Mechanisms of VT: Idiopathic, ischemic, non-ischemic

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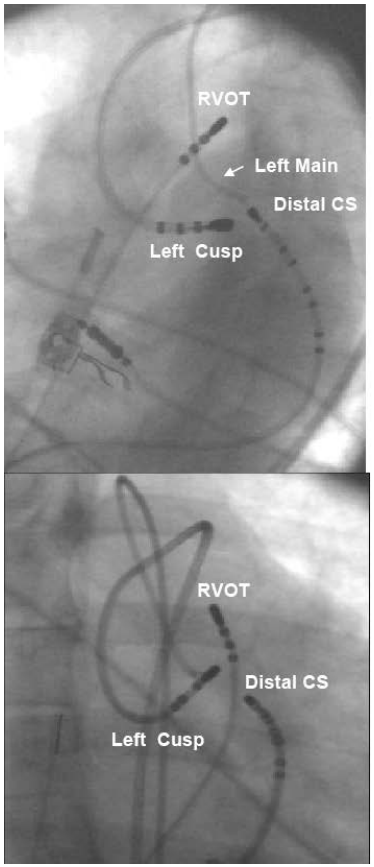
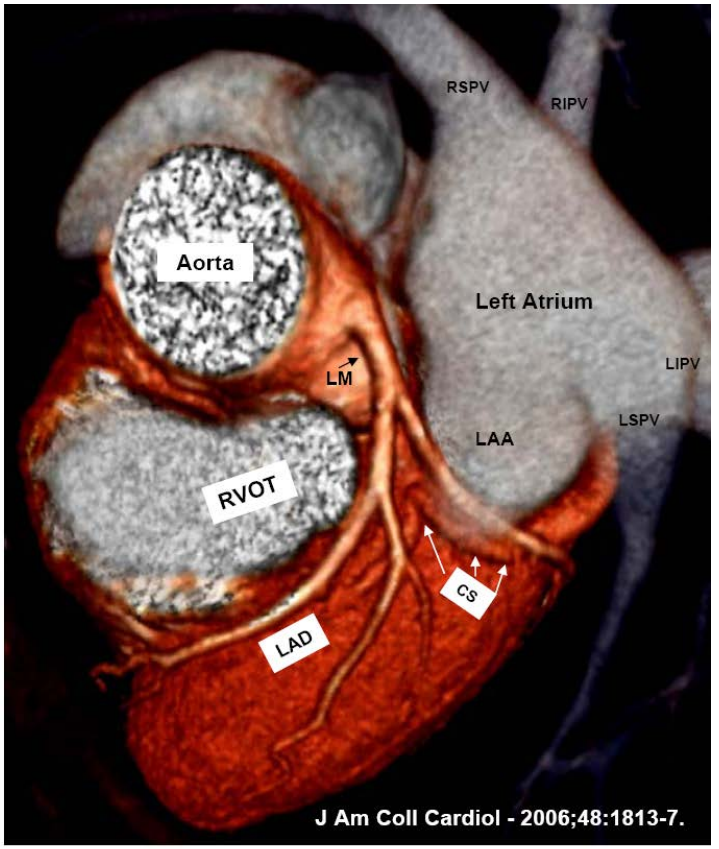
Idiopathic

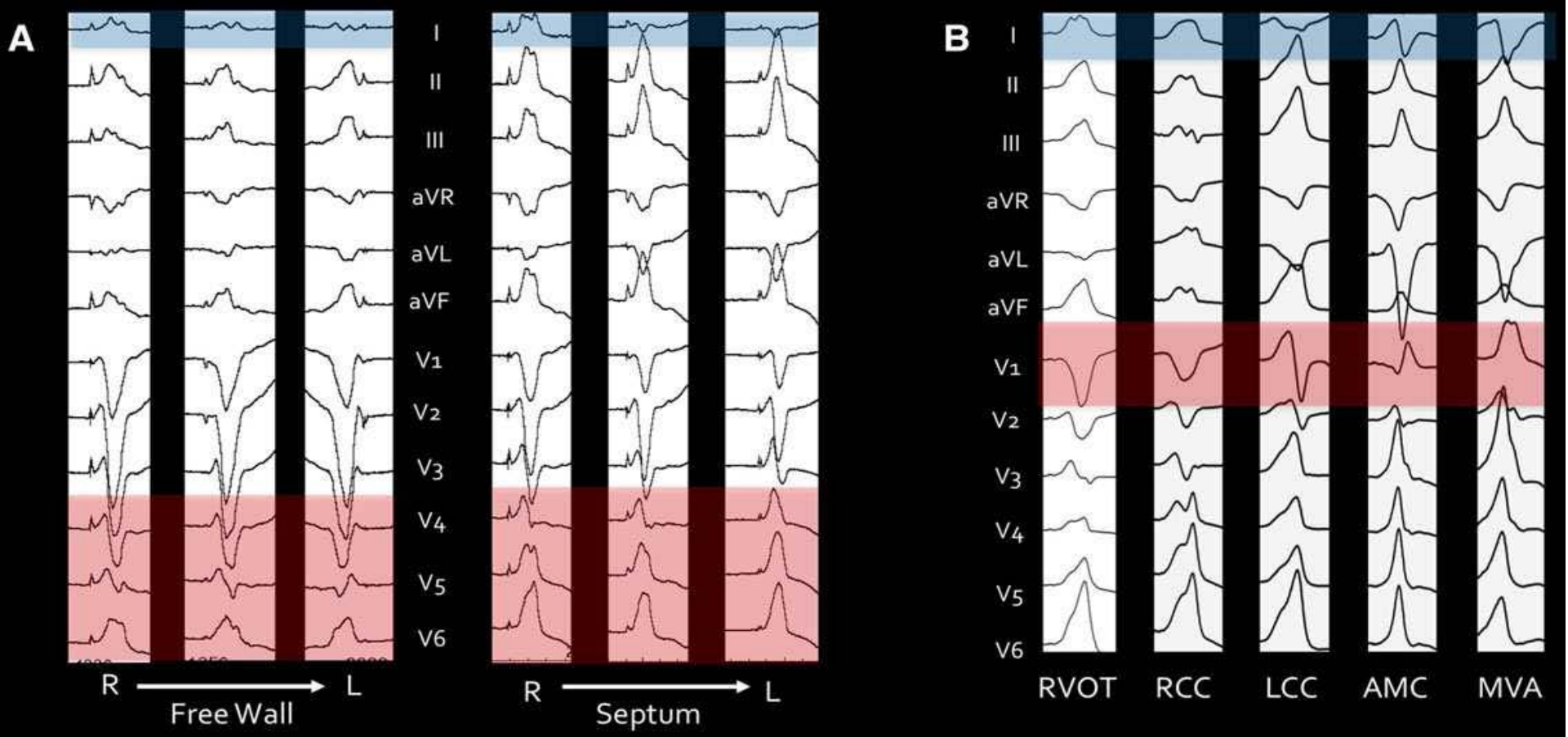
Idiopathic VT with inferior axis

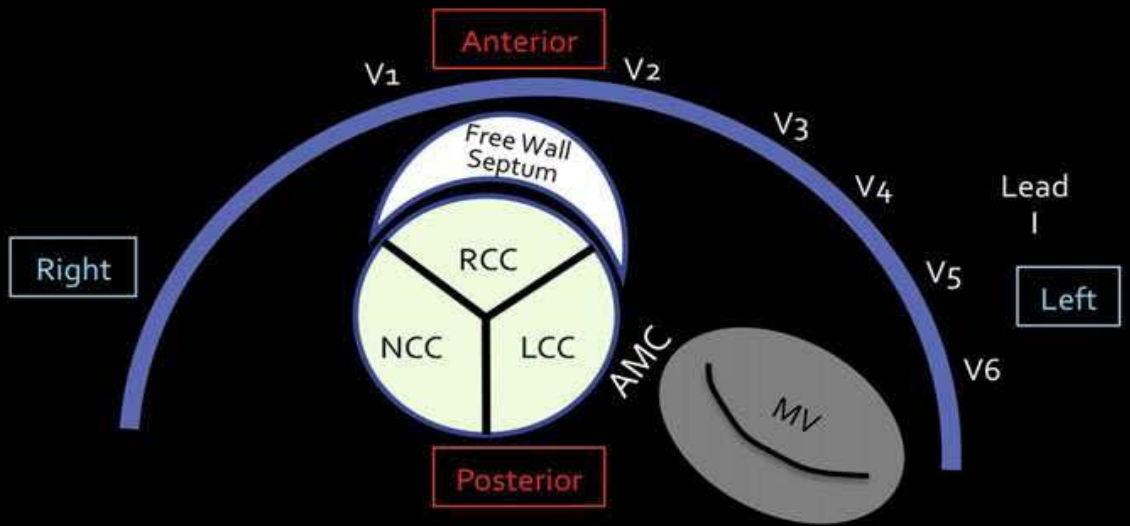
“Bermuda triangle”

- **RVOT (or above)**
- **Left pulmonary artery**
- **Sinuses of Valsalva**
- **LVOT**
- **Coronary veins (GCV-AIV)**
- **Anterior epicardium**









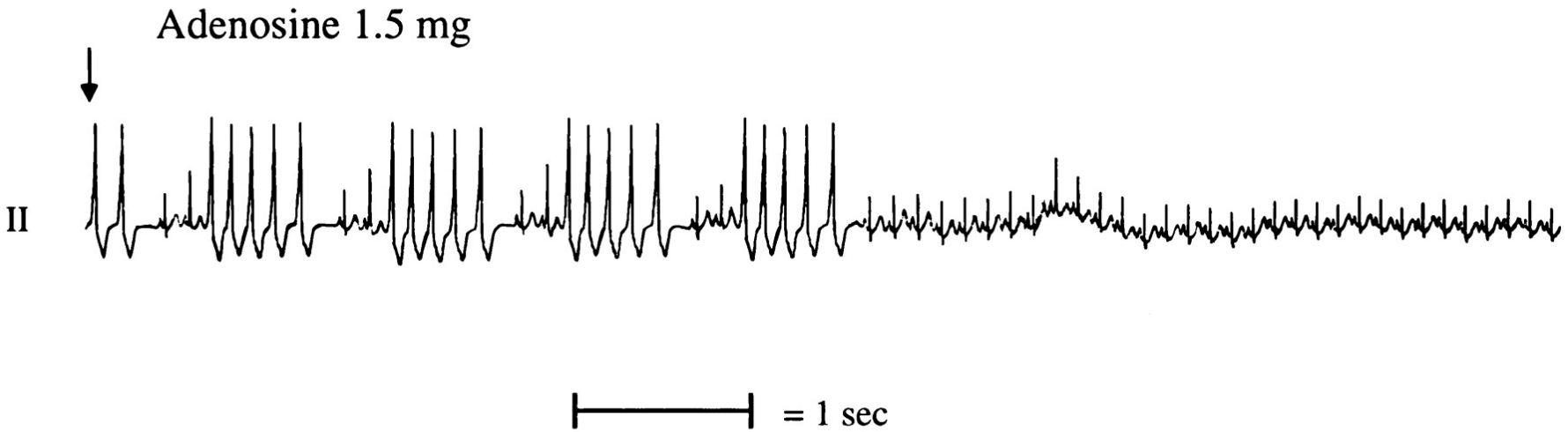
GARCIA et al. J Cardiovasc Electrophysiol, 2013;1189-97

Idiopathic RVOT arrhythmias

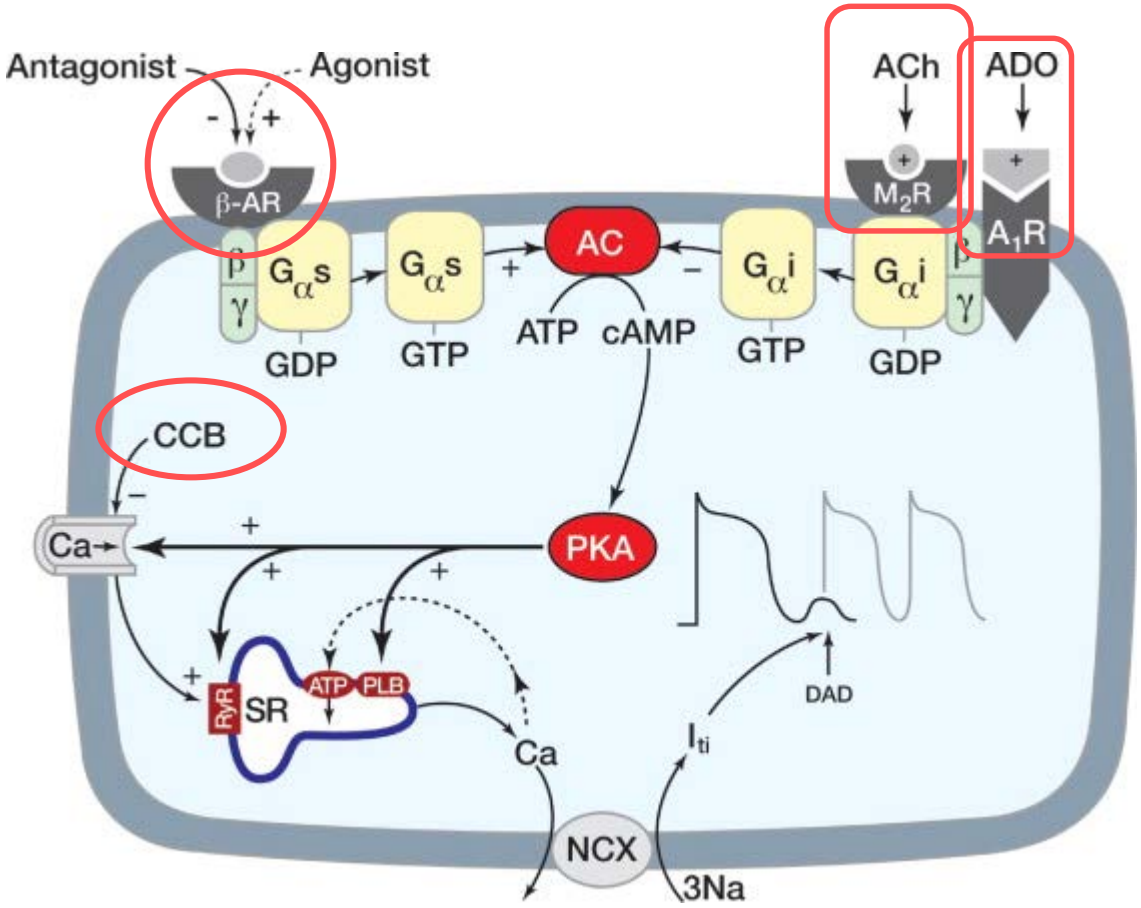
Pharmacology

- **β-blockers, Adenosine, Ca-channel antagonists, vagal maneuvers**

Would fit with abnormal automaticity



Signal transduction schema for initiation and termination of cAMP-mediated triggered activity



Lerman B. Heart Rhythm 2007;4:973–976

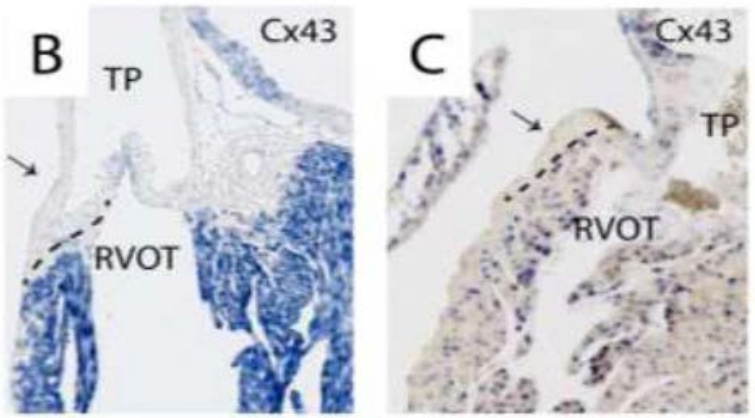
AC = adenylyl cyclase; ACh = acetylcholine; ADO = adenosine; A_1R= A_1-adenosine receptor; β-AR = β-adrenergic receptor; CCB = calcium channel blocker; DAD = delayed afterdepolarization; I_{ti} = transient inward current; M_2R = muscarinic receptor; NCX = Na^+/Ca^{2+} exchanger; PLB = phospholamban; PKA = protein kinase A; RyR = ryanodine receptor; SR = sarcoplasmic reticulum.

Idiopathic RVOT arrhythmias

Is there a developmental basis?

Primary “nodal” cells

There is a ring of primary myocardium just below the pulmonary valve (Cx43 negative)



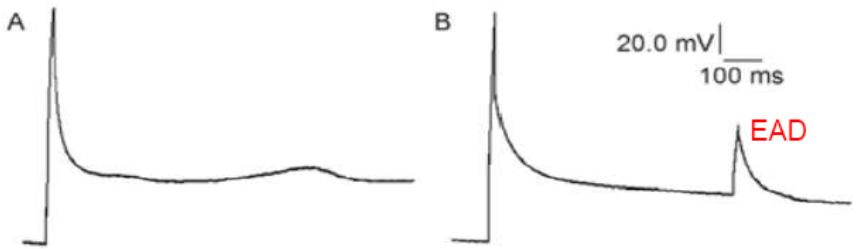
Fetal heart
- > 8 weeks in human
- ED 17.5 in mouse

Adult heart
- 8 weeks in mice

Boukens et al Circ Res 2013

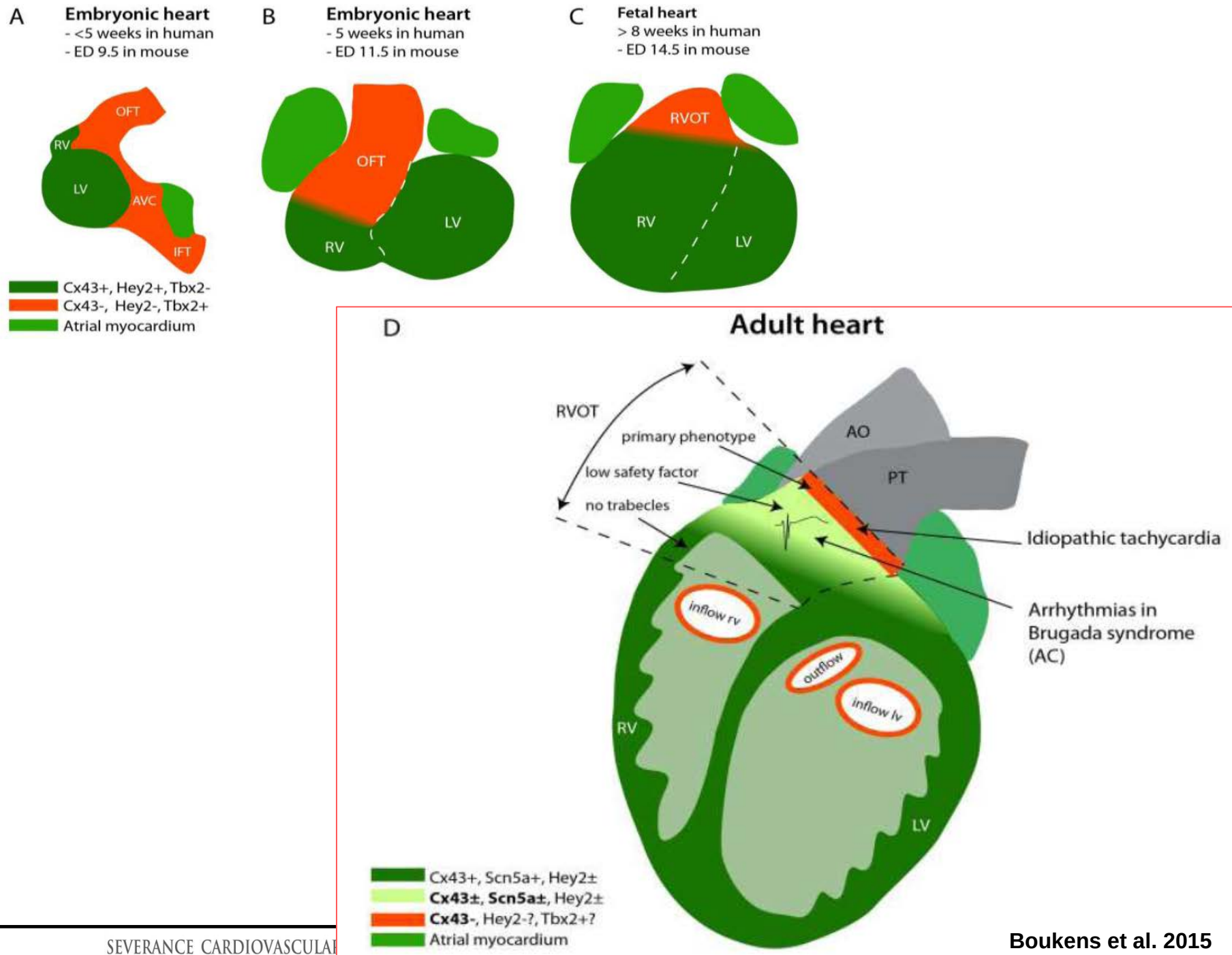
Spontaneous depolarization

Fraction of myocytes isolated from RVOT develop spontaneous EAD (Calcium dependent)



