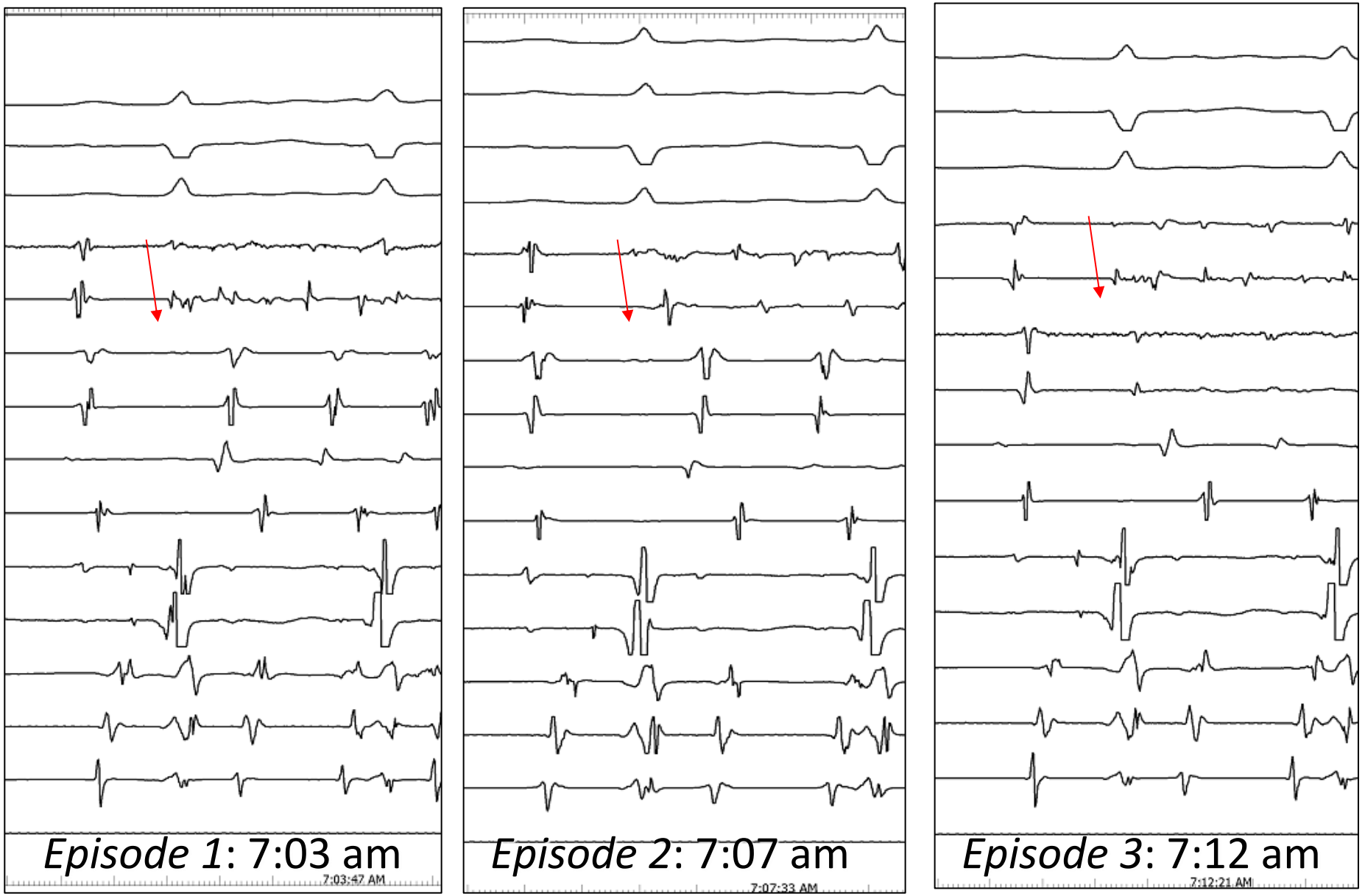
2/1997

Common Site of Focal Trigger for A Fib



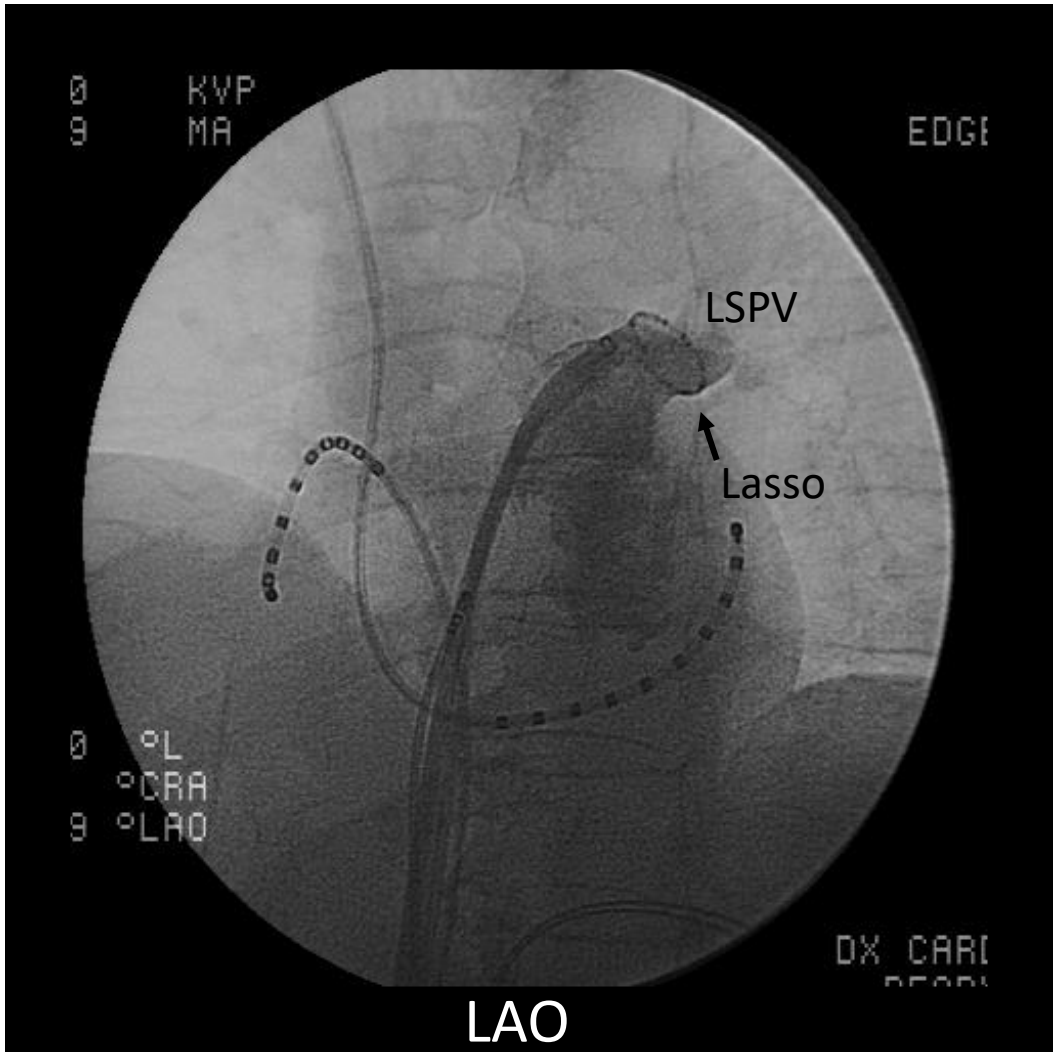
HAÏSSAGUERRE et al NEJM 1998;339-659-66

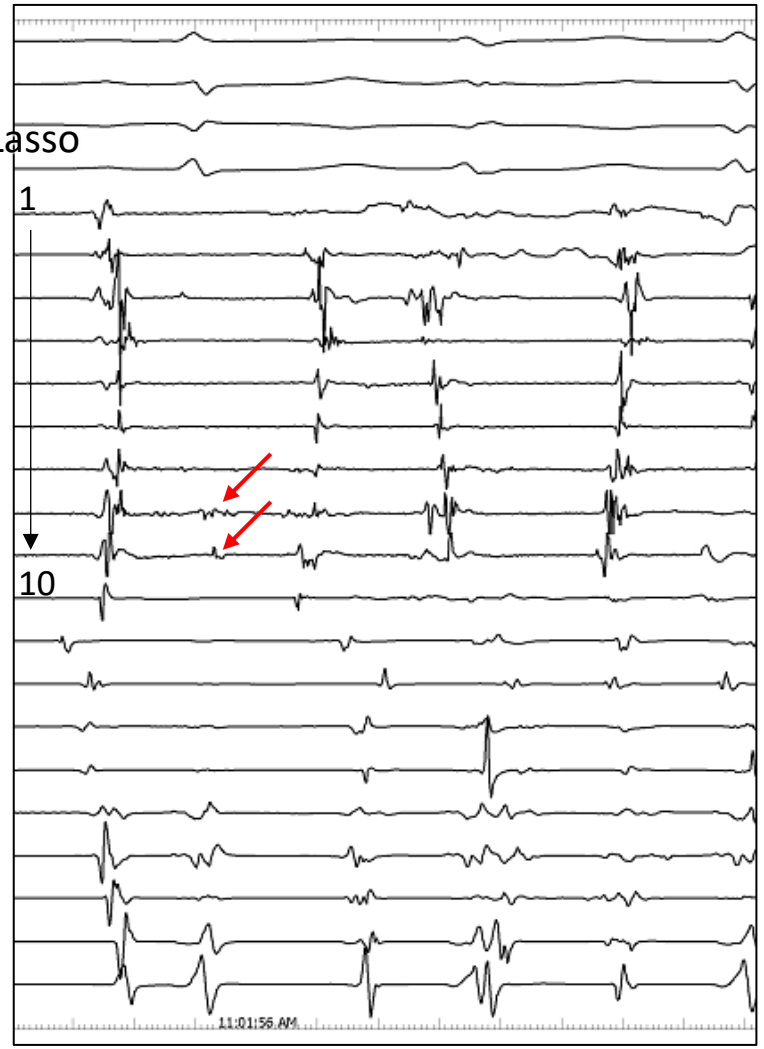
Re-initiation focus of A. fib from Right Superior PV in paroxysmal Afib Pts



3/2000

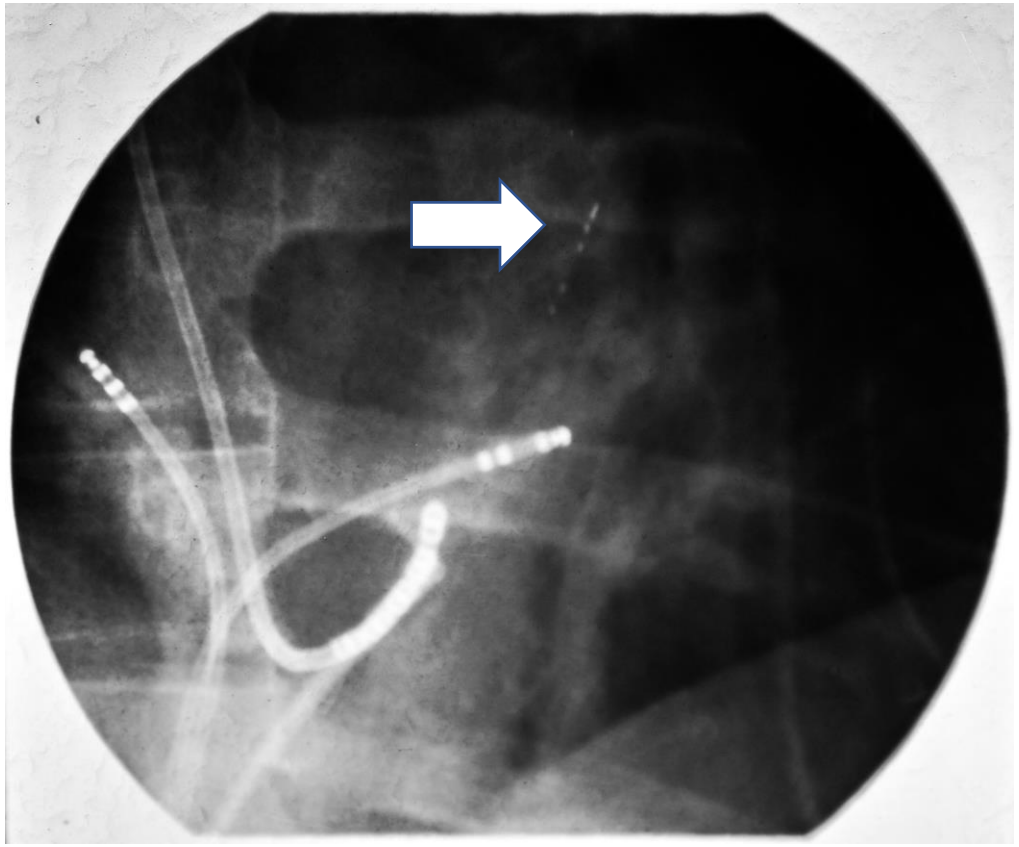
Circumferential Mapping of PV (Lasso Catheter) for PV Trigger Exit block for **PV Isolation**



