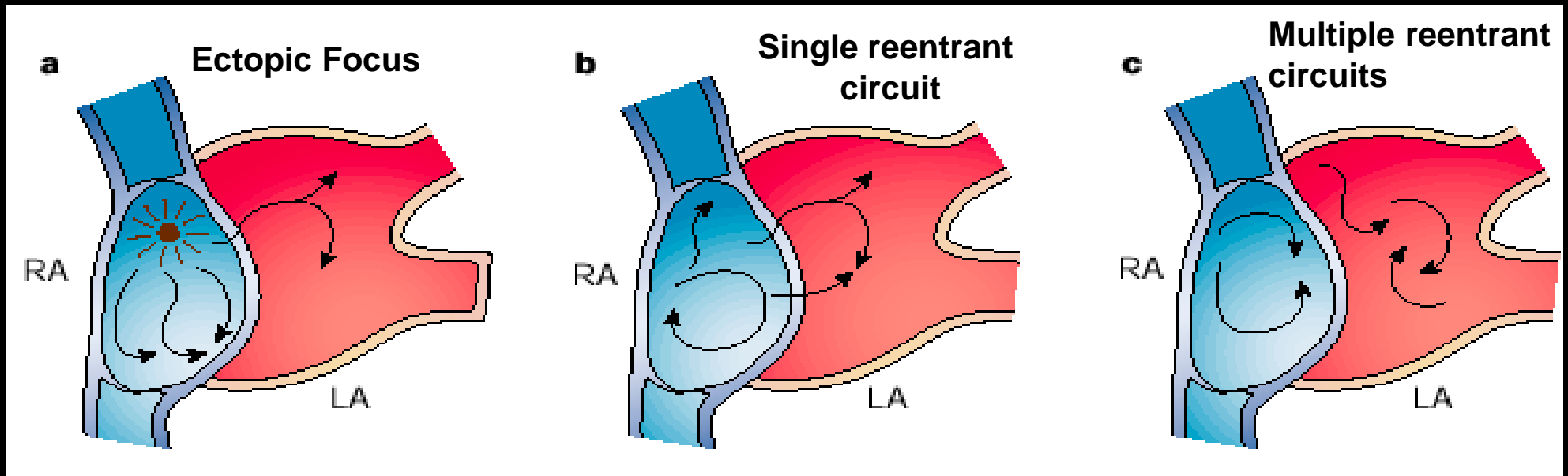


# **Electrophysiological determinants of atrial fibrillation**

**Andrew Grace**

**Consultant Cardiologist, Papworth Hospital  
University of Cambridge**

# Conventional conceptual models of atrial fibrillation



Engelmann  
Rothberger  
Winterberg

Lewis

Garrey  
Mines

adapted from Nattel, *Nature* 2002;415:219-226

# Who Gets Atrial Fibrillation ..?



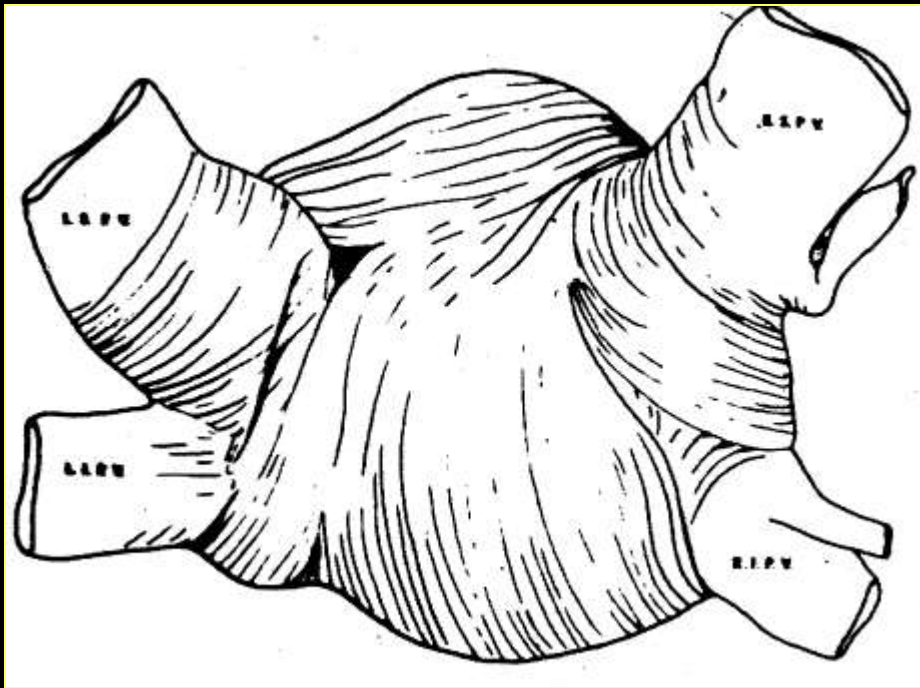
# Who Gets Atrial Fibrillation ..?



- 30-55 years of age
- 'Paroxysmal' AF
- Structurally normal heart
- No other co-morbidity
- His brother has it
- His mother had a stroke

# SUBSTRATE FOR ATRIAL FIBRILLATION

## MUSCULATURE OF THE PULMONARY VEINS

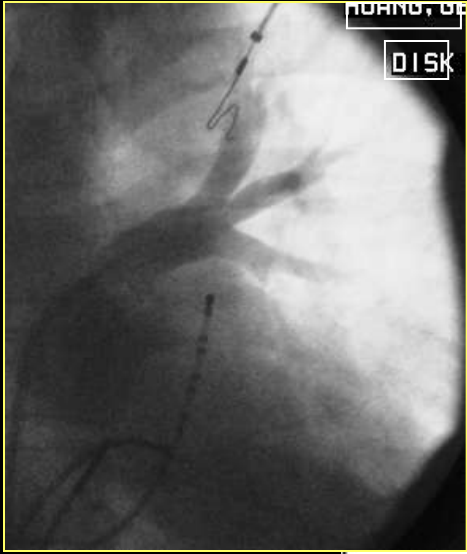


Nathan and Eliakim Circulation 1966; 34:412



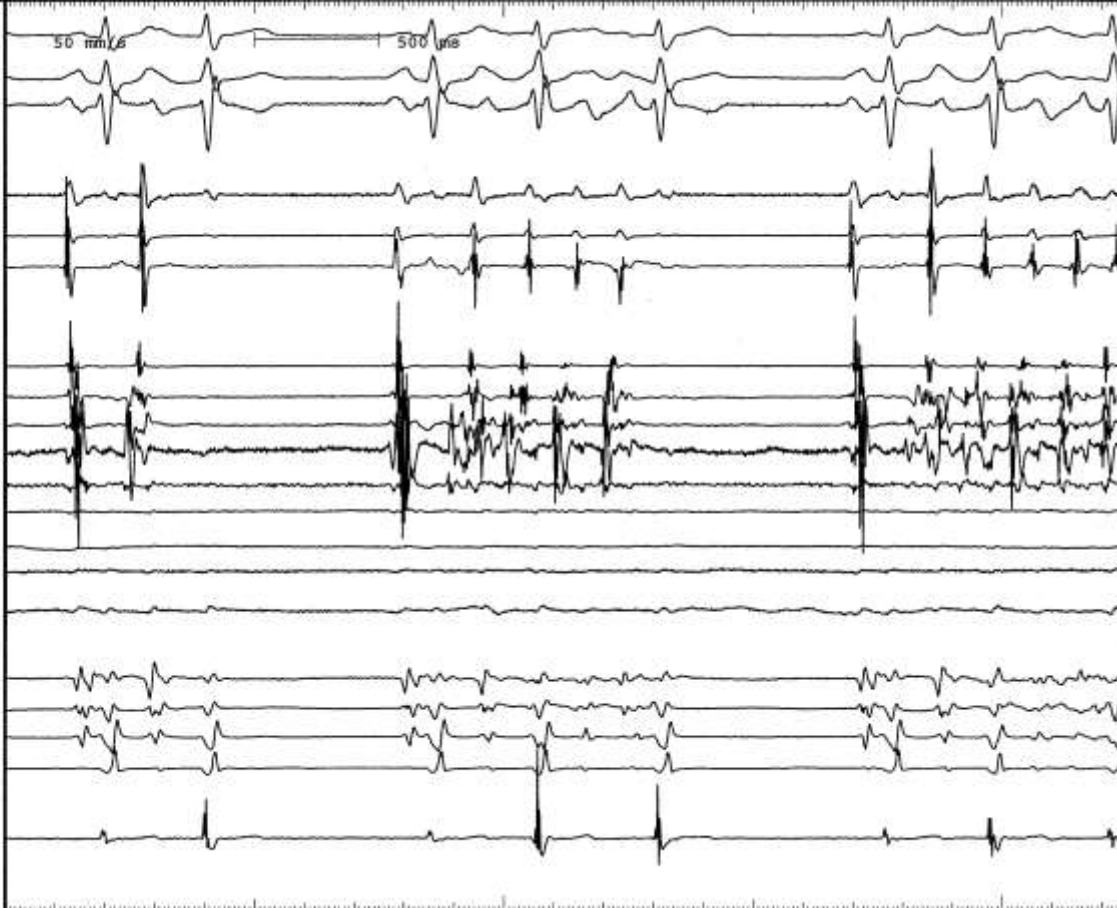
Haissaguerre *et al.* N Engl J Med 1998; 339:659

# FOCAL PV FIRING

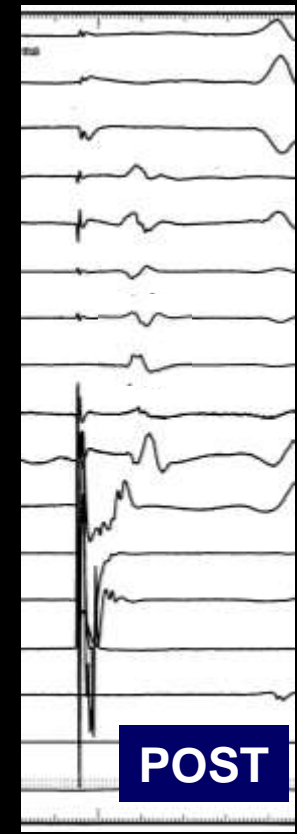
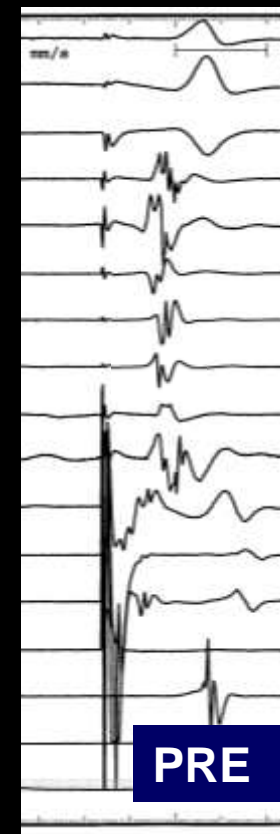
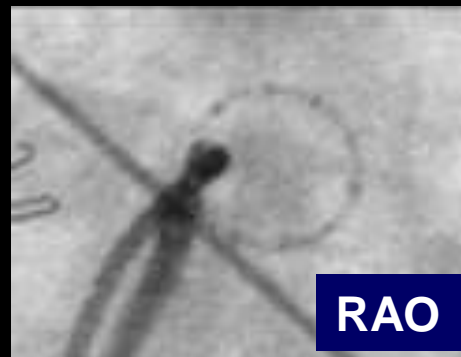
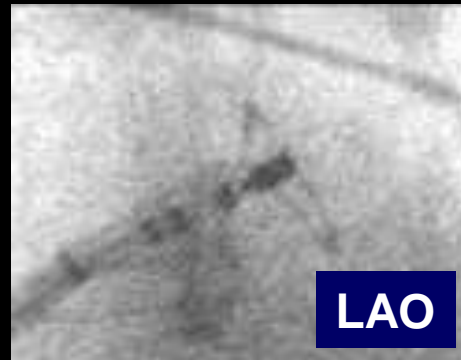