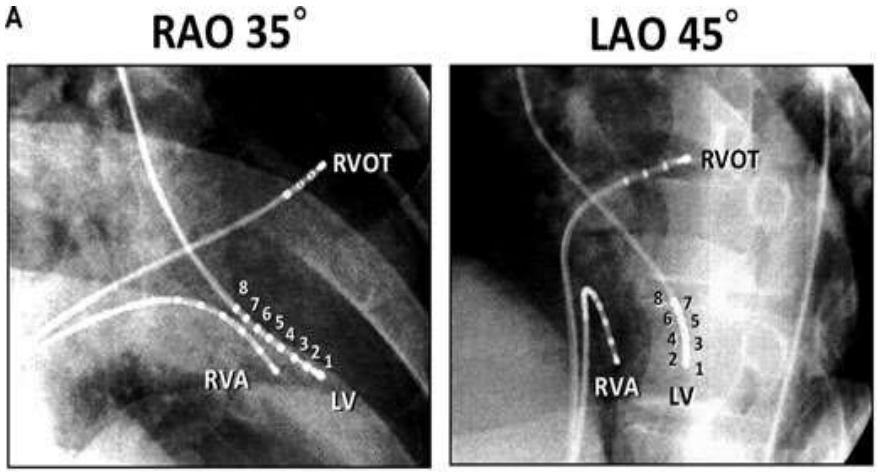
Rabbit

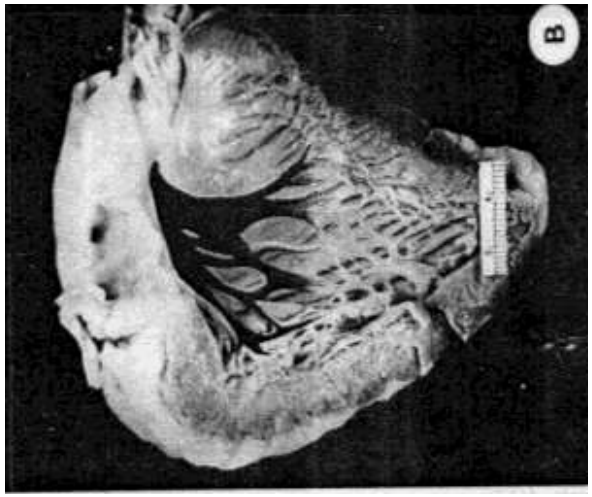
Liang et al Sci China Life Sci 2012

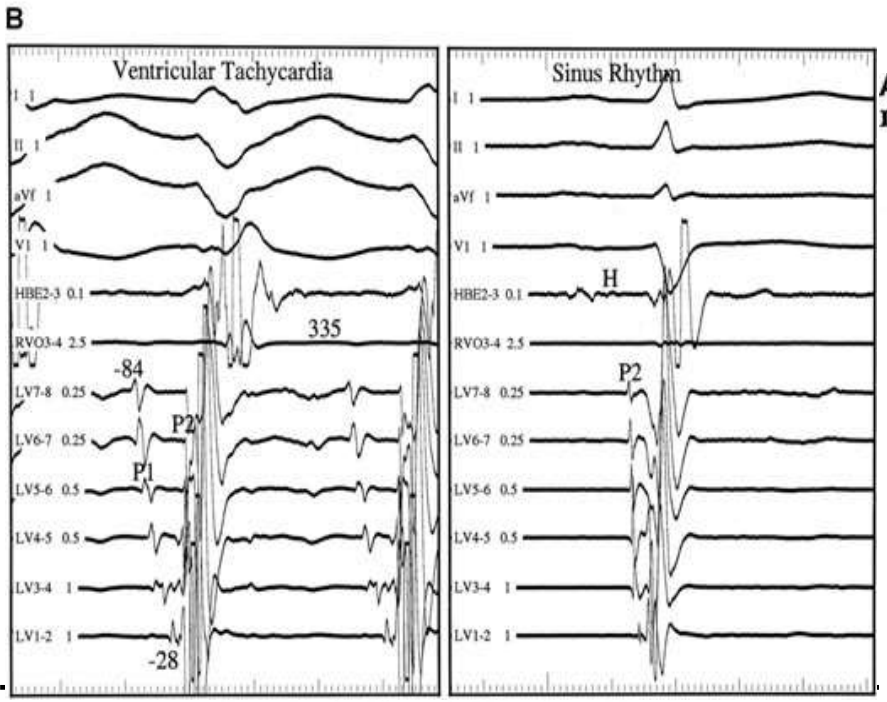


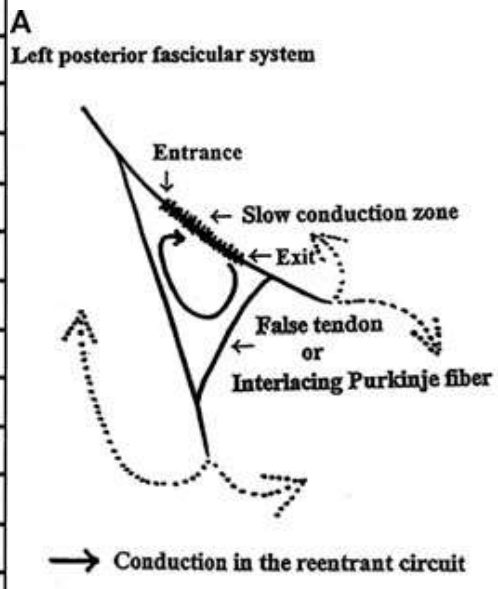
Boukens et al. 2015

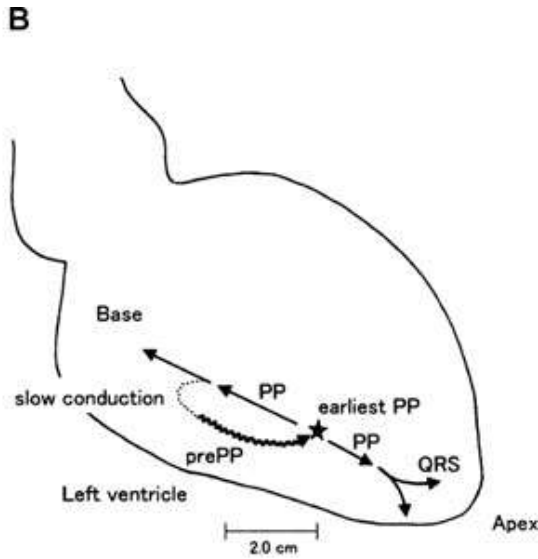
Idiopathic LV fascicular VT



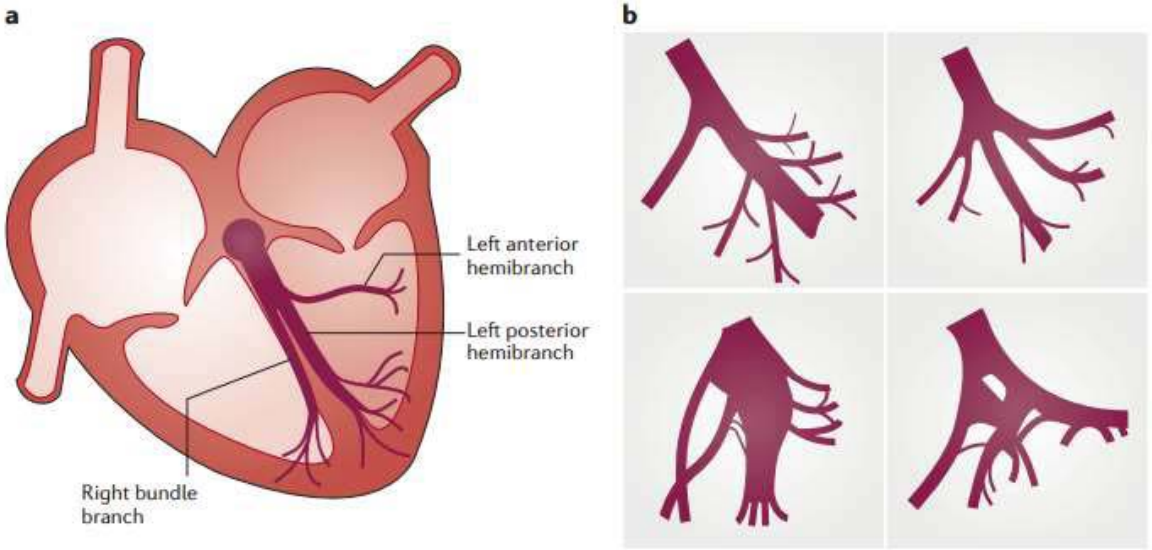




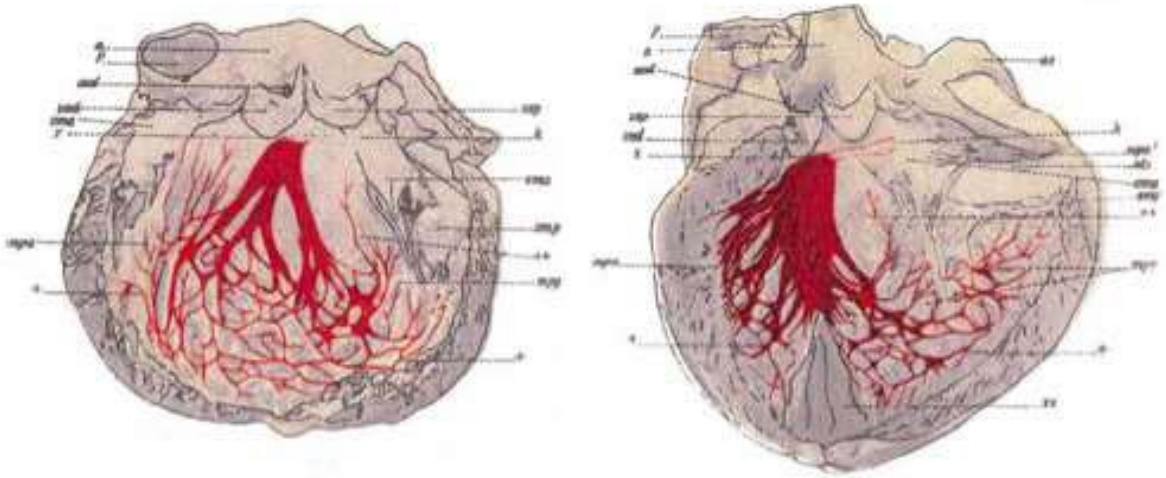




NOGAMI A. PACE 2011



Left Fascicular System



Tawara

Tawara. Jena, Verlag von Gustav Fischer 1906
M Haissaguerre. Nature review Cardiology, 2016

Supposed mechanisms of VF and PVT triggered by Purkinje system

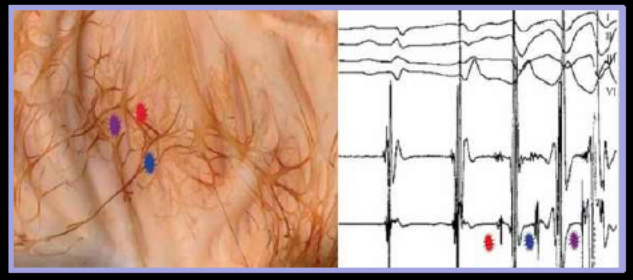
- Initiated PVCs
  - Triggered activity from Purkinje system
  - Abnormal automaticity
- Initiation and Maintenance of VF and PVT
  - Purkinje system and its surrounding tissue

    (Local reentry due to abnormal “gating mechanism”)

Purkinje Cells as Arrhythmic Triggers

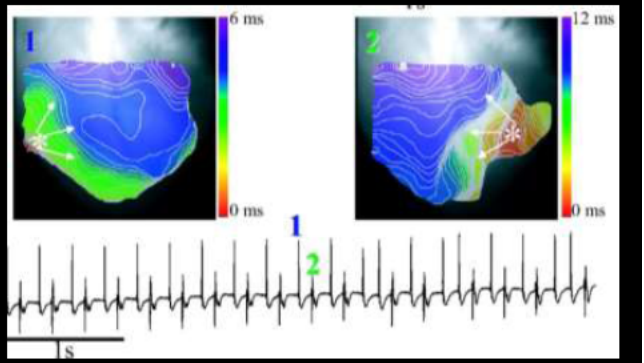
Bundle branch reentry	Haissaguerre et al, *Lancet* 2002
Post-MI VT	Boyden et al,*Circ*, 1994; Hayashi et al, *Heart Rhythm*, 2006; Bogun et al. *JACC*. 2006; Hirose et al. *Circ AE*, 2008
Ischemic VT	Arnar et al. *Am J Physiol*, 2001;
Acquired LQTS	Gintant et al. *Journal of Card Pharm*, 2001
CHF	Maguy et al. *Circ Res*. 2009
Idiopathic VF	Haissaguerre et al, *Circulation*, 2002
Multifocal PVCs	Laurent et al, *JACC*, 2012
Heritable LQTS	Ben Caref et al, *Europace*, 2008; Sampson et al, *J. Phys*, 2010; Iyer et al, PLoS One, 2014
CPVT	Cerrone et al, *Circ Res* 2007; Kang et al, *Circ Res*, 2010

Purkinje triggers leading to VF in patient



Haissaguerre et al, *EMBO Mol Med, 2010*

Purkinje triggers leading to bidirectional VT in CPVT model



Cerrone et al, Circ Res 2007

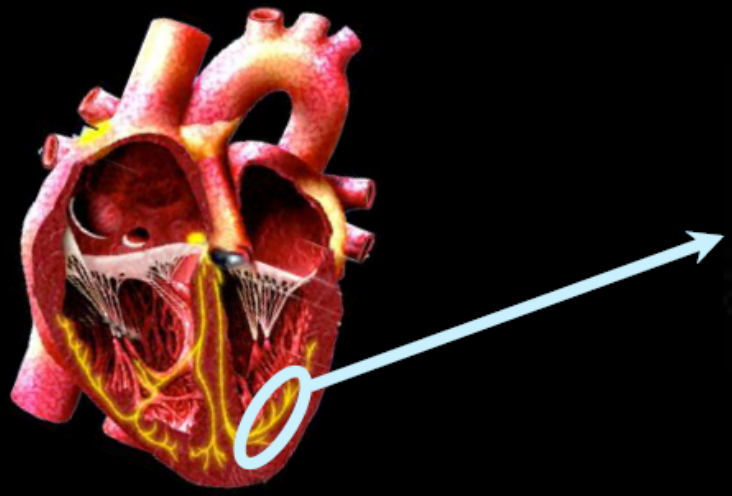
Purkinje Cells as Arrhythmic Triggers

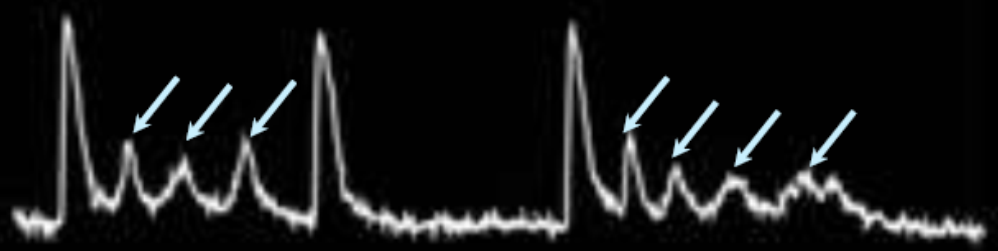
Cell autonomous properties

- unique complement of ionic currents
- prominent phase 1 repolarization
- prolonged APD
- pacemaker currents
- unique $[Ca^{2+}]_i$ handling properties
- propensity for EADs and DADs

Cell-cell/network interactions

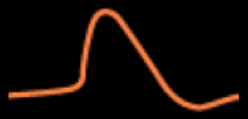
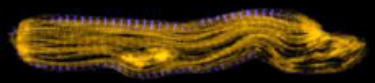
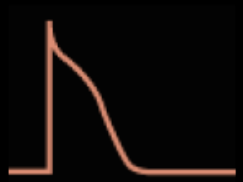
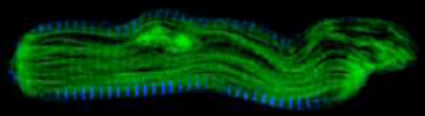
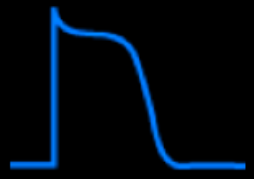
- unique complement of connexins
- cable structure
- branching network
- source/sink relationships at Purkinje-ventricular junctions



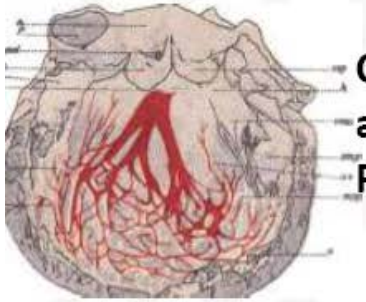


Triggered activity

Purkinje Cell Molecular Signature

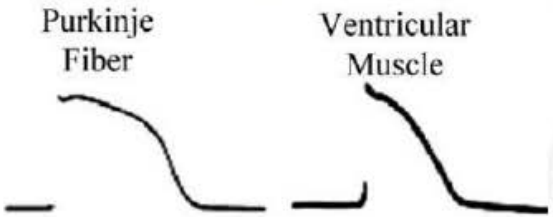
	Action Potential	Ion Channels	Transcription Factors
 Pacemaker cells		HCN4++ Cx45++ $Ca_V3.1$	Nkx2-5 +/- Tbx5 + Tbx18 ++
 Atrial cells		$Na_v1.5$ +++ Cx40 ++++	Nkx2-5 +++ Tbx5 ++
 **Purkinje cells**		**$Na_v1.5$ ++++** **$Na_v1.8$ ++** **Cx40 ++++** **HCN4 +; $Ca_V3.1$**	**Nkx2-5 ++++** **Tbx5 +++** **Irx3 ++** **Tbx3 +**
 Ventricular cells		$Na_v1.5$ ++ Cx43 +++	Nkx2-5 ++ Tbx5 +

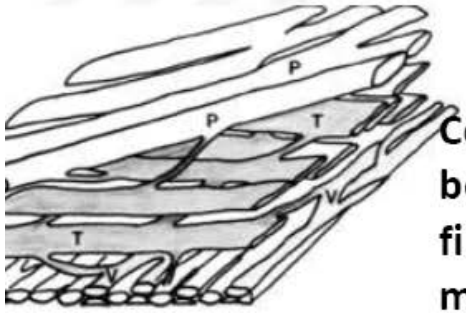
Complex Structure and Function of Purkinje Cells