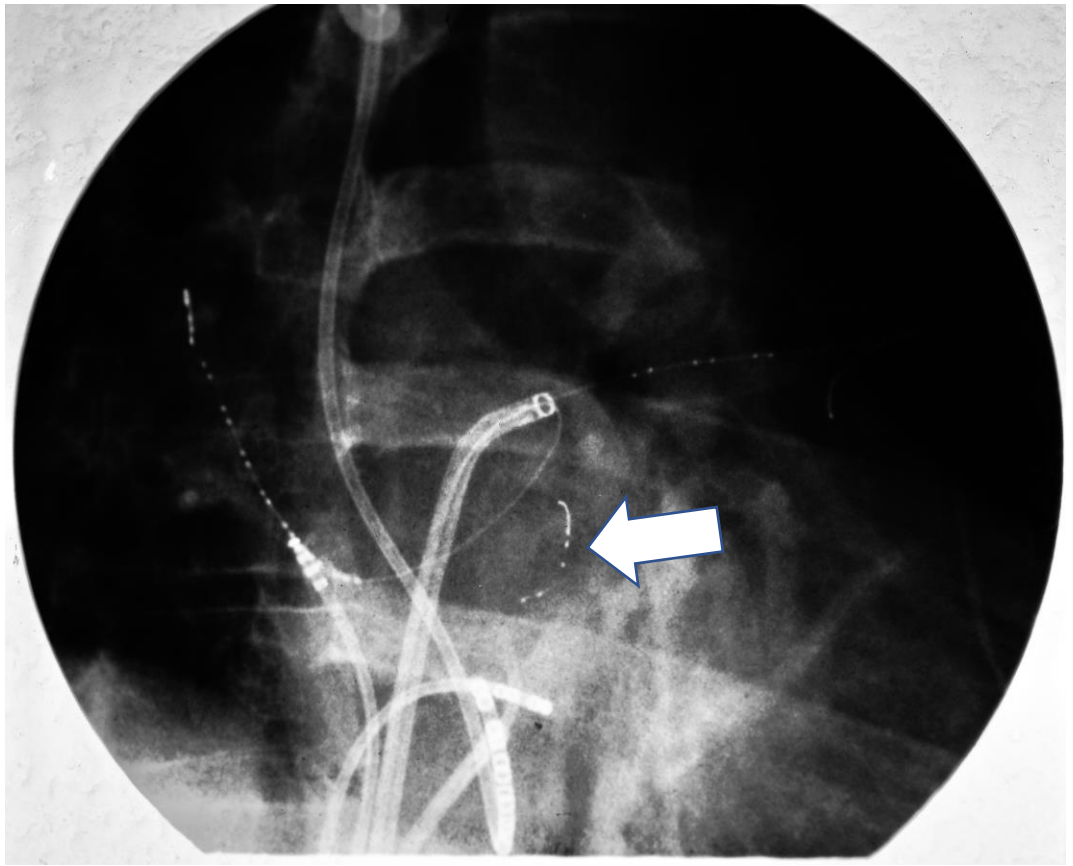


9/1999 (1st Lasso Catheter Mapping at UVRMC)

Focal A fib from Ligament of Marshall
(vein of Marshall mapping) image from case 3/1998

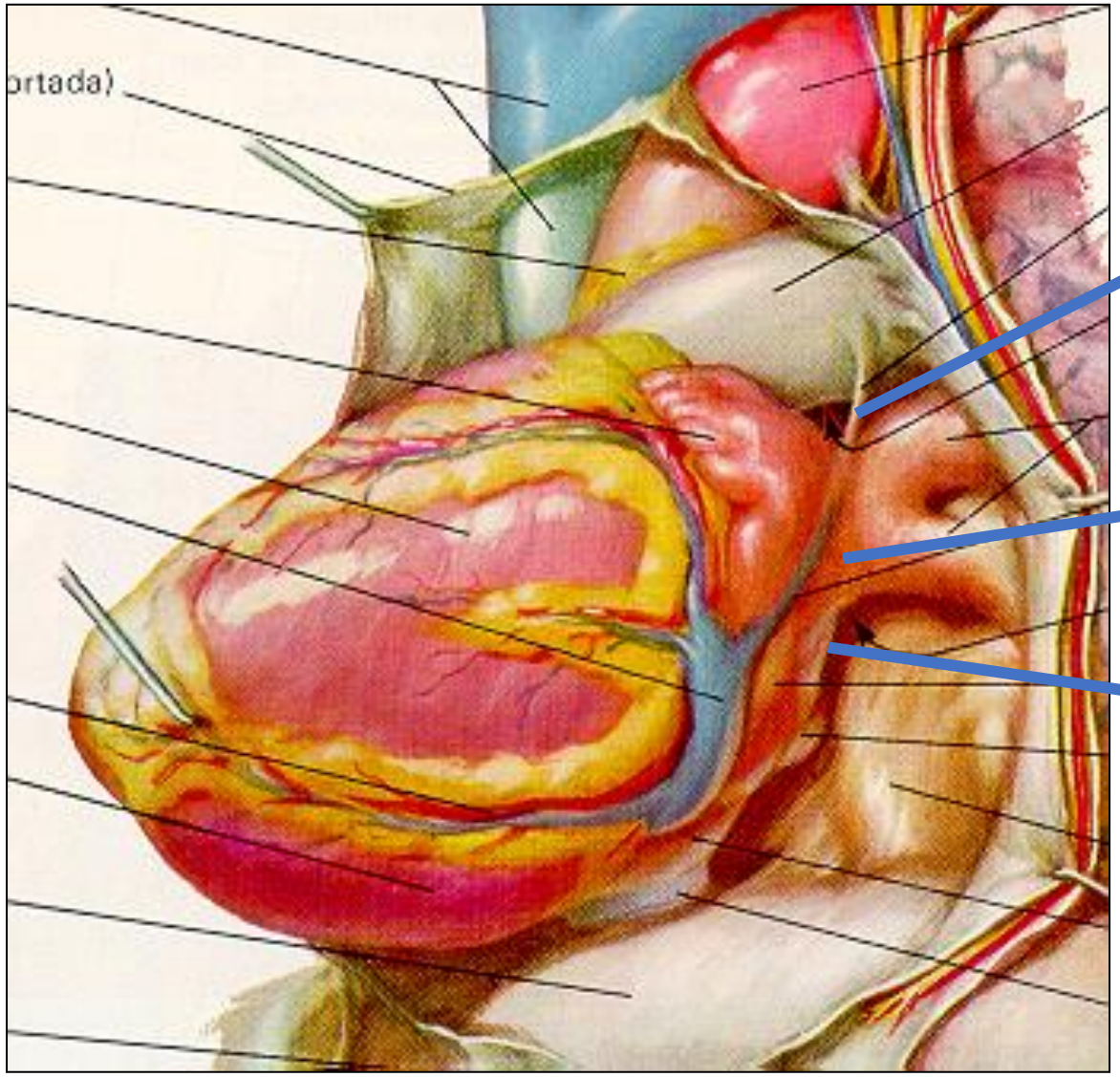


RAO



LAO

Anatomy of vein and Ligament of Marshall Anatomy



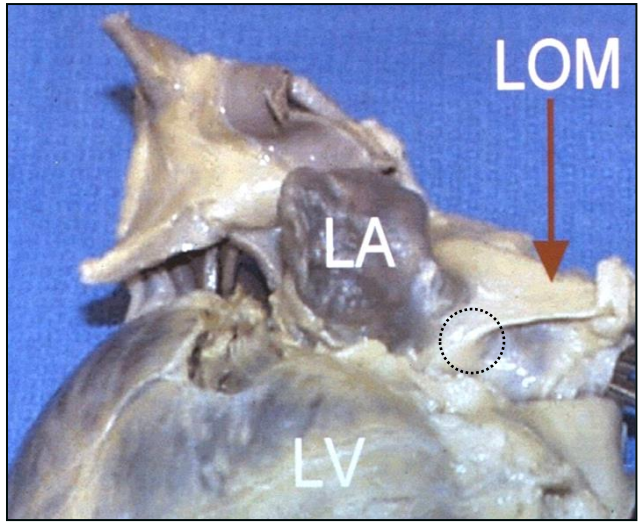
Distal segment: Ligament of Marshall (electrical inactive)

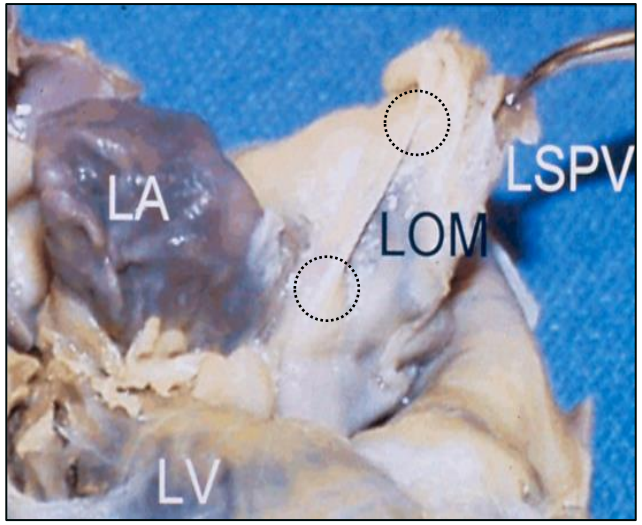
Mid segment: Vein of Marshall

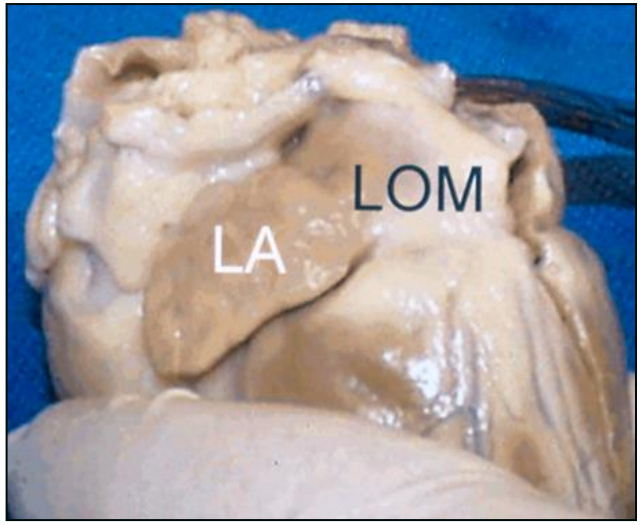
Proximal segment: Vein of of Marshall

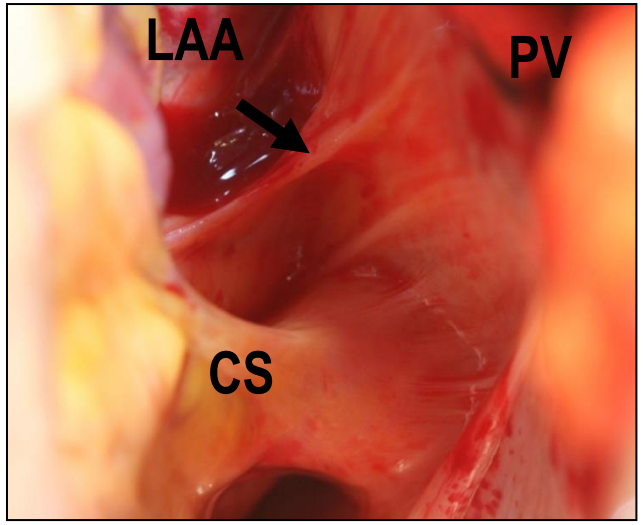
From F. Netter cardiac ant. atlas

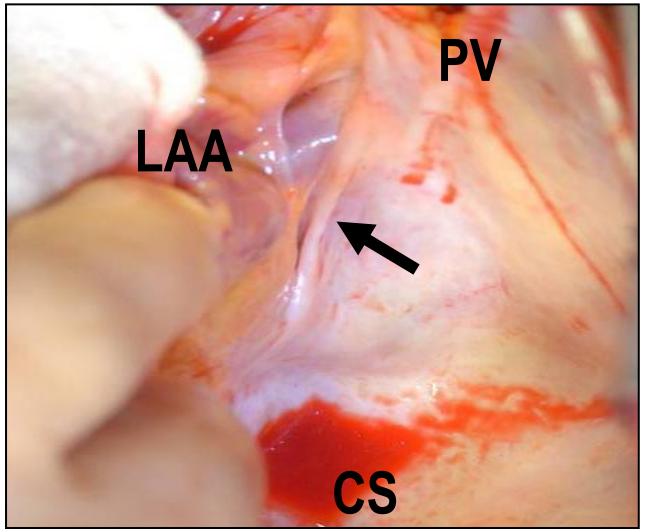
Anatomical Variations of Marshall Bundle in Patient under going Cardiac Surgery

