



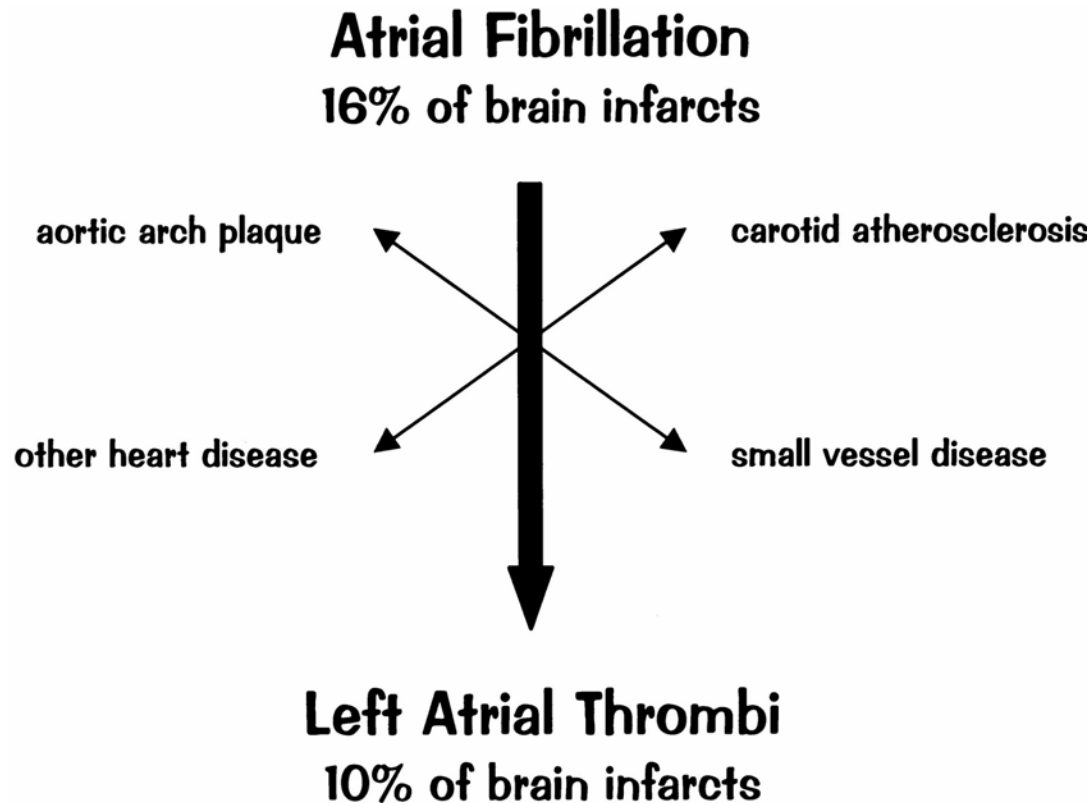
# **What “drives” the prothrombotic state in atrial fibrillation?**

***World College of Cardiology  
September 4, 2006***

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Cleveland Clinic,  
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# LAA thrombi are a primary cause of TIA and stroke



While the  
culprit is  
**obvious...**

the causes  
are less  
clear



# Virchow's triad...

Formation of a thrombus is dependent on:

- Abnormal blood flow, and/or
- Abnormal vessel (atrial) wall, and/or
- Abnormal blood clotting

For an interesting commentary on Virchow's point of view:  
DJ Brotman et al., Southern Medical J. 97(2):213-4, 2004.