Complex arborization of Purkinje network

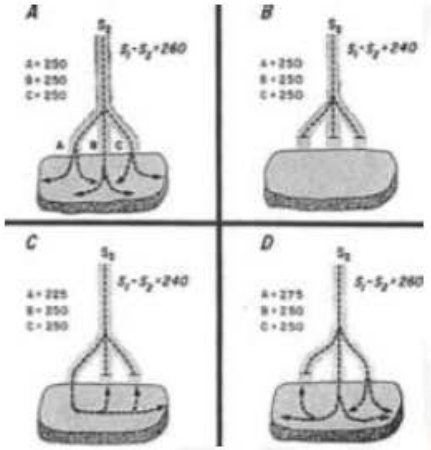
Longer APD

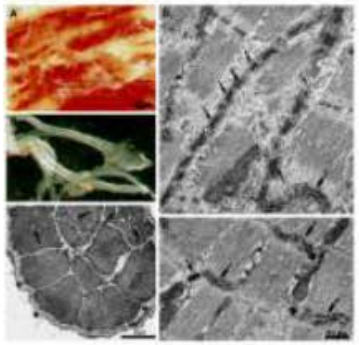




Complex junctions between Purkinje fibers and ventricular muscle

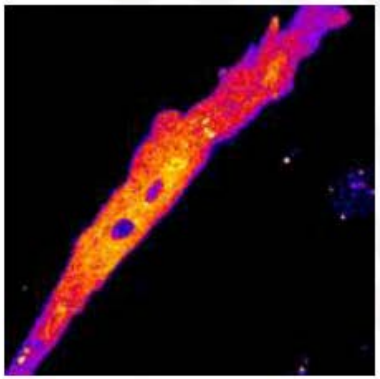
longest APD at junction





Specific cellular architecture of Purkinje fibers

Spontaneous Ca2 waves can occur spontaneously

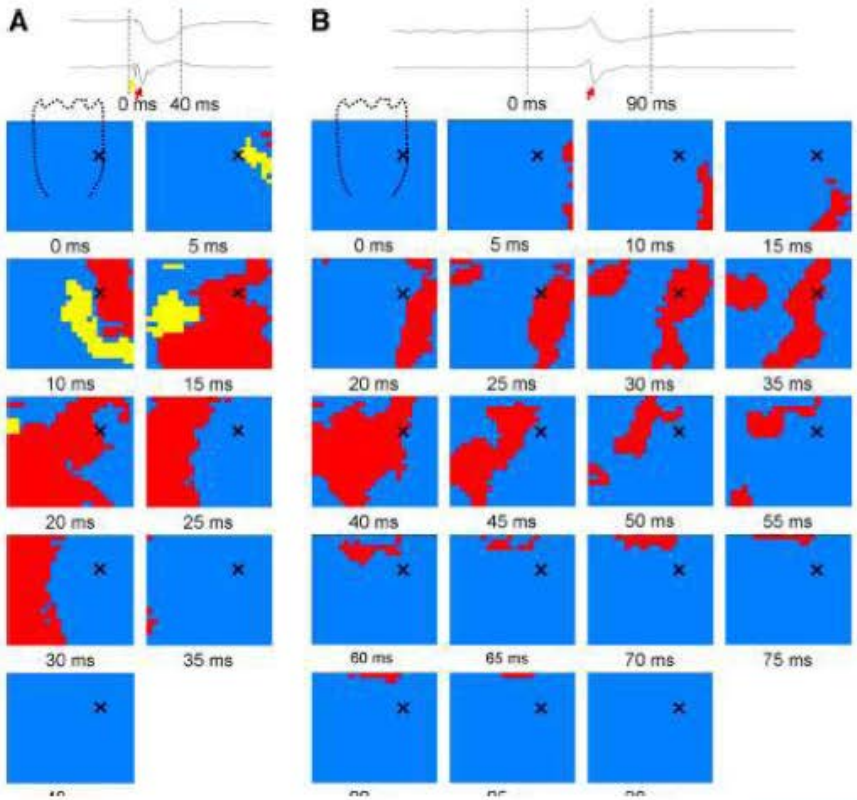


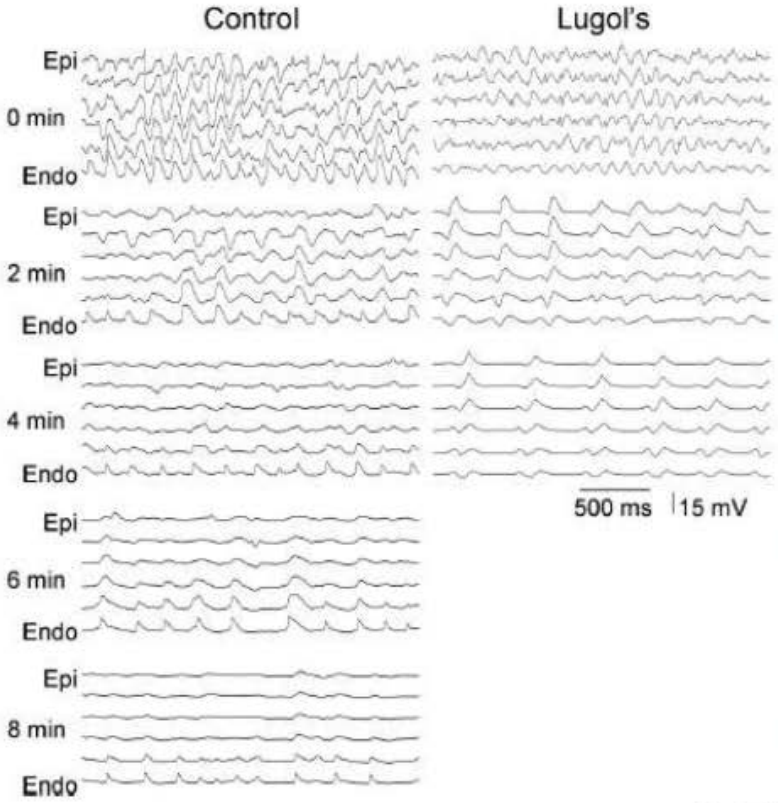
Tawara, Desmoulins ,Tranum-Jensen, Myerburg, Boyden, Stuyvers

Role for Purkinje network in VF maintenance

Derek J. Dosdall,[1] Paul B. Tabereaux,[2] Jong J. Kim,[1] Gregory P. Walcott,[2] Jack M. Rogers,[1]
Cheryl R. Killingsworth,[2] Jian Huang,[2] Peter G. Robertson,[2]
William M. Smith,[1,2] and Raymond E. Ideker[1,2,3]
Departments of [1]Biomedical Engineering, [2]Medicine, and [3]Physiology, University of Alabama at Birmingham, Birmingham, Alabama

12 Dog hearts endocardium treated with Lugol solution



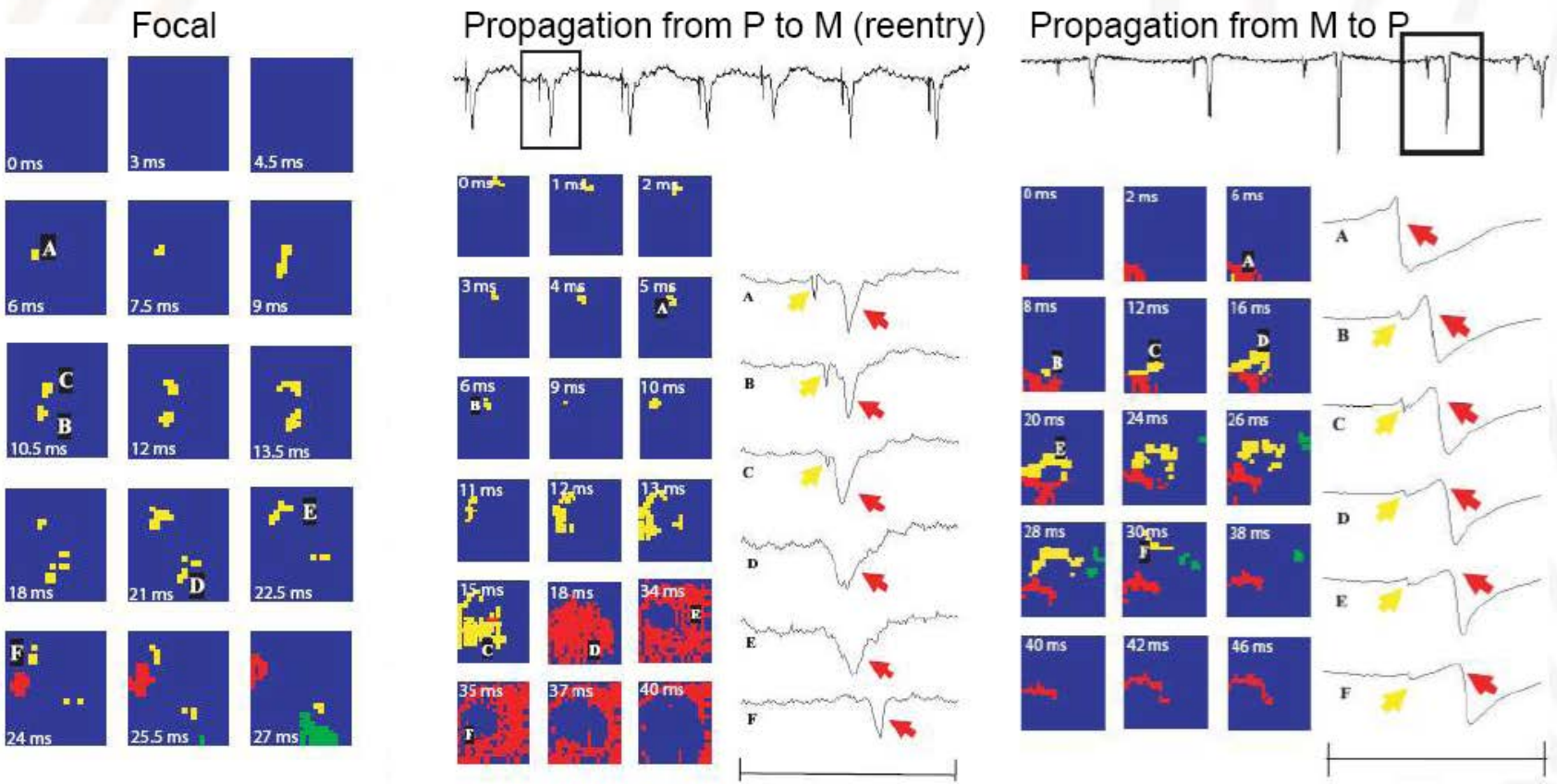


AJP 2008

Activation Patterns of Purkinje Fibers During Long-Duration Ventricular Fibrillation in an Isolated Canine Heart Model

Paul B. Tabereaux, MD, MPH; Greg P. Walcott, MD; Jack M. Rogers, PhD; Jong Kim, MS; Derek J. Dosdall, PhD; Peter G. Robertson, MD; Cheryl R. Killingsworth, DVM, PhD; William M. Smith, PhD; Raymond E. Ideker, MD, PhD

High density mapping (504-electrode array) of VF during first 10 min in canine hearts



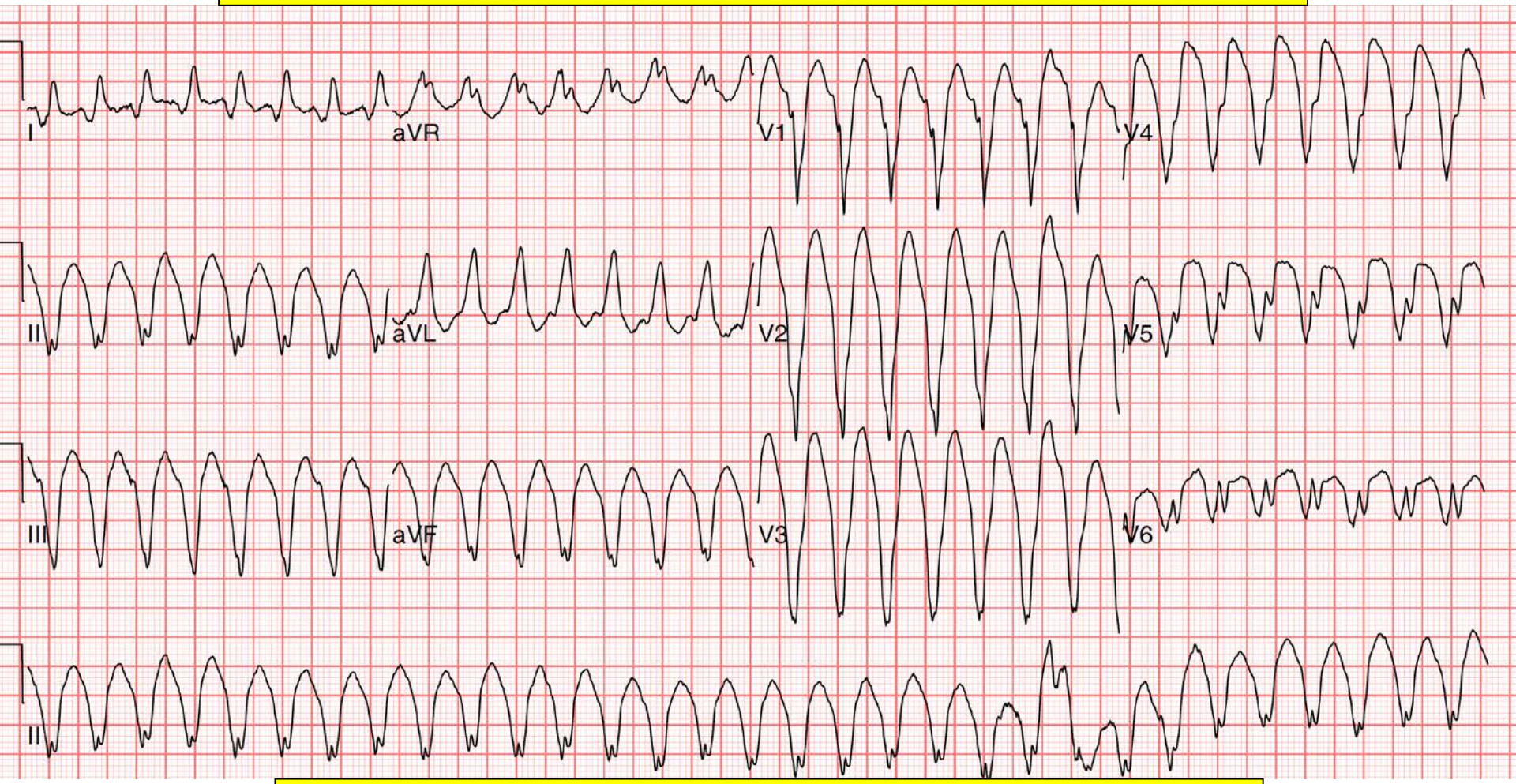
Circulation 2007

Ischemic VT

OH CW, # 5941458

M/55, Gardener, s/p PCI at p-LAD for Ant MI
Palpitation, dyspnea, dizziness for 1 hour

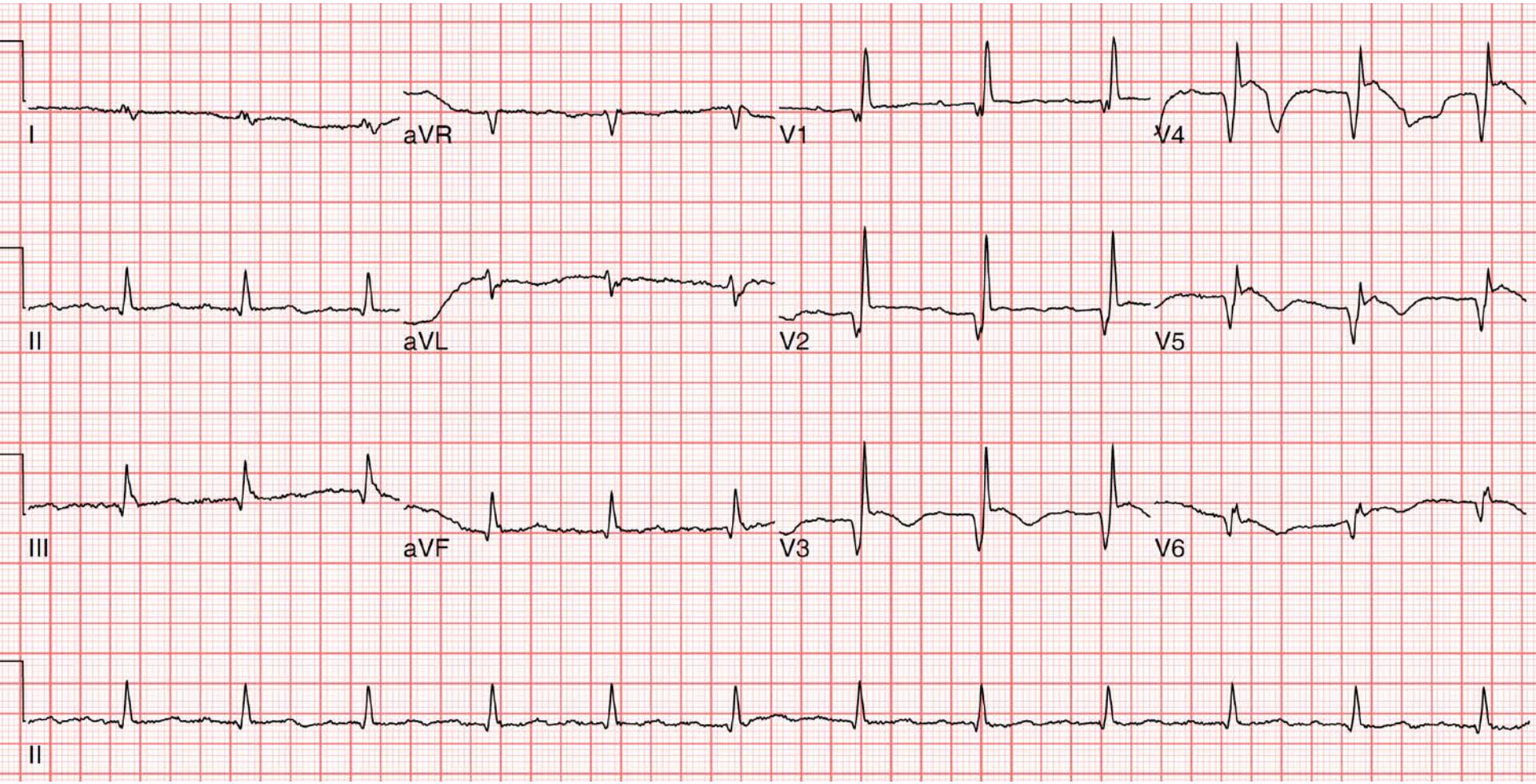
HR 188 bpm, Negative concordance, LAD, BP 70/40 mmHg



→ Patent stent, IABP, DC shock (x 25)