LSPV

21-HIS 8-7  
24-HIS 4-3  
25-HIS 2-1  
  
35-AM 18-17  
36-AM 16-15  
44-AM 14-13  
45-AM 12-11  
43-AM 10-9  
46-AM 8-7  
42-AM 6-5  
47-AM 4-3  
48-AM 2-1  
  
27-CS 8-7  
28-CS 6-5  
29-CS 4-3  
30-CS 2-1  
  
20-RVA 4-3

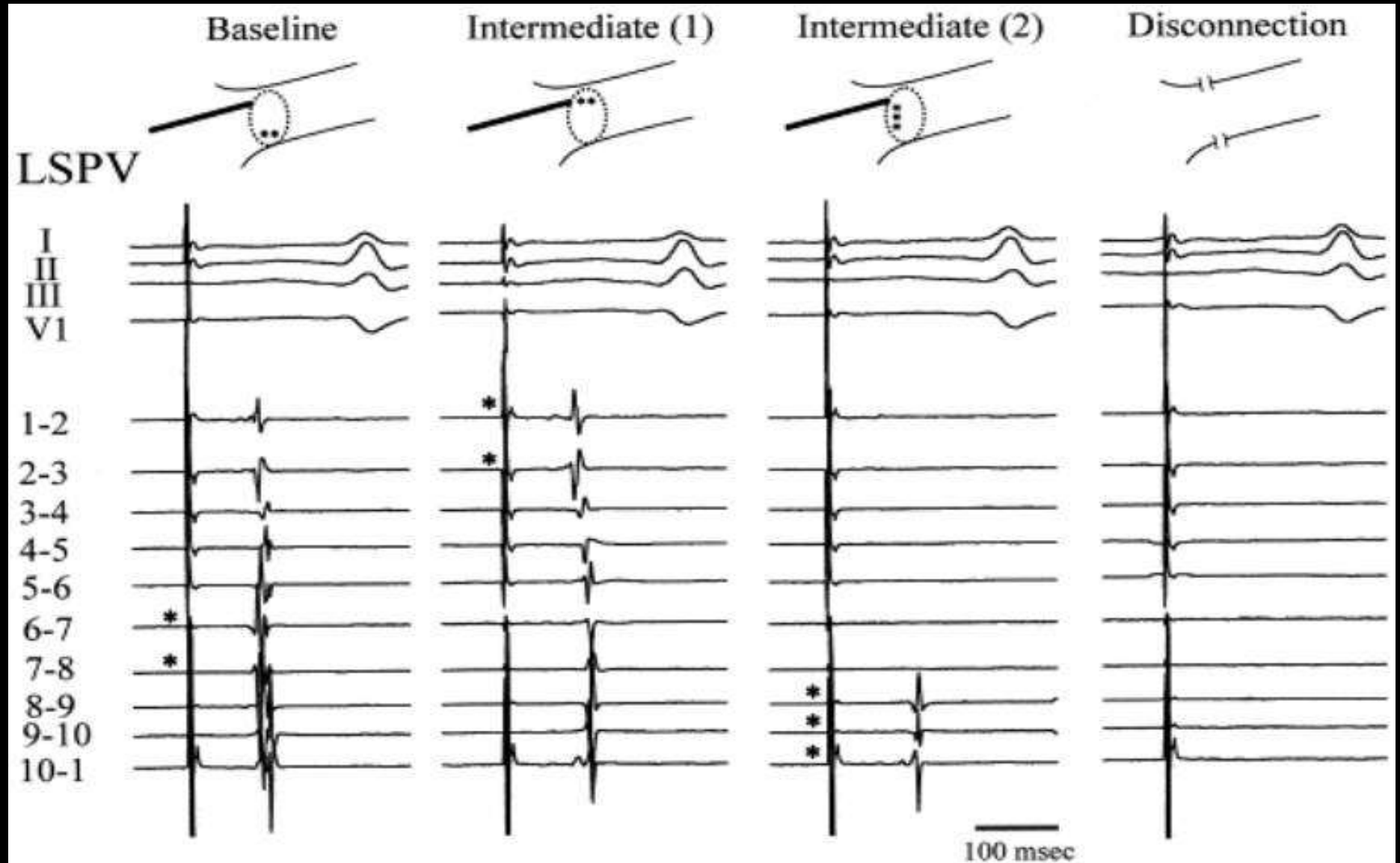


# CIRCUMFERENTIAL OSTIAL MAPPING - LSPV

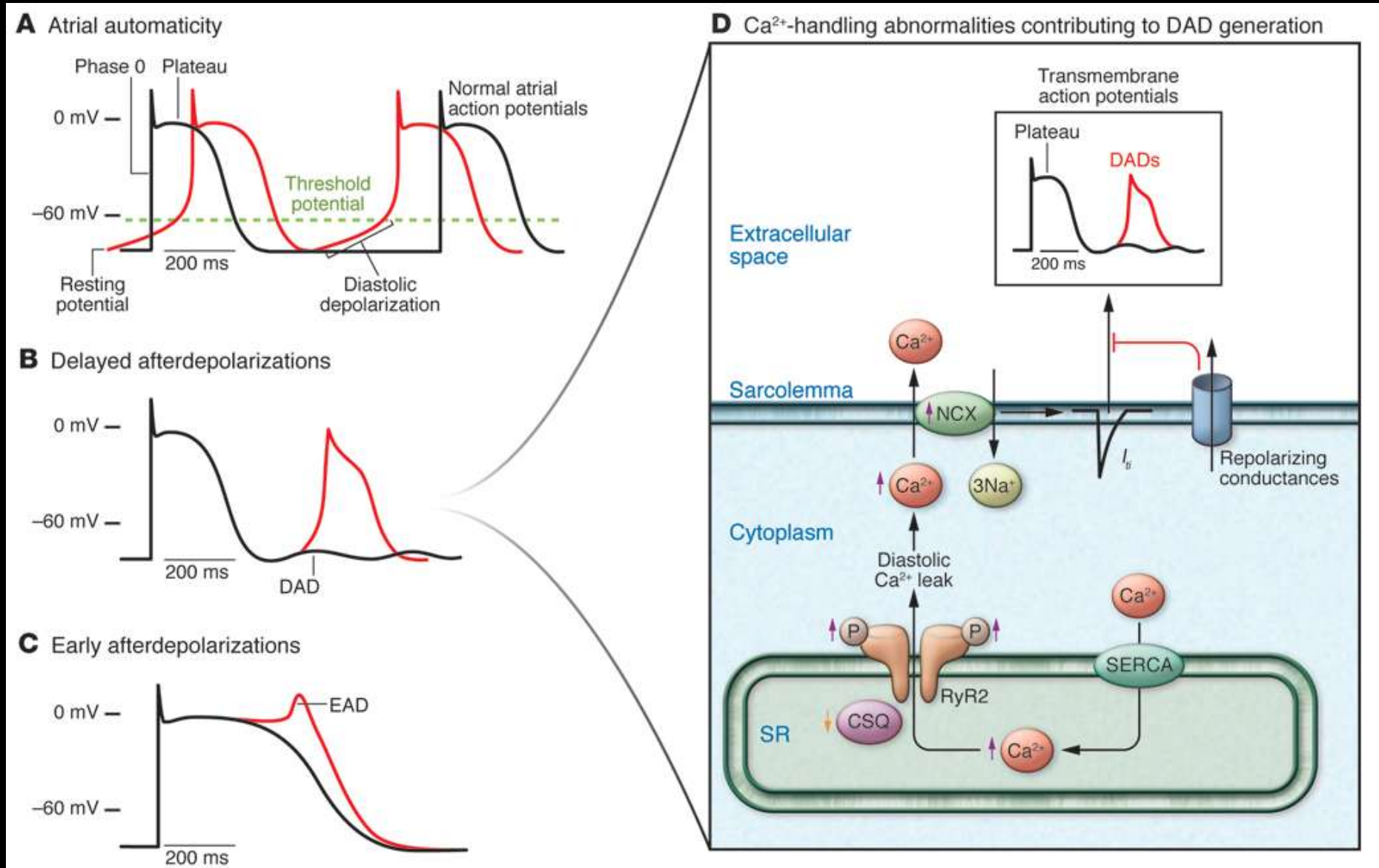


LASSO CATHETER

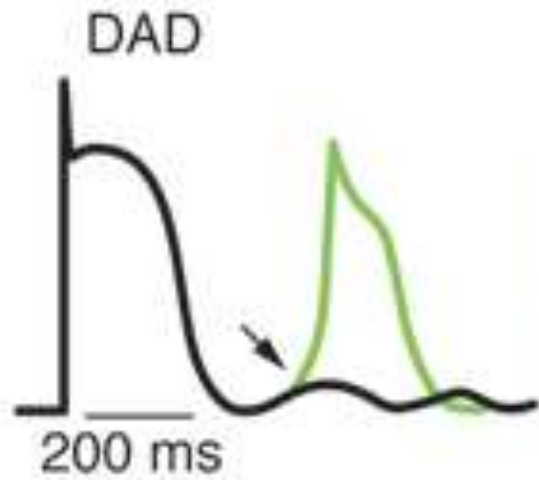
# Segmental ablation of all 4 veins



# Cellular Mechanisms underlying focal ectopic activity



# Genetic Mechanisms underlying focal ectopic activity



Single-gene mutation

Single nucleotide polymorphism

Gain of function

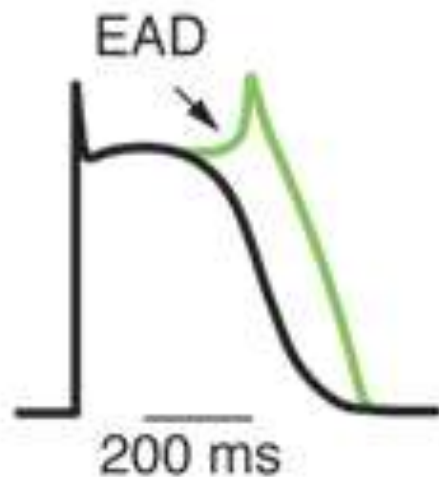
Loss of function

Unknown function

*ANKB*

*SLN*

*PITX2?*



Single-gene mutation

Single nucleotide polymorphism

Gain of function

Loss of function

Unknown function

*SCN5A*

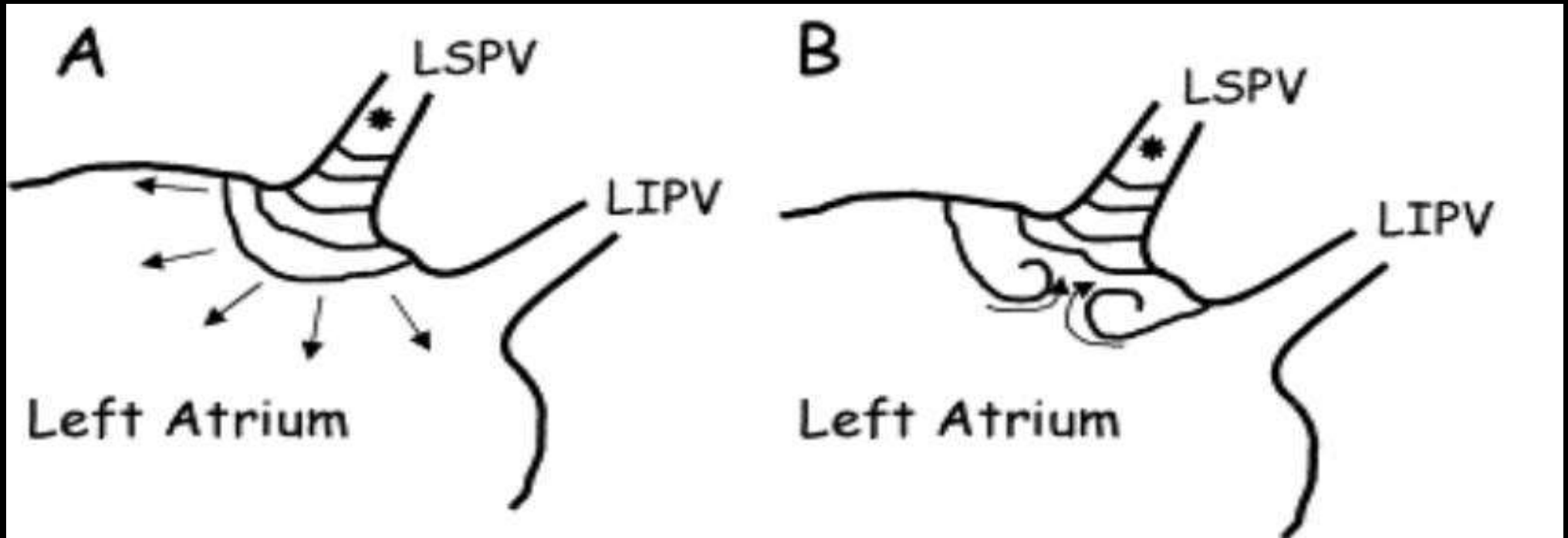
*KCNQ1*  
*KCNH2*  
*KCNA5*

*KCNE1*

*KCNN3?*

# Mechanisms of Perpetuation AF

- **Activation at highest frequency sites due to rapid firing/vortices of reentry**
- **Differences in activation frequency during AF**
  - Higher frequency sites in left atrium
  - Often occur at PV ostia, LAA, LA septum
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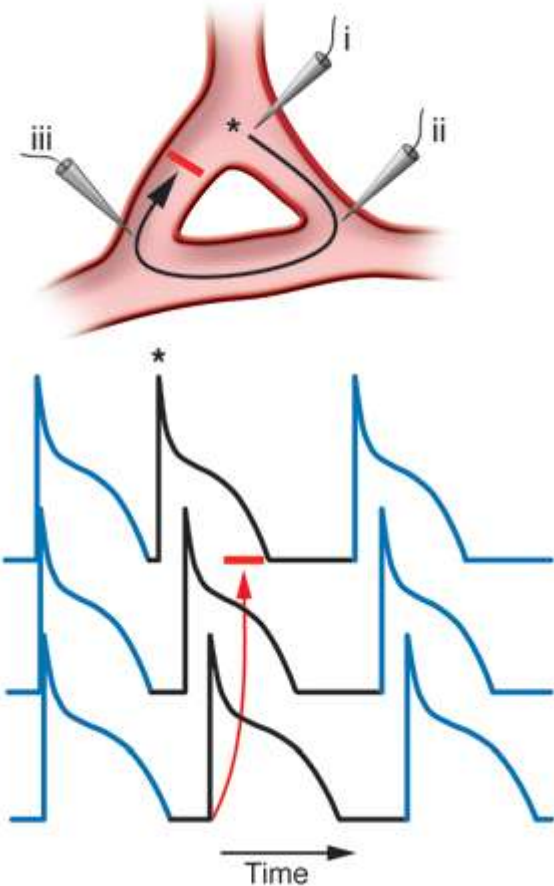


**Ectopic focus leads to wavefront from LSPV invading LA body**

**Appropriate conditions of heterogeneity lead to wave break with counter-rotating vortices**

# Factors underlying re-entrant excitation

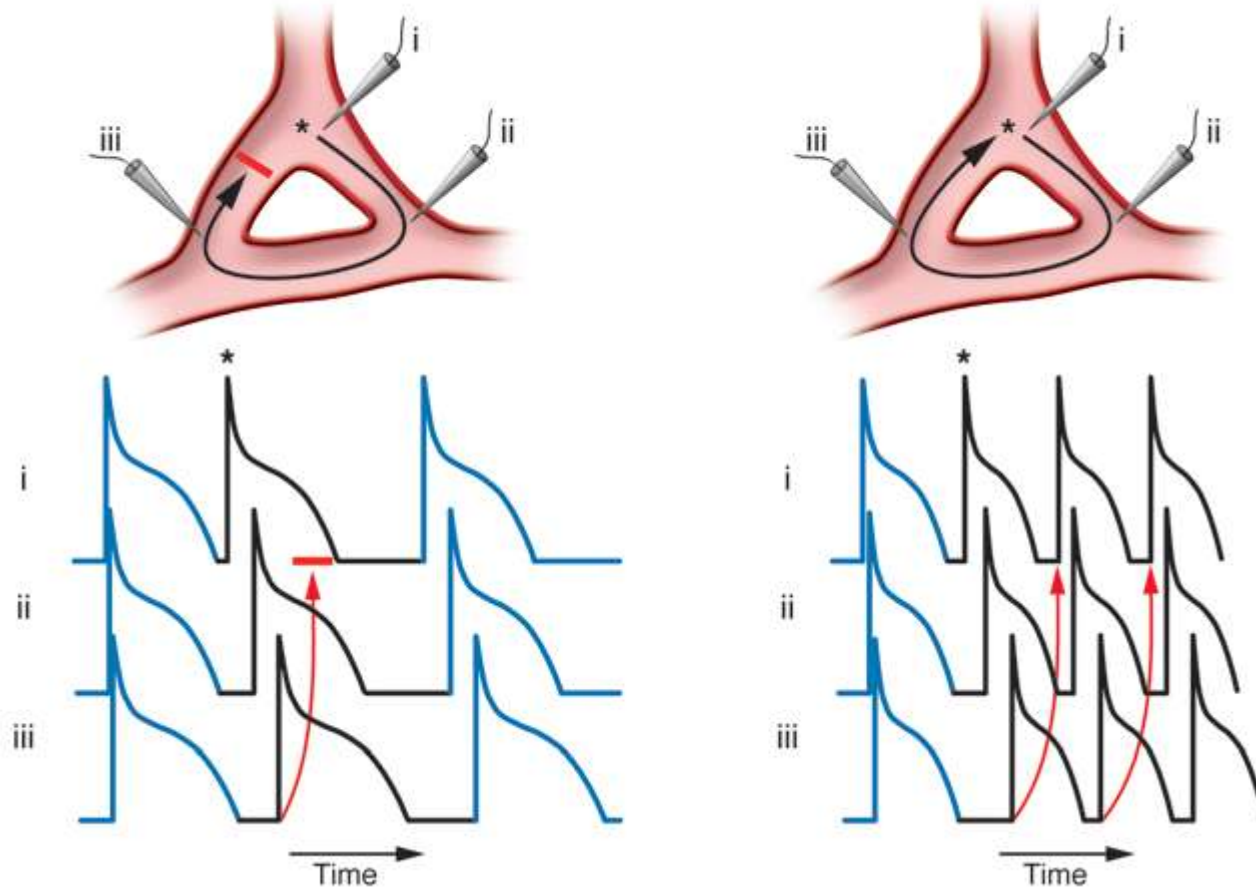
**A** Functional substrate, normal condition