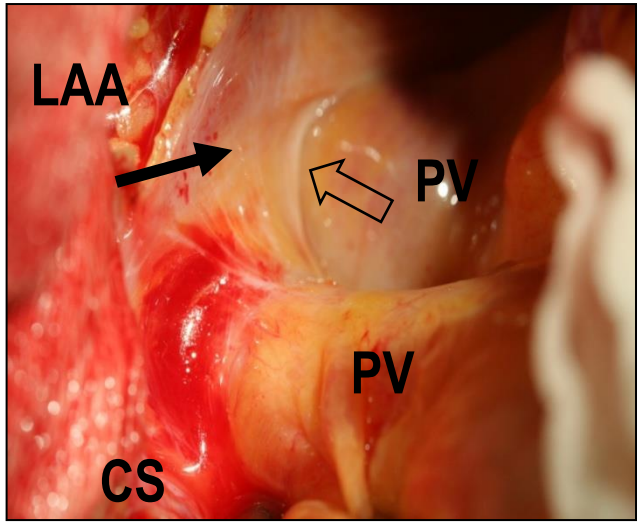






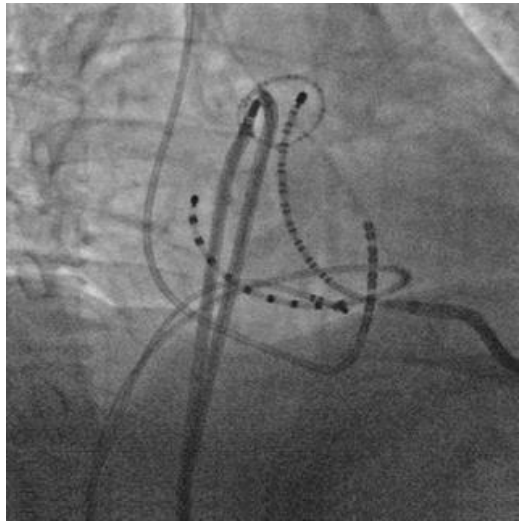


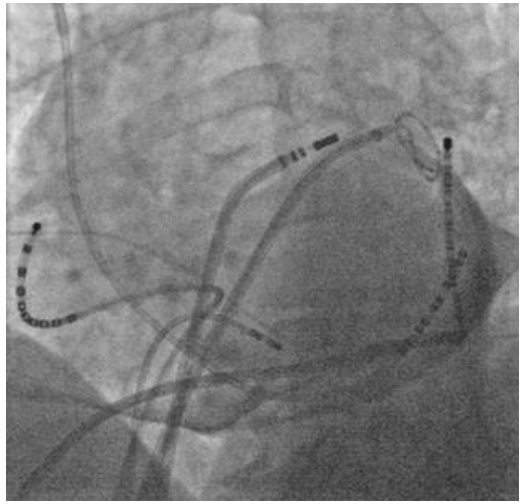


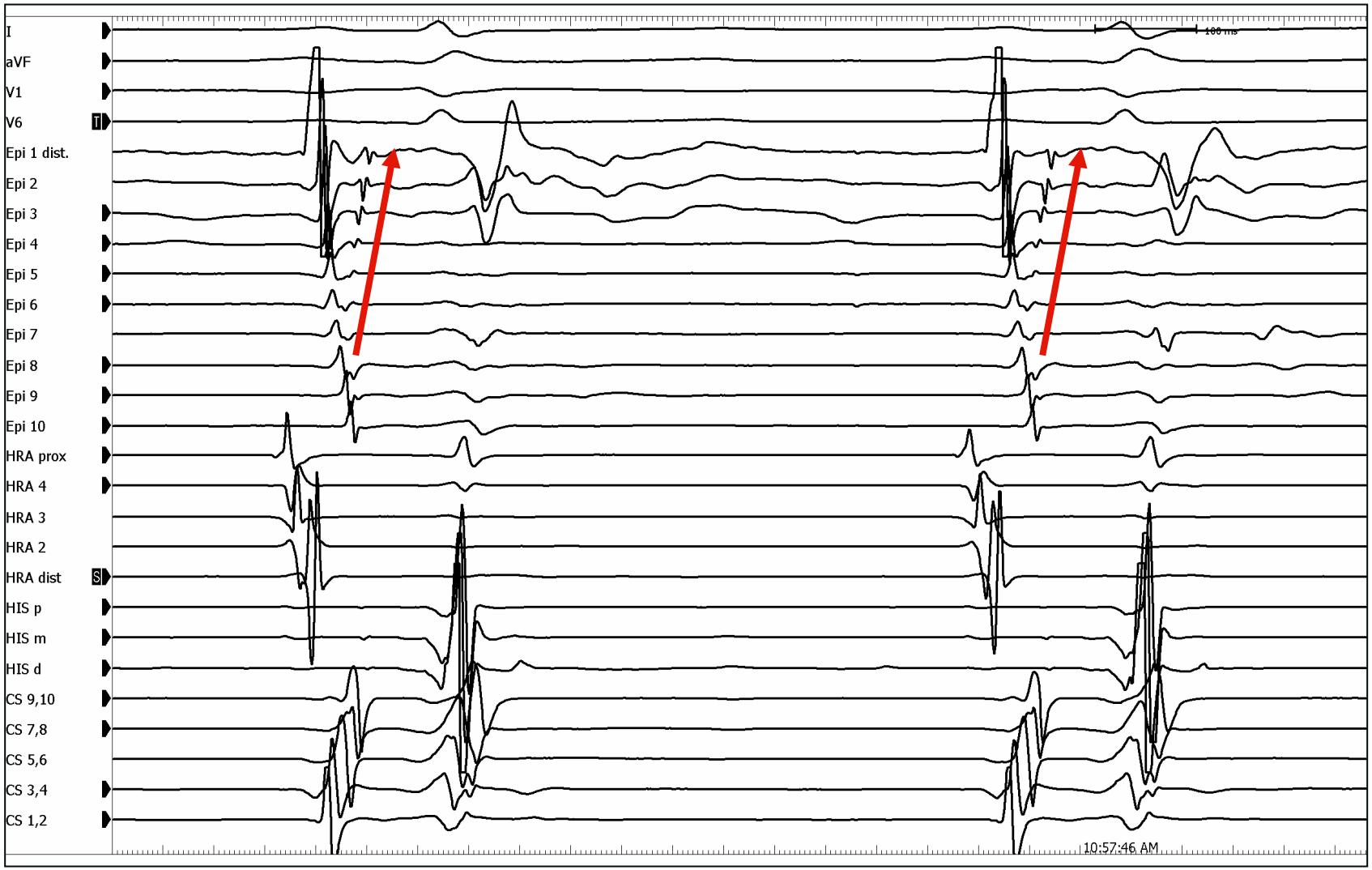


CS connection	CS + PV anterior carina connections	Multiple connections
5/53	21/53	27/53

Epicardial and endocardial LoM & Left Lateral Ridge Mapping

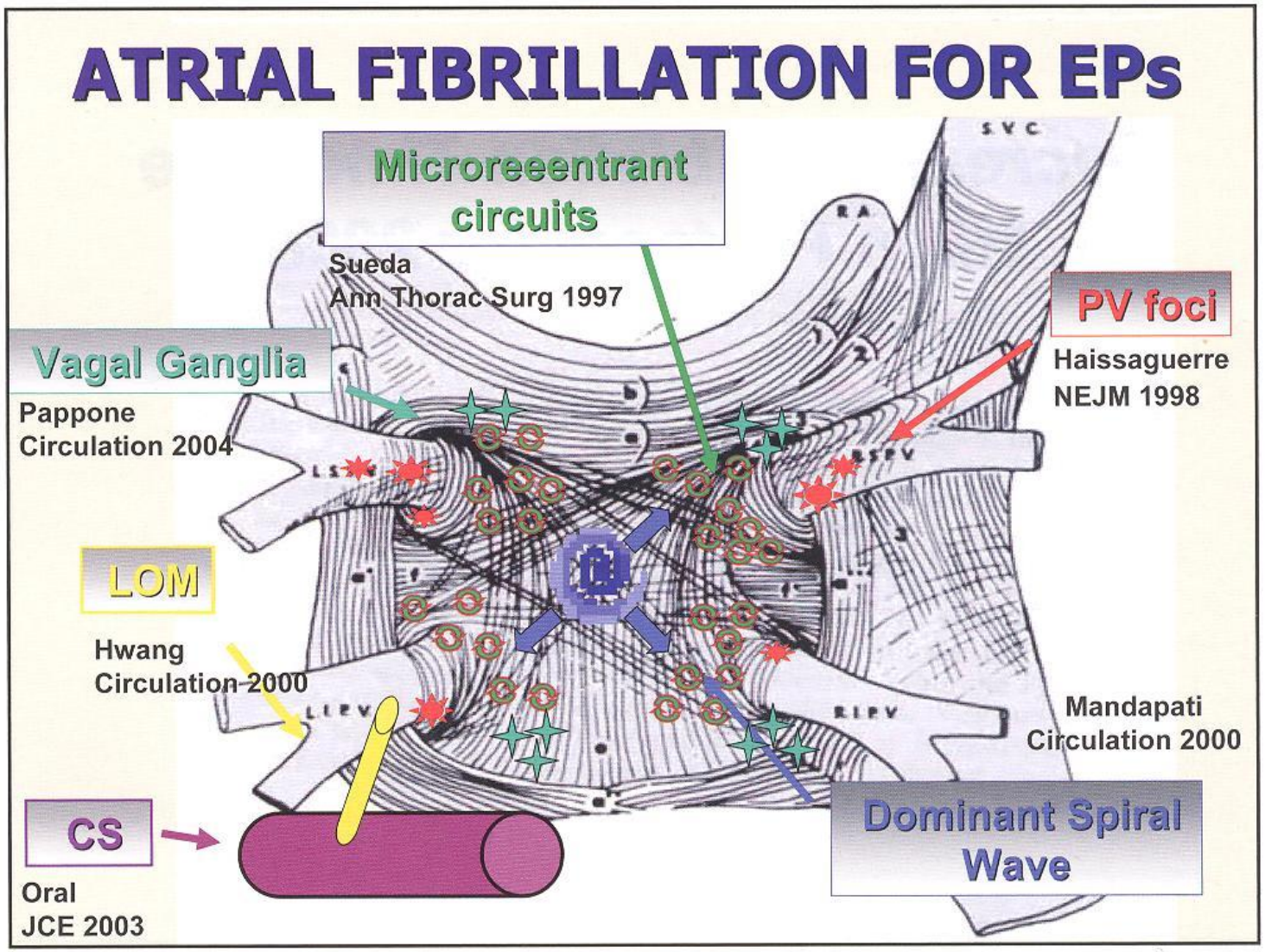






12/1999

Reported Mechanisms of A Fib



From Afib Summit 5/2007

Risk Factors &Pathophysiology of AF
Focal trigger and Reentrant mechanisms

Table 1. AF Risk Factors

Risk Factor	Estimated Increased Risk	Comments
Established		
Age	≈2	Per decade
Male sex	1.5	
Hypertension	1.2–1.5	BP >140/90 mm Hg
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Familial and genetic	1.85	AF in ≥1 parent
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Inflammation	1.47–1.77	Independent predictive value unclear
Pericardial fat	1.28–5.30	Risk related to thickness and volume of pericardial fat
Tobacco use	1.51–2.05	

AF indicates atrial fibrillation; BP, blood pressure; LV, left ventricular; and N/A, not available.

Cellular changes in A fib

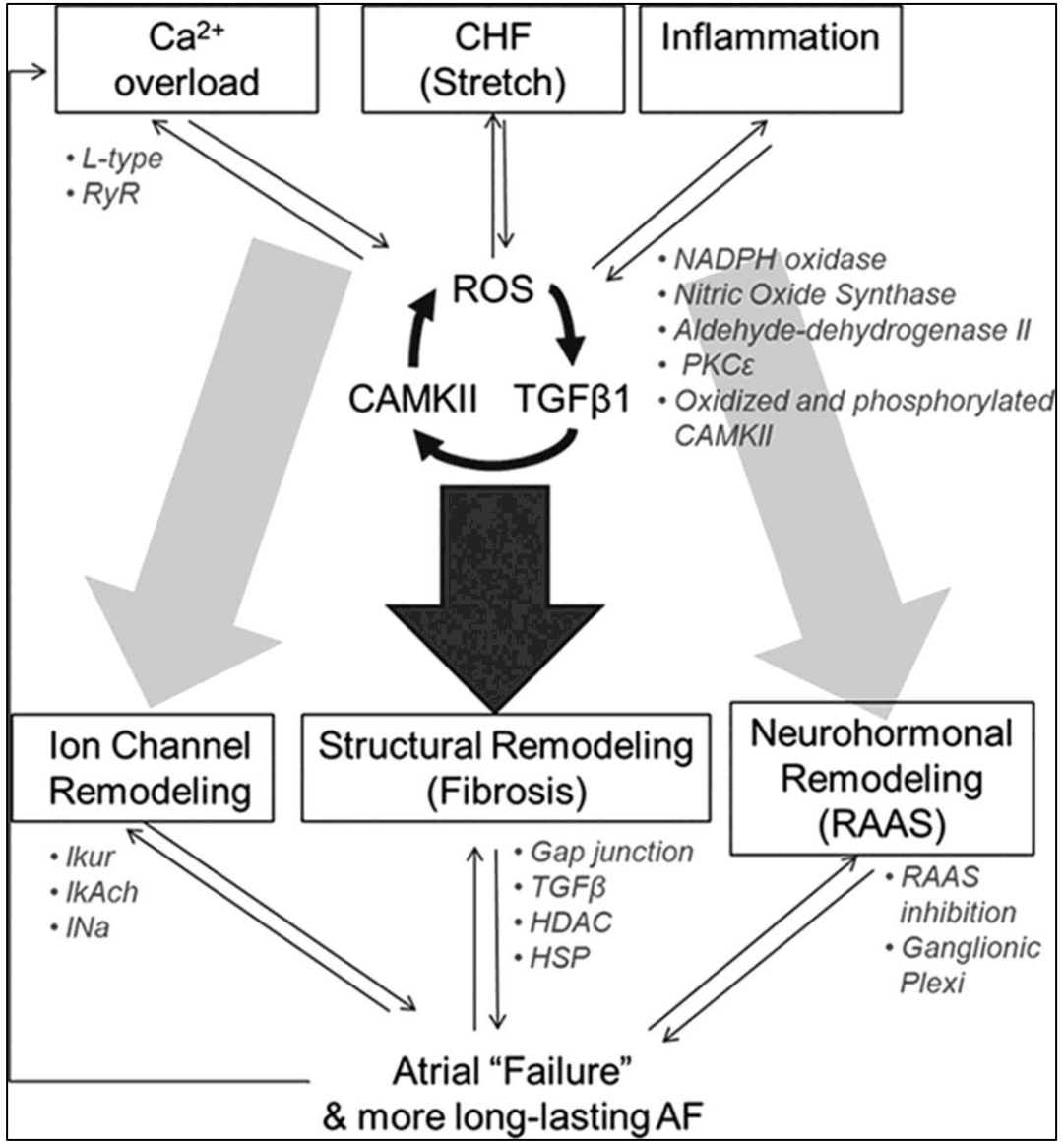
- Ion channel dysfunction inherited and acquired
- Ca2+-handling abnormalities,
- Structural remodeling
- Autonomic neural dysregulation

AF

Progression of atrial fibrillation

- Clinical observations showed that paroxysmal Afib progressed to persistent and then long standing persistent
- Atrial remodeling associated anatomical changes that also affect contractile myocardial units including gap junction to ion channels function.
- M Alexis study showed that **progressive remodeling** creates self perpetuating concept of "**atrial fibrillation begets atrial fibrillation**.