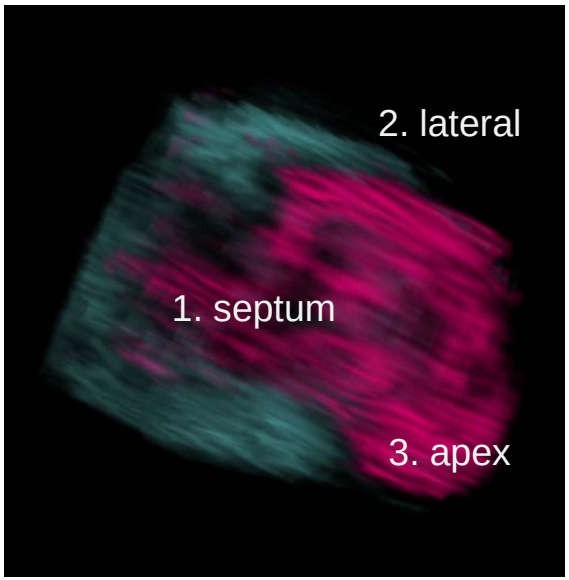
Sinus Rhythm

HR 73 bpm, PR=244ms



ECHO & MRI

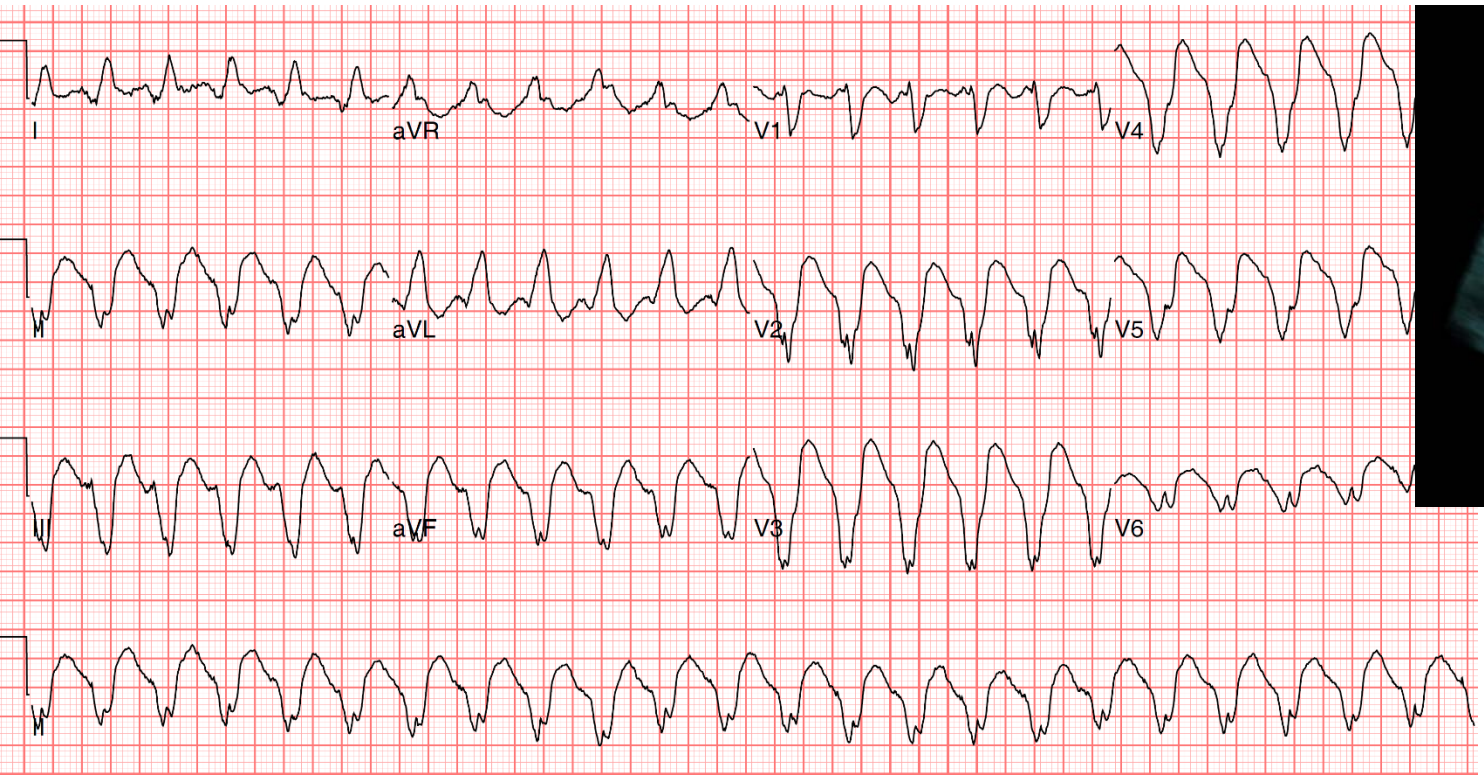
- **TTE: Akinesia with thinning and scarring at LAD territory, aneurysmal change in apex - LVEDD=65mm, LVEF=20%**

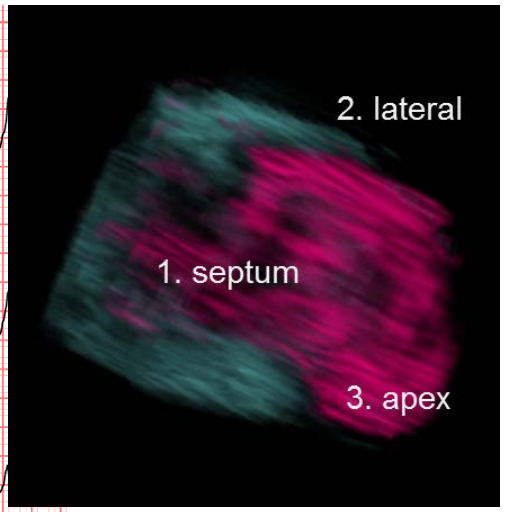


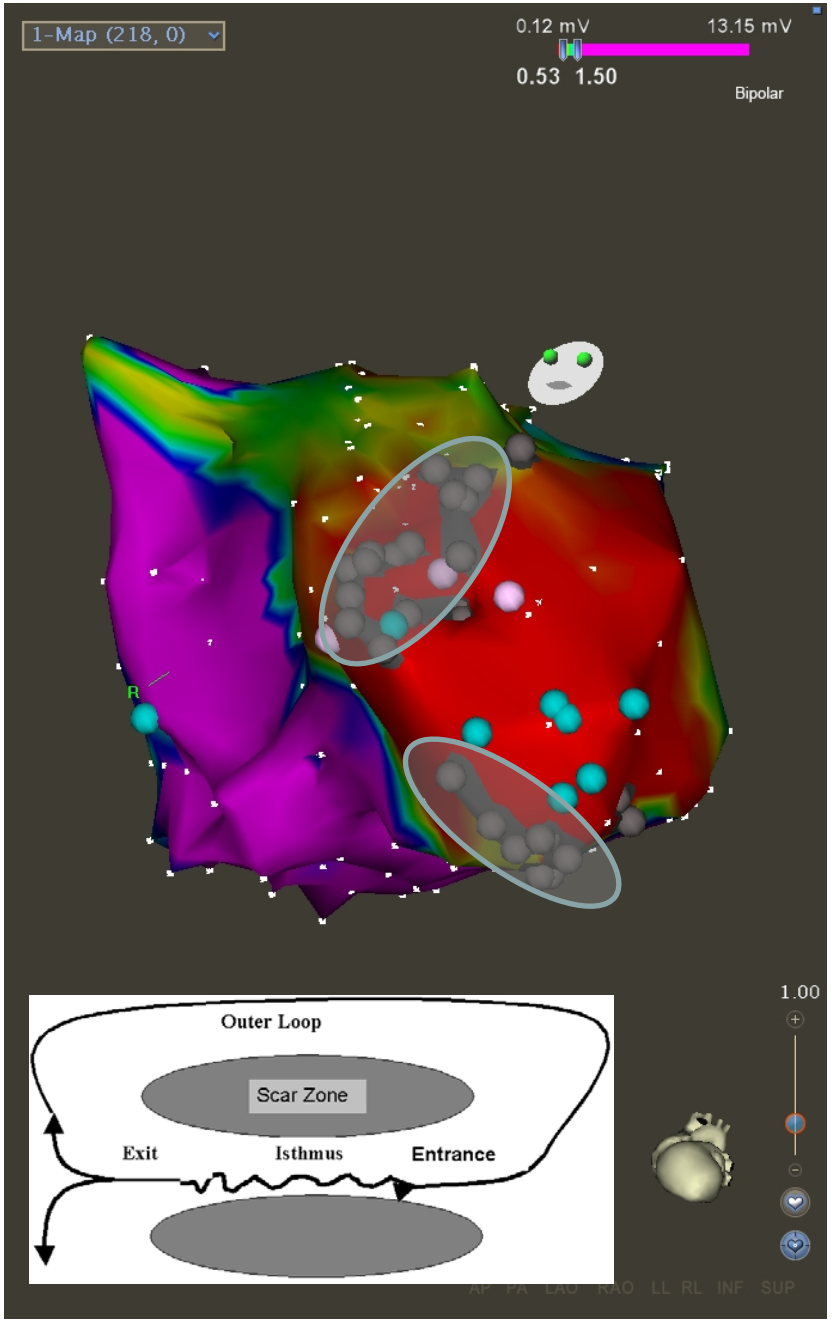
Q. Exit site ?

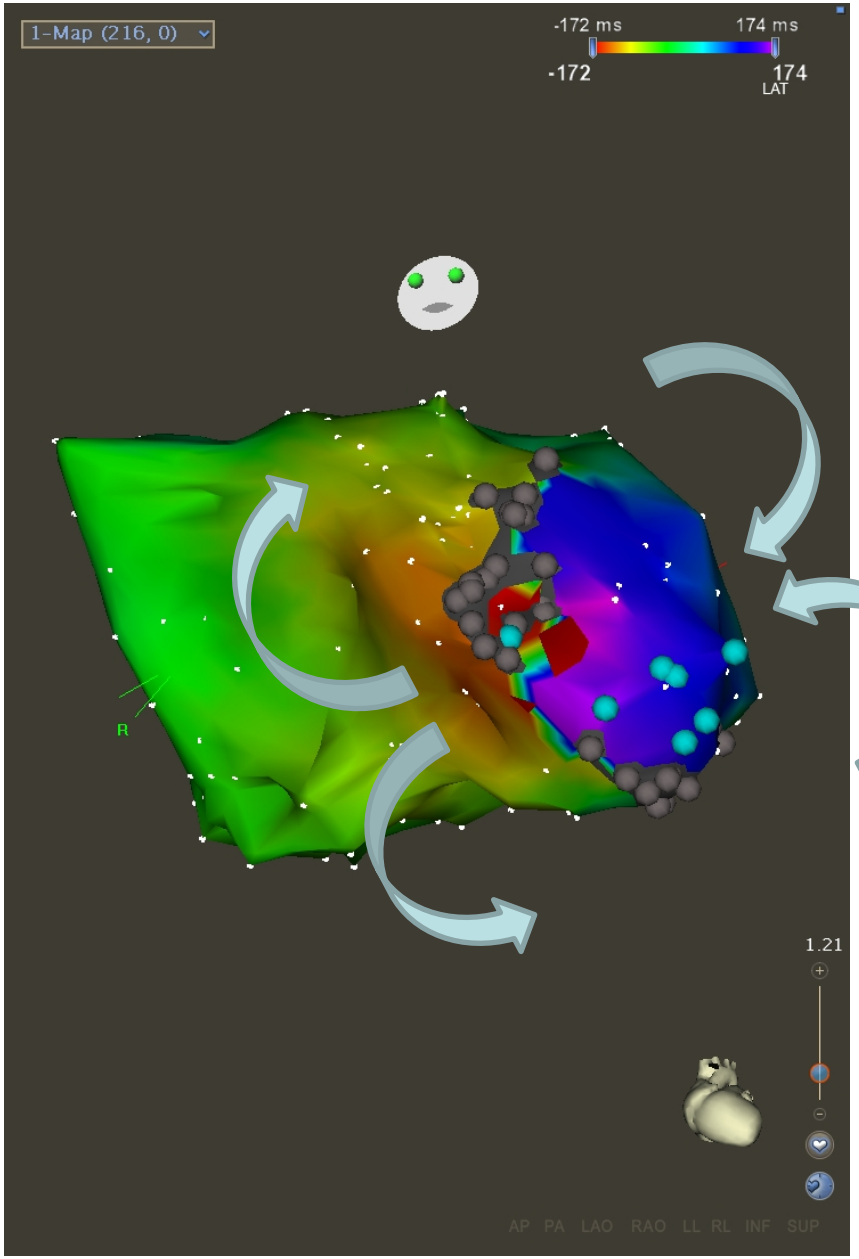
Recurrent VT, slow HR

HR 140 bpm, BP 90/50 mmHg, Negative concordance, LAD

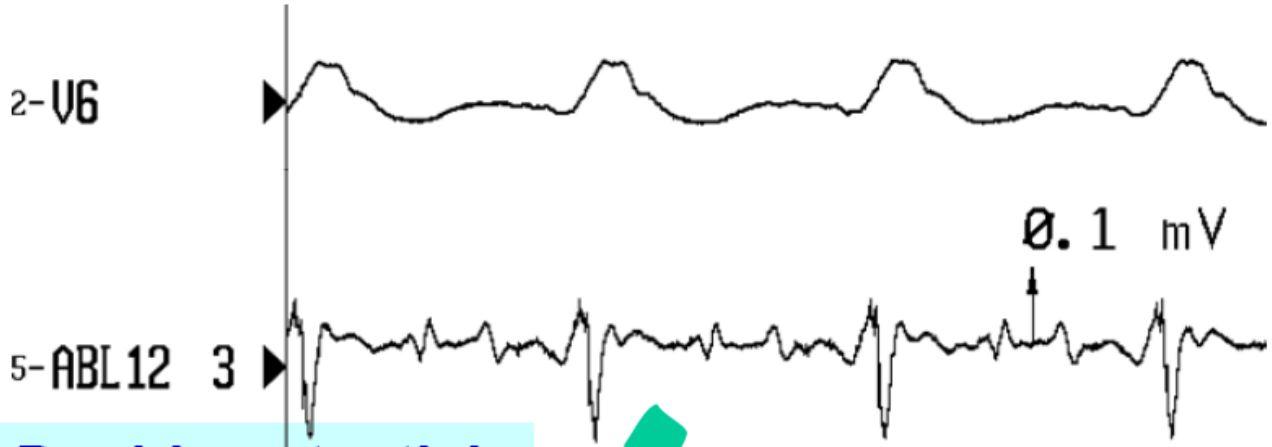





1-Map (218, 0)
0.12 mV
13.15 mV
0.53 1.50
Bipolar
R
Outer Loop
Scar Zone
Exit
Isthmus
Entrance
1.00
AP PA LAO RAO LL RL INF SUP

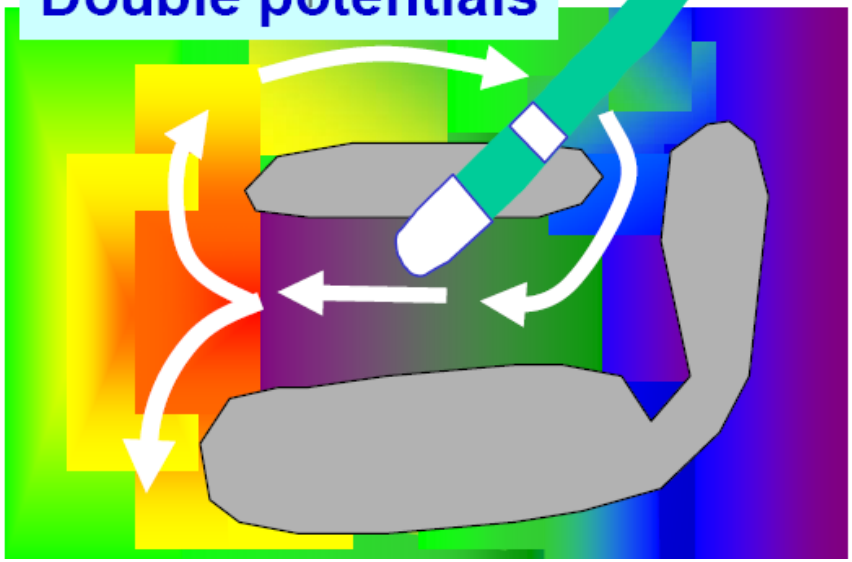

1-Map (216, 0)
-172 ms
174 ms
-172
174
LAT
R
1.21
AP PA LAO RAO LL RL INF SUP

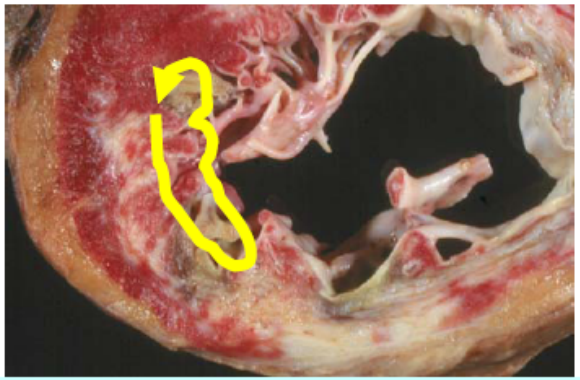
Post-pacing Interval Fundamental assumption: The potential used for measurement indicates depolarization at the pacing site.



Local vs Far-field potentials

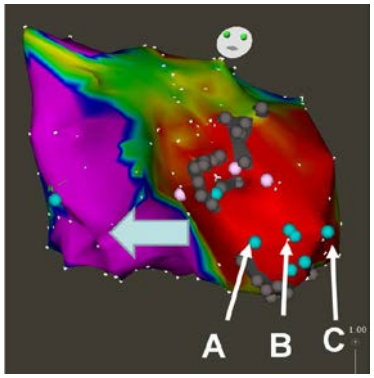
Double potentials

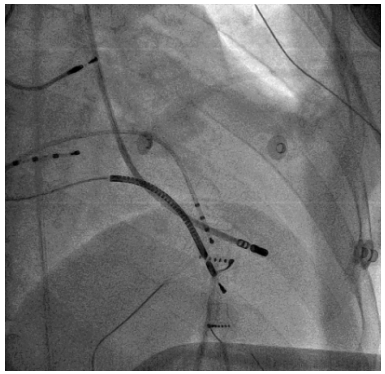


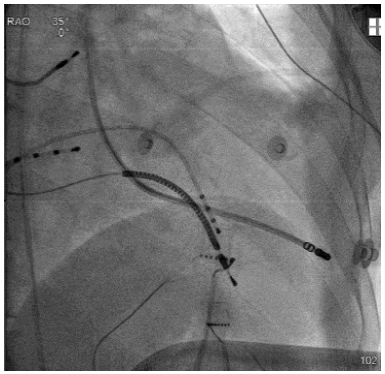


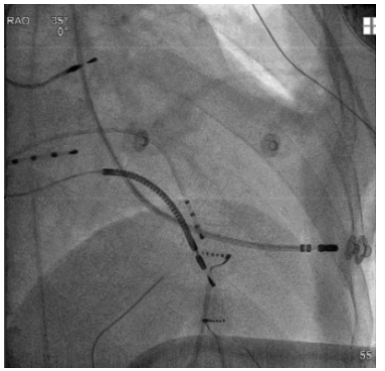
Tung et al. Recognition of far-field electrograms during entrainment mapping of VT. JACC 2003;42:110-5.

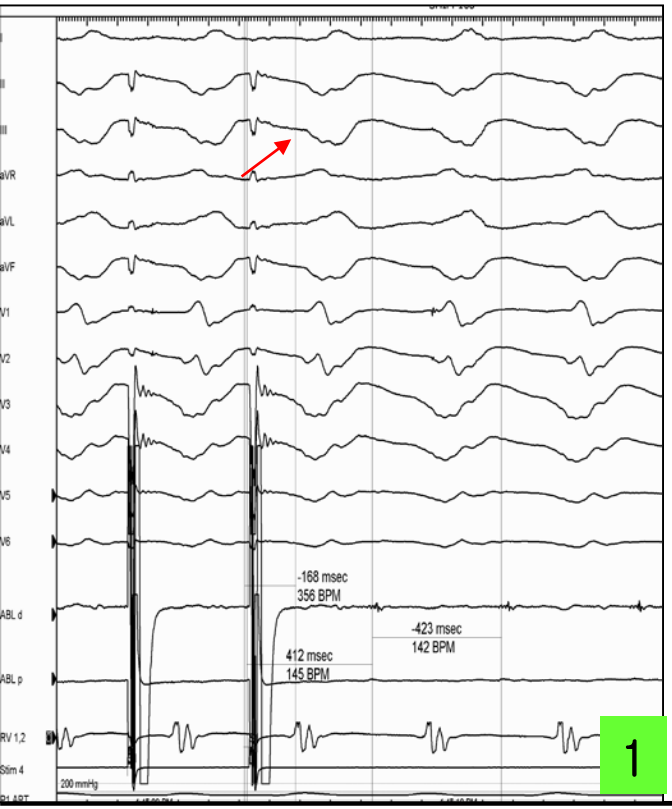
Q. Site A, B, C ?



