Mechanism of atrial fibrillation

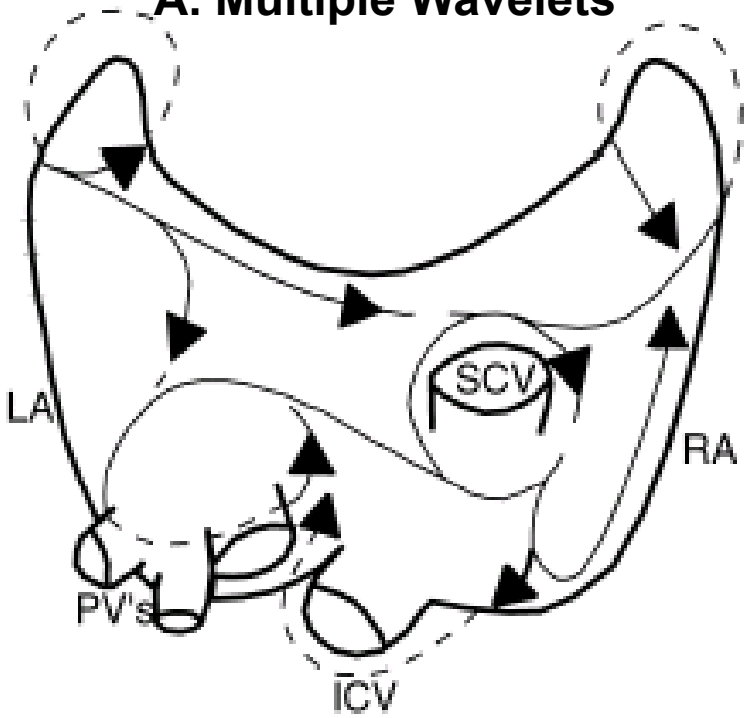
연세대학교
정보영

Mechanism of atrial fibrillation

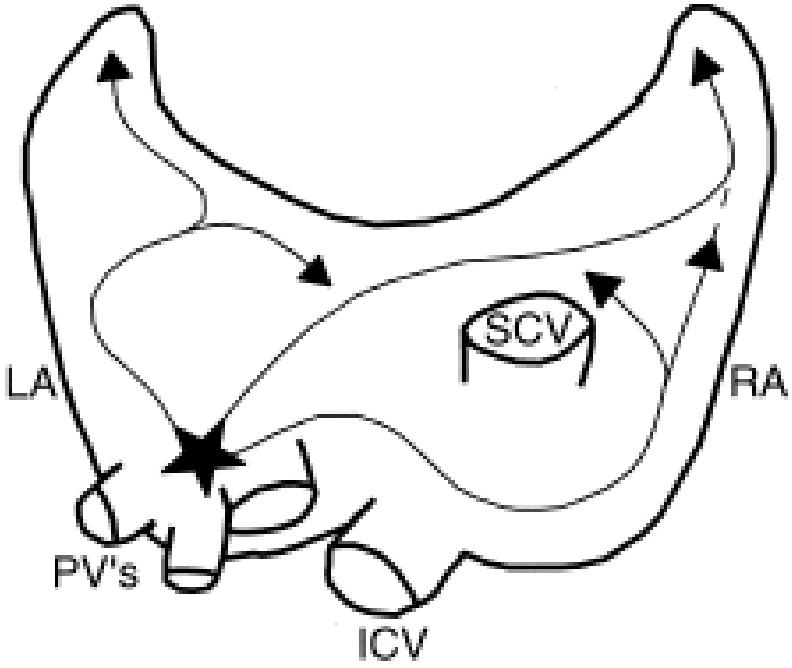
- **1. Rotors and wavelets**
- **2. Electrical, contractile and structural remodeling**
- **3.** 세포내 칼슘 대사 변화
- **4. Modulating factors**

Principal electrophysiological mechanisms of AF

A. Multiple Wavelets

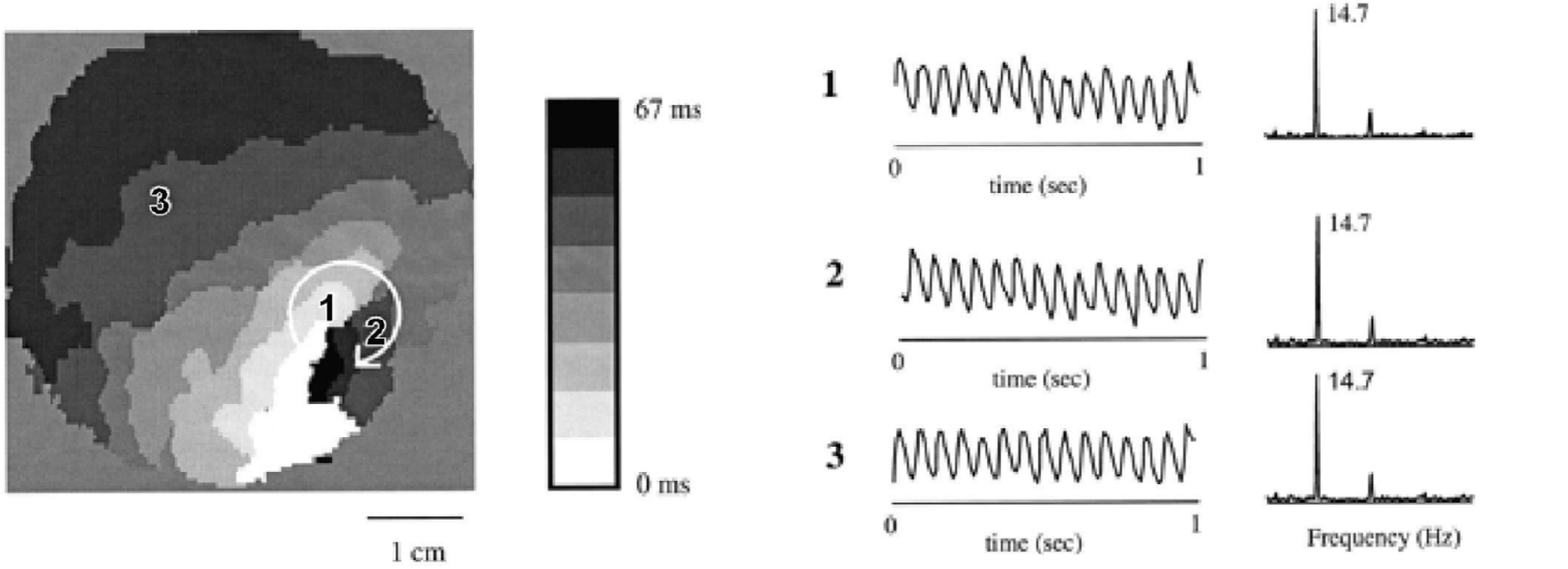


B. Focal Activation



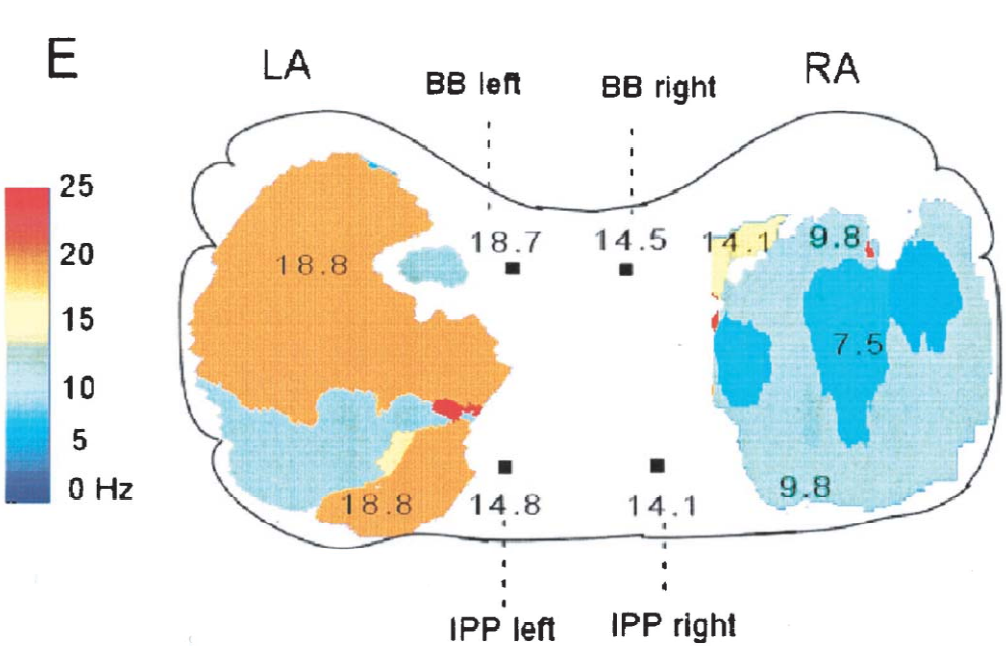
A. Moe GK. Arch Int Pharmacoldyn Ther 1962;140:183
B. Konings KTS, et al. Mapping of electrically induced AF in humans. 1999

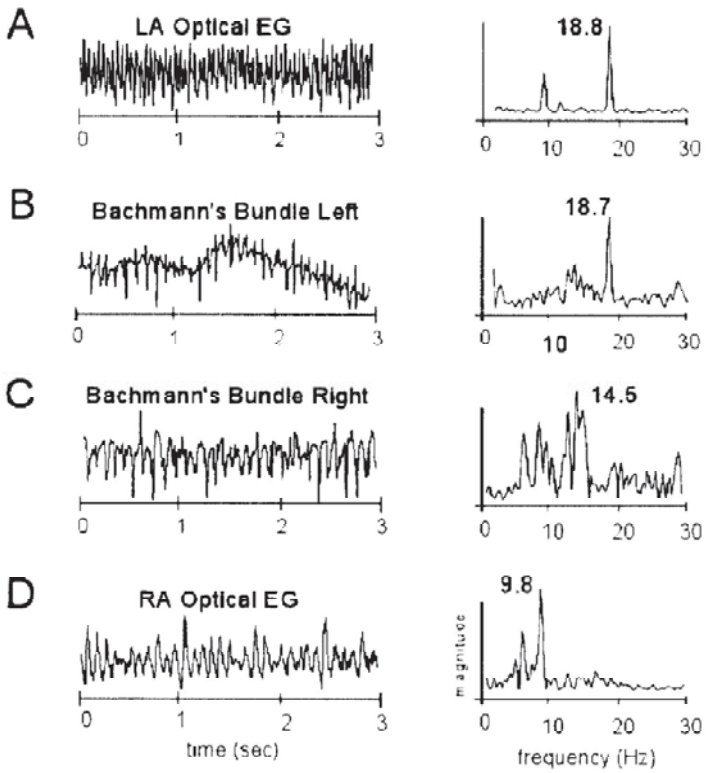
Microrentrant source of AF



Mandapati R, Jalife J. Circulation. 2000;101:194-9.

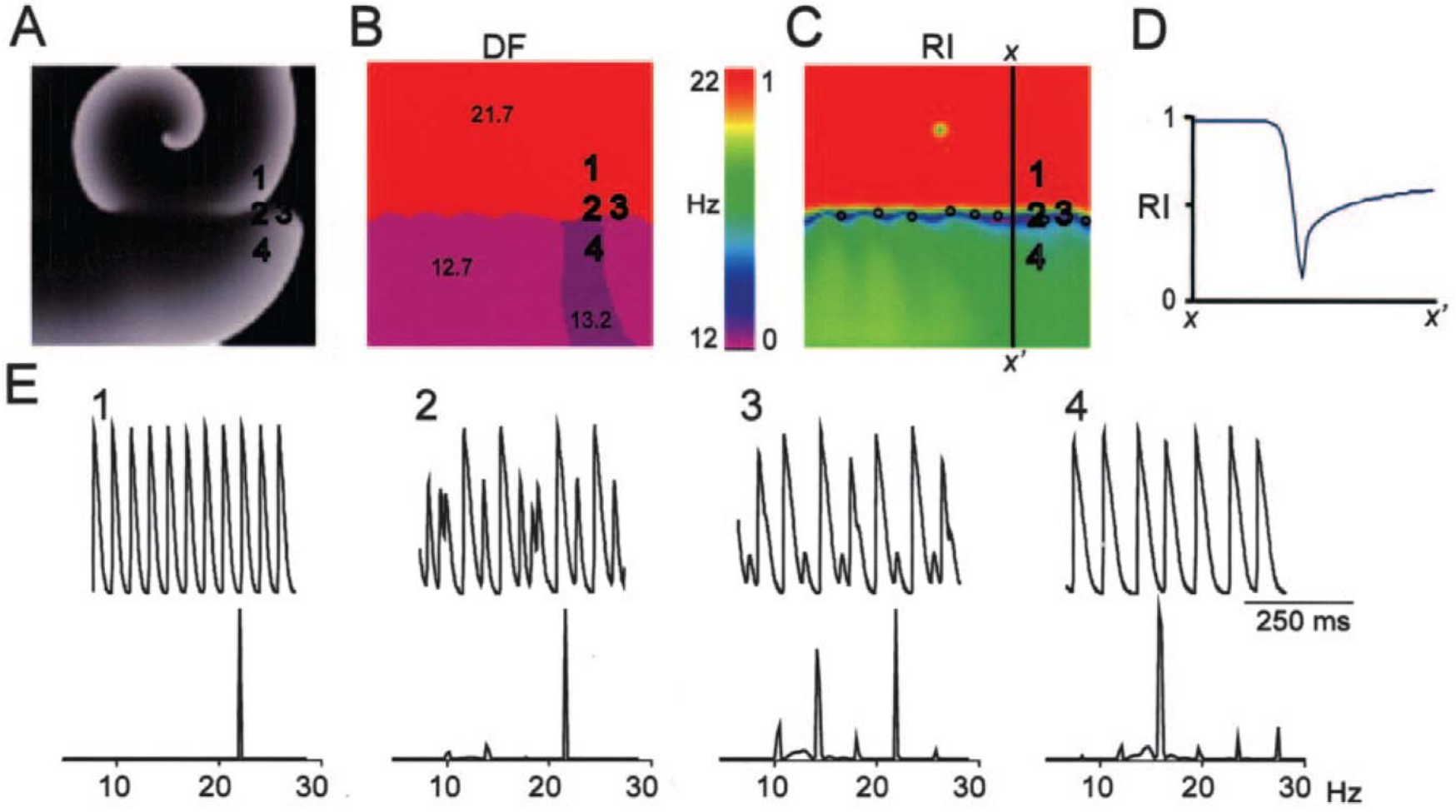
Left-to-right decrement of DFs





Mansour M, Jalife J. Circulation 2001;103:2631-6

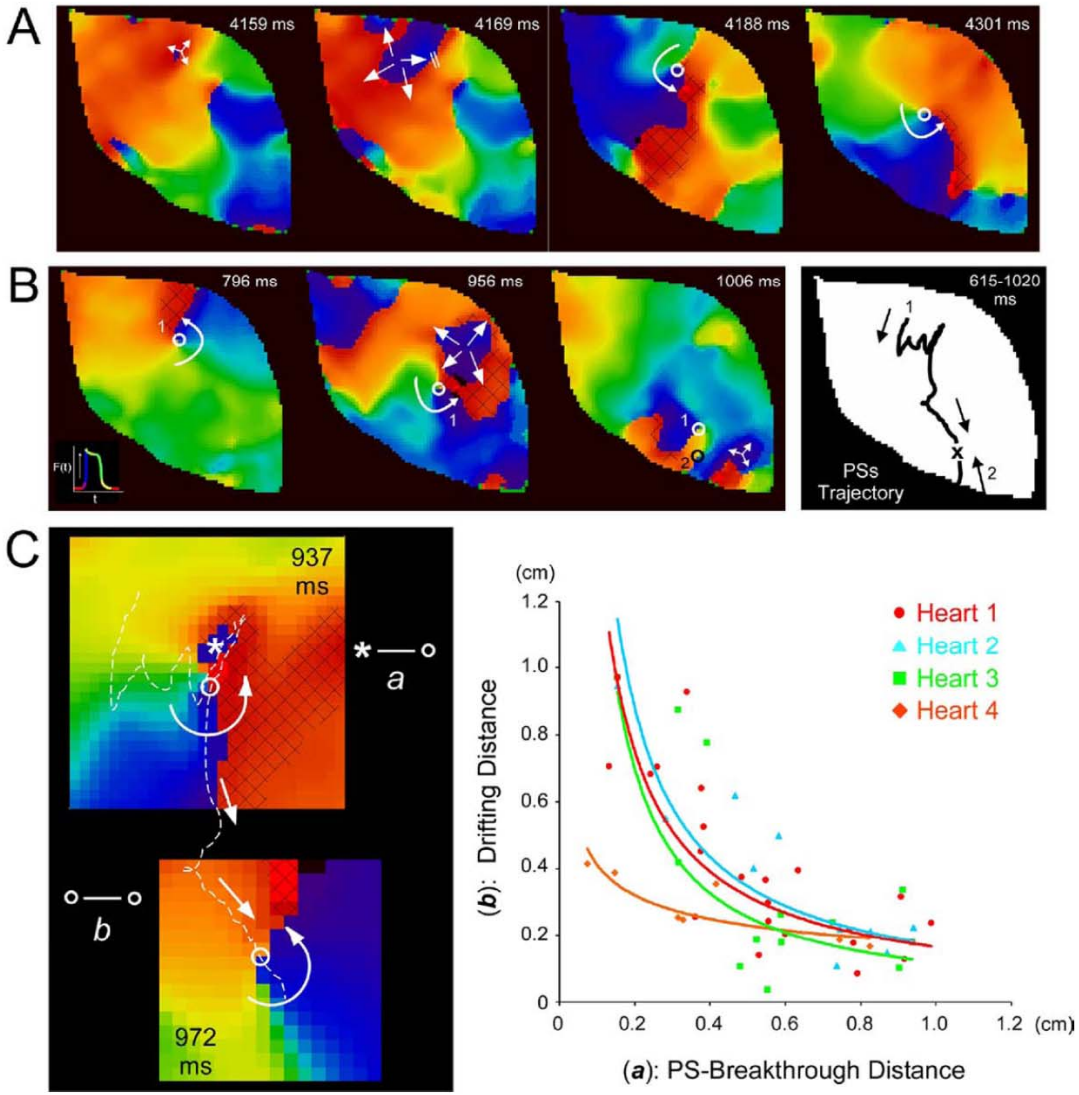
Wave Fractionation at Boundaries of High-Frequency Excitation