# Factors underlying re-entrant excitation

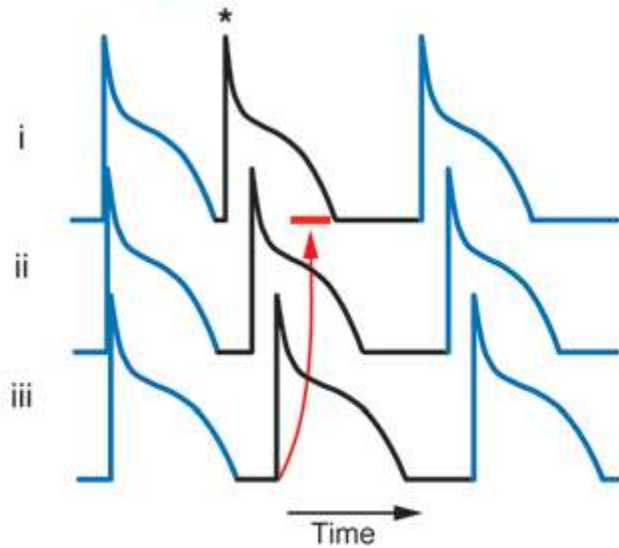
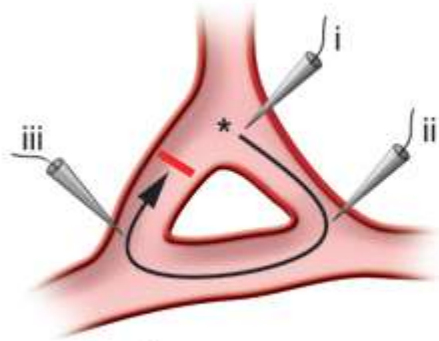
**A** Functional substrate, normal condition

**B** Abbreviated refractoriness

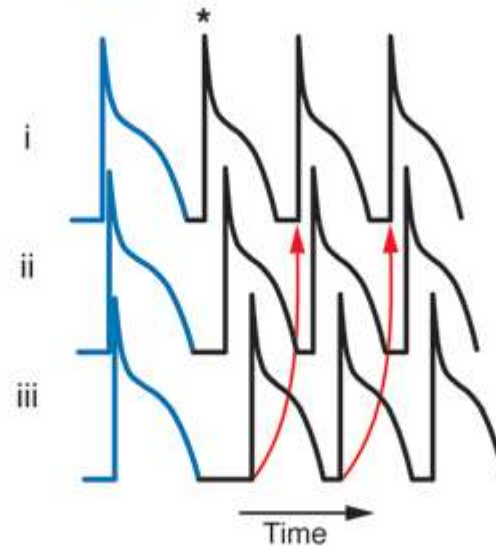
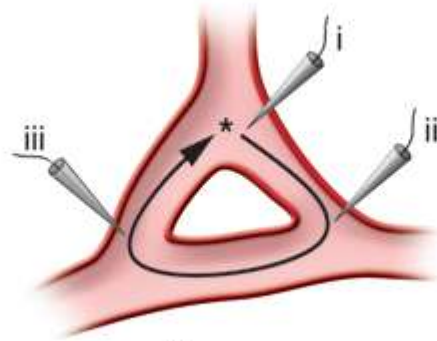


# Factors underlying re-entrant excitation

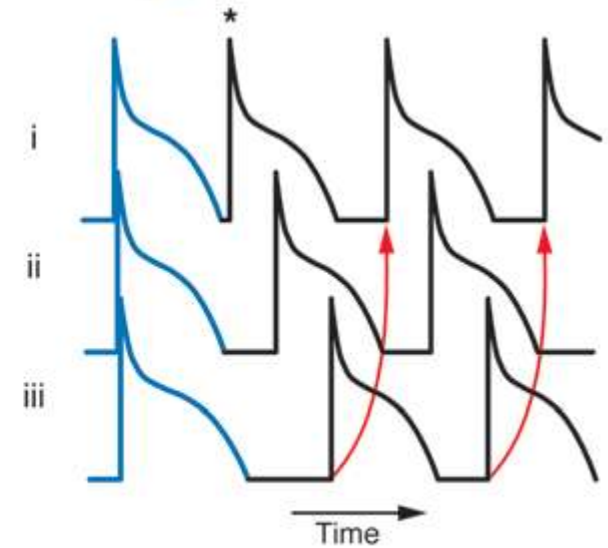
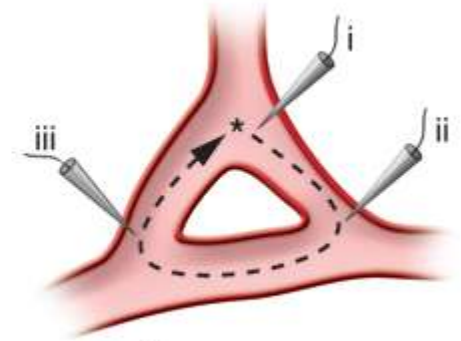
**A** Functional substrate, normal condition



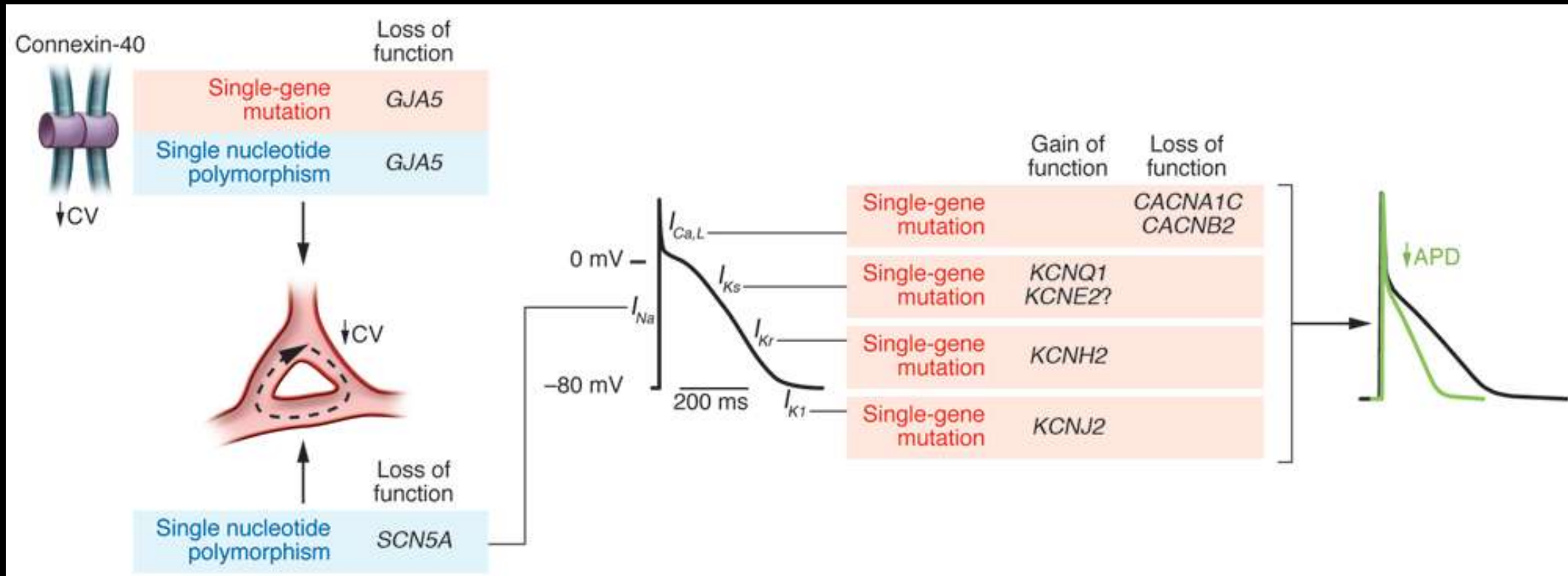
**B** Abbreviated refractoriness



**C** Slowed conduction

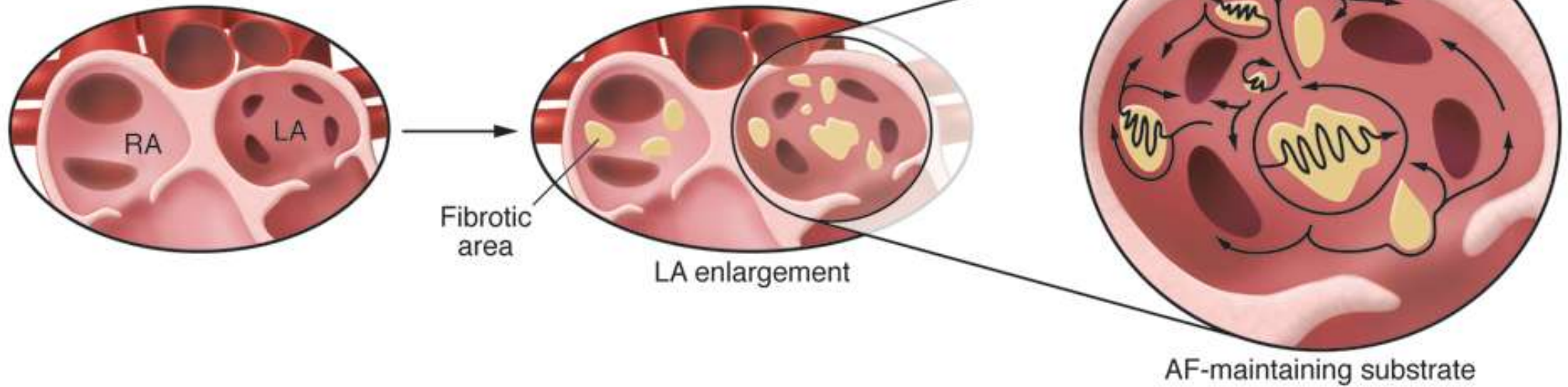


# Genetic factors underlying re-entrant excitation

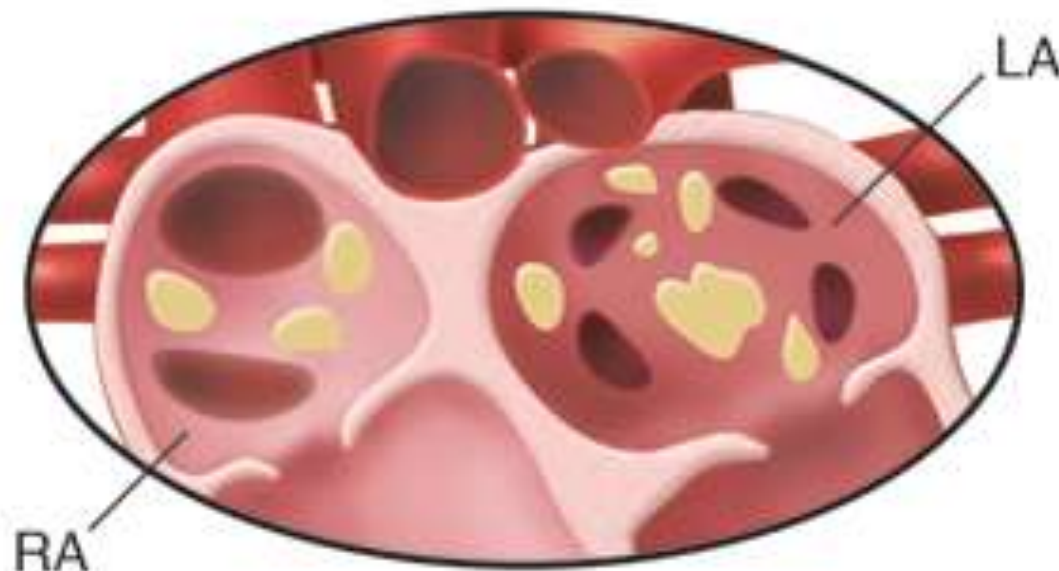


# Structural substrate underlying re-entrant excitation

## D Structural substrate



# Genetic factors underlying fixed re-entry

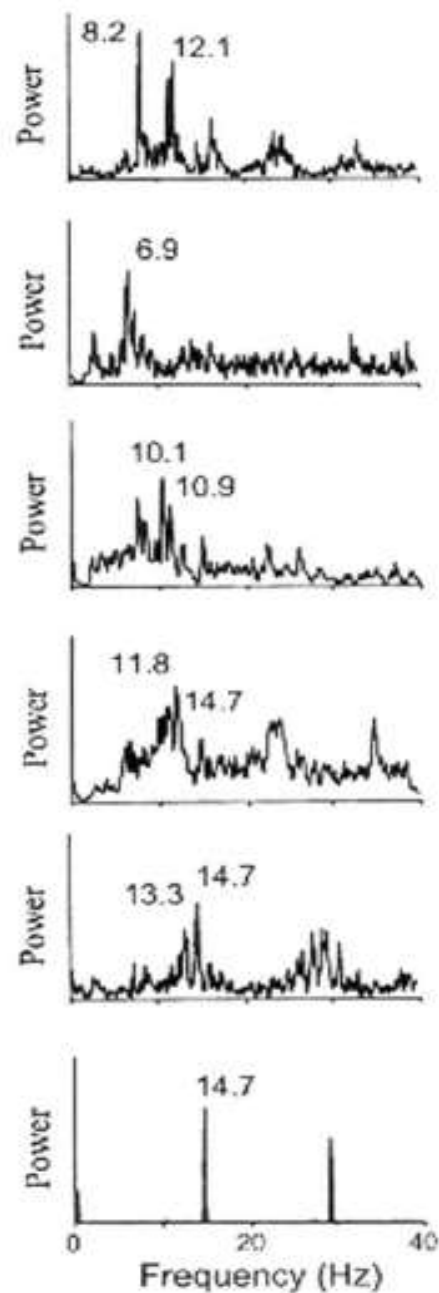
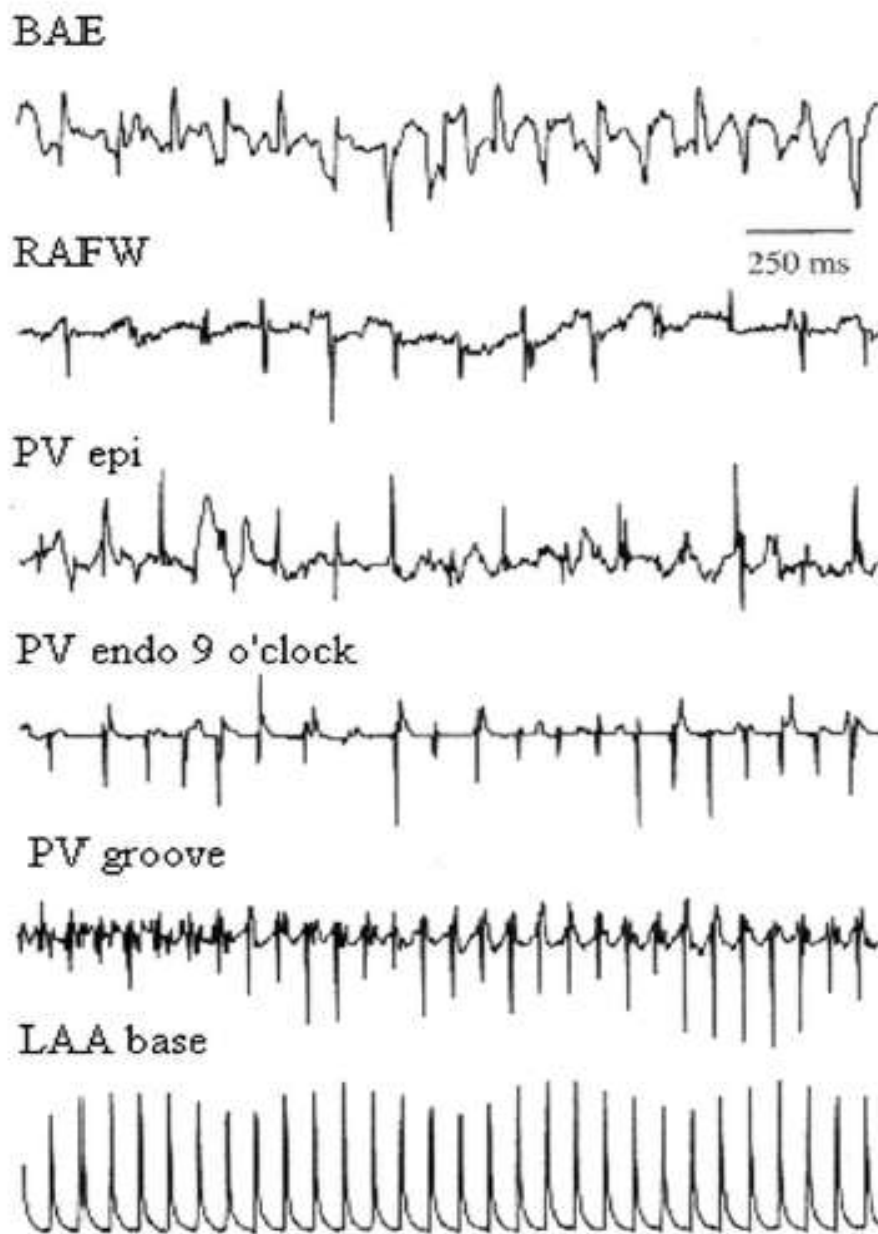


	Gain of function	Loss of function	Unknown function
Single nucleotide polymorphism	ACE		MMP2 IL10 PITX2? ATBF1/ZFH3?