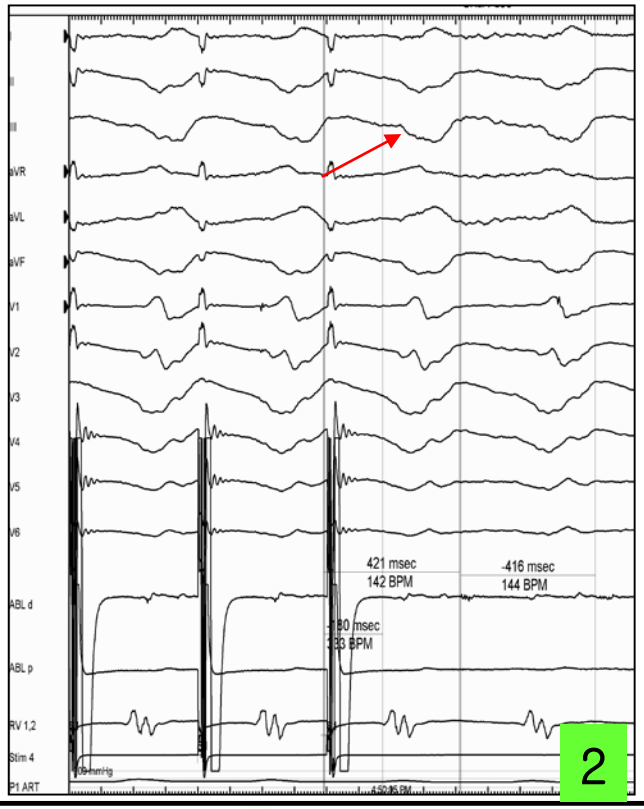




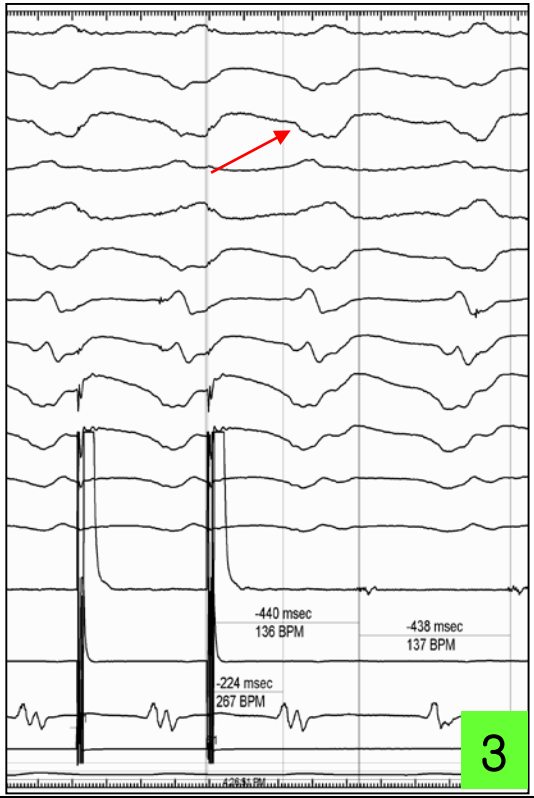




S-QRS= 168ms, PPI-TCL= 11ms

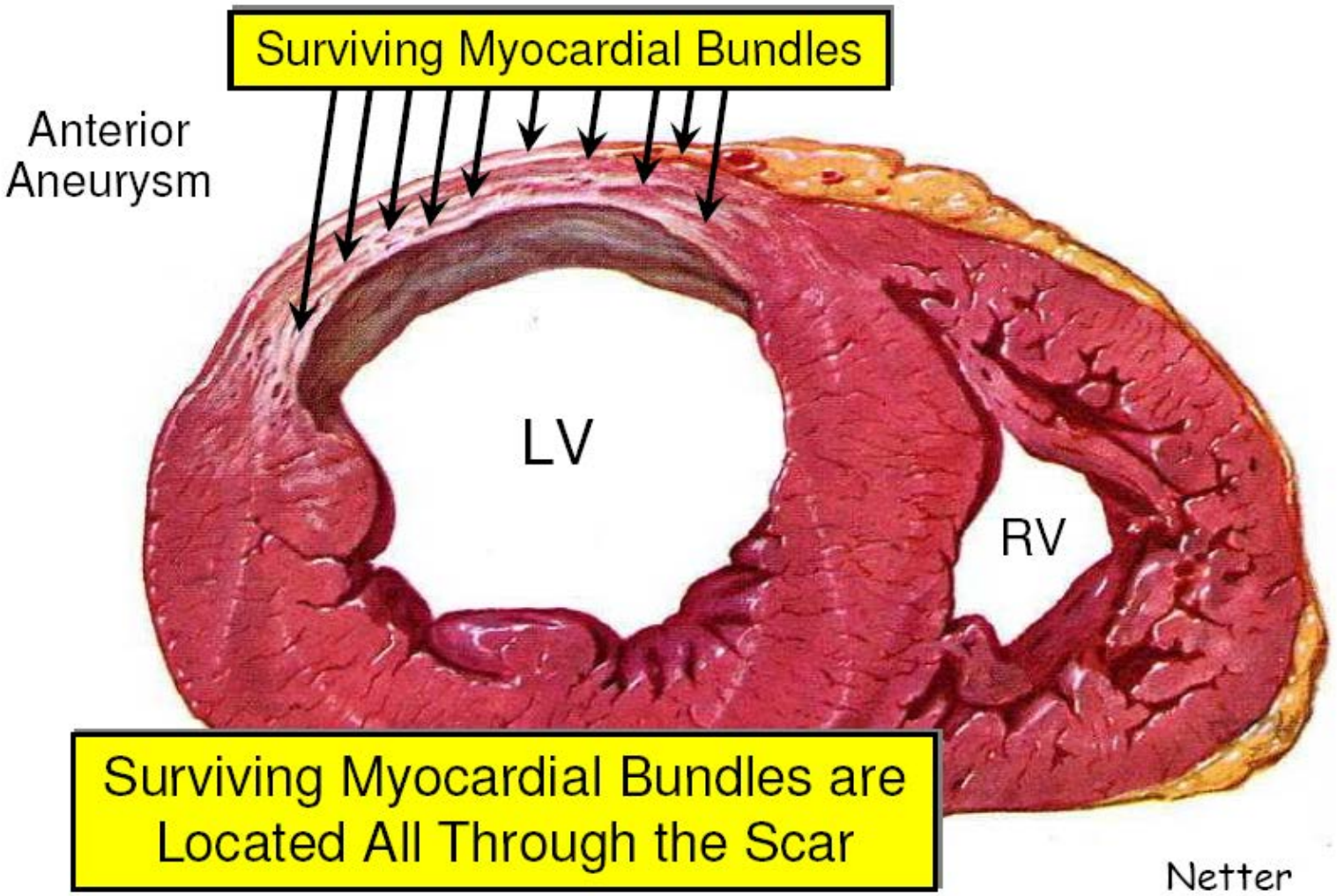


S-QRS= 180ms, PPI-TCL= 5ms

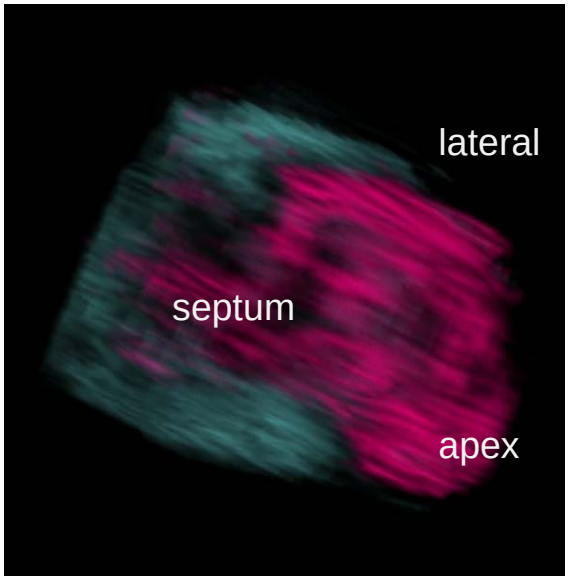


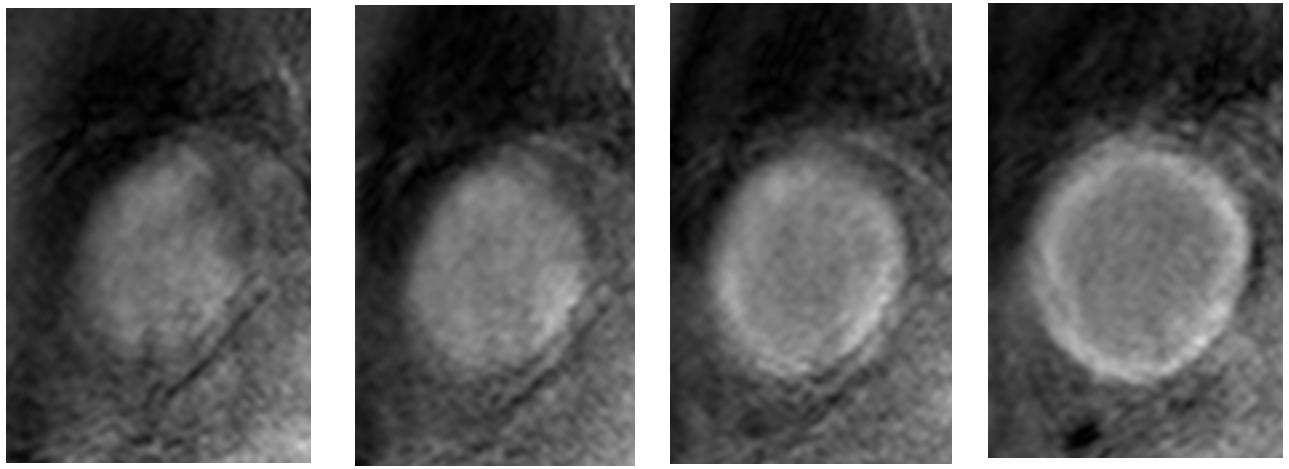
S-QRS= 224ms, PPI-TCL= 2ms

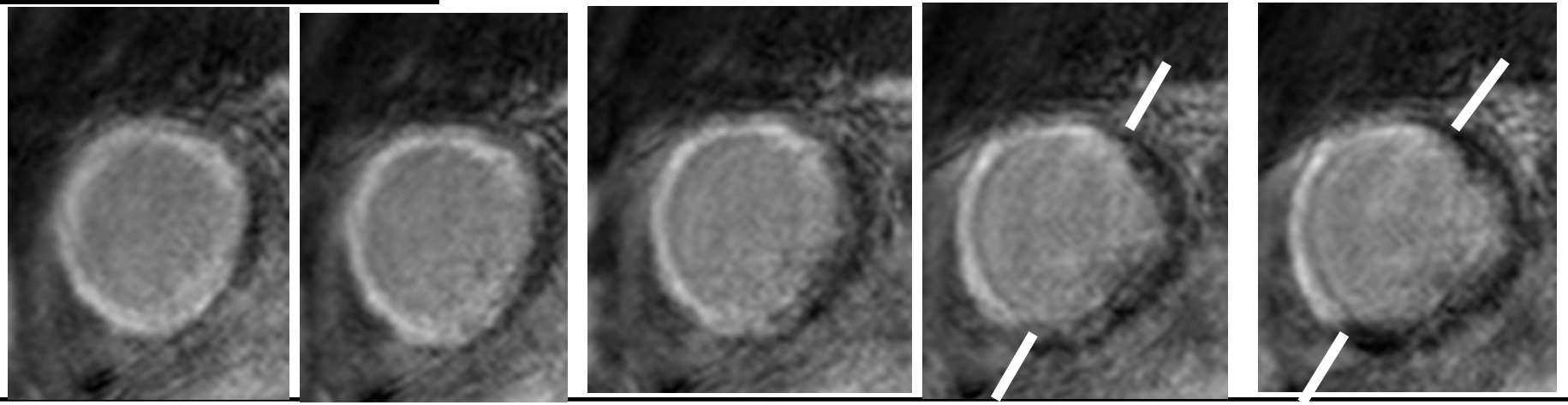
Substrate for Ventricular Tachycardia



Q. Amount of myocardium for electrical conduction?

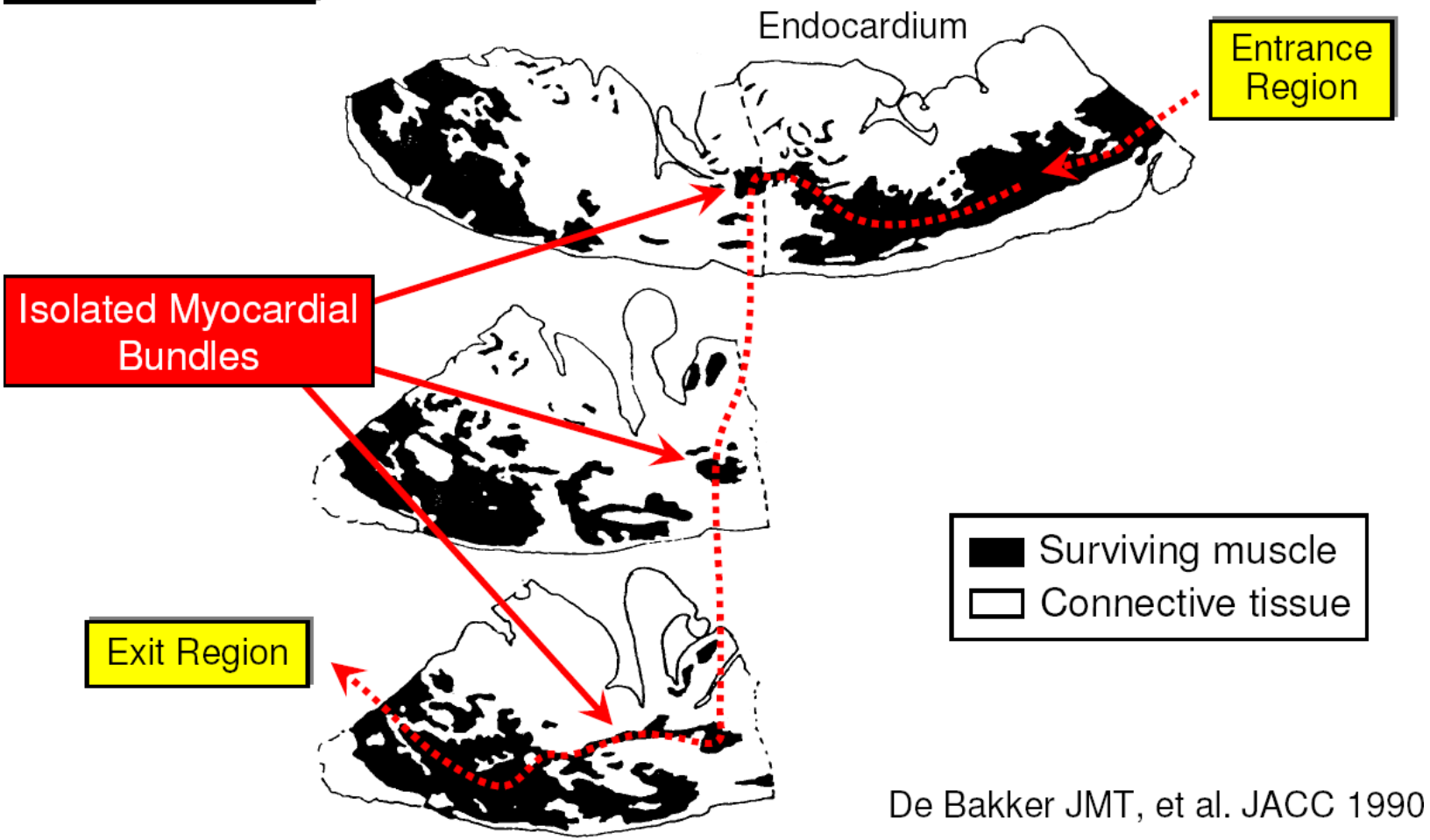






Explanted Human Heart – Prior MI

Mapping Ventricular Tachycardia (Needle Electrodes)



De Bakker JMT, et al. JACC 1990

Tunnel Propagation of Postshock Activations as a Hypothesis for Fibrillation Induction and Isoelectric Window

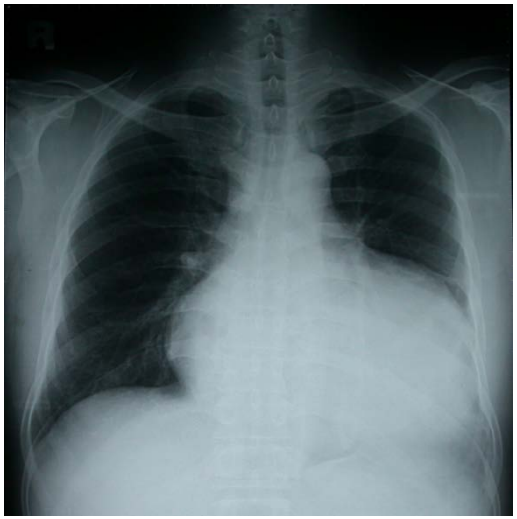
Takashi Ashihara, Jason Constantino, Natalia A. Trayanova

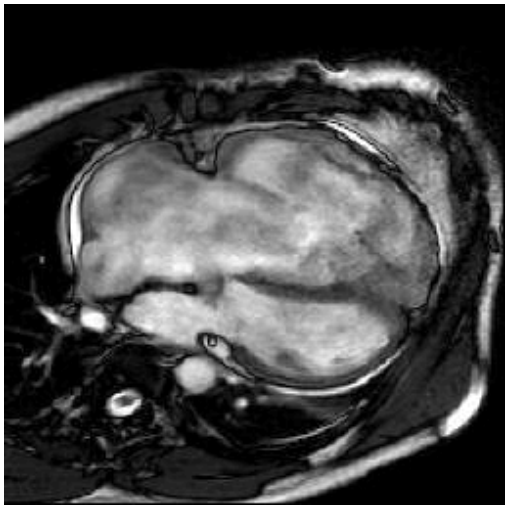
Abstract—Comprehensive understanding of the ventricular response to shocks is the approach most likely to succeed in reducing defibrillation threshold. We propose a new theory of shock-induced arrhythmogenesis that unifies all known aspects of the response of the heart to monophasic (MS) and biphasic (BS) shocks. The central hypothesis is that submerged "tunnel" propagation of postshock activations through shock-induced intramural excitable areas underlies fibrillation induction and the existence of isoelectric window. We conducted simulations of fibrillation induction using a realistic bidomain model of rabbit ventricles. Following pacing, MS and BS of various strengths/timings were delivered. The results demonstrated that, during the isoelectric window, an activation originated deep within the ventricular wall, arising from virtual electrodes; it then propagated fully intramurally through an excitable tunnel induced by the shock, until it emerged onto the epicardium, becoming the earliest-propagated postshock activation. Differences in shock outcomes for MS and BS were found to stem from the narrower BS intramural postshock excitable area, often resulting in conduction block, and the difference in the mechanisms of origin of the postshock activations, namely intramural virtual electrode–induced phase singularity for MS and virtual electrode–induced propagated graded response for BS. This study provides a novel analysis of the 3D mechanisms underlying the origin of postshock activations in the process of fibrillation induction by MS and BS and the existence of isoelectric window. The tunnel propagation hypothesis could open a new avenue for interventions exploration to achieve significantly lower defibrillation threshold. (*Circ Res*. **2008;102:737-745.**)

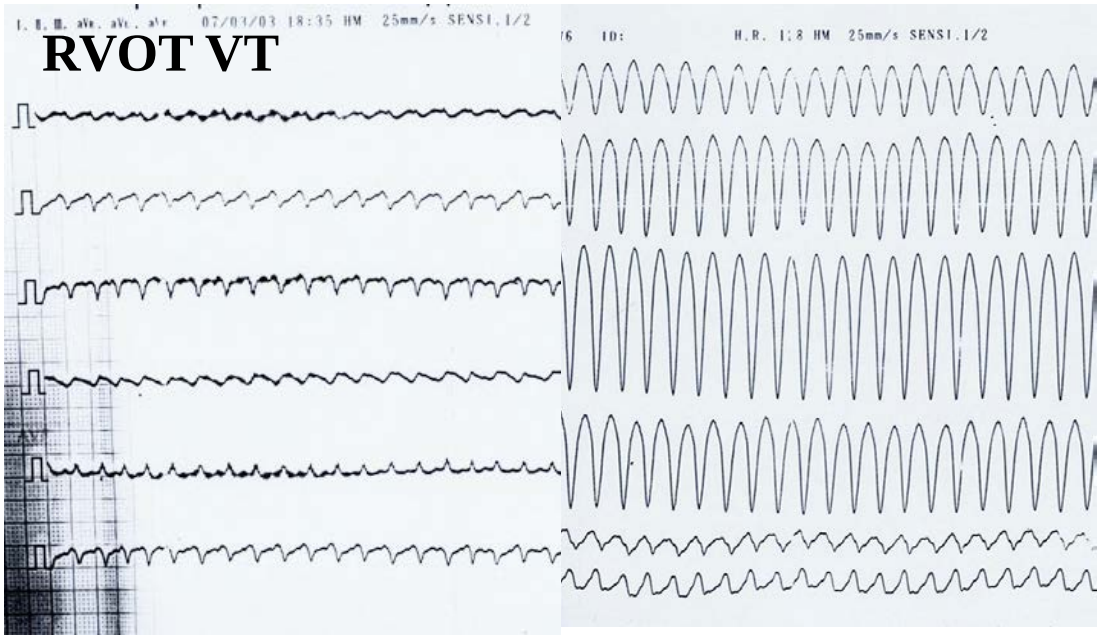
Key Words: ventricular fibrillation ■ electric shock ■ postshock activation ■ bidomain model ■ spiral wave

