

# Cellular and Molecular Pathophysiology of AF:

*Lessons for Cardiology*

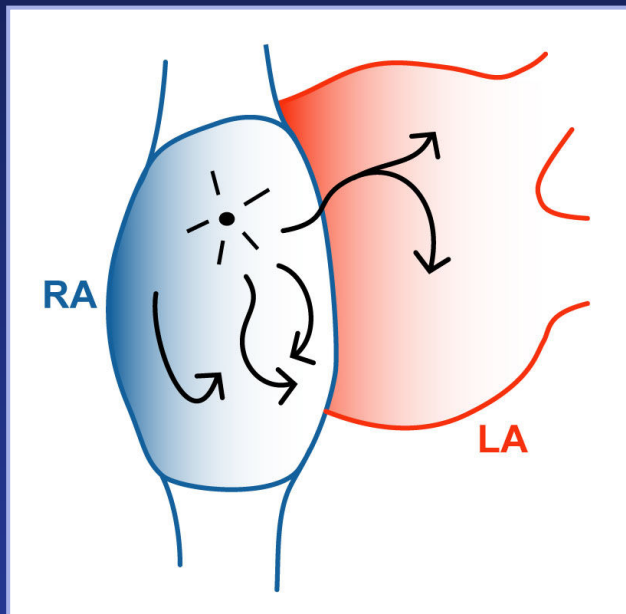
***Stanley Nattel, MD***

**Montreal Heart Institute  
University of Montreal**



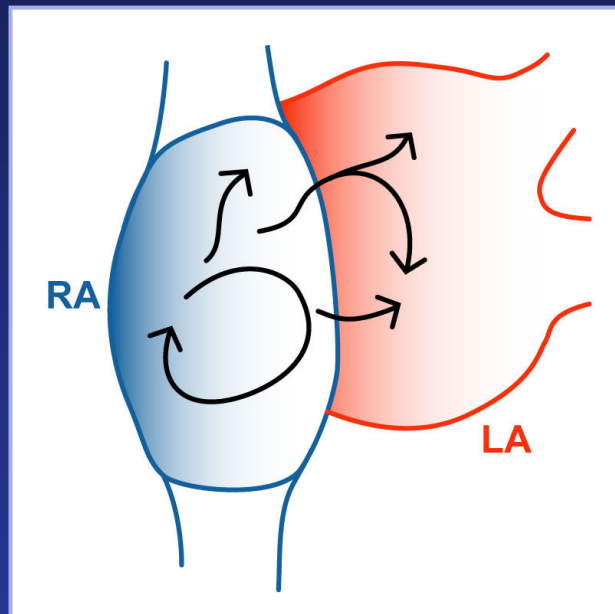
# Mechanisms of AF: Ideas of Early 20<sup>th</sup> Century

**A** Ectopic focus



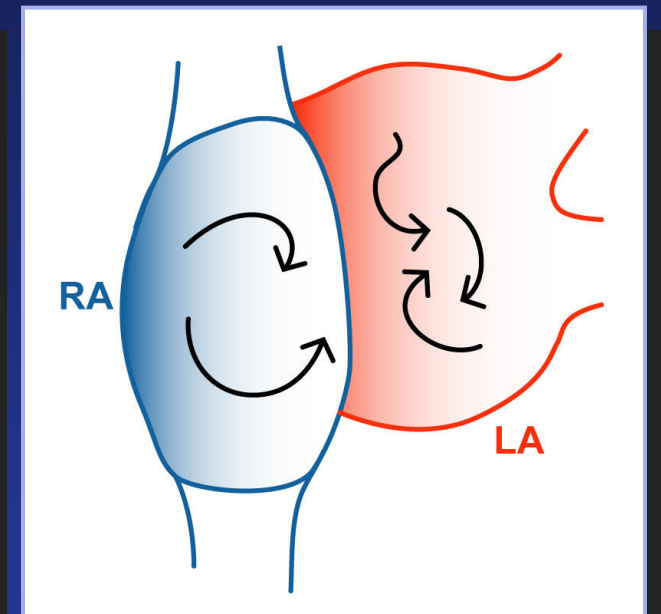
*Engelmann, Winterberg*

**B** Single-circuit reentry



*Lewis*

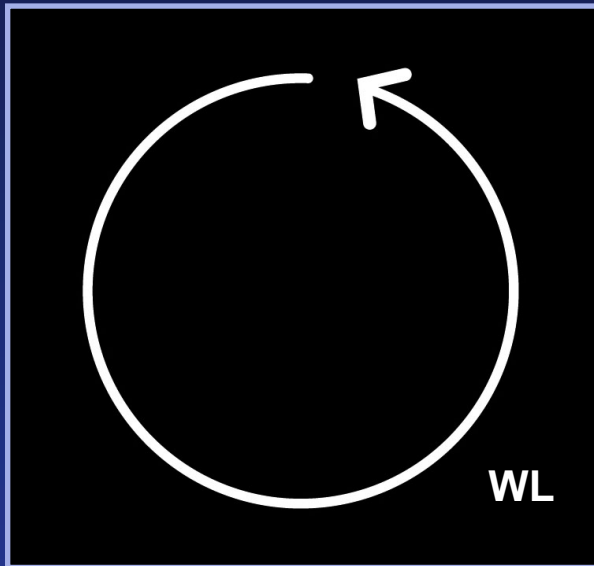
**C** Multiple-circuit reentry



*Garrey, Mines*

# Classical Concepts: Role of Refractory Period and Wavelength Changes

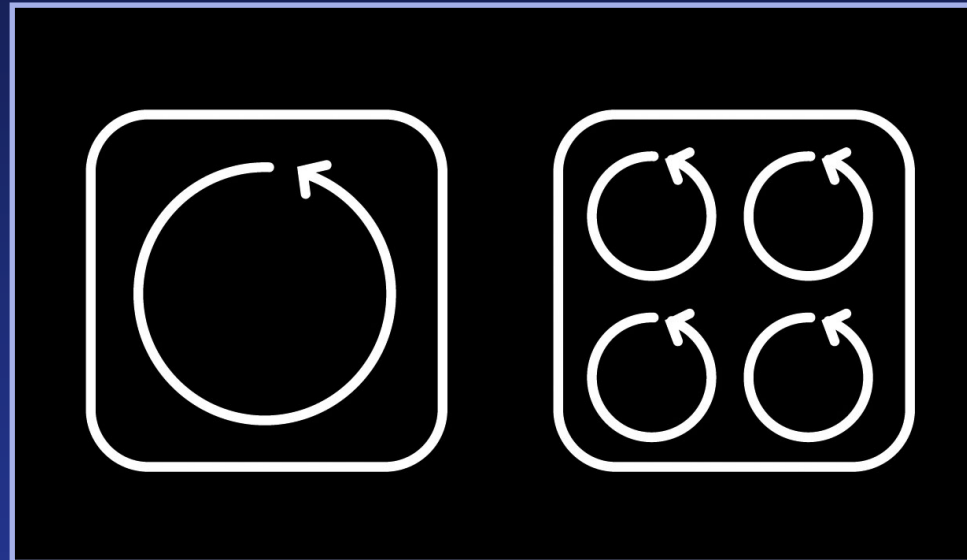
**A**



**Wavelength (WL) =**  
refractory period x conduction velocity

- minimal path length for reentry
- size of functional reentry circuits

**B**



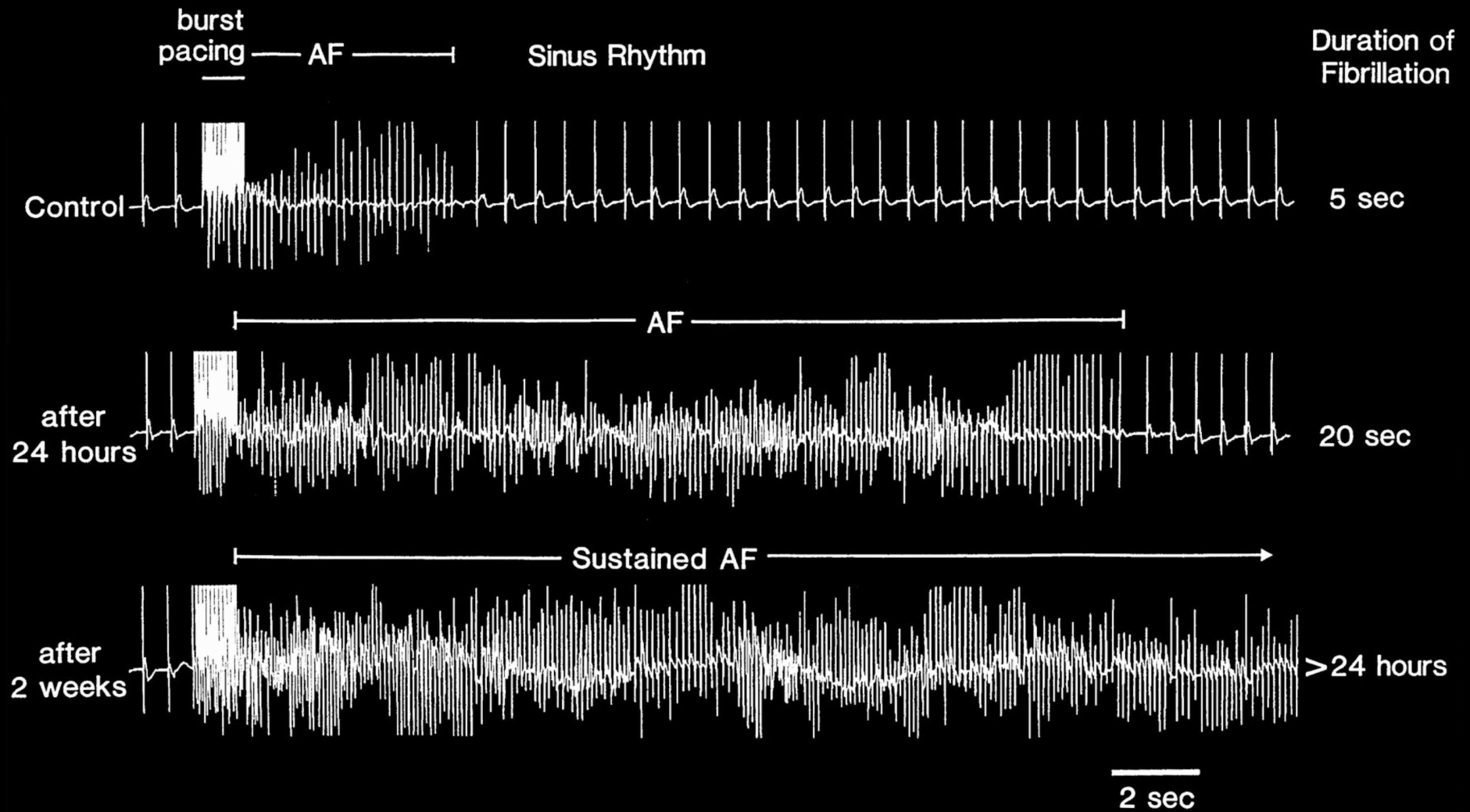
**Normal atrial size**  
**Normal WL**

- AF not sustained

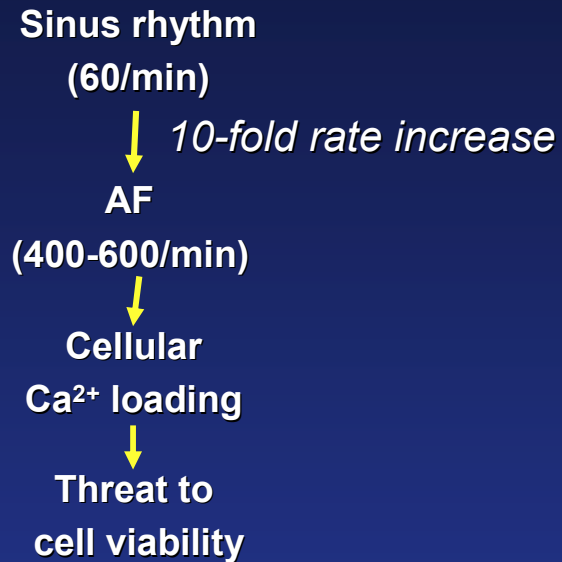
**Normal atrial size**  
**Short WL**

- AF sustained

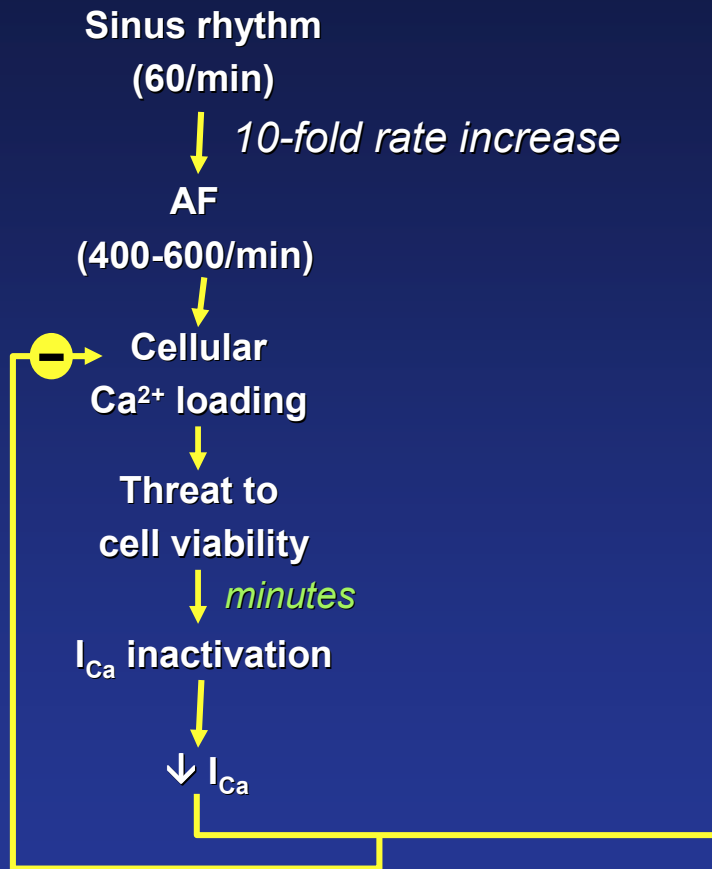
# Atrial tachycardia remodeling: AF Begets AF



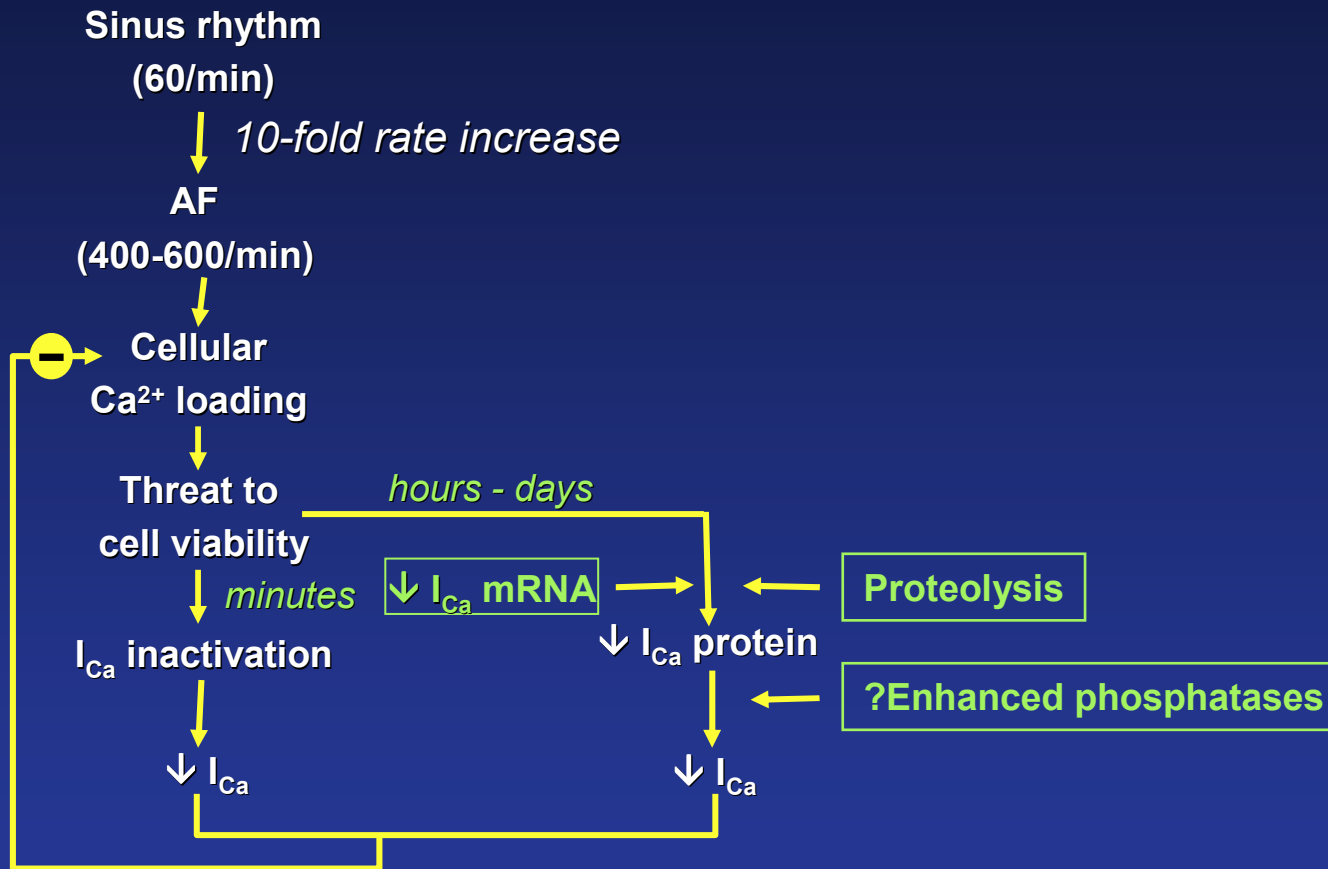
# Atrial tachycardia remodeling (“AF begets AF”)



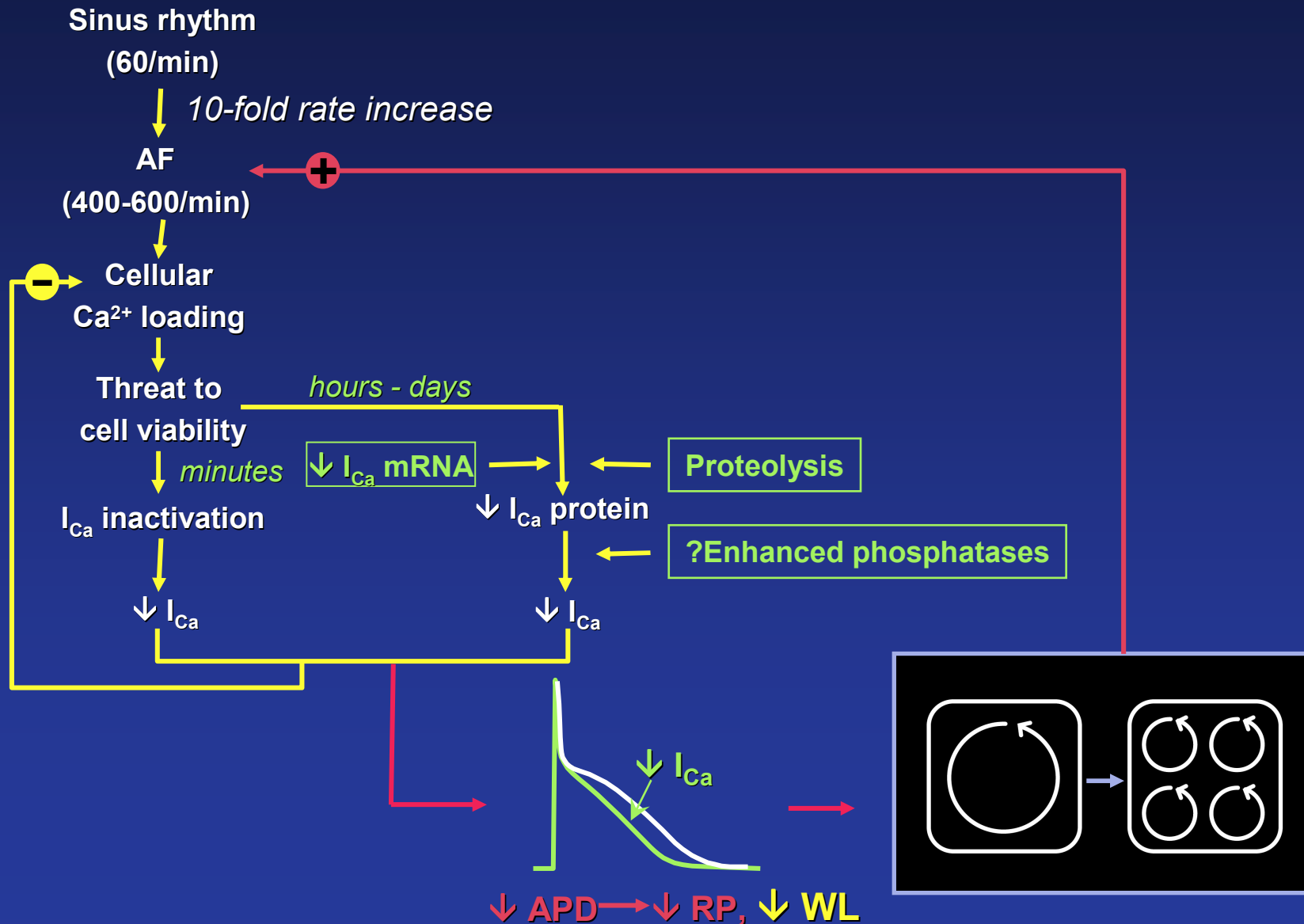
# Atrial tachycardia remodeling (“AF begets AF”)



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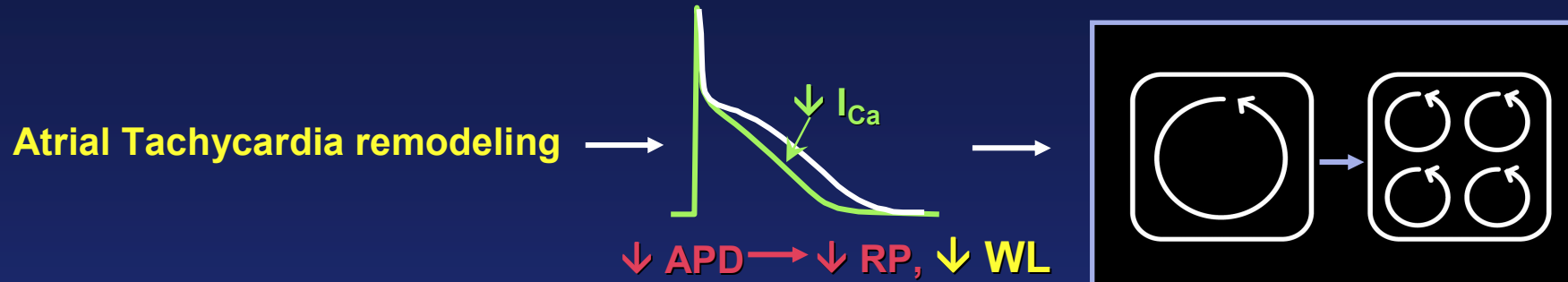


# Atrial tachycardia remodeling (“AF begets AF”)

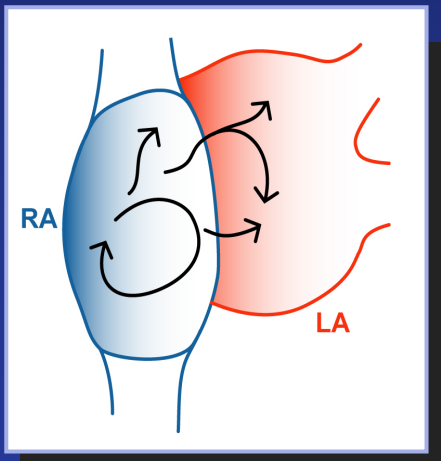




# Conceptual Models of AF are Linked

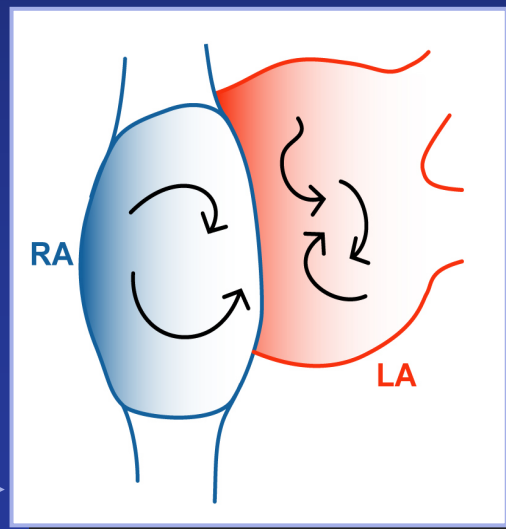


## Single-circuit reentry



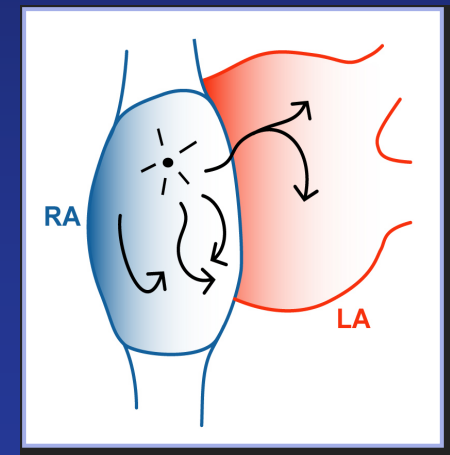
*Atrial tachycardia remodeling*

## Multiple-circuit reentry



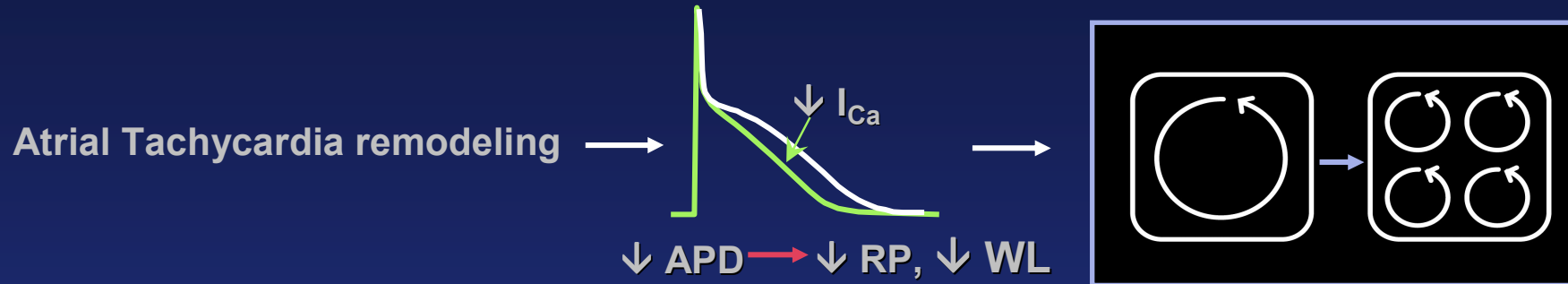
*Final common pathway*

## Ectopic focus

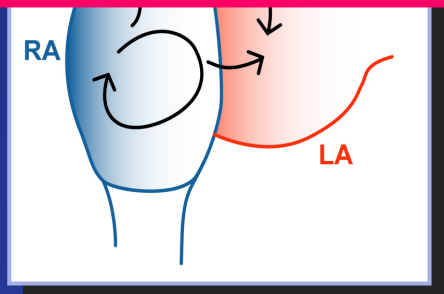


*Atrial tachycardia remodeling*

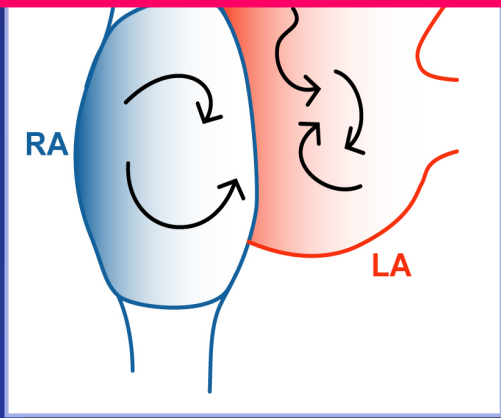
# Conceptual Models of AF are Linked



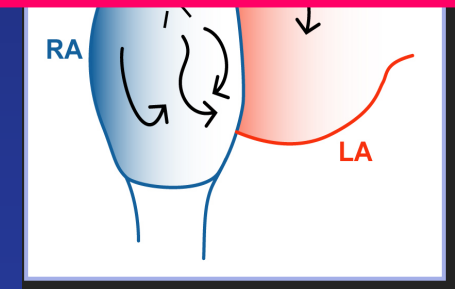
Could this process be a target for drug therapy?