RI: regularity index

Kalifa J. Circulation. 2006;113:626-633

Breakthroughs induce wave break, rotor drifting, and termination



Yamazaki M, Heart Rhythm 2009;6:1009 –1017

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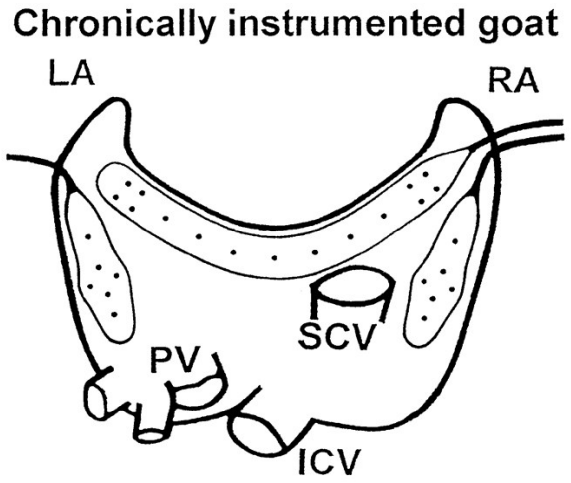
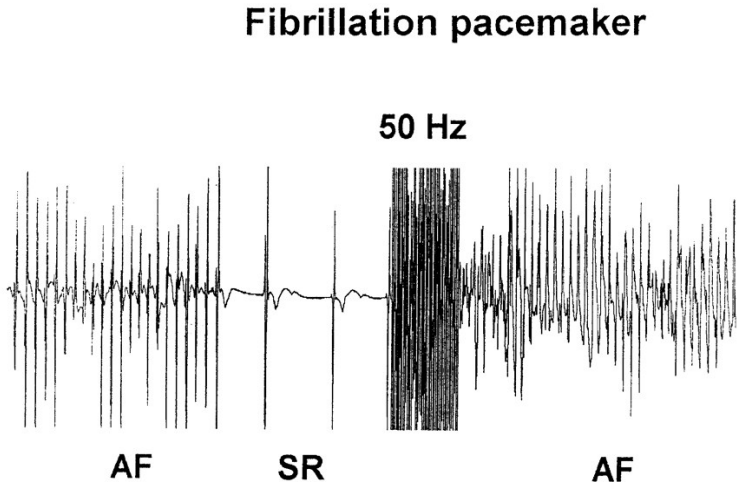
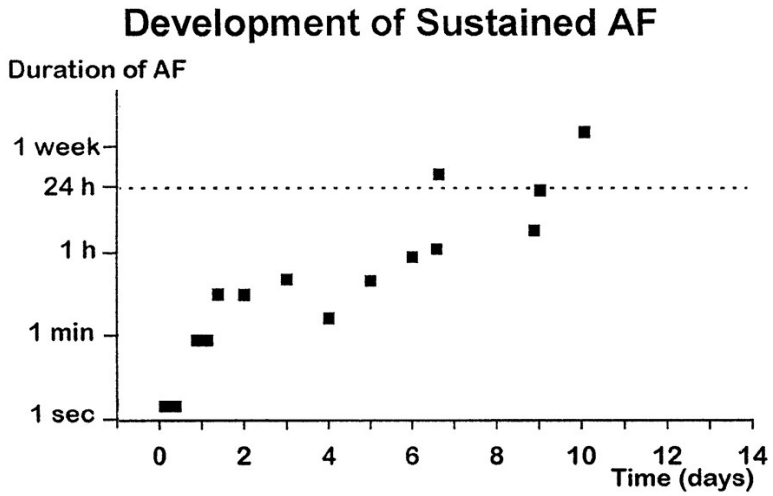
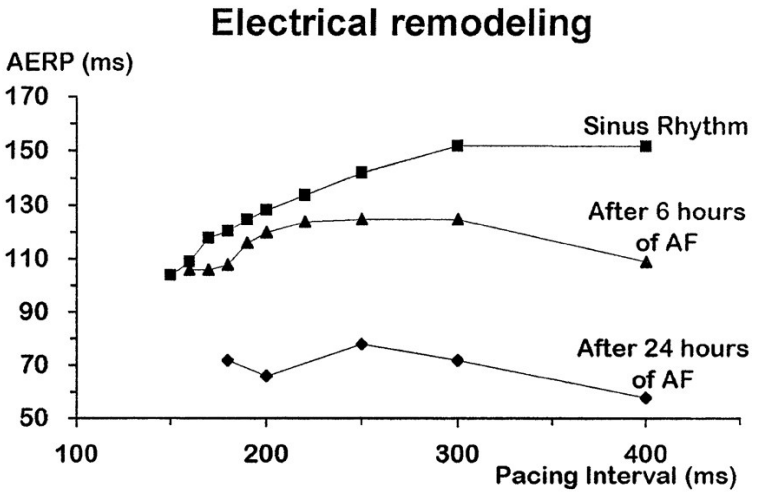
Changes in tissue electrical properties

"Atrial Fibrillation Begets Atrial Fibrillation"



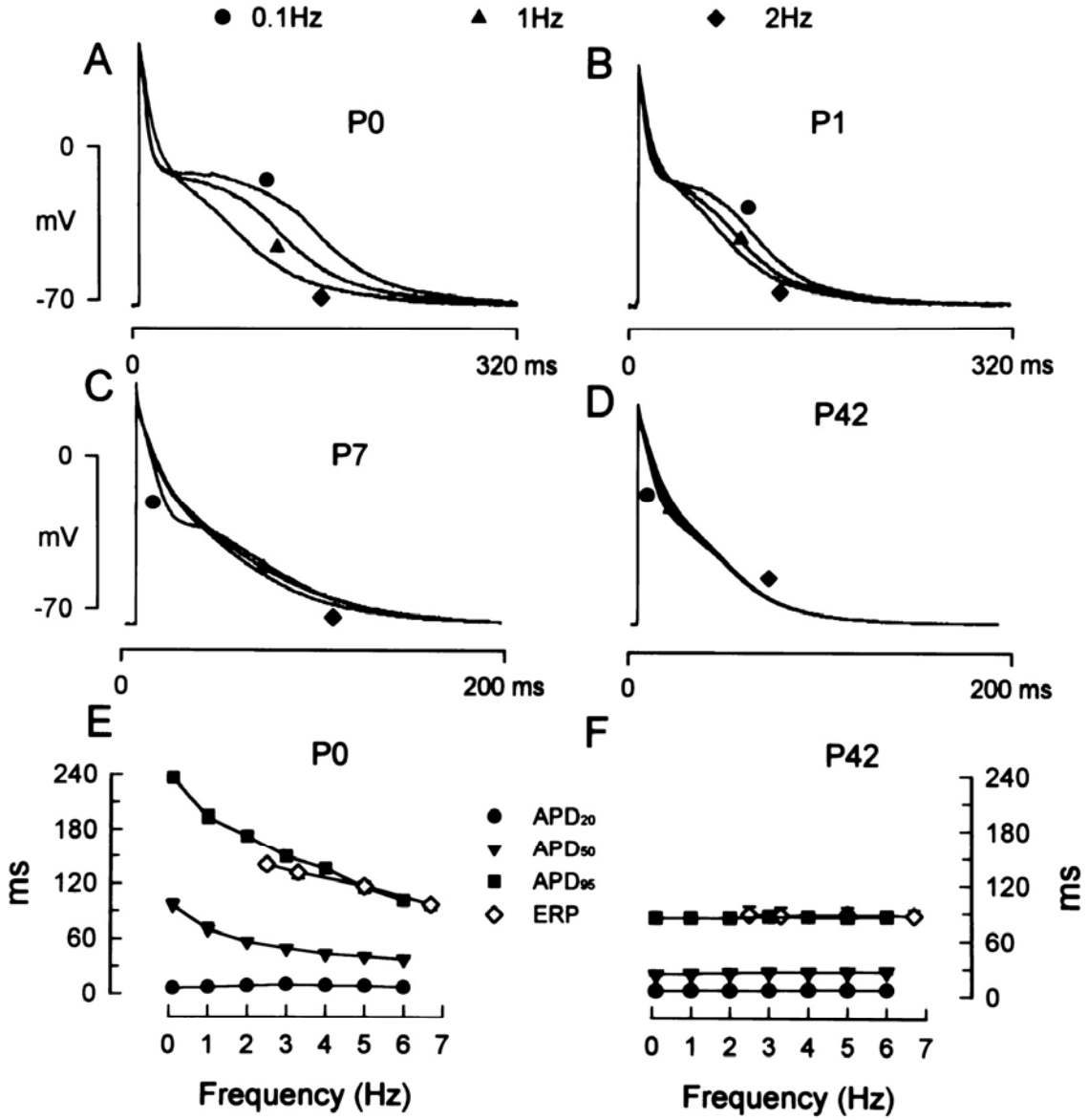






Wijffels M, et al. Circulation. 1995;92:1954-1968

Underlying cellular and ionic bases

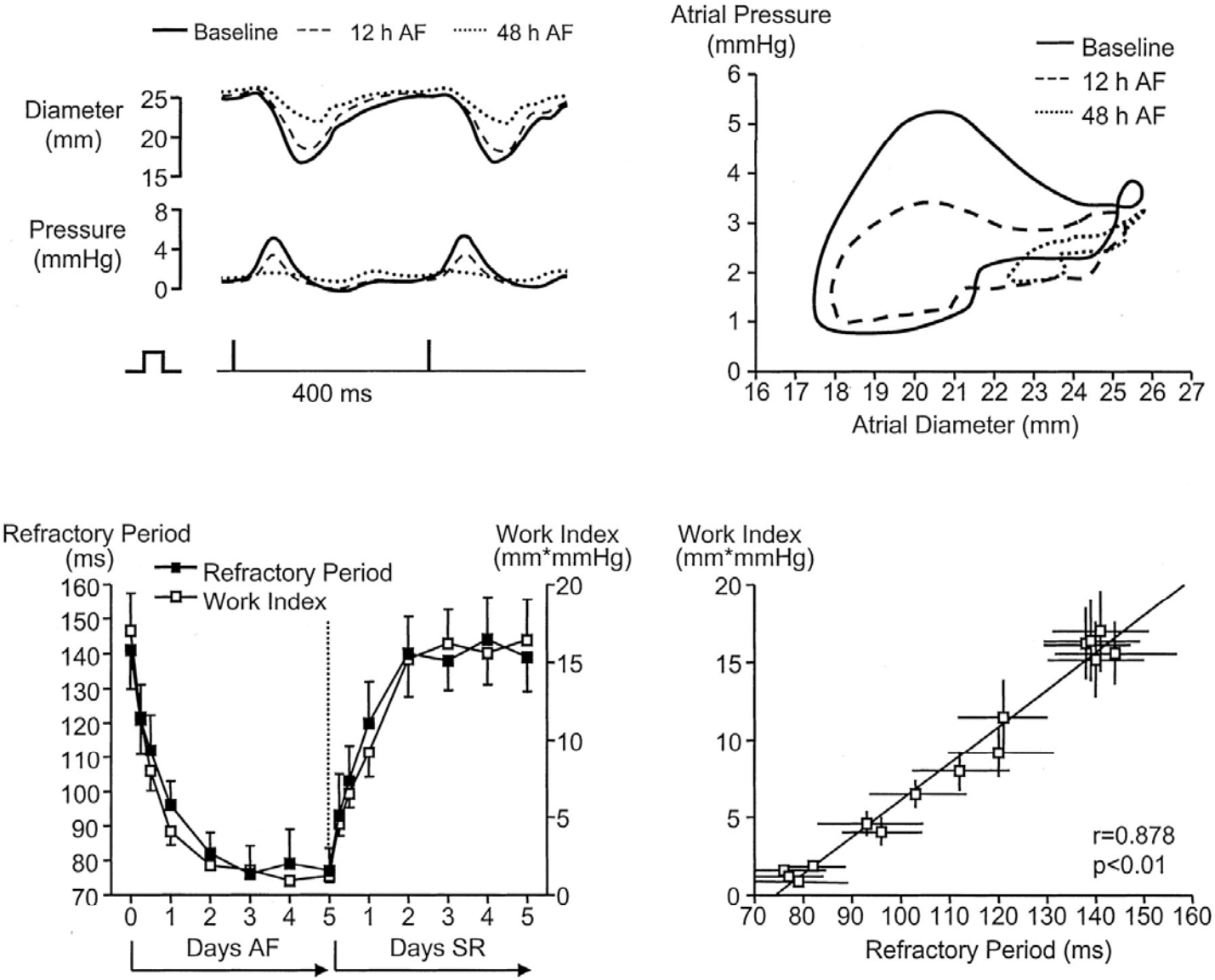


$\downarrow I_{CaL}$, $\uparrow I_{K1}$, $\uparrow I_{KACH}$, $\downarrow I_{to}$, $\downarrow I_{Kur}$

$\downarrow I_{Na}$

Yue L, et al. Circulation Research. 1997;81:512-525

Time course of electrical and contractile remodeling during first days of AF



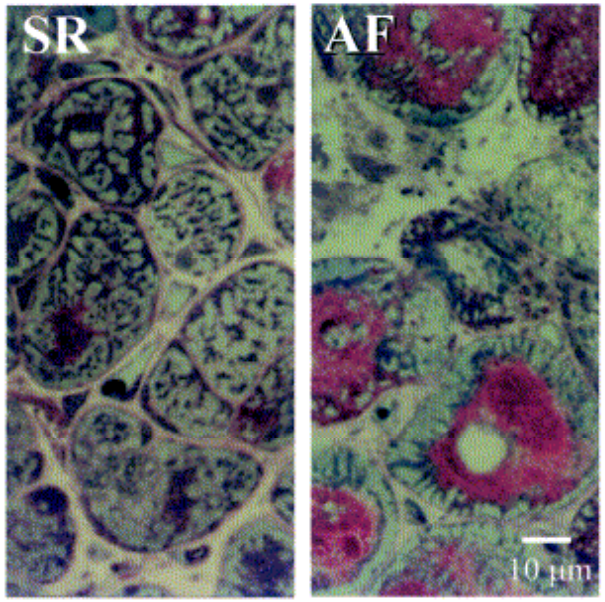
Schotten U, et al. Circulation 2003;107:1433-9