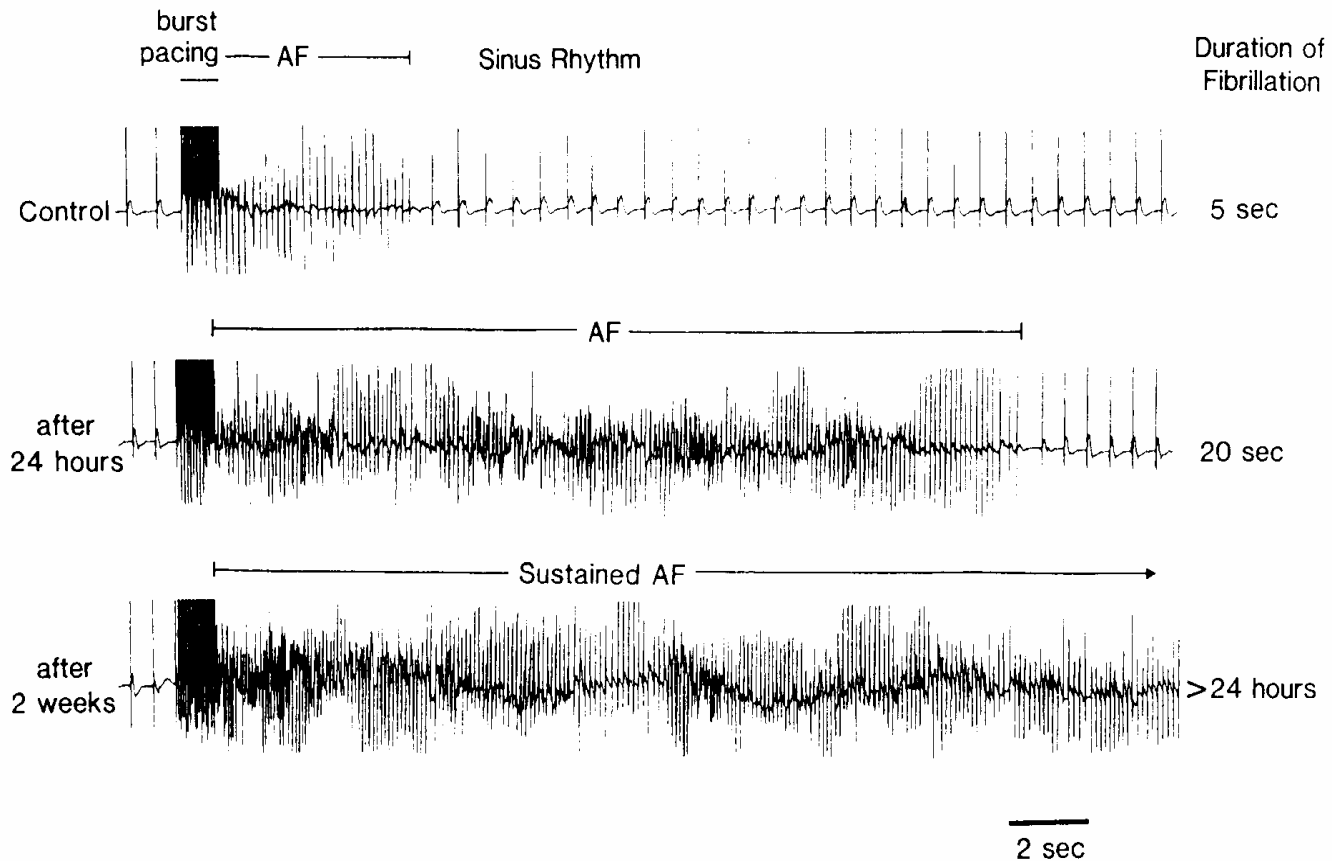
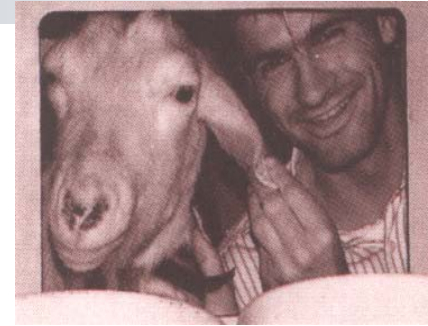