*Atrial tachycardia remodeling*

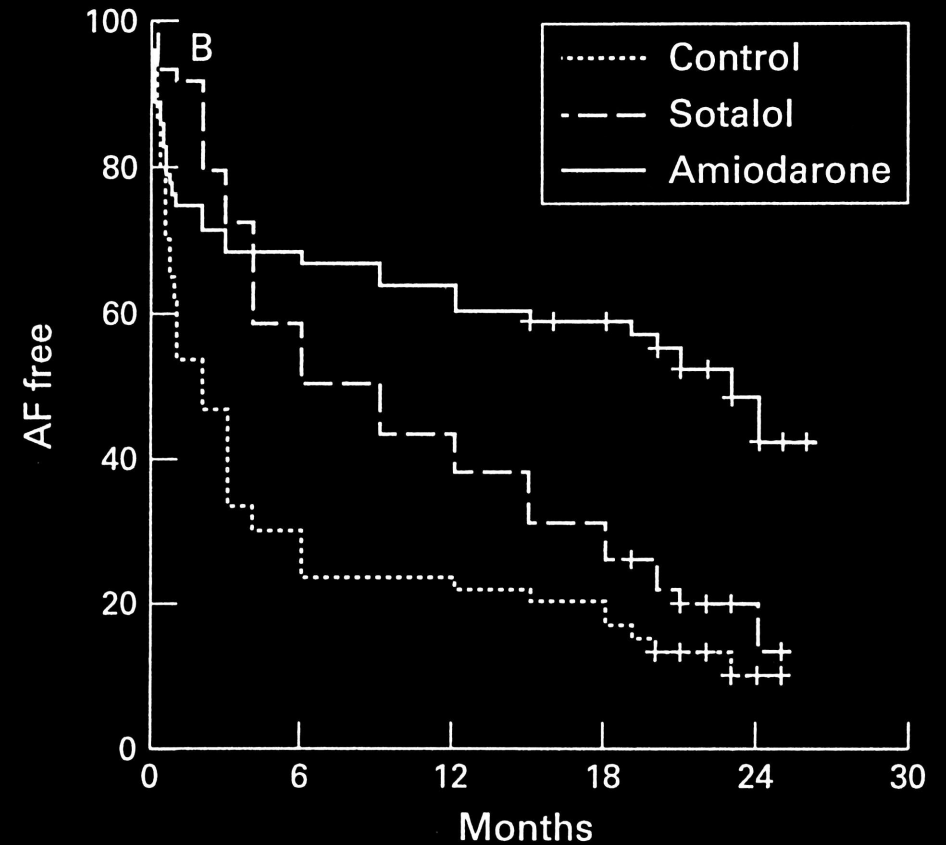
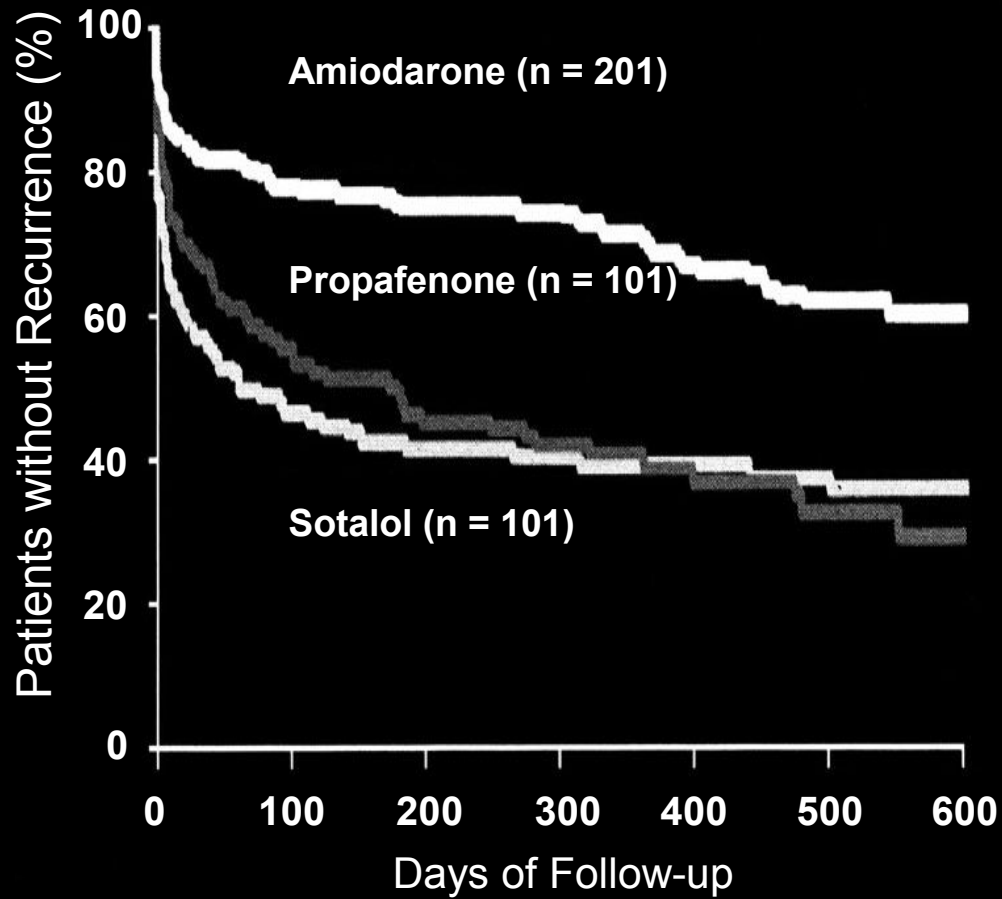


*Final common pathway*

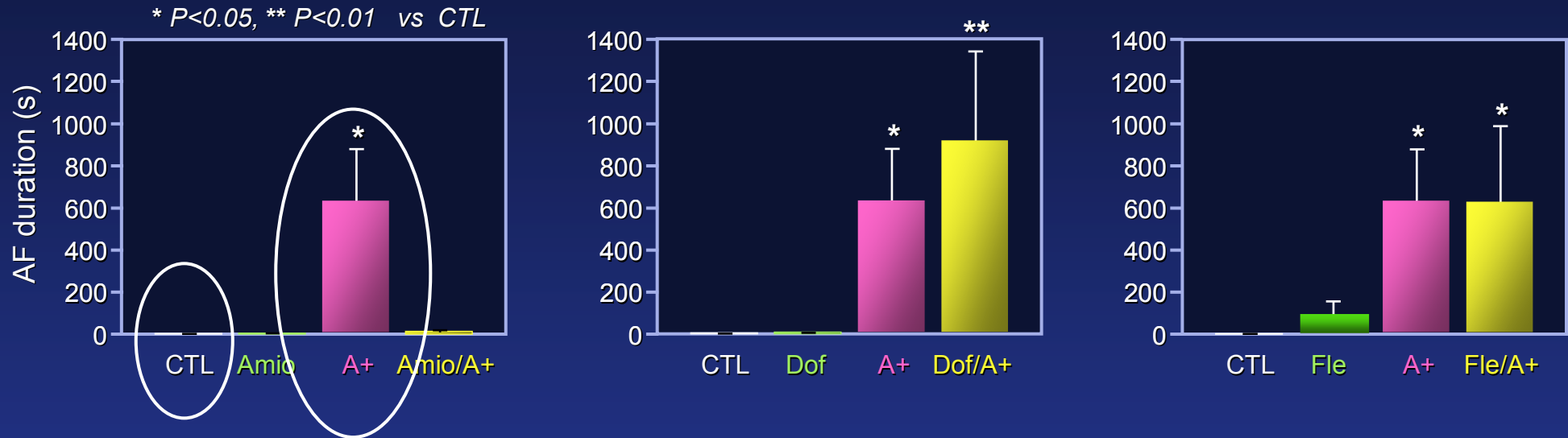


*Atrial tachycardia remodeling*

# Superiority of Amiodarone in AF

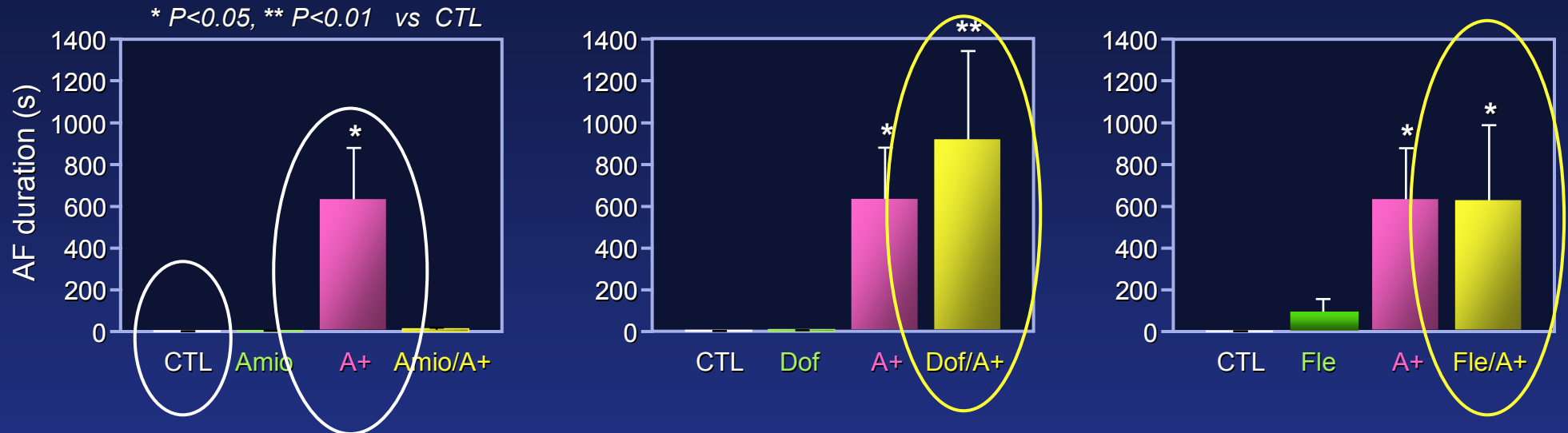


# Effects of antiarrhythmic drugs on AF



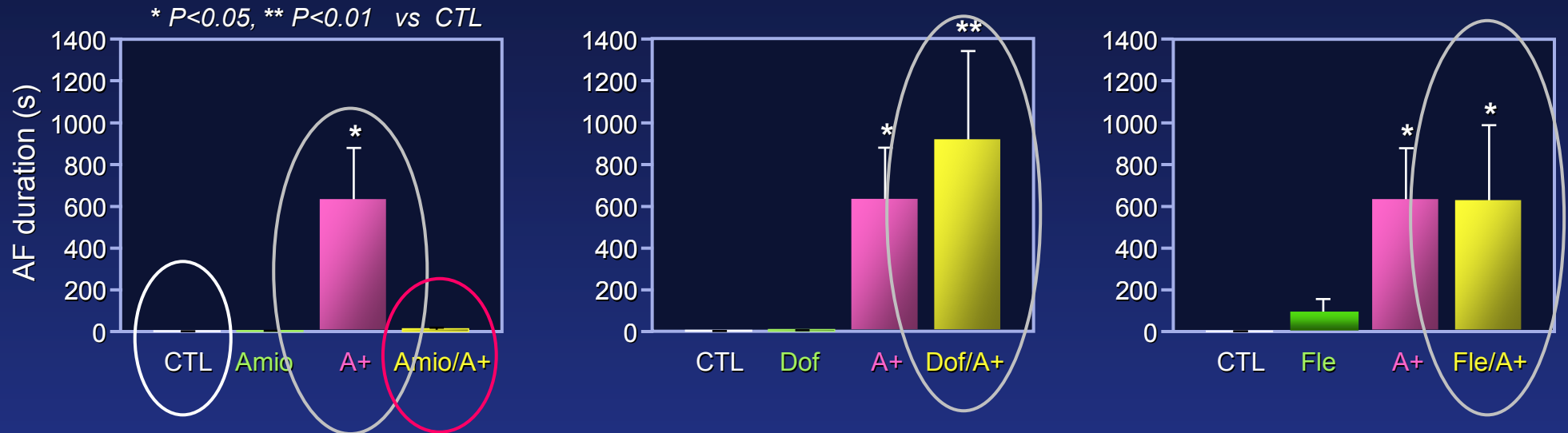
AT-remodeling (A+) increases AF duration.

# Effects of antiarrhythmic drugs on AF



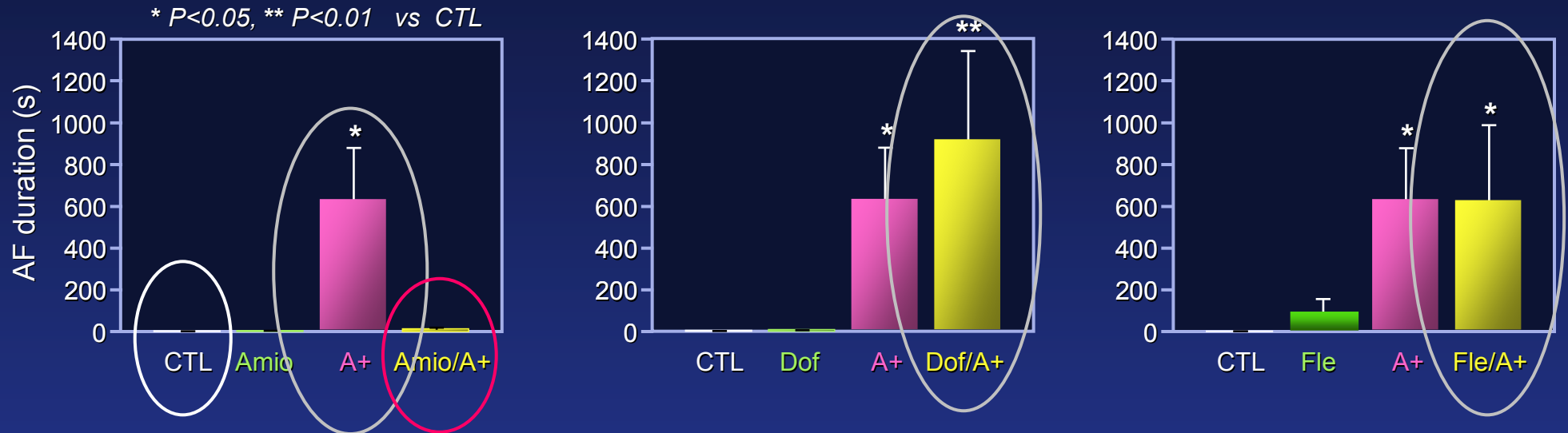
AT-remodeling (A+) increases AF duration.  
Dofetilide (DOF) and Flecainide (Flec) have no protective effects

# Effects of antiarrhythmic drugs on AF



AT-remodeling (A+) increases AF duration.  
Amiodarone prevents AF-duration increase caused by AT-remodeling.

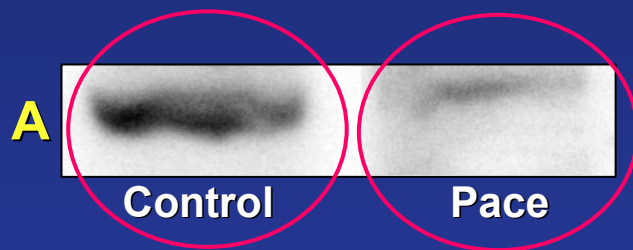
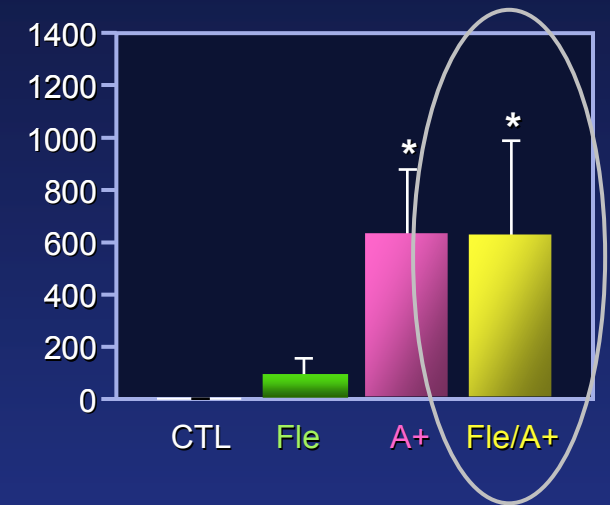
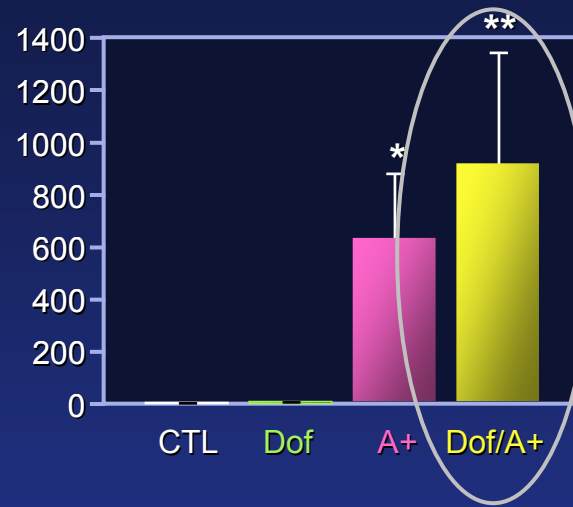
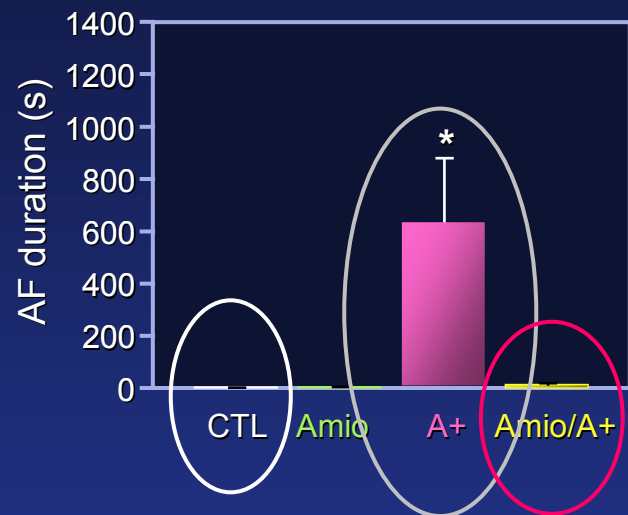
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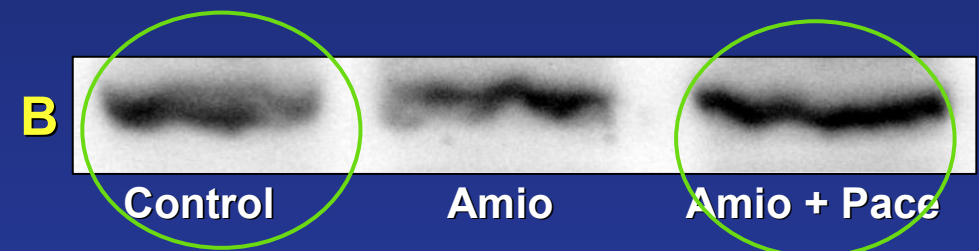
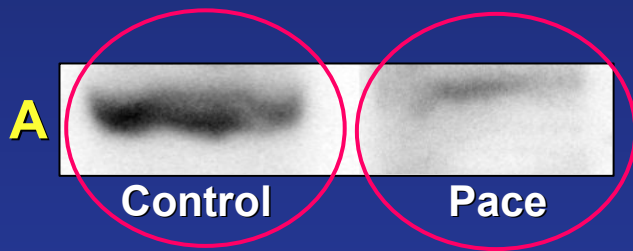
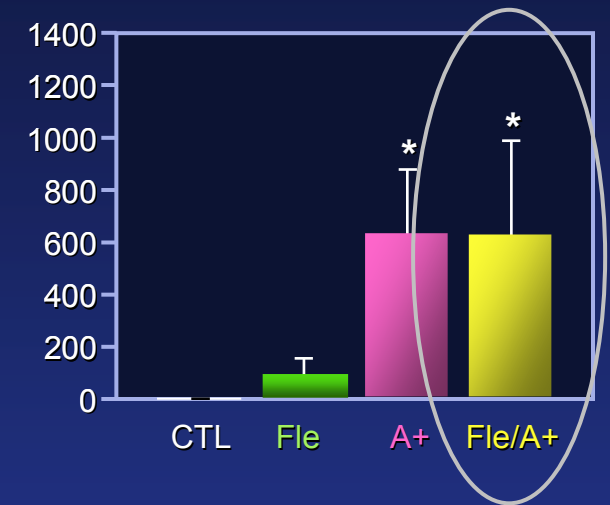
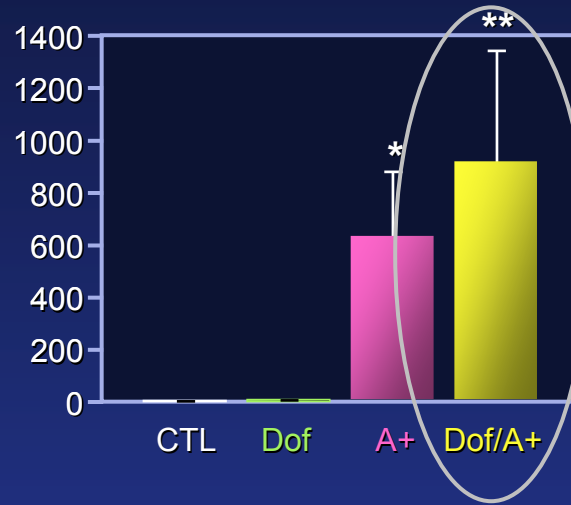
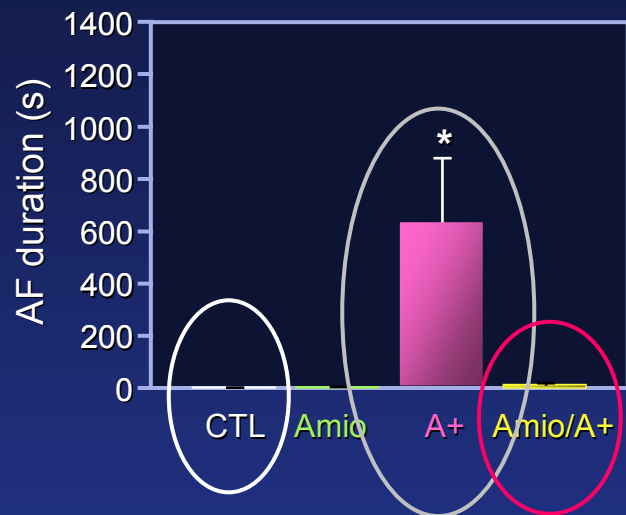
***Is this effect of amiodarone due to remodeling prevention?***