Non-ischemic

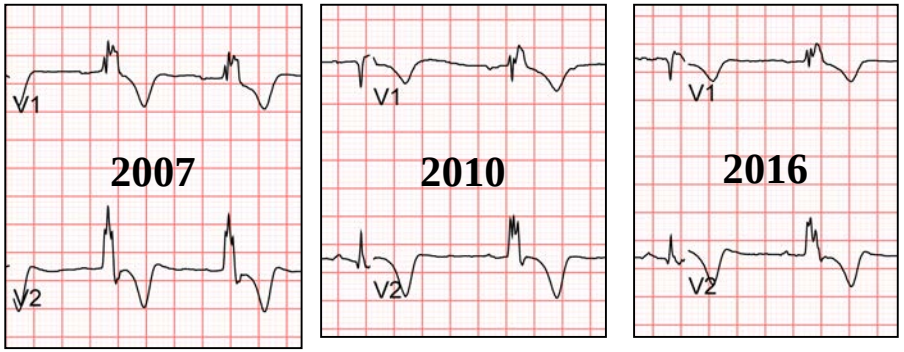
ARVD



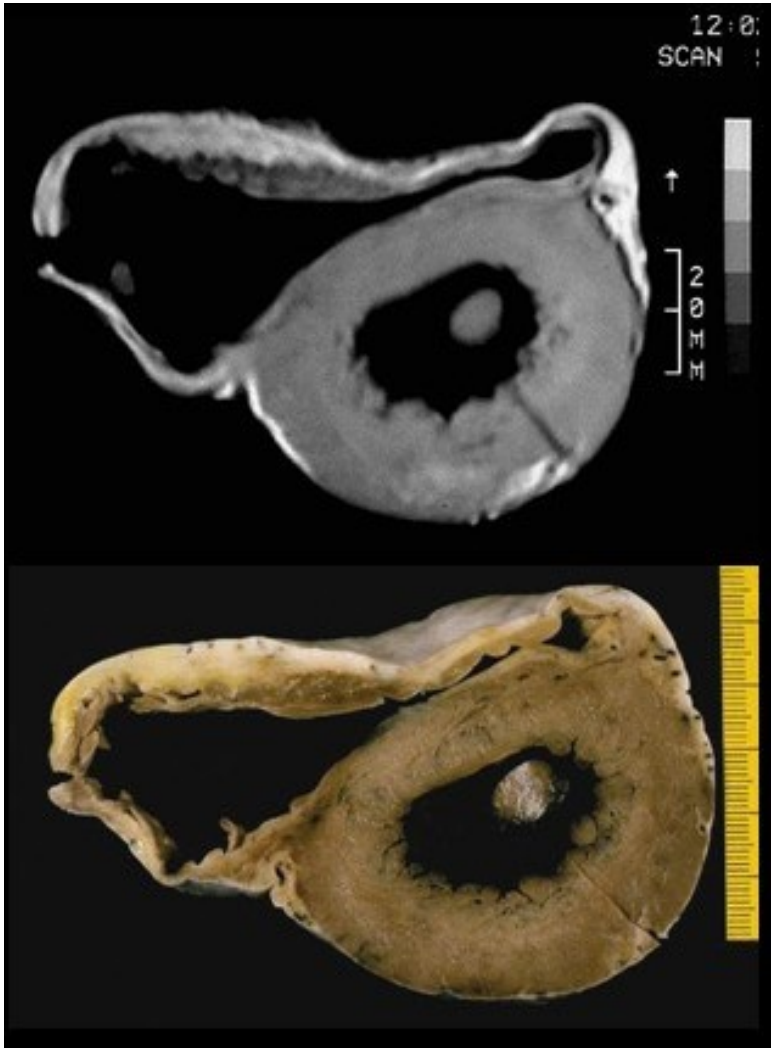


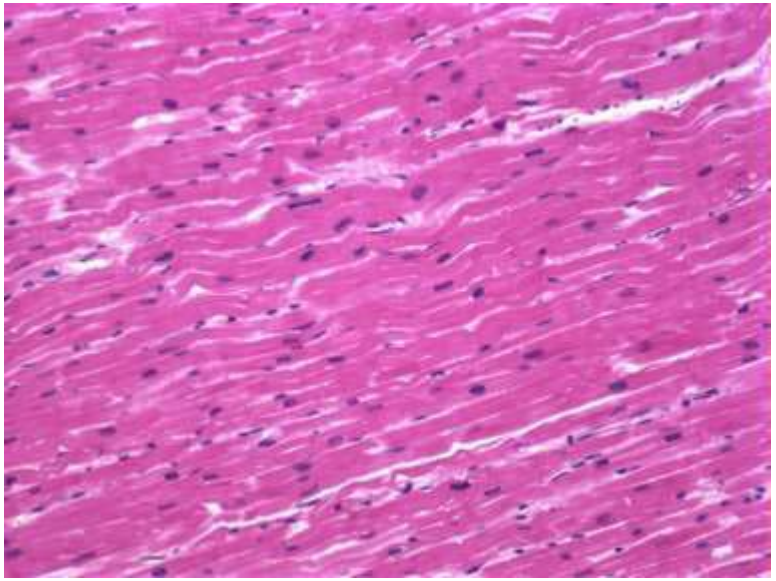


Epsilon wave

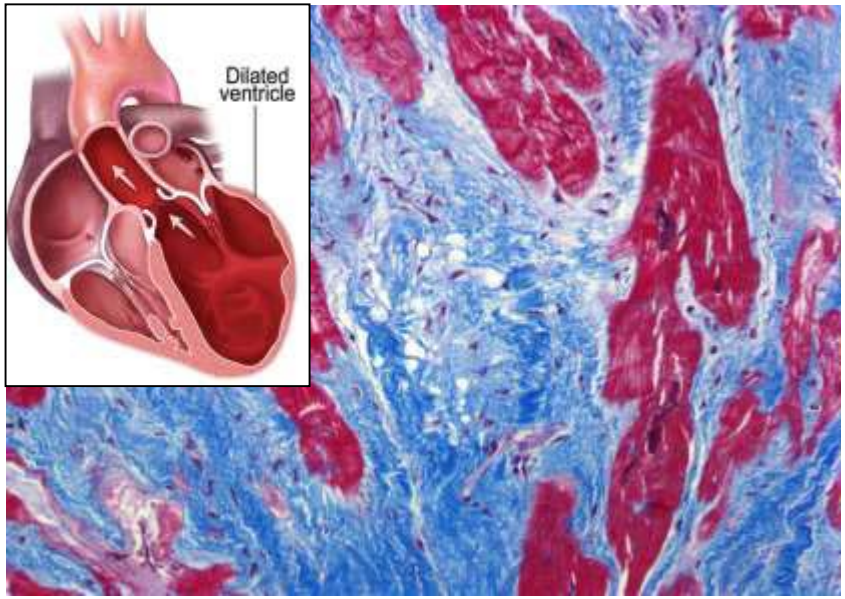


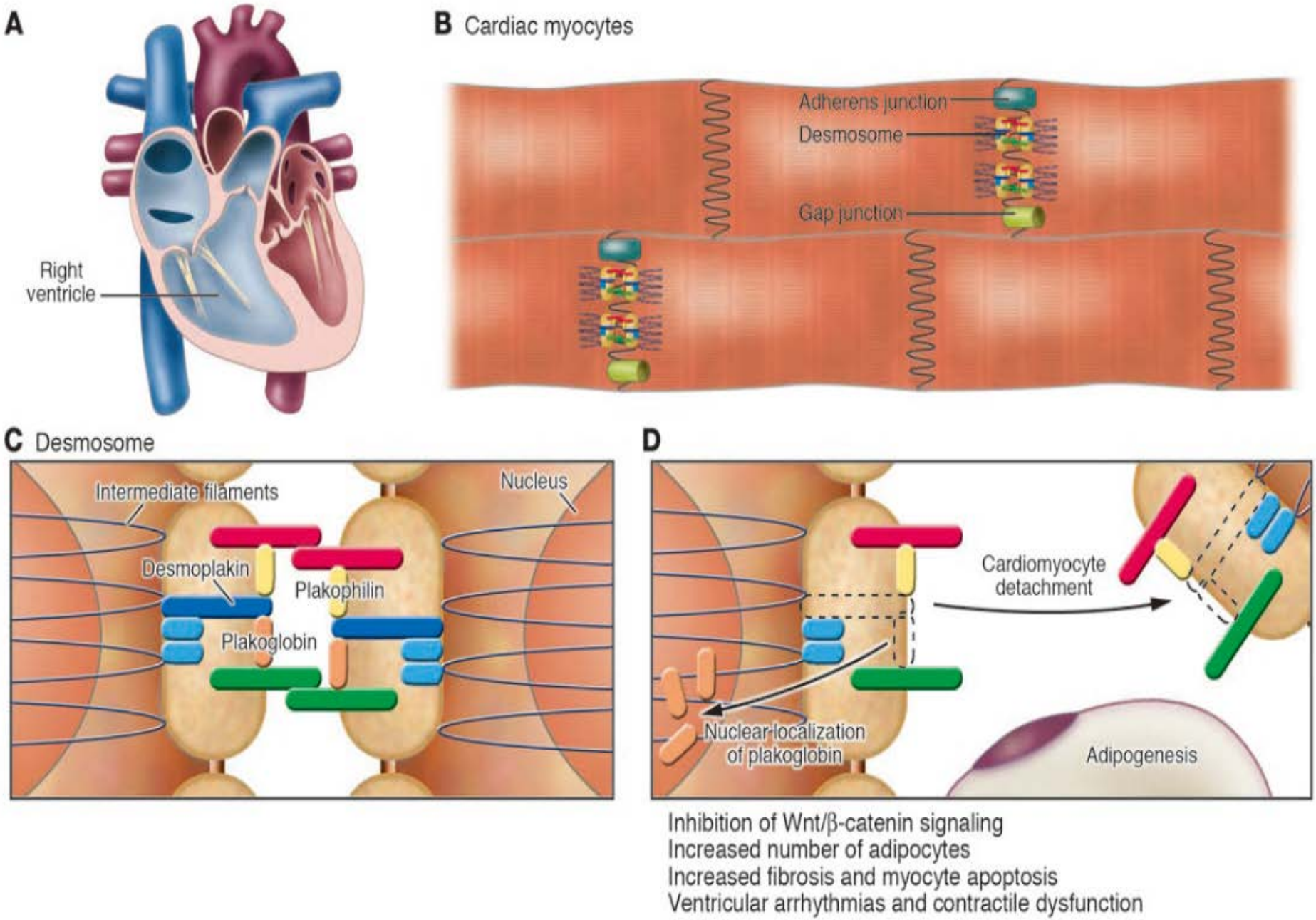
MRI



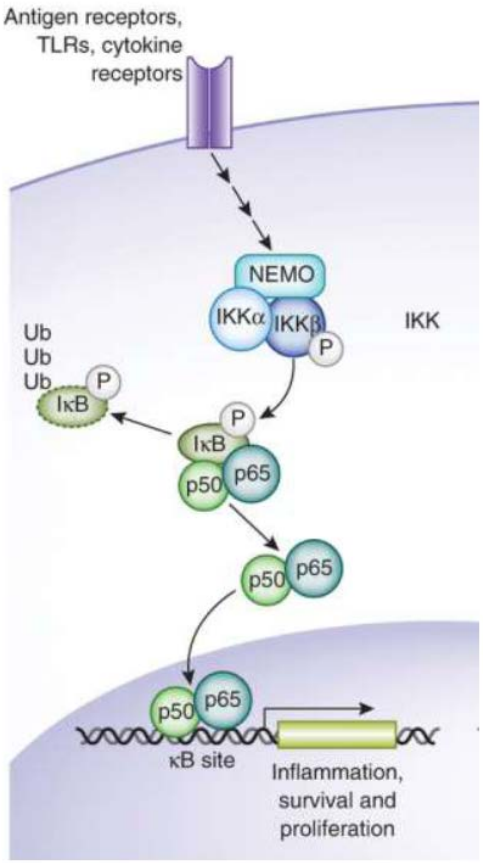


Early/Concealed ARVC: minimal/no structural remodeling

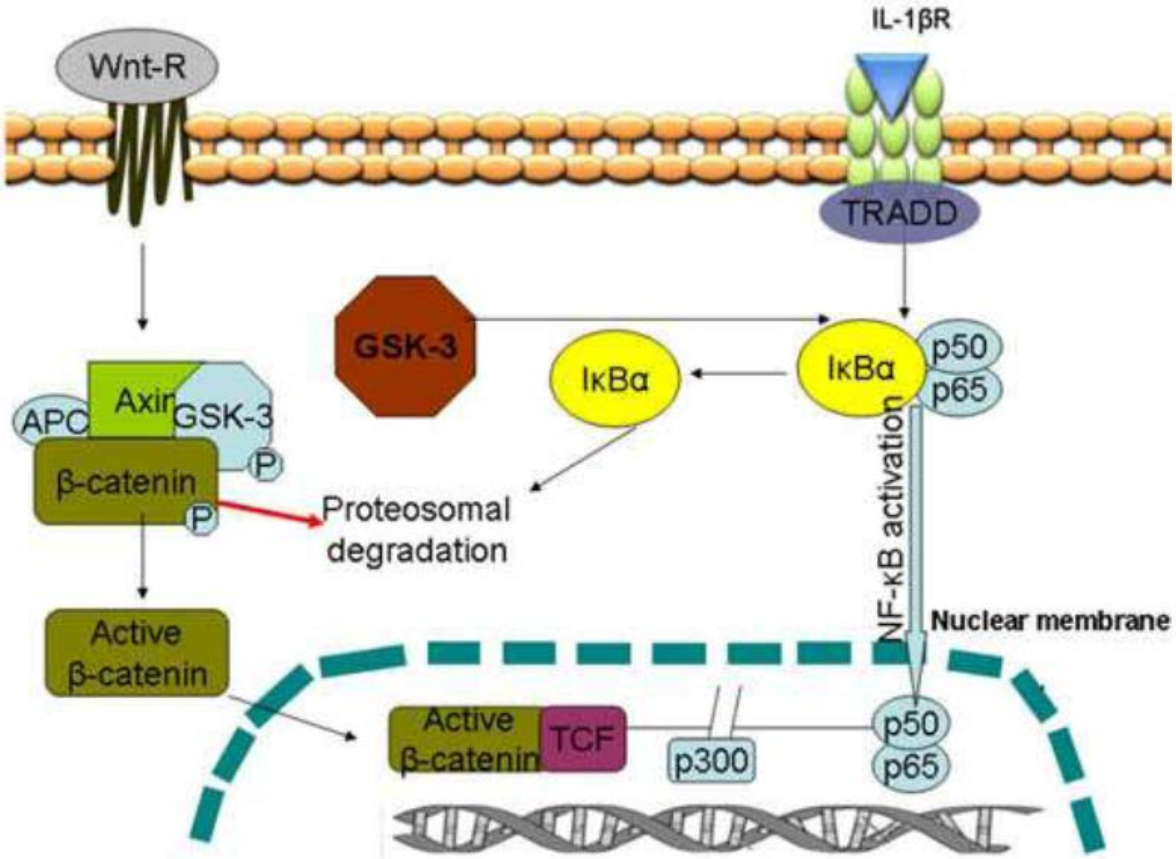



A
Right ventricle
B Cardiac myocytes
Adherens junction
Desmosome
Gap junction
C Desmosome
Intermediate filaments
Nucleus
Desmoplakin
Plakophilin
Plakoglobin
D
Cardiomyocyte detachment
Nuclear localization of plakoglobin
Adipogenesis
Inhibition of Wnt/β-catenin signaling
Increased number of adipocytes
Increased fibrosis and myocyte apoptosis
Ventricular arrhythmias and contractile dysfunction

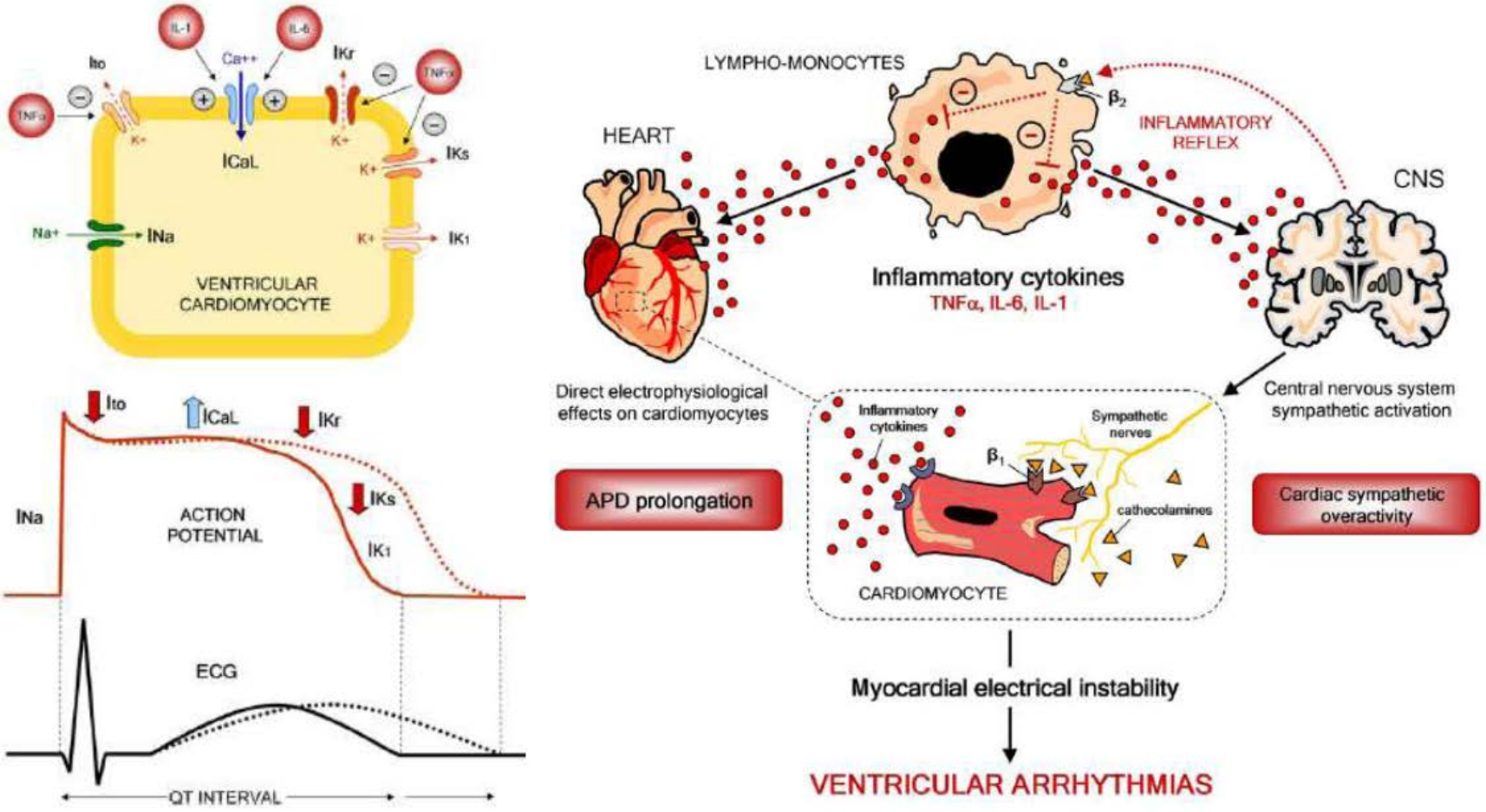
The Canonical NFκB Signaling Pathway



The Canonical NFκB Signaling Pathway is Activated by GSK3β

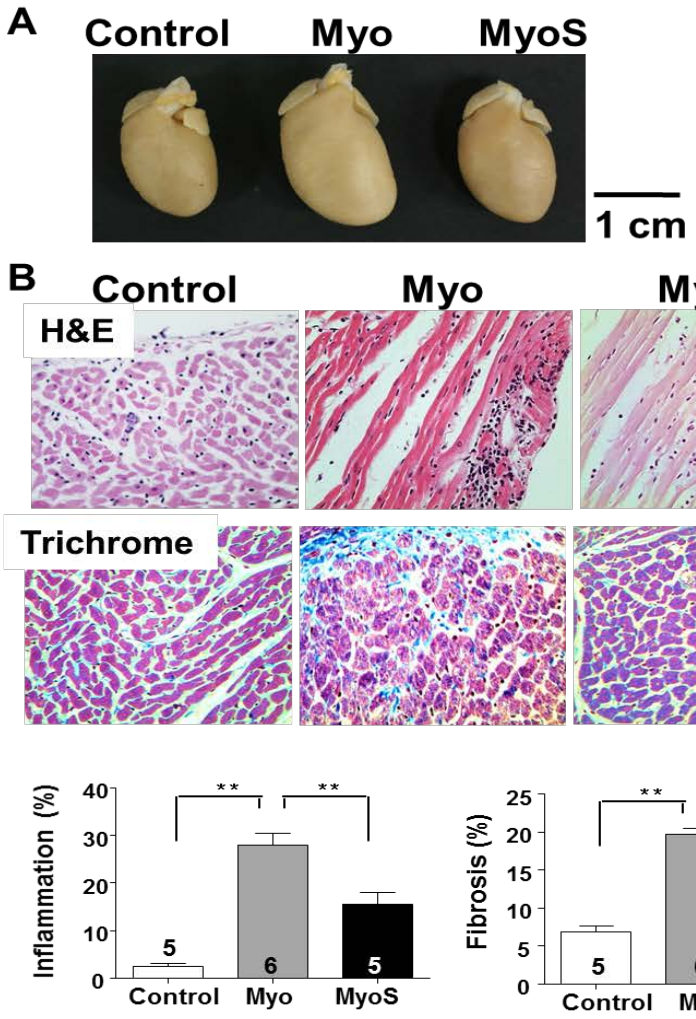


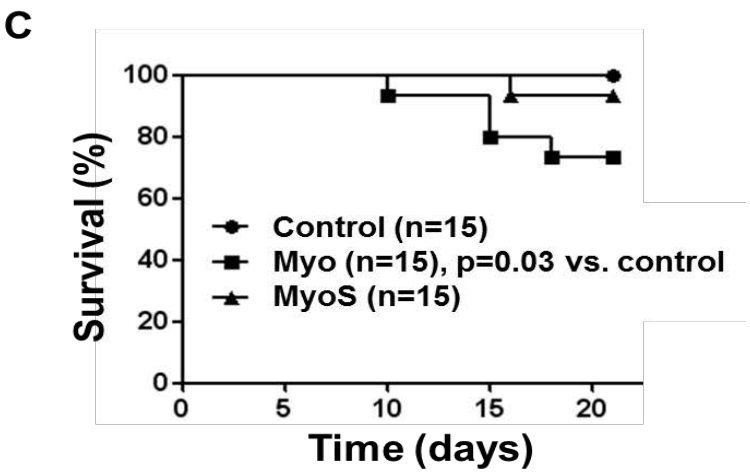
Systemic Inflammation and Ventricular Arrhythmias
Potential Pathways and Mechanisms

