

# 'AF Begets AF'

## The Role of Early Action

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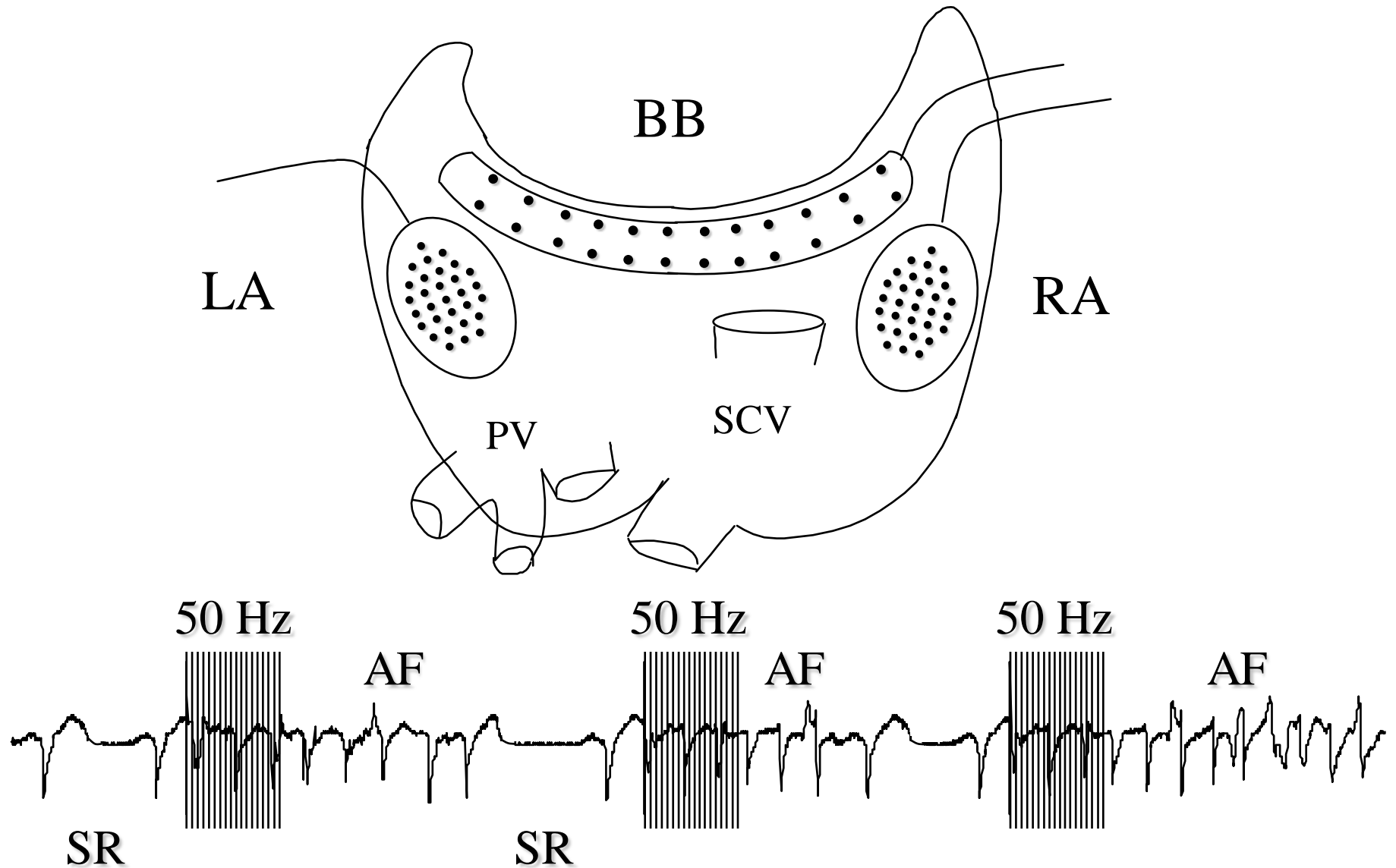
Maastricht, The Netherlands

# 1995

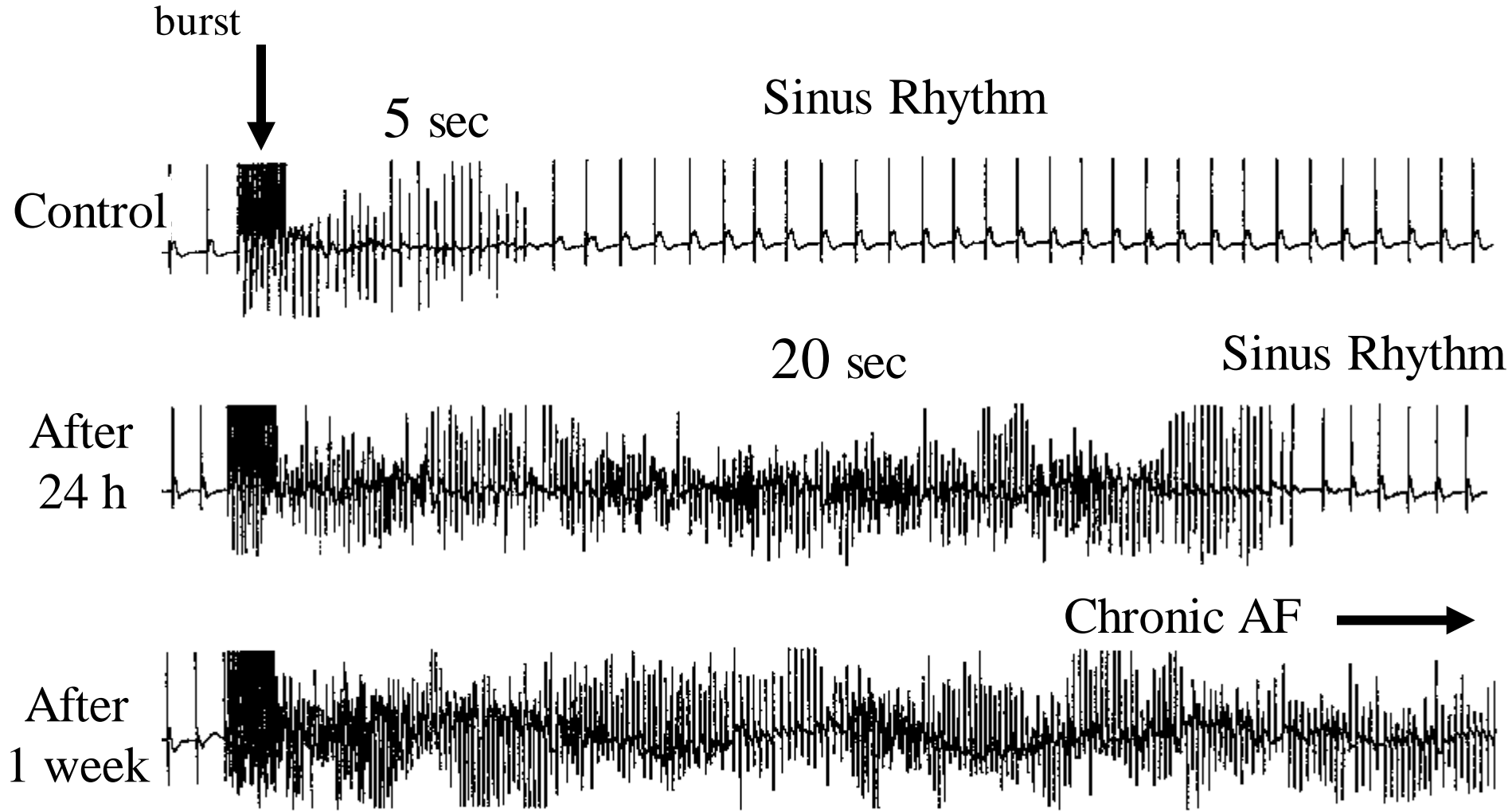
## Atrial Remodeling

- *Morillo et al. Circulation 1995; 91: 1588-1595*  
Chronic Rapid Atrial Pacing  
Structural, functional, electrophysiological characteristics  
of a new model of sustained atrial fibrillation (dog)
- *Wijffels et al. Circulation 1995; 92: 1954-1968*  
Atrial Fibrillation Begets Atrial Fibrillation  
A study in awake chronically instrumented goats