# Mechanisms of Perpetuation AF

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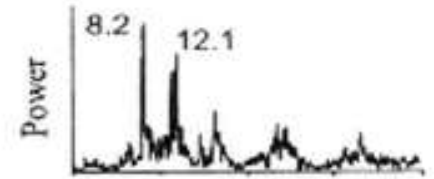
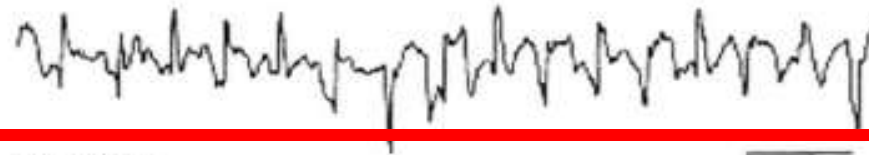
# Left-to-right frequency gradients in isolated sheep heart



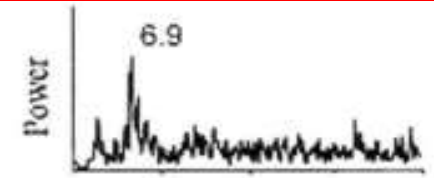
Mansour *et al.*  
Circ 2001; 103:2631-6

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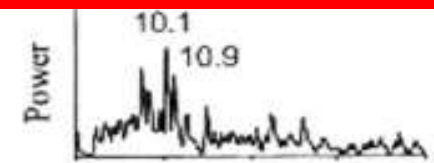
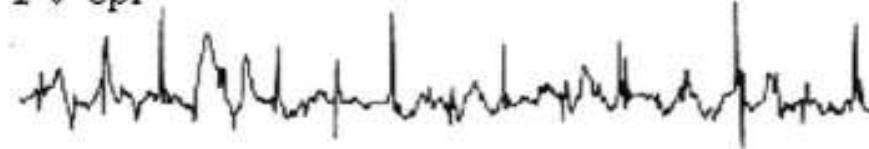
BAE



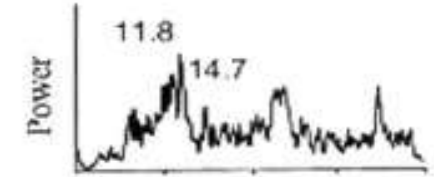
RAFW



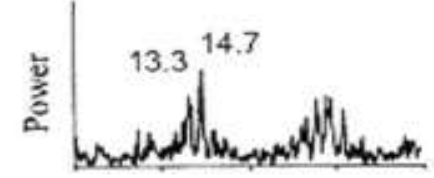
PV epi



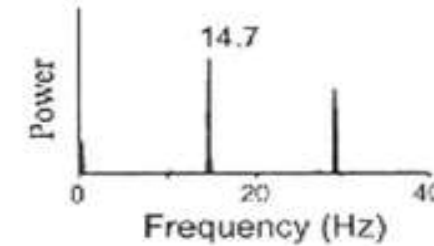
PV endo 9 o'clock



PV groove



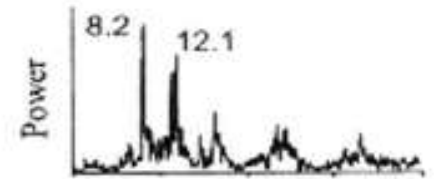
LAA base



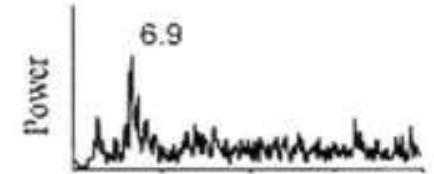
Mansour et al.  
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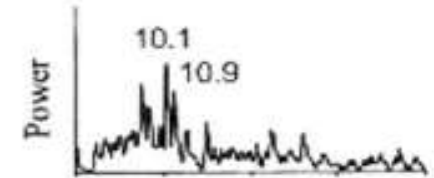
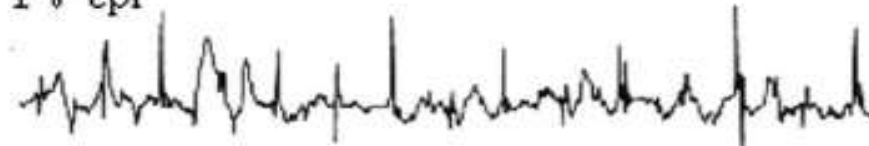
BAE



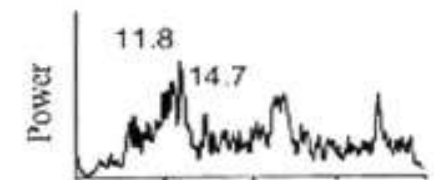
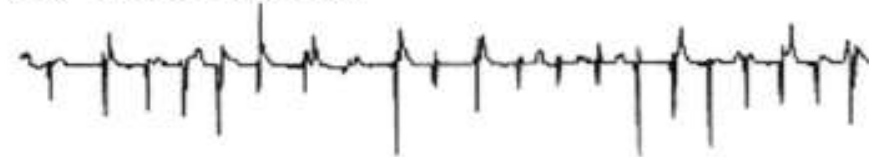
RAFW



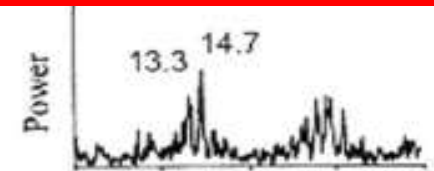
PV epi



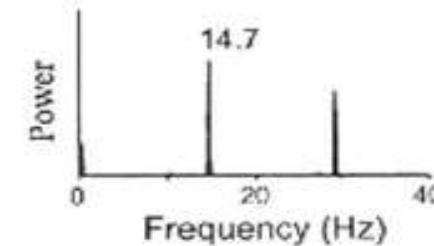
PV endo 9 o'clock



PV groove

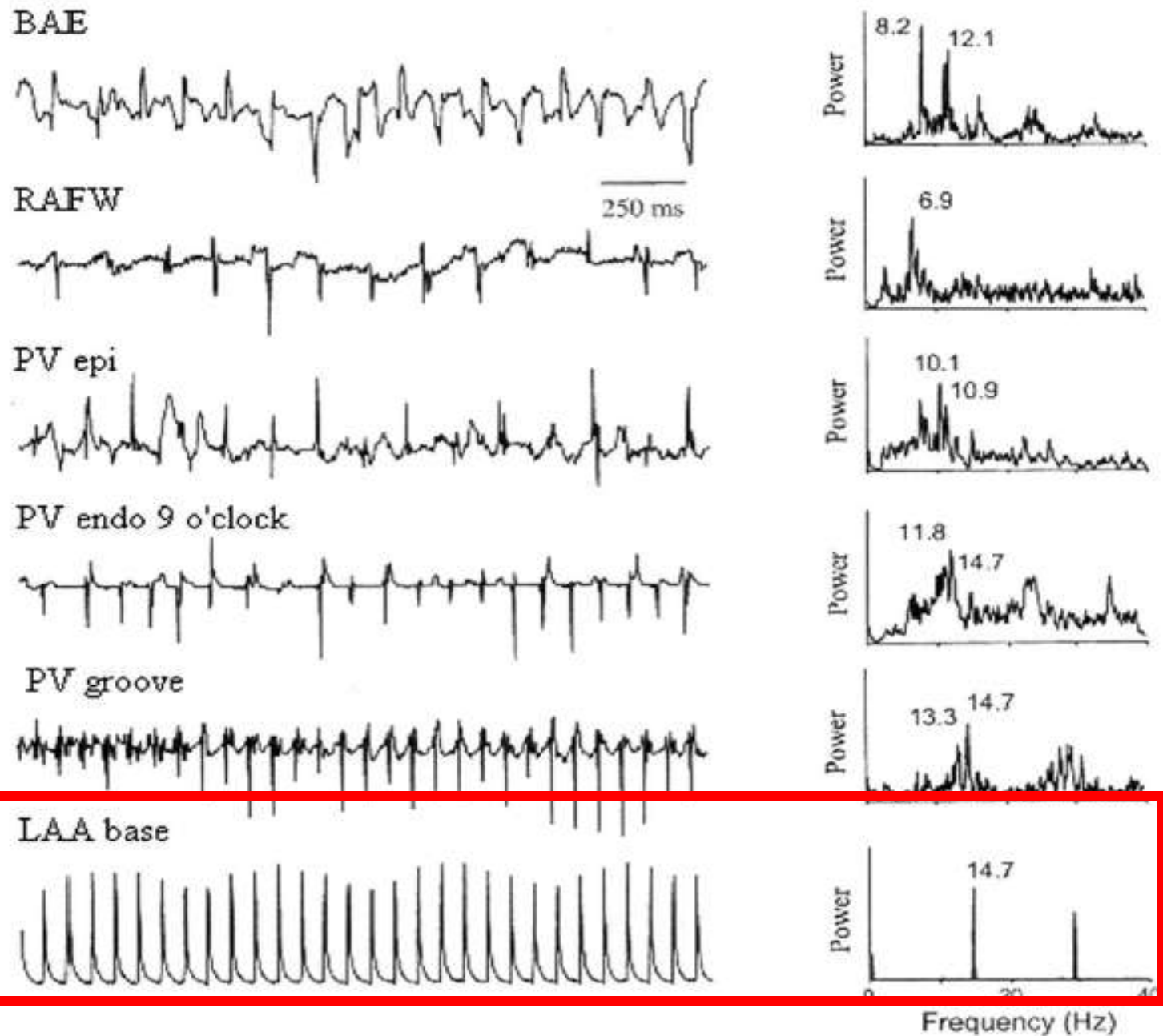


LAA base



Mansour et al.  
Circ 2001;103:2631-6

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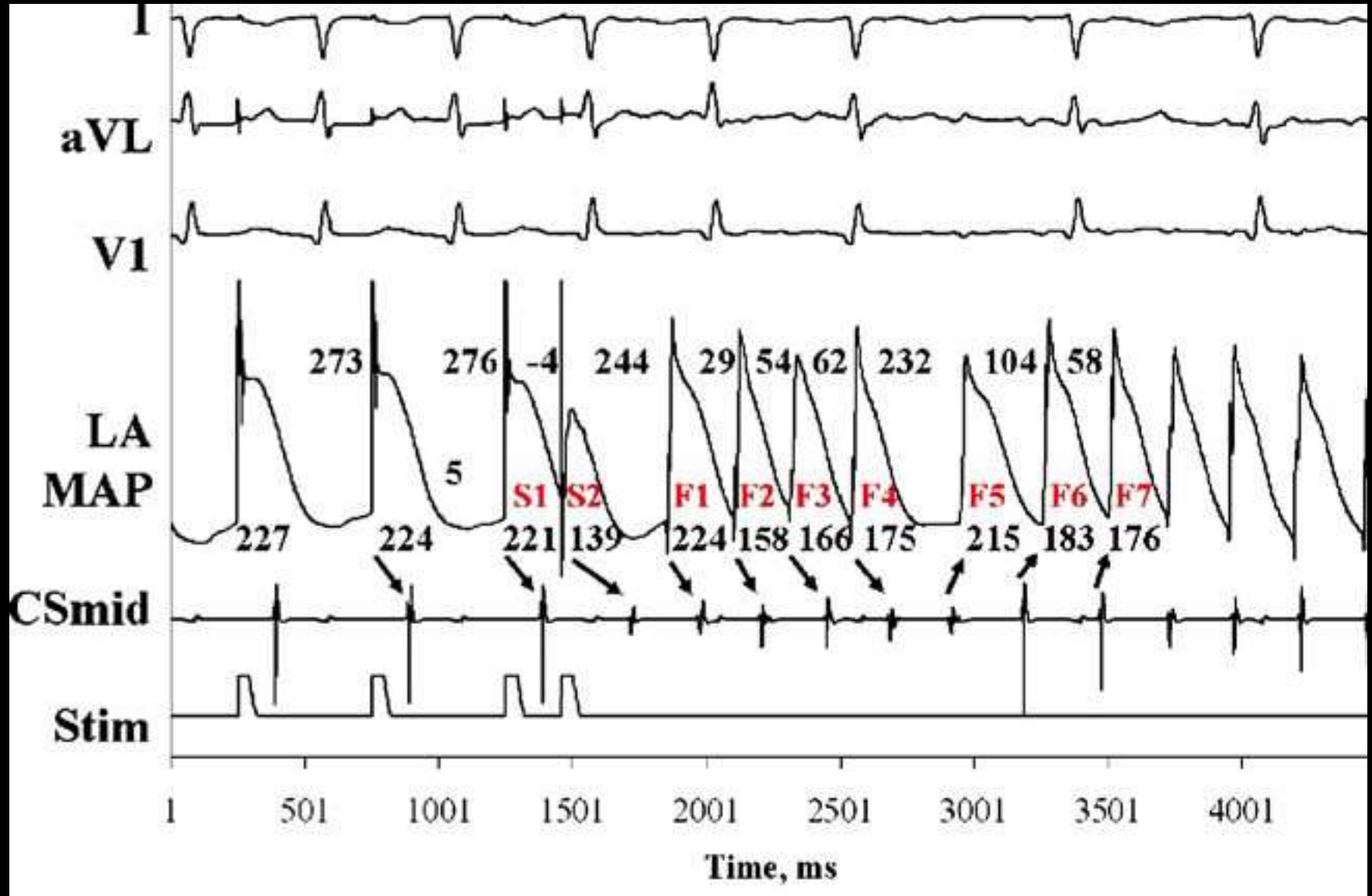