# AT- remodeling suppresses $\alpha_{1c}$ (L-type $\text{Ca}^{2+}$ channel) subunit expression

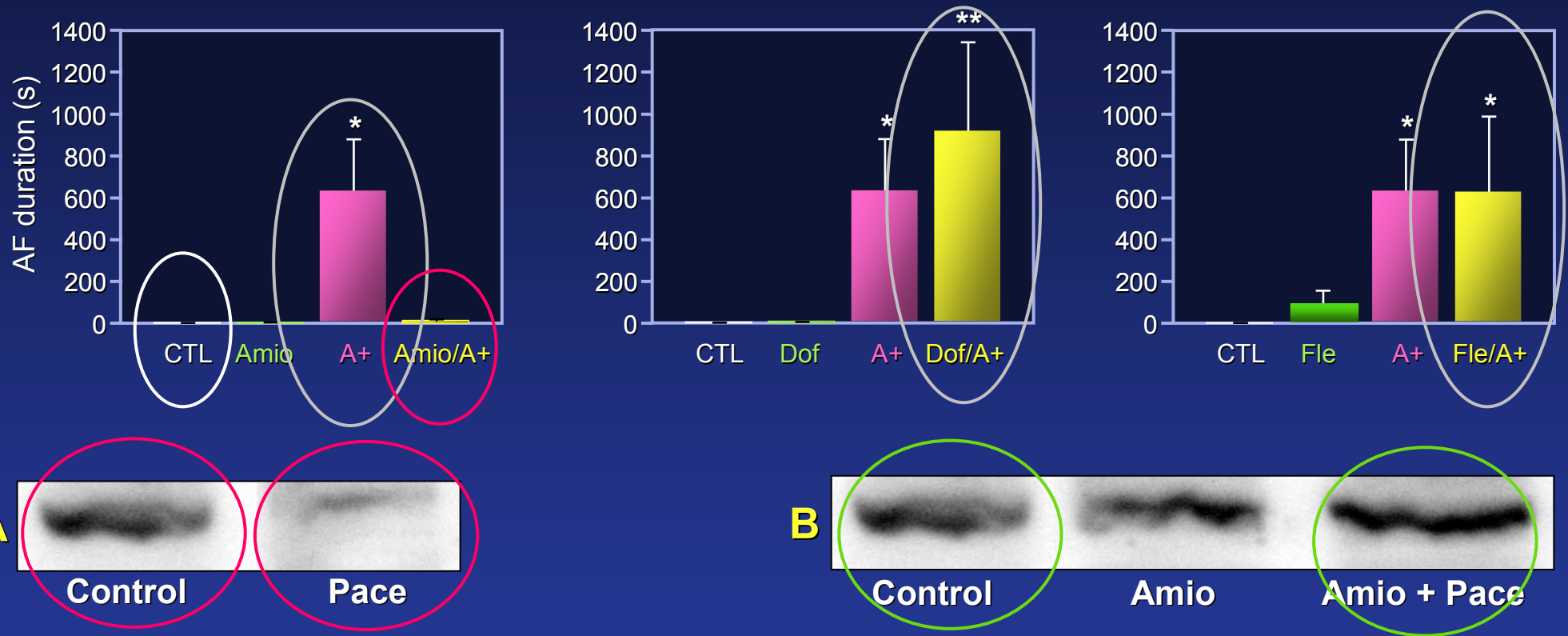




# Amiodarone prevents AT- remodeling suppression of $\alpha_{1c}$ (L-type $\text{Ca}^{2+}$ channel) subunit expression

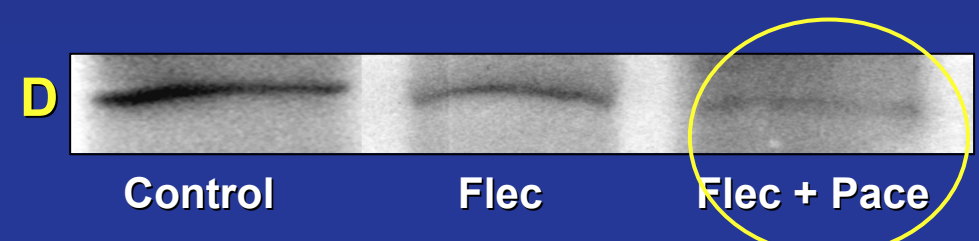
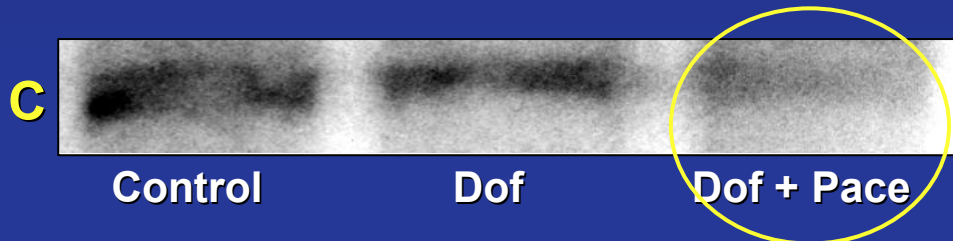
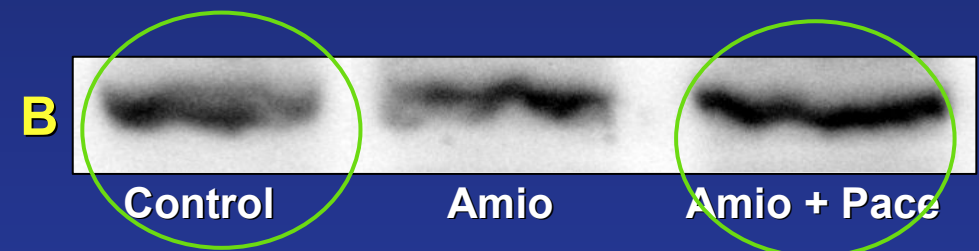
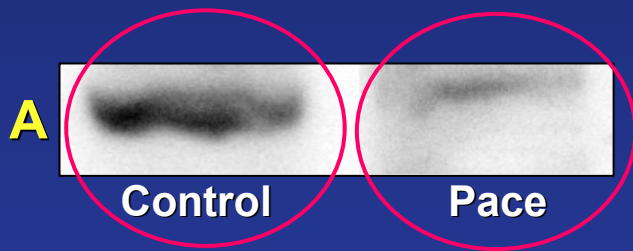
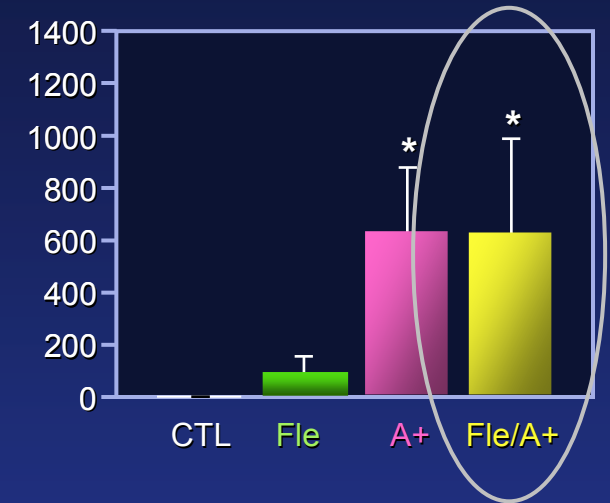
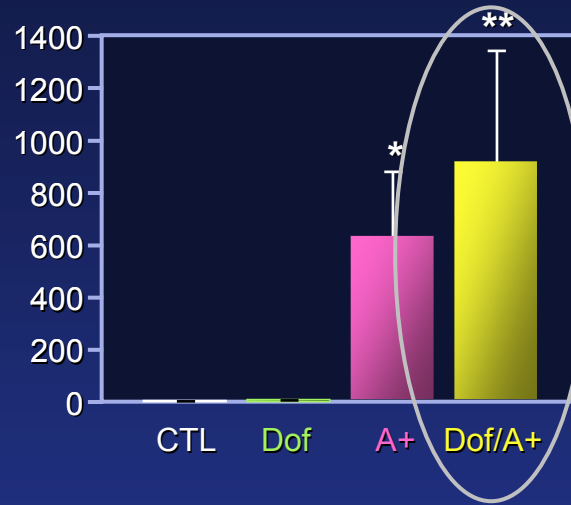
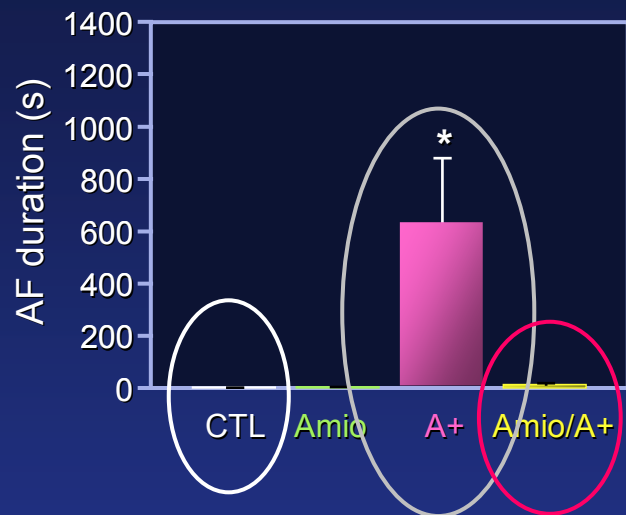


# Amiodarone prevents AT- remodeling suppression of $\alpha_{1c}$ (L-type $\text{Ca}^{2+}$ channel) subunit expression



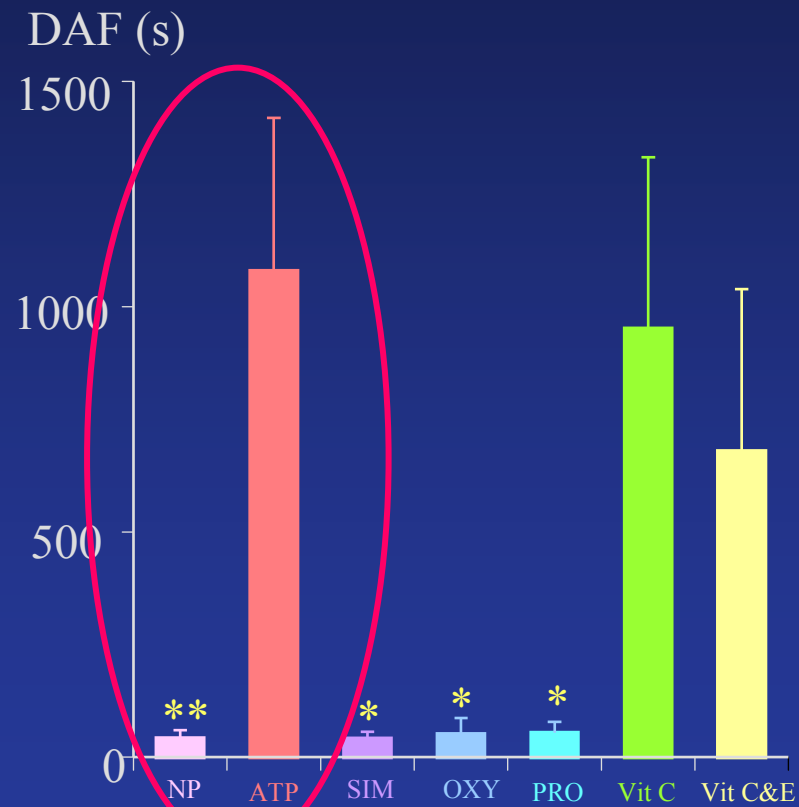
This is evidence of a direct effect to prevent remodeling

# Dofetilide and flecainide do not prevent AT-remodeling suppression of $\alpha_{1c}$ subunit expression



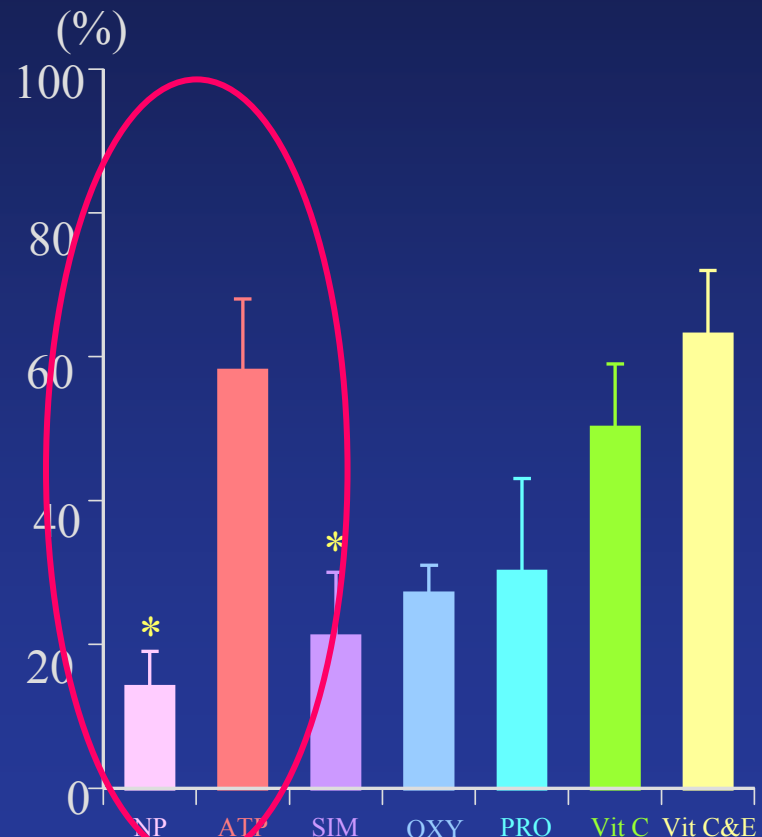
# Effects of agents interacting with redox mechanisms on atrial-tachycardia remodeling

## Mean AF duration (D7)



\*:p<0.05 vs ATP, \*\*:p<0.01 vs ATP

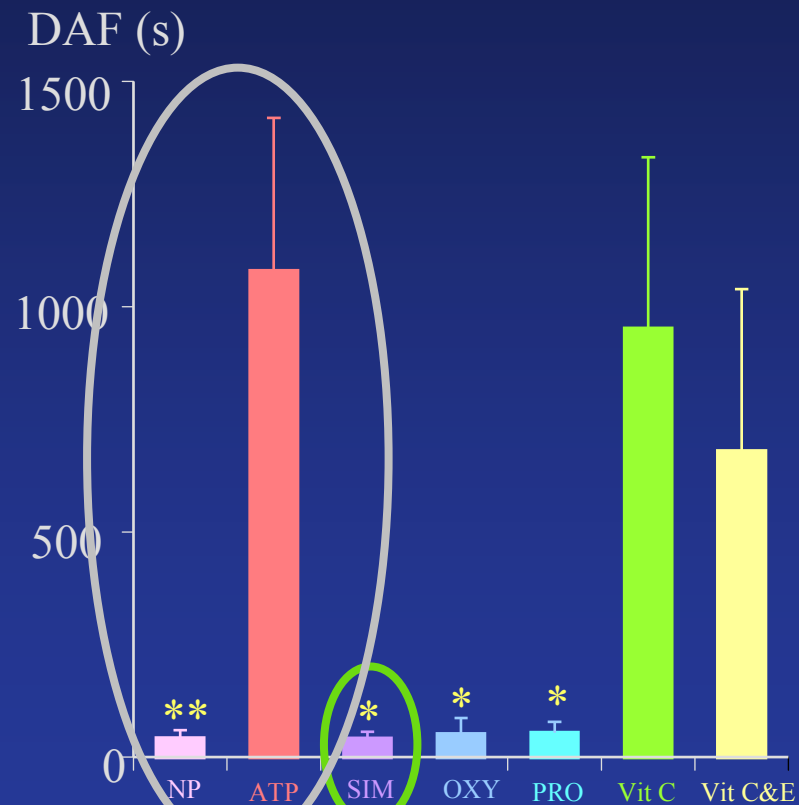
## AF vulnerability (D7)



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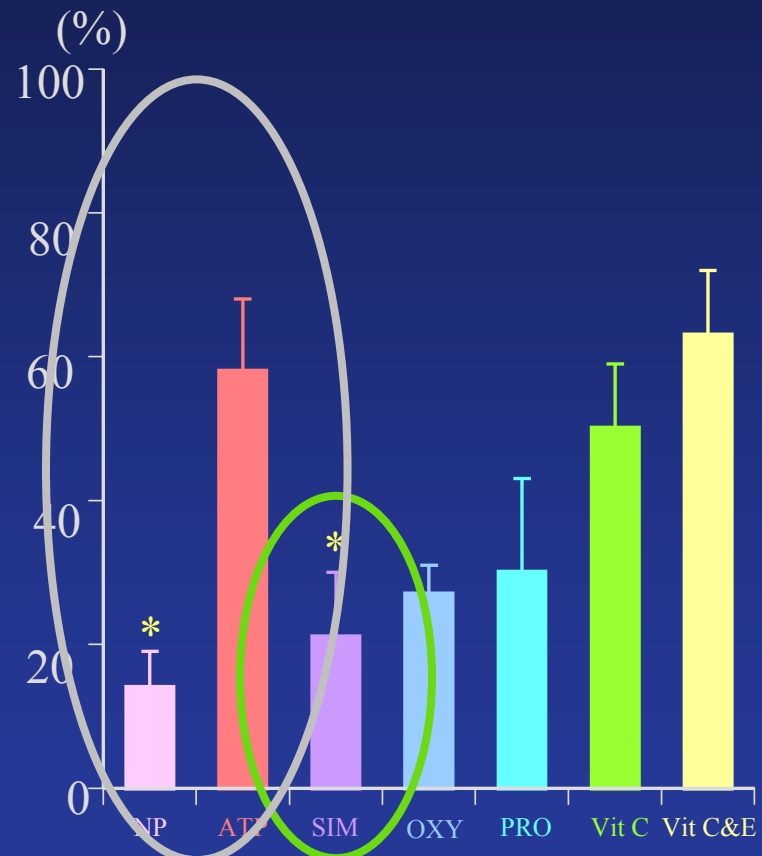
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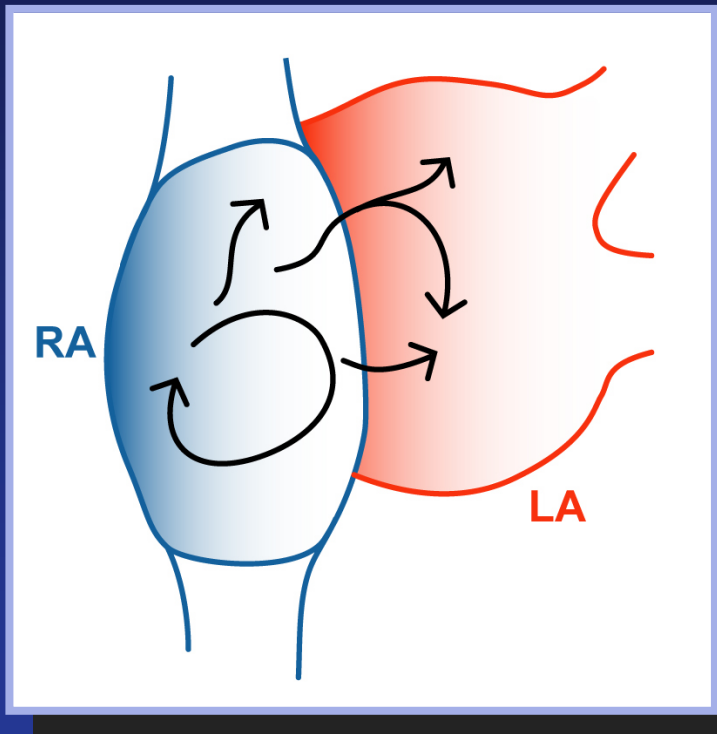


\*:p<0.05 vs ATP

# Can Single-Circuit Reentry Underlie AF?

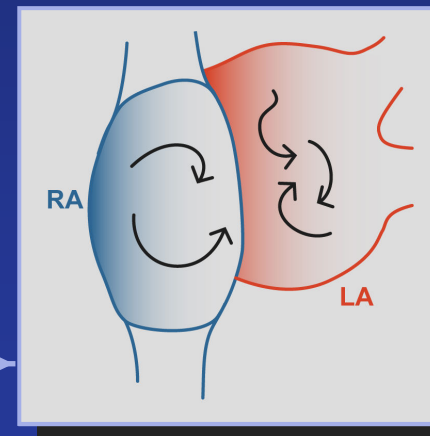
## Single-circuit reentry

? →



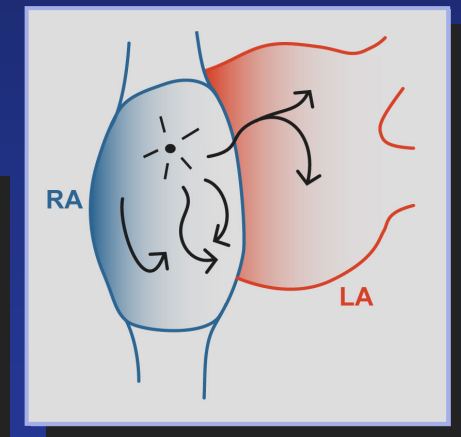
*Atrial tachycardia remodeling*

## Multiple-circuit reentry



*Final common pathway*

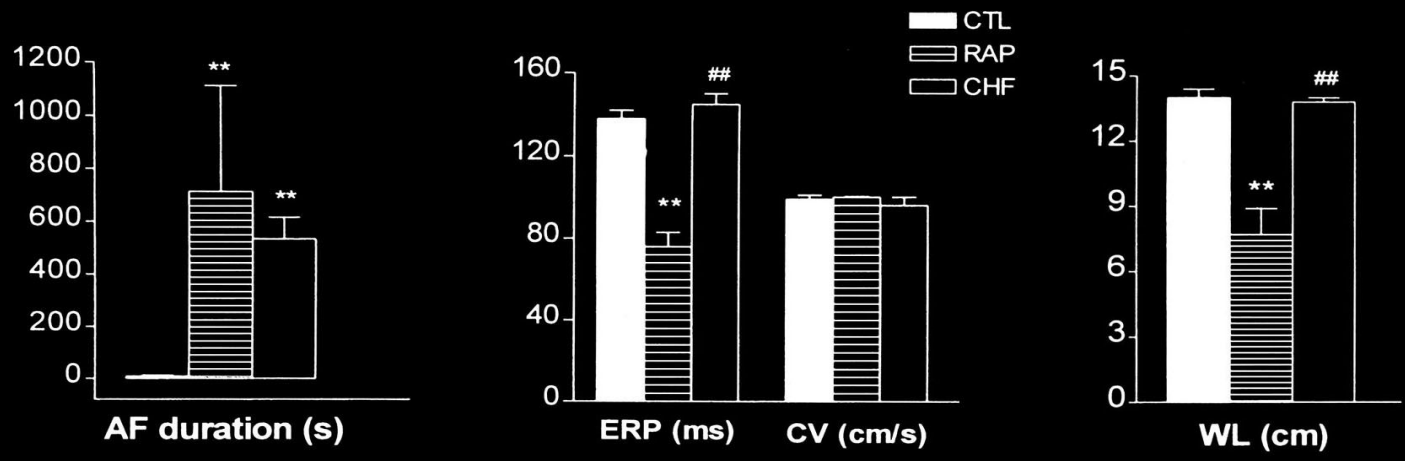
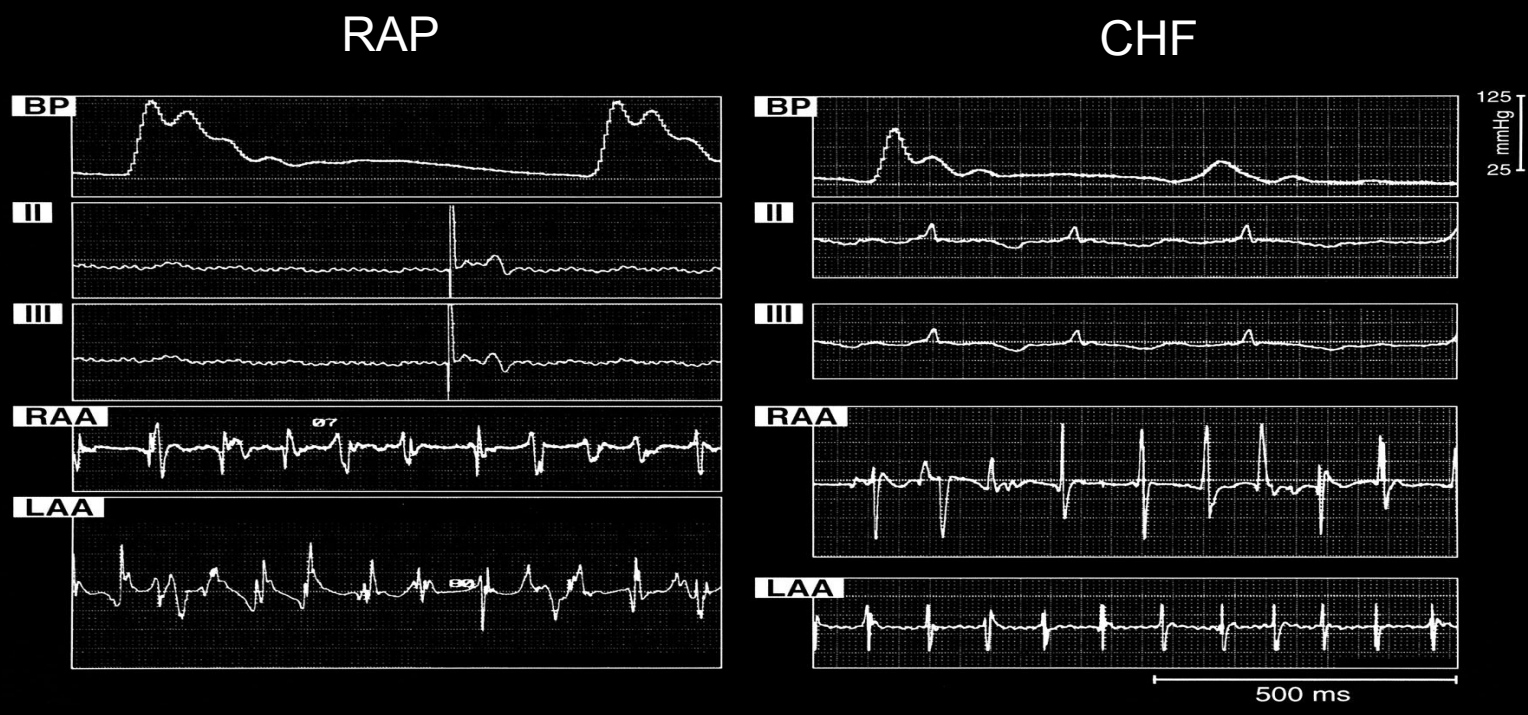
## Ectopic focus