# The Goat model of AF

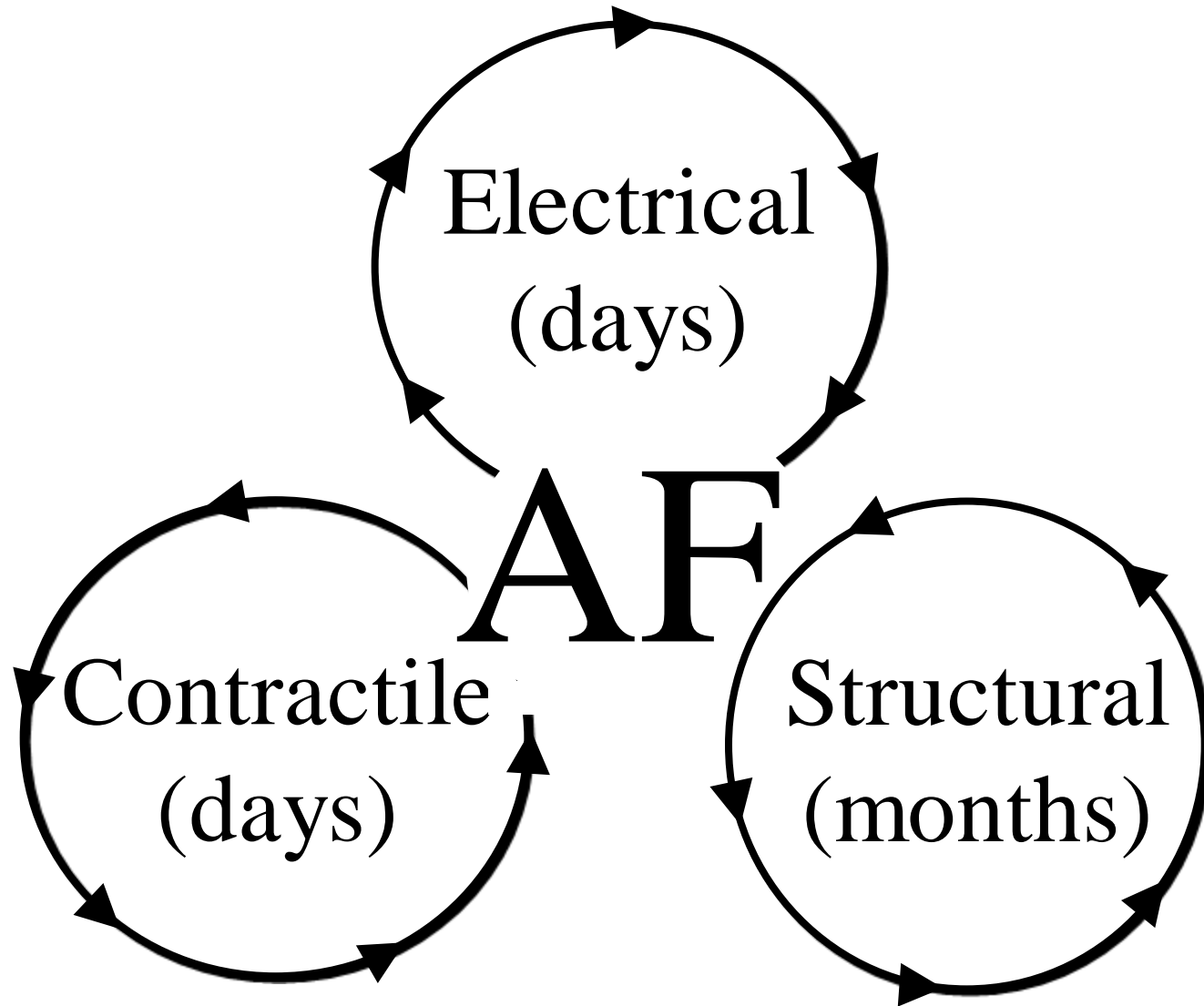


# Paroxysmal → Persistent AF



*Wijffels et al. Circulation 1995*

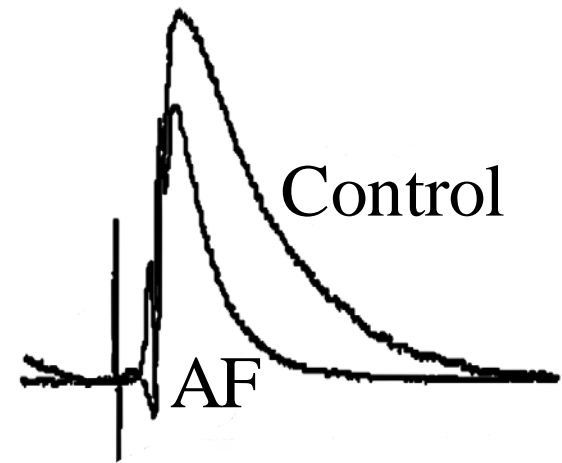
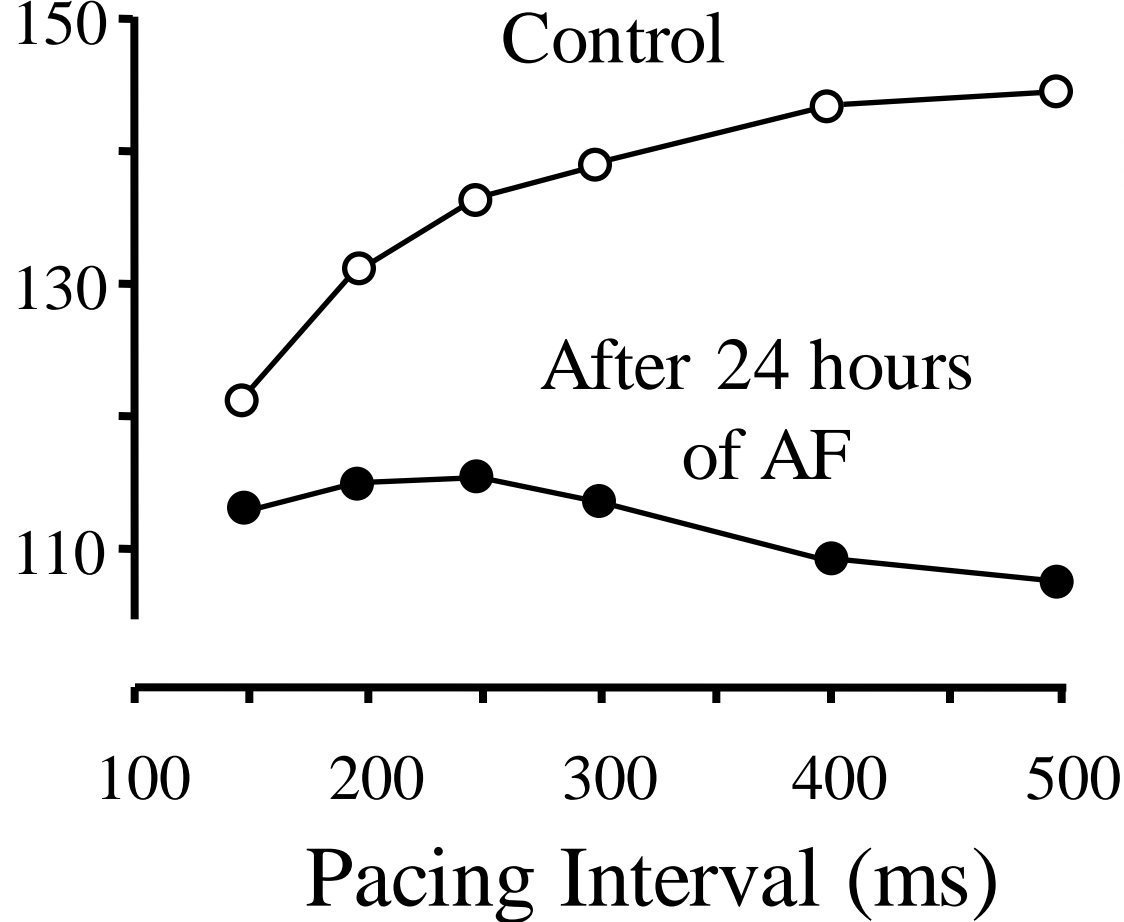
# The 3 Wheels of Atrial Remodeling



# The First Days....

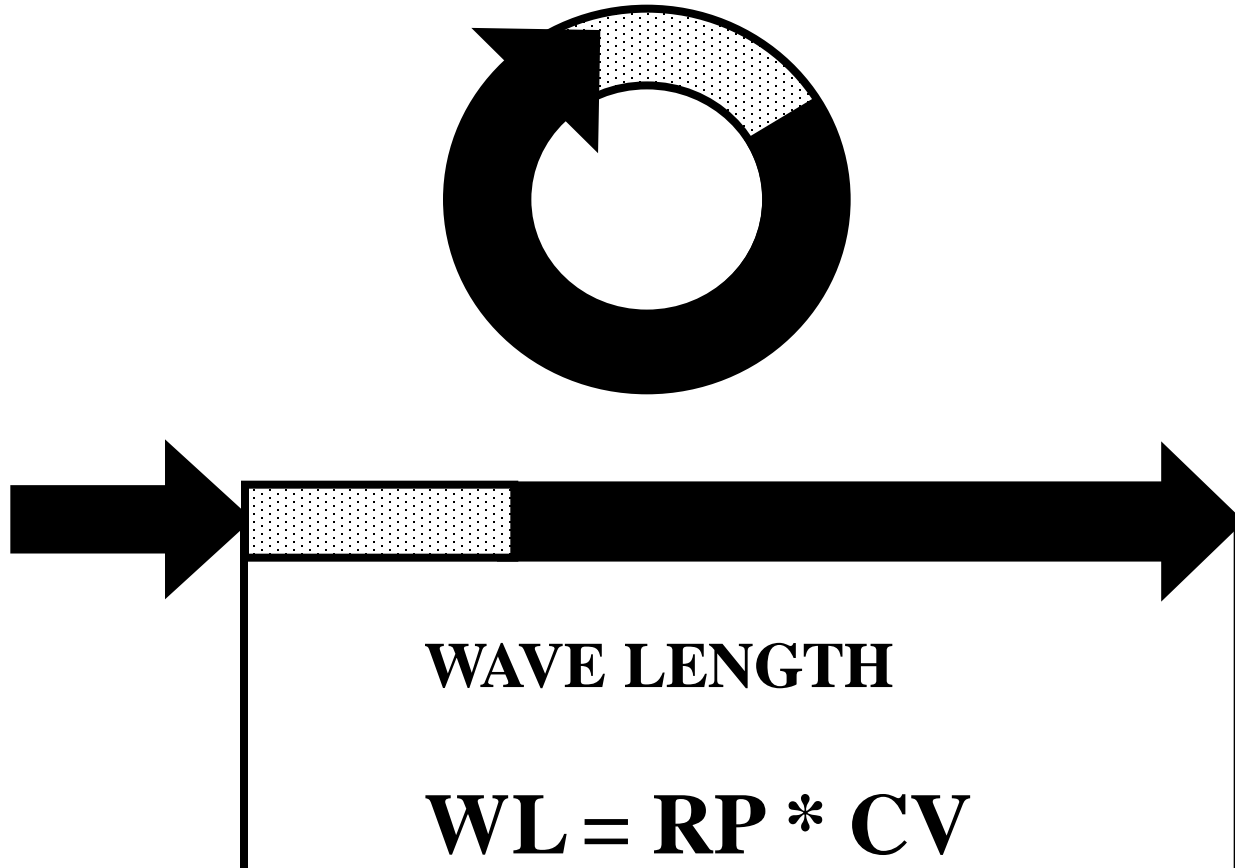
AERP

(ms)