# Impaired blood flow

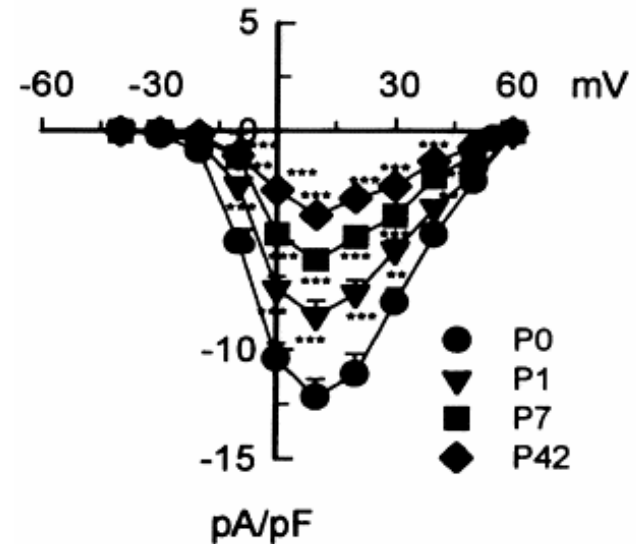
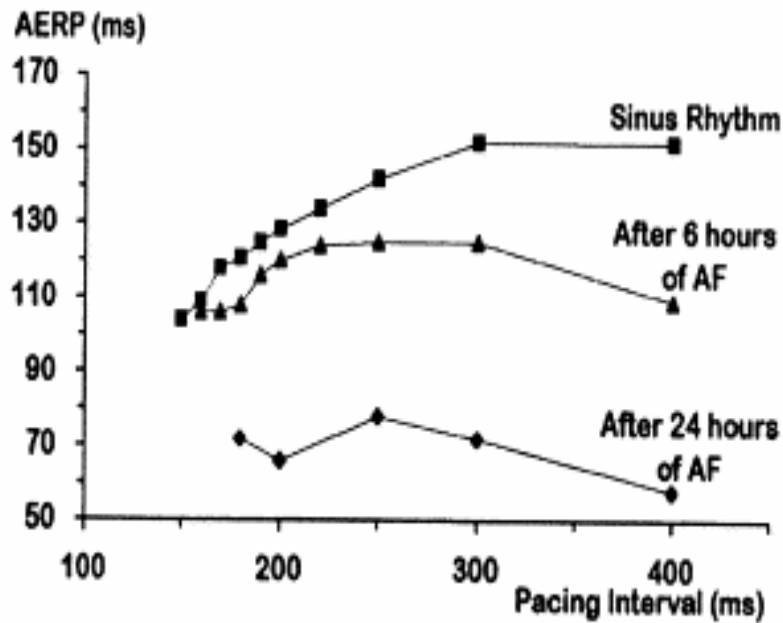
Is due to electrical remodeling  
and altered atrial contractility



# AF begets AF



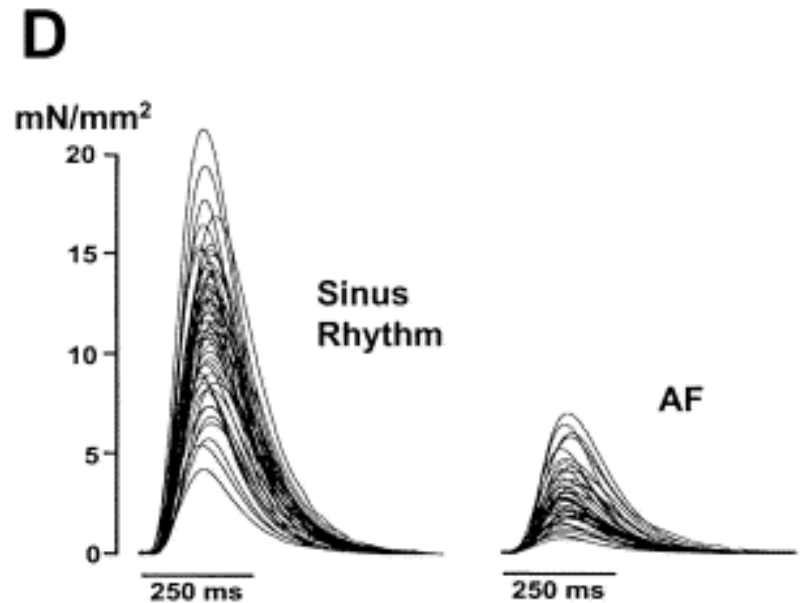
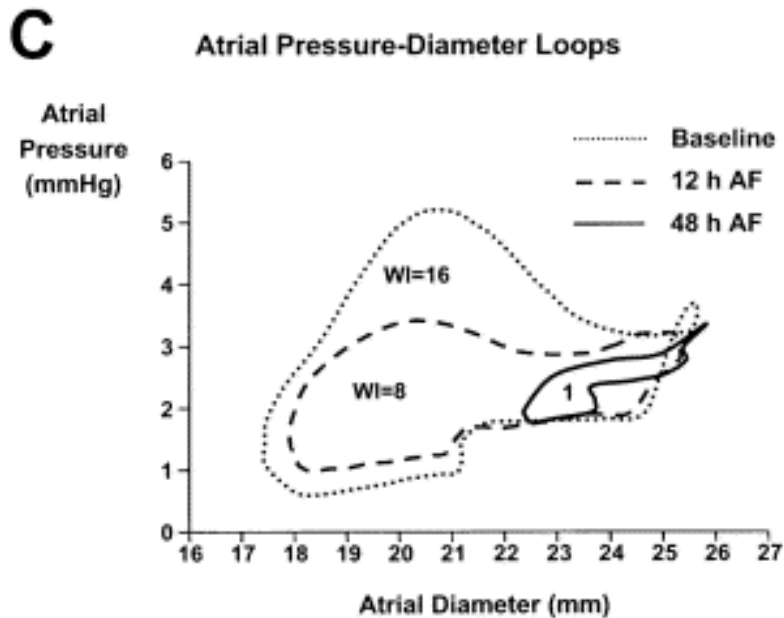
# Electrical remodeling occurs *rapidly* and is due to loss of $I_{Ca}$