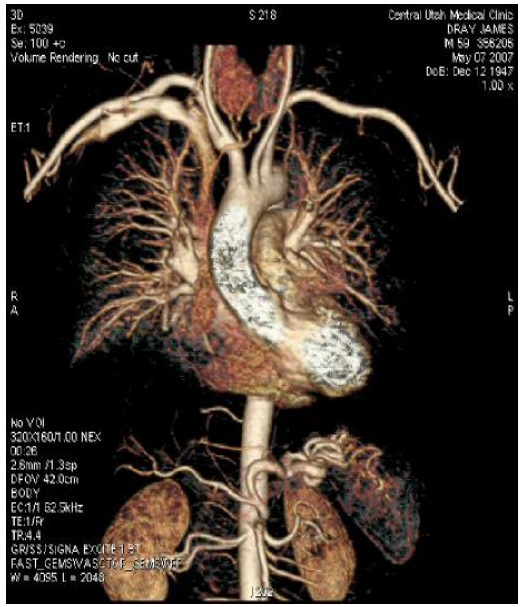
A fib Mechanisms of Remodeling



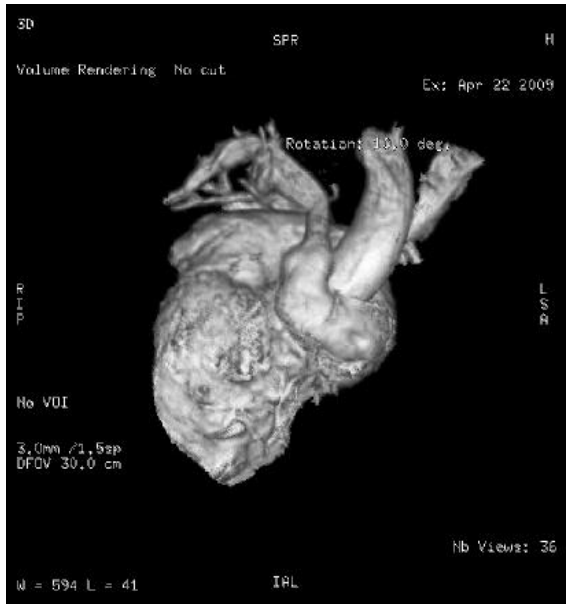
Woods et al (*Circ Res*. 2022;114:1532-1546.)

3-D Imaging

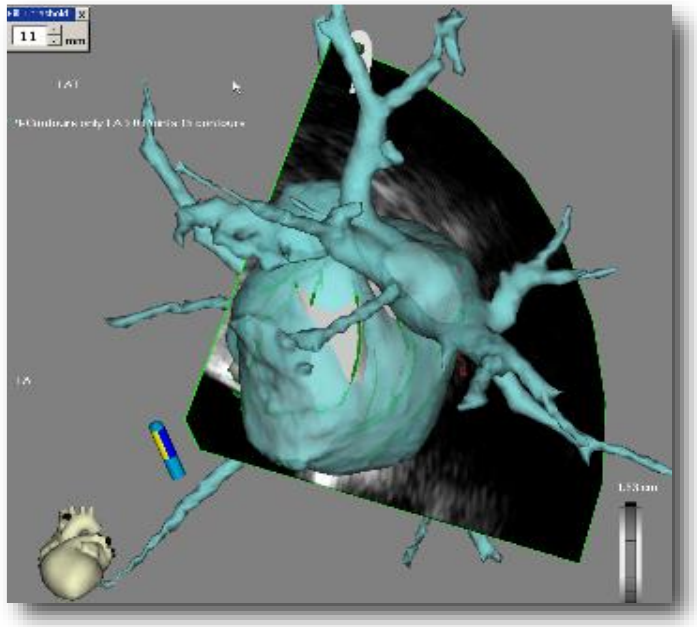
Pre-procedure and Real-time imaging with ICE for evaluation of anatomy and mapping to guide atrial fib ablation



CT angio



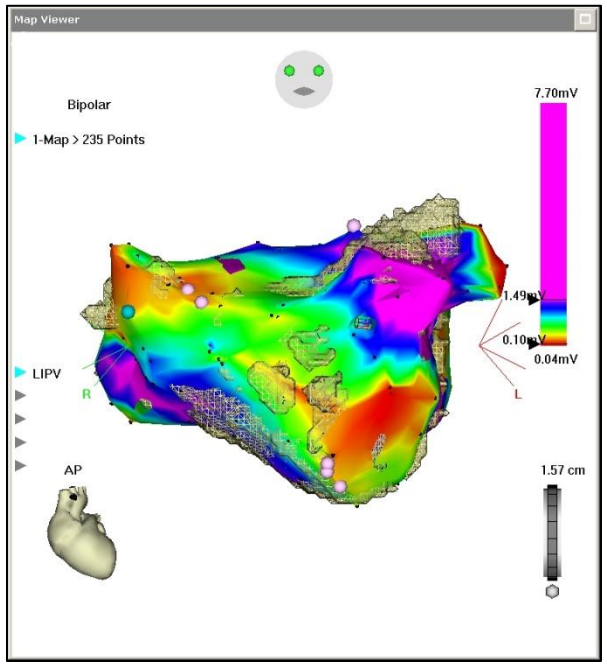
Cardiac MR
(PLSVC)



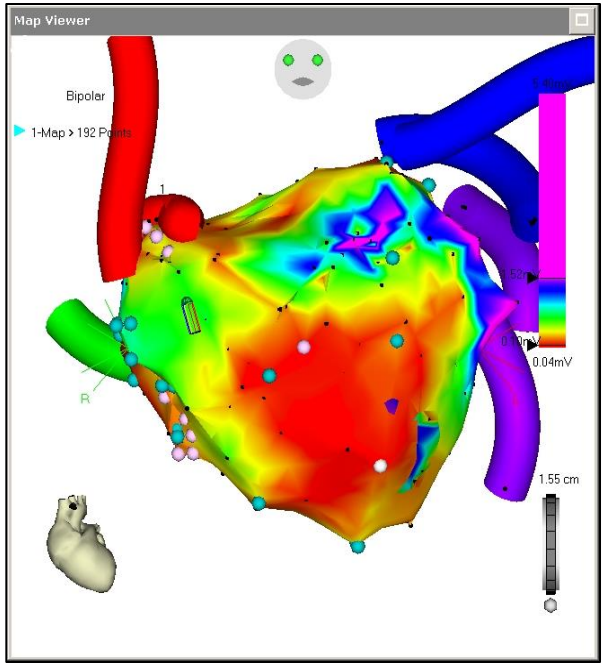
Intra cardiac echo

3-D Electro-Anatomical Mapping (1999)

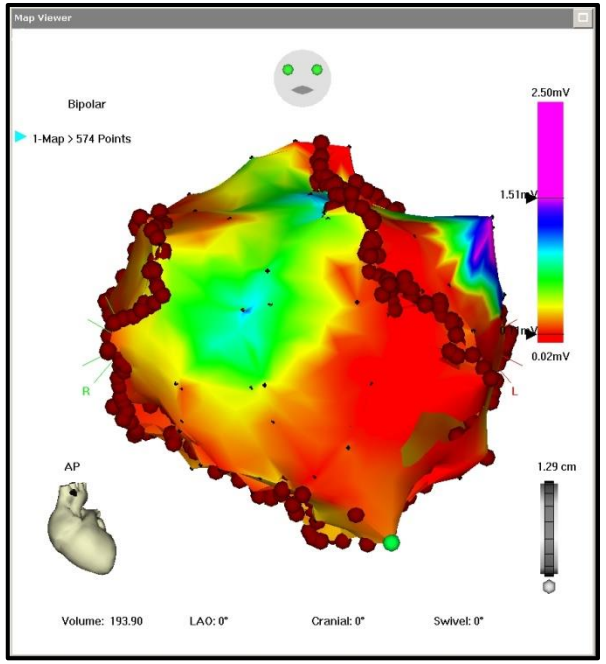
LA Volume and Voltage Map



LAV = 95 ml



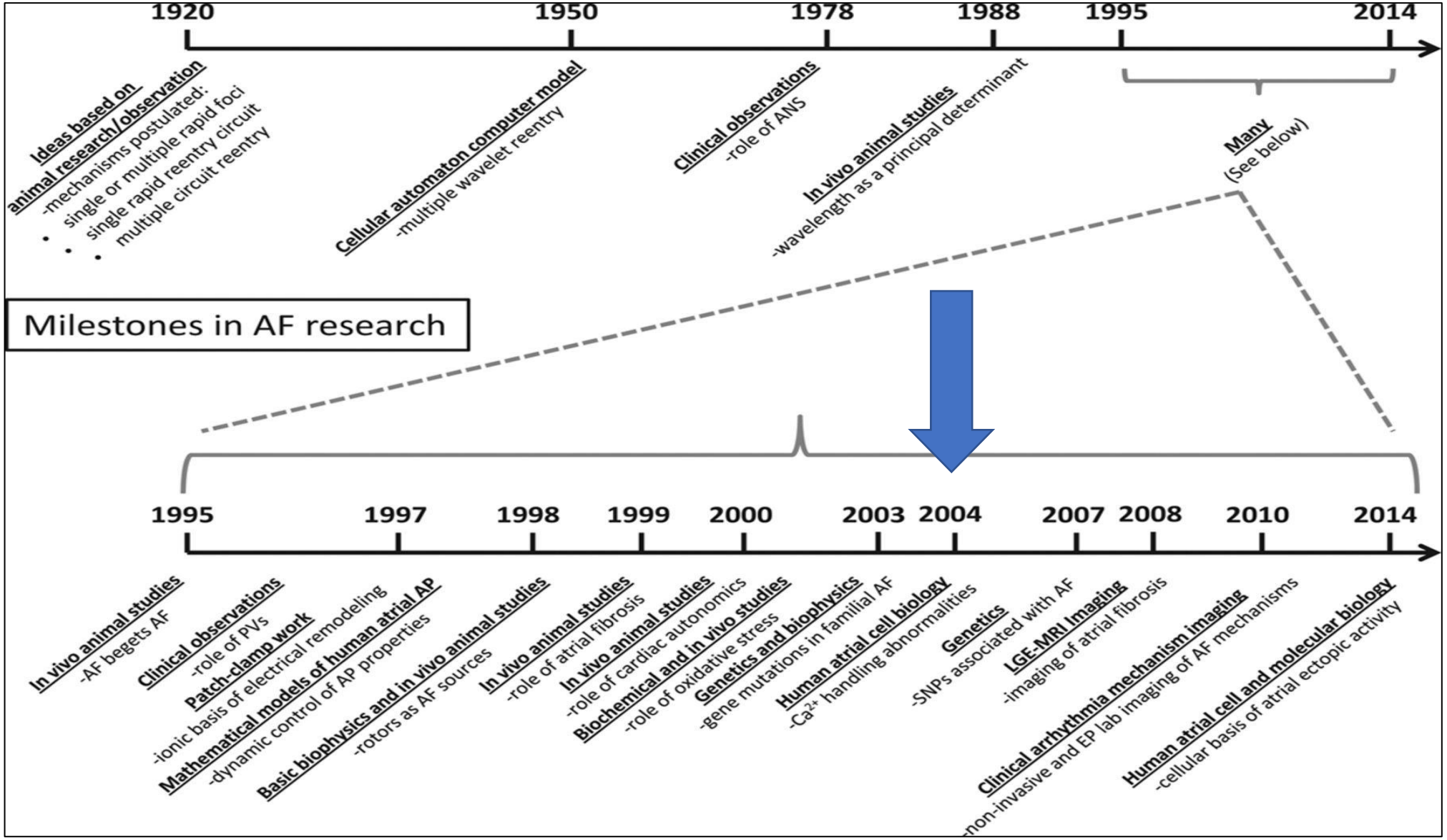
LAV = 179 ml



LAV = 234 ml

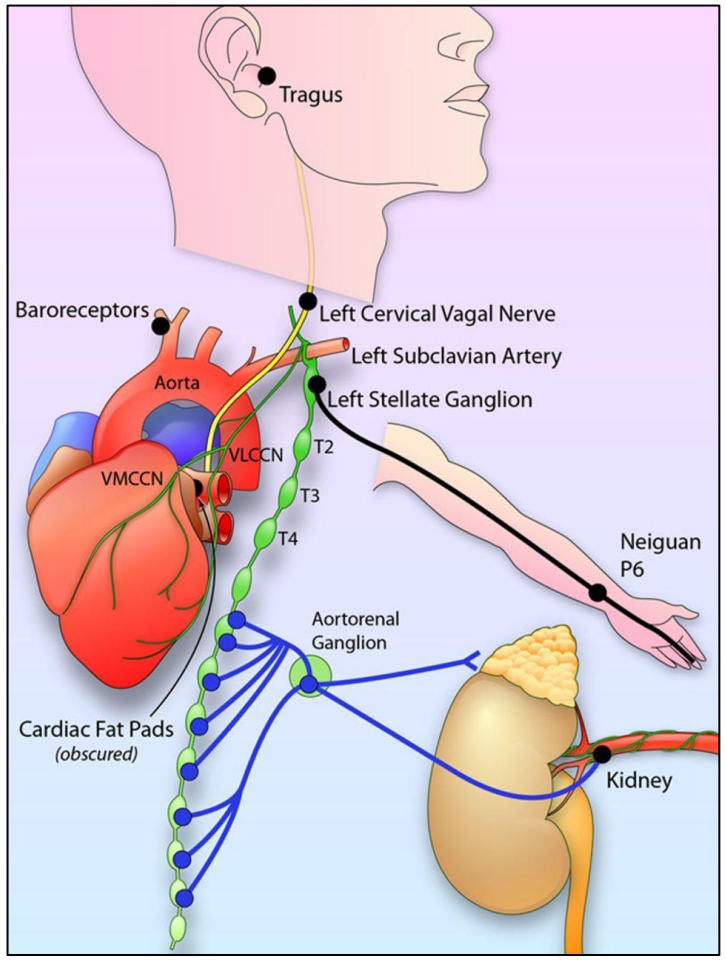
Progressive remodeling decreased overall atrial myocardial voltage and increased scared area