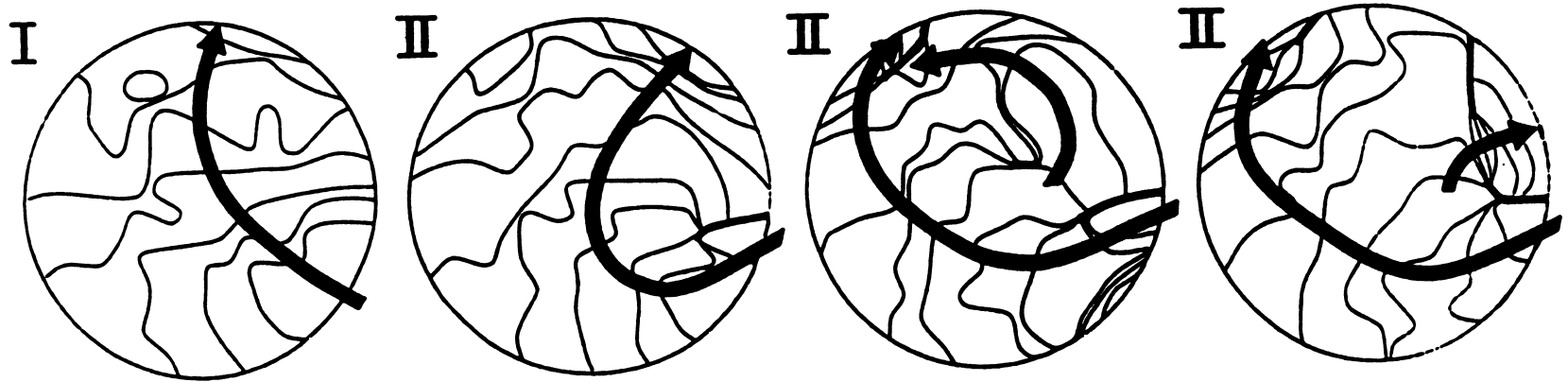
*Wijffels et al.  
Circulation 1995*

# Shortening of the Wavelength

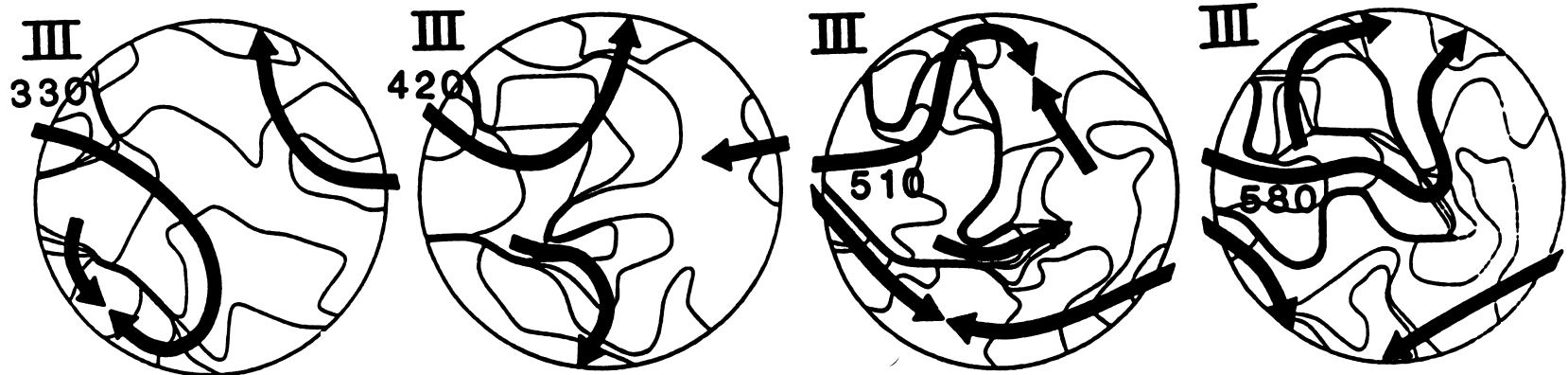


# Increased Number of Wavelets

## Acute AF

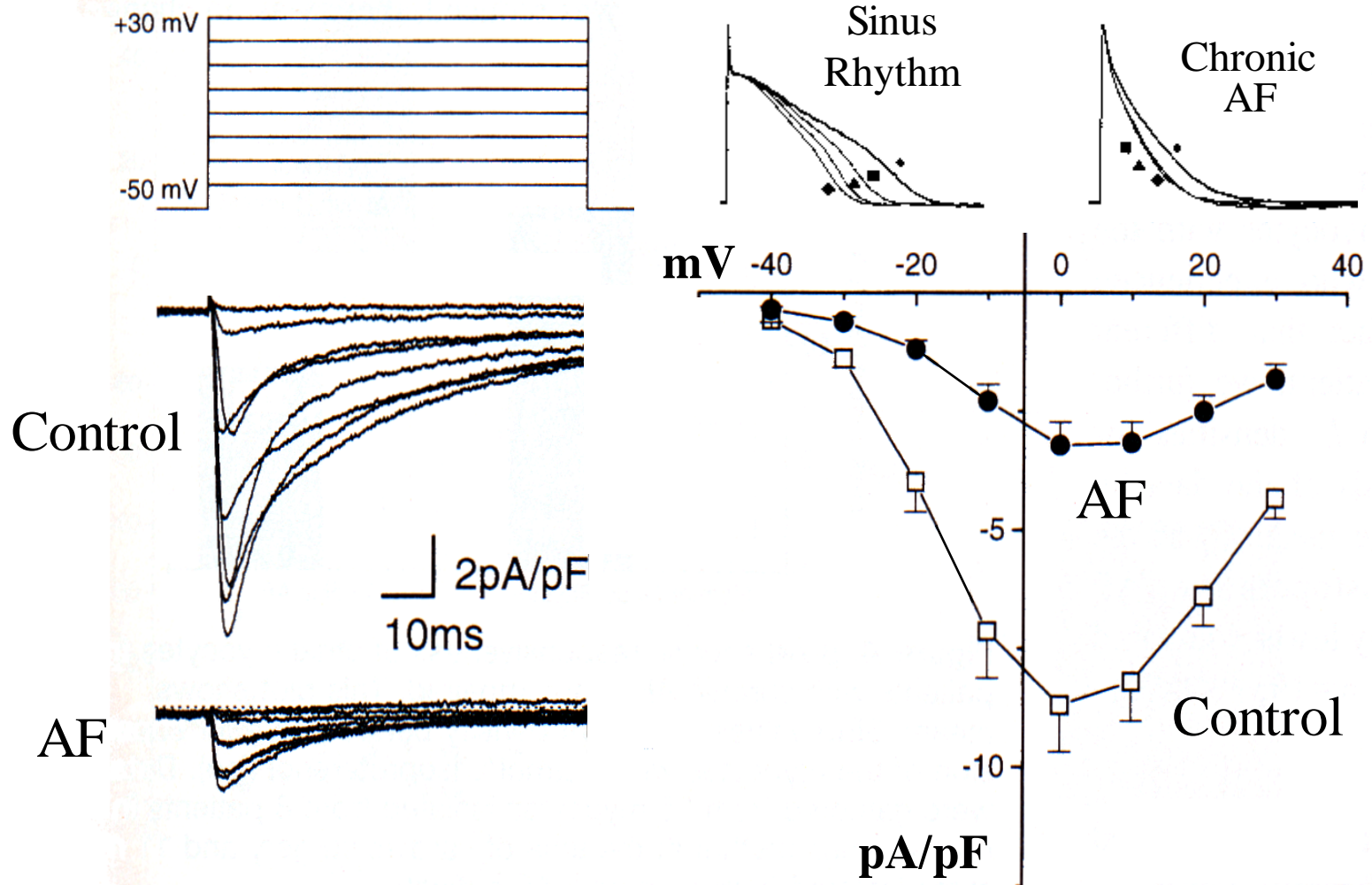


## Persistent AF

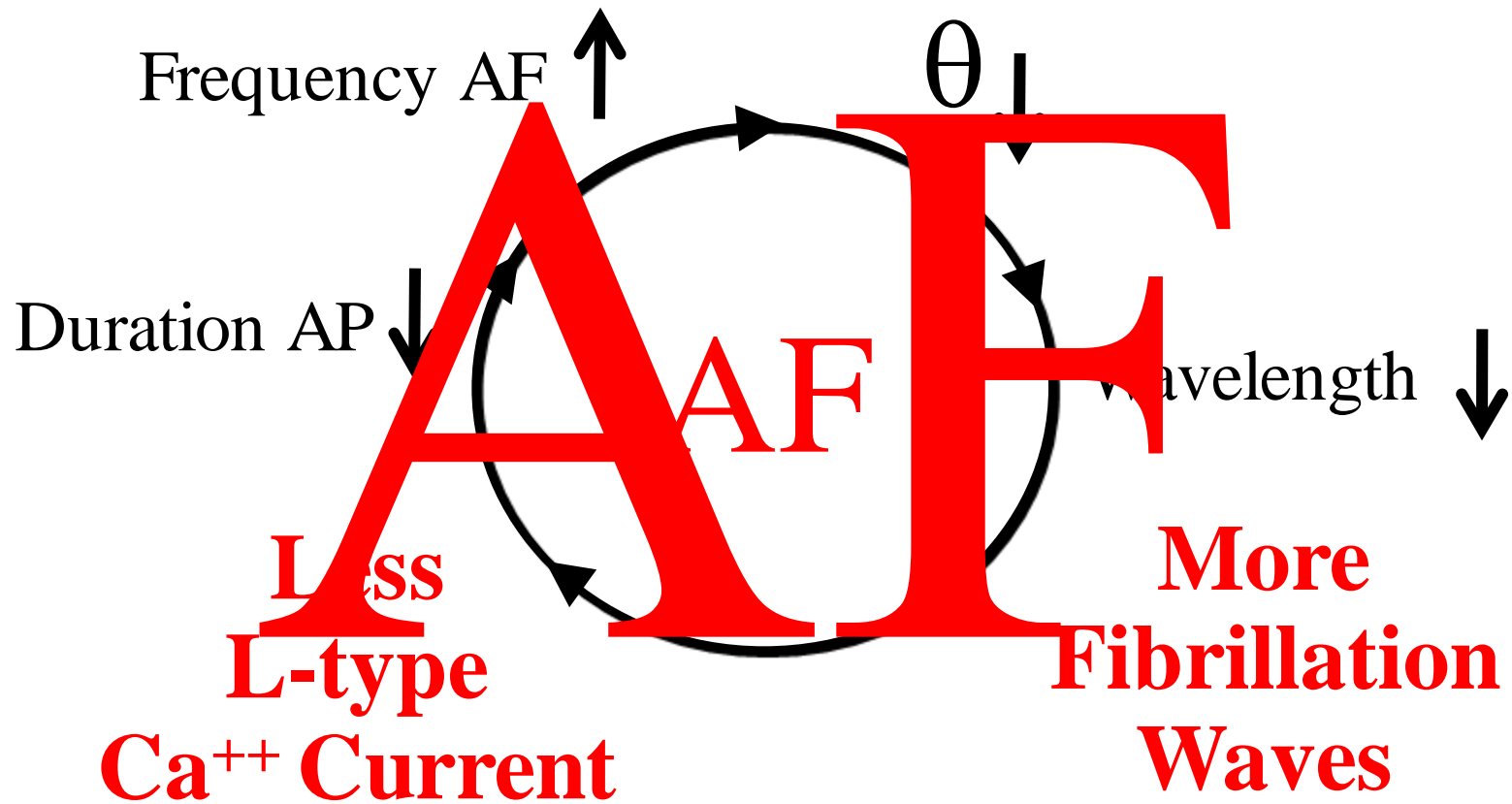




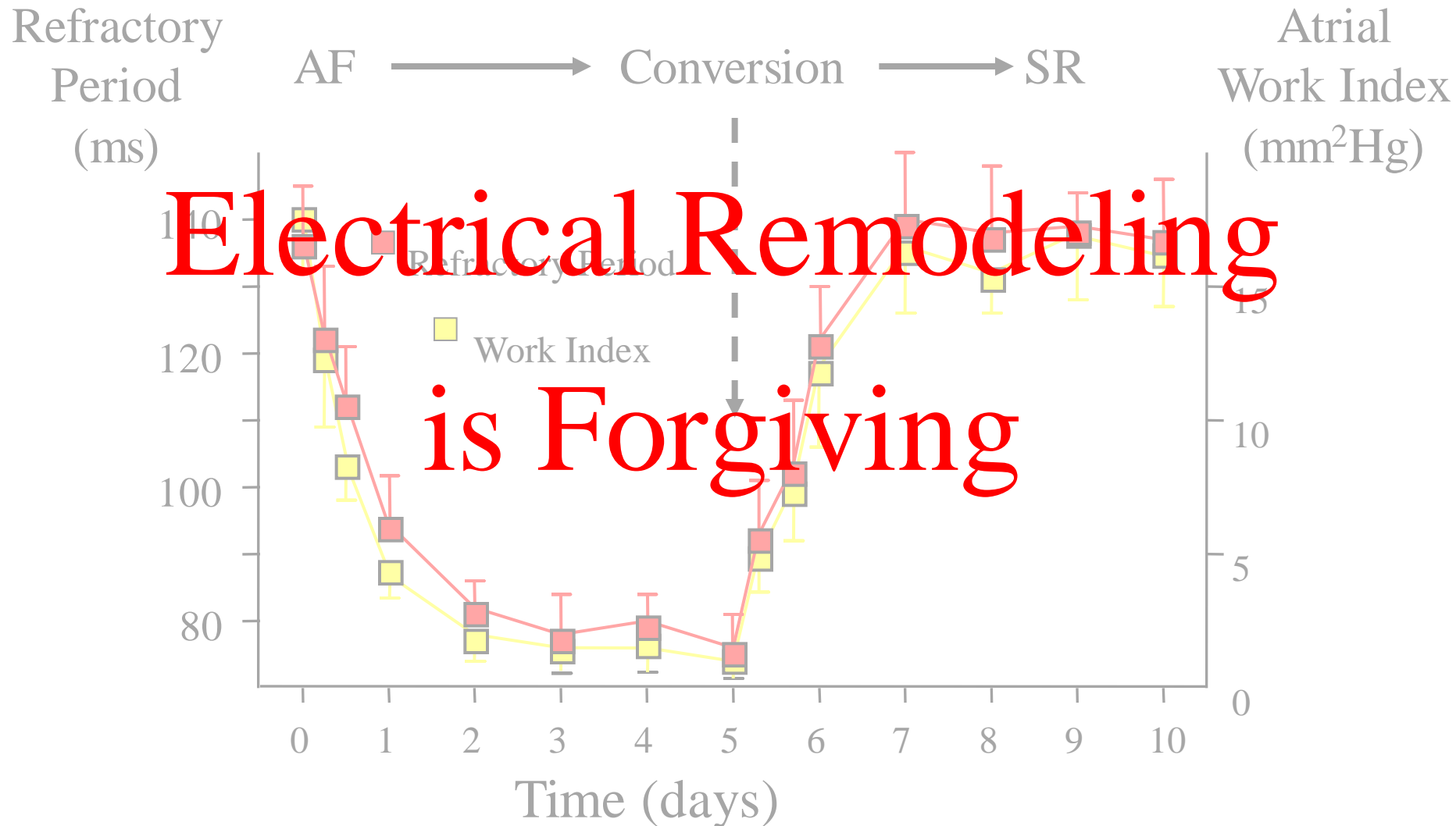
# Downregulation of L-type $\text{Ca}^{++}$ in Human AF



# ‘AF Begets AF’: Electrical Remodeling:

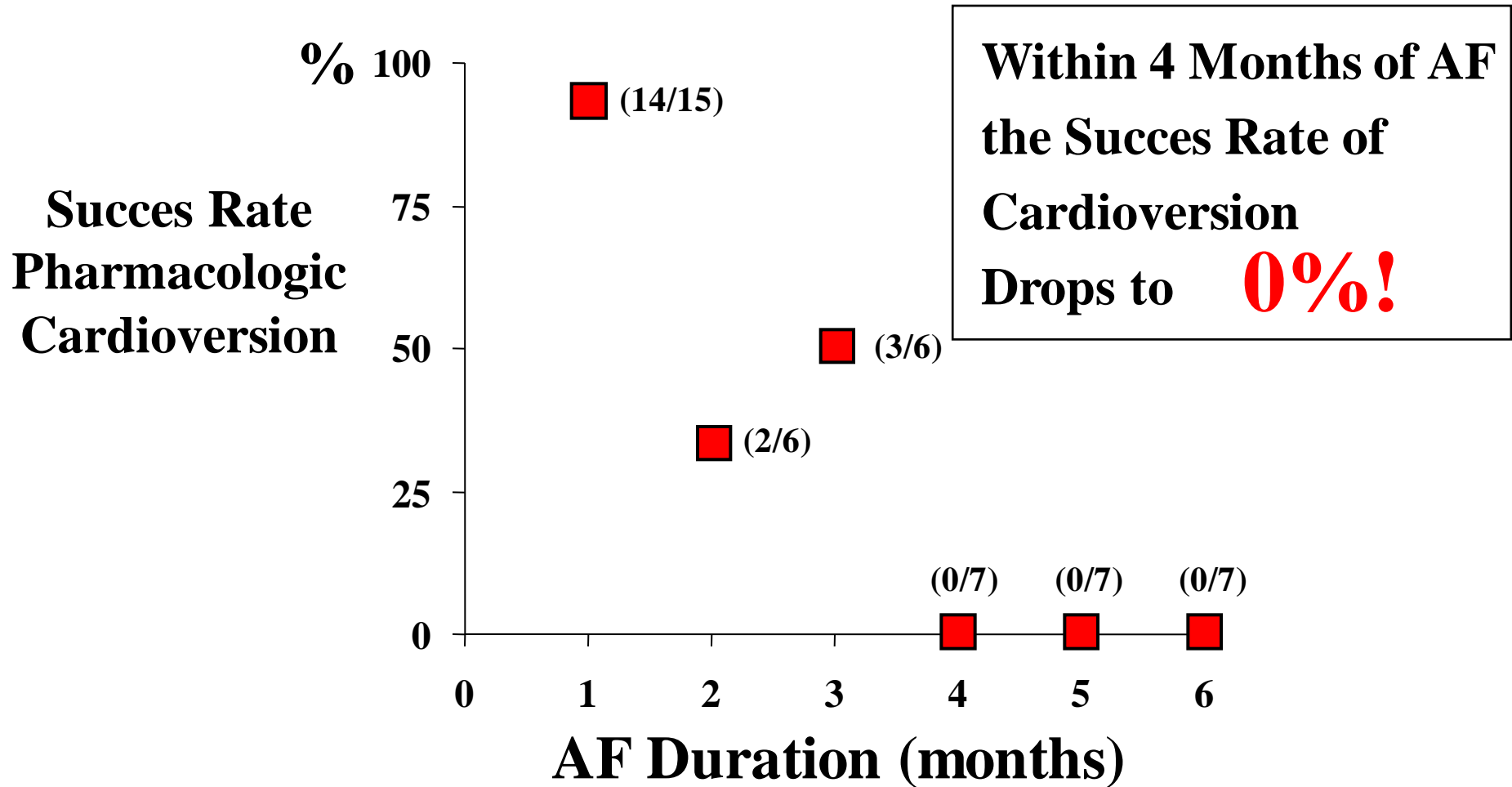


# Contractions and Electrical Coupling ‘Go Hand in Hand’



# However ...

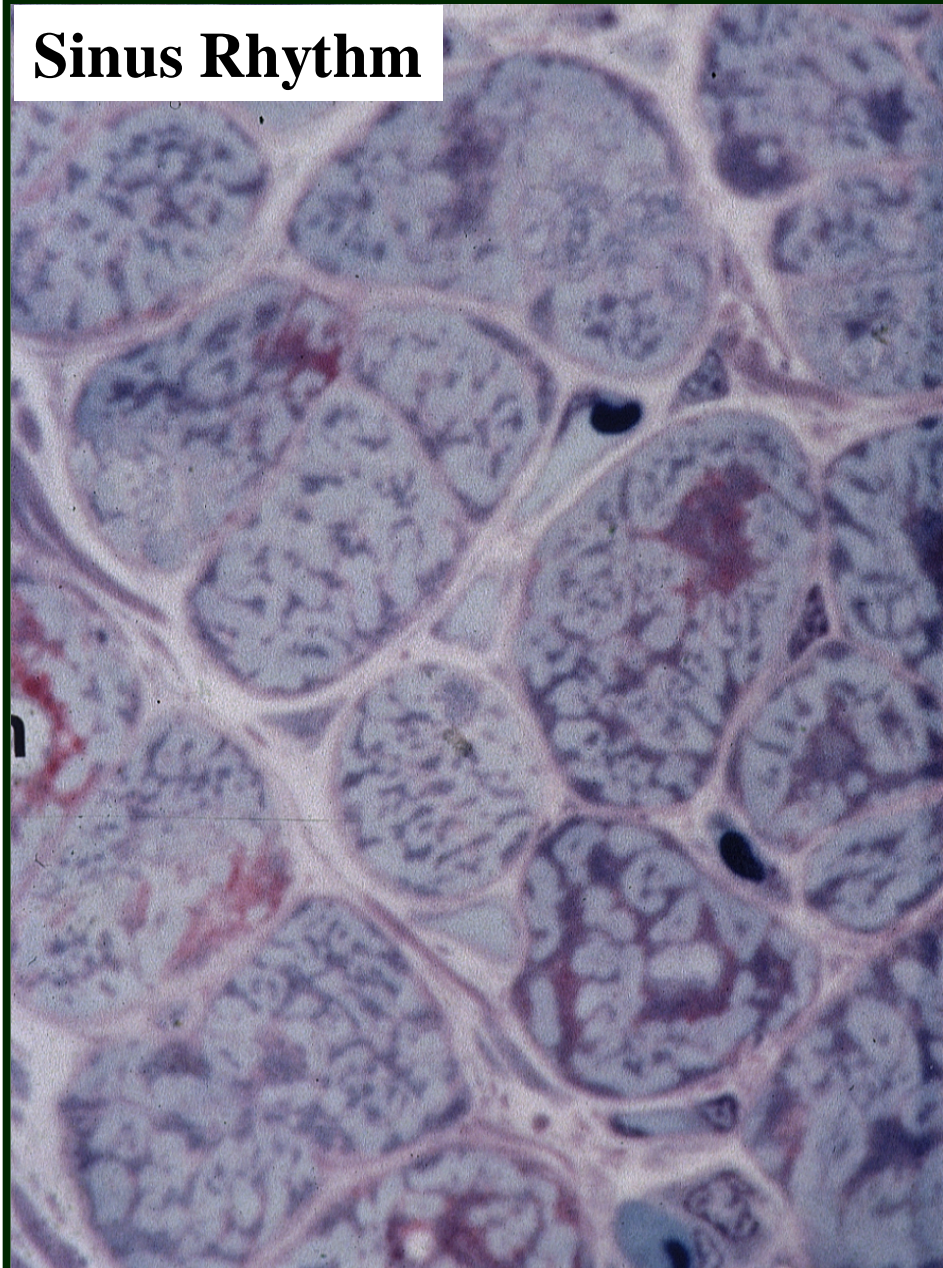
## There Must be a 'Second Factor'