Structural remodeling of atrial myocytes after 4 months of AF in the goat

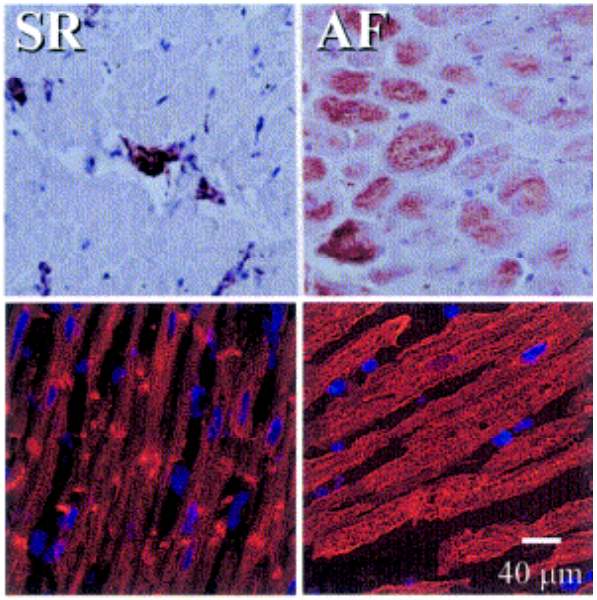
1. Loss of sarcomeres (blue) and accumulation of glycogen (red)
2. fetal α–smooth muscle actin (red) desmin (red) nuclei (blue DAPI).
3. Cx40 (green) and Cx43 (red)
4. Chromatin (arrow) small donut shape mitochondria (arrow head)

Ausma et al. Circulation 1997;96:3157-3163
Van der Velden et al. J Cardiovasc Electrophysiol 2000;11:1262-1269

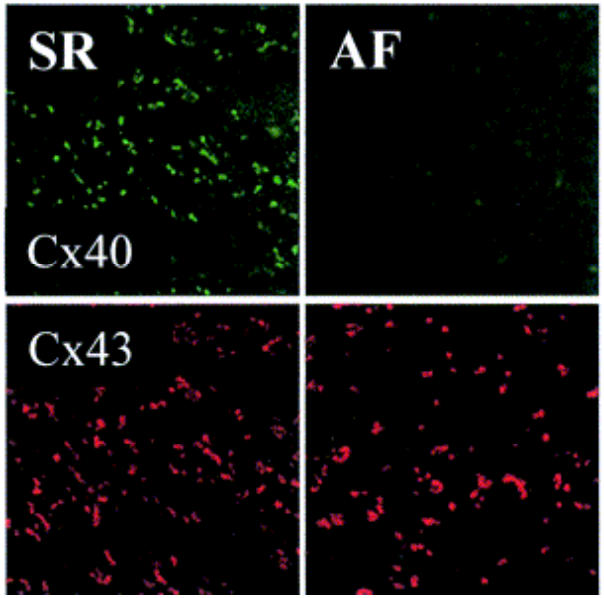
Myolysis



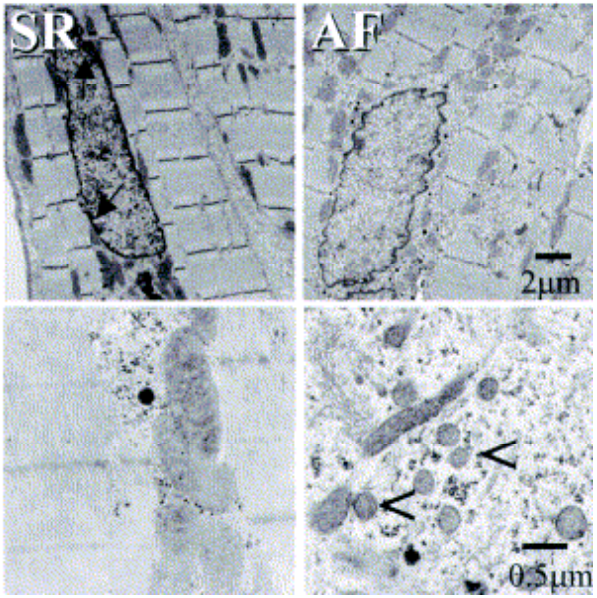
Dedifferentiation



Connexins



Ultrastructure



Changes in connexin expression in AF and atrial tachycardia remodeling

Reference	Cx40	Cx43	Population (n)*	Remarks
			Experimental studies	
Elvan et al. (86)	ND	P↑	ATR dogs (AV block for rate control)	
Van der Velden et al. (327)	M/P↔	M/P↔	AF-induced ATR goats	Heterogeneous Cx40 in AF
Van der				40/43 P
Sakabe				staining
Polontc				dxn (rats)
Dupont				
Kostin				
Nao et				
Kanagaratnam et al. (143)	P↔	P↔	CAF (13) vs. SR (27)	Increased Cx40 heterogeneity in AF
Wetzel et al. (341)	P↑	P↑	Lone AF (43); CAF-MVD (31); SR (15)	LA tissue
Wilhelm et al. (344)	P↓	P↔	CAF (12); post-op AF (12); SR (20)	Cx40↓ in CAF only; ↓Cx40/43 in CAF and post-op AF

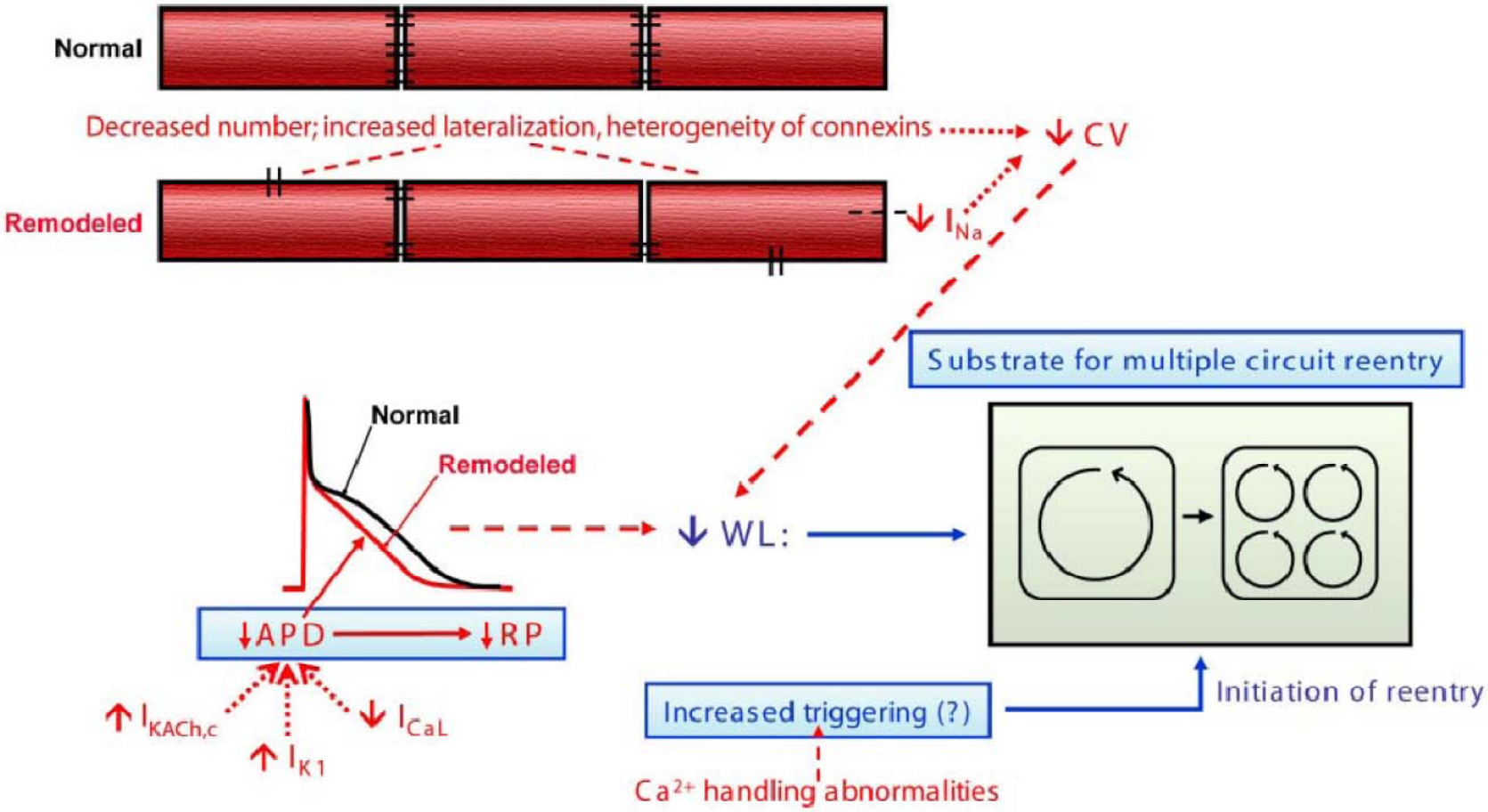
The most consistent findings of connexin changes

1. ↑ **Lateralization.**
2. ↑ **Dephosphorylation**
3. ↑ **Heterogeneity.**

P, protein; M, mRNA; ND, not done; CAF, persistent (chronic) atrial fibrillation; SR, sinus rhythm; MVD, mitral valve disease; ATR, atrial tachycardia remodeling; CHF, congestive heart failure; Cx, connexin; ↑, increase; ↓, decrease; ↔, no change. * For clinical studies, the number of patients in each group is indicated in parentheses.

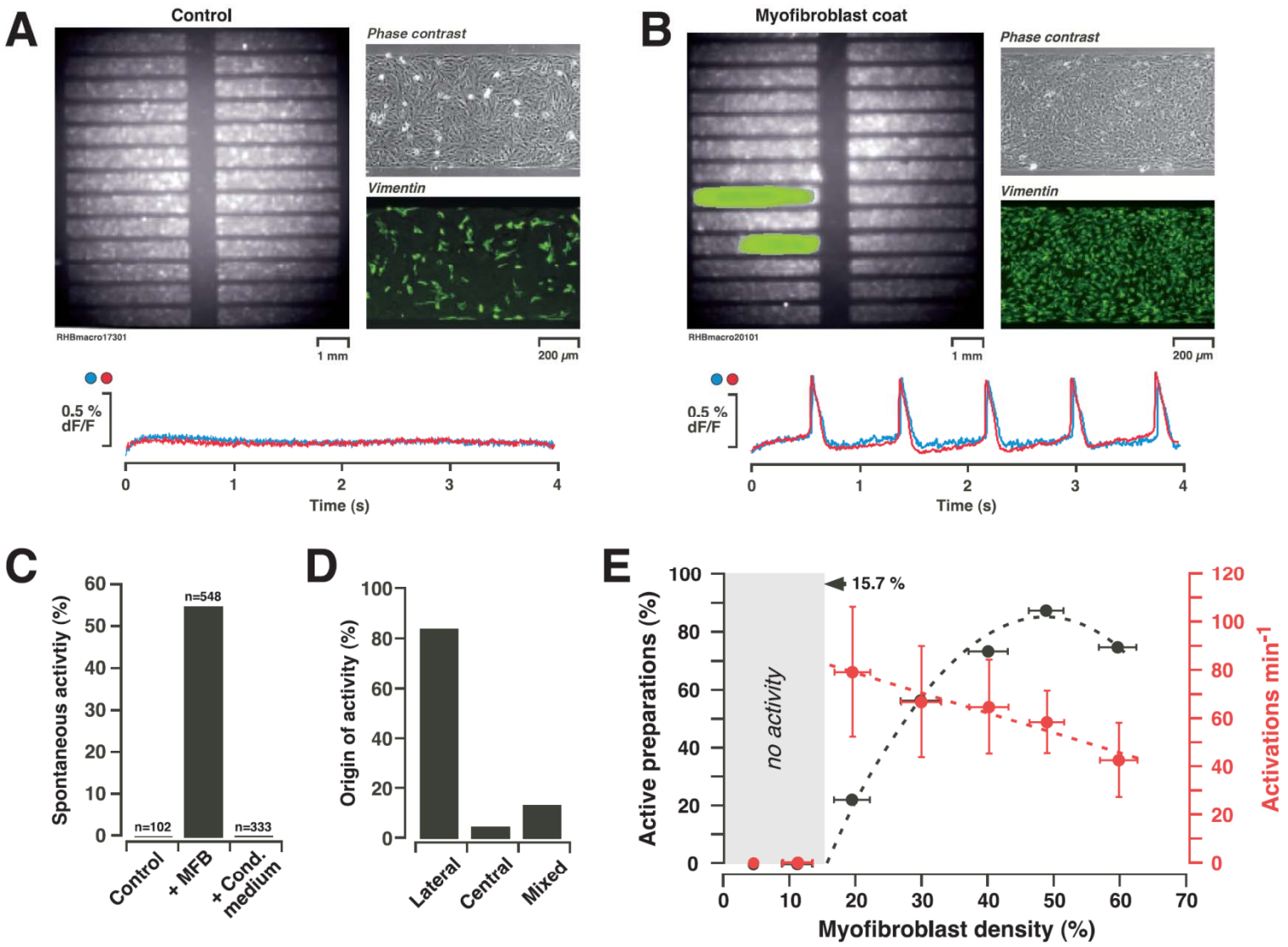
Nattel S. Physiol Rev 2007;87: 425–456

Pathophysiology of AF promotion by atrial-tachycardia remodeling



Nattel S. Physiol Rev 2007;87: 425–456

Induction of spontaneous activity in strands of cardiomyocytes by myofibroblasts



Miragoli M, Rohr S. Circ Res 2007;101:755–758.