*Atrial tachycardia remodeling*

# Electrophysiology of Sustained AF

## Substrate in Rapid Atrial Paced (RAP) vs CHF Dogs



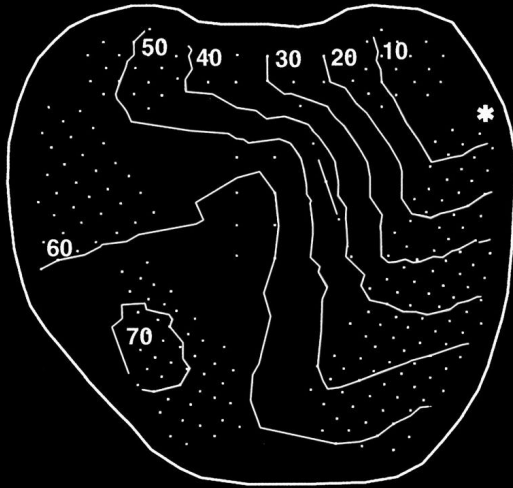
LI et al, Circulation 1999; 100:87-95



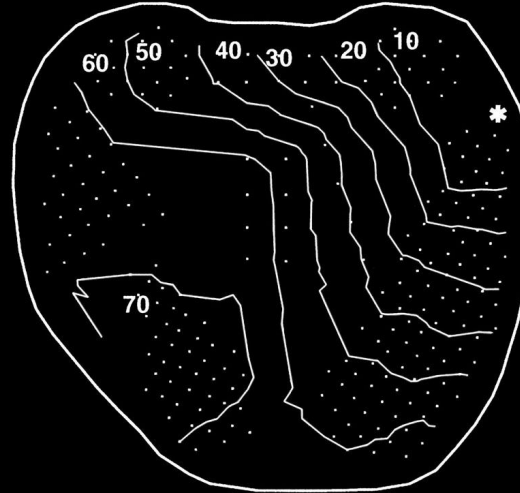
# Conduction Abnormalities and Atrial Fibrosis in CHF (Structural remodeling)

## Epicardial maps

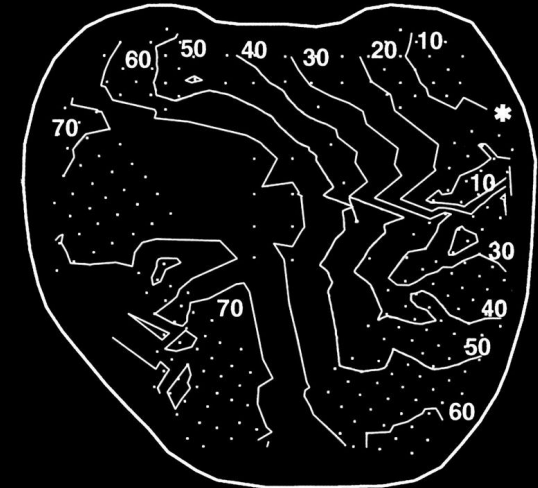
Control



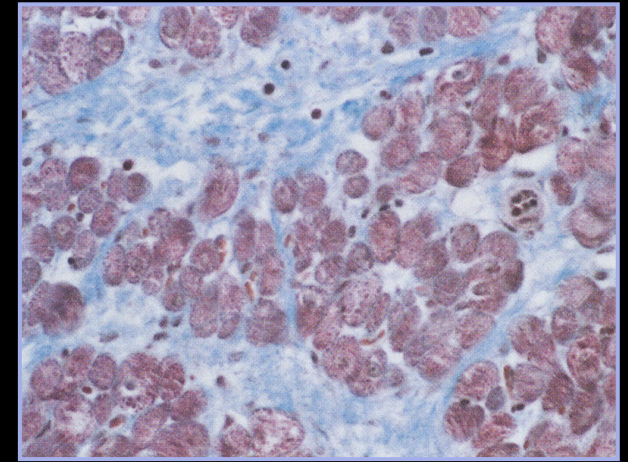
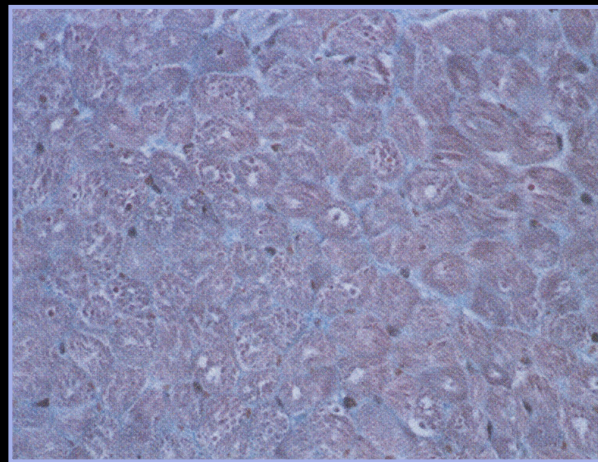
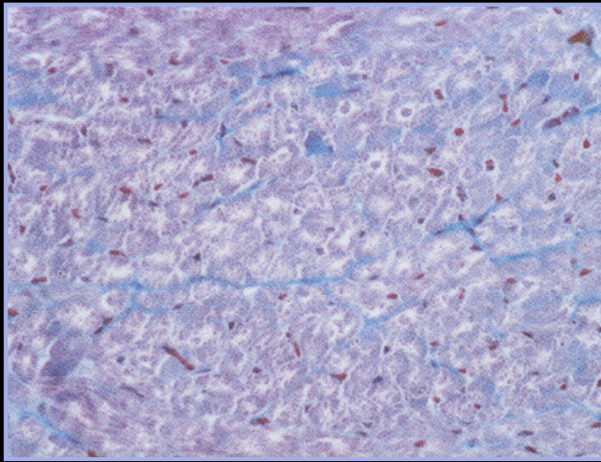
Atrial tachycardia



CHF

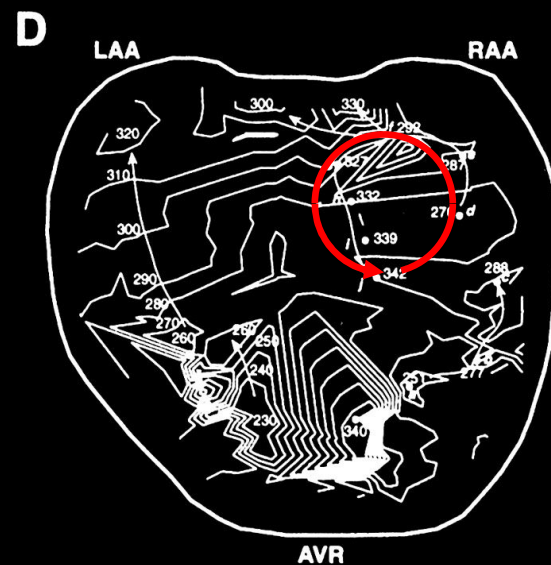
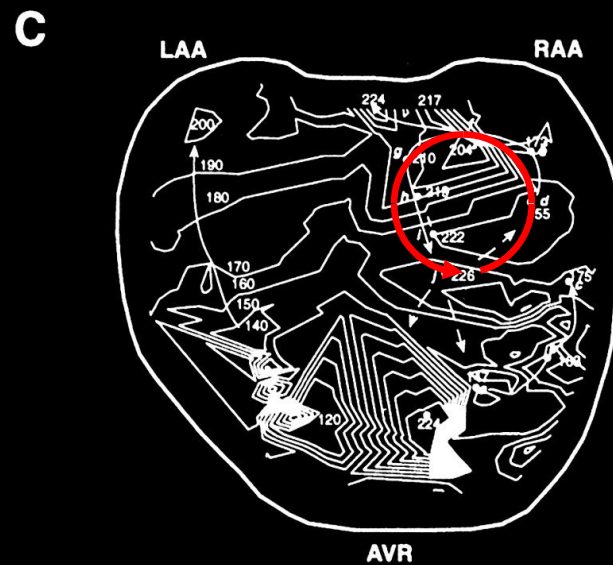
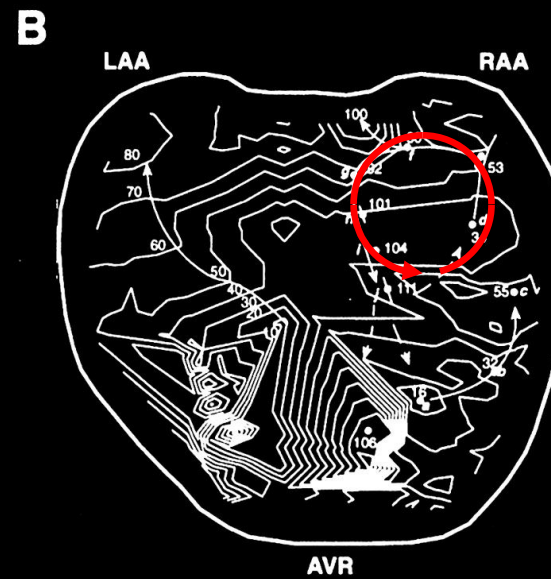
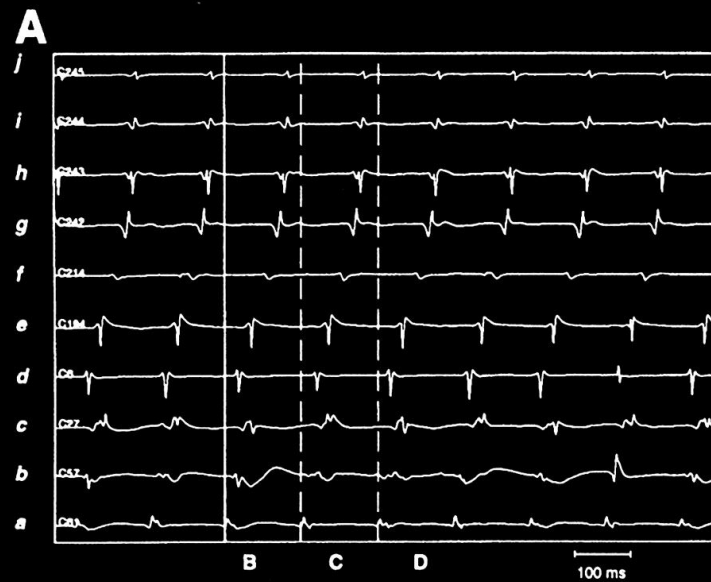


## Histology



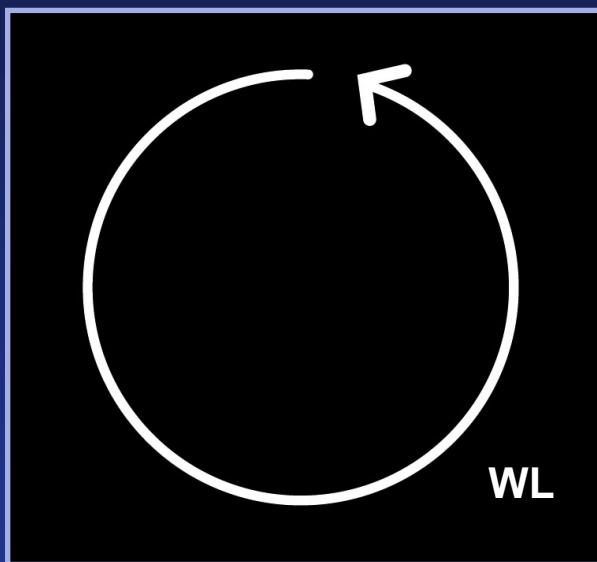


# Mapping of Sustained AF in a Dog with CHF



# Reentry: Stabilization by Conduction Abnormalities

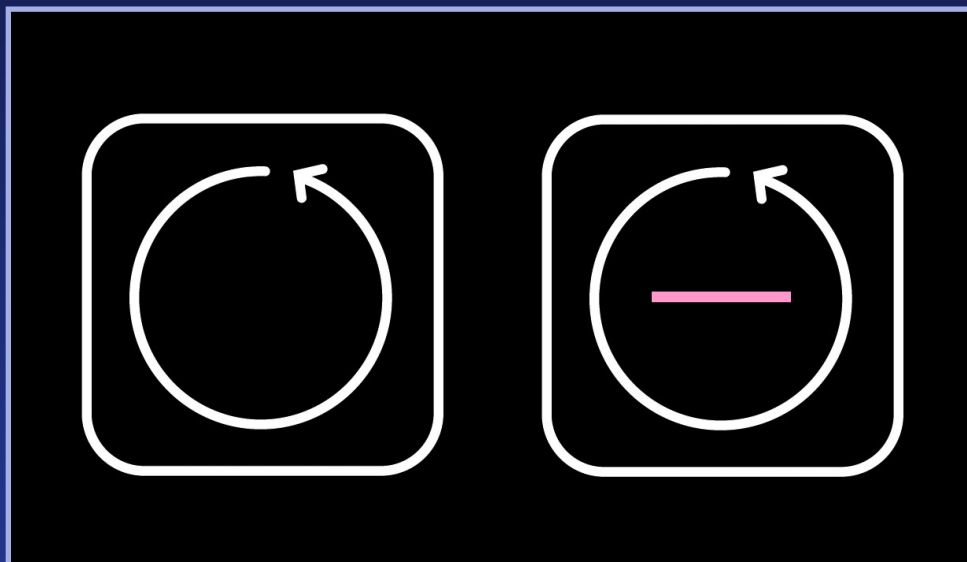
**A**



**Wavelength (WL) =**  
refractory period x conduction velocity

- minimal path length for reentry
- size of functional reentry circuits

**B**



**Normal atrial size**  
**Normal WL**

- reentry unstable
- AF not sustained

**Normal atrial size**  
**Normal WL**

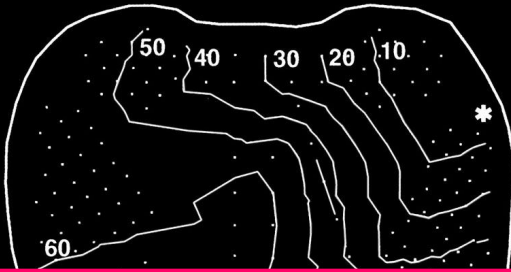
**Local conduction abnormality**

- reentry stabilized
- Fast, irreg. condxn = AF

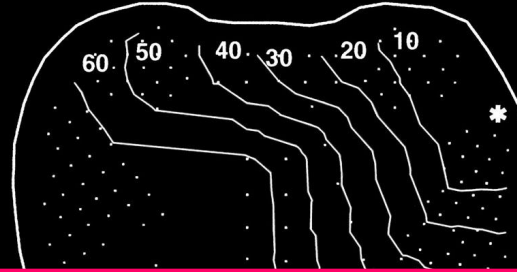
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Control



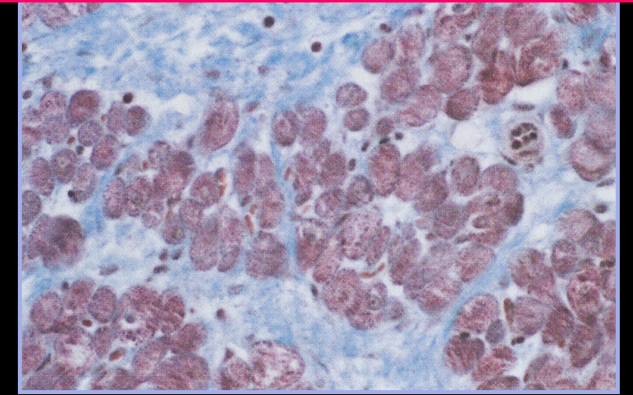
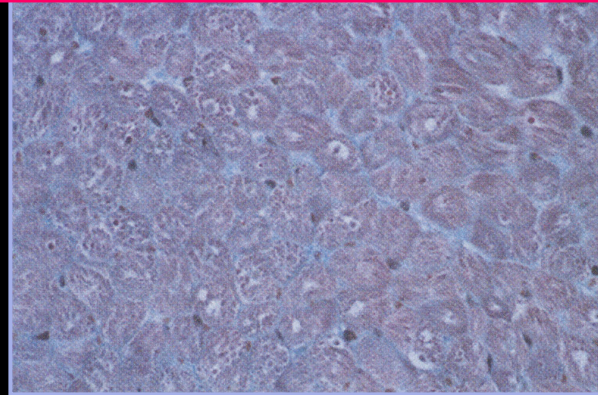
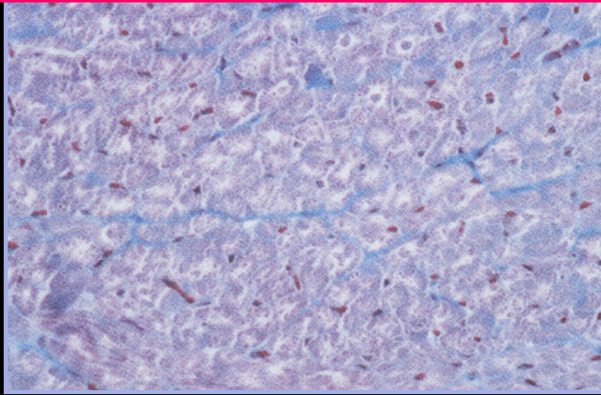
Atrial tachycardia



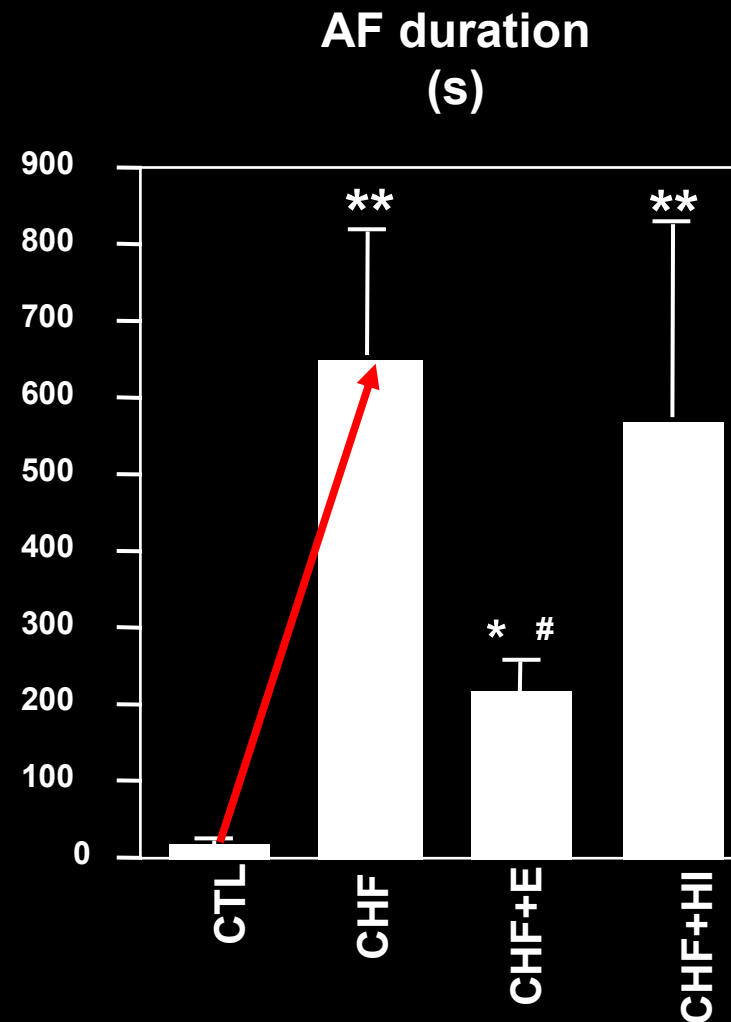
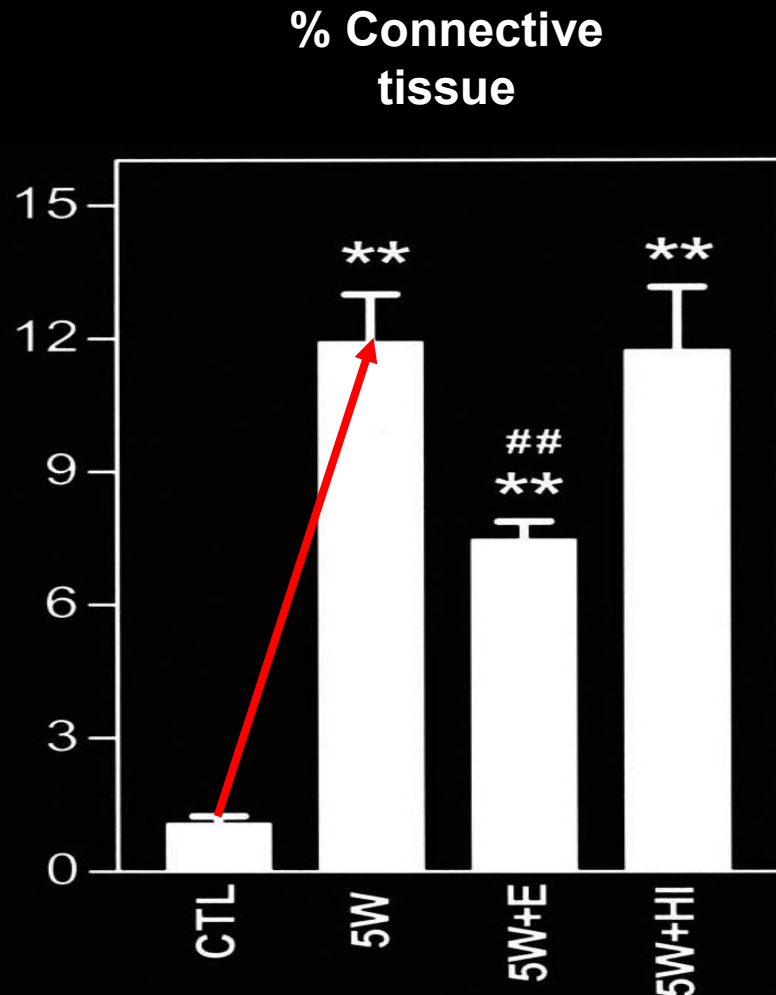
CHF



Could this process be a target for drug therapy?