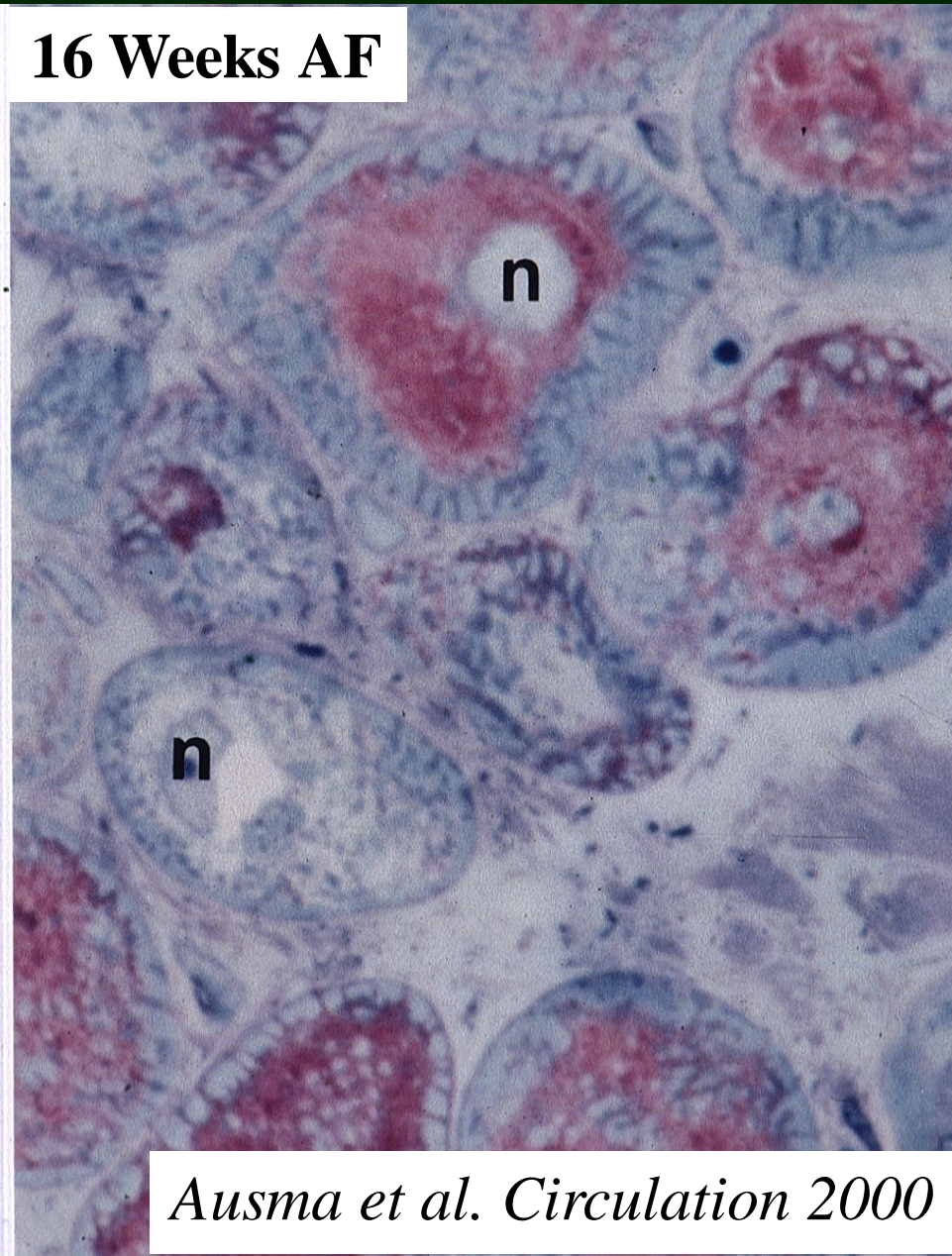


# AF-Induced Structural Remodeling

Sinus Rhythm



16 Weeks AF



*Ausma et al. Circulation 2000*

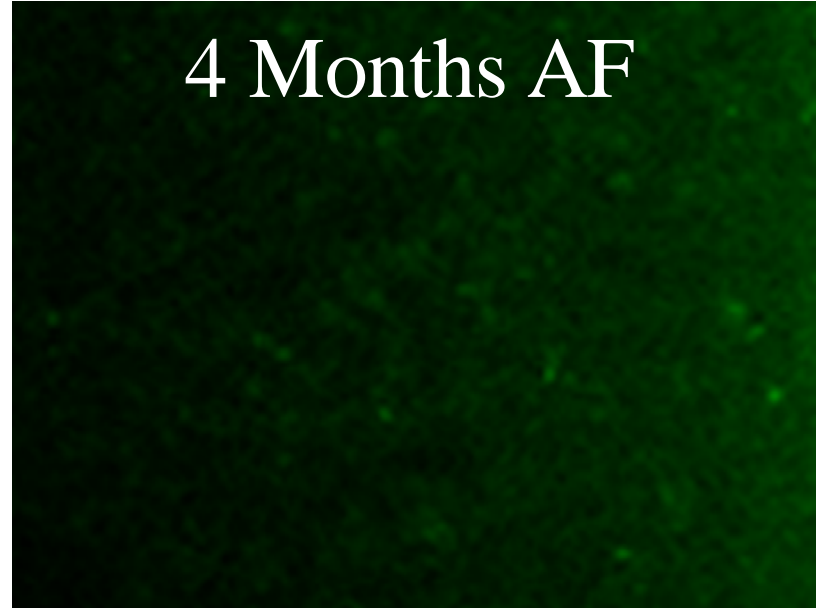
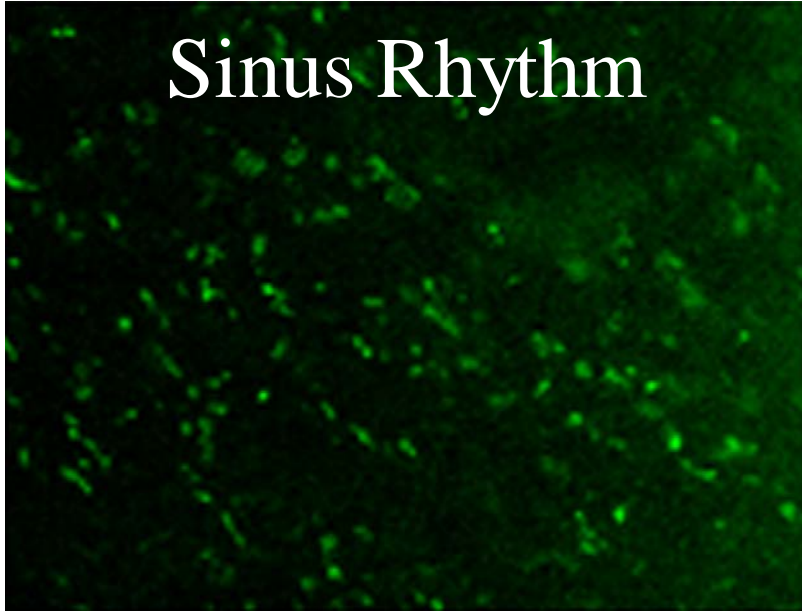


# Down Regulation of Connexin 40

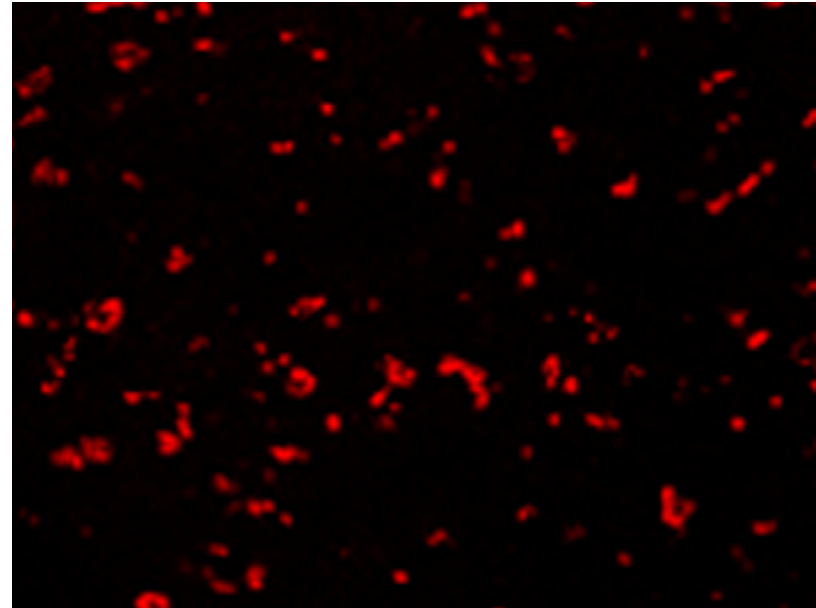
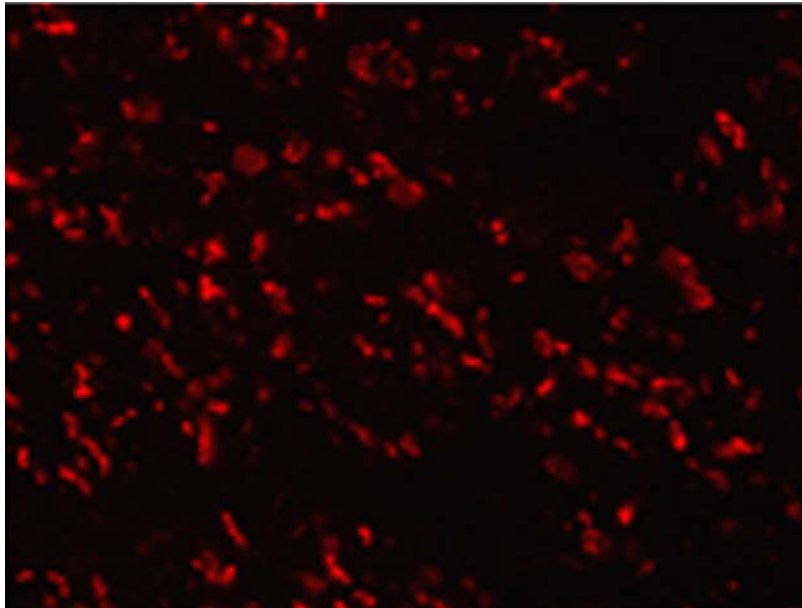
Sinus Rhythm

4 Months AF

Cx40



Cx43



# Structural Remodeling is a Slow Process

Duration of AF	0	2	4	8	16 Weeks
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Myolysis in

Right Atrium	1.3	3.9	4.2	10.0	12.2 %
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Myolysis in

Left Atrium	2.0	2.7	4.9	7.6	10.2 %
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*Ausma et al. Circulation 2000*

# Reversibility Slow and Incomplete

Myolysis  
(% of cells)

	Control	16 weeks	2 months	4 months
Severe:	1.4±1.6	8.9±7.2	3.5±3.1	1.8±1.6
Mild:	6.5±5.1	27.8±12.1	34.2±4.6	25.4±6.2
Total:	7.9±6.0	36.7±12.3	37.7±4.7	27.1±7.7

Structural Remodeling

is NOT Forgiving



# Many Structural Changes

Dilatation?

Architecture?

Myolysis?

Hypertrophy?

Fibrosis?

Anisotropy?

Connexins?

Amyloidosis?

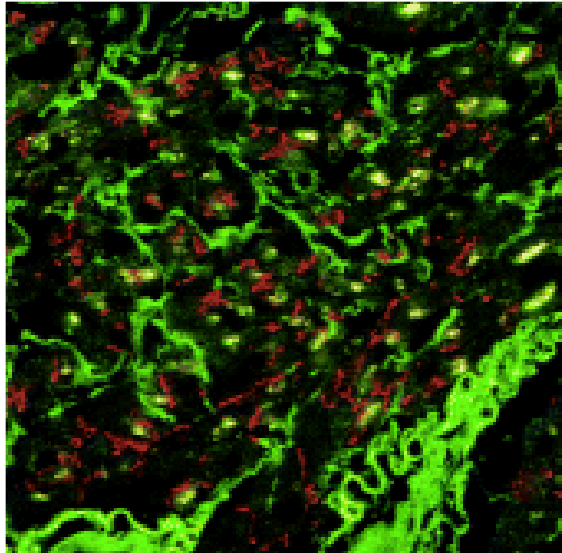
Fatty Infiltration?