Mansour et al.  
Circ 2001;103:2631-6

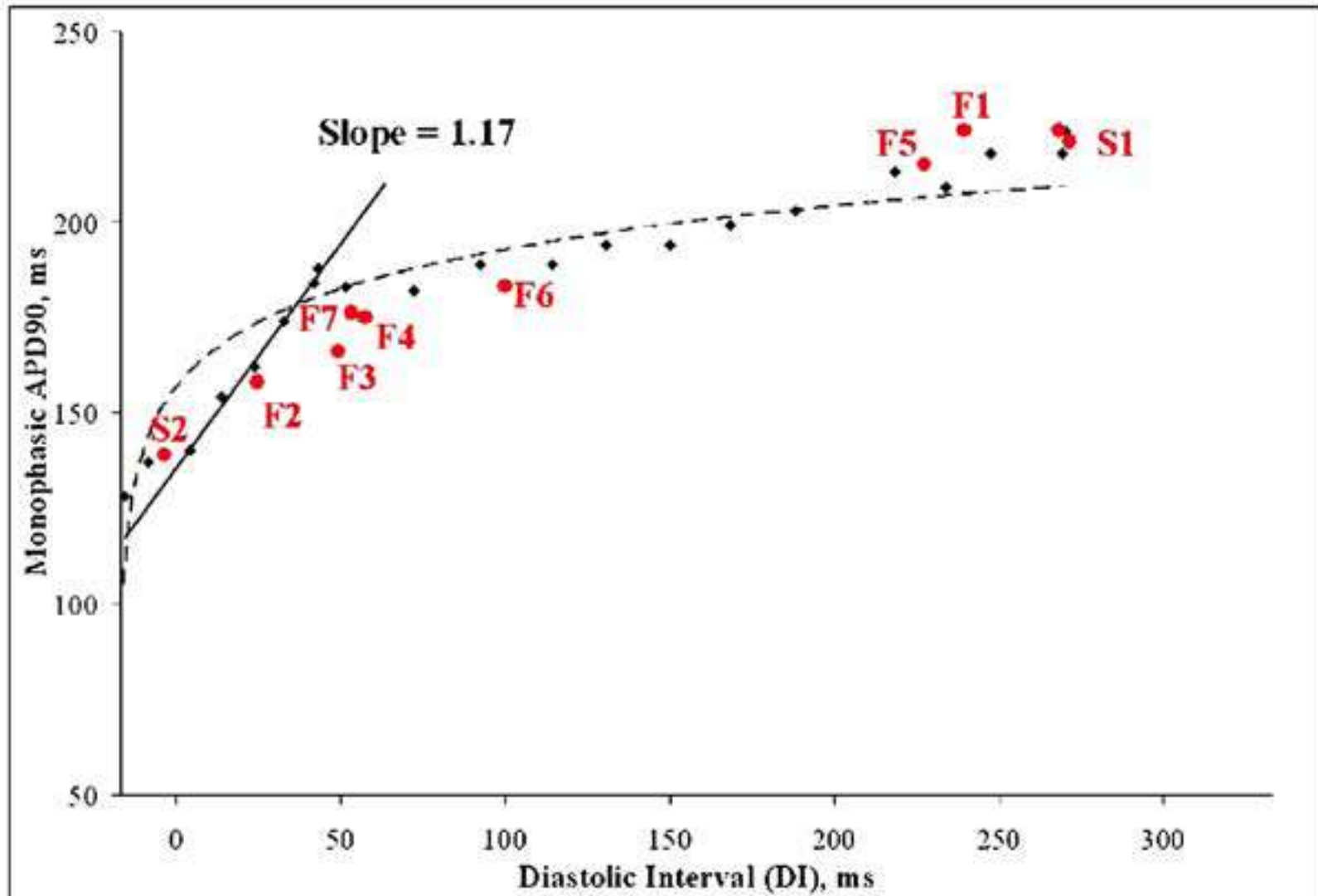
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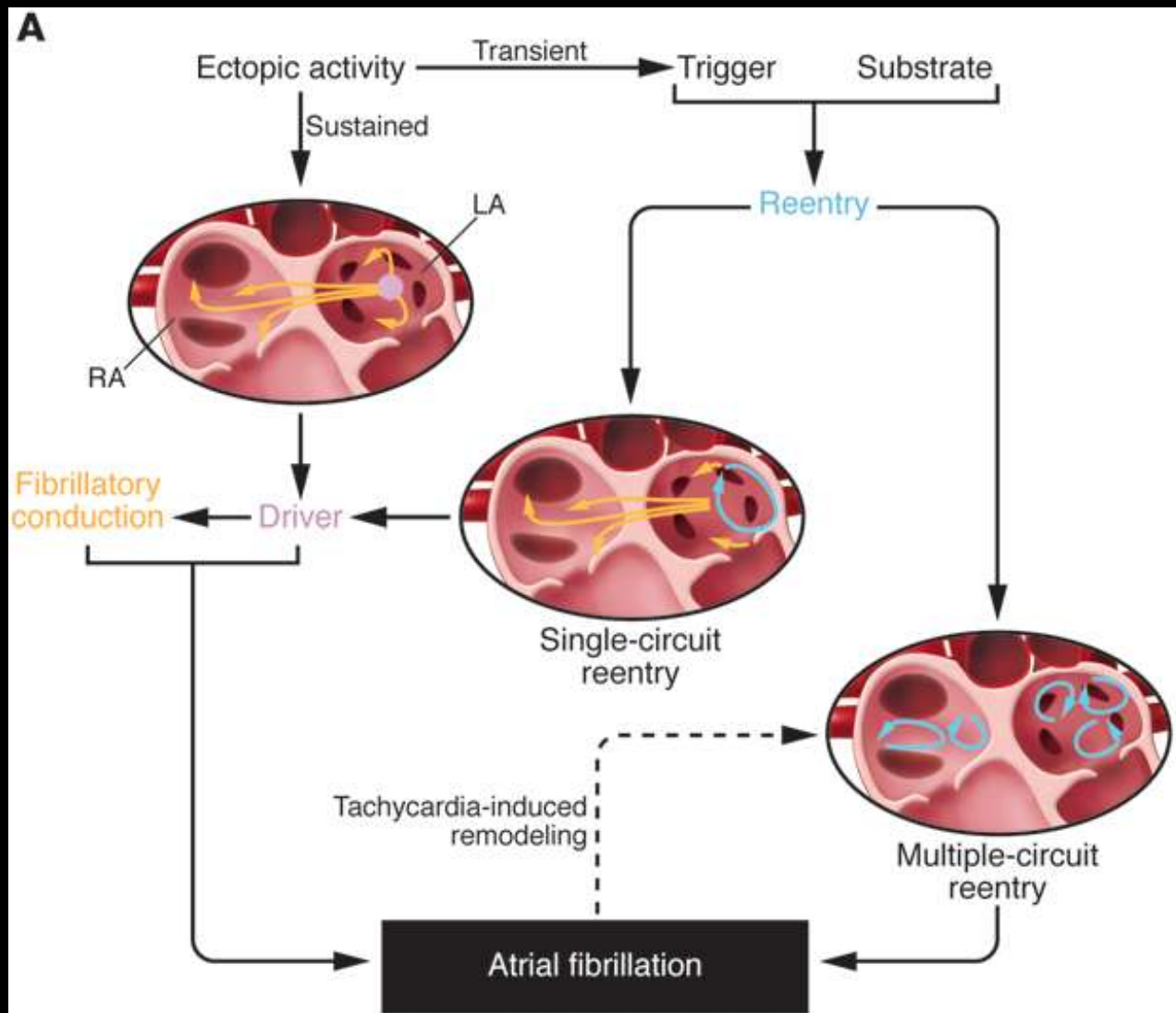
# Contribution of steep APD restitution to AF initiation



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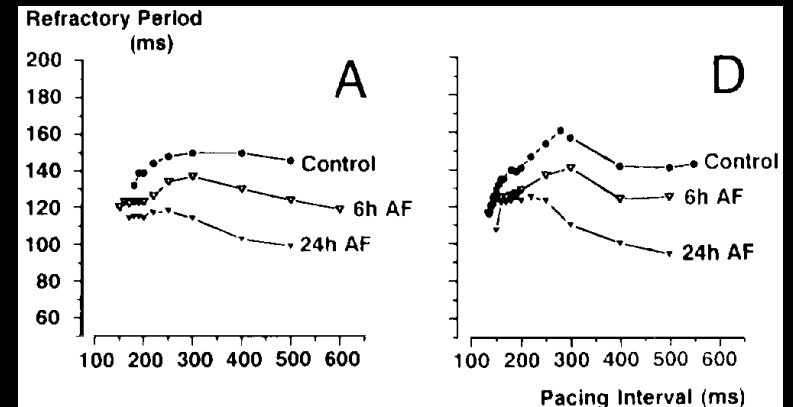
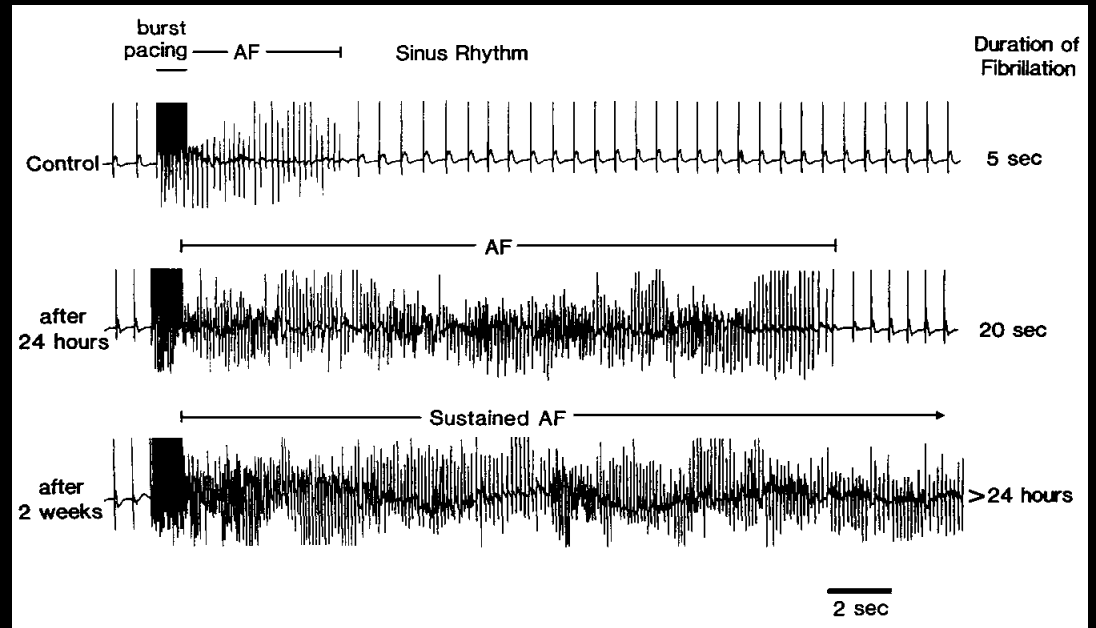


# Tissue factors leading to atrial fibrillation

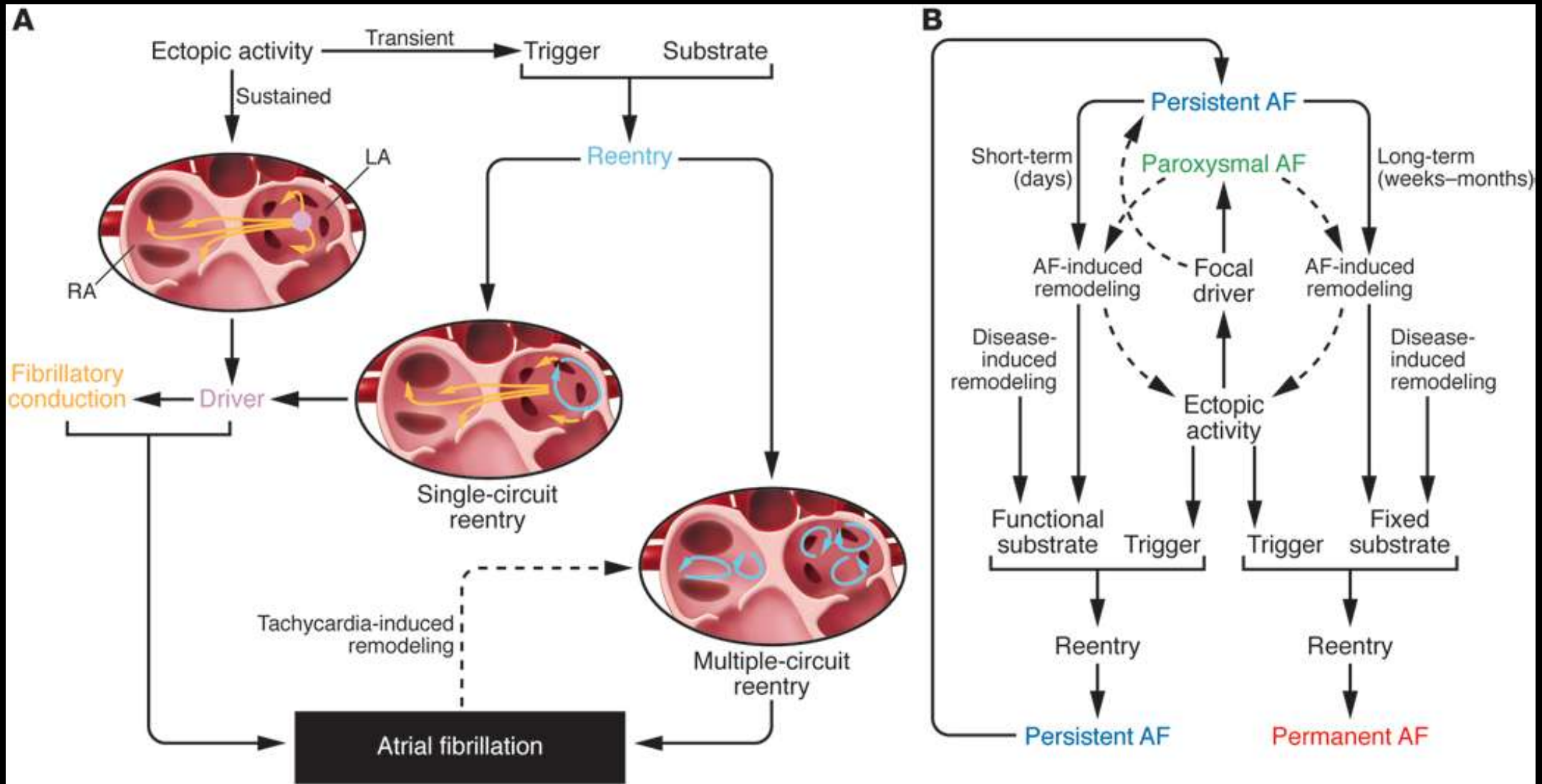


# Repetitive pacing/remodelling and atrial fibrillation

- AF artificially maintained in 12 chronically instrumented goats
- Progressive increase in AF duration
- Electrical remodeling:  $\downarrow$ AERP
- Related to rate, not stretch, ischemia, autonomic tone, ANF\*