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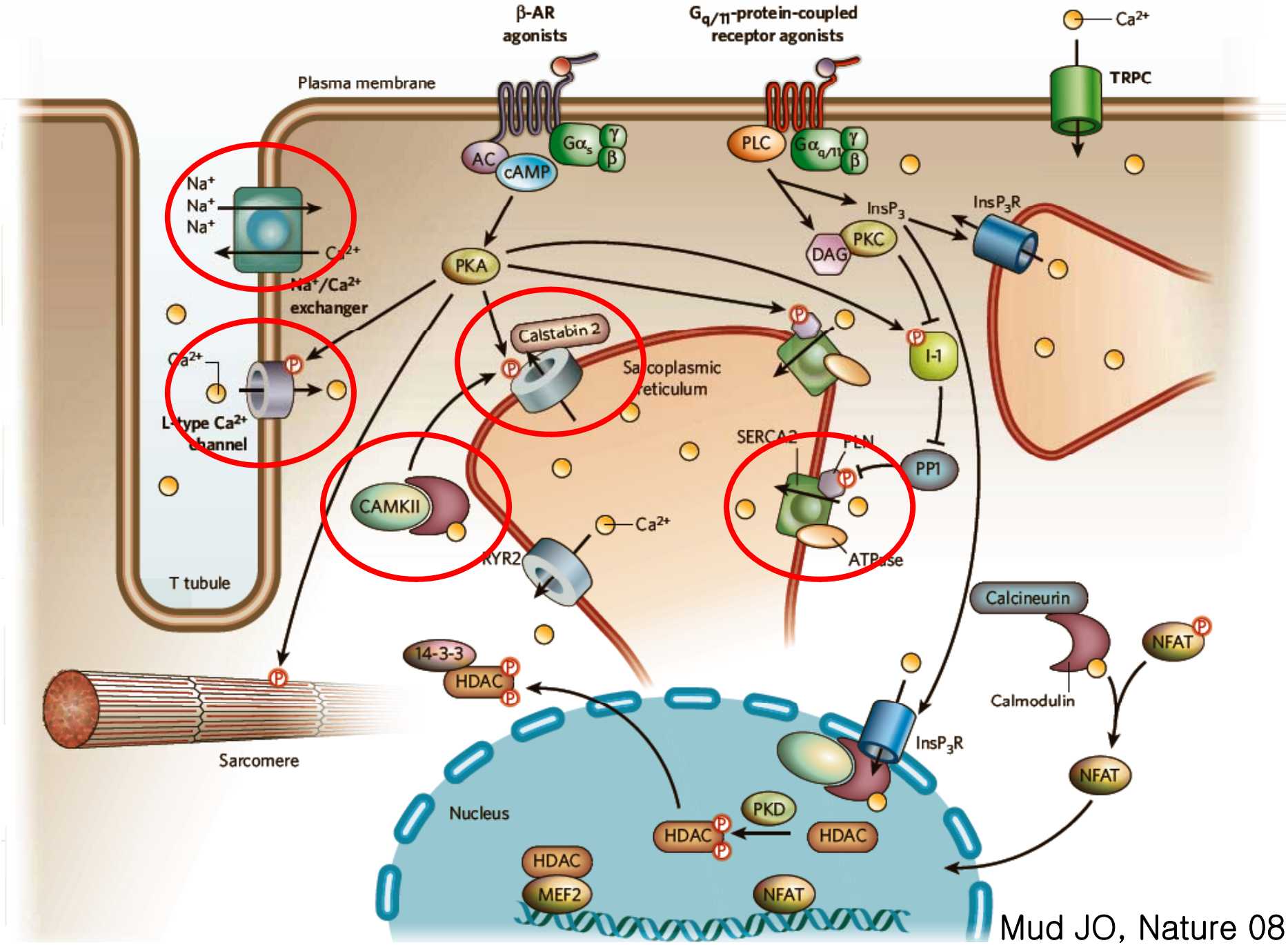
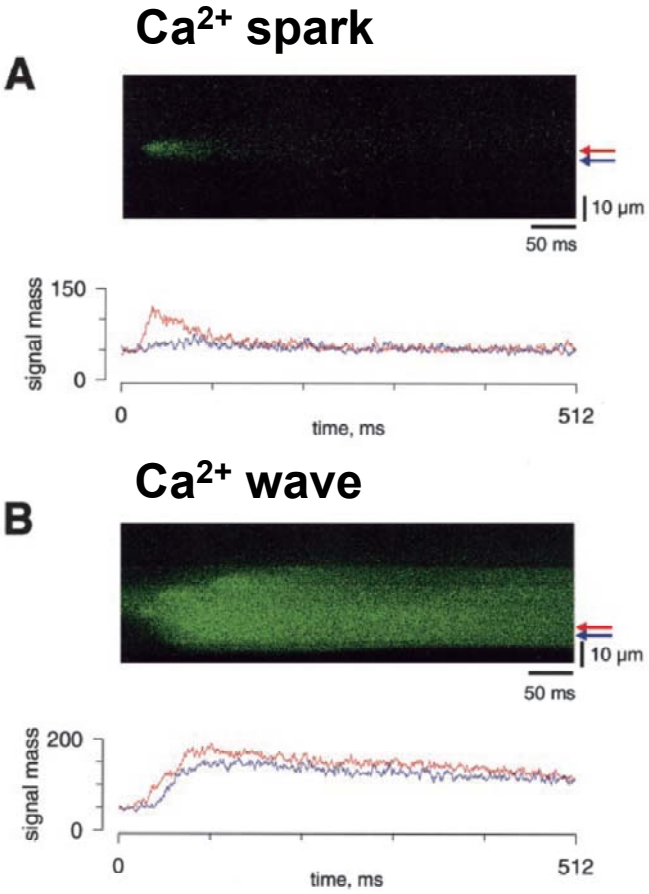
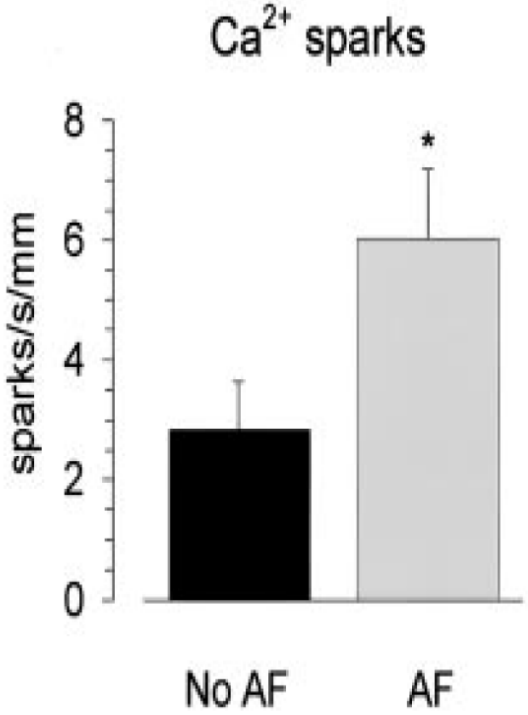
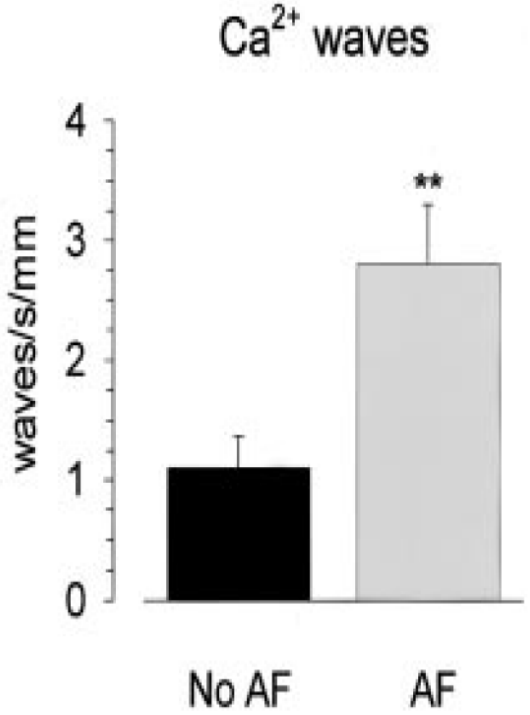


Mud JO, Nature 08

Increased SR Ca^{2+} release in Human AF

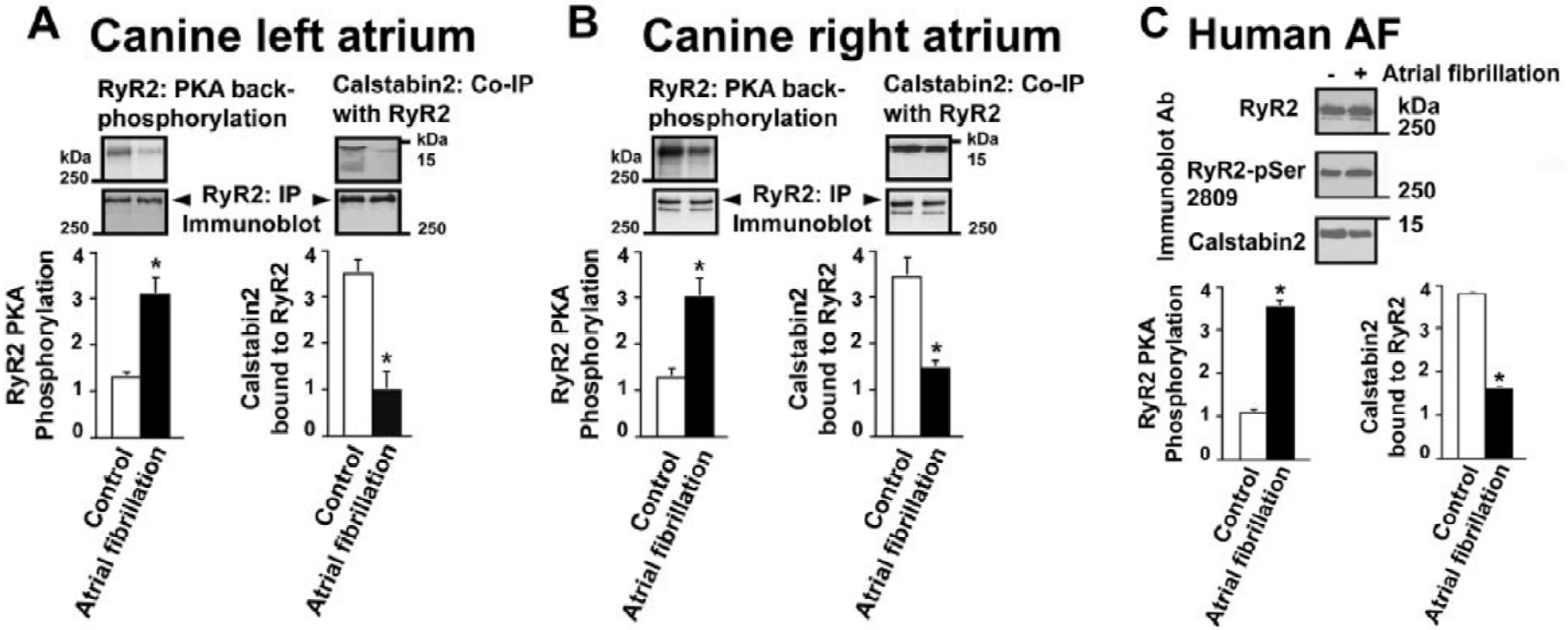






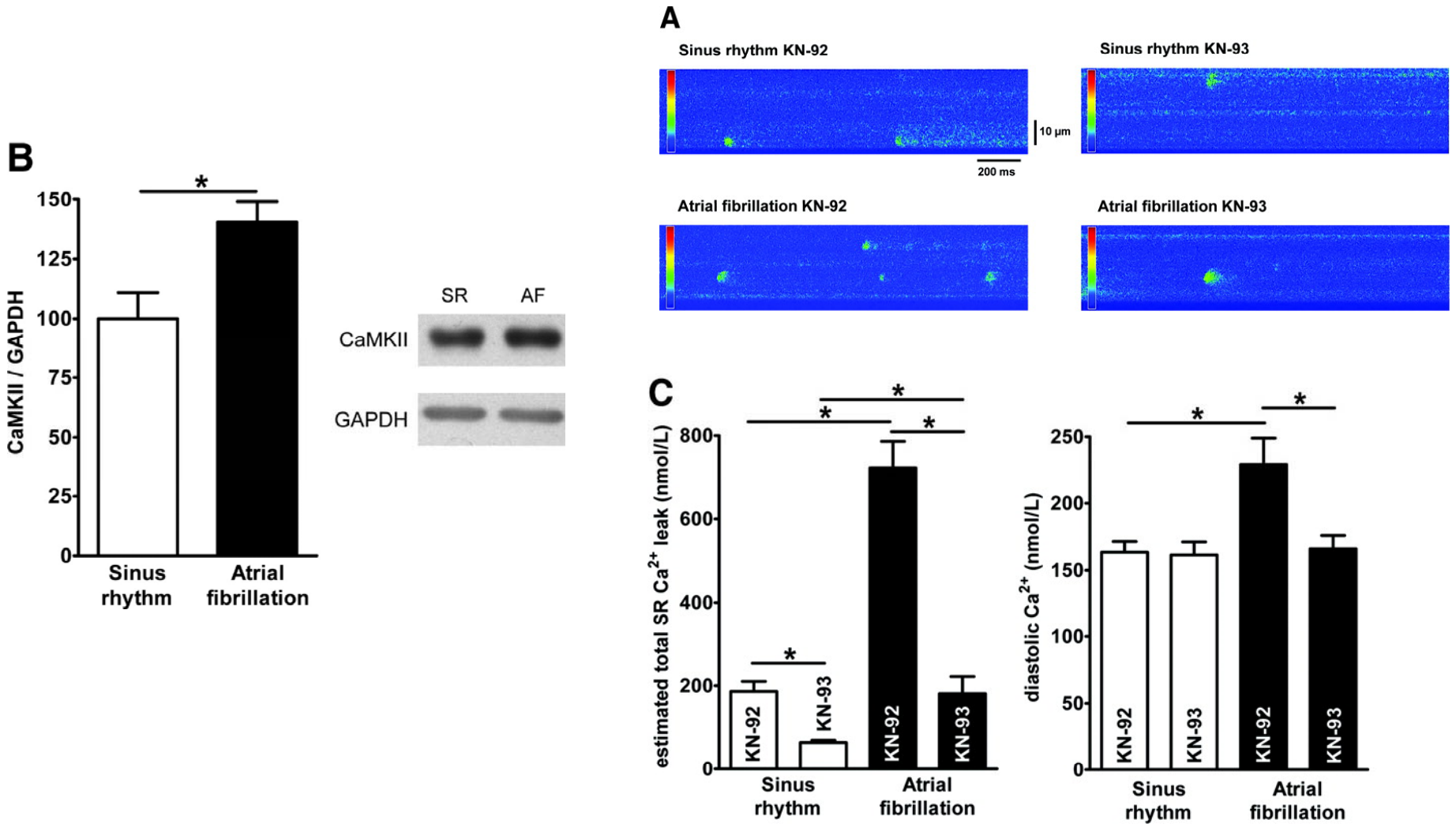
Hove-Madsen L, Circulation. 2004;110:1358-1363

PKA hyperphosphorylation of RyR2 in canine and human AF



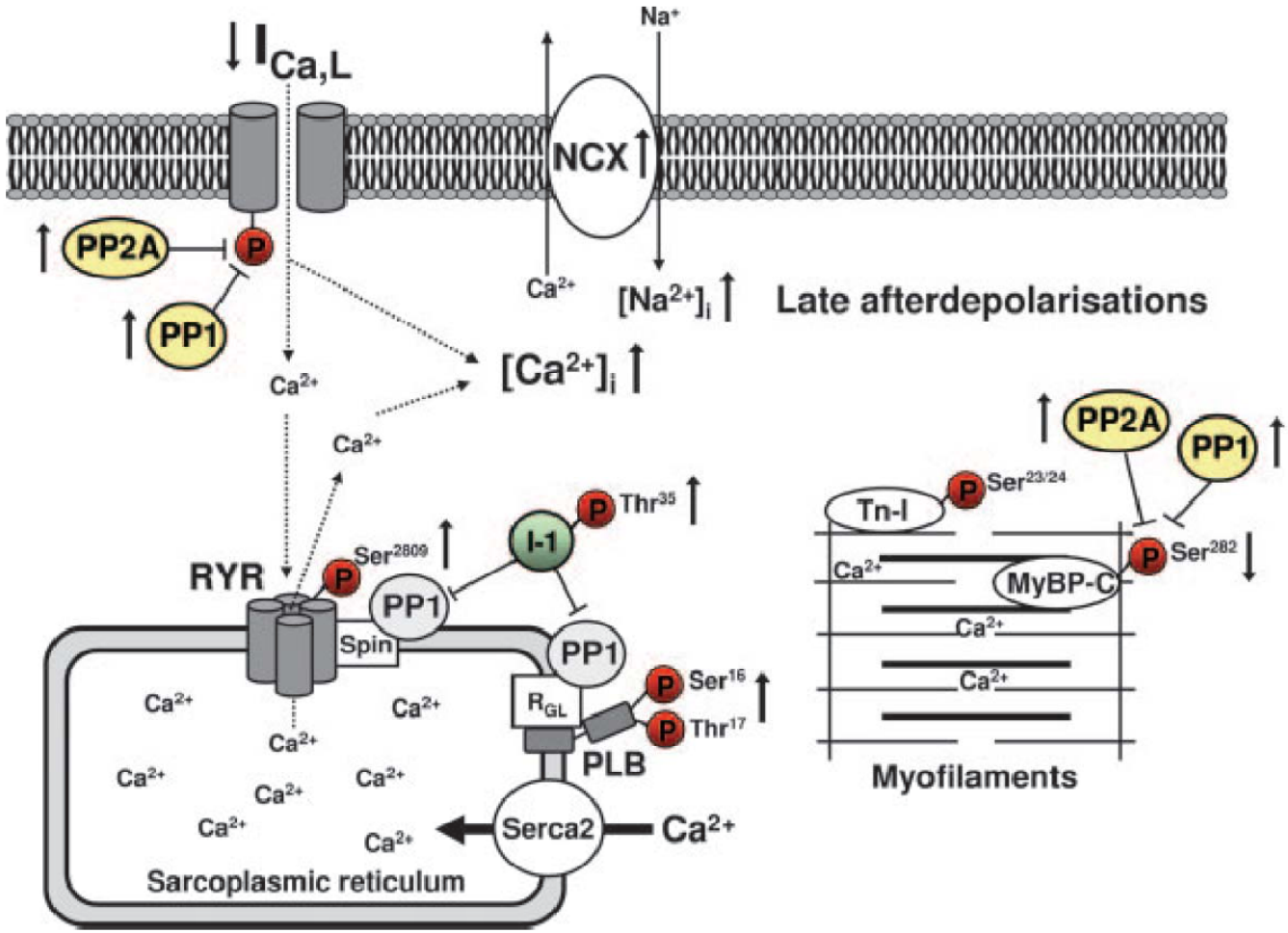
Vest J, Marks A. Circulation 2005;111:2025-32

CaMKII-Dependent Diastolic SR Ca^{2+} Leak and Elevated Diastolic Ca^{2+} Levels in RA Myocardium of Patients With AF