Structural Proteins?

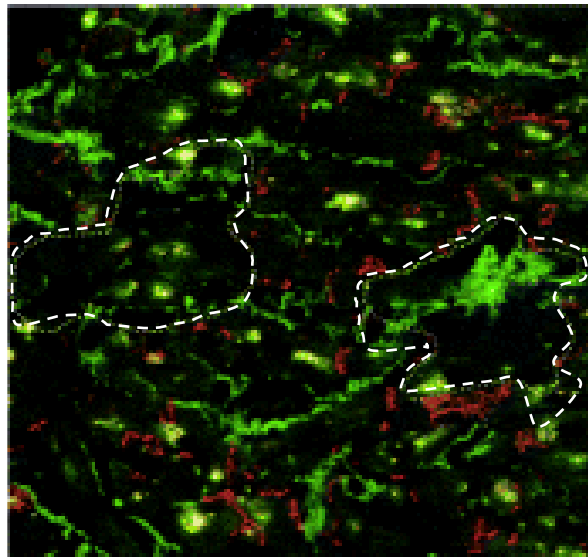
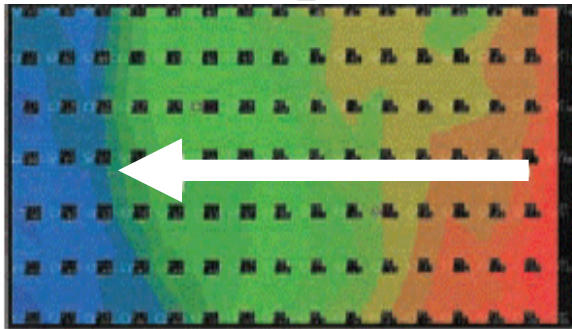
**What Makes the Atria  
Such a Perfect Host  
for AF?**

# Is It Small Islands without Connexins?

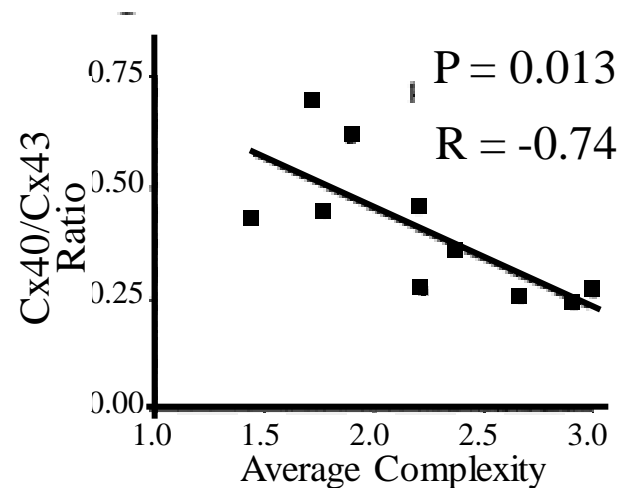
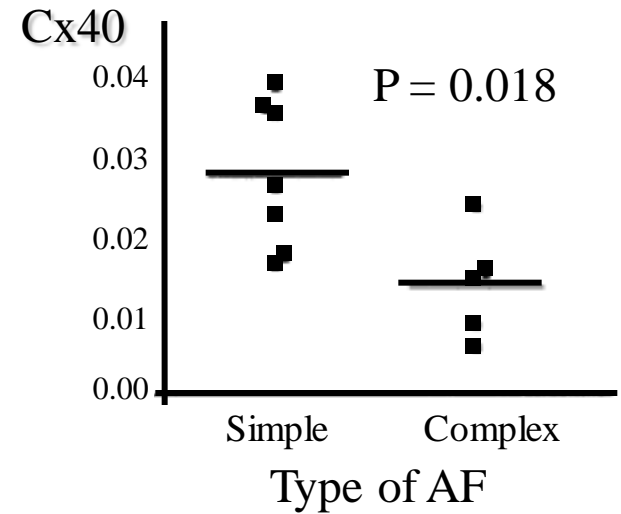
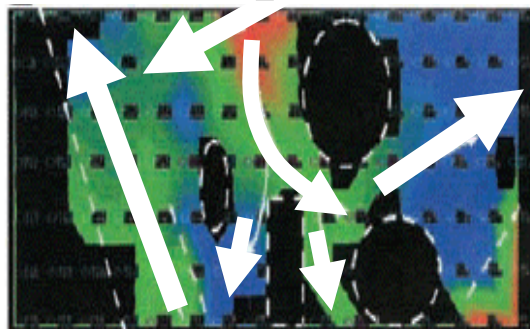
## AF $\longrightarrow$ More Complex



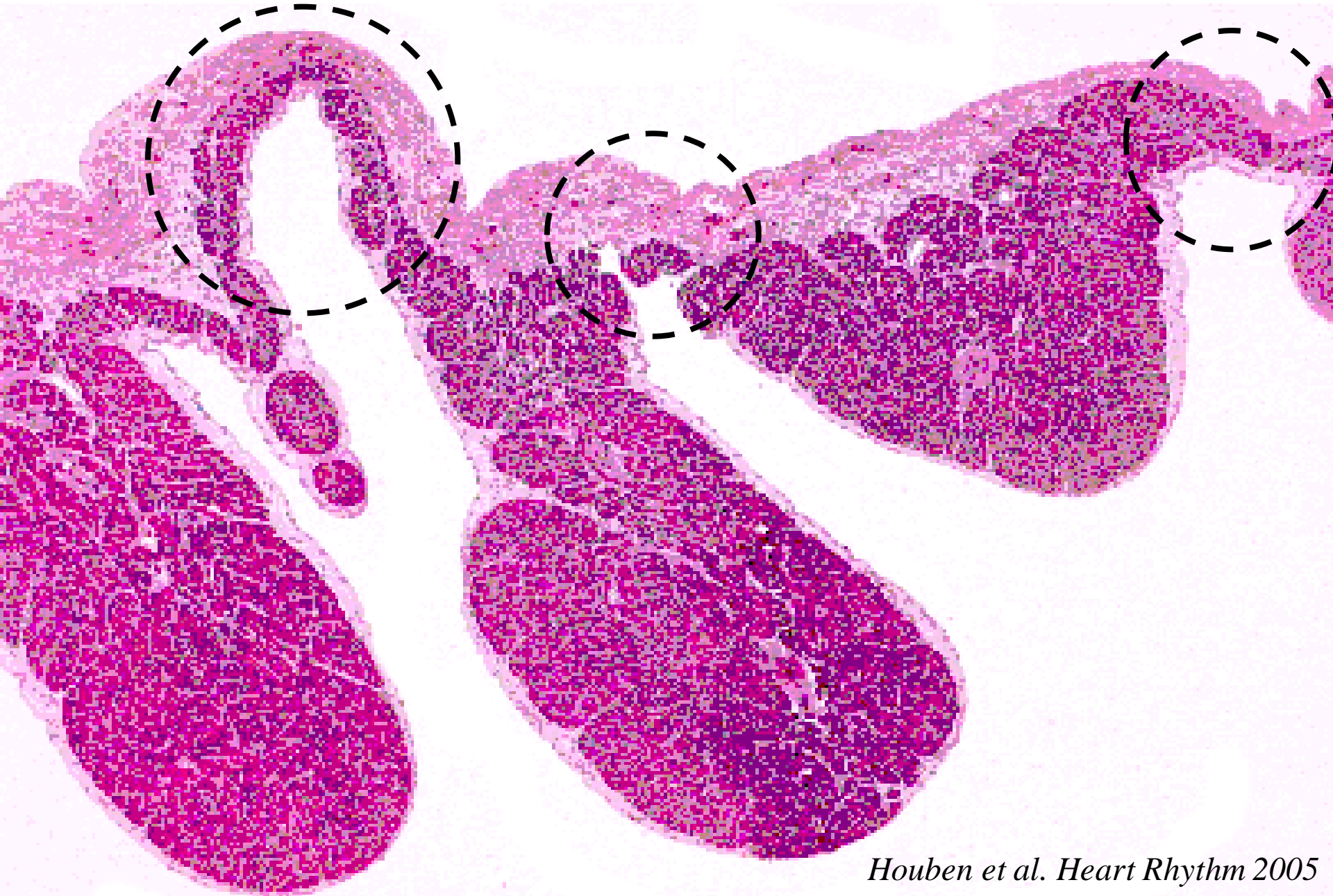
Simple



Complex



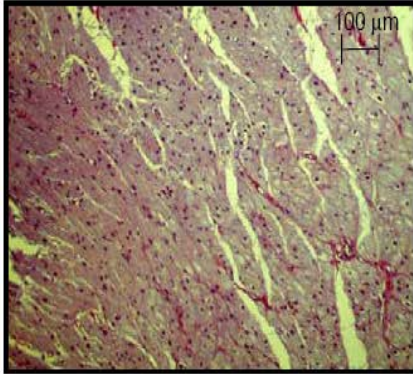
# Is It Conduction Defects due to Stretch?



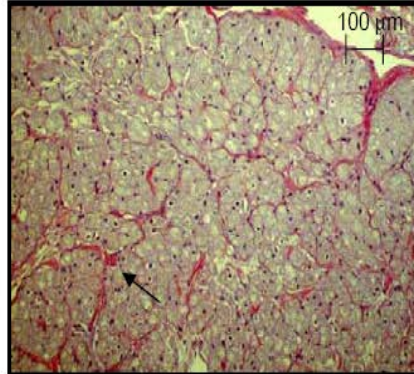
*Houben et al. Heart Rhythm 2005*

# Is it Atrial Fibrosis?

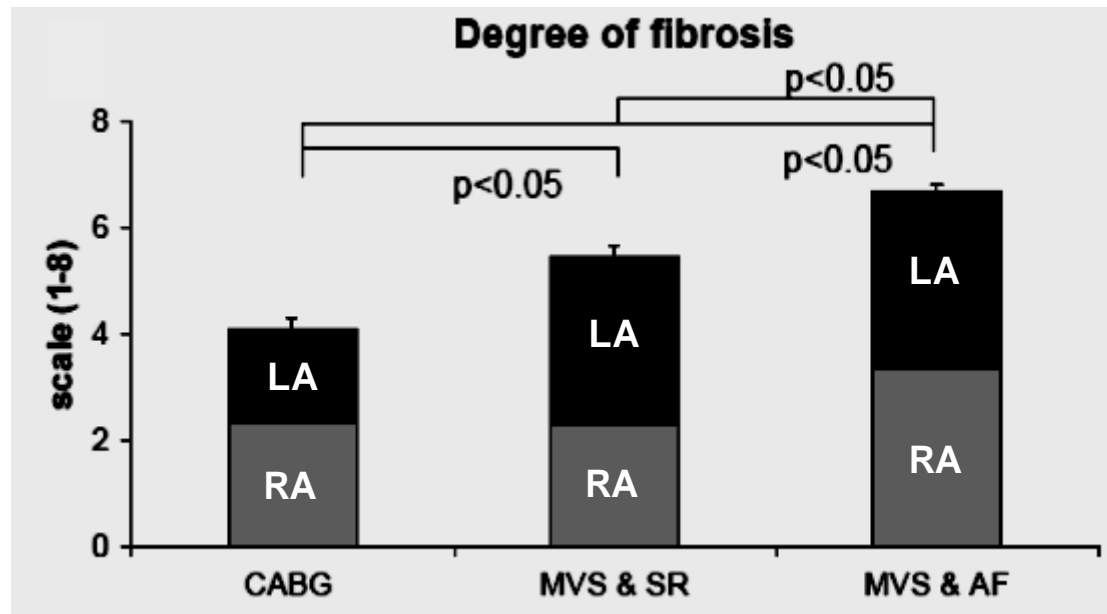
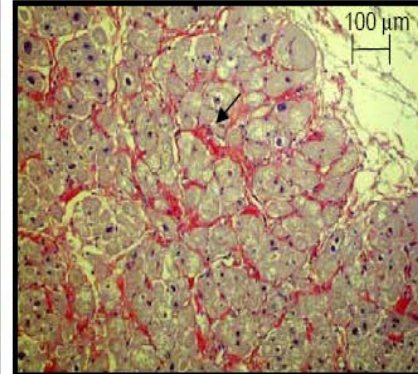
**CABG SR**