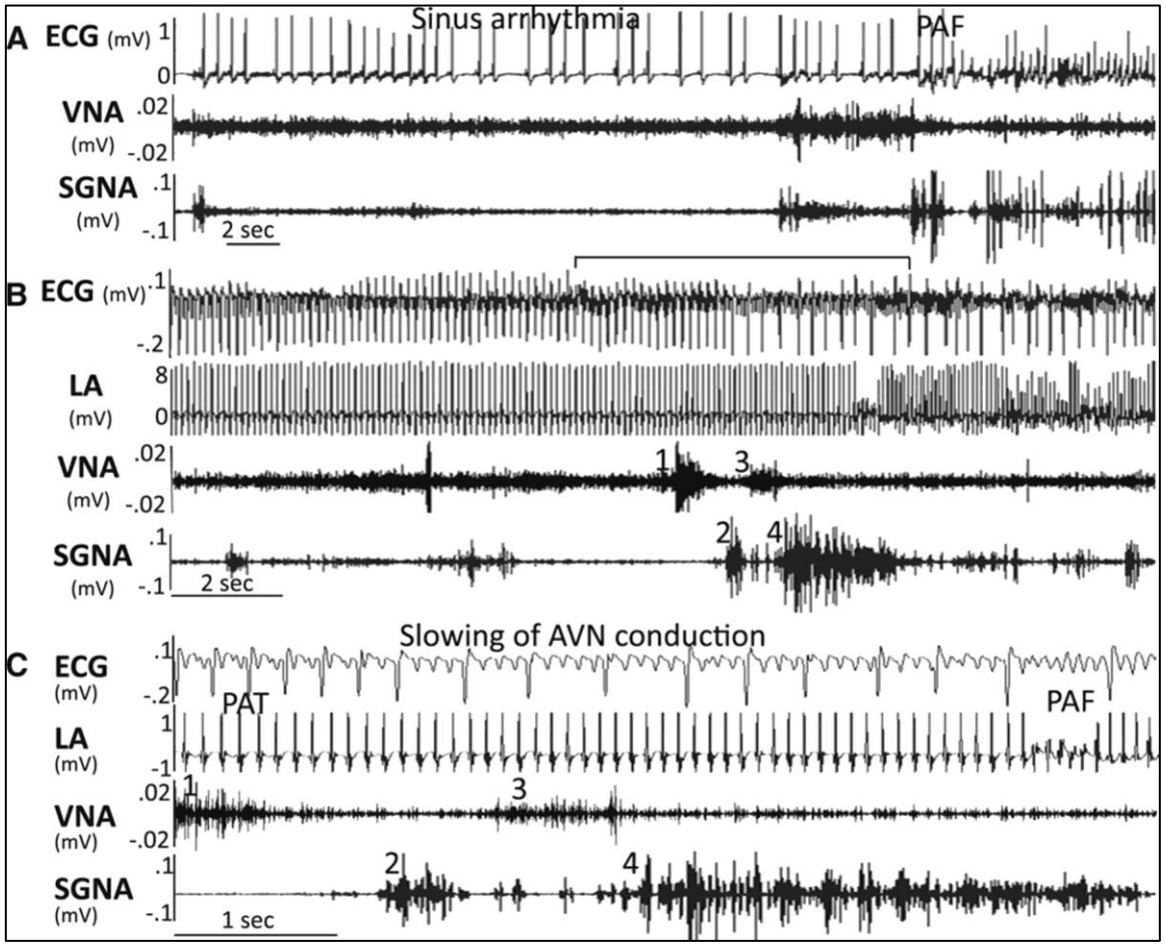
Schematic representation of the history of atrial fibrillation (AF) research



Modified from Nishida et al (***Circ Res*. 2014;114:1447-1452.**)

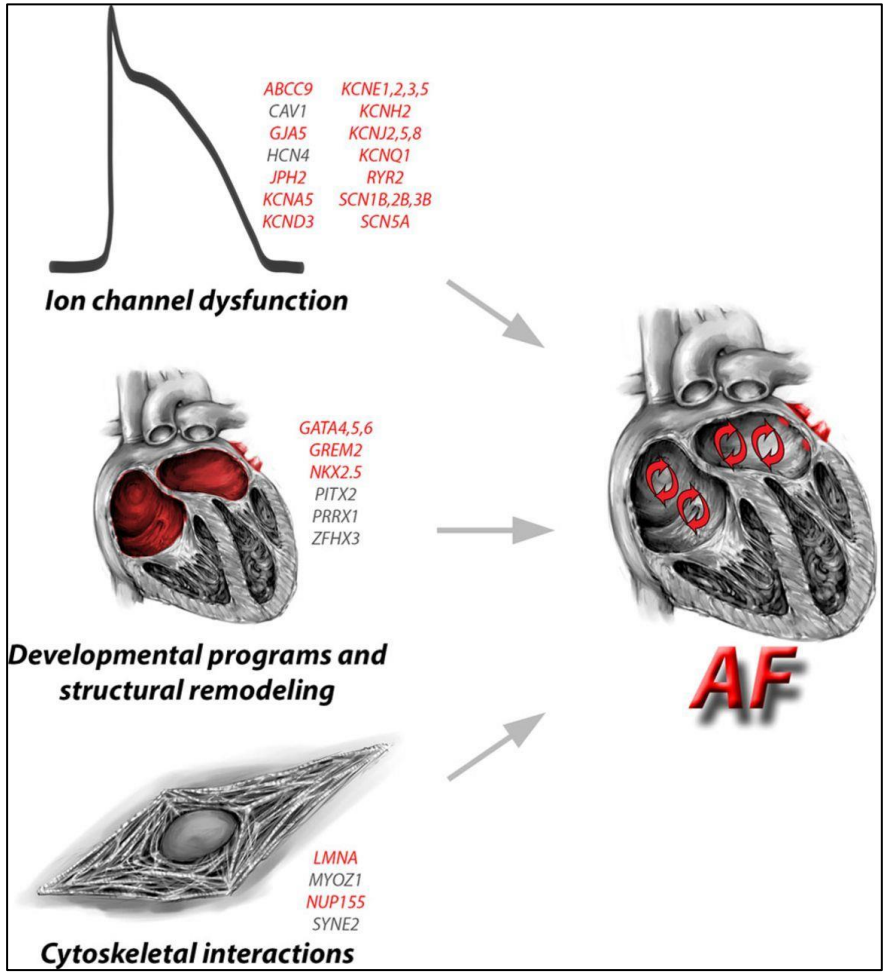
Role of the Autonomic Nervous System in Atrial Fibrillation

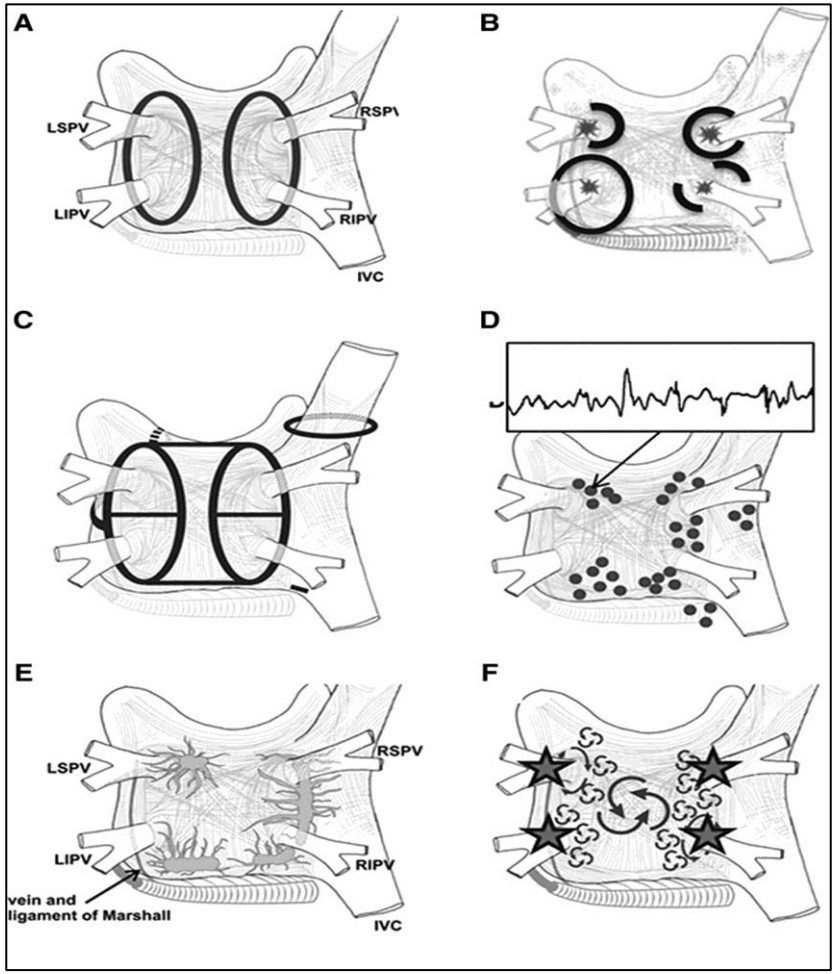




Chen et al (*Circ Res*. 2012;114:1500-1515.)

Known genetic pathways for atrial fibrillation (AF) pathogenesis.

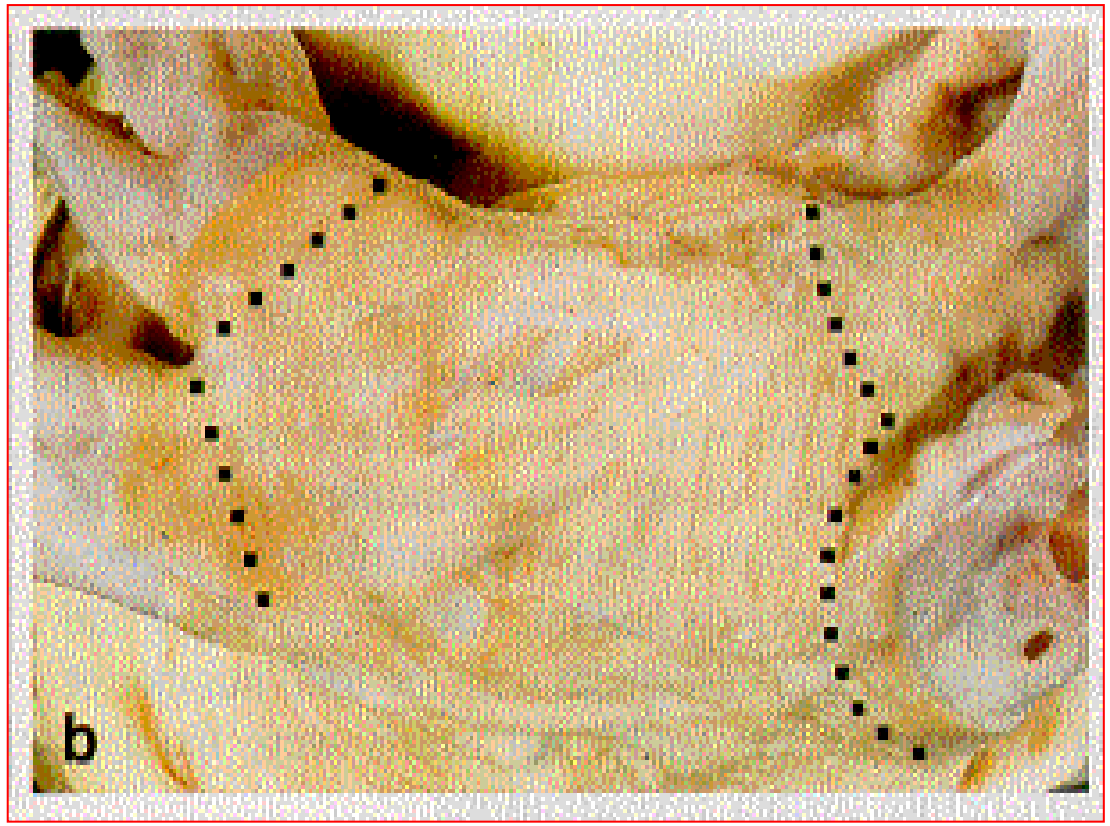




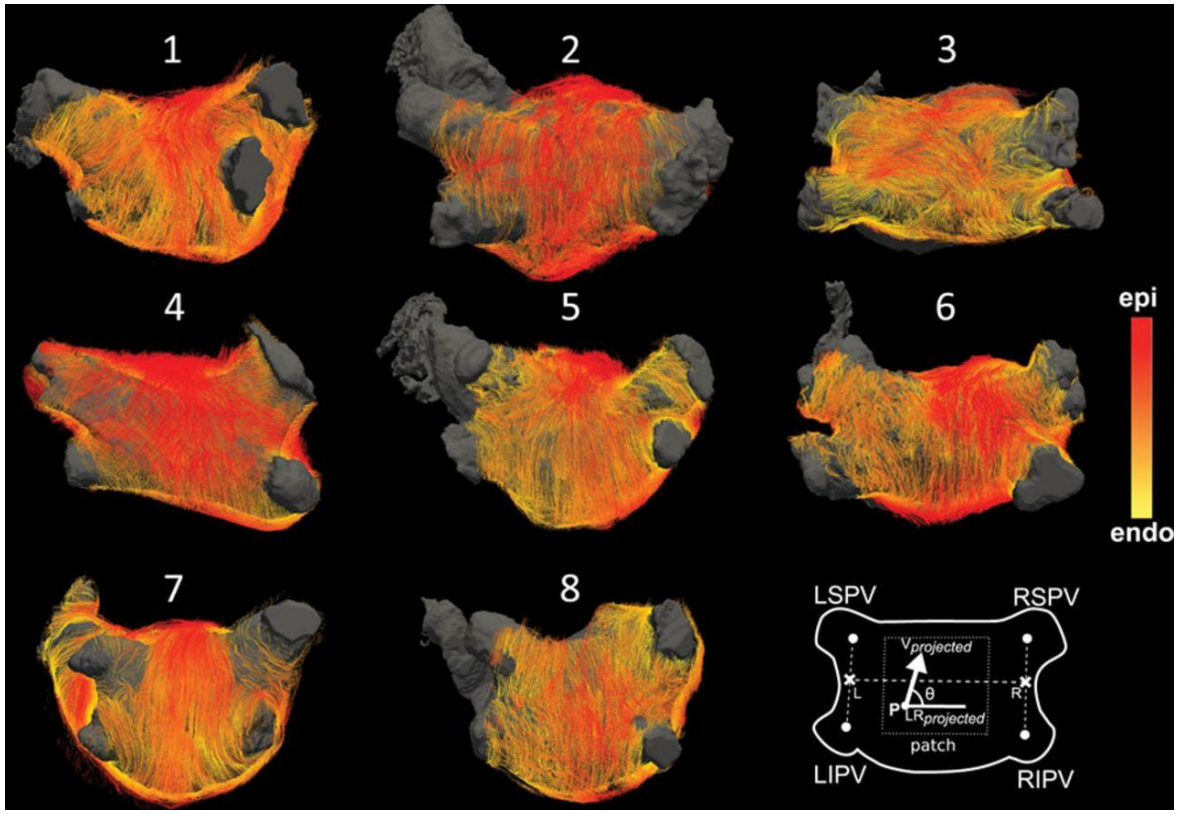
Tucker et al. (*Circ Res*. 2014;114:1469-1482.)