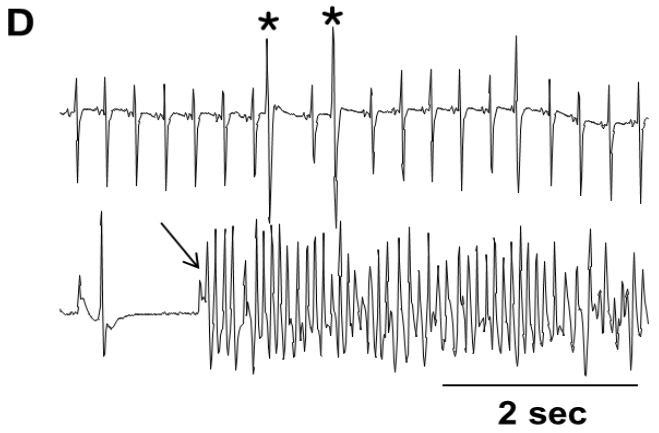


from Lazzerini et al, Eur Heart J 2016 Jun 1. pii: ewh208

Myocarditis and arrhythmia

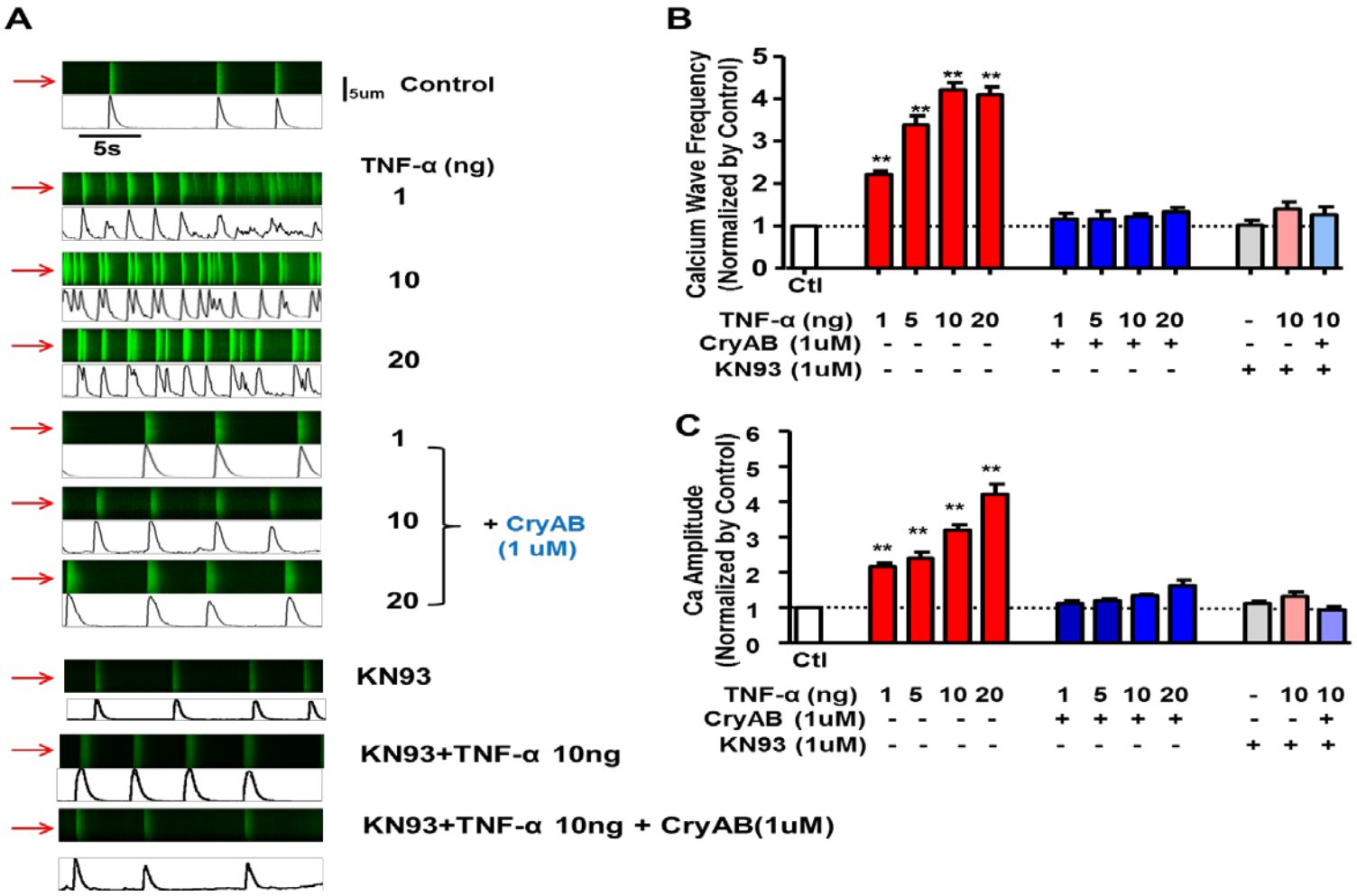






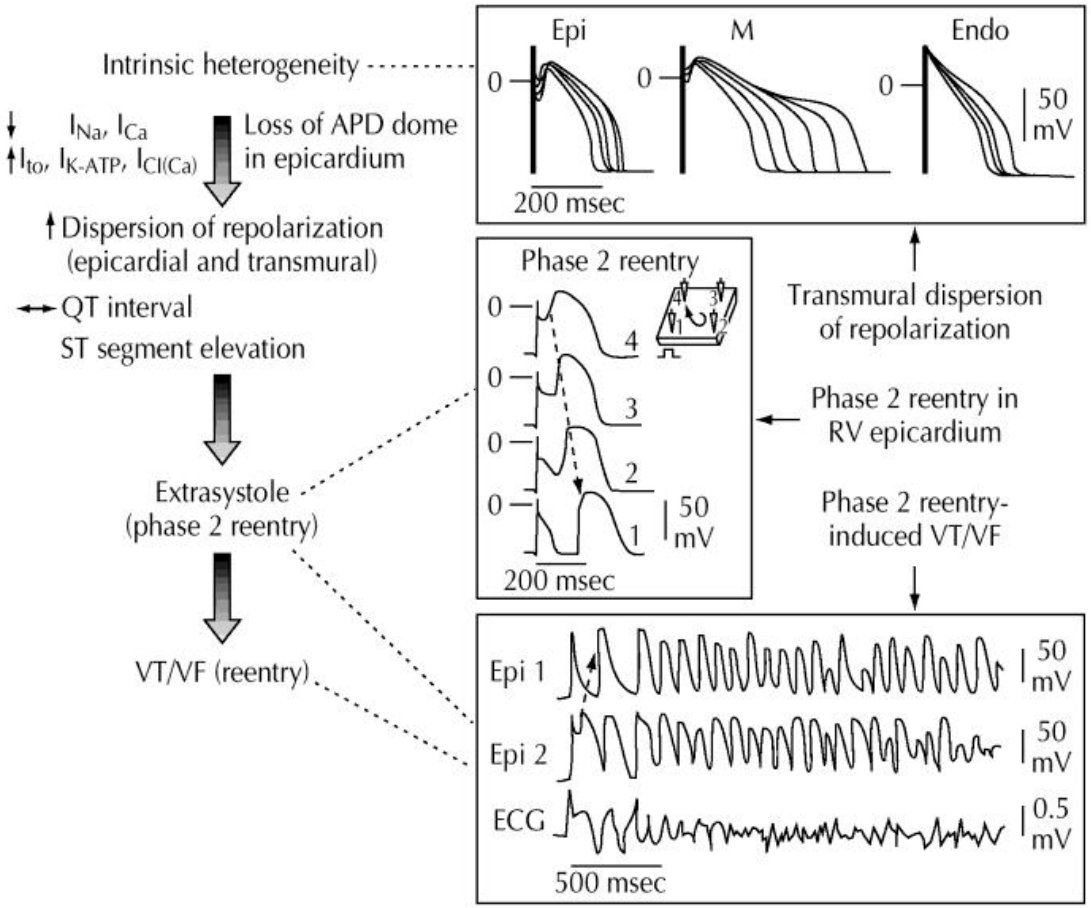
Park H, et al. Circ J. 2014;78(9):2292-301

Spontaneous Ca^{2+} release in rat neonatal myocytes treated with TNF-α



Park H, et al. Int J Cardiol. 2015;182:399-402.

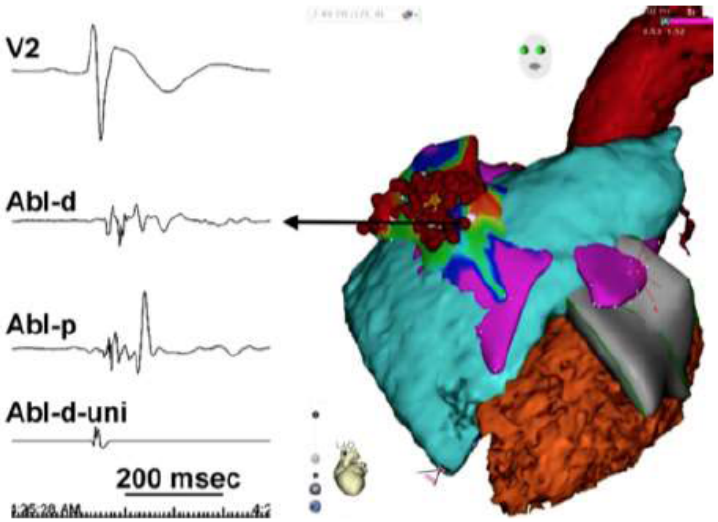
Brugada syndrome



Antzelevitch et al. JCE 2001;12:268–72.

The EGMs recorded from RVOT epicardium

Substrate ablation



Abnormal EGMs (n=9pts)
≤1mV, split or fractionated ≥2 distinct components, wide >80-120ms, beyond QRS

Endpoint

Elimination of al abnormal EGMs 24.8min RF

Non-inducibility of VF 7/9

Disappearance of type 1 Brugada ECG pattern (5/9 acute, 3/9 delayed)

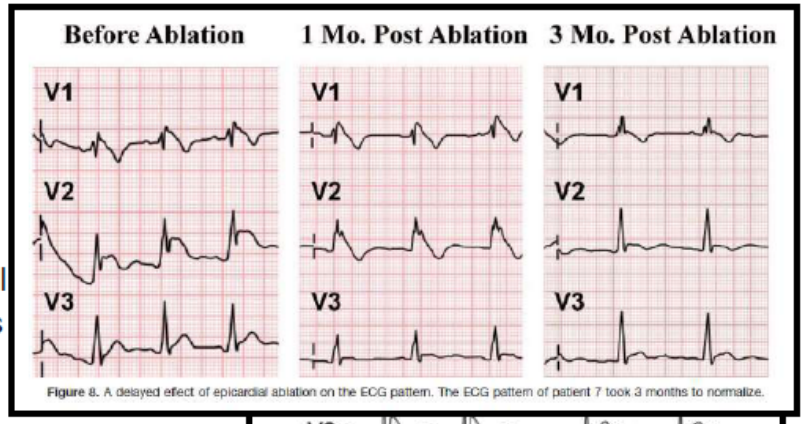


Figure 8. A delayed effect of epicardial ablation on the ECG pattern. The ECG pattern of patient 7 took 3 months to normalize.

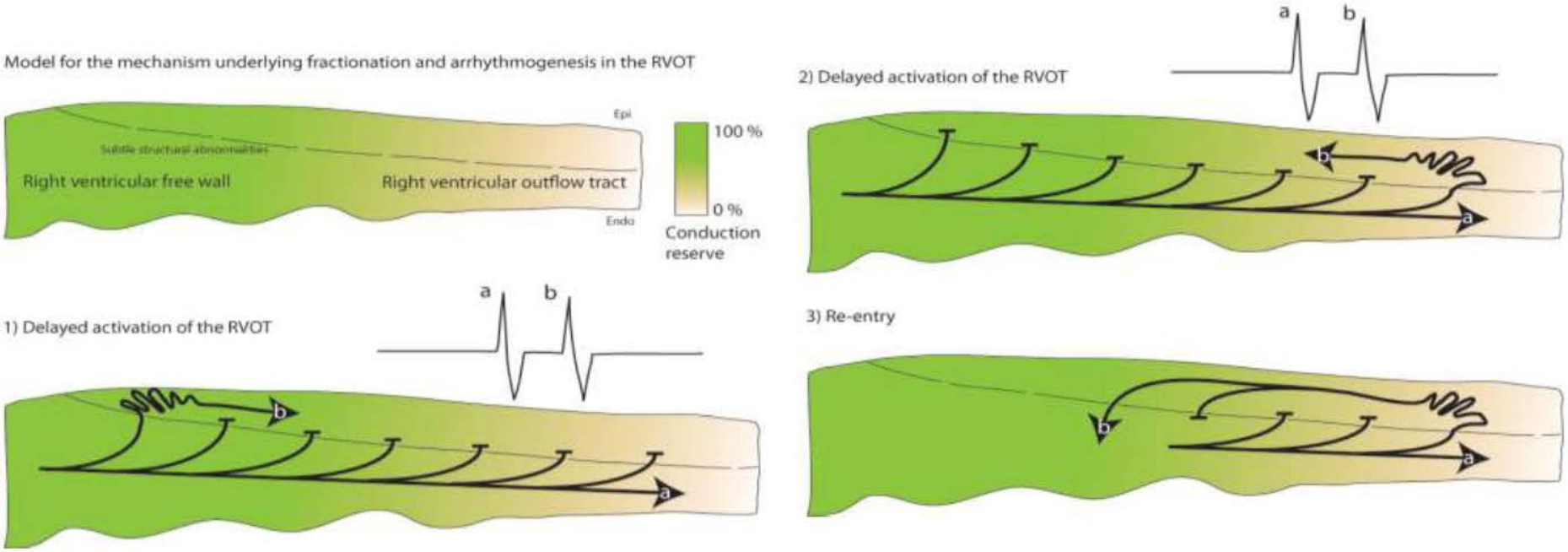
No complications
Follow-up 20±6 months 1/9 VF recurrence

No use of sodium channel blocker during ablation

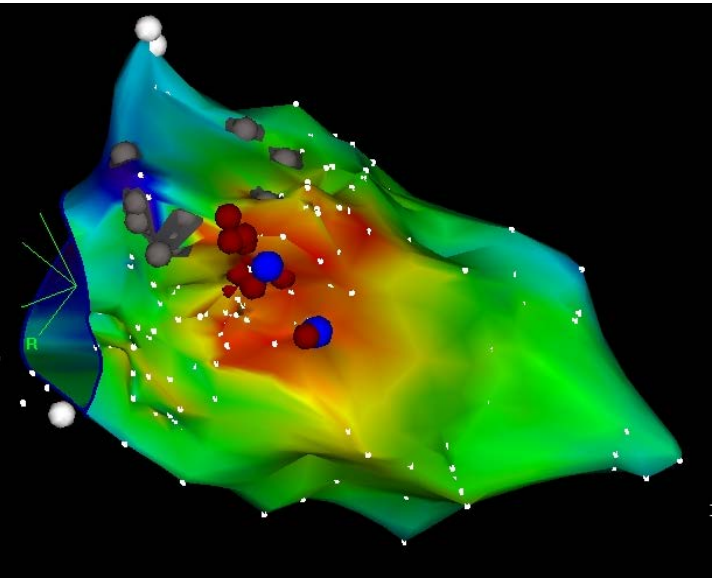
Nademanee K, et al. Circulation. 2011;123:1270–1279.
Nademanee et al. Heart Rhythm 2017;14:457–461

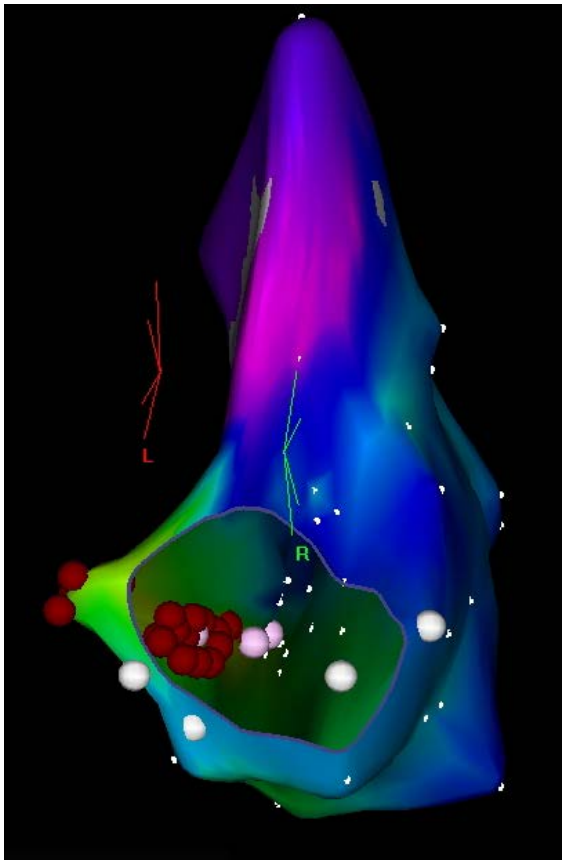
Brugada syndrome
Is there a developmental basis?