**MVS SR**



**MVS AF**



# Epicardial Mapping of Longstanding Persistent AF during Cardiac Surgery

24 Patients

# of Epicardial Maps

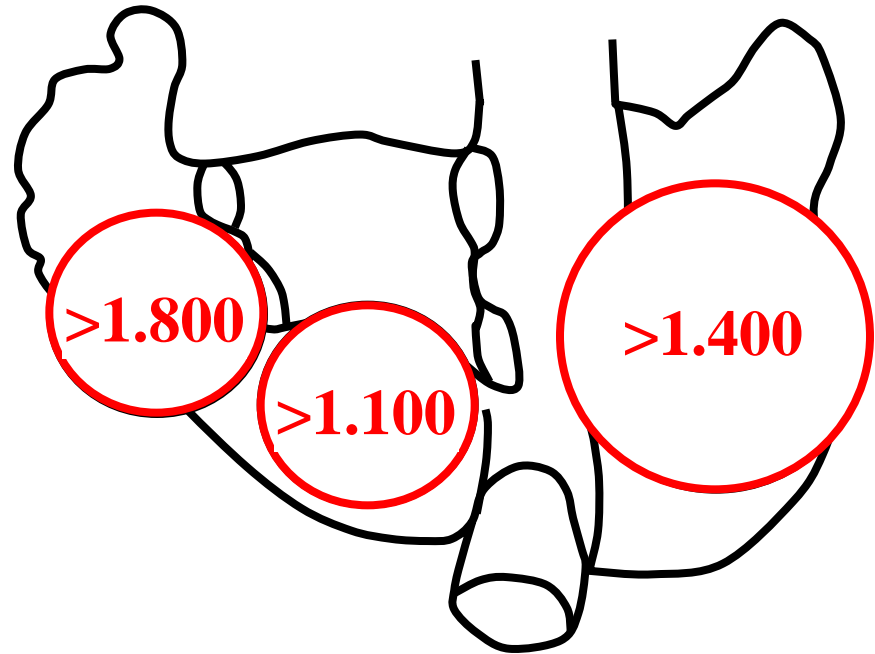
Persistent AF > 1 Year

♂15 ♀9

Age:  $64 \pm 9$

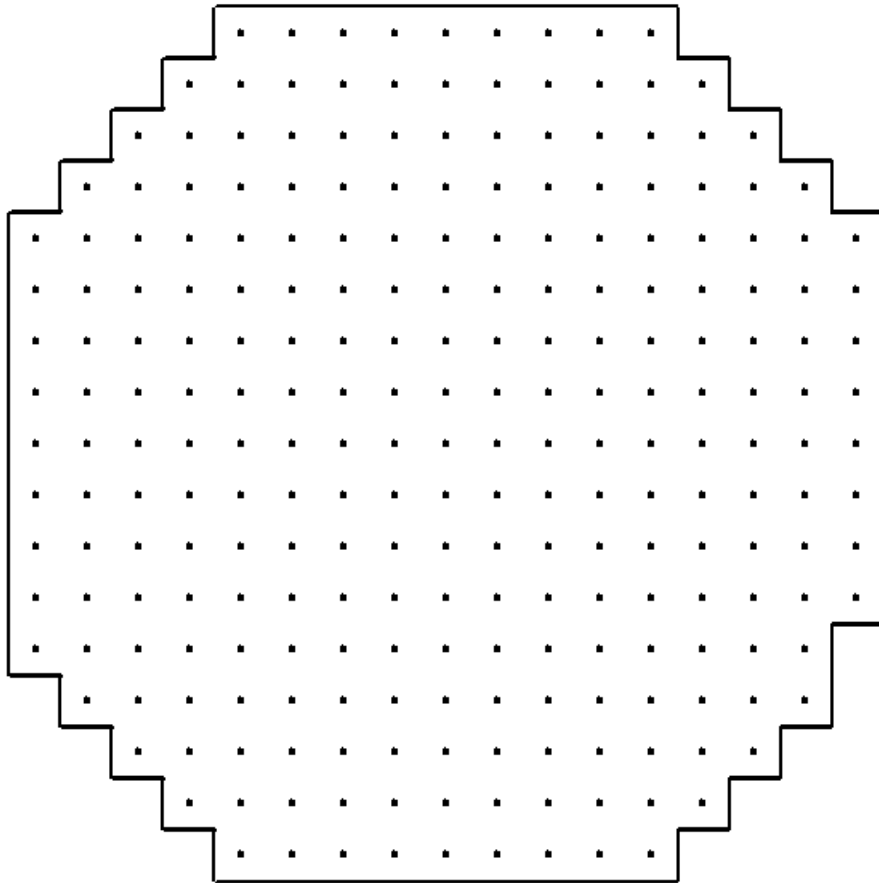
Mitral Valve Disease

Left Atrial Size:  $59 \pm 9$  mm



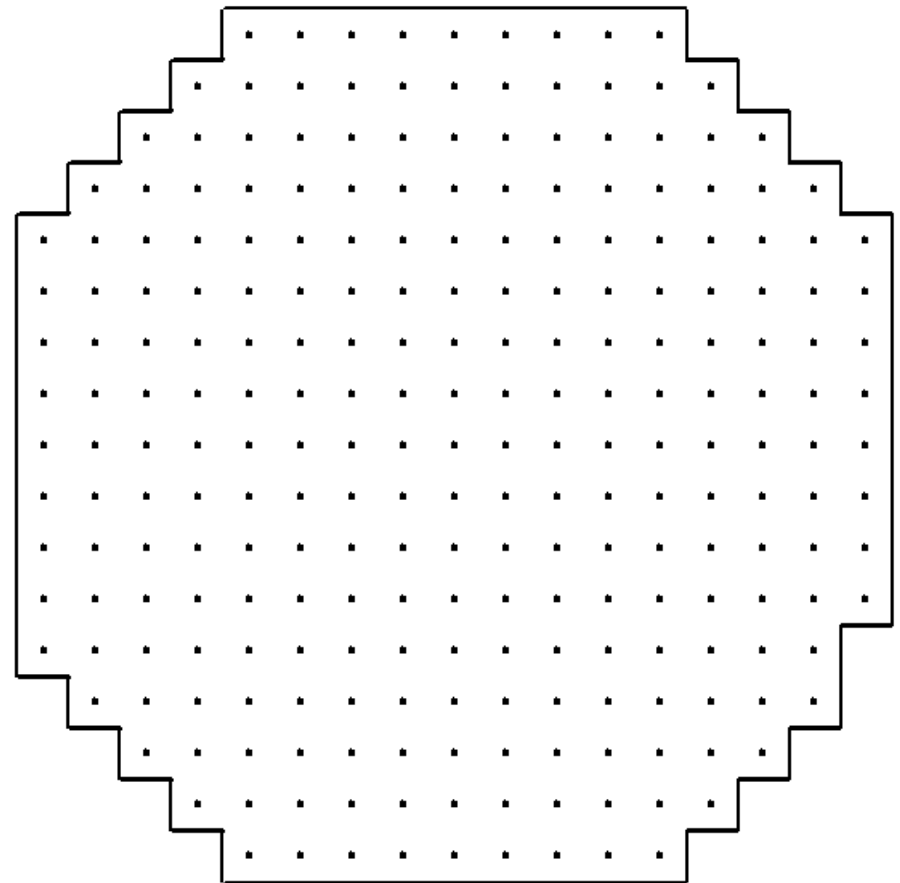
# Wave Mapping of Human AF

Fibrillation Waves  
Acute AF  
Fuse and Collide



3 cm

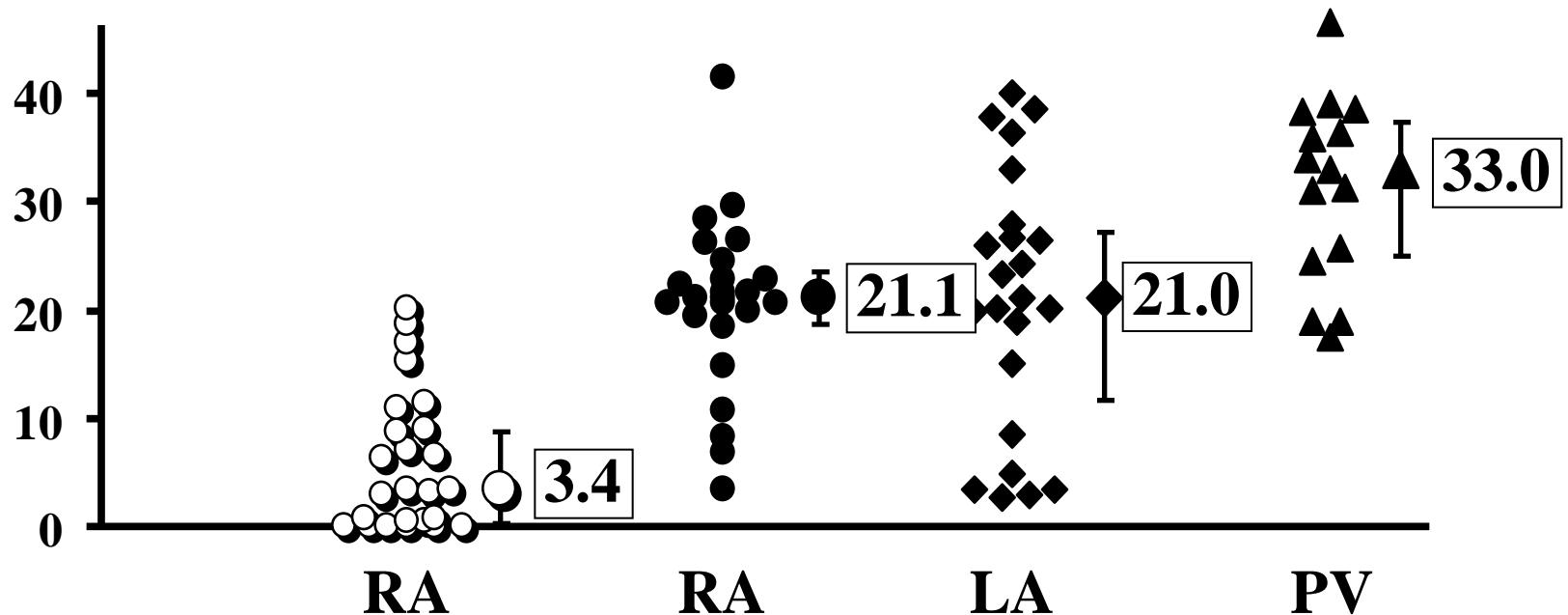
Waves are Separated  
Persistent AF  
by Line of Block



3 cm

# 6-10 Times More Intra-atrial Block in Patients with Persistent AF

Length of lines of block  
(mm/cm<sup>2</sup>/AF-cycle)

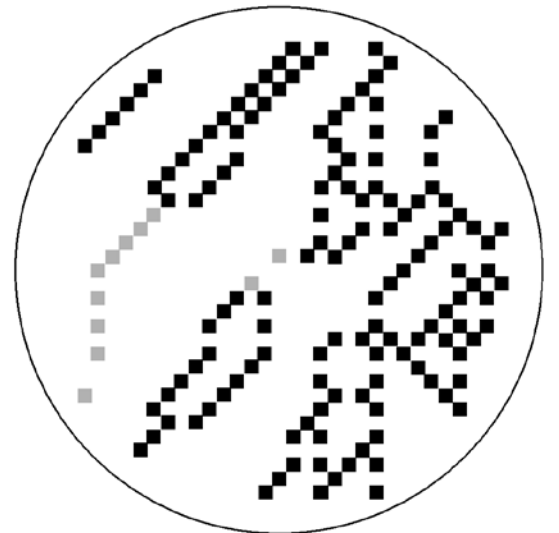
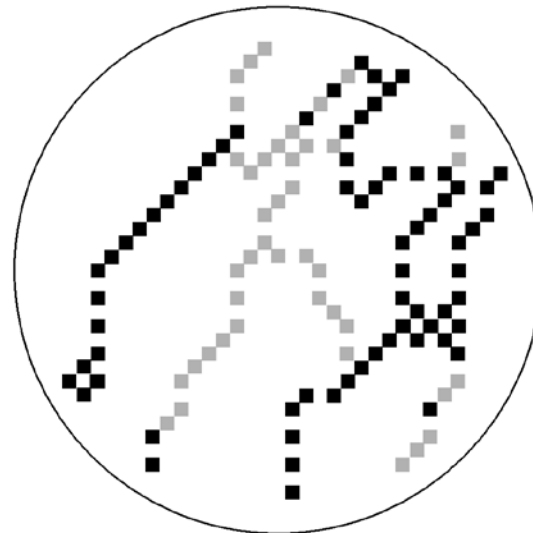
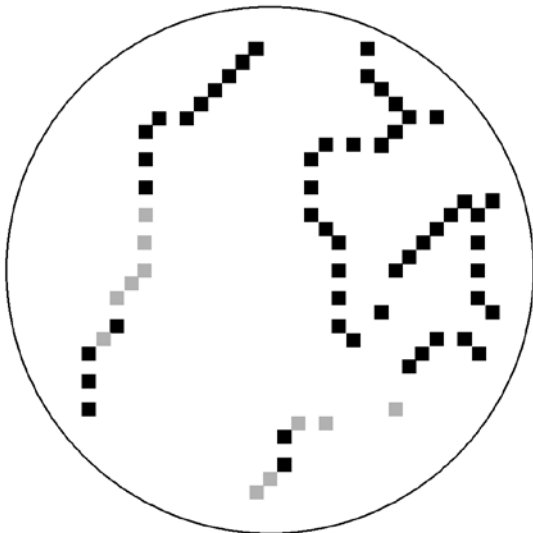


**Acute AF**  
(25 patients)

**Persistent AF**  
(24 patients)

*Allessie et al.*  
*Circ AE 2010*

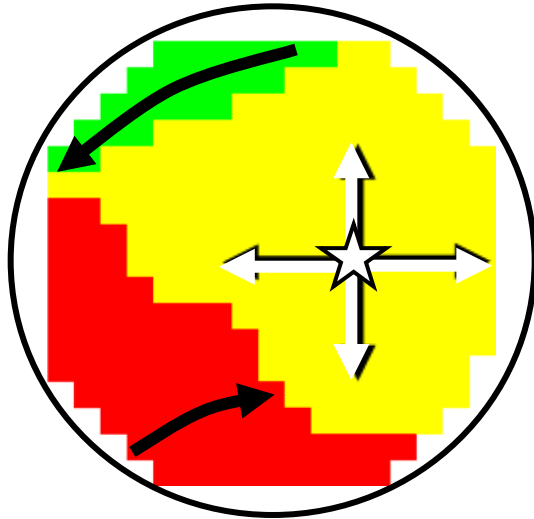
# Macroscopic Longitudinal Dissociation of Atrial Muscle Bundles