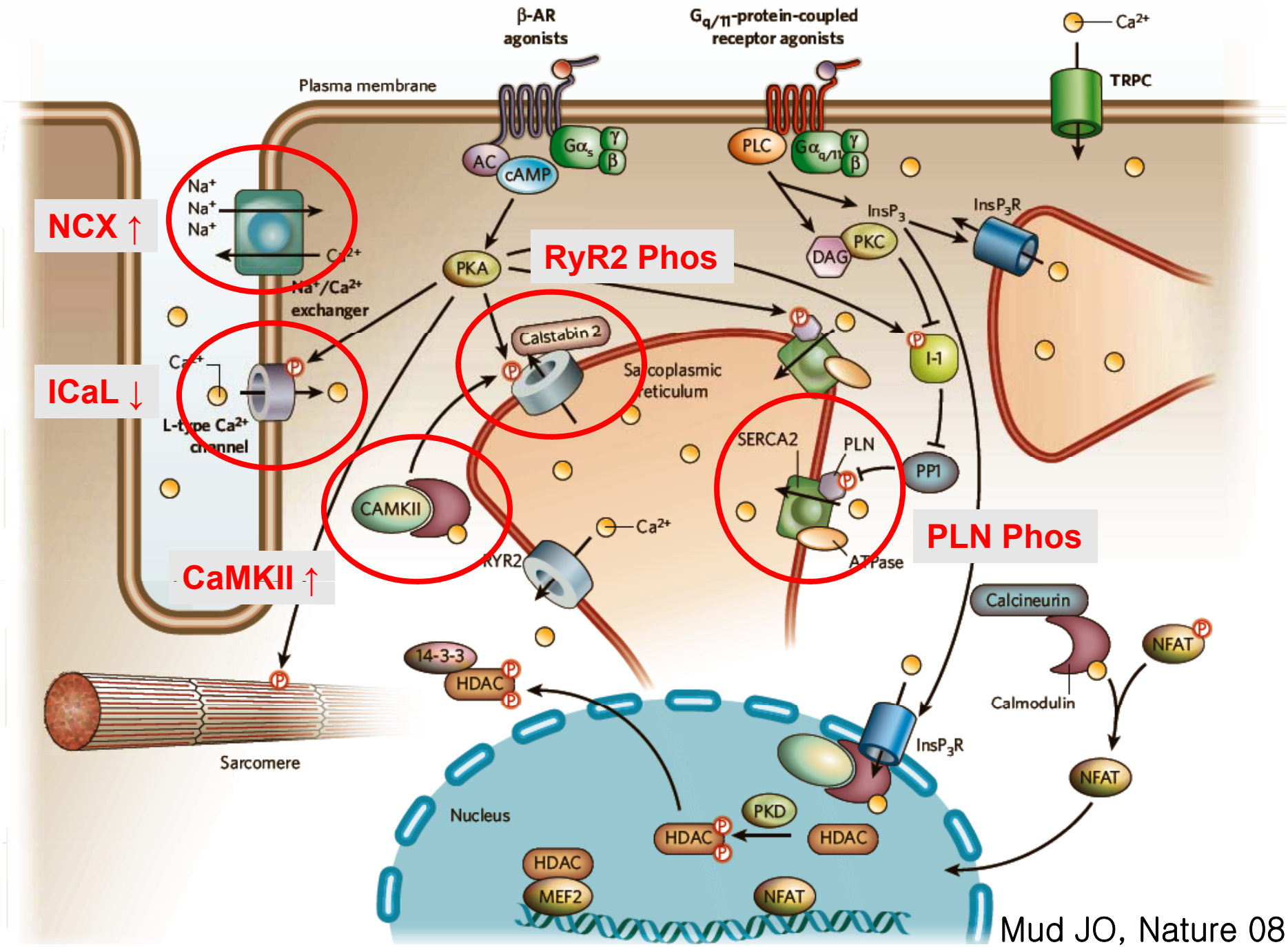
Neef S. Circ Res. 2010;106:1134

Model of impaired phosphorylation dependent regulation of Ca^{2+} handling and contractility in human cAF



- PP1: serine/threonine protein phosphatase type 1, PP2A: type 2A,
- I-1: phosphatase inhibitor-1
- Ser16 of PLB : PKA, Thr 17 of PLB : CaMKII.

El-Armouche A. Dobrev D. Circulation. 2006;114:670-680.



Mud JO, Nature 08

Table 4. Comparison of Characteristics of Arrhythmogenic Foci Between Paroxysmal and Persistent AF

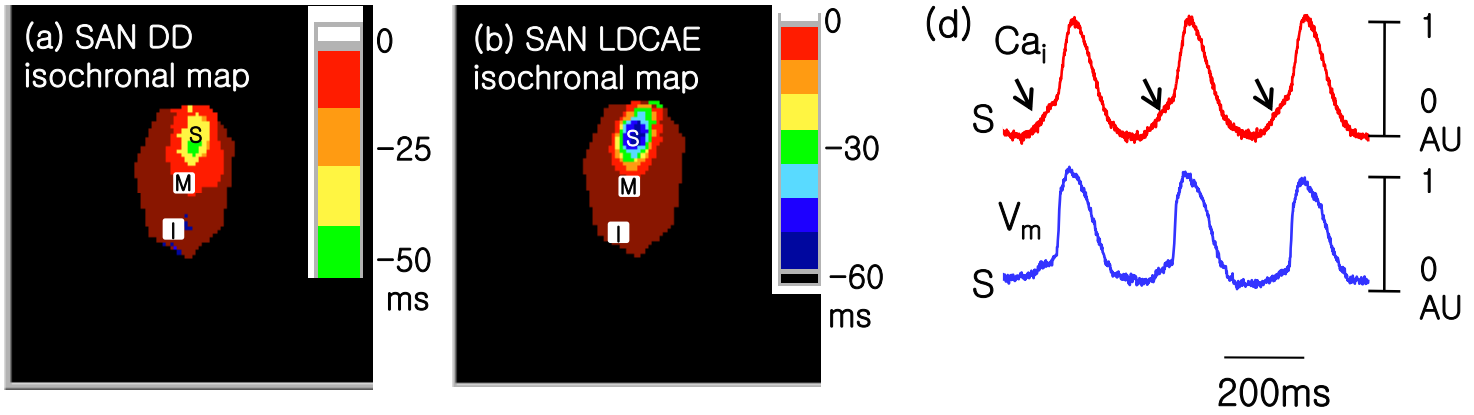
	Paroxysmal (n=170)	Persistent (n=44)	*P* Value
PV foci, %	89	93	0.40
Non-PV foci, %	45	61	0.041
Total No. of foci, counts	2.28±0.12	3.03±0.14	<0.001
No. of non-PV foci, counts	0.98±0.14	2.23±0.16	<0.001
Foci in the left atrium, %	90	96	0.26
Foci in the right atrium, %	28	56	<0.001
Multiple foci (>2)	65%	88%	0.002

No. of foci are expressed as mean±SEM.

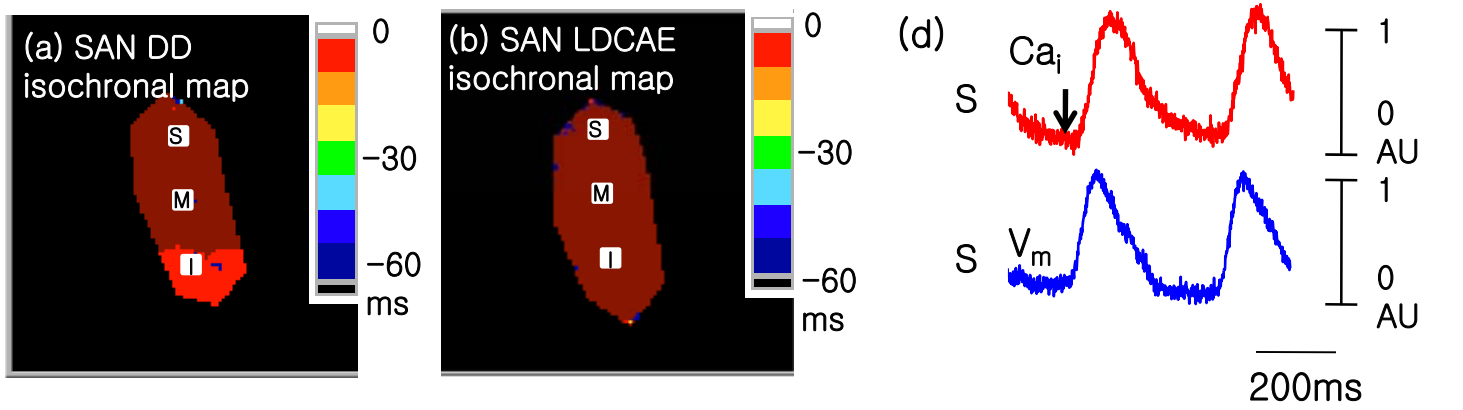
Kurotobi T. Circ Arrhythm Electrophysiol. 2010;3:39-45.

Mechanism of SAN dysfunction in AF

Control



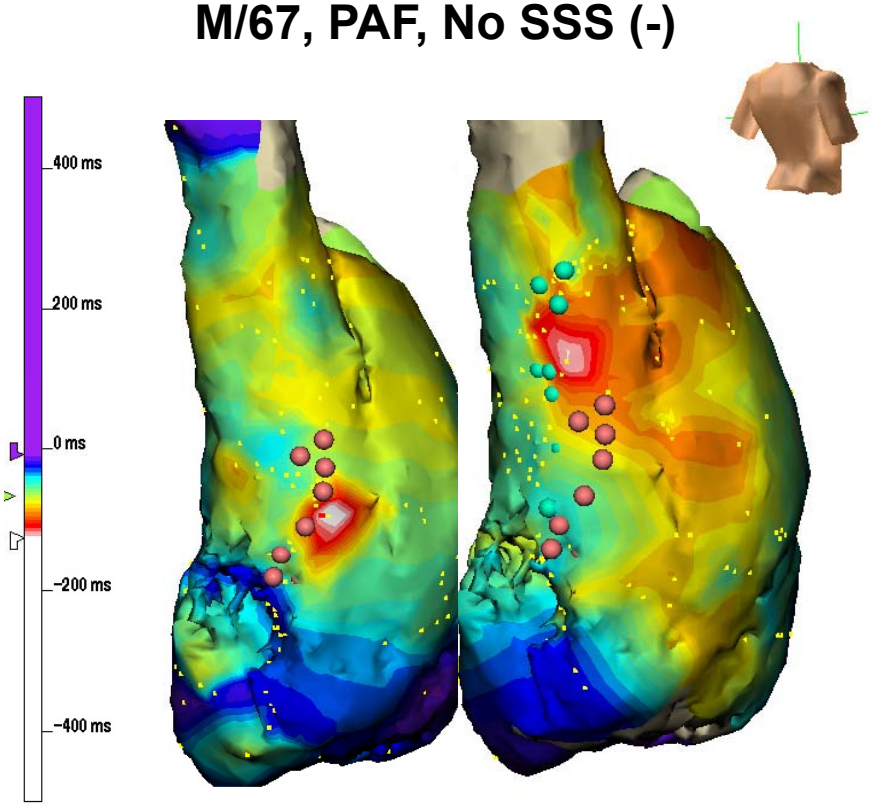
AF Dog



Joung B. Heart Rhythm 2010;7:88-95

Impaired Response of SAN in Human AF with SSS

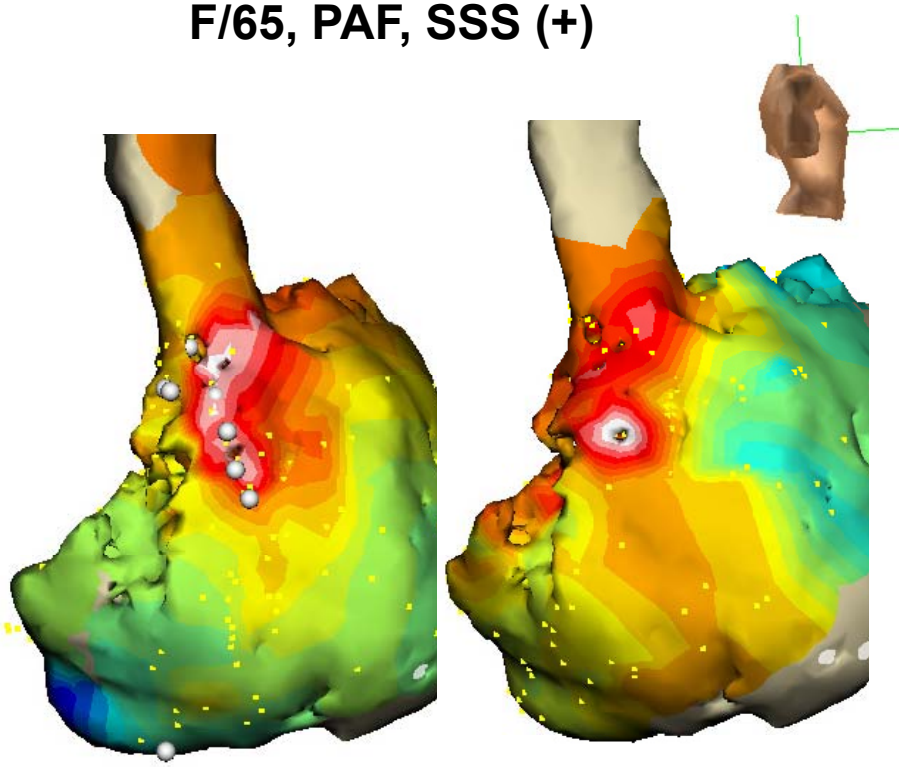
M/67, PAF, No SSS (-)



Baseline
HR 80 bpm

ISO
HR 130 bpm

F/65, PAF, SSS (+)