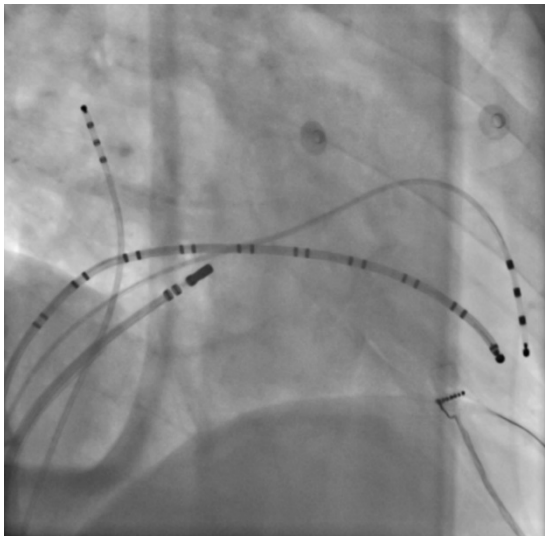
The RVOT has a lower safety for cardiac conduction compared to RV

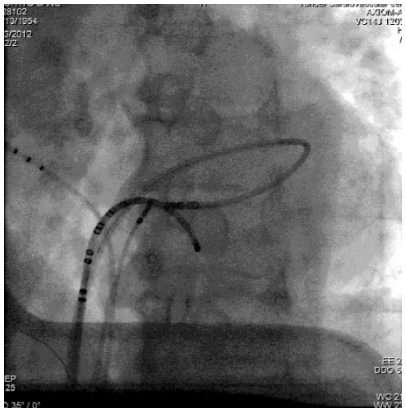


Sarcoidosis

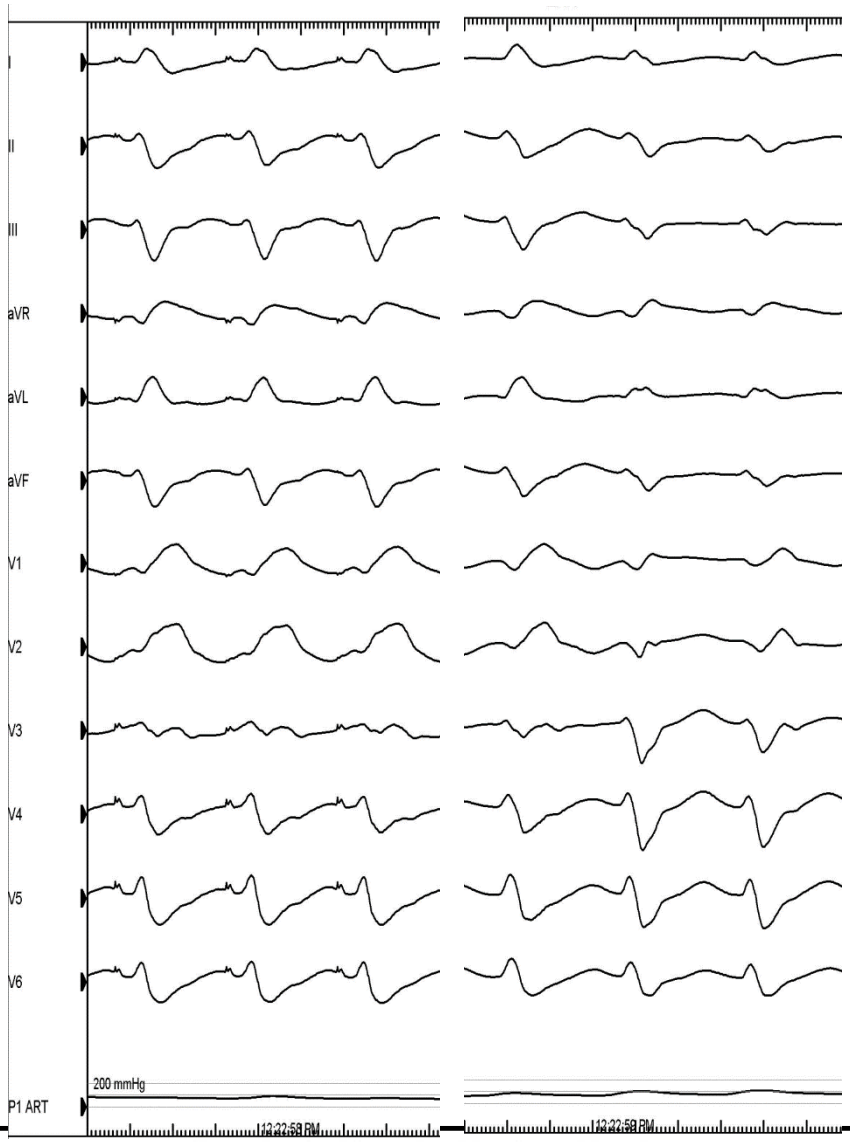


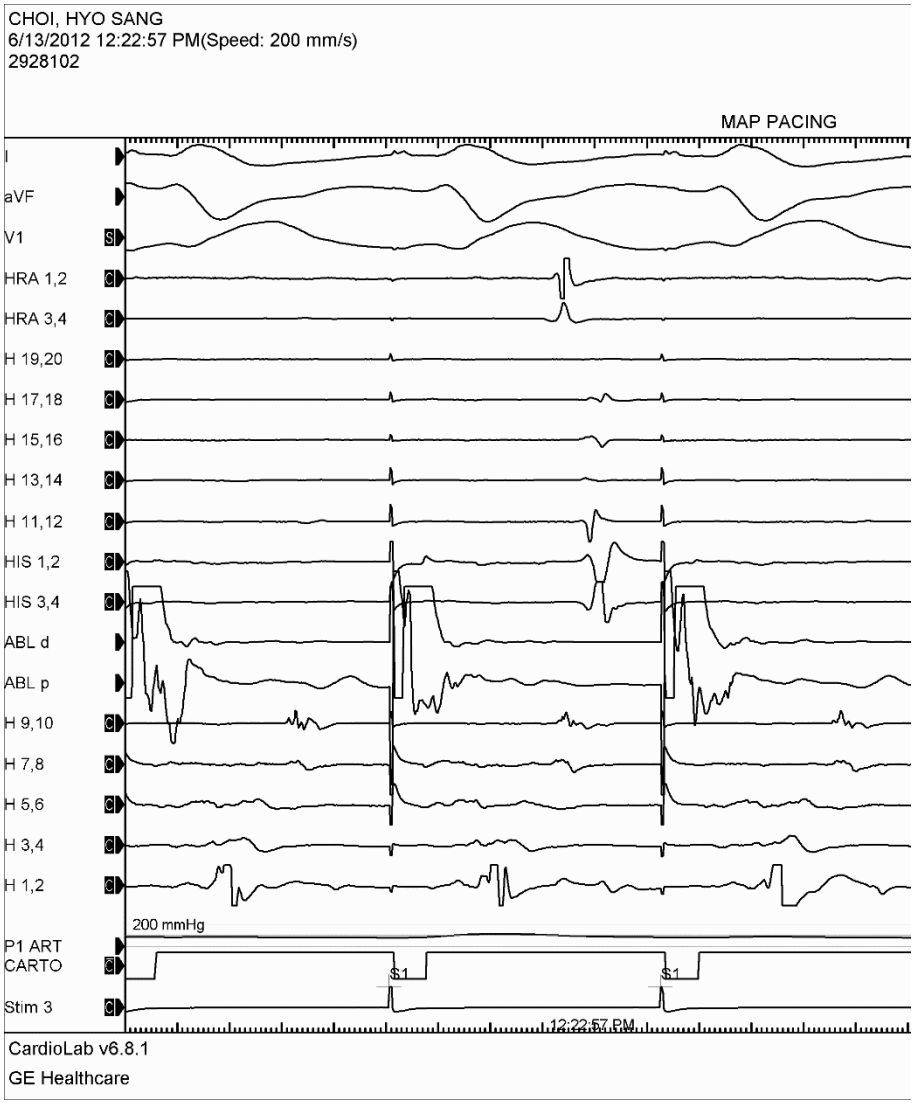


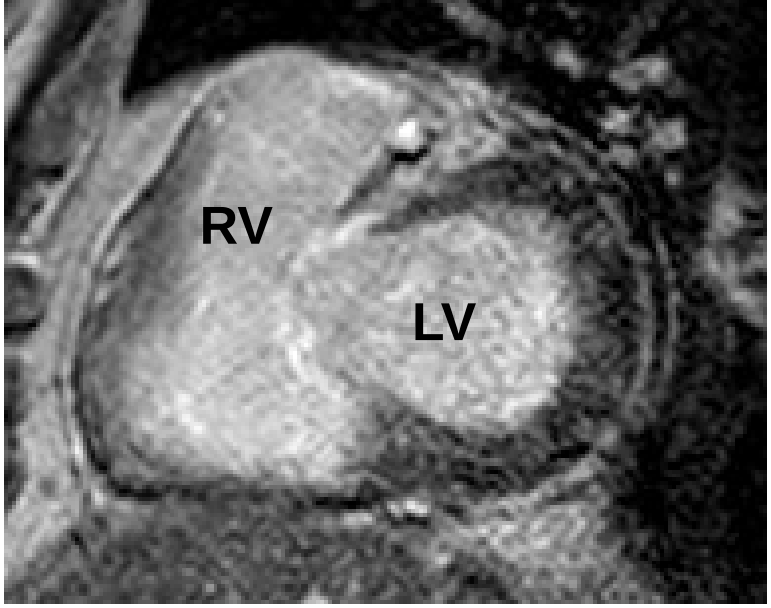


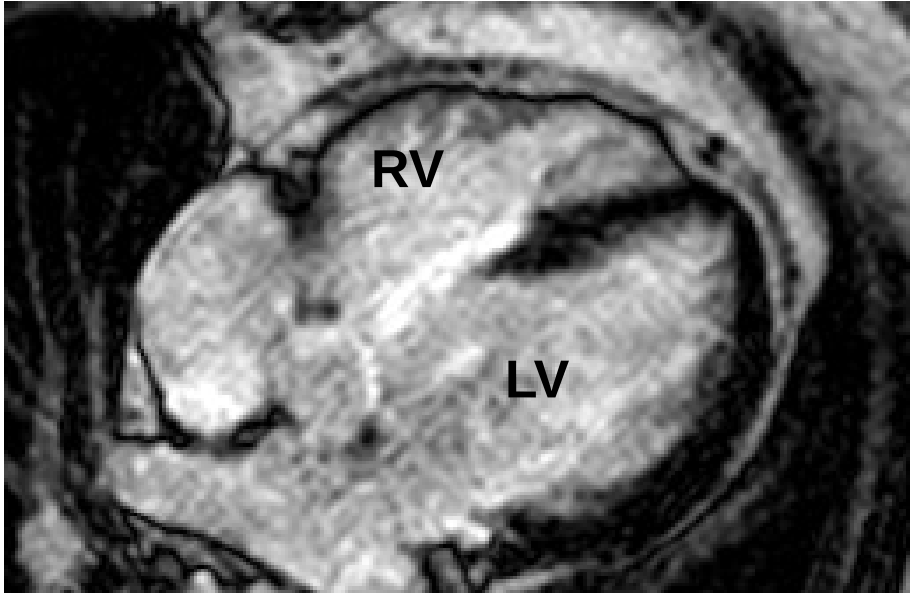


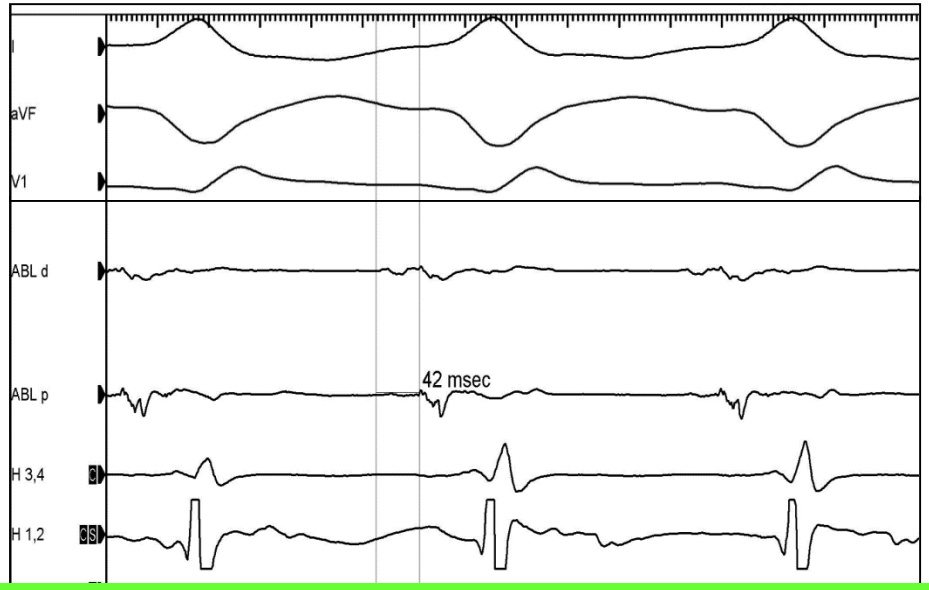
Map pacing

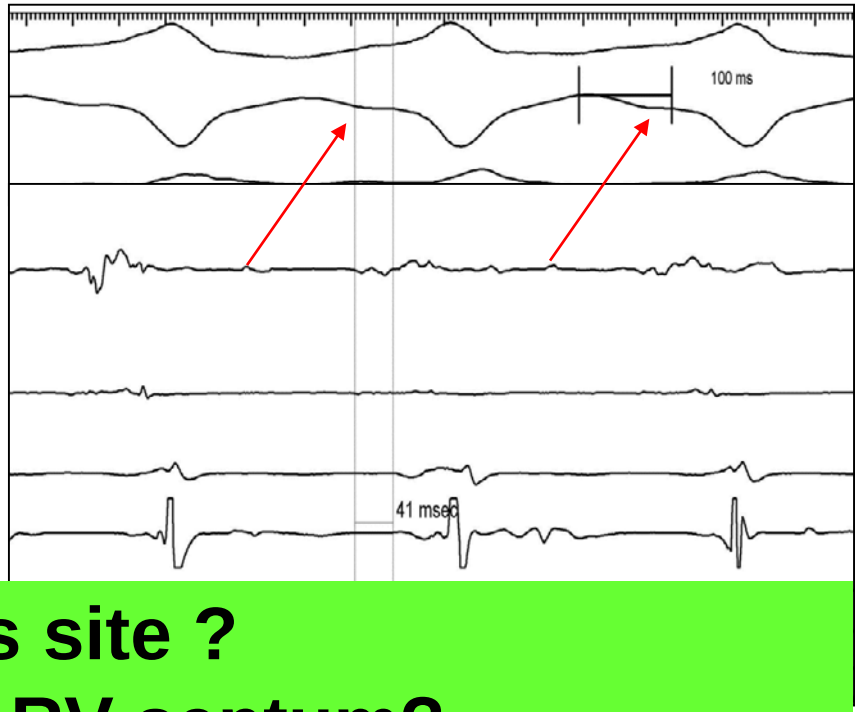

I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
200 mmHg
P1 ART


CHOI, HYO SANG
6/13/2012 12:22:57 PM(Speed: 200 mm/s)
2928102
MAP PACING
I
aVF
V1
HRA 1,2
HRA 3,4
H 19,20
H 17,18
H 15,16
H 13,14
H 11,12
HIS 1,2
HIS 3,4
ABL d
ABL p
H 9,10
H 7,8
H 5,6
H 3,4
H 1,2
200 mmHg
P1 ART
CARTO
Stim 3
S1
S1
12:22:57 PM
CardioLab v6.8.1
GE Healthcare









Q. Success site ?

1) LV septum, 2) RV septum?

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Pattern of late gadolinium enhancement predicts arrhythmic events in patients with non-ischemic cardiomyopathy

Dong Geum Shin [a,1], Hye-Jeong Lee [b,1], Junbeom Park [c], Jae-Sun Uhm [a], Hui-Nam Pak [a], Moon-Hyoung Lee [a], Young Jin Kim [b,*], Boyoung Joung [a,*]

[a] Division of Cardiology, Yonsei University College of Medicine, Seoul, Republic of Korea
[b] Department of Radiology, Research Institute of Radiological Science, Yonsei University College of Medicine, Seoul, Republic of Korea
[c] Department of Cardiology, School of Medicine, Ewha Womans University College, Seoul, Republic of Korea

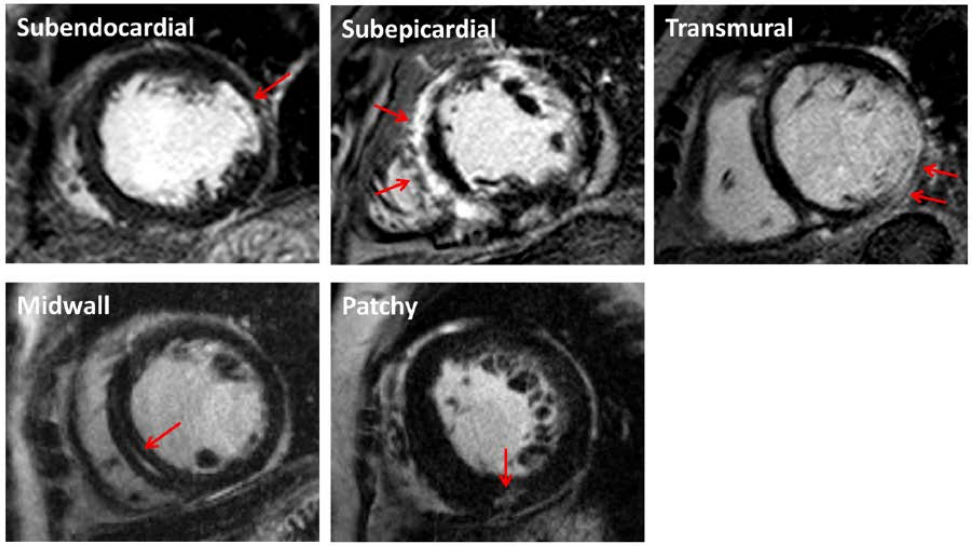
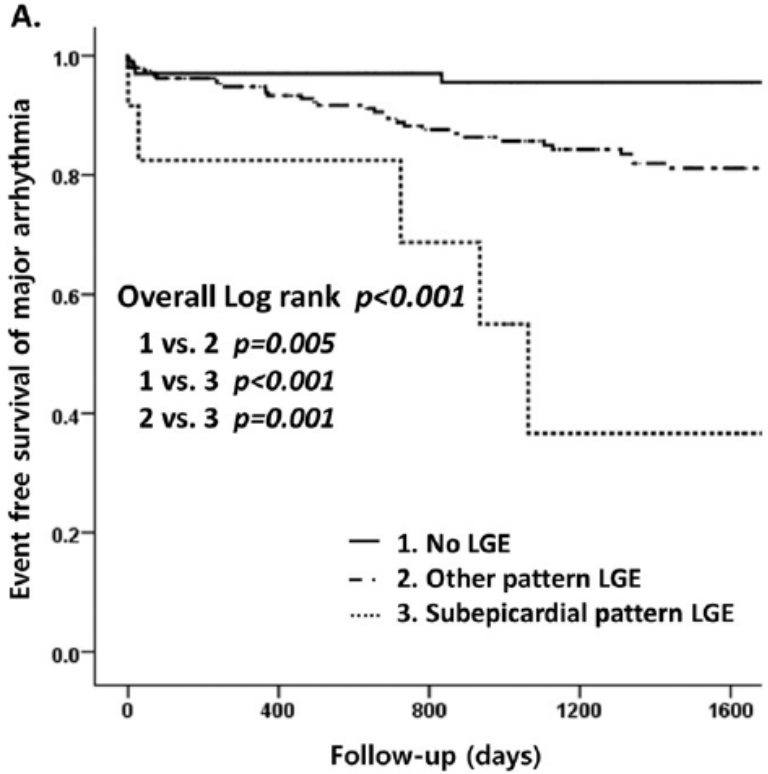


Fig. 1. Examples of patterns of left ventricular late gadolinium enhancement (arrow) shown by delayed contrast-enhanced short-axis cardiac magnetic resonance imaging.



Summary

1. Idiopathic VT
   - Outflow tract VT는 cAMP-mediated triggered activity가 관여하며, 다른 이온 채널 구성을 보인다.
   - Purkinje cells are important arrhythmic triggers, Initiation and Maintenance of VF and PVT.
2. Ischemic VT는 slow conduction을 유발하는 substrate가 관여한다.
3. Non-ischemic VT
   - ARVC는 plakoglobin re-distribution, gap junction remodeling, apoptosis, inflammation 등이 특징이다.
   - Brugada syndrome은 RVOT epicardium EGM 이상과 연관된다.

Thank you for your attention!