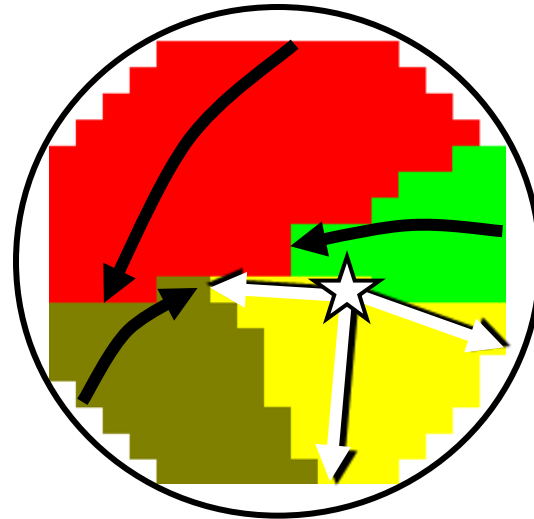


# Epicardial Breakthroughs

31 ms



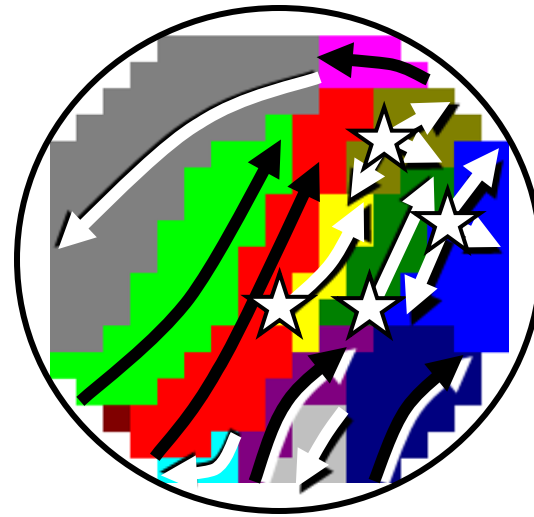
43 ms



149 ms

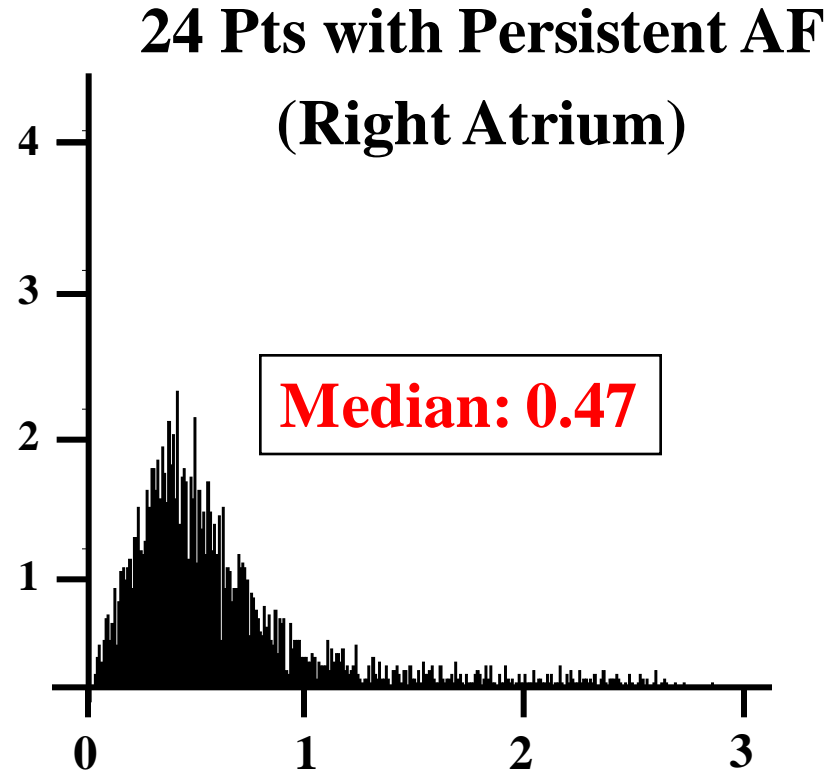
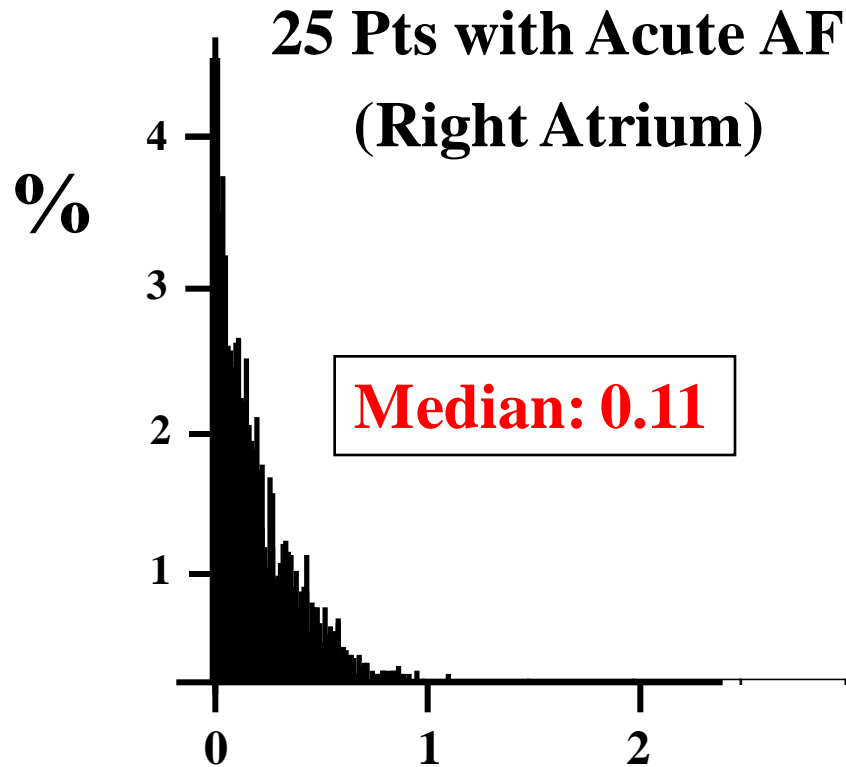


171 ms

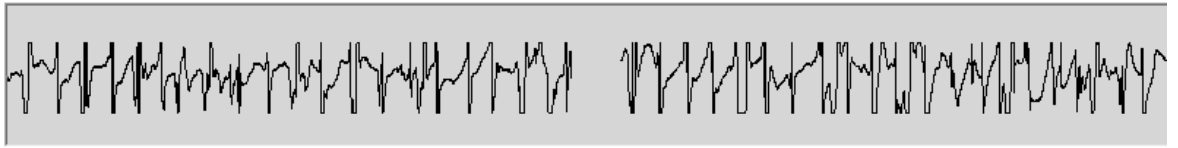


3cm

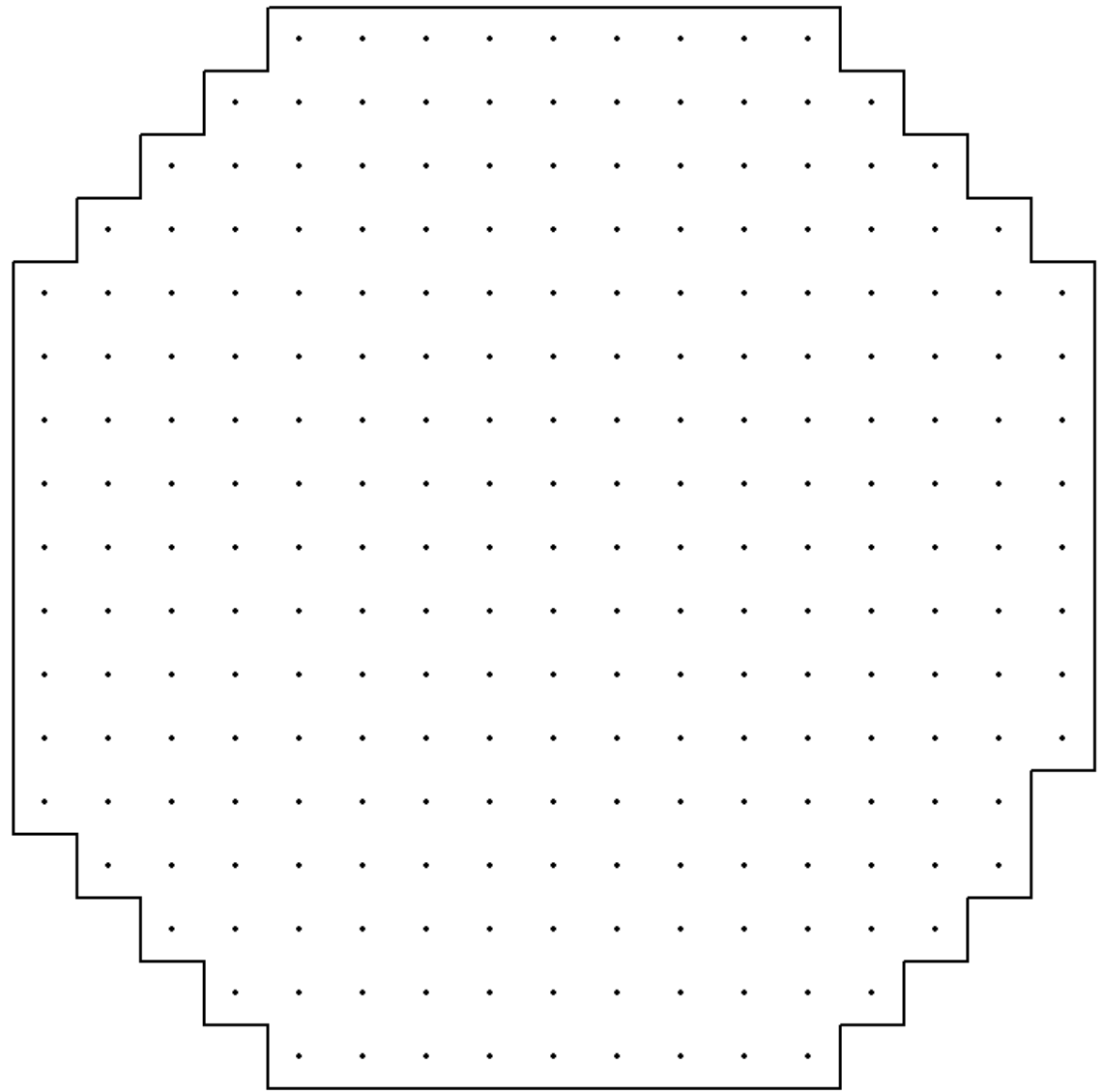
# 4-fold Higher Incidence of Epicardial Breakthroughs



**Number of Epicardial Breakthroughs per AF-cycle/cm<sup>2</sup>**



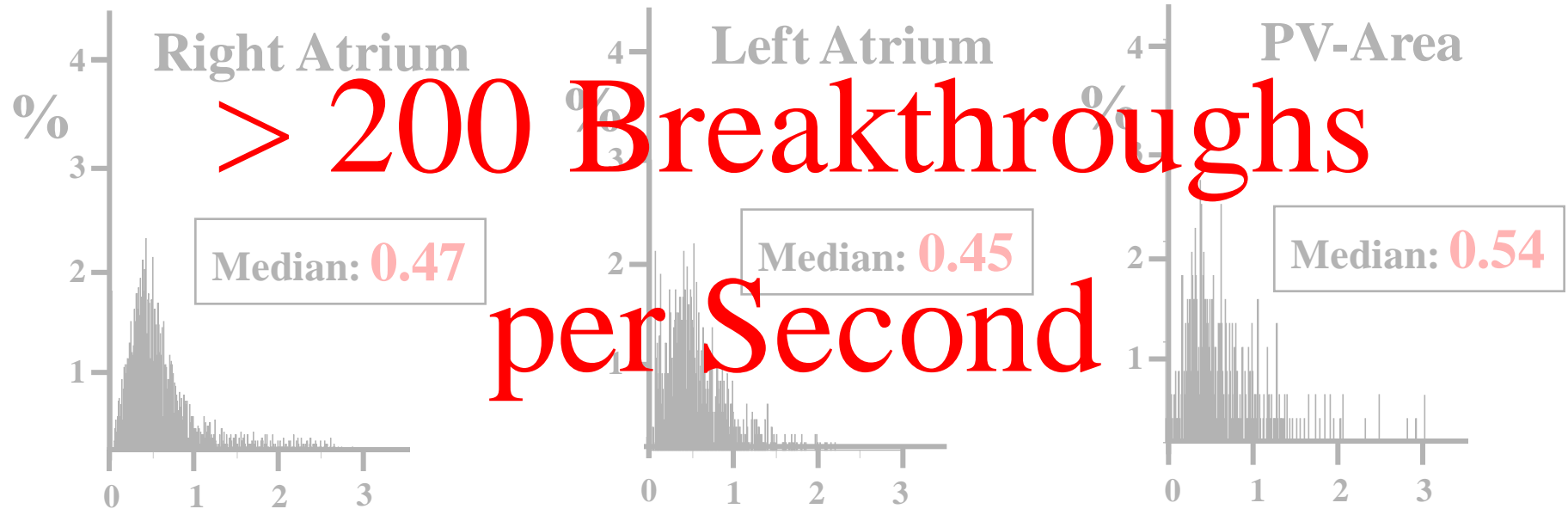
As Many as  
115 Epicardial  
Breakthroughs in  
the Right Atrium  
during 8 seconds  
of Longstanding  
Persistent AF