# Can Inhibiting Ang-II Formation Prevent Development of the Substrate for AF?



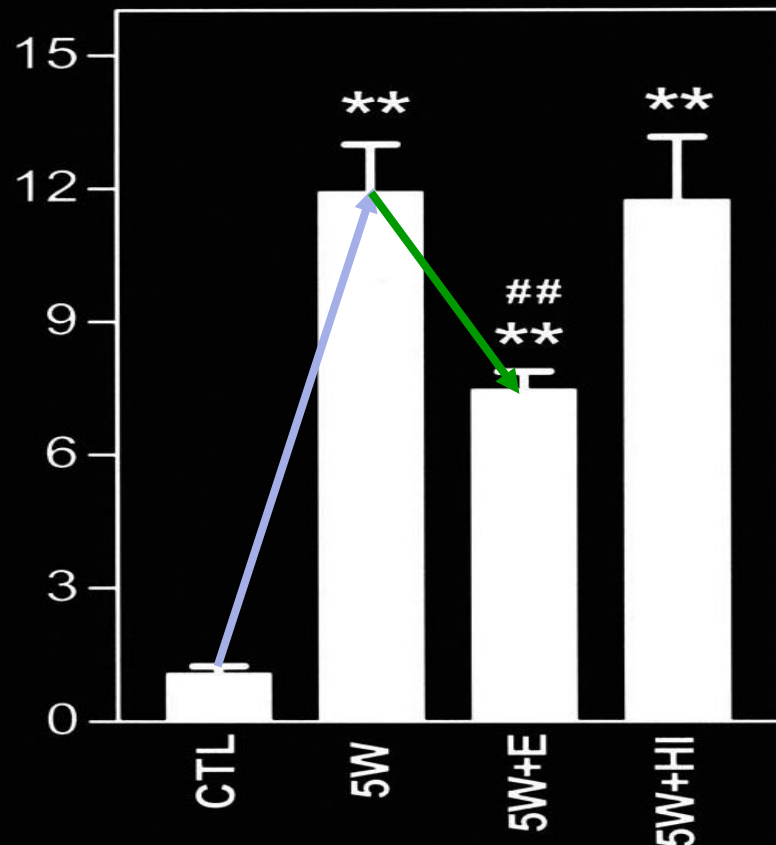
E = enalapril; HI=hydralazine/isosorbide

CHF induces fibrosis and increases AF duration

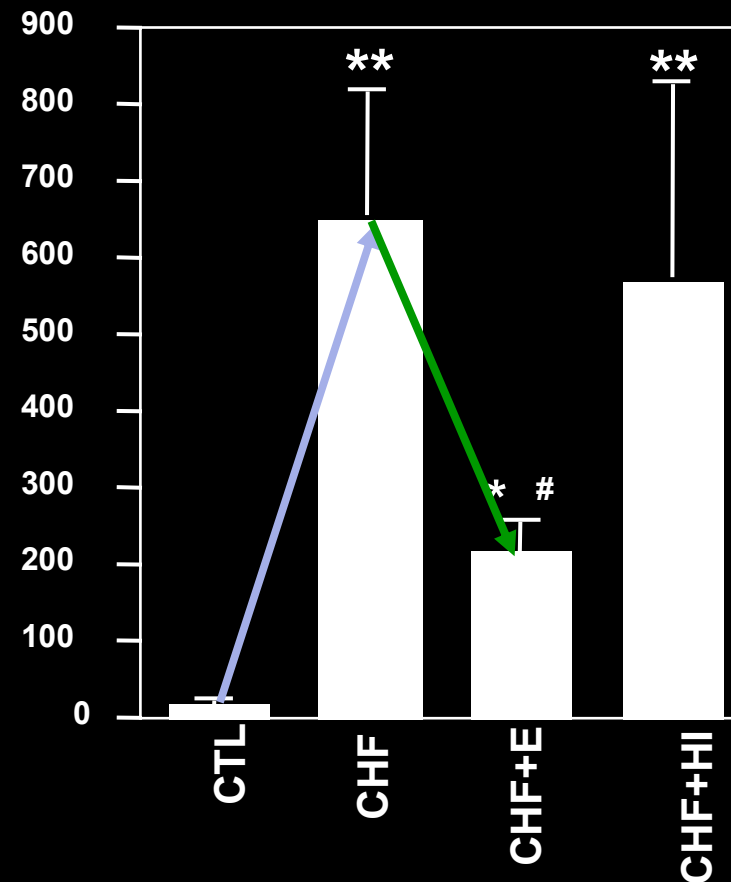
LI D et al, Circulation 104: 2608-2614, 2001

# Can Inhibiting Ang-II Formation Prevent Development of the Substrate for AF?

% Connective tissue



AF duration (s)



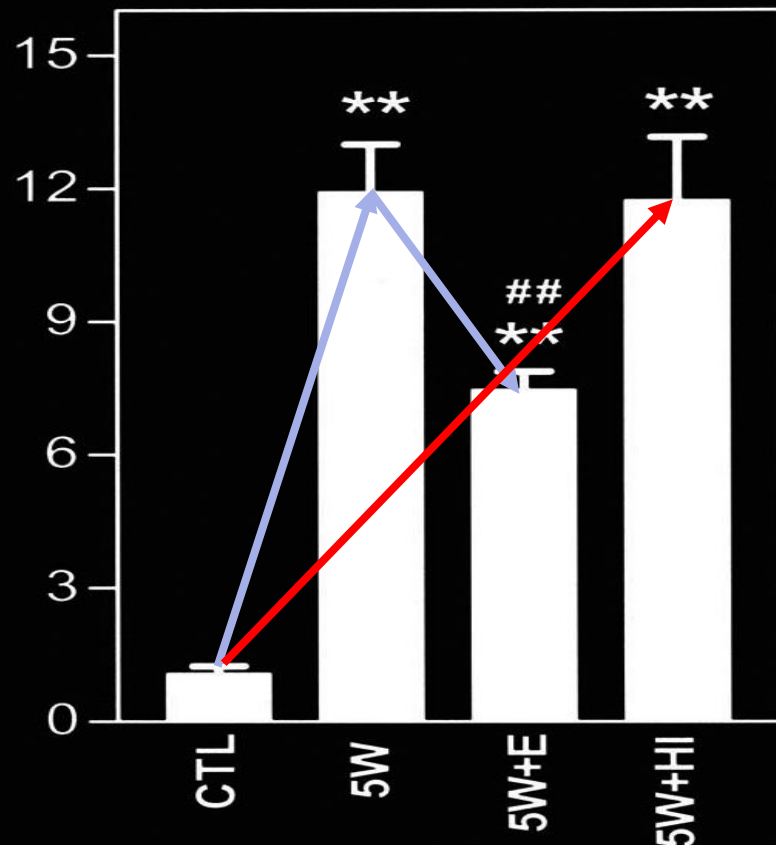
E = enalapril; HI=hydralazine/isosorbide

Enalapril attenuates fibrosis and AF duration increases

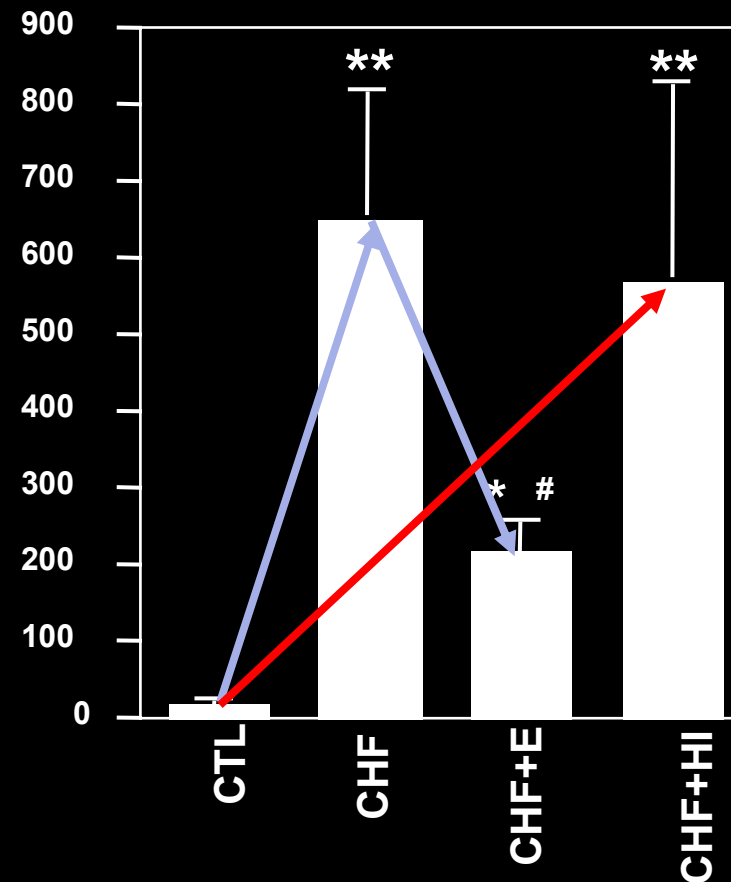
LI D et al, Circulation 104: 2608-2614, 2001

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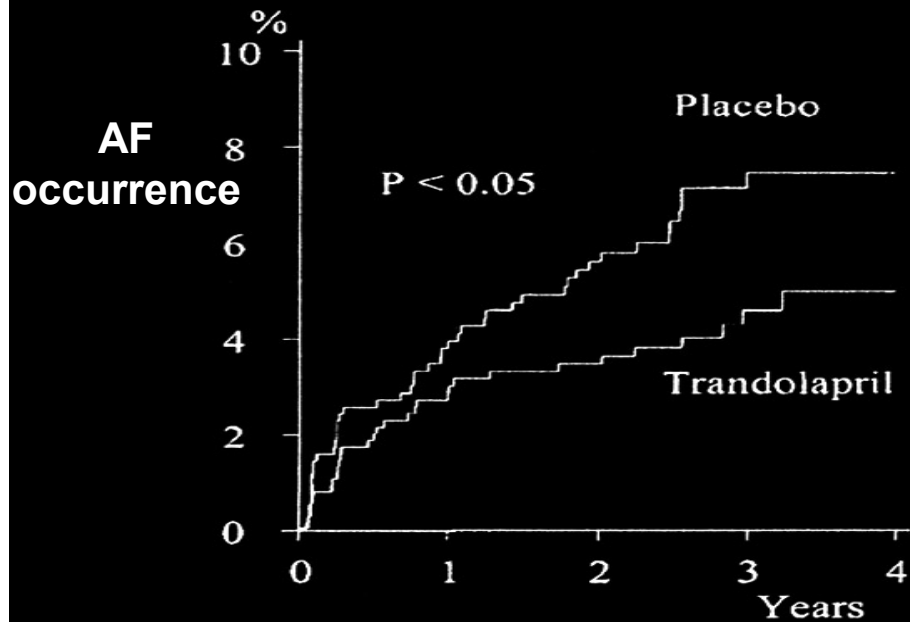
Vasodilator therapy does not mimic enalapril effects

LI D et al, Circulation 104: 2608-2614, 2001



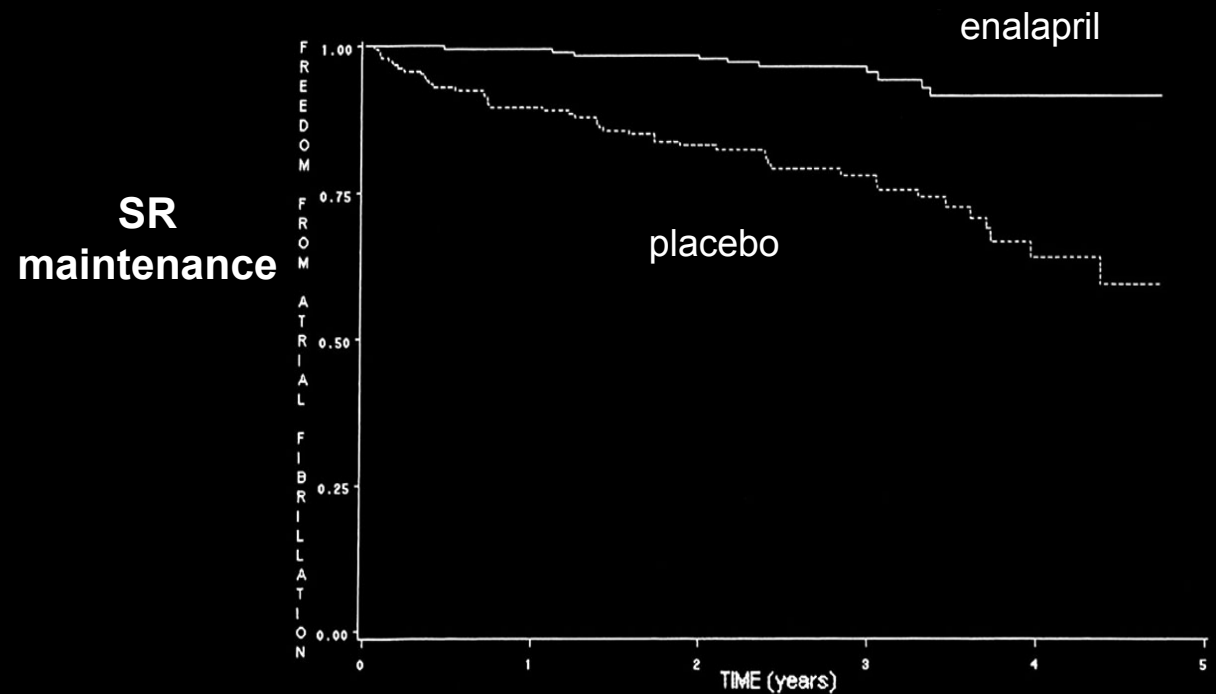
# ACE antagonism and clinical AF in LV dysfunction

AF in post-MI patients with LVD



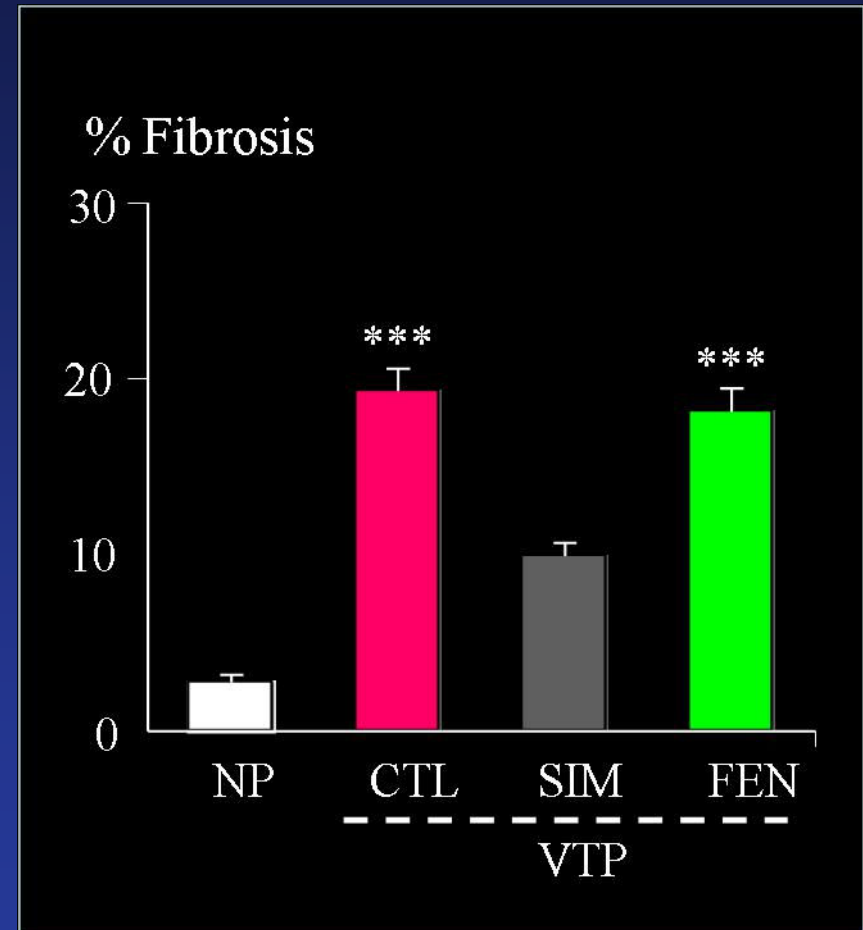
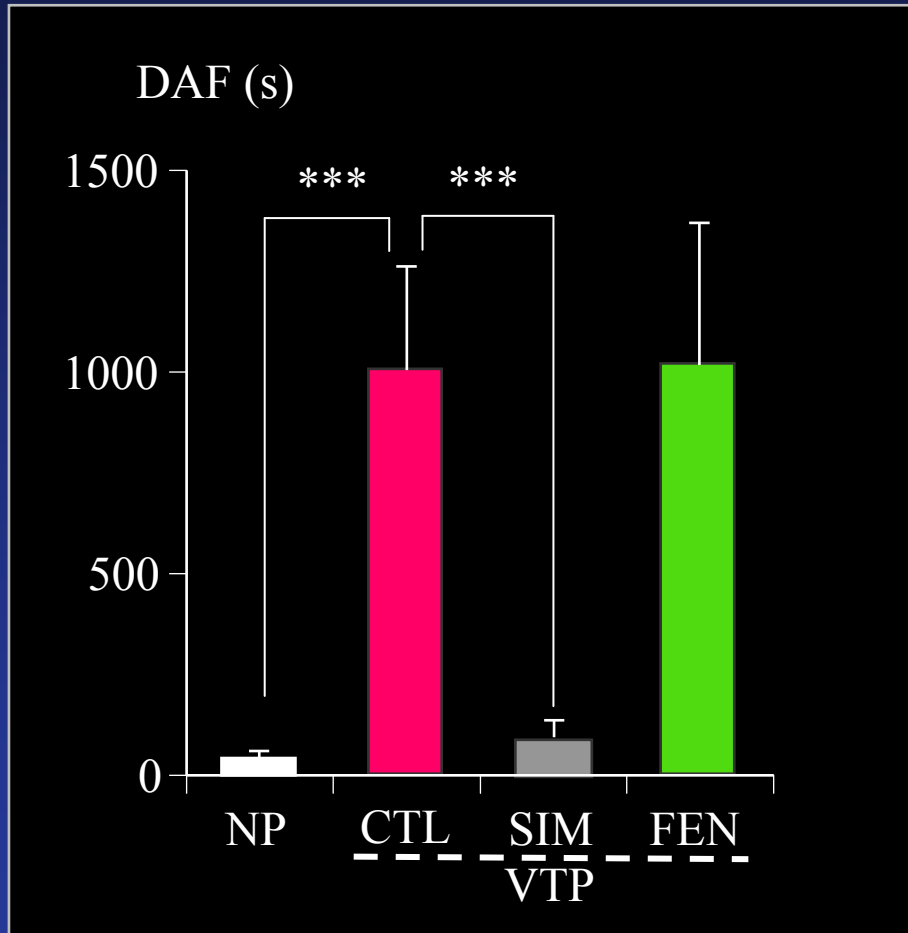
*Pedersen et al, Circulation 1999; 100: 376-380*

AF in SOLVD patients



*Vermes et al, Circulation 2003; 107: 2926-2931*

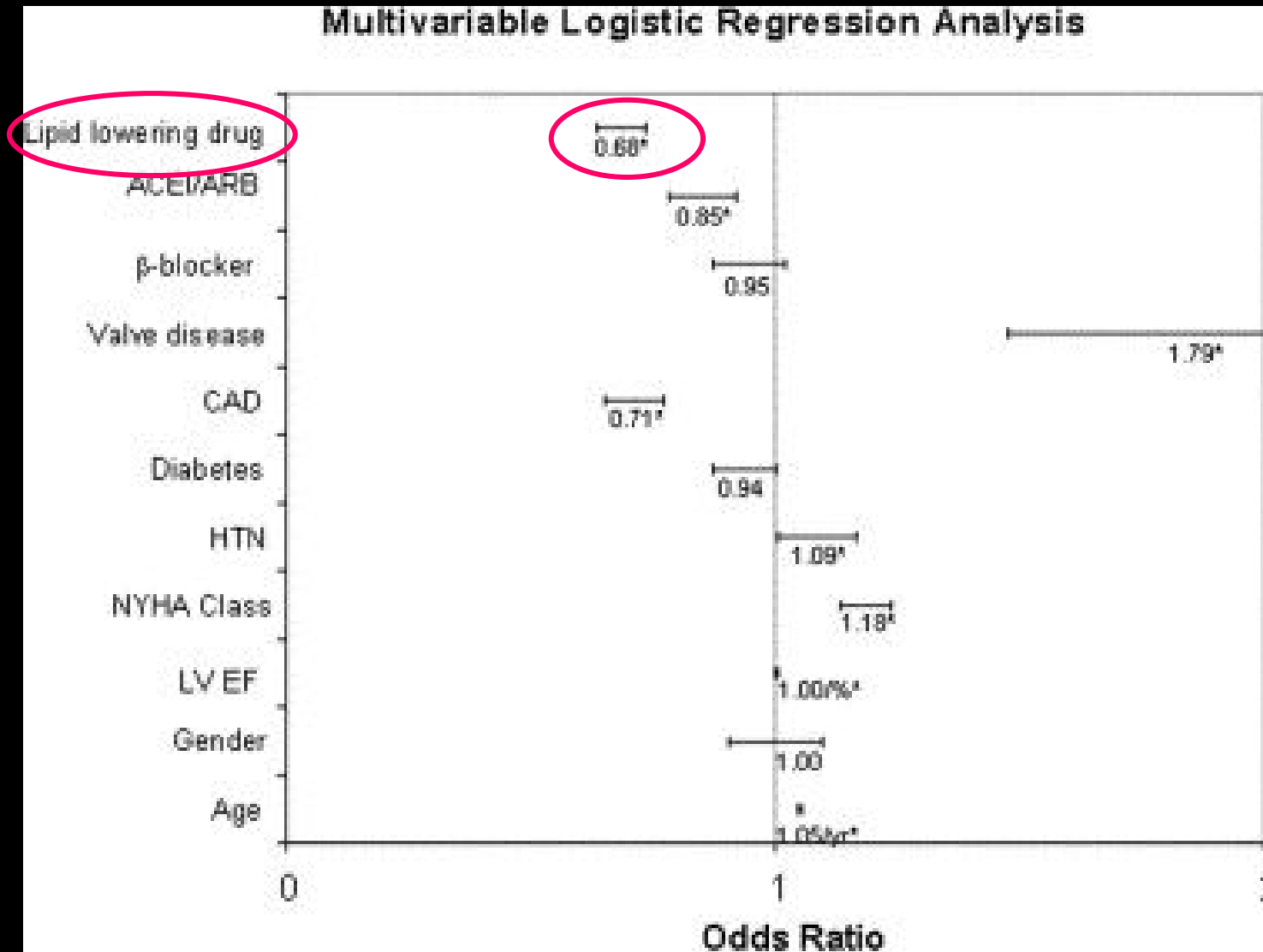
# Effects of simvastatin and fenofibrate on AF duration and atrial atrial fibrosis in CHF