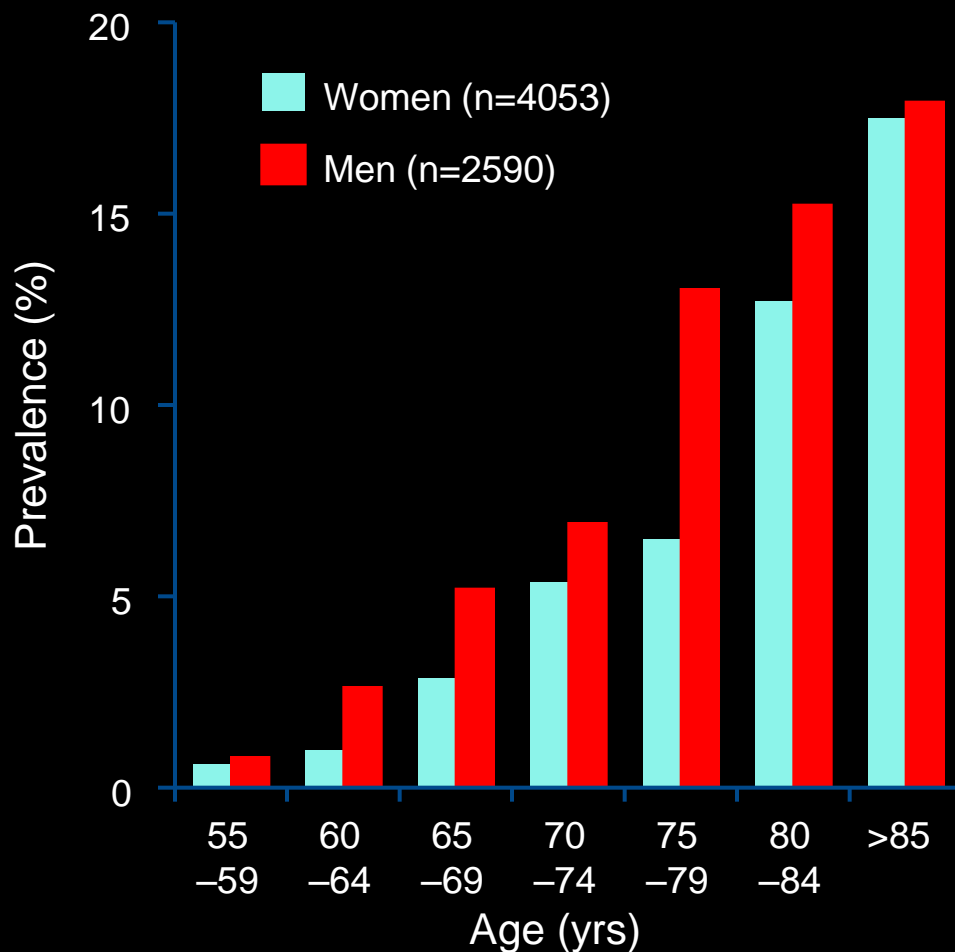


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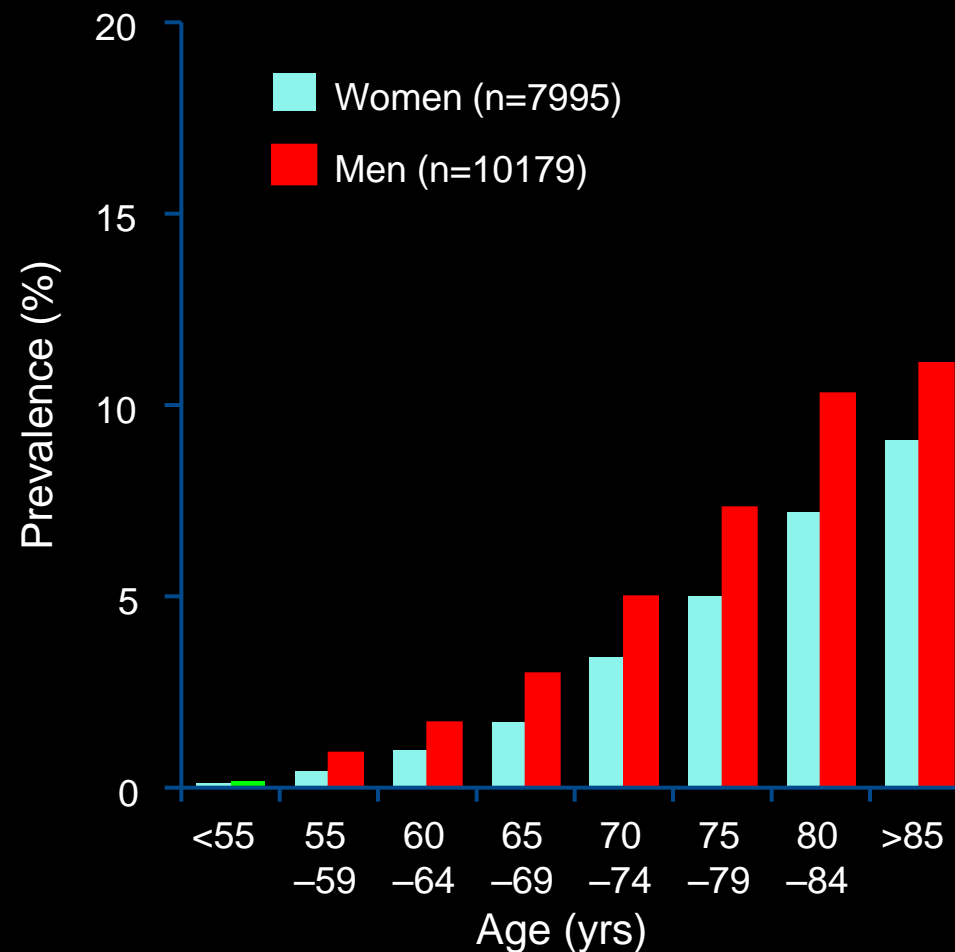


# Prevalence of AF increases with age

European age-related prevalence<sup>1</sup>

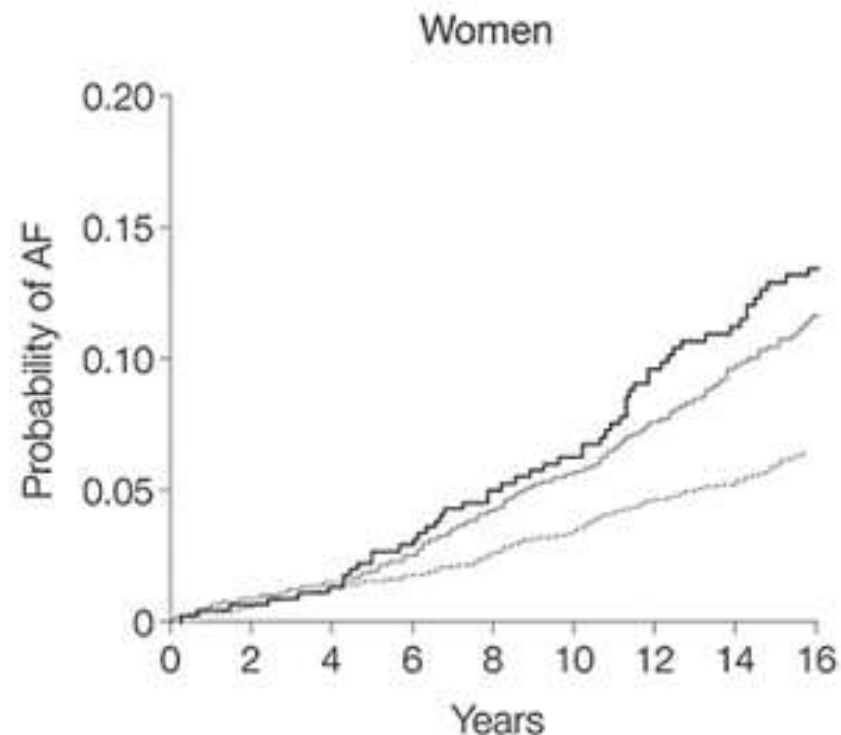
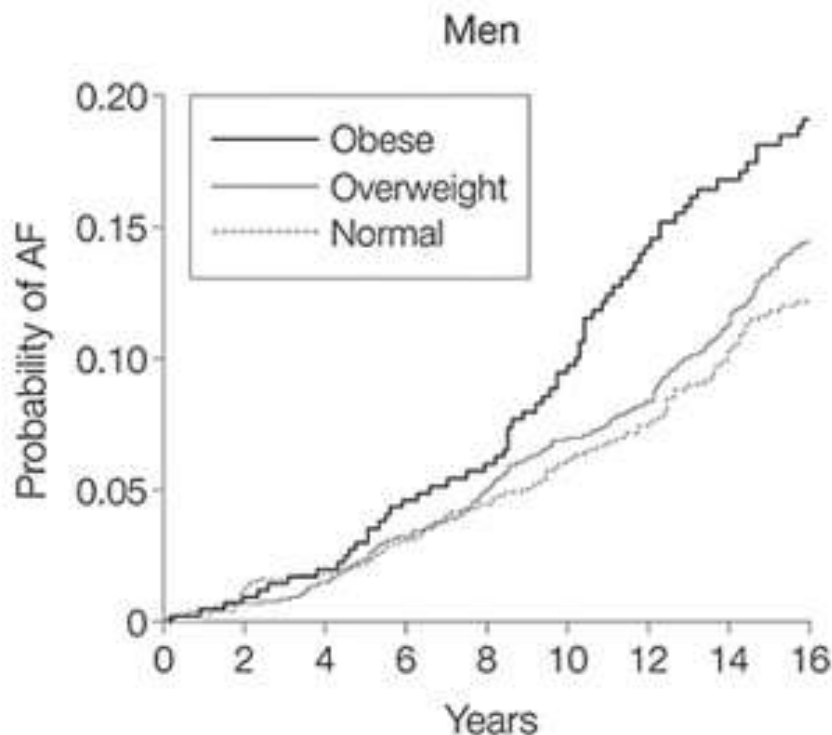


US age-related prevalence<sup>2</sup>



1. Heeringa J et al. Eur Heart J 2006;27:949-53; 2. Go AS et al. JAMA 2001;285:2370-5

# OBESITY AND AF RISK



No. at Risk

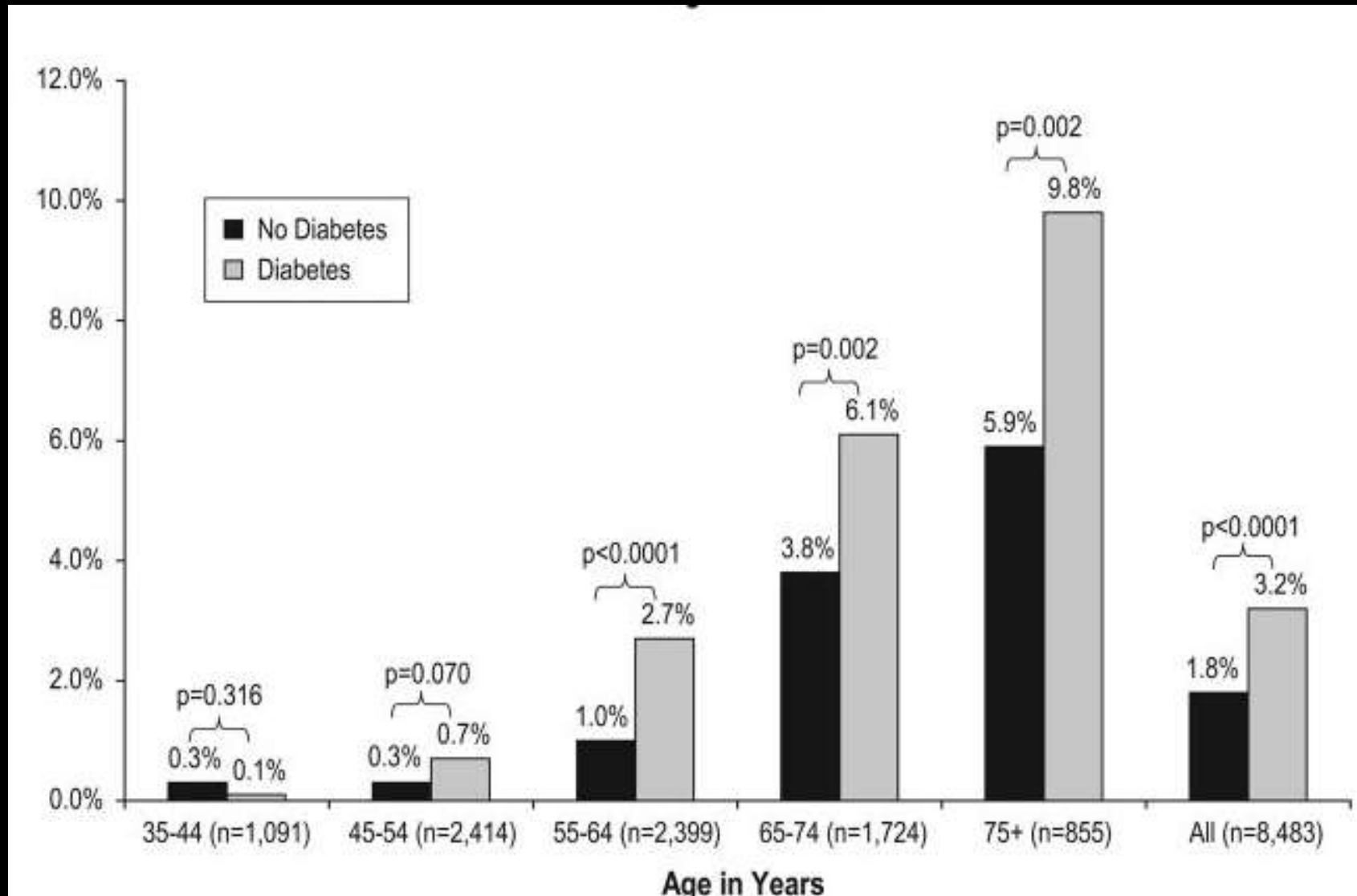
Obese	413	380	336	280	238
Overweight	1216	1143	1023	908	776
Normal	755	699	614	557	482