3cm

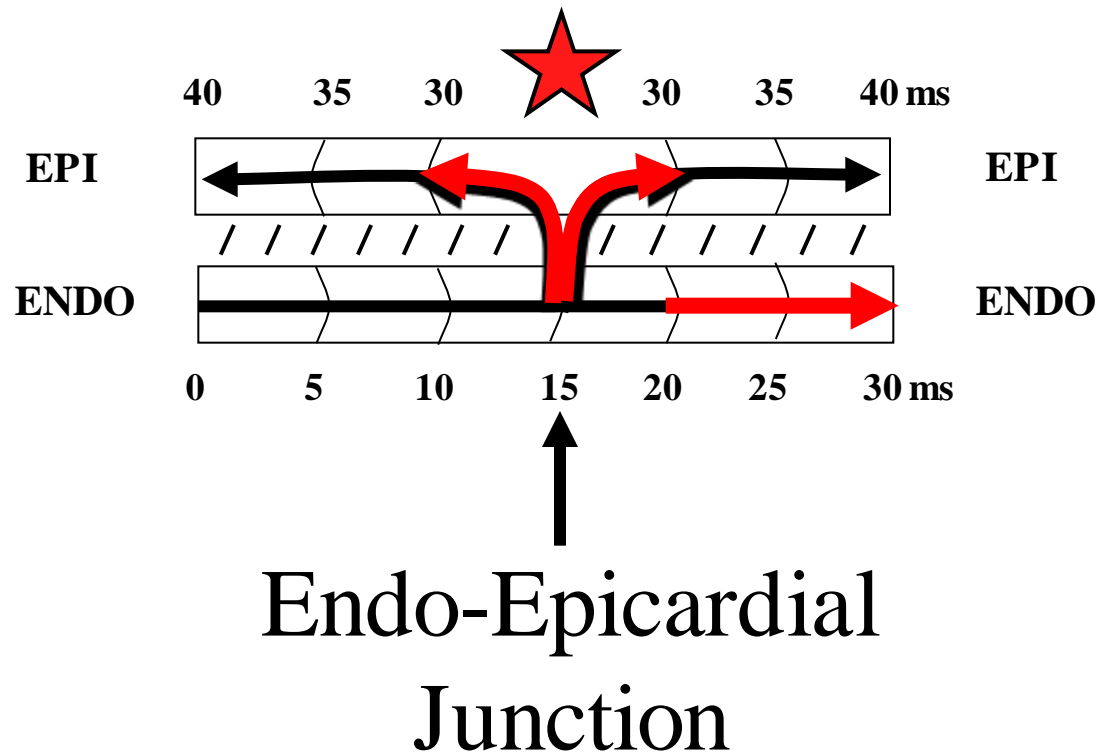
In 24 Patients with Longstanding Persistent AF,  
on Average 3-4 Breakthroughs per second  
in Each Square cm of the Atrial Wall  
**This Means a Total of**

**> 200 Breakthroughs  
per Second**



Number of Epicardial Breakthroughs per AF-cycle/cm<sup>2</sup>

# The 'Hidden' Reservoir of AF-Sources is **Right Under Your Feet!**



# Simultaneous Endo-Epicardial Mapping of Persistent AF in the Goat

*Eckstein et al.  
Cardiovasc Res 2011*



**Epicardial  
Layer**

**18ms**



**8ms**

**Endocardial  
Layer**

# Progressive Endo-Epicardial Dissociation in the Goat

# Goat 1

# Goat 2

# Goat 3

# Goat 4

# Goat 5

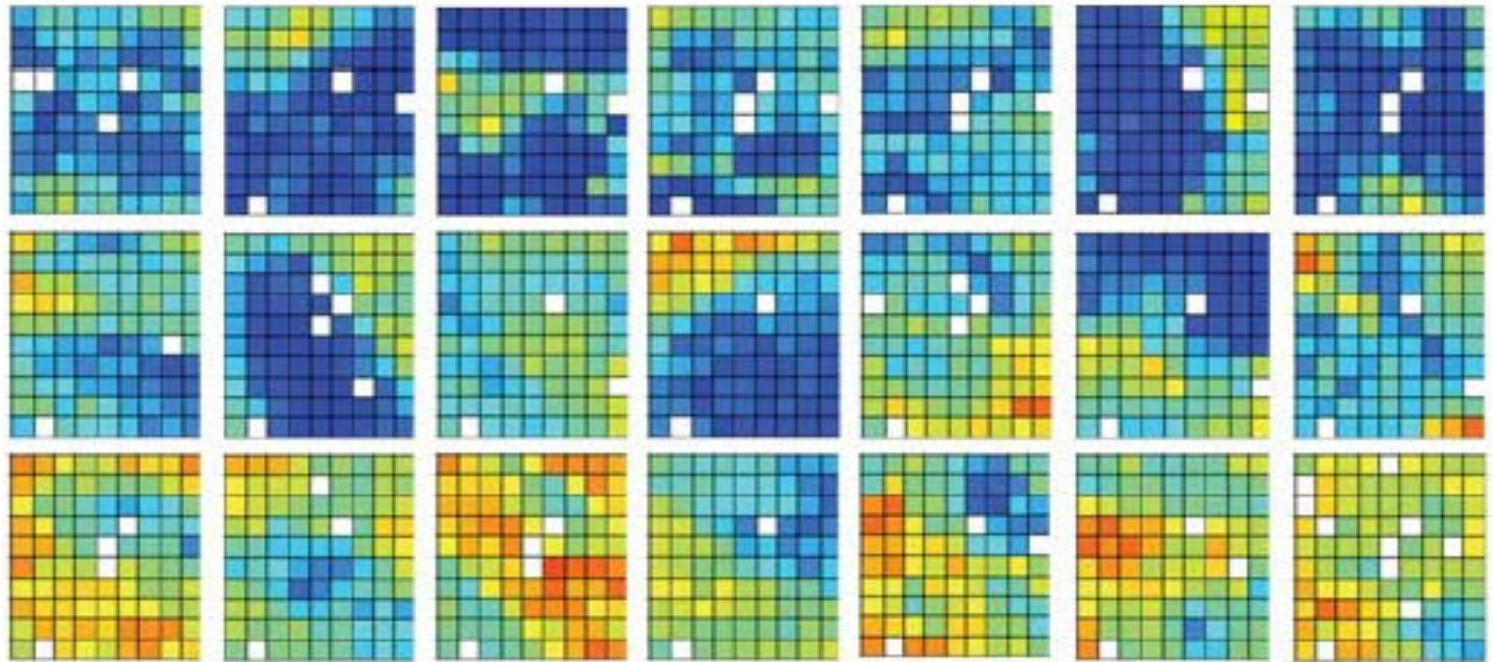
# Goat 6

# Goat 7

## Acute AF

# 3 Weeks of AF

## 6 Months of AF



Low

# High

# Degree of Endo-Epicardial Dissociation

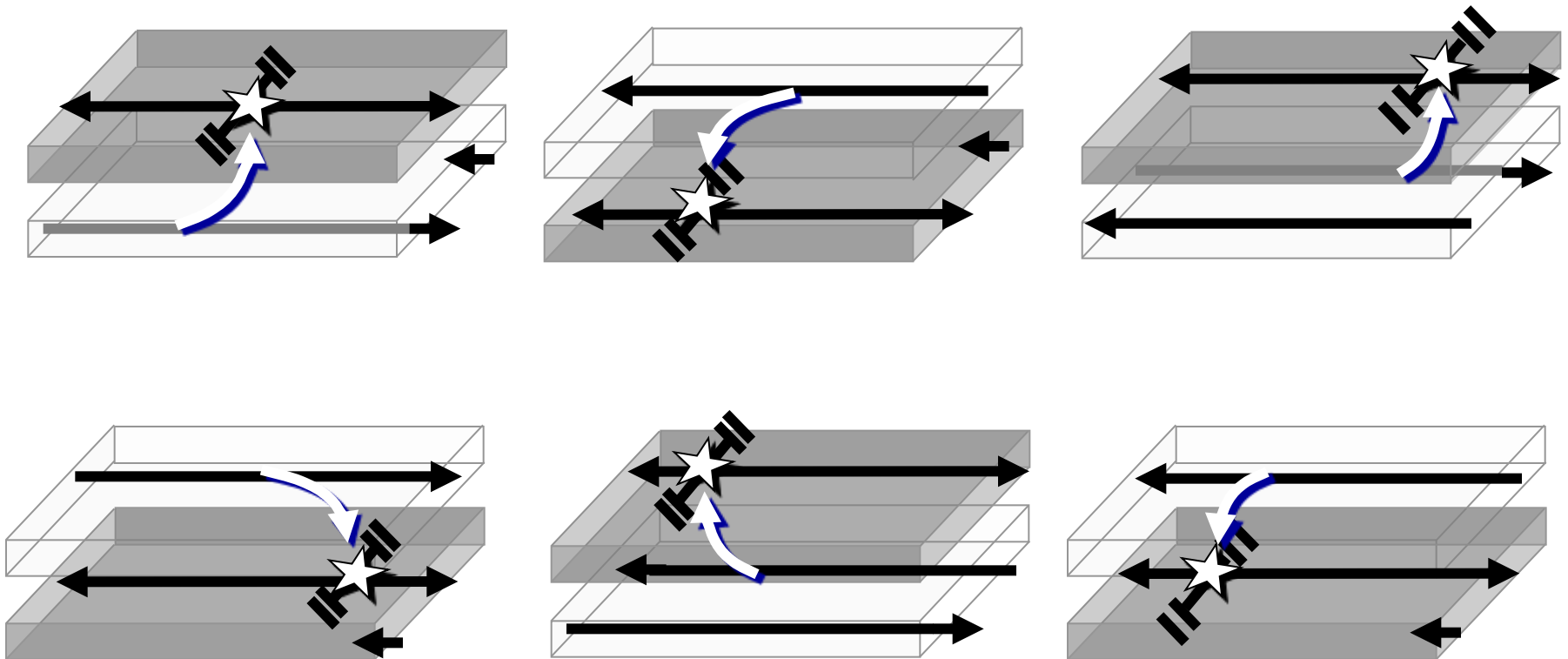
In Patients with Longstanding AF  
the Atria have been Transformed  
into a **Double Layer** of  
Dissociated Muscle Bundles



# Two Layers of Dissociated Fibrillation

## Waves that Constantly

## 'Feed' Each Other



# Double Layer AF:

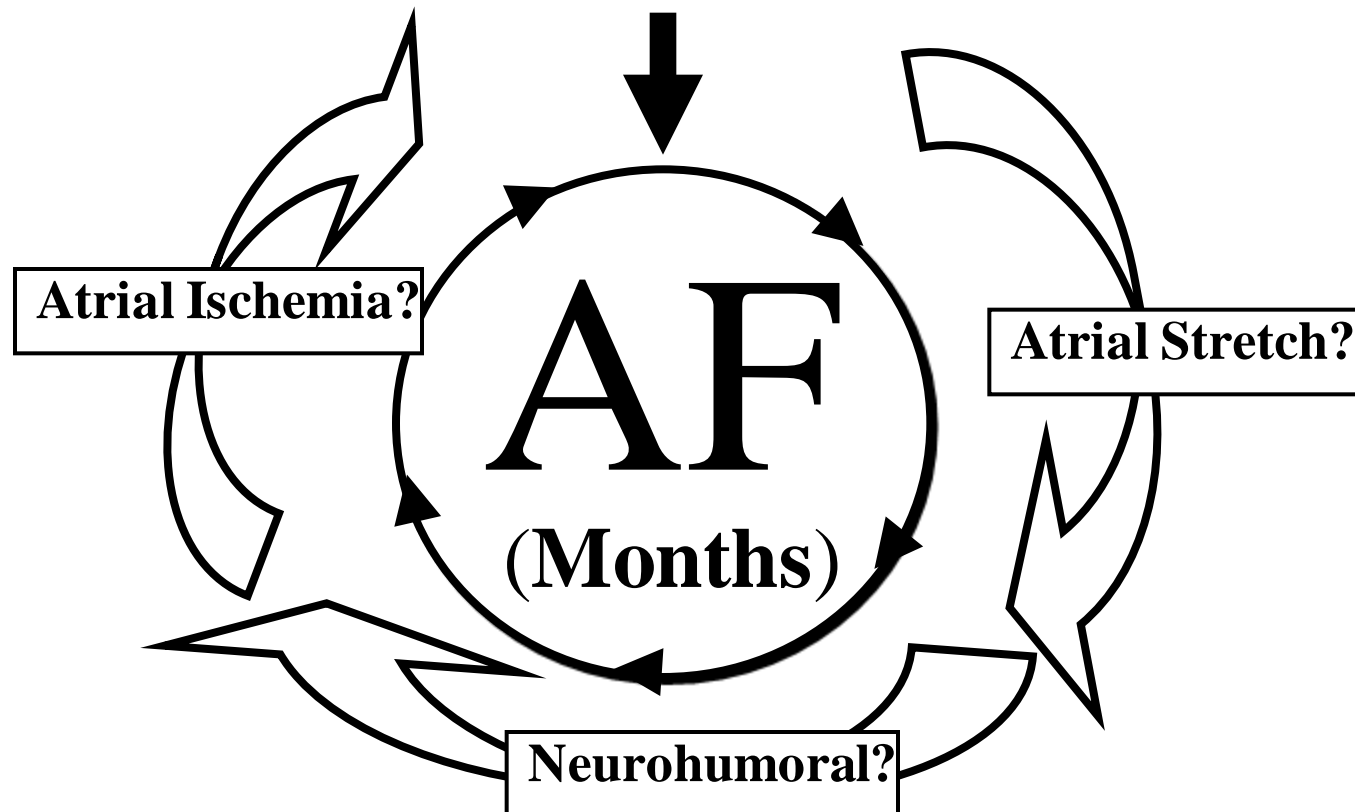
- ❖ Perpetuation of AF **Independent** of Presence of Rotors or Rapid Foci
- ❖ Each Layer of Dissociated Wavelets Serves as a **Multi-Site Generator** for the Other Layer
- ❖ Will **Not Be Easy** to **Ablate**

# The Role of Early Action:

1) **Prevention** of Structural Remodeling

# But How?

Advancing Age, Hypertension, Valvular Disease,  
Left Ventricular Dysfunction ..... **→ Years**



# The Role of Early Action:

- 1) **Prevention** of Structural Remodeling
- 2) **Diagnosis** of the Stage of the  
Electropathological Substrate of AF
- 3) **Don't Ablate When it is Too Late**