Baseline
HR 80 bpm

ISO
HR 110 bpm

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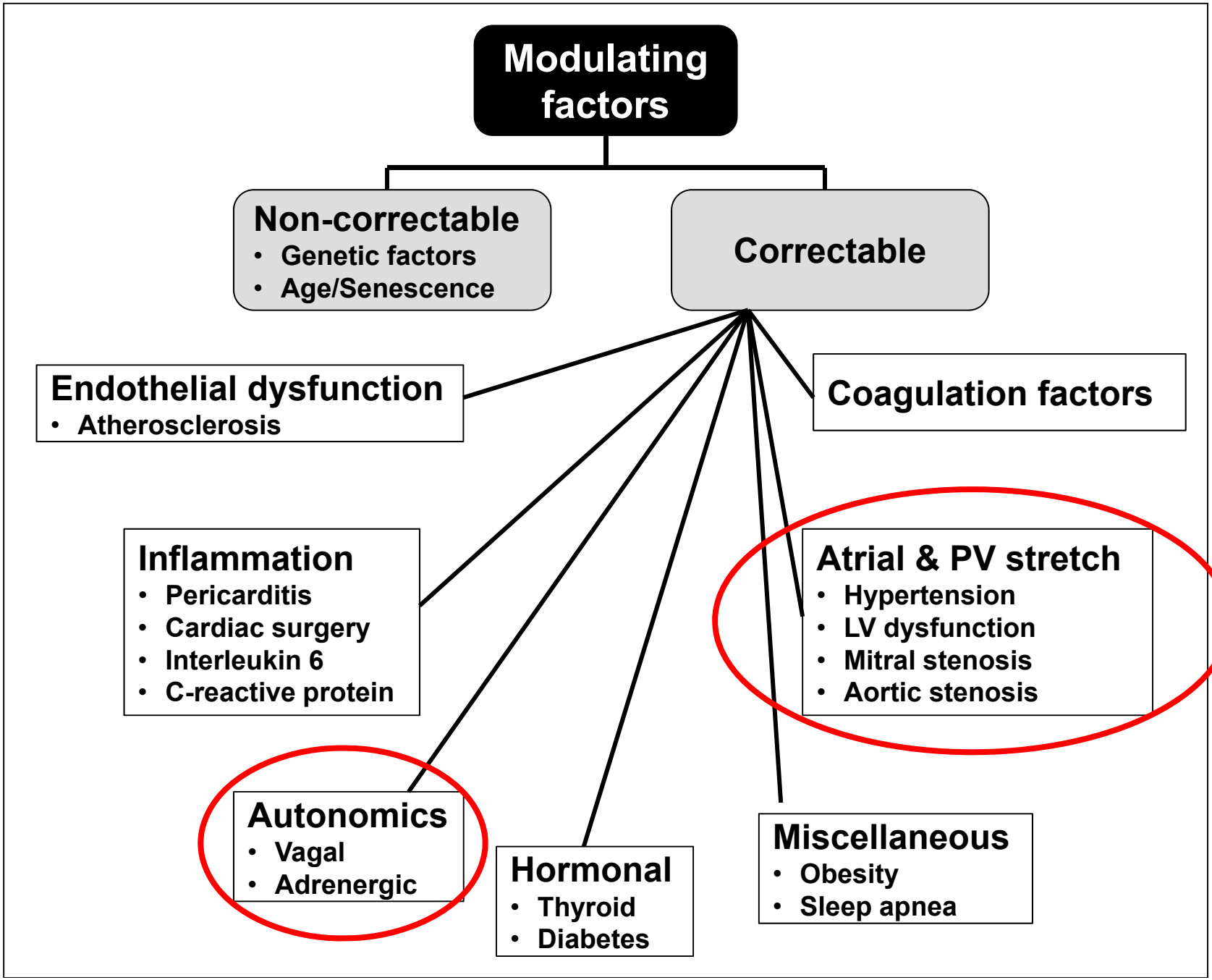
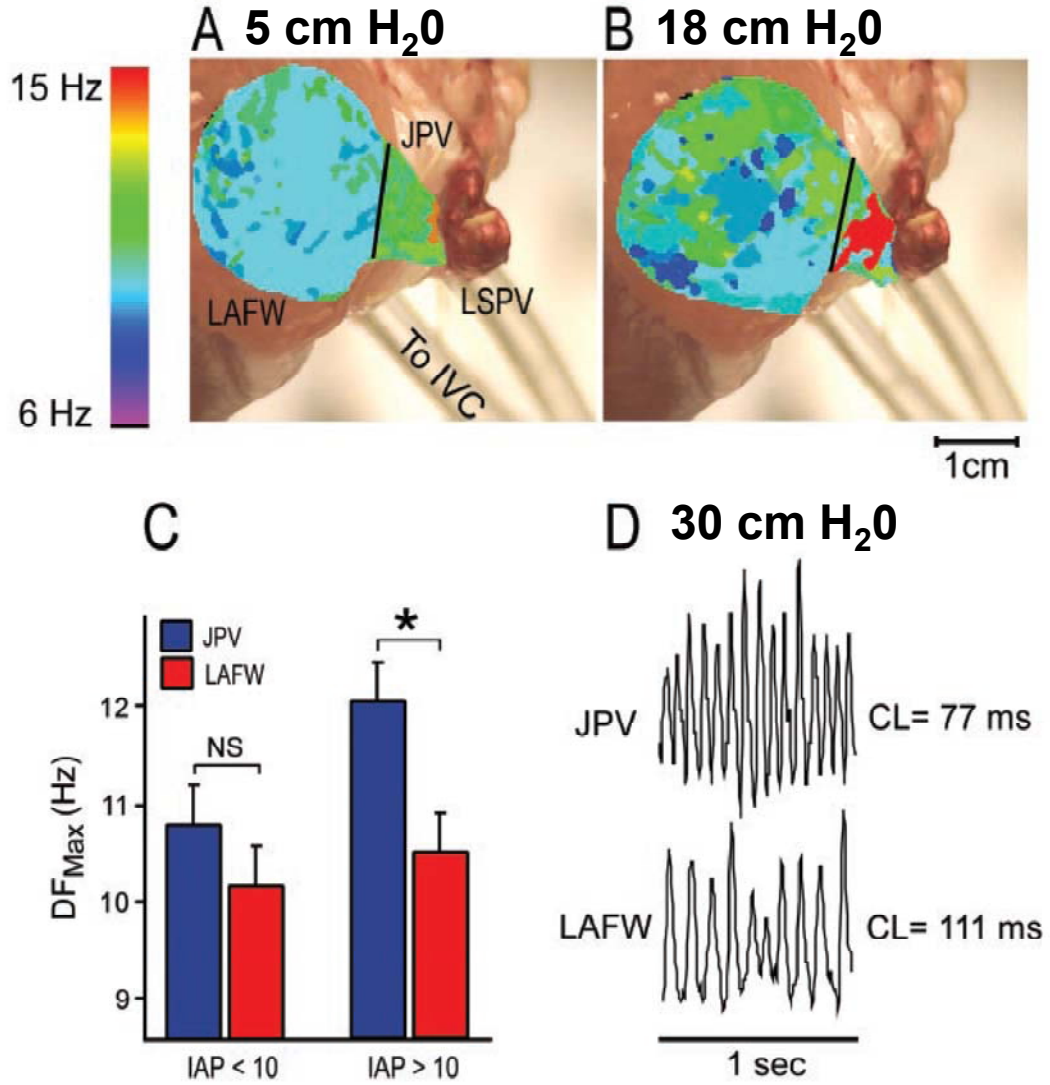
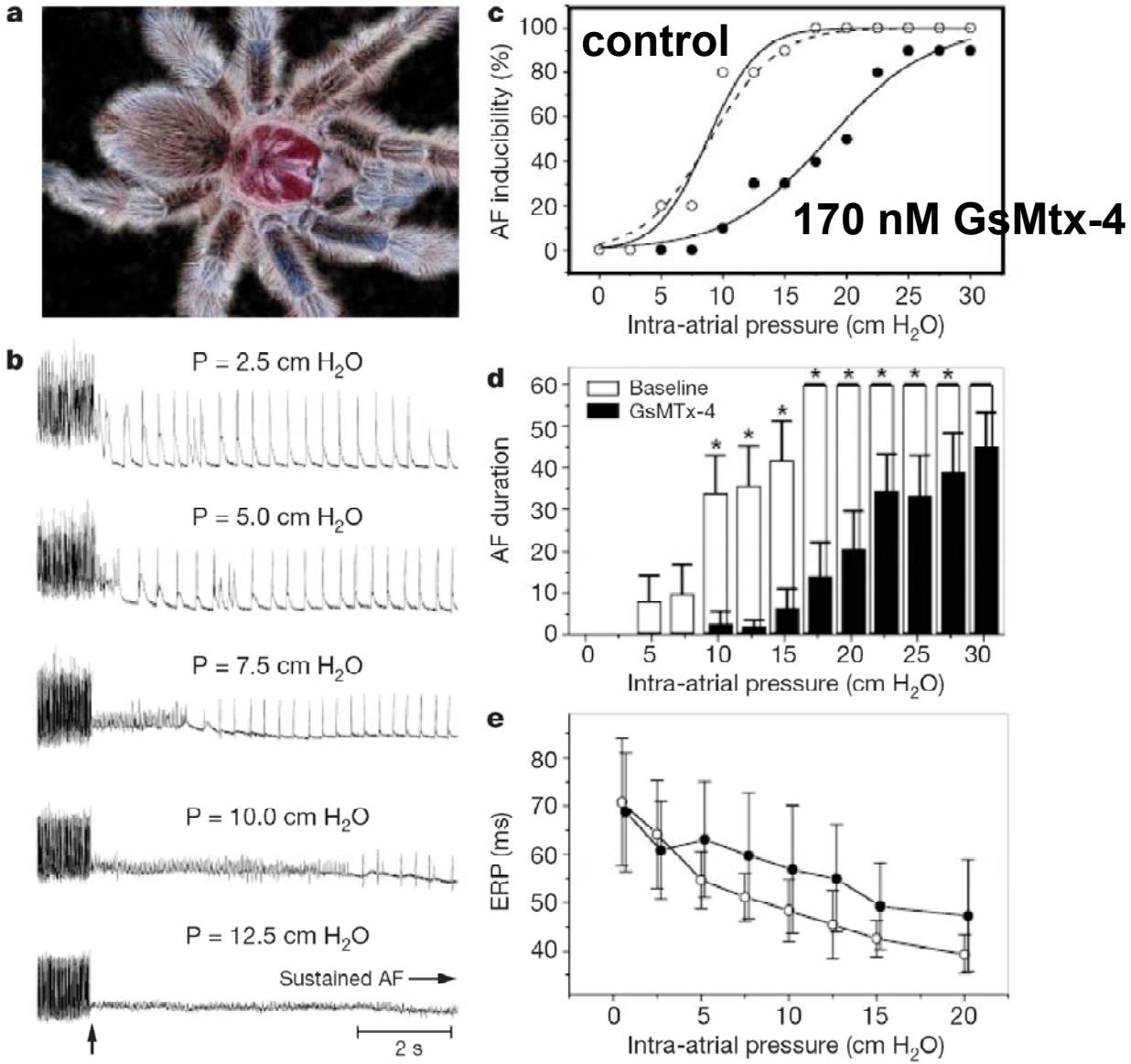

Modulating factors
Non-correctable
• Genetic factors
• Age/Senescence
Correctable
Endothelial dysfunction
• Atherosclerosis
Coagulation factors
Inflammation
• Pericarditis
• Cardiac surgery
• Interleukin 6
• C-reactive protein
Atrial & PV stretch
• Hypertension
• LV dysfunction
• Mitral stenosis
• Aortic stenosis
Autonomics
• Vagal
• Adrenergic
Hormonal
• Thyroid
• Diabetes
Miscellaneous
• Obesity
• Sleep apnea

Pulmonary veins and atrial function



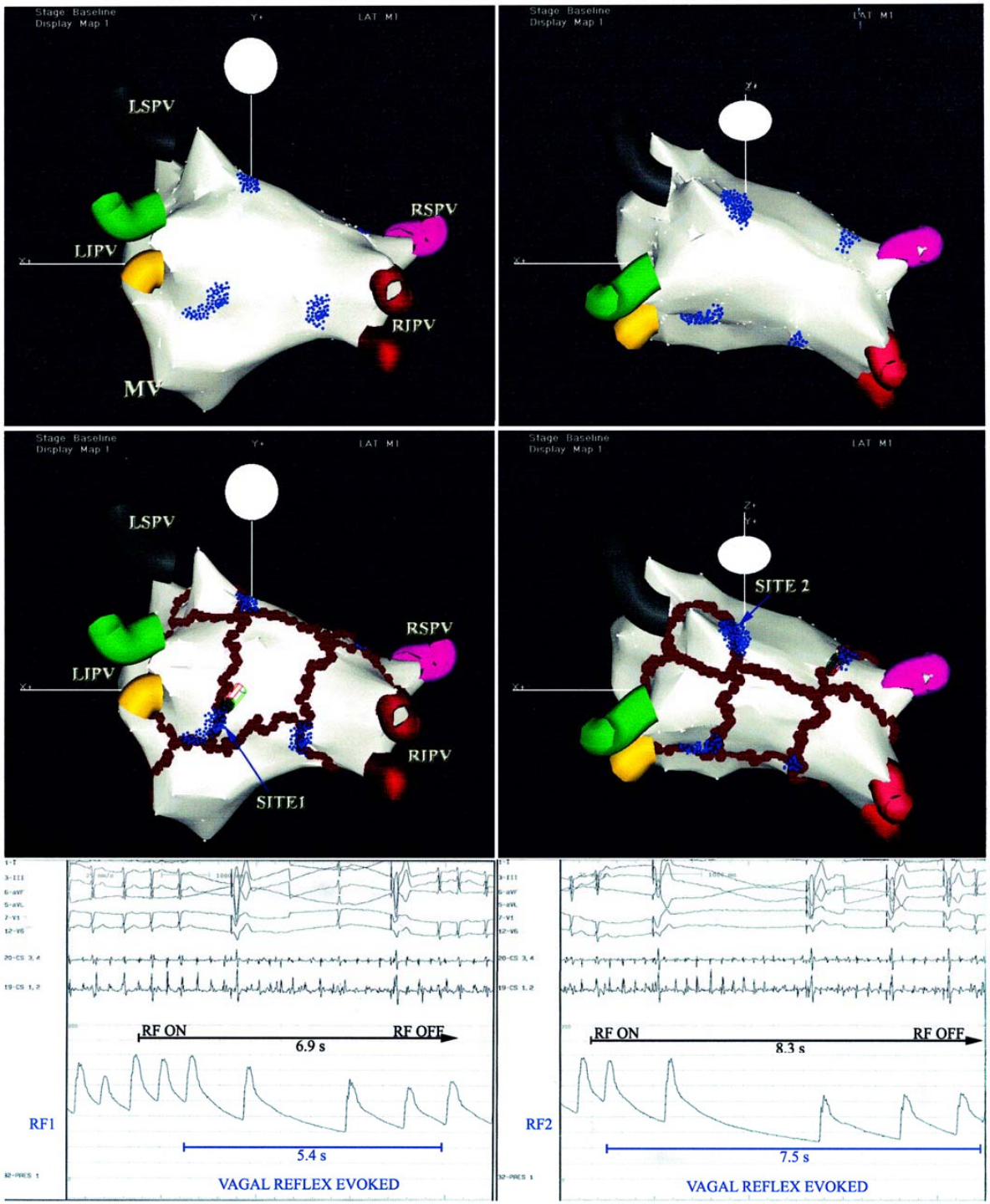
Kalifa J, Jalife J, Nattel S. Circulation 2003;108:668-71

Tarantula peptide inhibits atrial fibrillation



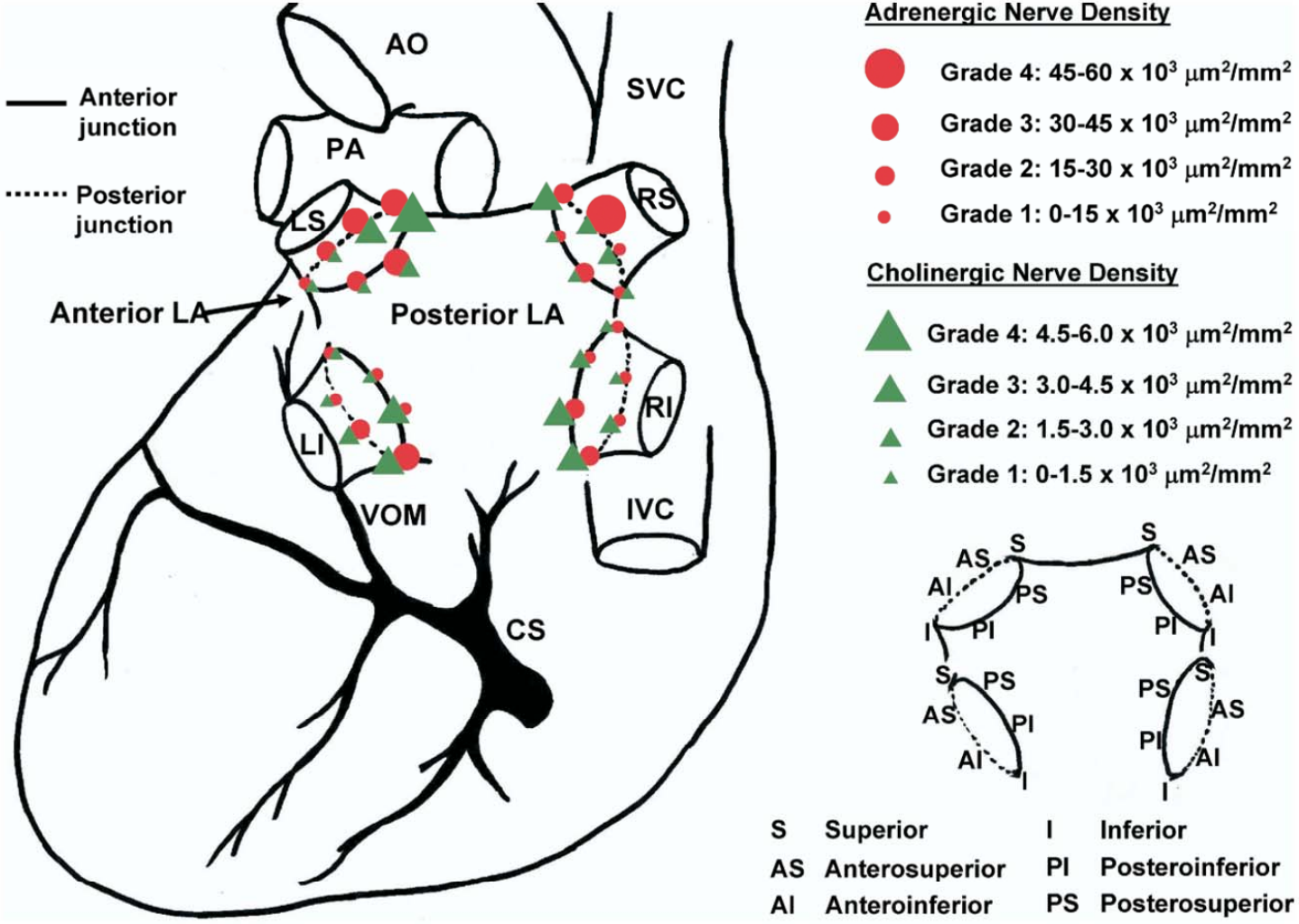
Bode F, nature 2001;409:35-36

PV Denervation Enhances Long-Term Benefit After Circumferential Ablation for Paroxysmal Atrial Fibrillation



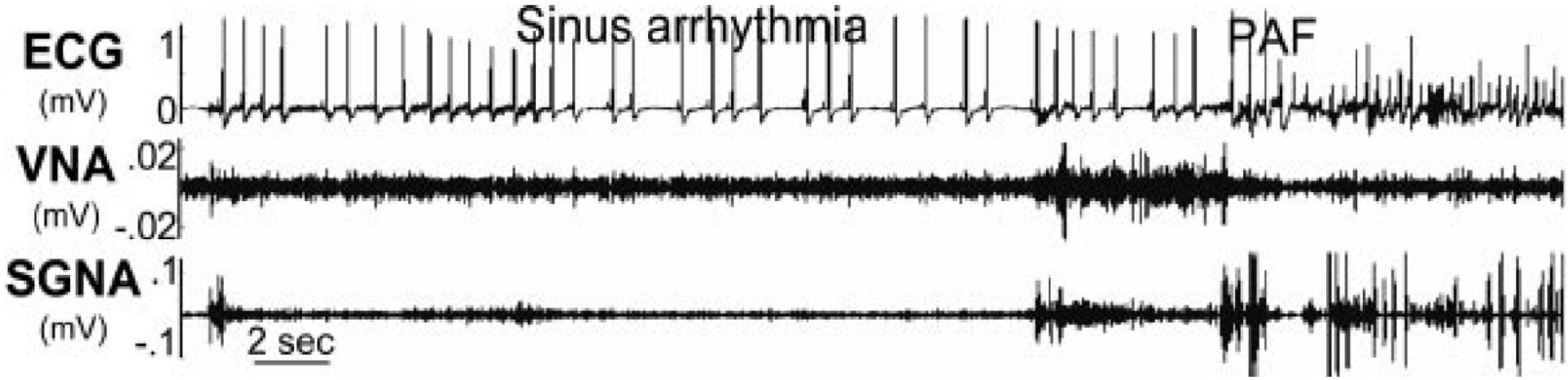
Pappone et al.
Circulation 2004;109:327-334

Circumferential distribution of autonomic nerves at the PV-LA junction



Tan A. J Am Coll Cardiol 2006;48:132–43.