Ultra Structure of Left Atrium Myocardial Layers Post-Mortem Anatomical Studies

"There is no other same heart in human"



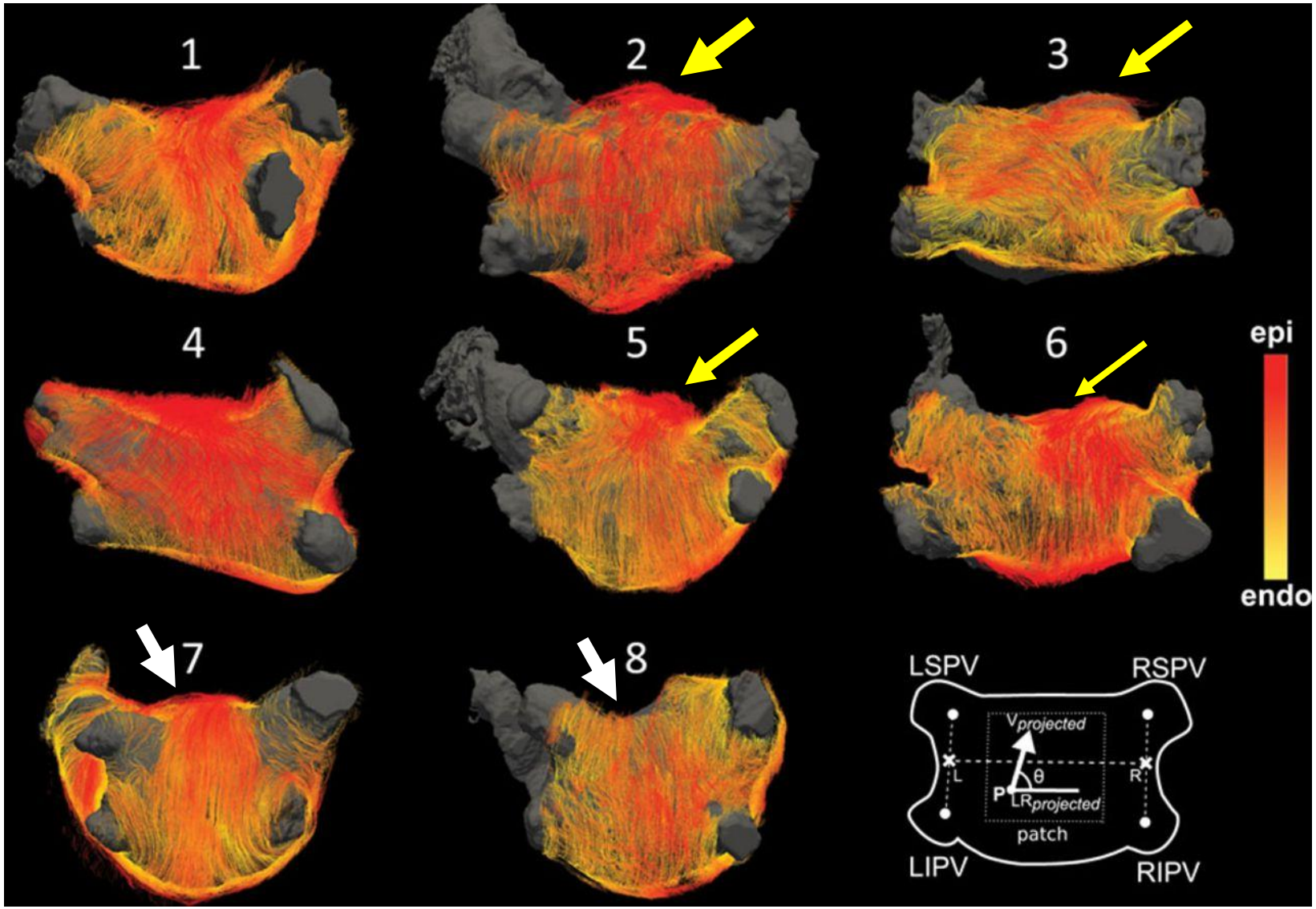
Ito el al JCE 2001



Farhad Pashakhanloo et al. Circ Arrhythm Electrophysiol. 2016;9:e004133

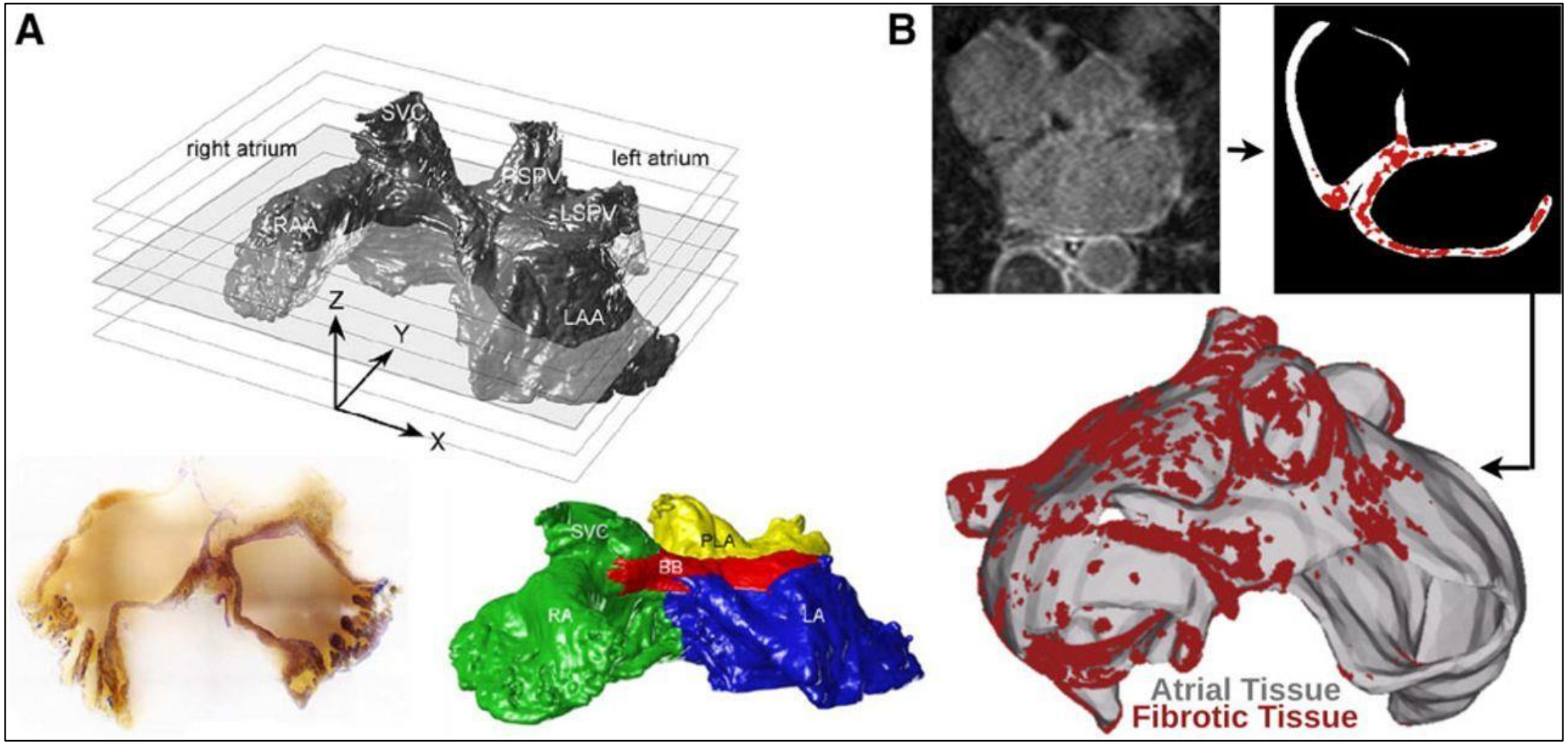
Anatomical of LA: Epicardial Septal Pulmonary bundle varaitions

Posterior view of DT MRI fiber tractography in 8 hearts (endocardial ablation limitations)



Farhad Pashakhanloo et al. Circ Arrhythm Electrophysiol. 2016;9:e004133

Mathematical Geometric modeling of the atria.

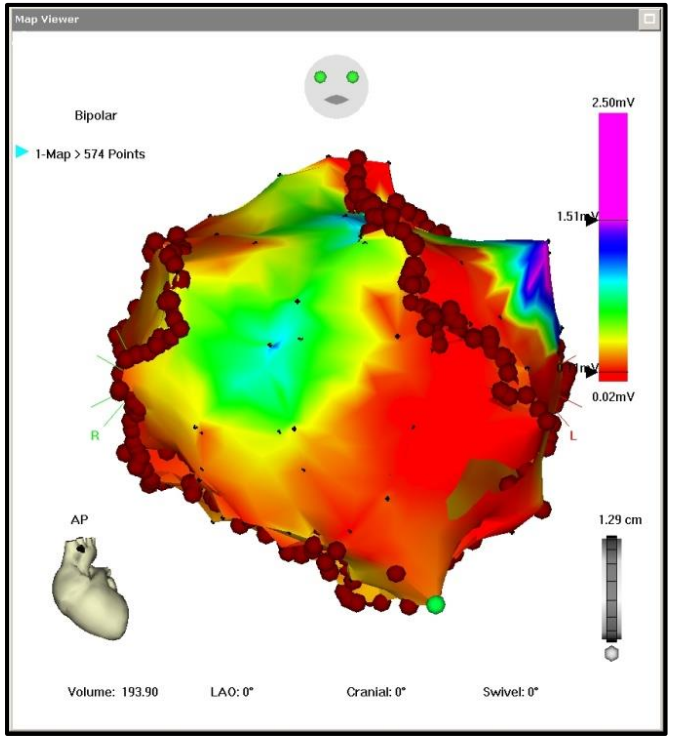


Traianova (*Circ Res* 2019;114:1516-1531.)

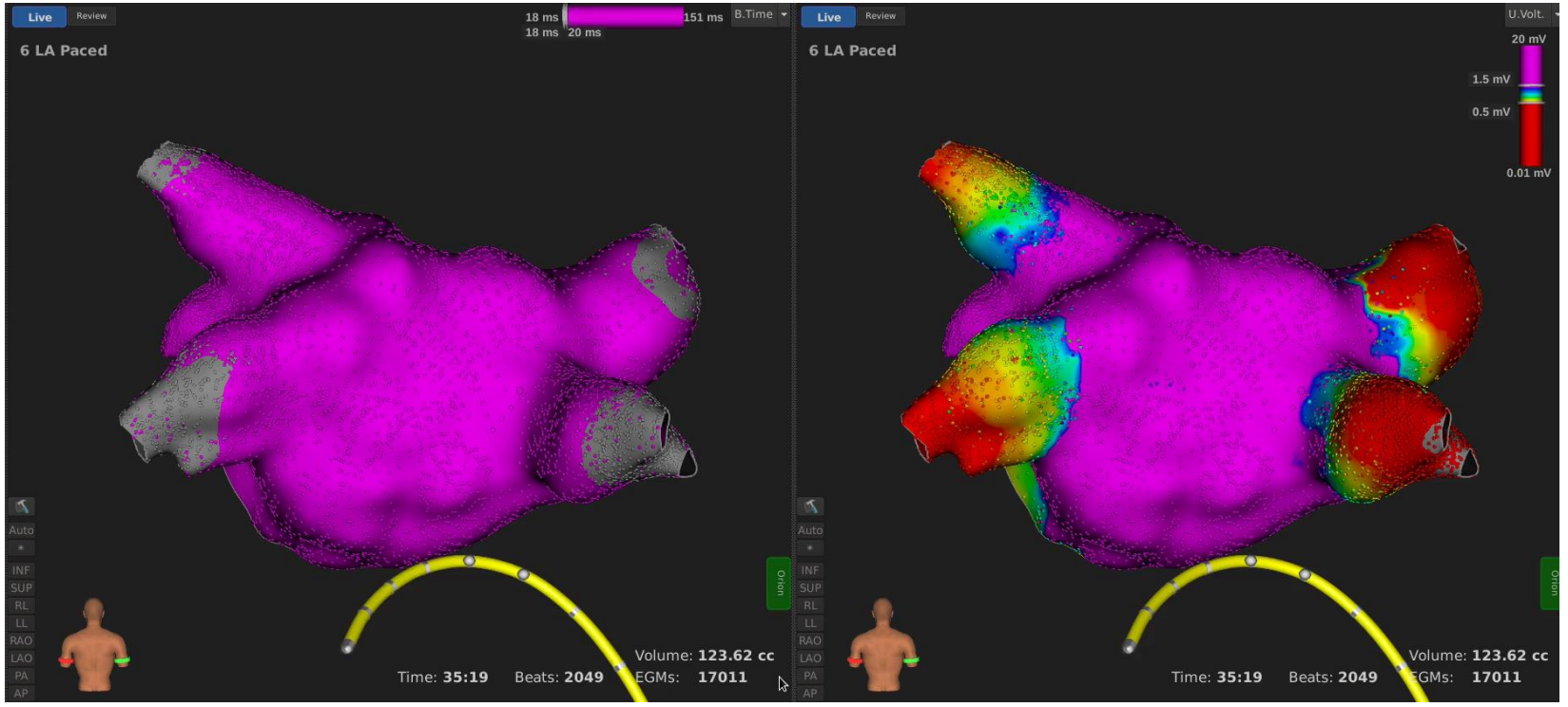
New Ablation and mapping technologies to create more accurate larger and deeper lesions

- Ablation energies: **Radio-frequency**, Laser, Ultra sound, Cryo and Pulse field (electroporation using high energy shock)
- Delivery ablation lesions: Catheters, Balloon
- New catheter design: Irrigation flat, Circumferential, Orion.
- Robotic system: Stereotaxis, Hansen, Magnetics
- 3-D HD mapping system: Carto-3, NAVX-X, Rhythmia