	464	444	397	345	299
	898	852	776	696	614
	1536	1476	1394	1282	1180

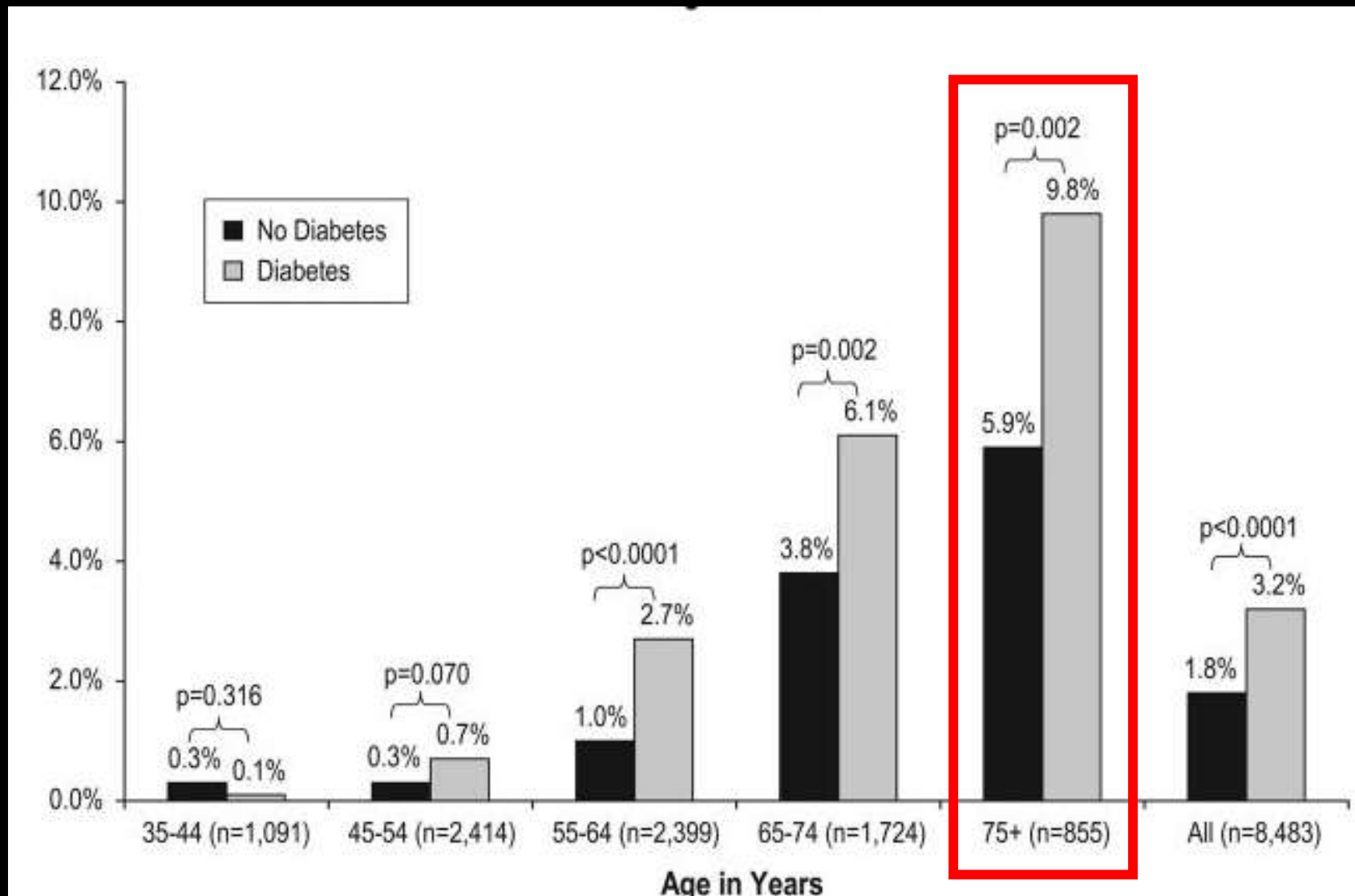
**Adjusted HR 1.5 with obesity, attributable to increased LA size**

Wang *et al*, JAMA 2004; 292:2471

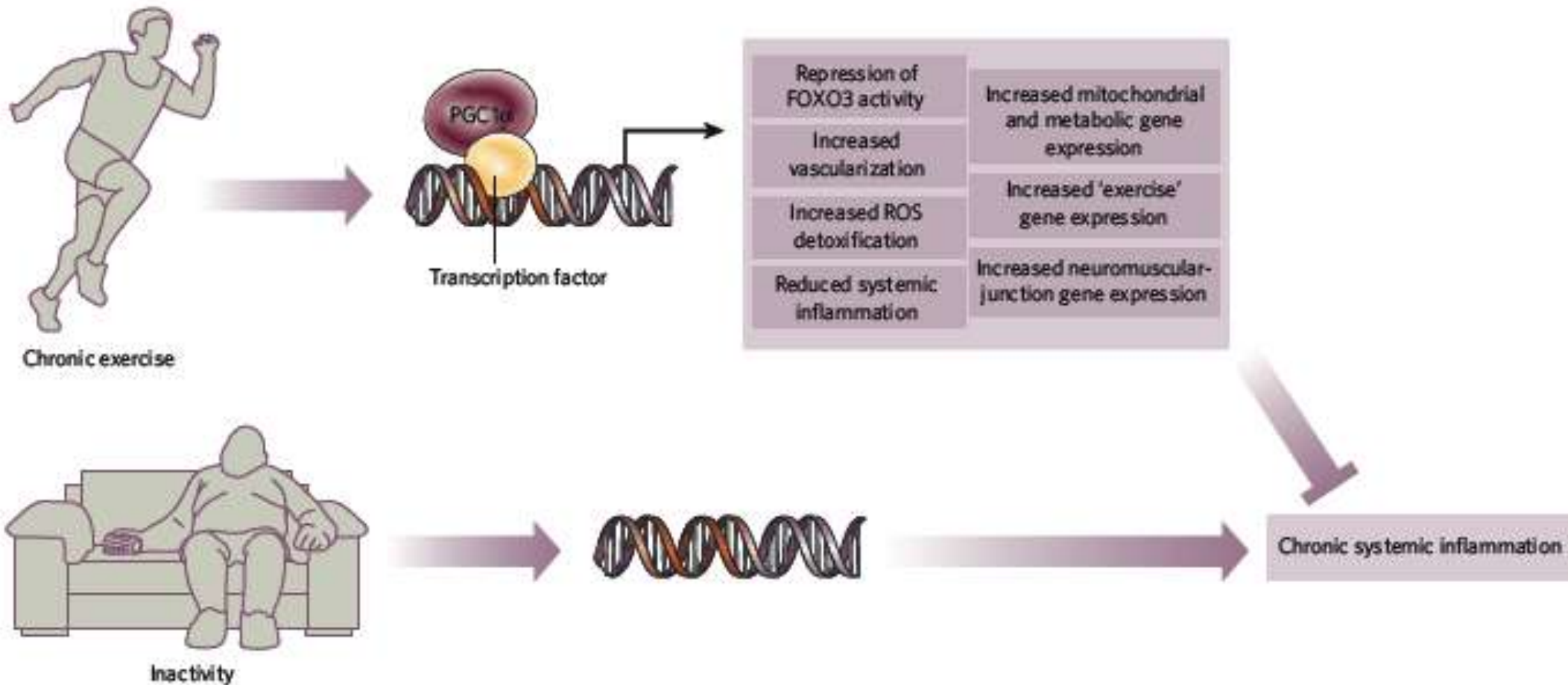
# Risk of Atrial Fibrillation and Diabetes (Women)



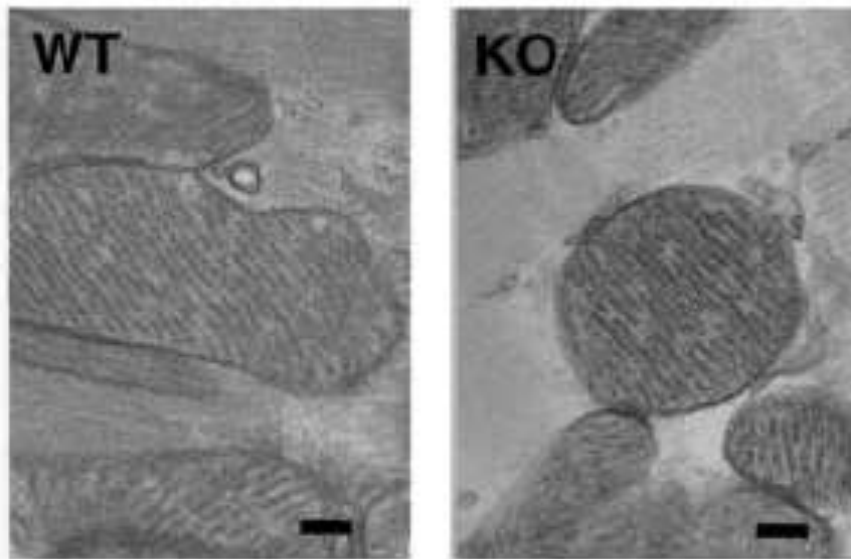
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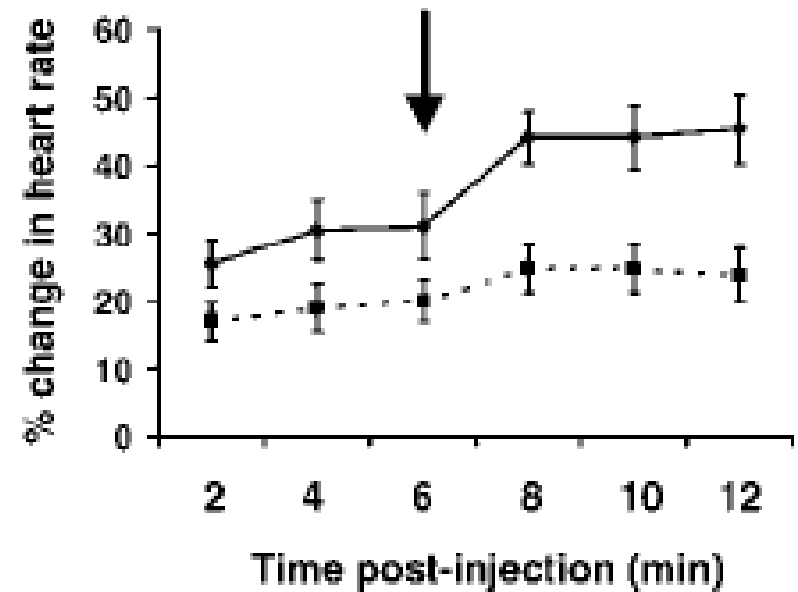
# Hypothesis: Role of exercise and PGCs in disease



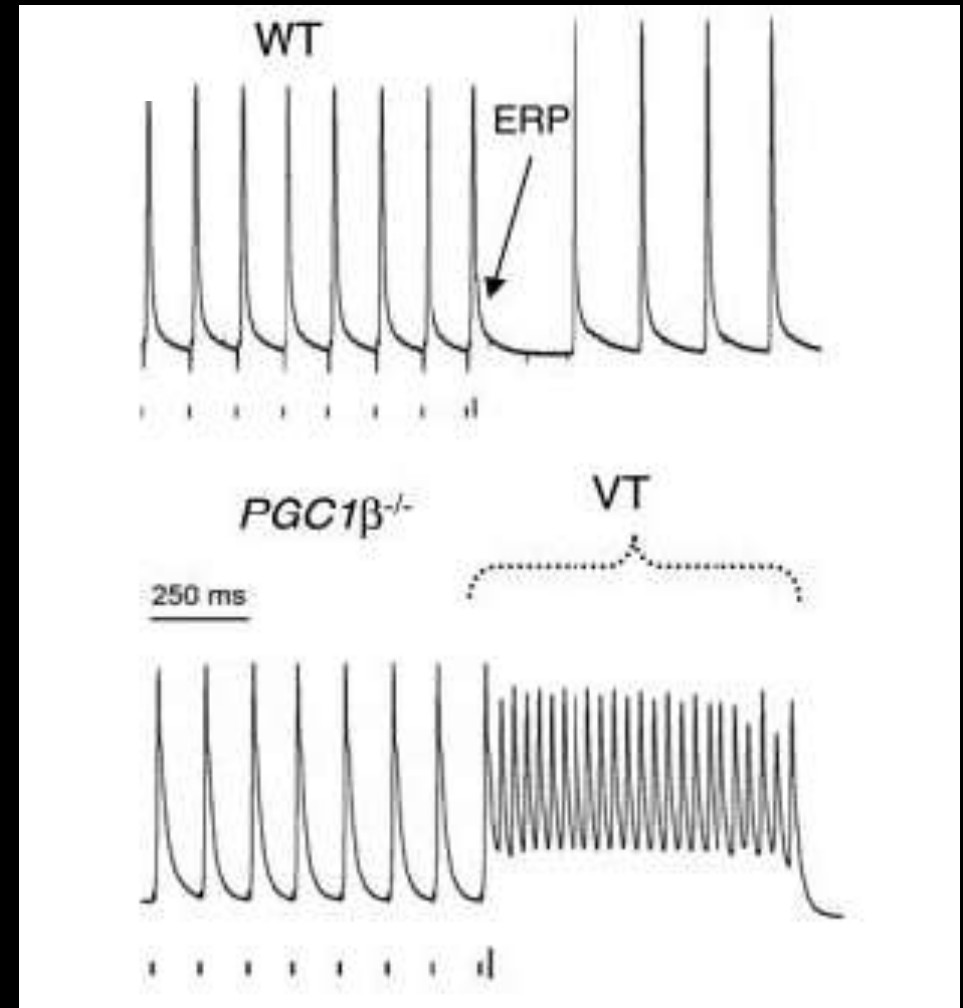
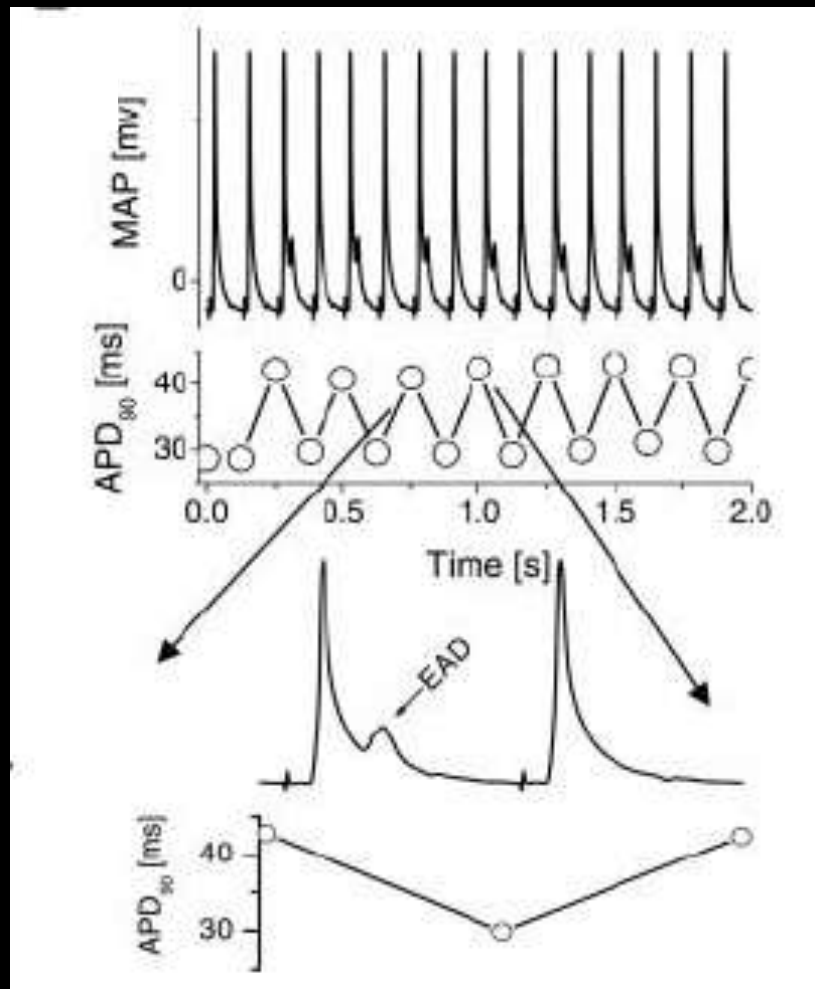
# PGC-1 $\beta$ ablation results in a major defect in mitochondrial biogenesis