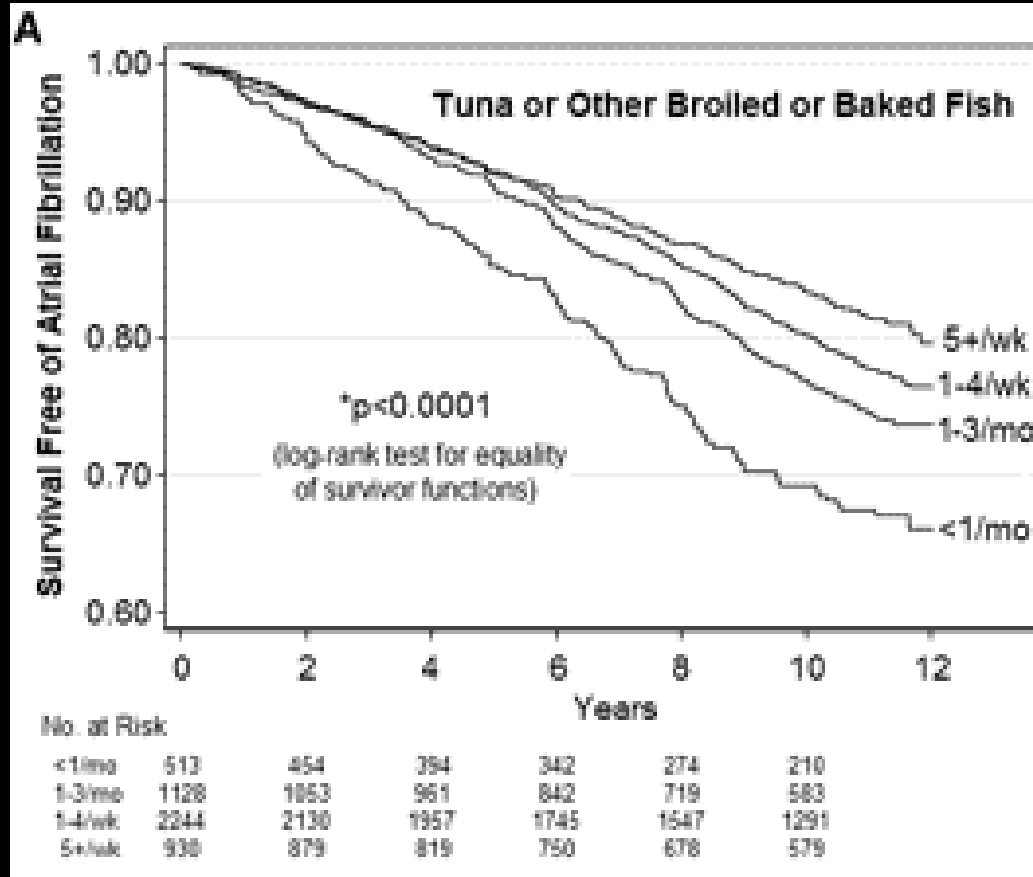


# Factors predicting AF in patients with LV dysfunction

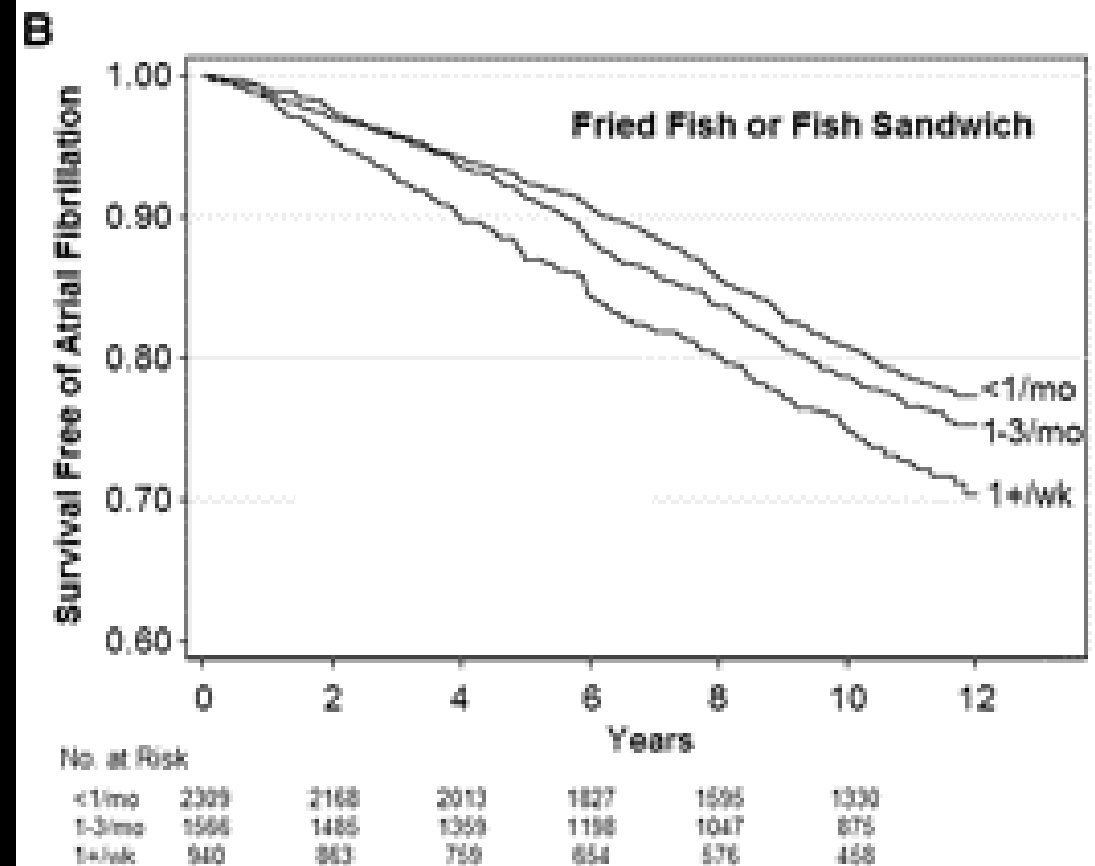
92% statins



# Effects of fish consumption on AF occurrence

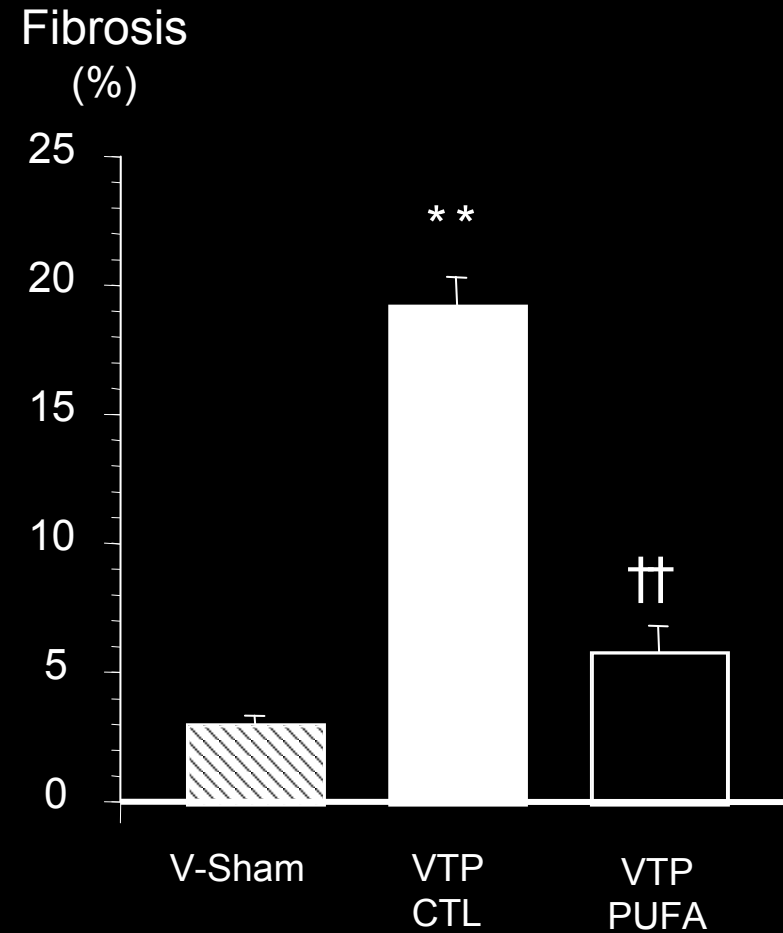
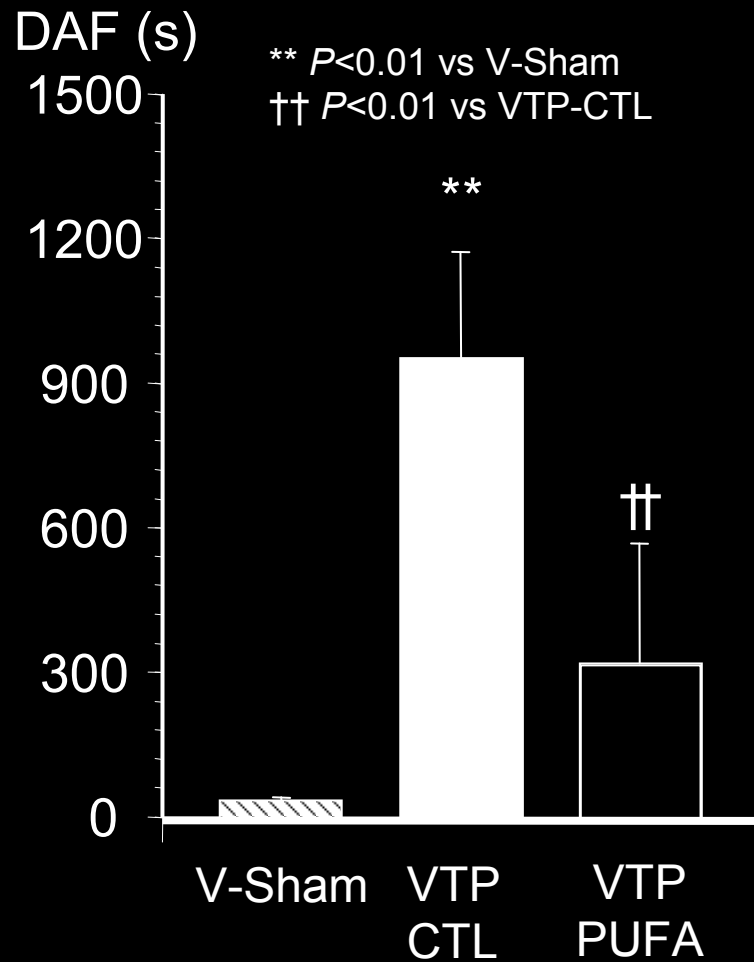


Ω-3 FA determined by ingestion



Ω-3 FA not determined by ingestion

# Effects of polyunsaturated acids on structural remodeling

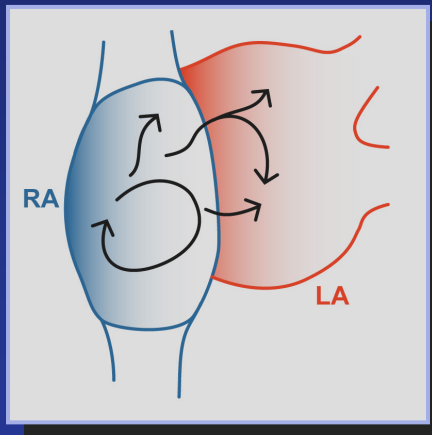


# What is the Role of Ectopic Foci?

## Ectopic focus

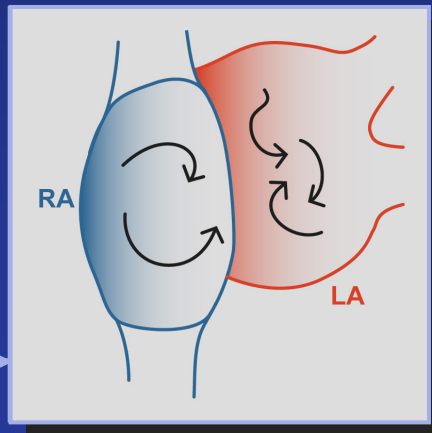
← ?

### Single-circuit reentry

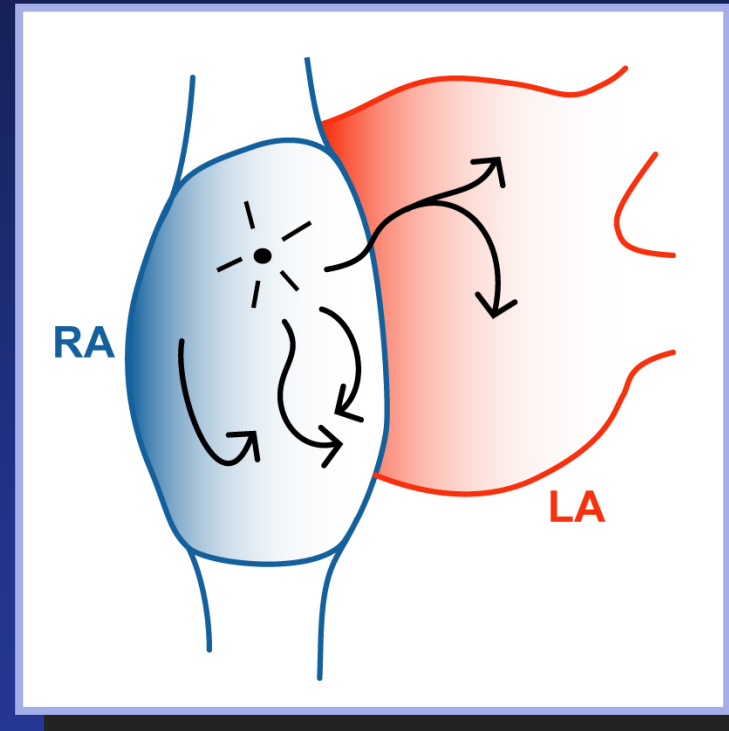


*Atrial tachycardia remodeling*

### Multiple-circuit reentry

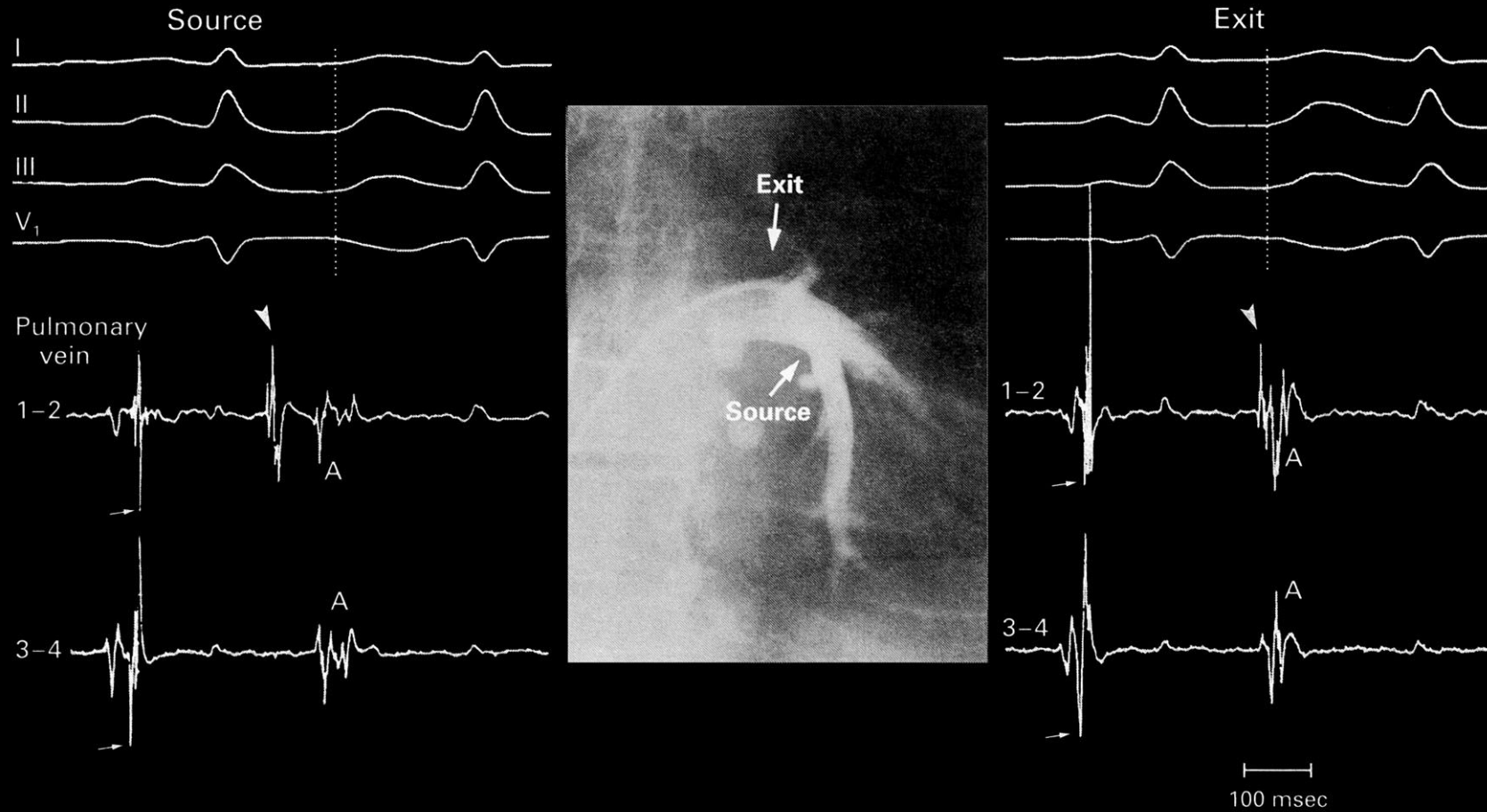


*Final common pathway*



*Atrial tachycardia remodeling*

# Etopic activity from a PV



# AF initiation from a PV



# Other Contributors

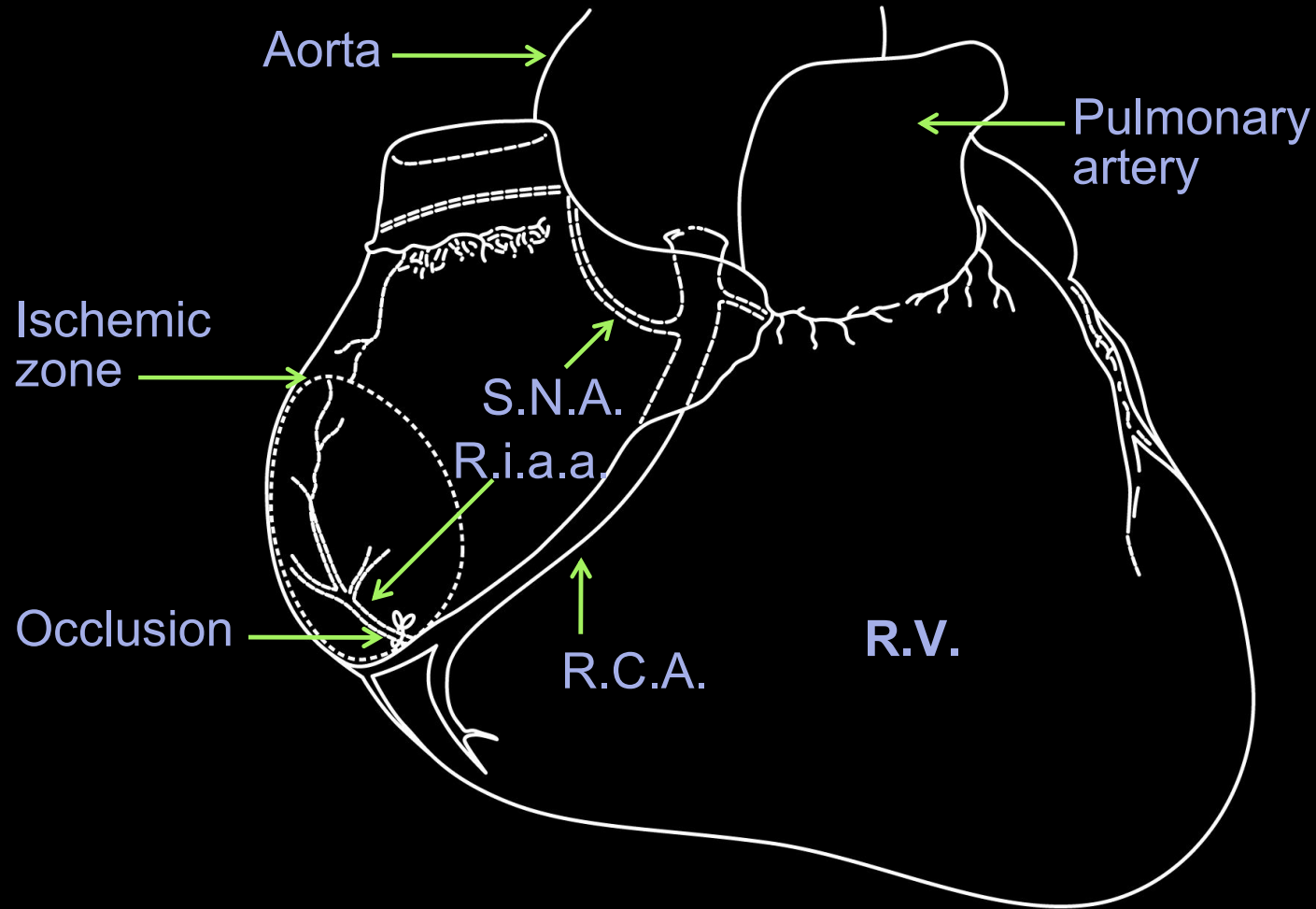
- **Atrial Ischemia**
  - **Inflammation**
  - **Atrial stretch**

# Other Contributors

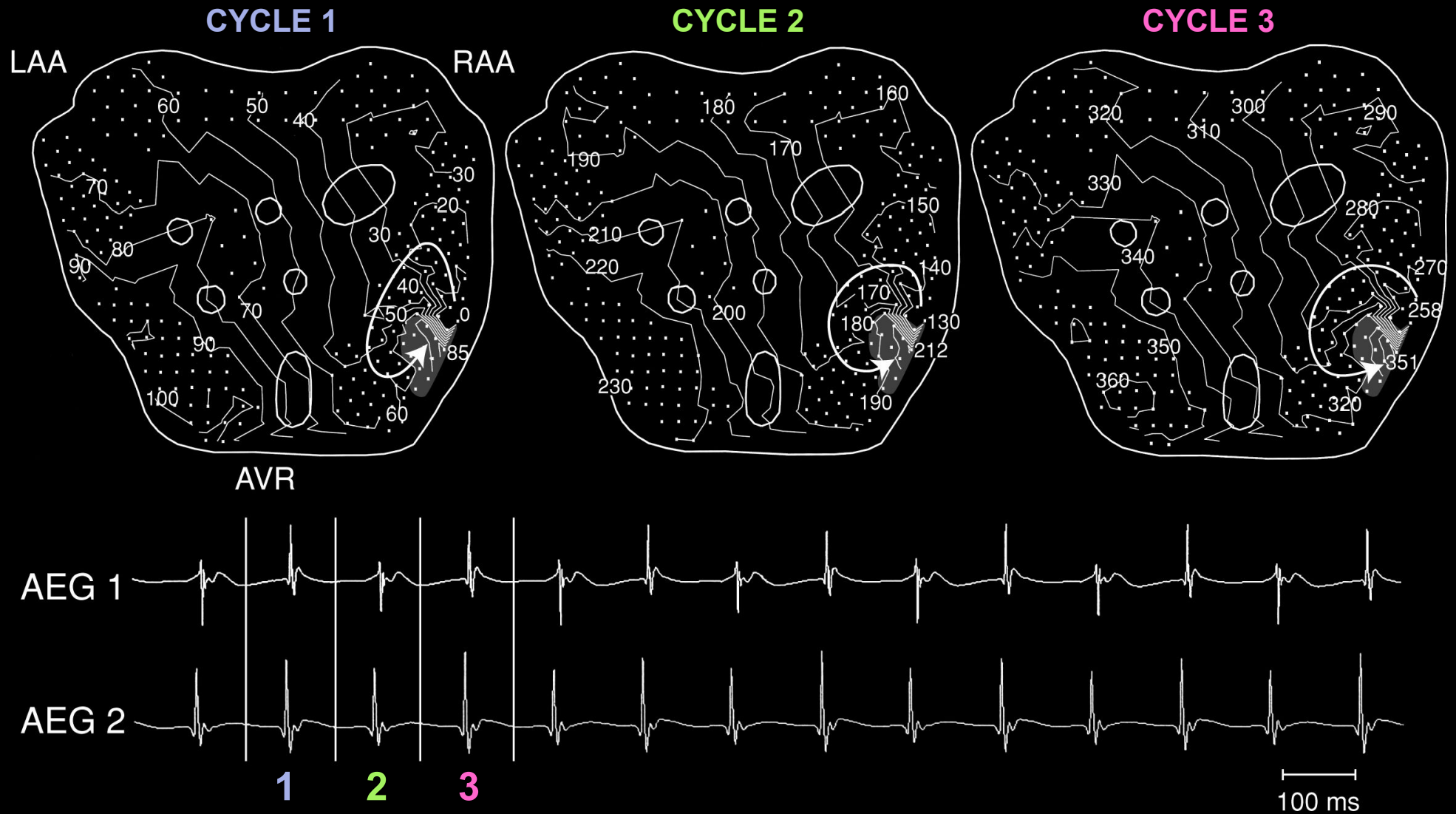
- **Atrial Ischemia**
  - **Inflammation**
  - **Atrial stretch**



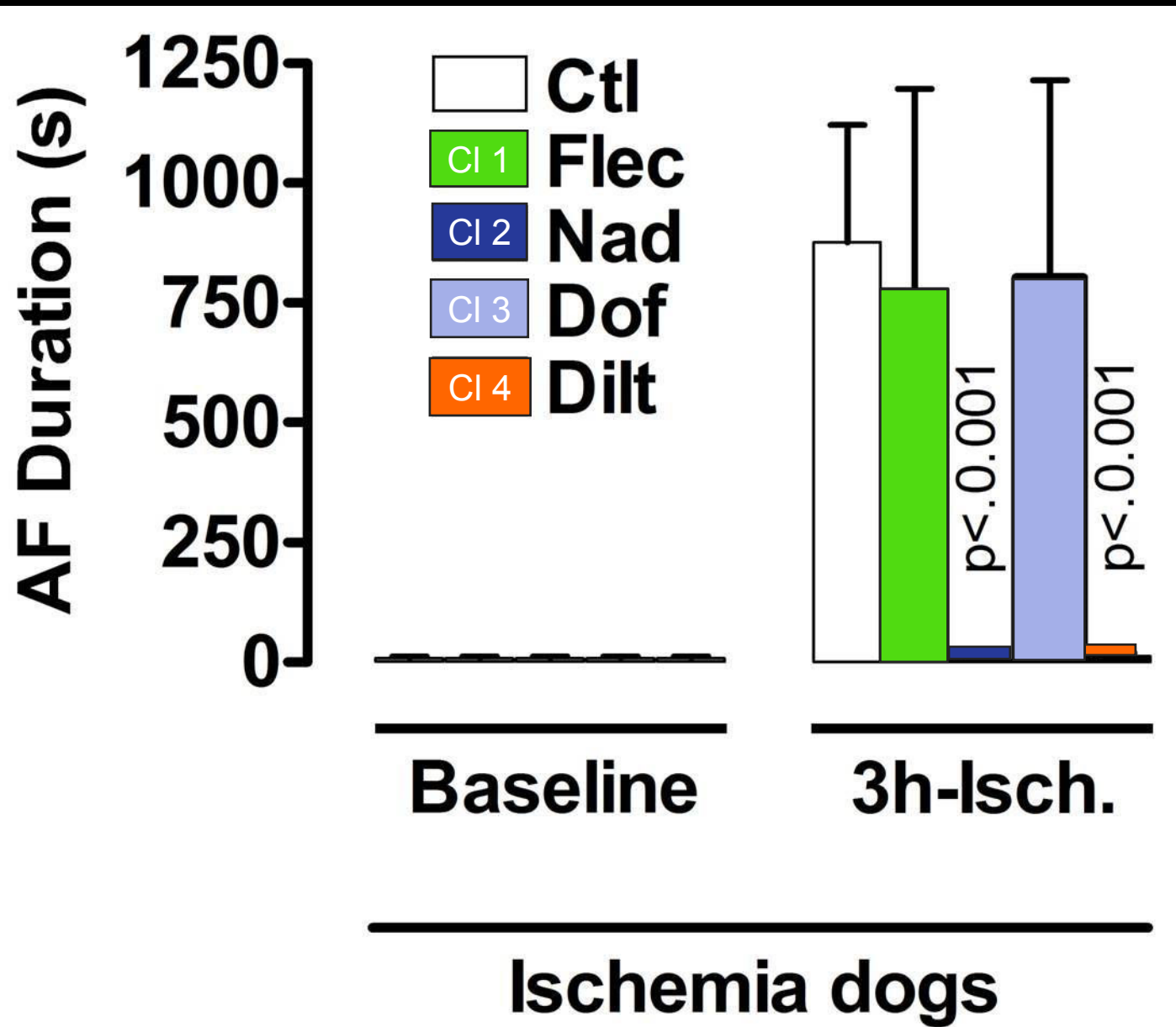
# Occlusion of Arterial Branch to RA



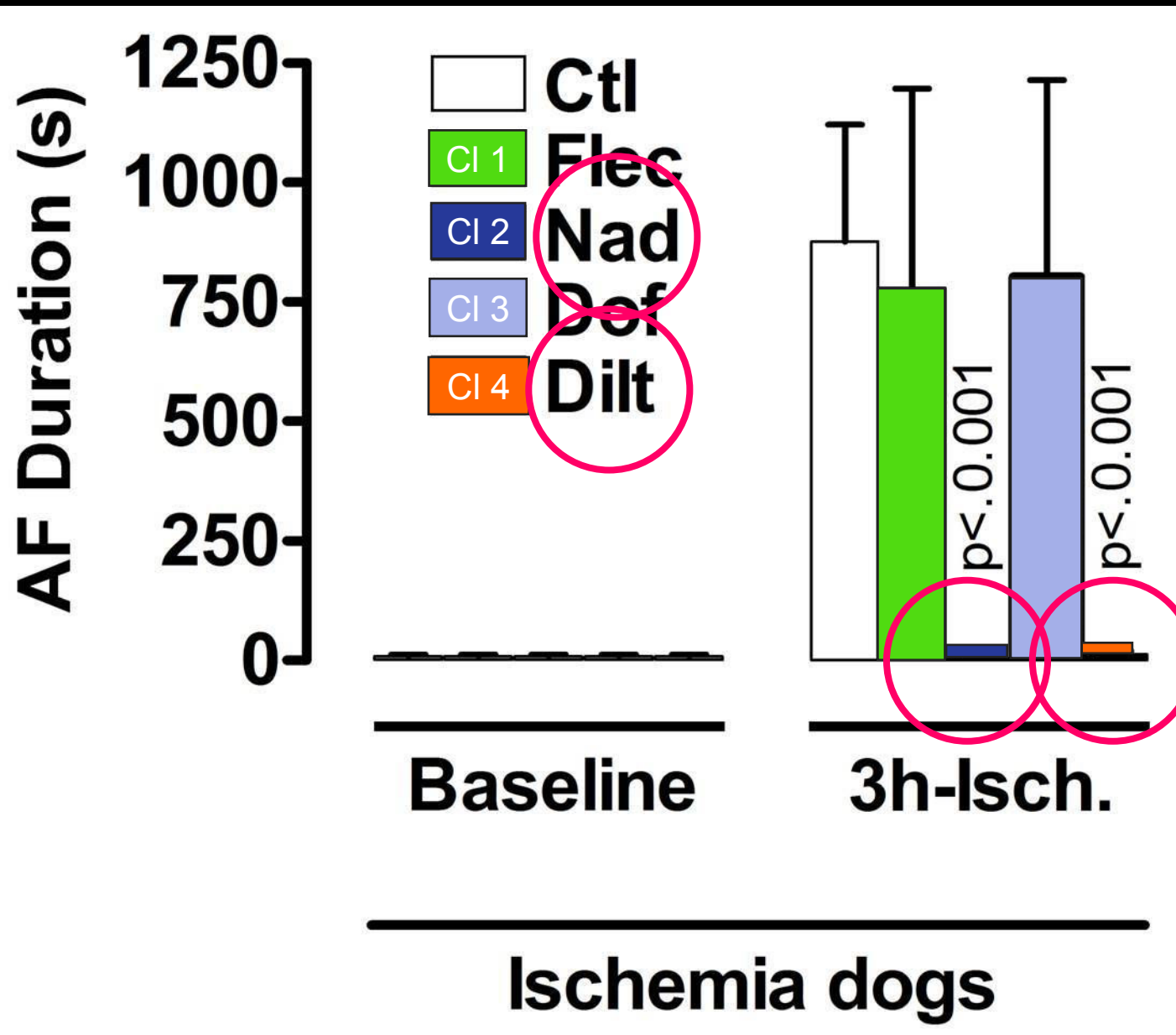
# Activation Mapping of AF during Atrial Ischemia