3-D HD mapping offers detailed electrophysiologic proprieties of left atrium voltage and propagation patterns and atrial remodeling



3-D map (1999)

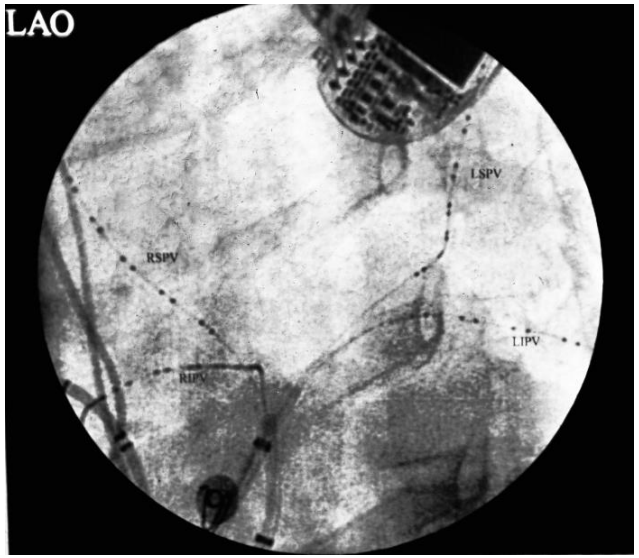


3-D High Density map (2015)

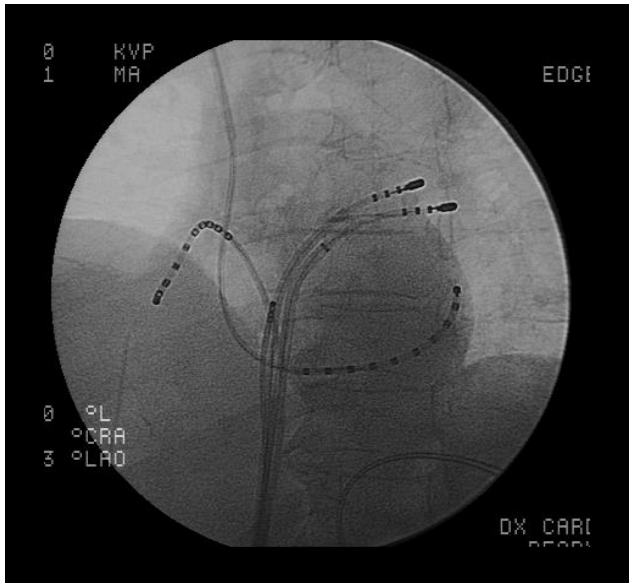
Progress in Mapping for focal trigger = focal ablation

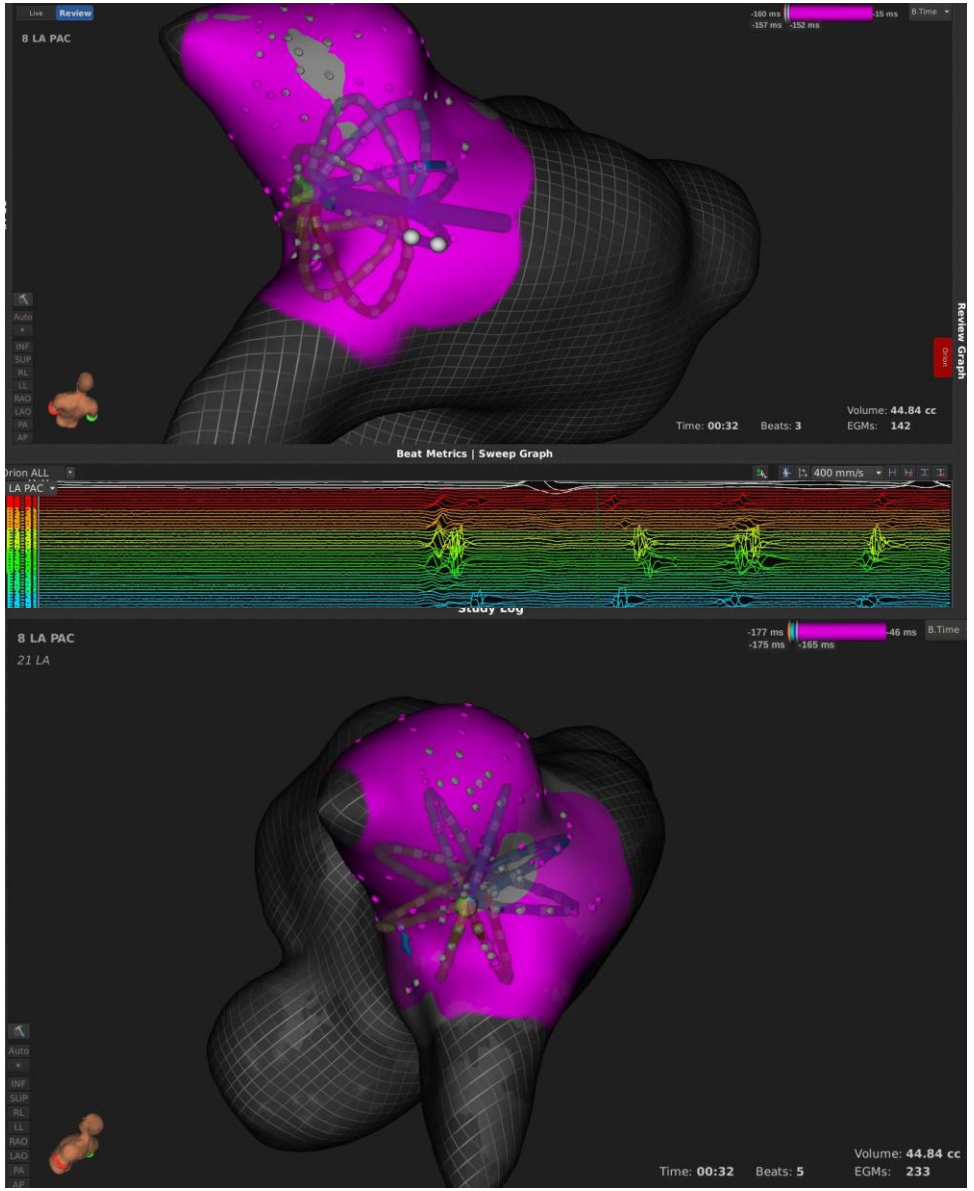
Higher resolution HD mapping of focal trigger from LPV sub-carina

1994



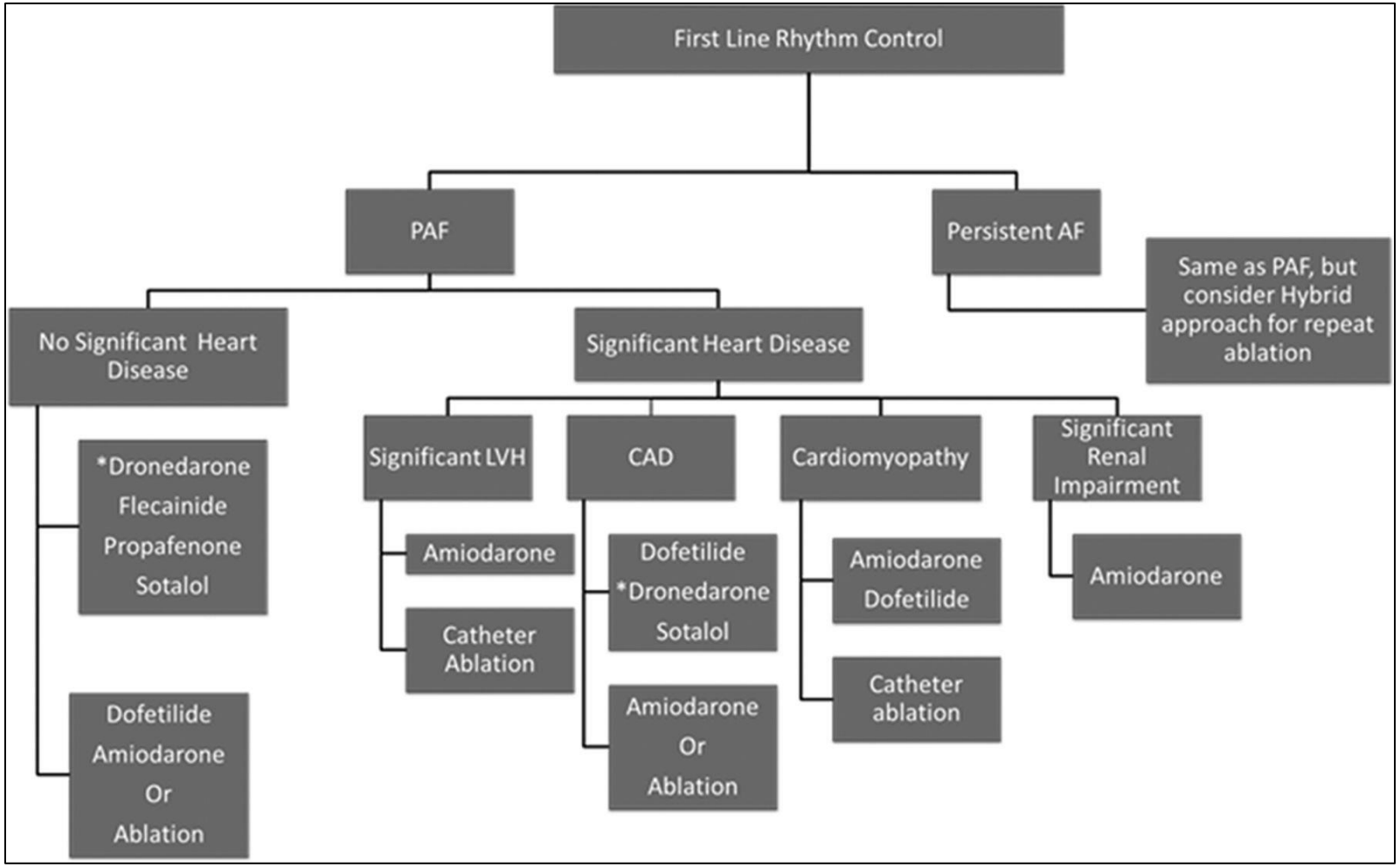
1997





2016

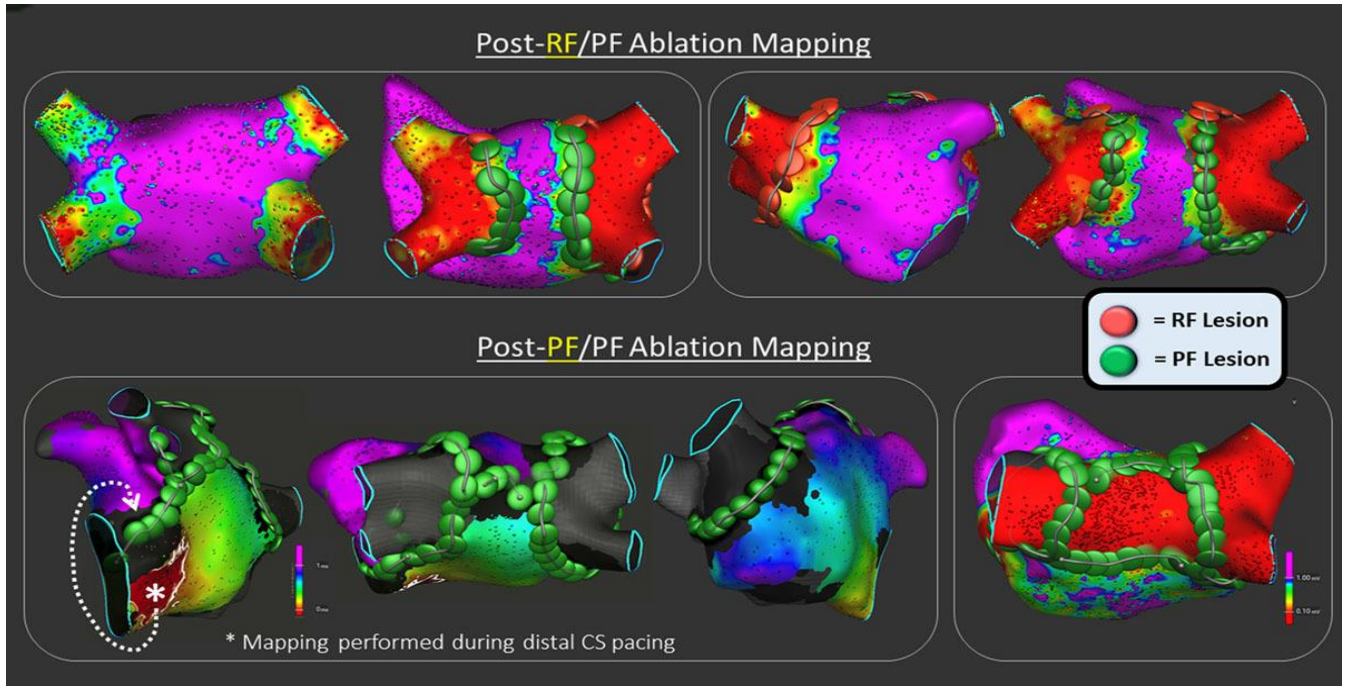
Propose guidelines for A fib Rhythm Control Therapy



Olgin et al. Circ EP. 2020

Current trend from last decades developments of new technologies for A fib ablation

Pulse Field Ablation (PFA) = Electroporation using high energy shock



Empiric PVI or antral ablation - PFA is better than RFA creating larger and deeper lesion.

Vivek Y. Reddy. Circulation: Arrhythmia and Electrophysiology., Volume: 13, Issue: 6, DOI: (10.1161/CIRCEP.2023)

RF: Simple and Quick ablation procedure with higher power: high power short duration

Cryo: Simple and quick ablation procedure with minimal mapping to address PVI only

PFA: Quicker PVI or linear lesion with minimal mapping with creation of bigger lesions

Current two diverging practices of A fib ablation

- 1) **Bigger lesion minimal mapping using Cryo or PFA (short procedure time):** that widely practice in developed countries (Europe and US) and currently expanding to higher social economic status Asian countries including Japan, South Korea, possibly Taiwan. No mapping required (from scientific stand point due to the no detailed mapping and potentially less hemodynamic improvement even after Afib control due to the significant atrial myocardial mass loss from large ablation lesions). Only approved for Afib ablation today

- **2) Traditional mapping and ablation using RF (longer procedure time)**: This approach is more technically demand requires mapping to do complete procedure. (mapping data that potentially can be used to develop more upstream treatments of ablation. Mapping can identifying critical atrial tissue substrate that responsible for the perpetuation of A fib). (data for development of AI guided technology). Approved for types of arrhythmia

Preventive measures and risk factors modifications are most cost effective therapy
Can be practiced in all countries of the world regardless socio-economic status.