Neural Mechanisms of Paroxysmal AF

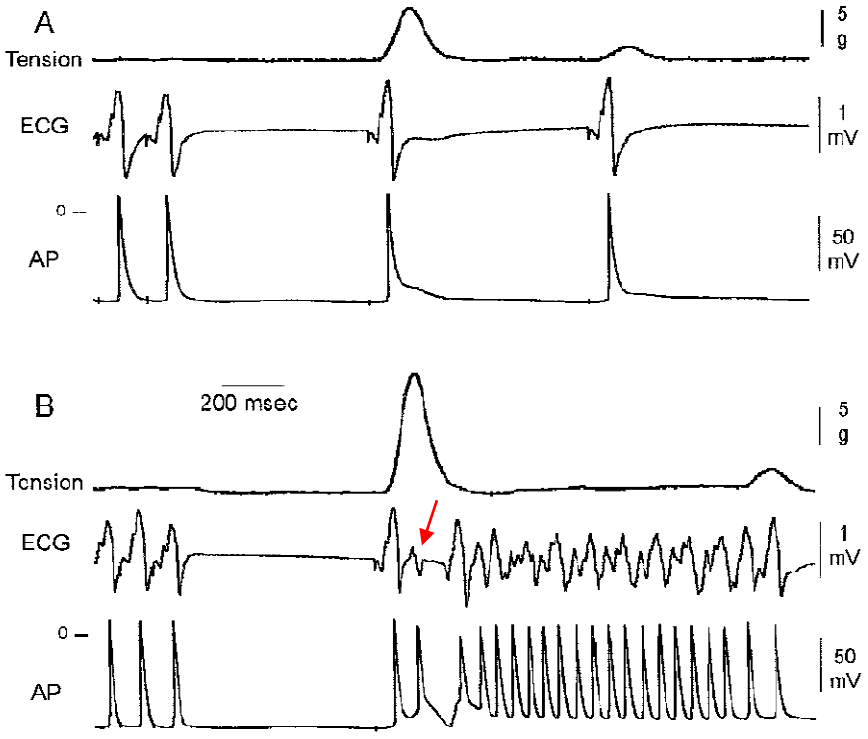


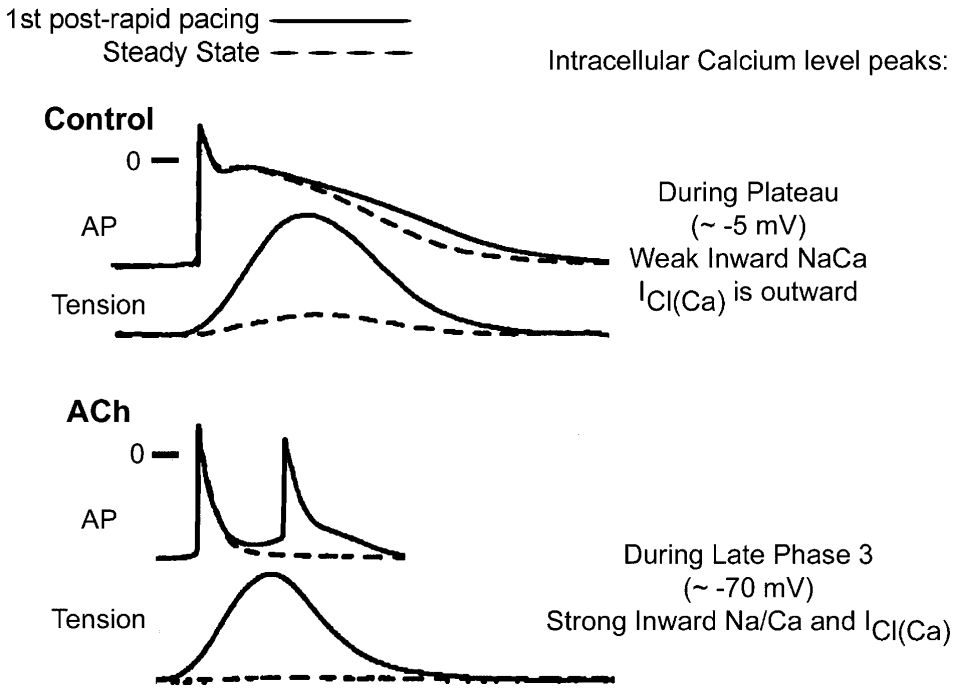
*** Cryoablation of extrinsic sympathovagal nerves eliminated paroxysmal atrial fibrillation and paroxysmal atrial tachycardia**

Tan A, Chen PS. Circulation. 2008; 118:916-925.

Late-phase 3 EADs.

responsible for the extrasystolic activity that reinitiates fibrillation in canine atrial tissues.

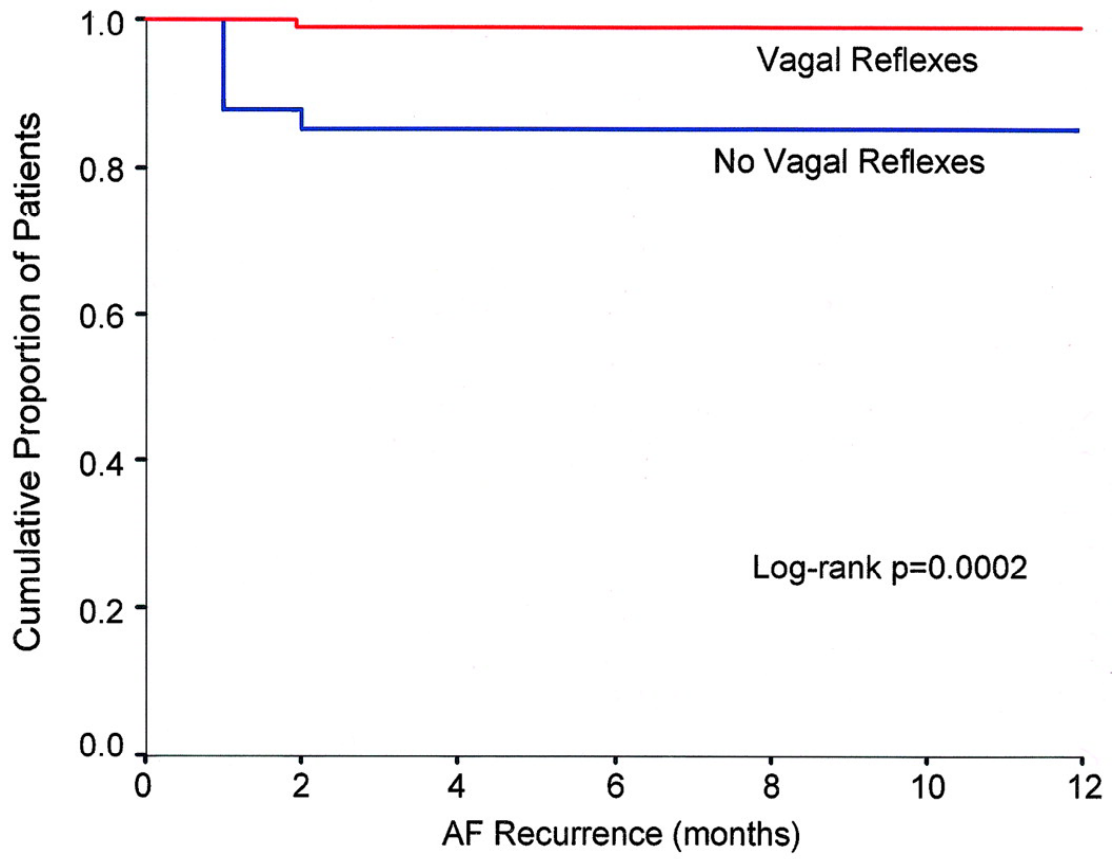




Burashnikov A, Antzelevitch C. Circulation 2003; 107:2355–2360.

경청하여 주셔서 감사합니다.

PV Denervation Enhances Long-Term Benefit After Circumferential Ablation for Paroxysmal AF

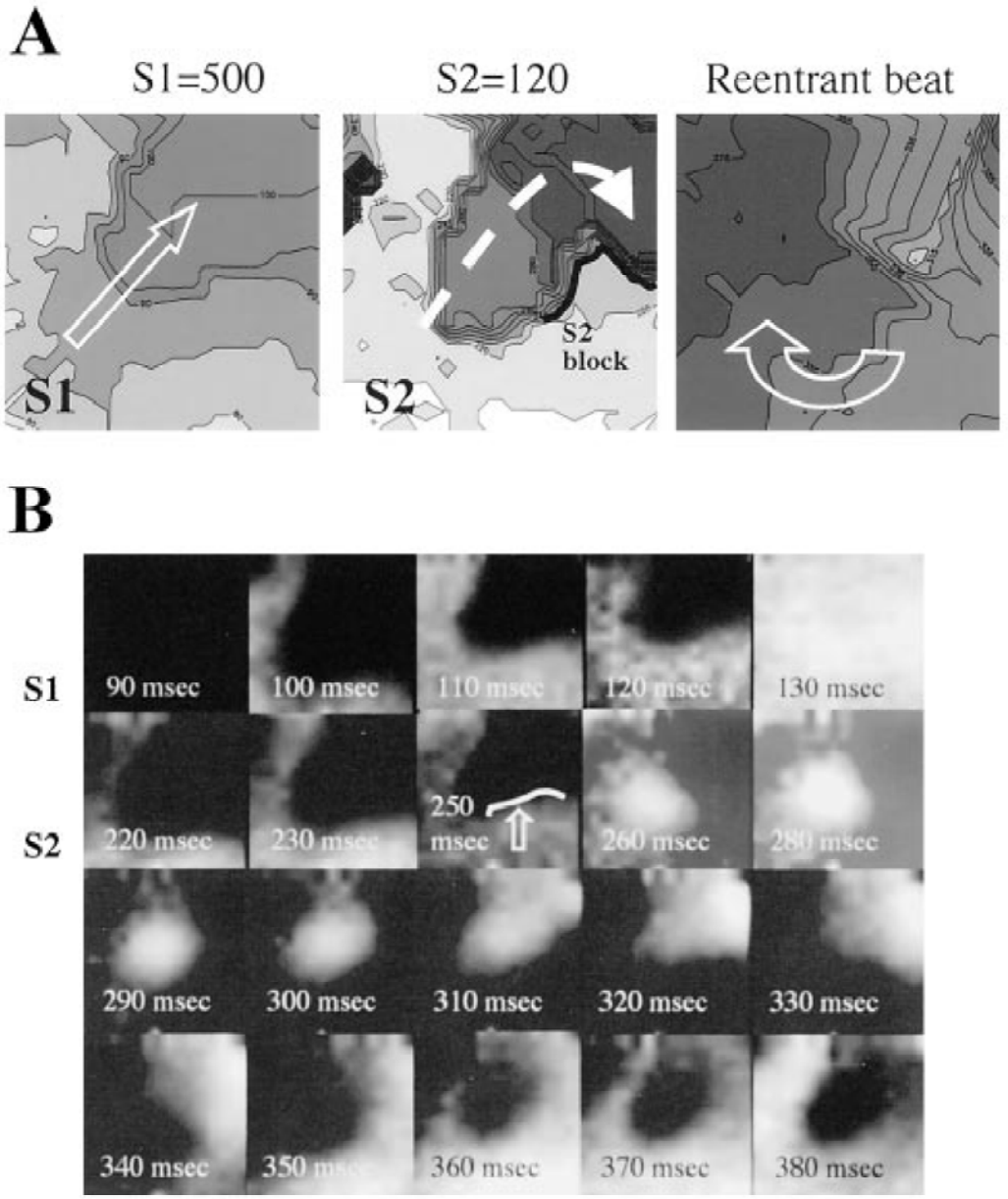


Number at risk

Vagal Reflexes:	102	101	101	101	101	101	101
No Vagal Reflexes:	195	166	166	166	166	166	166

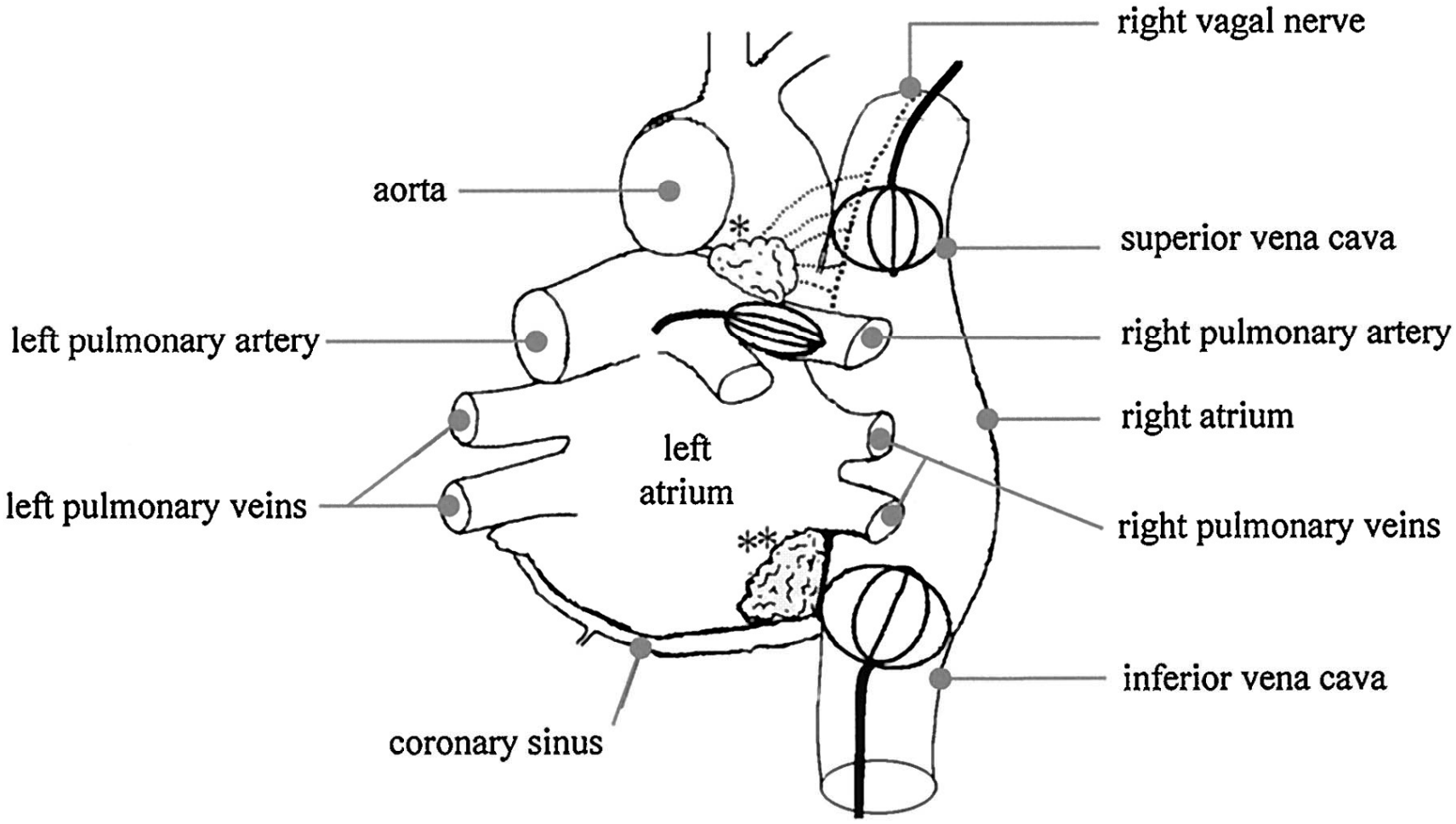
Pappone et al. Circulation 2004;109:327-334