# Drug effects on ischemic AF



# Drug effects on ischemic AF

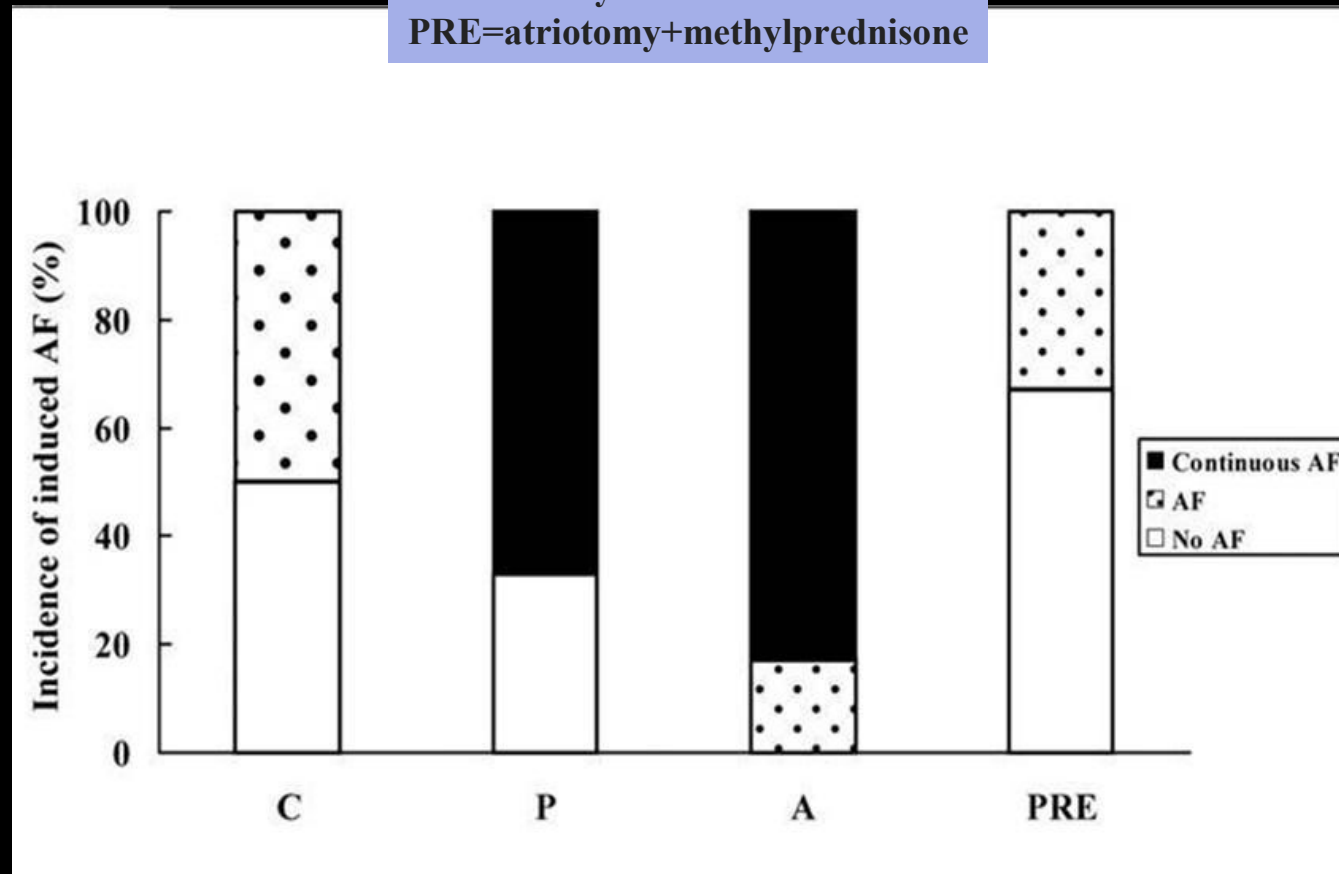


# Other Contributors

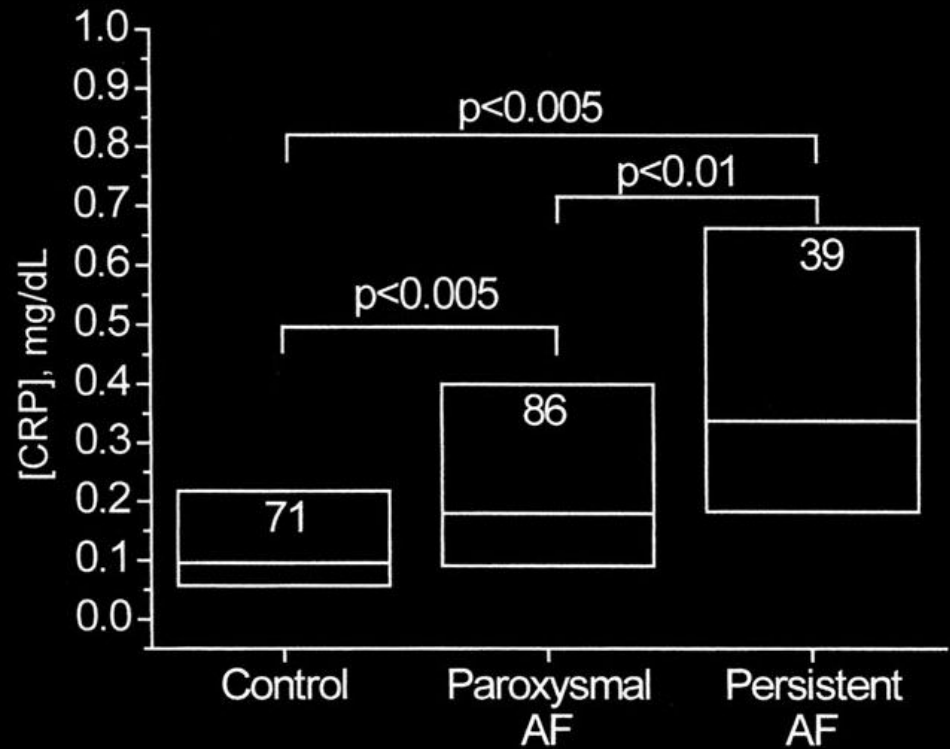
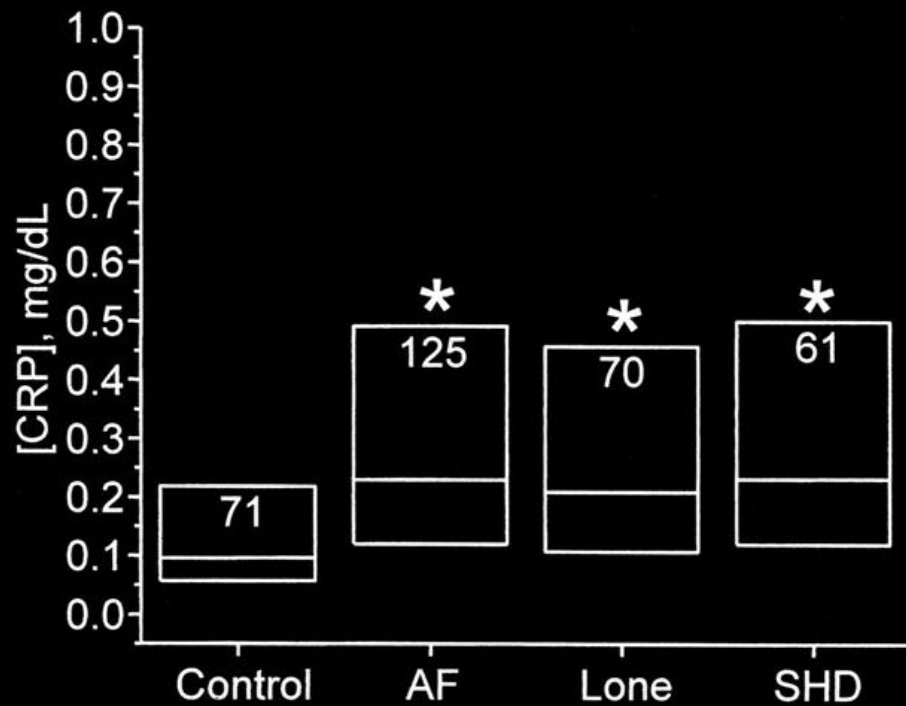
- **Atrial Ischemia**
  - **Inflammation**
  - **Atrial stretch**

# Effects of methylprednisolone on post-op AF in dogs

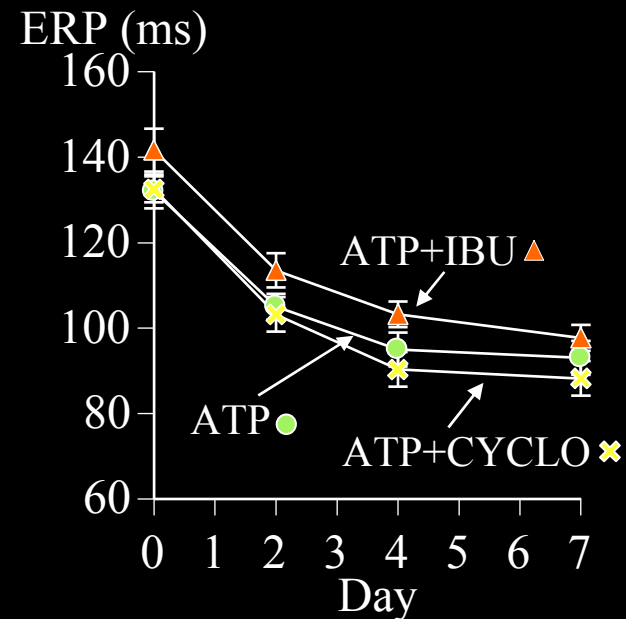
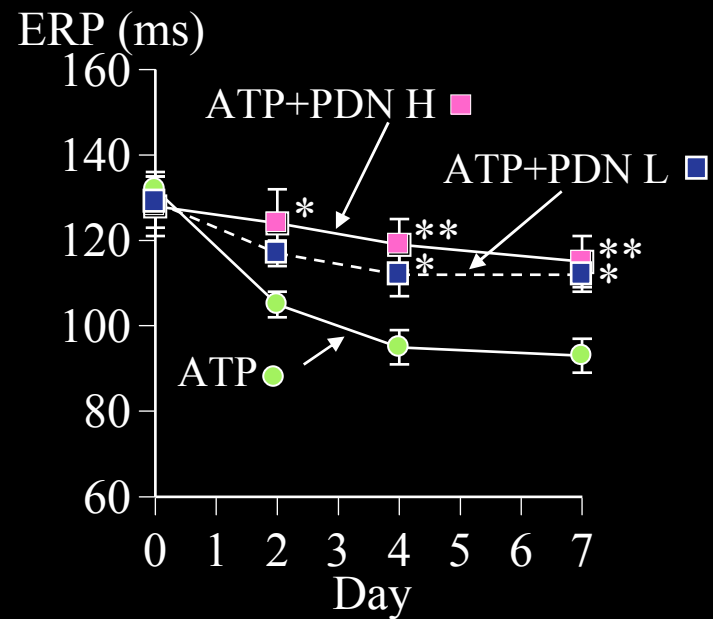
C=control  
P=pericardiotomy  
A=atriotomy  
PRE=atriotomy+methylprednisone



# Role of Inflammation/ C-Reactive Protein

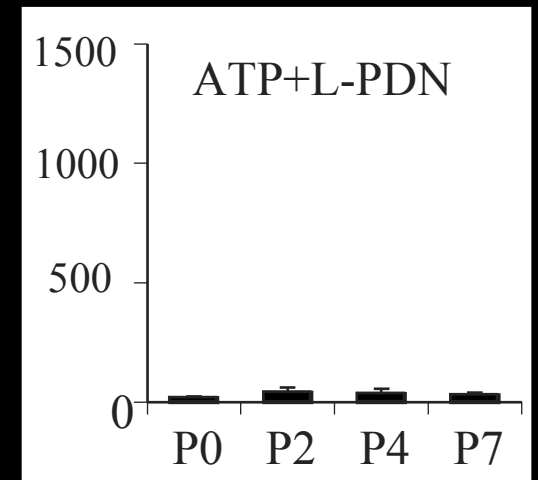
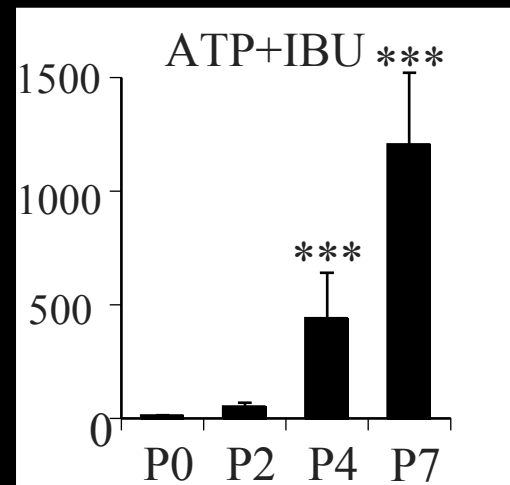
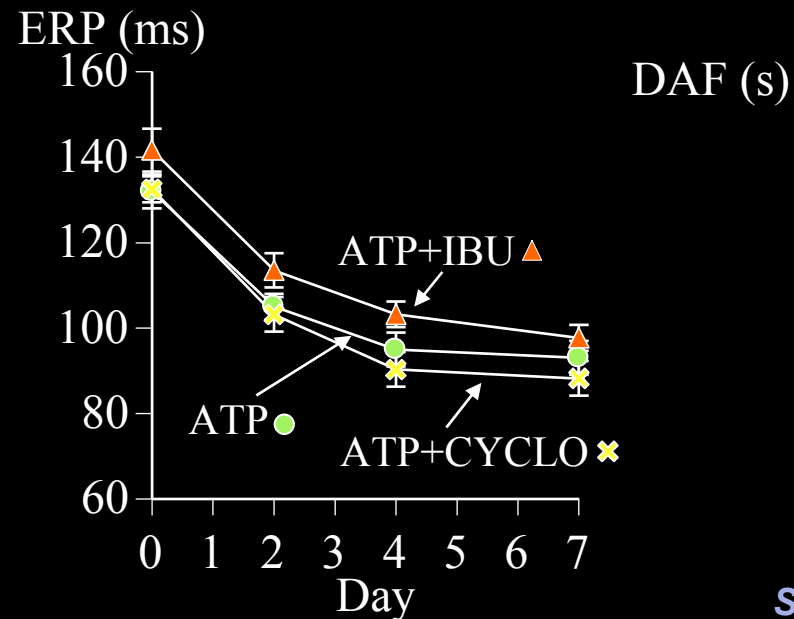
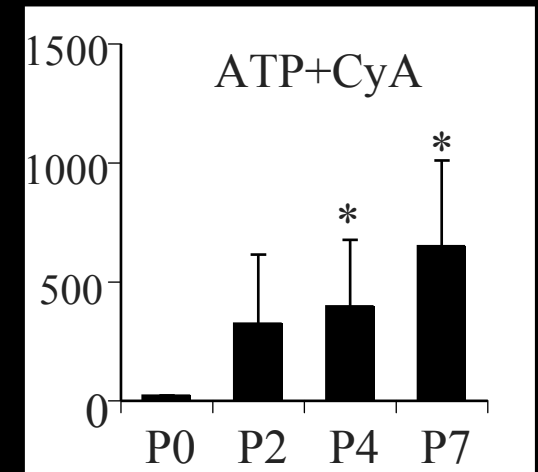
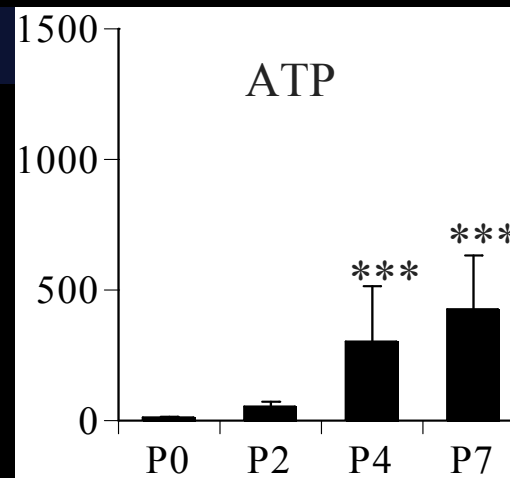
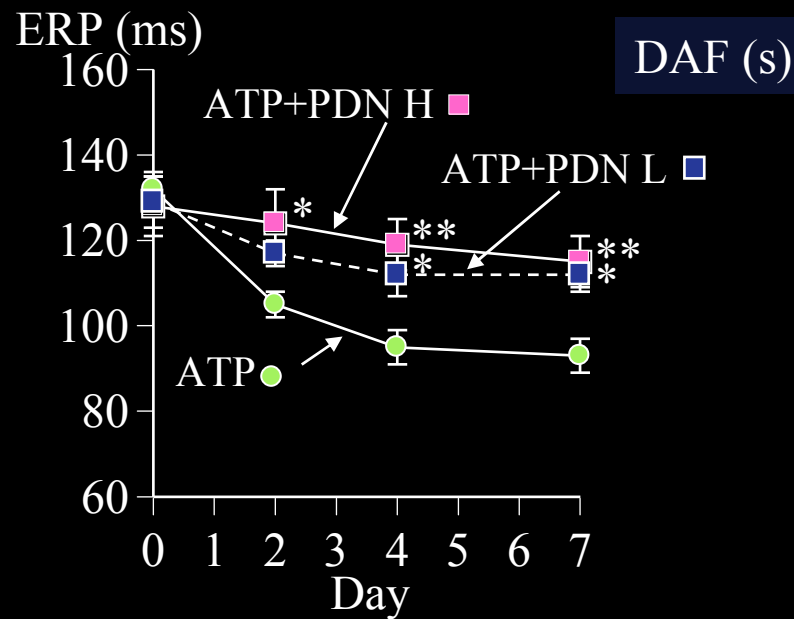


# Effects of prednisone on atrial-tachycardia remodeling





# Effects of prednisone on atrial-tachycardia remodeling

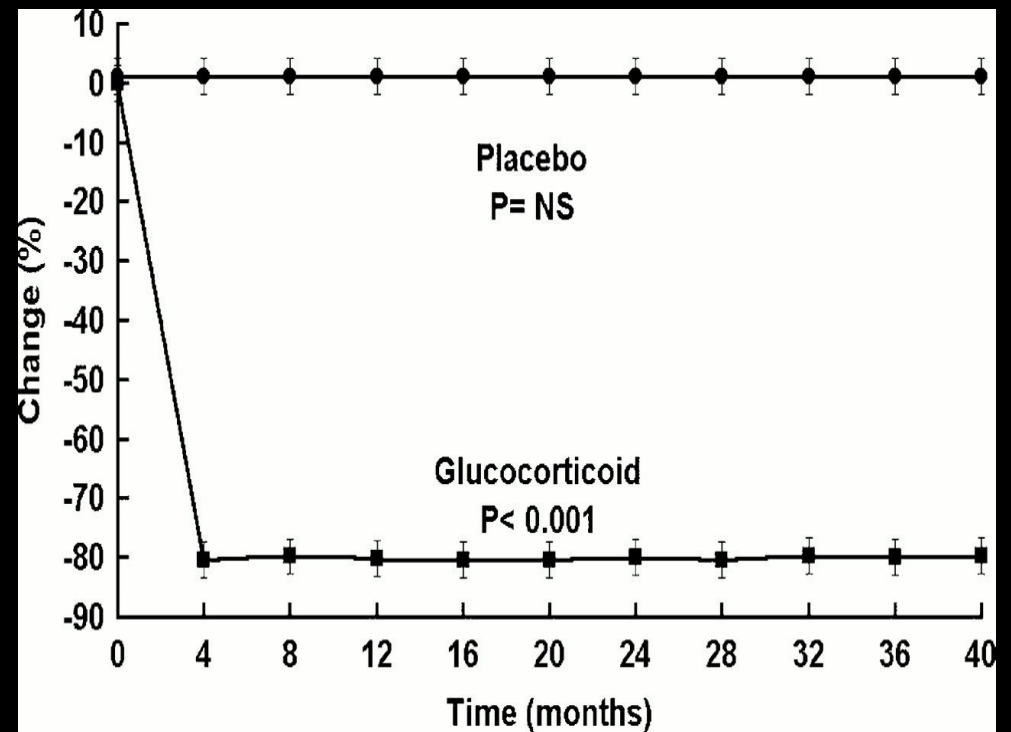
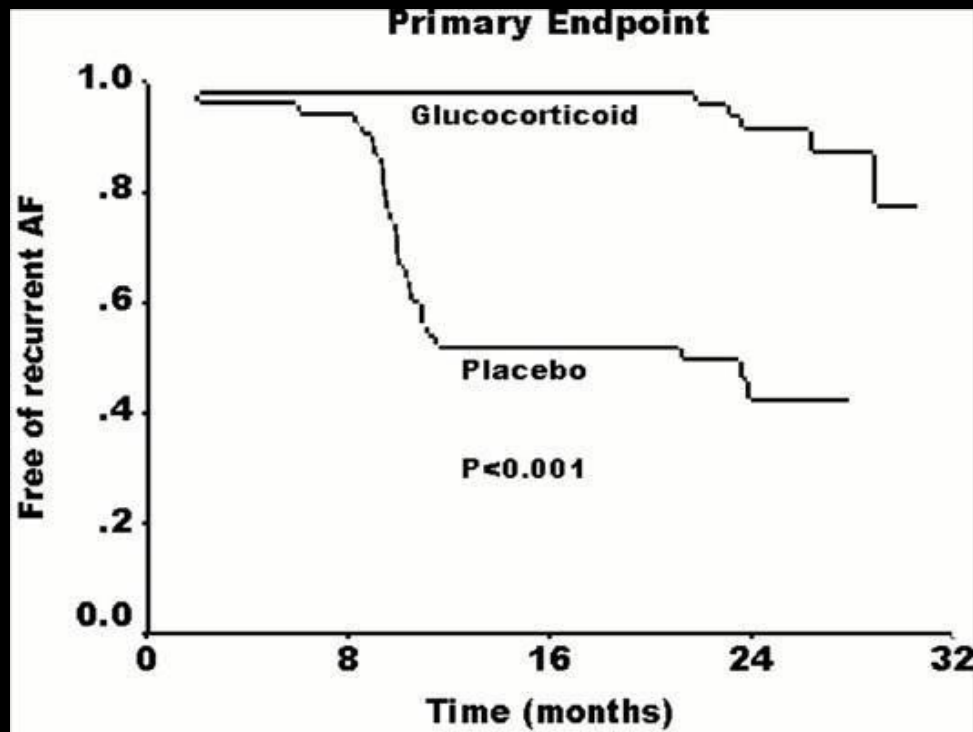


# Effects of Glucocorticoids on AF Recurrence

Patients presenting with persistent AF randomized to receive glucocorticoid or placebo.