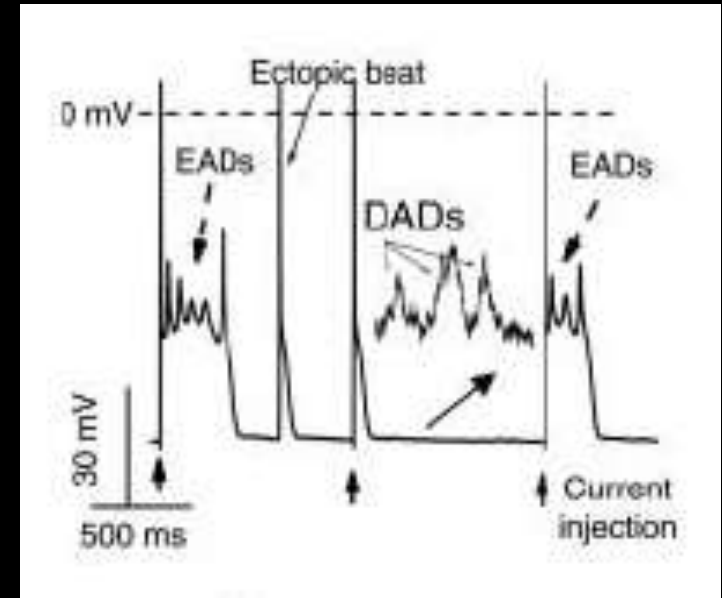
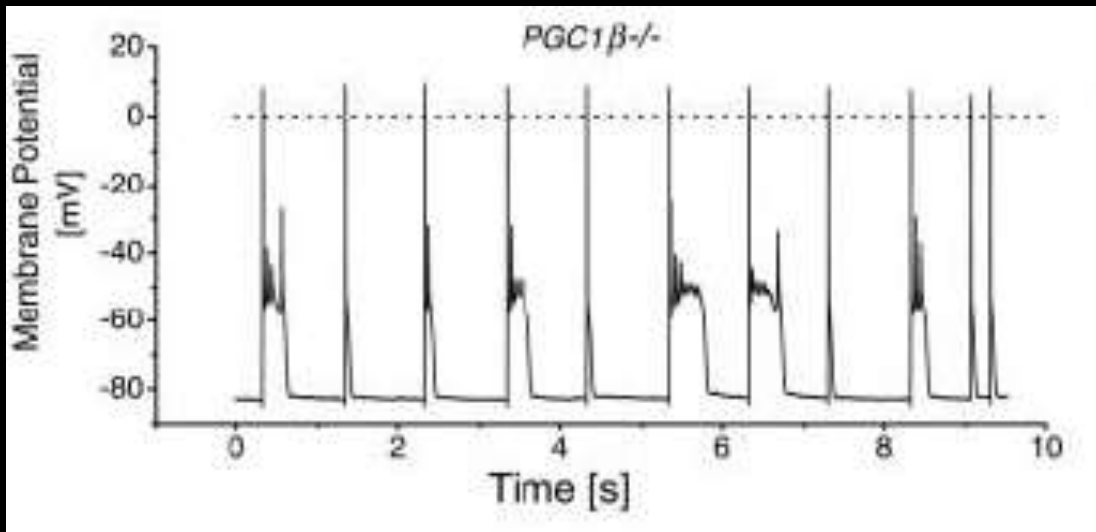
	WT	KO
Vv (%)	42.7 $\pm$ 2.8	35.3 $\pm$ 0.3*
Sv - outer ( $\mu\text{m}^2/\mu\text{m}^3$ )	5.73 $\pm$ 0.33	5.33 $\pm$ 0.66
Sv - inner ( $\mu\text{m}^2/\mu\text{m}^3$ )	10.17 $\pm$ 0.02	10.32 $\pm$ 1.18



# Cardiac Arrhythmia in PGC-1 $\beta$ -/- mice (Langendorff-perfusion)

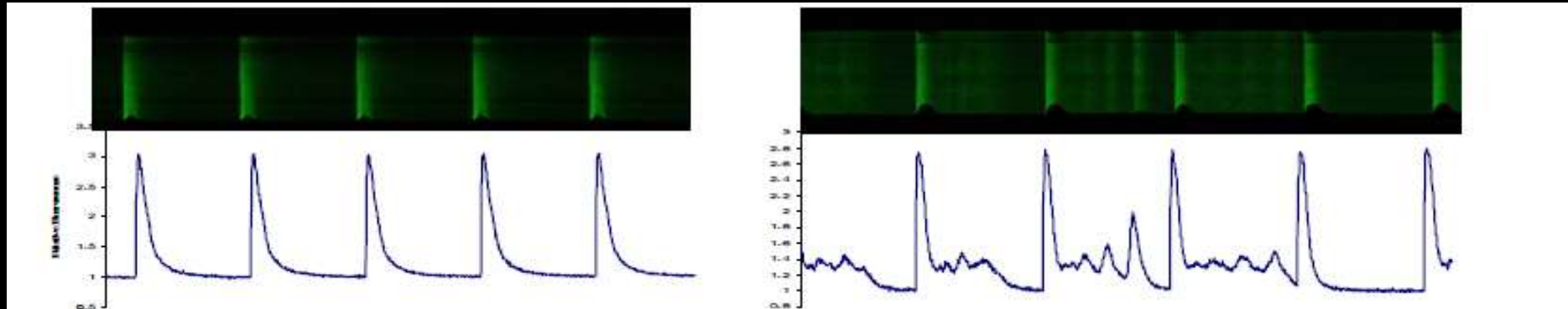


# Cardiac Arrhythmia in PGC-1 $\beta$ -/- mice (Isolated cells)



Wild-type

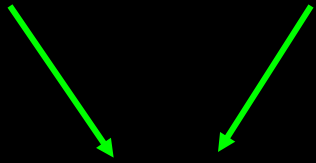
PGC1 $\beta$ -/-



# Transcriptional co-activators (PGCs) mitochondrial biogenesis and cardiac arrhythmias

Inactivity

Obesity and  
nutrient excess

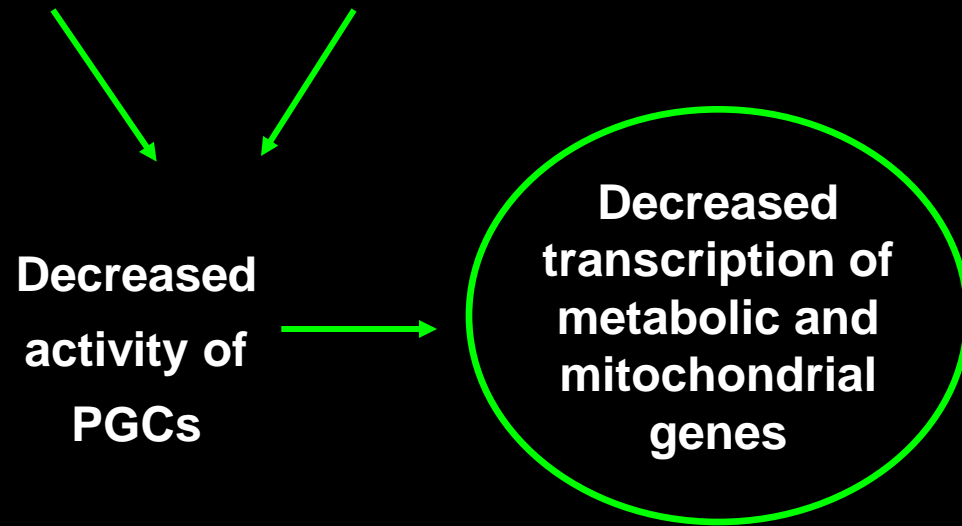


Decreased  
activity of  
PGCs

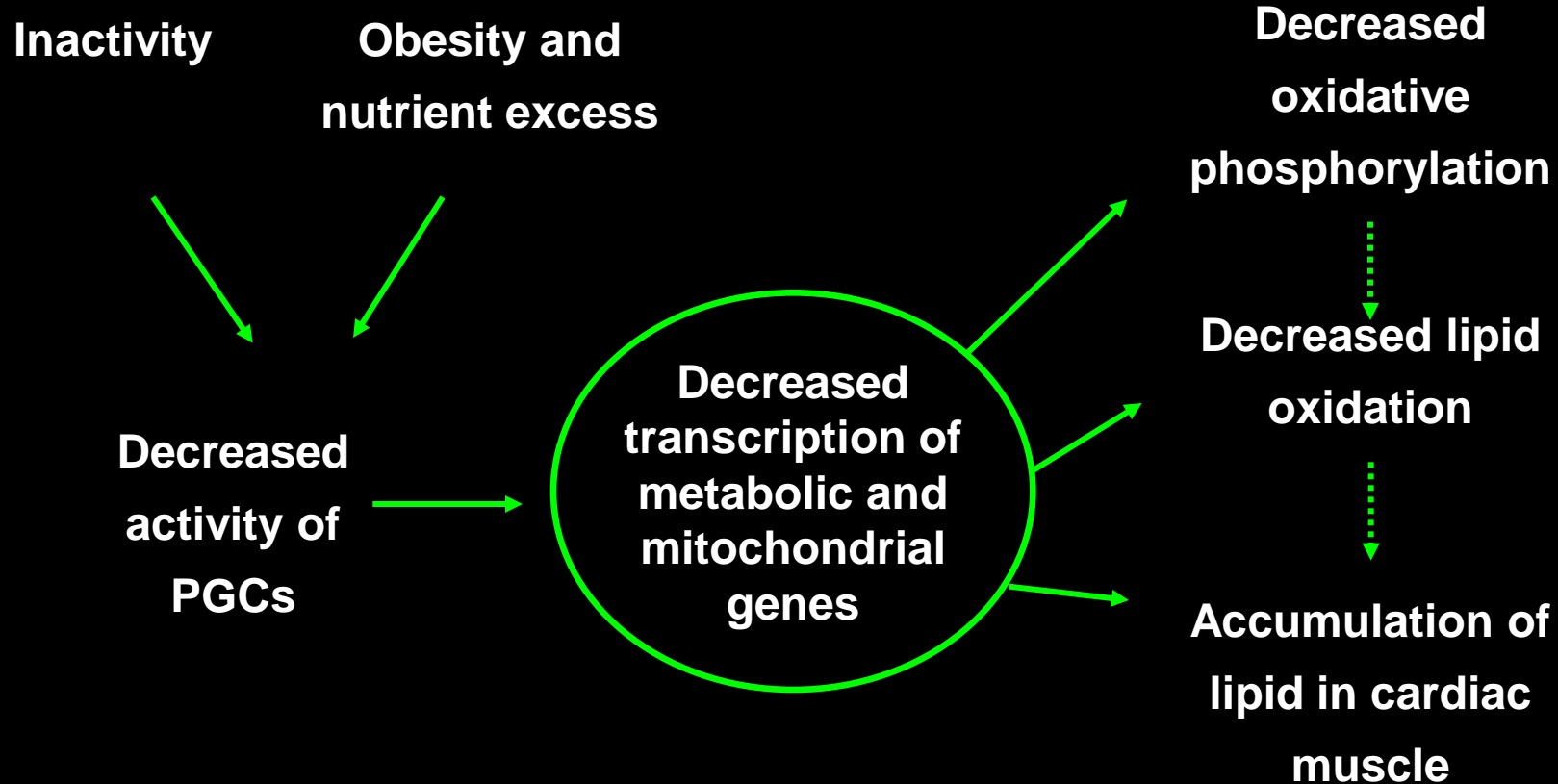
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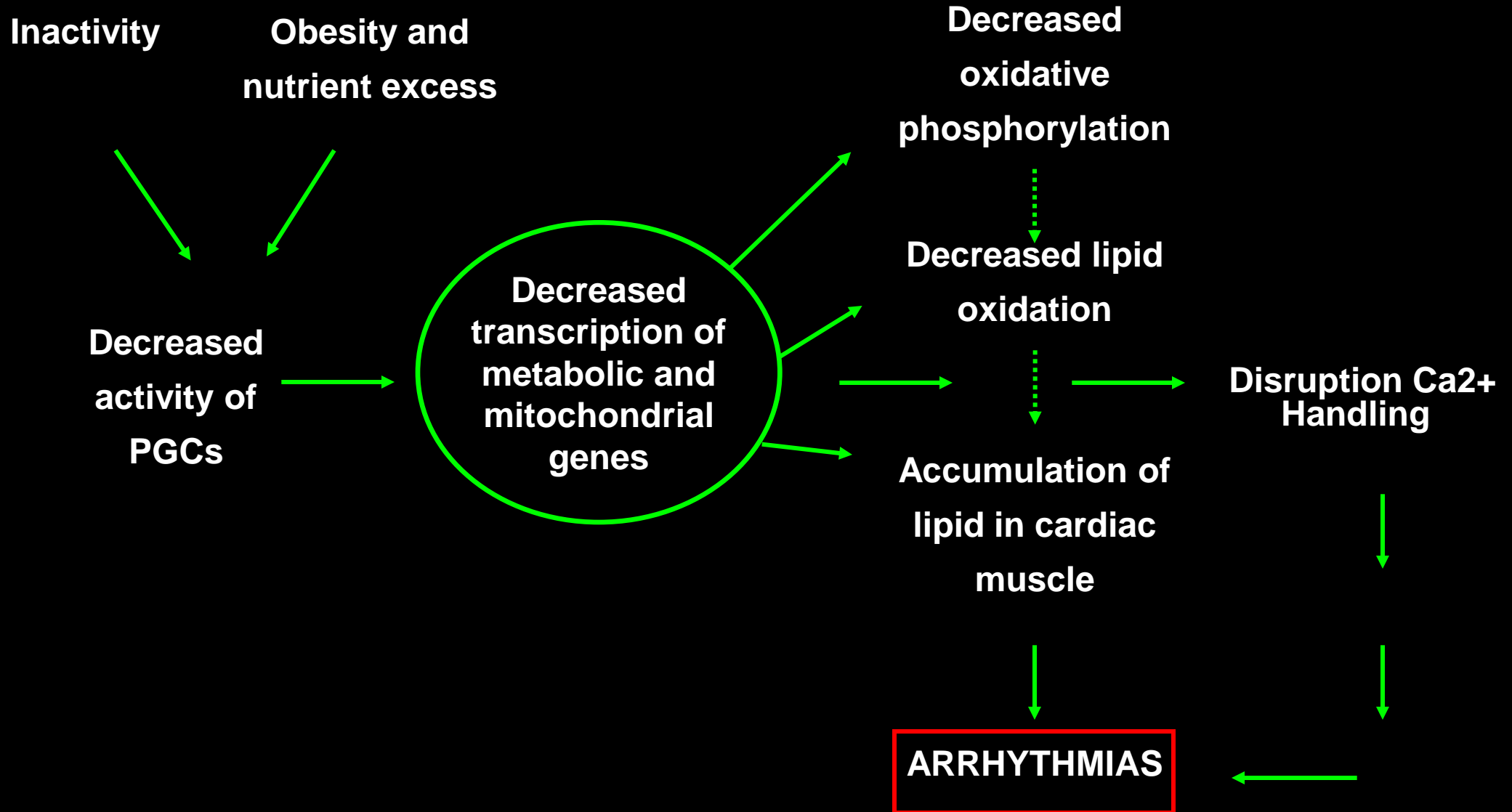
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# Transcriptional co-activators (PGCs) mitochondrial biogenesis and cardiac arrhythmias



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# Electrophysiological mechanisms AF

- **PVs critical triggers**

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  - **Genetic determination critical**
  - **Clear-cut risks - age, obesity, LA size**

# Electrophysiological mechanisms AF

- **PVs critical triggers**
- **Vulnerable atrium**
  - Genetic determination critical
  - Clear-cut risks - age, obesity, LA size
- **Inflammatory/metabolic stressors**  
(mitochondria/ROS etc.)