Reentry within PV



Arora R. Circulation. 2003;107:1816-1821

Illustration of parasympathetic innervation of atria



Schauerte et al. Circulation. 2000;102:2774

A comparison of ion current and transporter remodeling in CHF, healed MI and AF/ATR

Property	CHF	MI	AF	Remarks
*I*to	↓↓	↓↓	↓↓	
*I*K1	↓	↓	↑	Constitutive IKACh ↑ in AF
*I*Kr	↔	↓	↔	
*I*Ks	↓	↓	↔	
*I*CaL	↔(↓)	↓	↓↓	
SERCA	↓	↓	??	
CaRc	Ph ↑	DS	Ph ↑	
NCX	↑	↔	↔(↑)	
*I*Na	↓	↓	↔(↓)	
Connexins	↓	↓	??	Increased lateralization in MI and AF Increased heterogeneity in all
APD	↑	↑	↓	
CV	↓	↓	↓(↔)	
EADs	+	+	No	
DADs	+	+	?	
Reentry	+	+	+	

DS, dyssynchronous release

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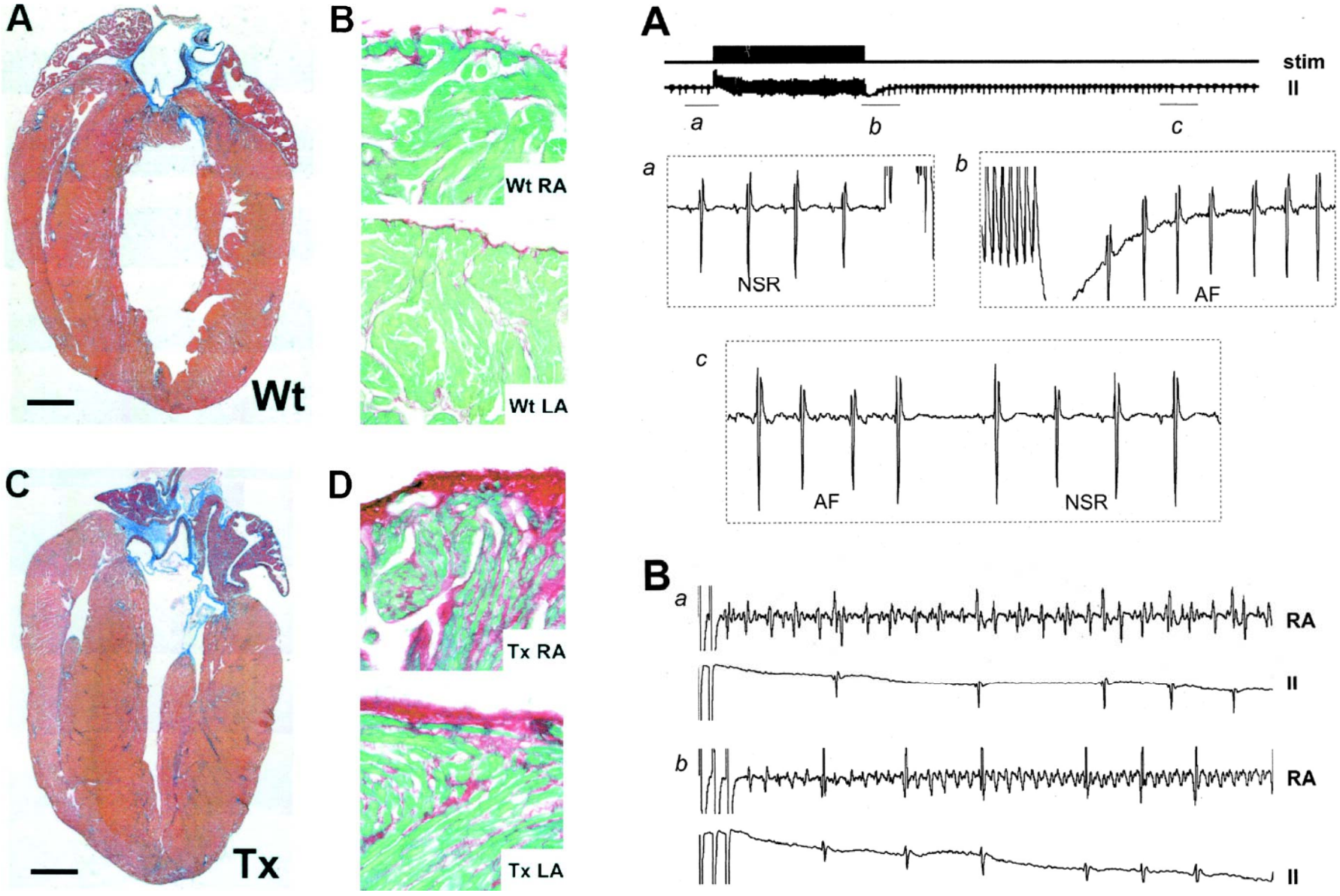
Increased vulnerability to AF in transgenic mice with selective atrial fibriosis caused by overexpression of TGF-β1



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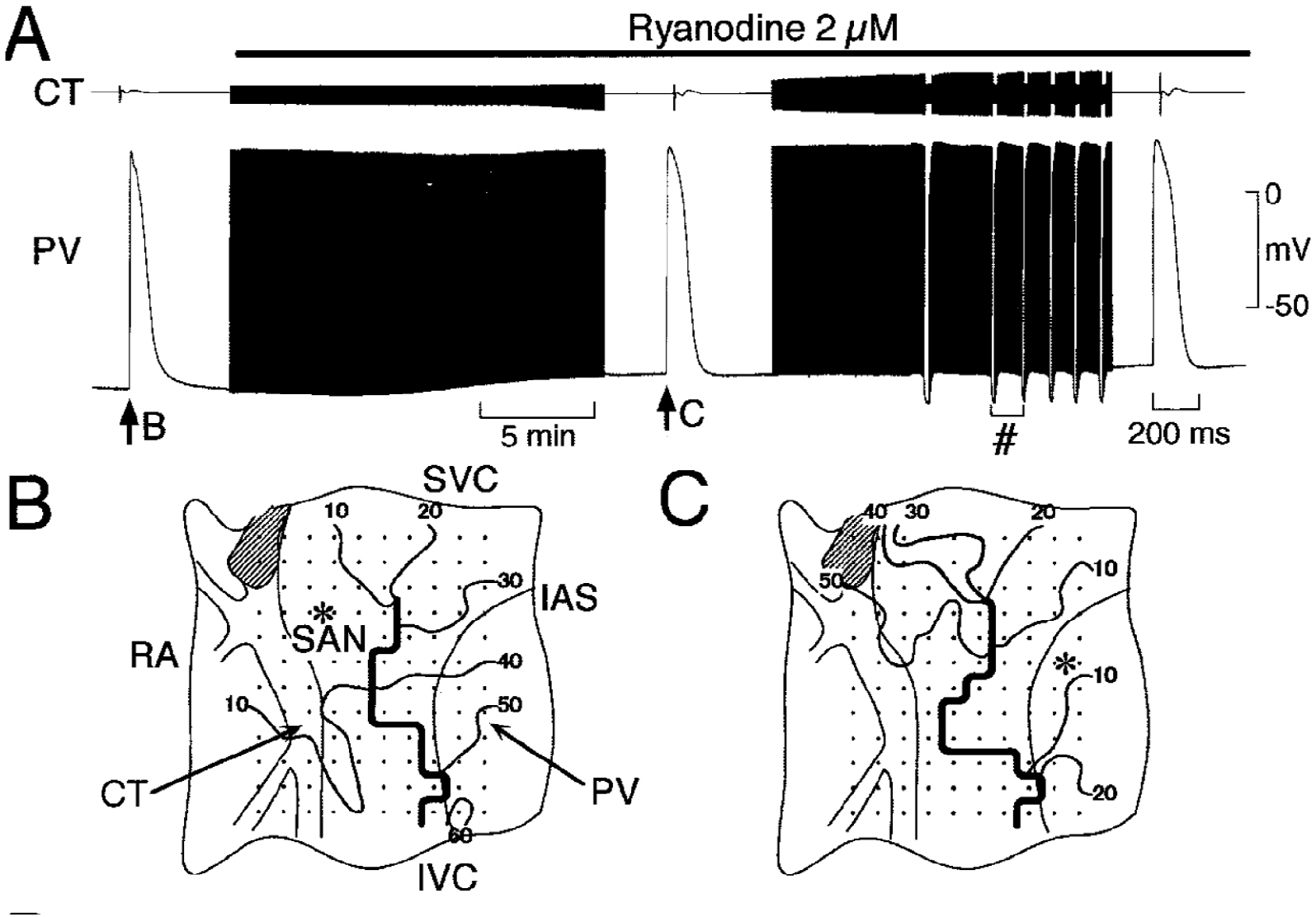
Ryanodine-induced PV firing - pacemaker shift



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TRPM7-Mediated Ca^{2+} Signals Confer Fibrogenesis in Human Atrial Fibrillation

Jianyang Du,* Jia Xie,* Zheng Zhang, Hiroto Tsujikawa, Daniel Fusco, David Silverman, Bruce Liang, Lixia Yue

Rationale: Cardiac fibrosis contributes to pathogenesis of atrial fibrillation (AF), which is the most commonly sustained arrhythmia and a major cause of morbidity and mortality. Although it has been suggested that Ca^{2+} signals are involved in fibrosis promotion, the molecular basis of Ca^{2+} signaling mechanisms and how Ca^{2+} signals contribute to fibrogenesis remain unknown.

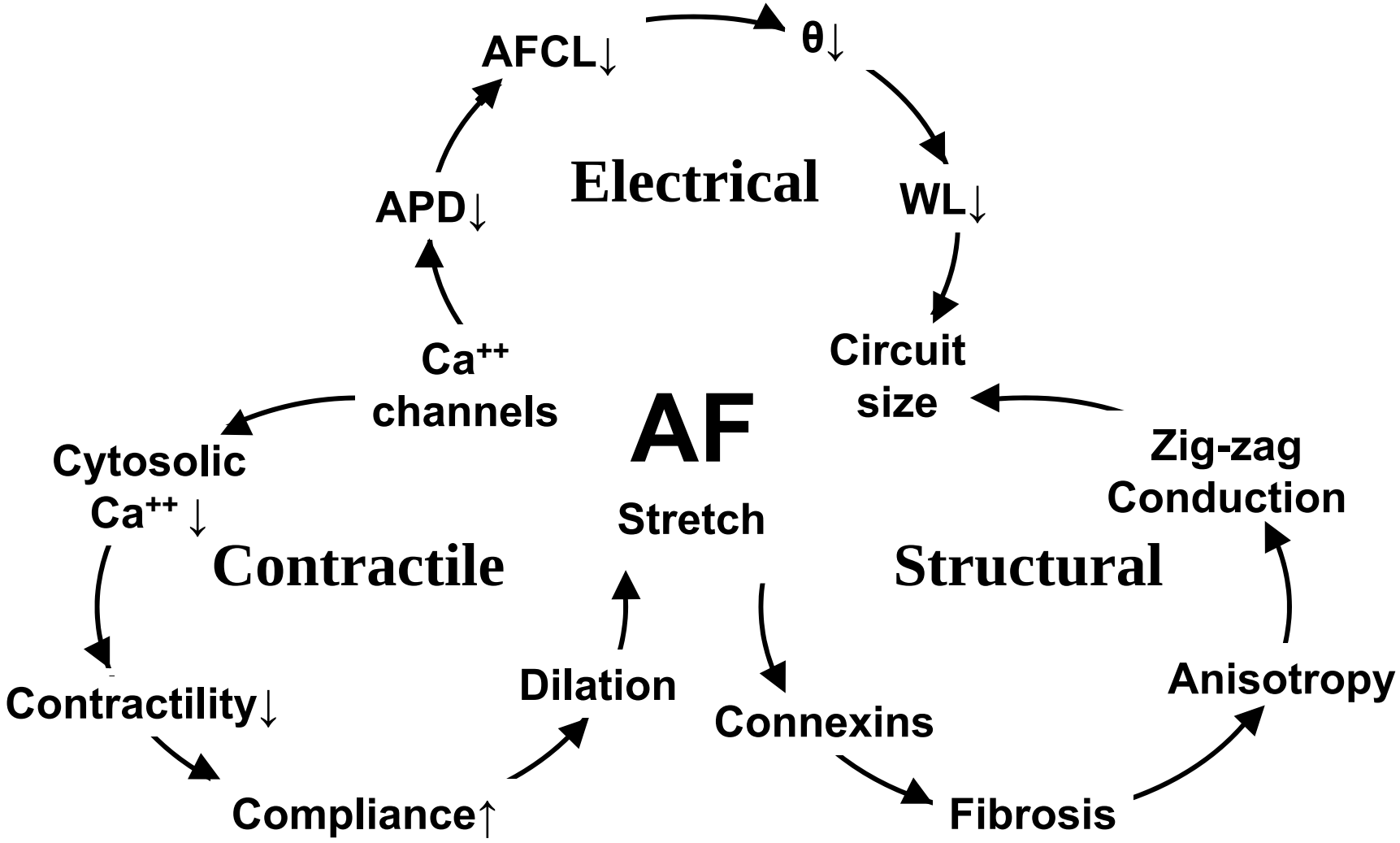
Objective: To determine the molecular mechanisms of Ca^{2+}-permeable channel(s) in human atrial fibroblasts, and to investigate how Ca^{2+} signals contribute to fibrogenesis in human AF.

Methods and Results: We demonstrate that the transient receptor potential (TRP) melastatin related 7 (TRPM7) is the molecular basis of the major Ca^{2+}-permeable channel in human atrial fibroblasts. Endogenous TRPM7 currents in atrial fibroblasts resemble the biophysical and pharmacological properties of heterologous expressed TRPM7. Knocking down TRPM7 by small hairpin RNA largely eliminates TRPM7 current and Ca^{2+} influx in atrial fibroblasts. More importantly, atrial fibroblasts from AF patients show a striking upregulation of both TRPM7 currents and Ca^{2+} influx and are more prone to myofibroblast differentiation, presumably attributable to the enhanced expression of TRPM7. TRPM7 small hairpin RNA markedly reduced basal AF fibroblast differentiation. Transforming growth factor (TGF)-β1, the major stimulator of atrial fibrosis, requires TRPM7-mediated Ca^{2+} signal for its effect on fibroblast proliferation and differentiation. Furthermore, TGF-β1–induced differentiation of cultured human atrial fibroblasts is well correlated with an increase of TRPM7 expression induced by TGF-β1.

Conclusions: Our results establish that TRPM7 is the major Ca^{2+}-permeable channel in human atrial fibroblasts and likely plays an essential role in TGF-β1–elicited fibrogenesis in human AF. (*Circ Res.* 2010;106:992-1003.)

Key Words: atrial fibrillation ■ TRPM7 ■ Ca^{2+} signaling ■ TGF-β1 ■ fibrogenesis

The potential interplay of electrical, contractile and structural feedback loops



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