Awareness and Education

Can be practiced all levels in health care

=

Table 1. AF Risk Factors

Risk Factor	Estimated Increased Risk	Comments
Established		
Age	≈2	Per decade
Male sex	1.5	
Hypertension	1.2–1.5	BP >140/90 mm Hg
Valvular heart disease	1.8–3.4	
LV systolic dysfunction	4.5–5.9	
Obesity	1.39–2.35	
Alcohol consumption	1.34–1.46	Heavy alcohol use (≥36 g/d)
Emerging		
Prehypertension	1.28	Systolic BP 130–139 mm Hg vs <120 mm Hg
Increased pulse pressure	1.26	Per 20-mm Hg increment
Obstructive sleep apnea	2.8–5.6	
Physical activity	2.87	Cumulative lifetime practice >1500 h
Diastolic dysfunction	3.33–5.26	
Familial and genetic	1.85	AF in ≥1 parent
Hypertrophic cardiomyopathy	4–6	
Congenital heart disease	N/A	
Potential		
Coronary artery disease	N/A	Data inconclusive
Chronic kidney disease	1.3–3.2	Graded risk
Inflammation	1.47–1.77	Independent predictive value unclear
Pericardial fat	1.28–5.30	Risk related to thickness and volume of pericardial fat
Tobacco use	1.51–2.05	

AF indicates atrial fibrillation; BP, blood pressure; LV, left ventricular; and N/A, not available.

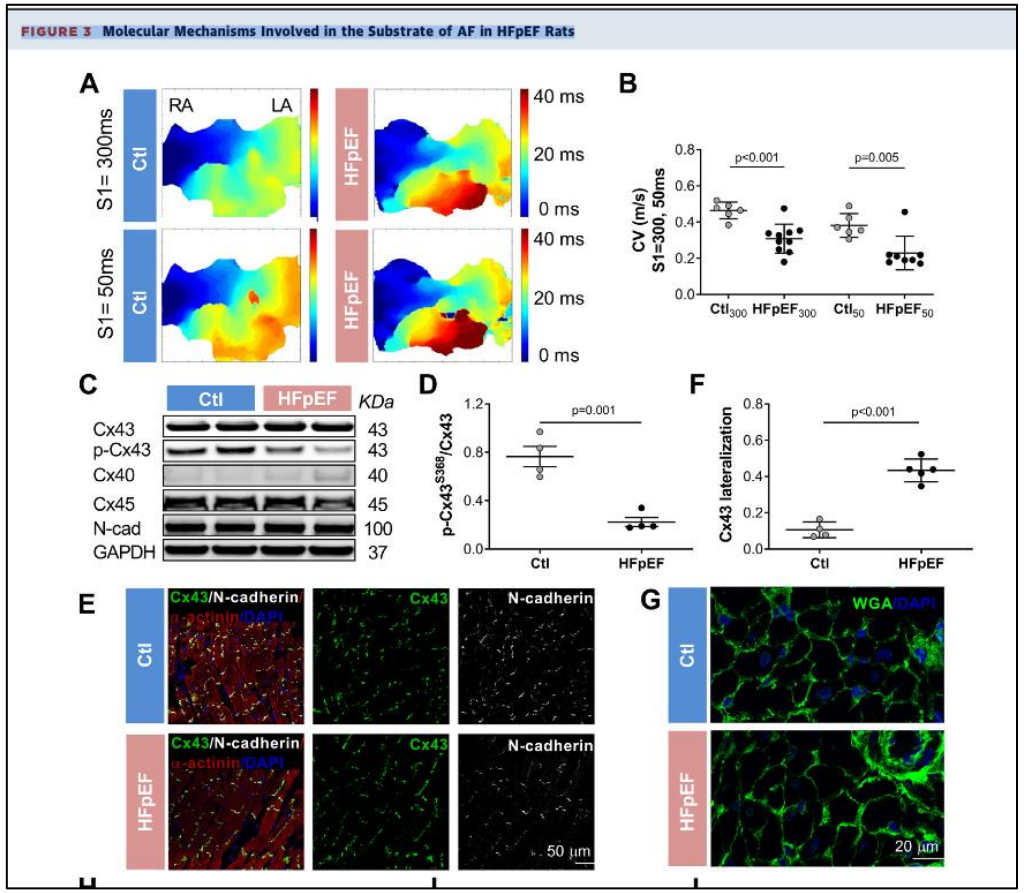
+

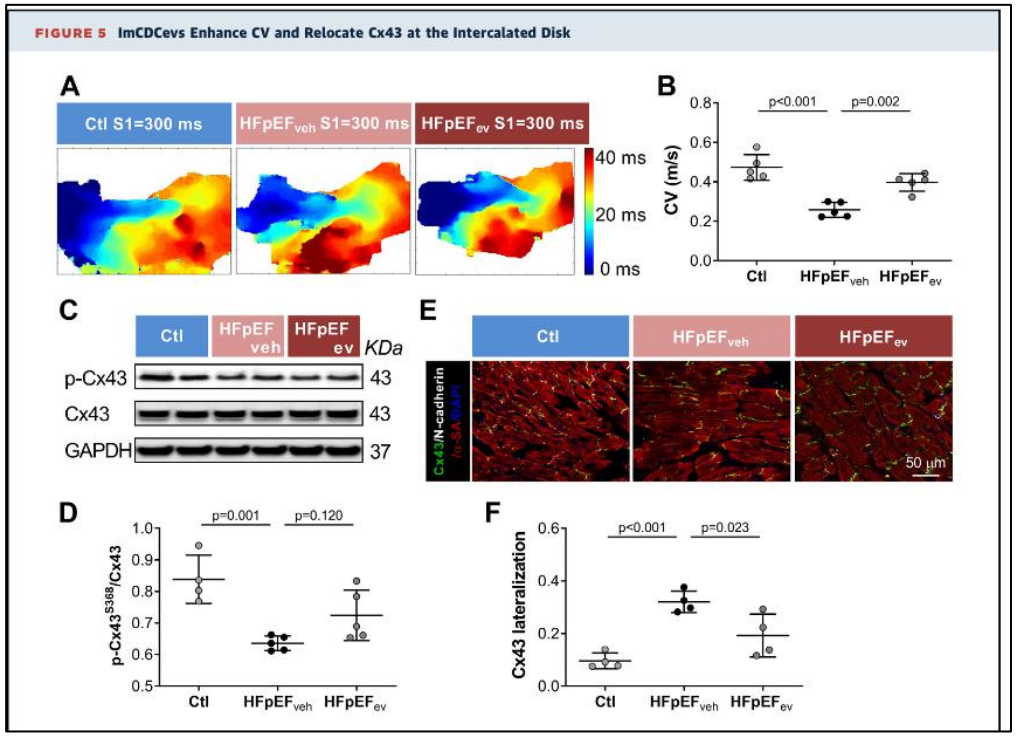
CVA prophylaxis with proper anti-coagulation therapy

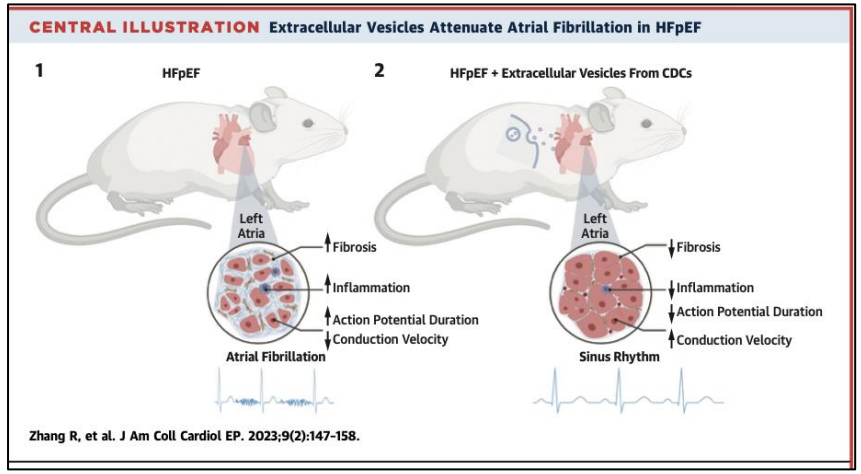
Future directions: Cell therapy

- Cardiosphere-derived cells (CDCs) are stem cells that come from cardiac tissue and can be used to treat heart disease and becoming intense research subject in HF arena.
- CDCs have cardioprotective effects on different diseases including HFpEF
- Most of the salutary effects of CDCs are mediated via secreted EVs (CDC EVs)
- EVs have the potential of reversing disease phenotypes by affecting fibrosis, angiogenesis, oxidative stress, and inflammation signaling pathways.
- Immortalized CDCevs are enriched with small RNAs (eg, miR-4488 and miR92a), which have been shown to be therapeutically active microRNA in arrhythmogenic cardiomyopathy and HF

Cardiosphere-derived extracellular vesicles (imCDCevs) Therapy in A fib/Hfpef animal model

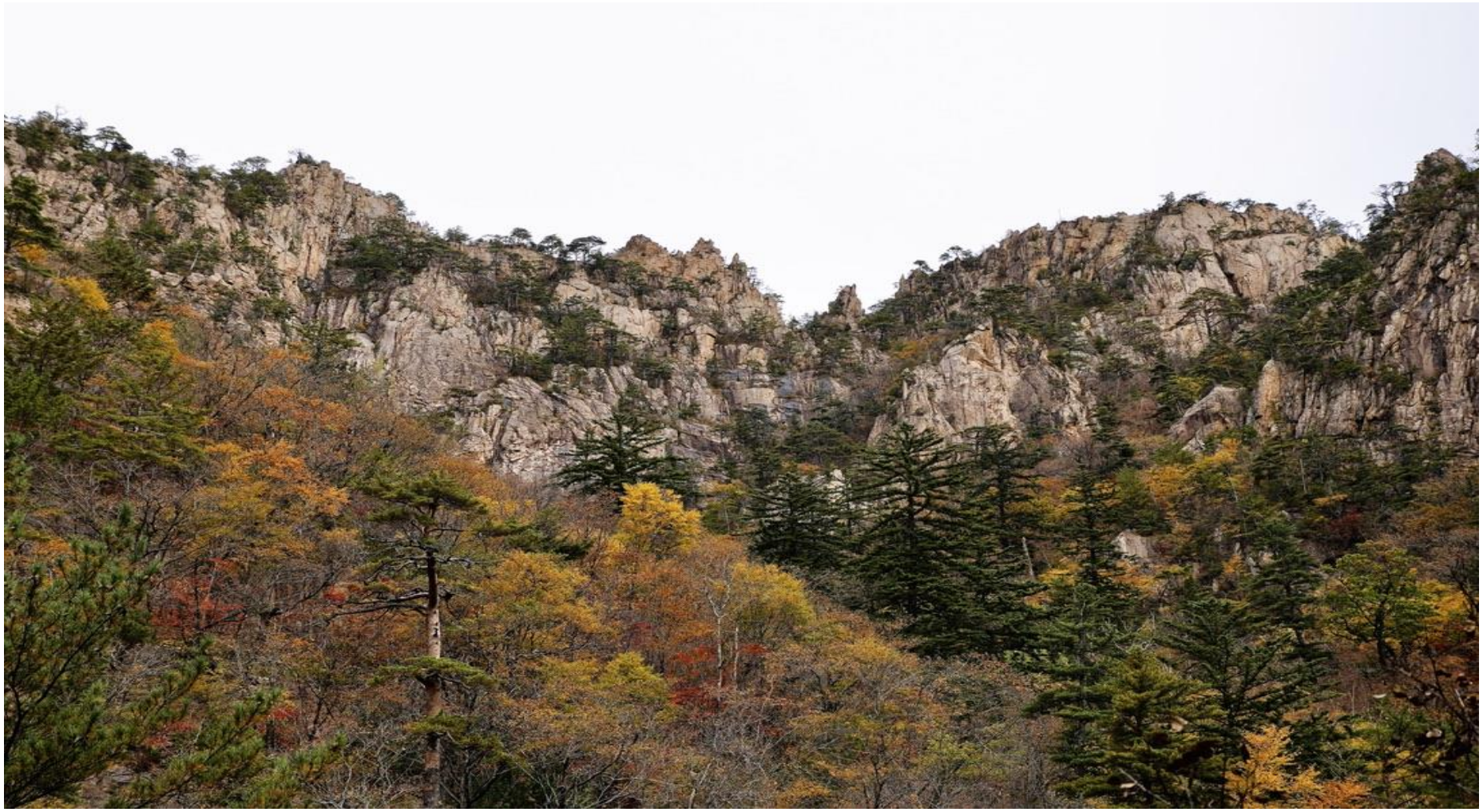






Lessons from A fib ablation studies

- AF is progressive condition that cannot be cured regardless etiology using currently available modalities of therapy but they can improve quality of life, reduce stroke and improve cardiac function
- Prevention and risks modifications with education is one of the most important part of care and needed in all pts. Also shown to reduce recurrences after successful ablation
- CVA prophylaxis with proper anti-coagulation is required for all pts who have increased risk for stroke (CHADvasc score $\geq$ 2) unless contraindicated
- AF pts that benefit the most from ablation: Early stage paroxysmal Afib and CHF pts with A fib.
- Ablation is destructive therapy regardless energy source and end result is more scarring of atrial myocardium. Therefore, should be practiced with proper indications and good judgment (less empiric approach is better)
- Future upstream rhythm control therapies are being developed using biological, engenered materials and possibly Ail modalities in near future. These can be less destructive and also can be adjuvant therapy to improve myocardial function and fibrosis (reversal of remodeling)



Thank you for the invitation, kind courtesy provided during my visit to Myanmar