Active Rx= methylprednisolone, 16 mg/d x 4 wks, then 4 mg/d x 4 months.

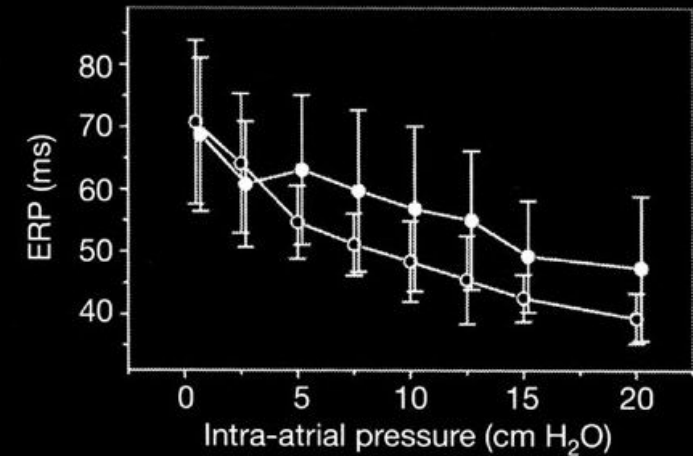
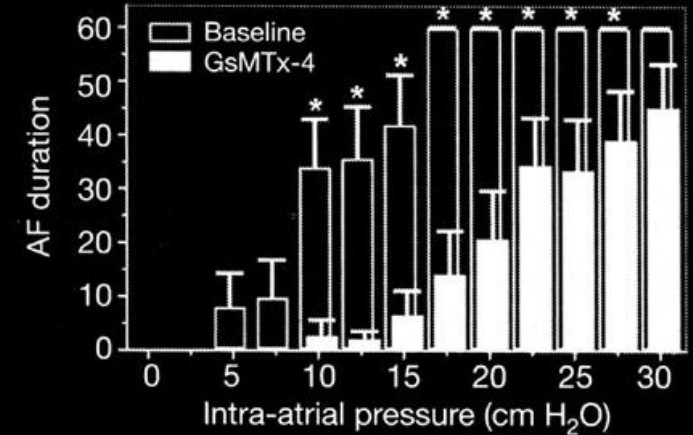
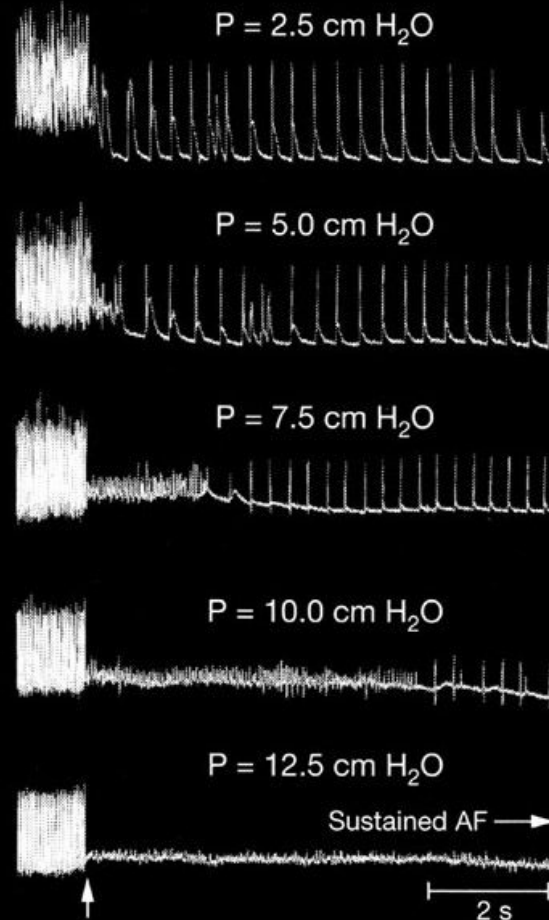
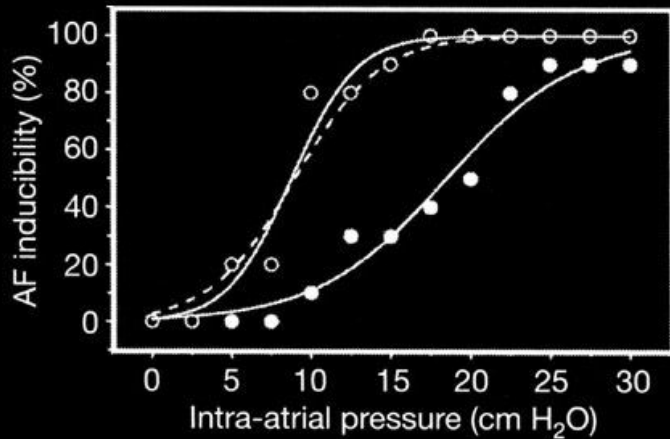
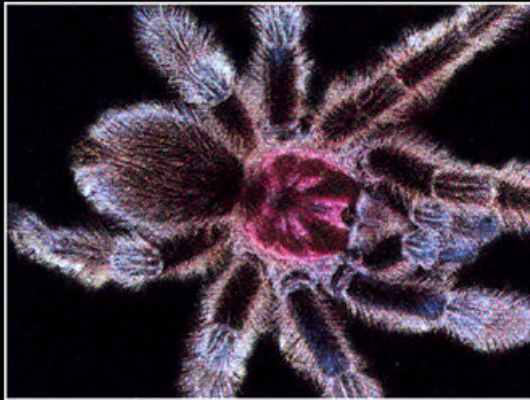
Primary end-point = recurrence of persistent AF.



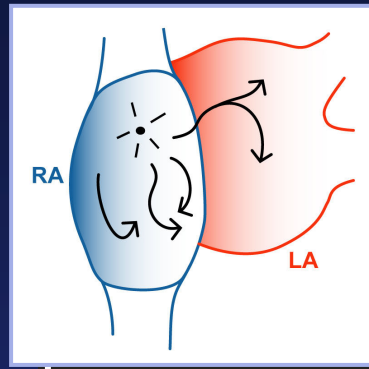
# Other Contributors

- Atrial Ischemia
  - Inflammation
  - Atrial stretch

# Inhibition of Atrial Fibrillation by GsMtx-4 during stretch



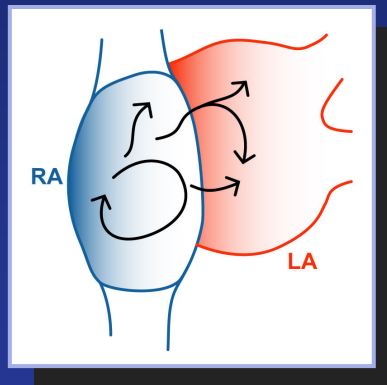
### Ectopic focus



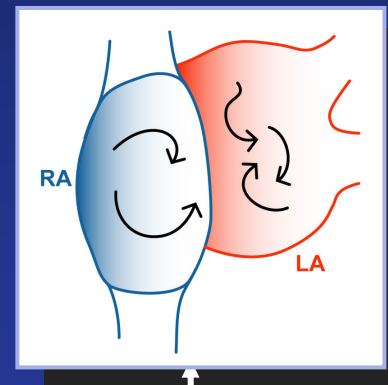
Pulmonary veins

Substrate Trigger

Single-circuit reentry



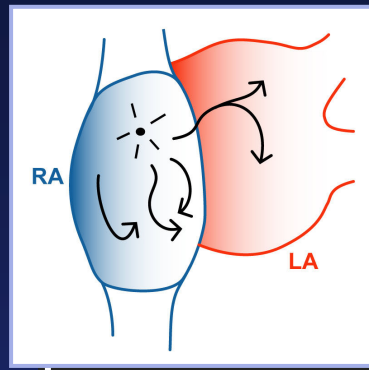
Multiple-circuit reentry



Trigger

Substrate

# Ectopic focus

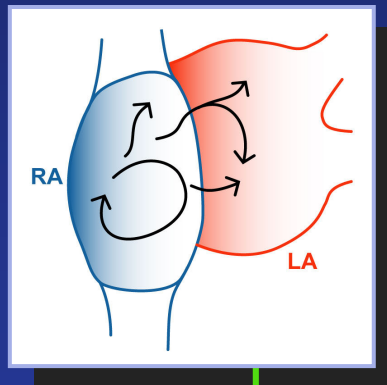


Pulmonary veins

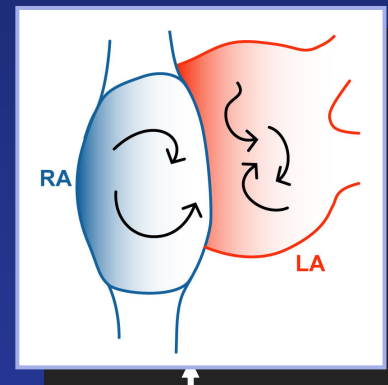
Fibrosis → Substrate Trigger

Angiotensin II ↑

Single-circuit reentry



Multiple-circuit reentry

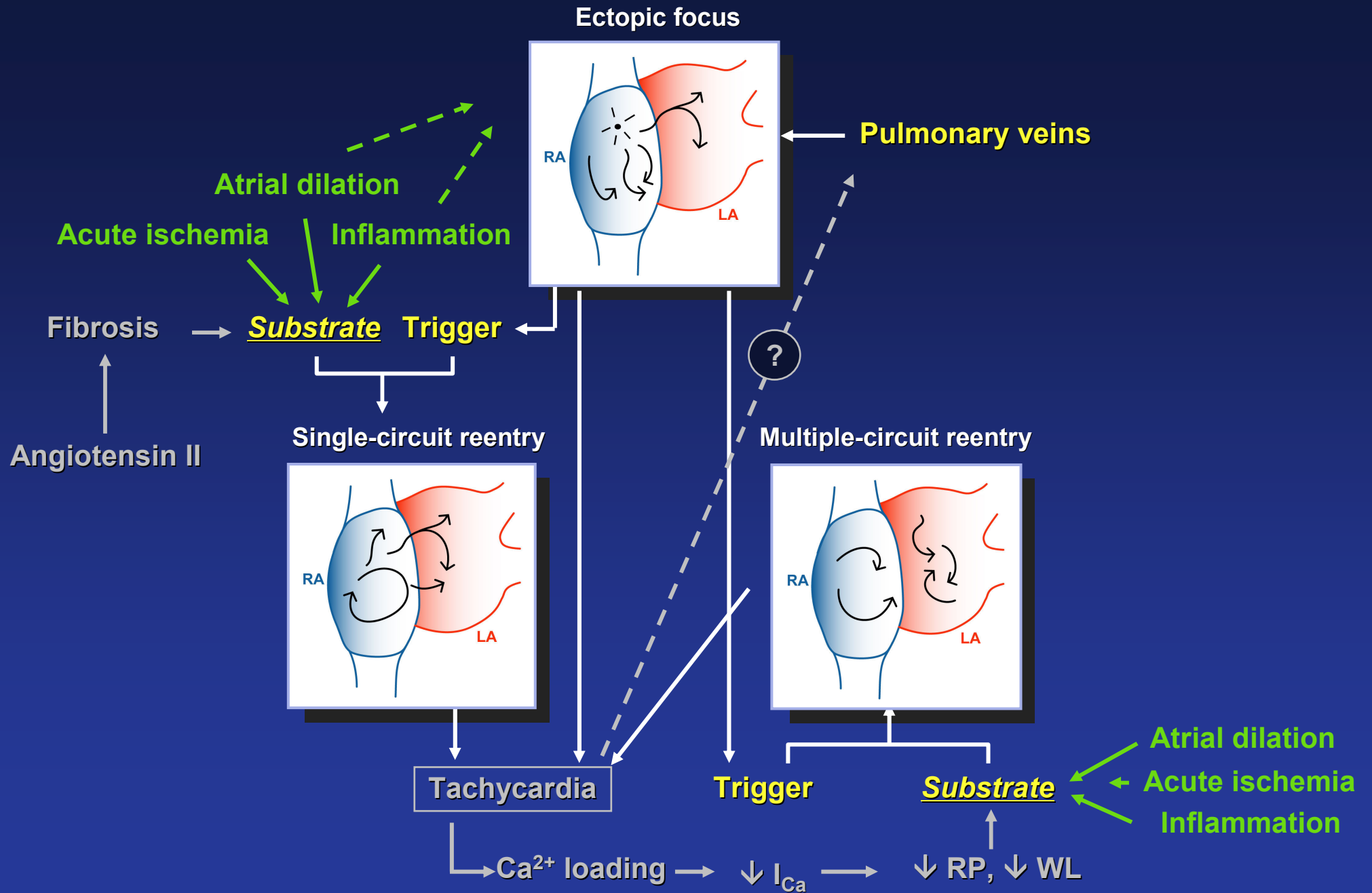


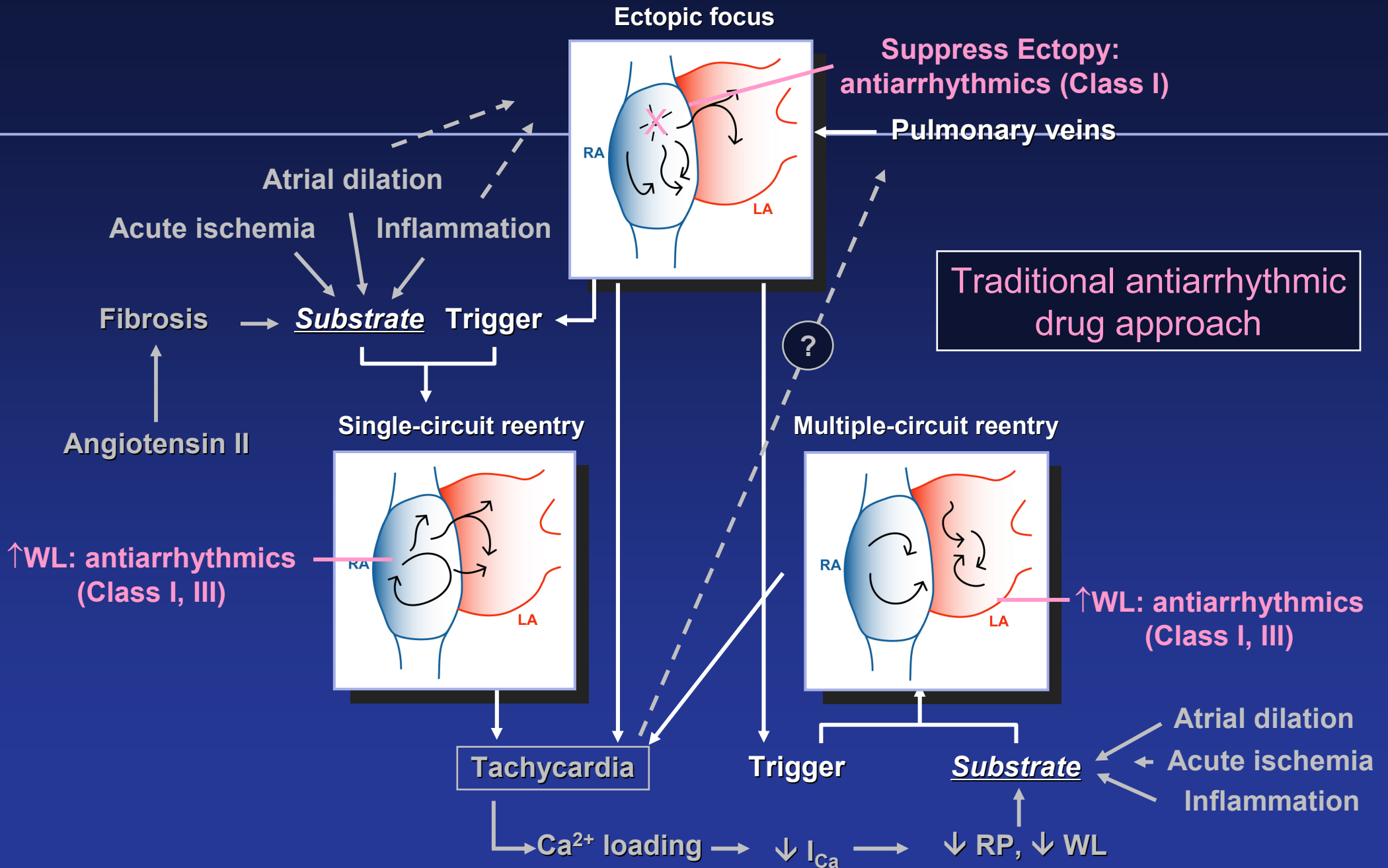
Tachycardia

Trigger

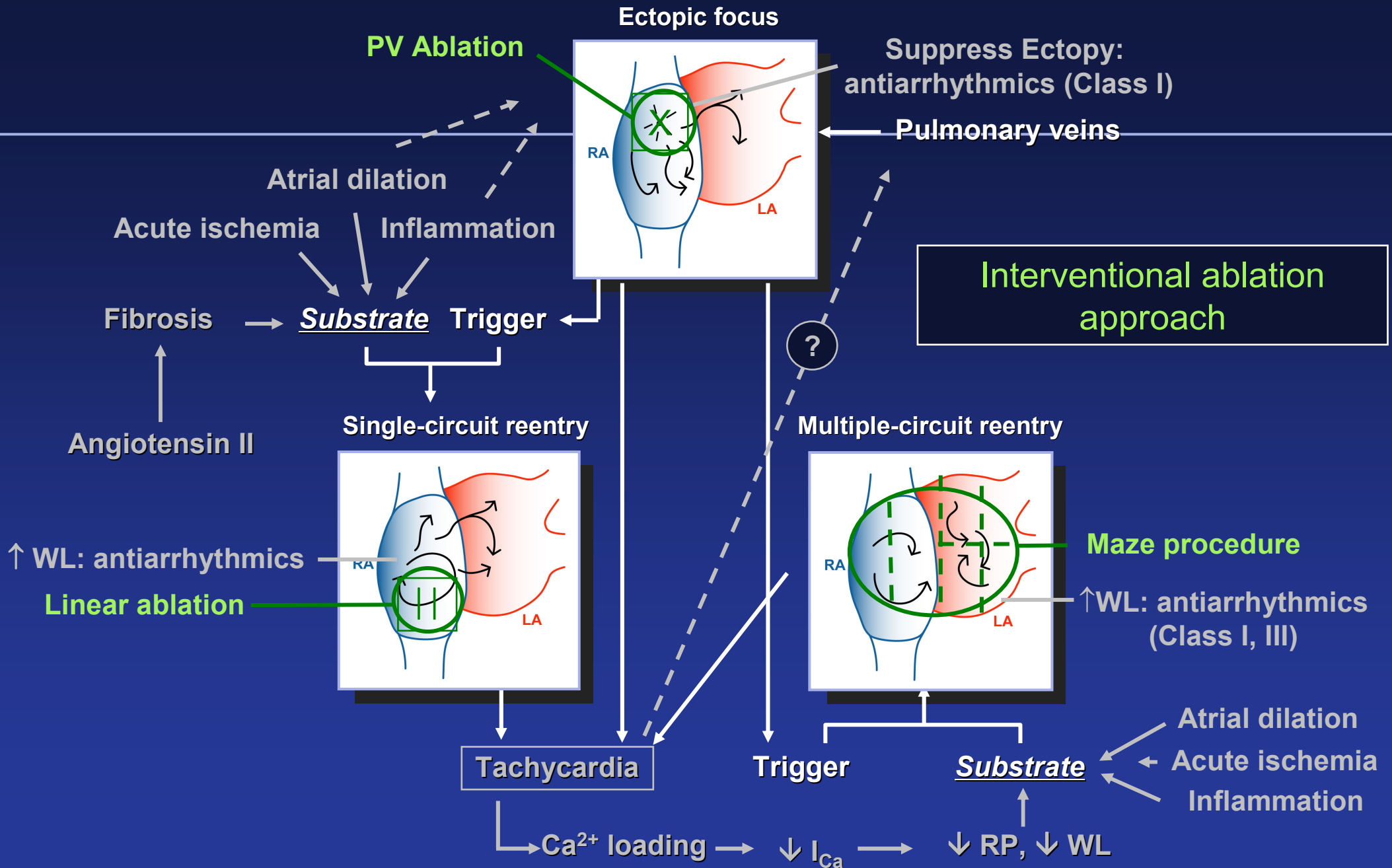
Substrate

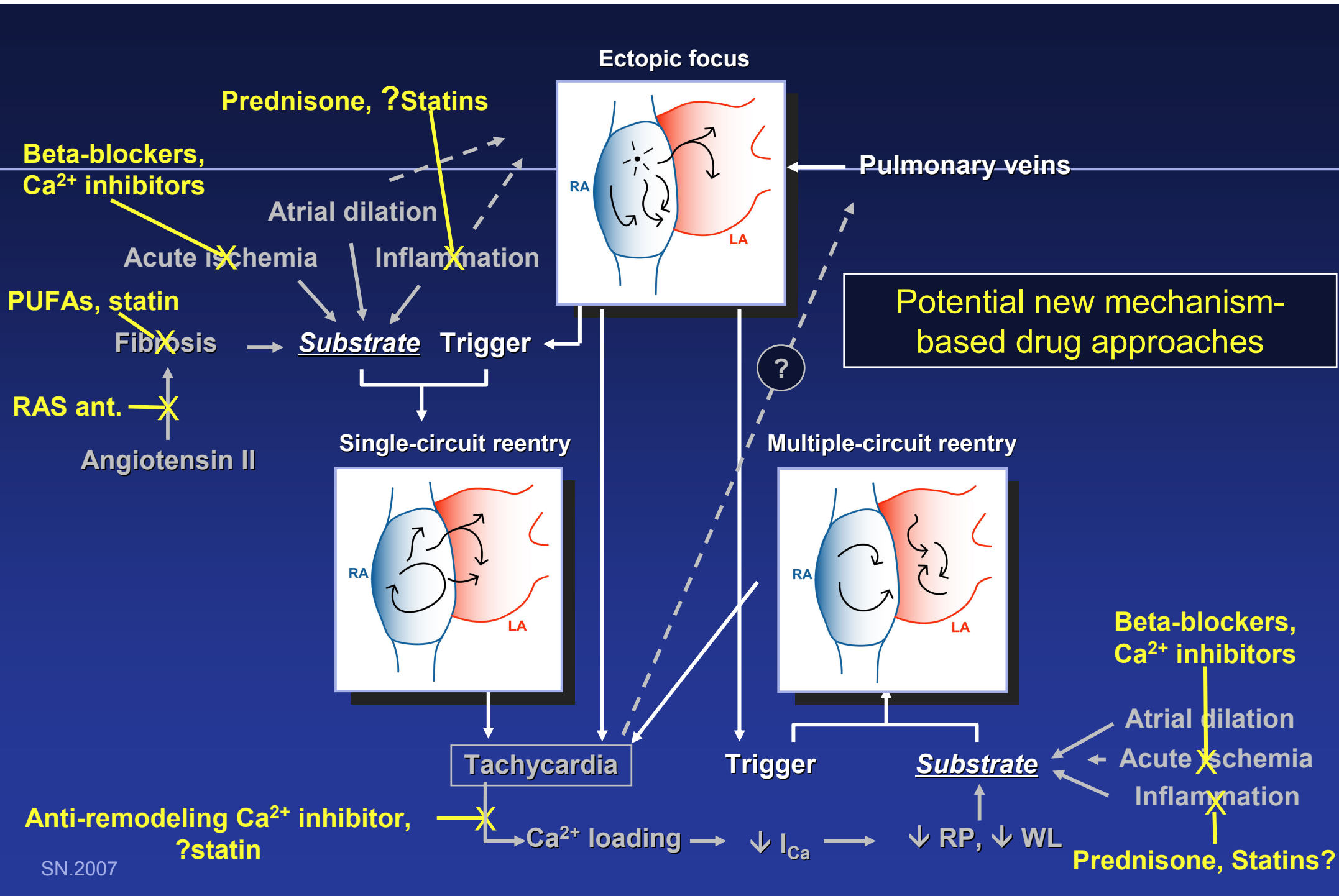
Ca<sup>2+</sup> loading → ↓ I<sub>Ca</sub> → ↓ RP, ↓ WL











# CONCLUSIONS

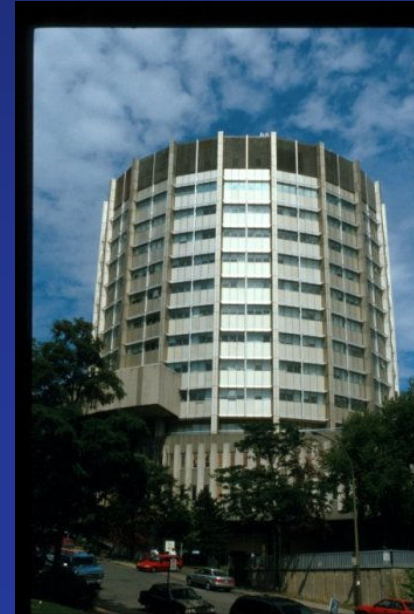
- **Atrial fibrillation can be due to one or a combination of single-circuit reentry, ectopic activity or multiple circuit reentry, with complex interactions possible**
- **Atrial remodeling contributes importantly to these mechanisms and may provide novel therapeutic targets**
- **The specific mechanisms of atrial fibrillation have important potential therapeutic consequences**



감사합니다

Thank you

Seoul



Montreal