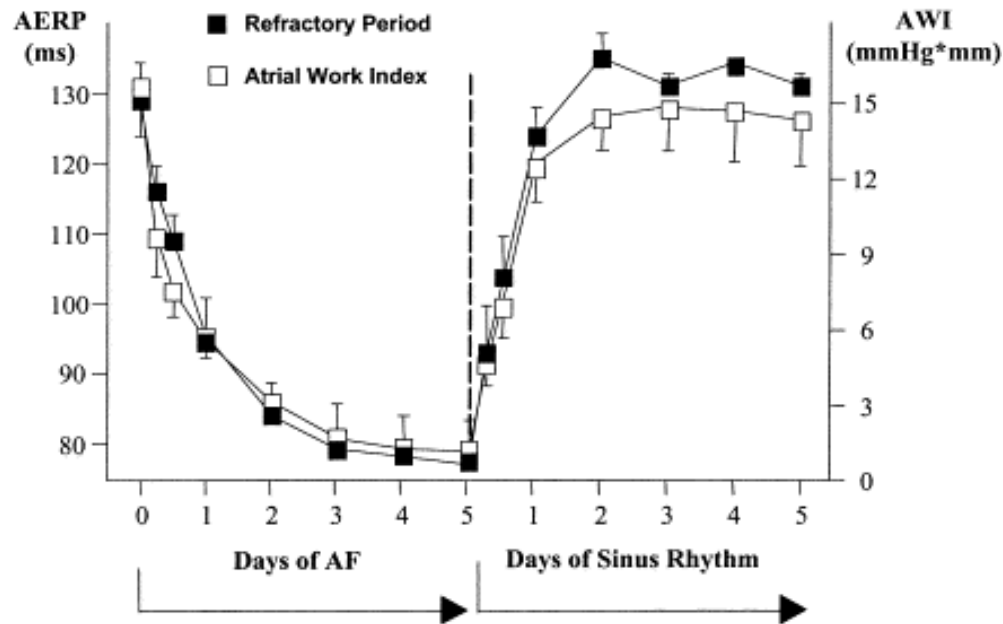
↓ERP is due to ↓ $I_{Ca}$



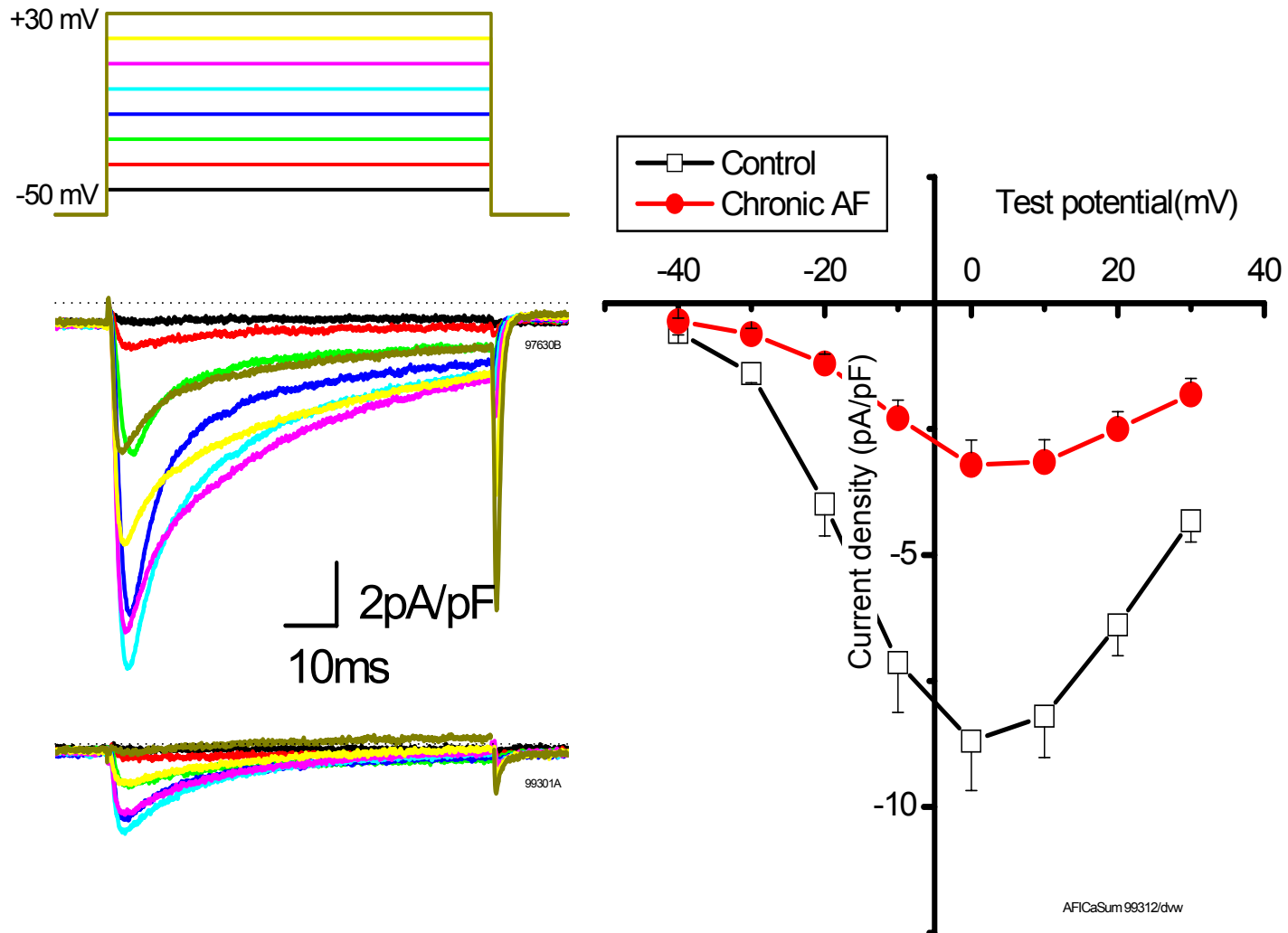
# Electrical remodeling leads to decreased atrial contractility



# Early changes in contractility closely follow the time course of electrical remodeling



# Basal $I_{Ca}$ is reduced in persistent AF



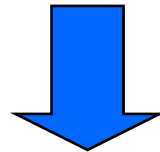
# Impaired contractility...

- Is driven by a loss of myocyte calcium current, and is initially reversible in parallel with the electrical remodeling
- A significant contractile impairment occurs within 12-48 hours of AF
- Restoration of sinus rhythm is associated with a *gradual* (not instantaneous) restoration of contractility
- *Risk of thrombosis due to impaired contractility remains elevated following cardioversion*



# Cardiac response to injury

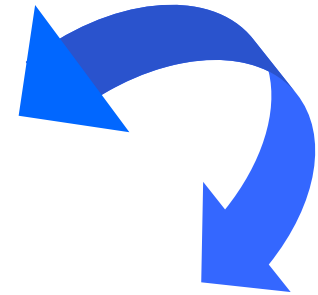
**Ca<sup>2+</sup> overload**



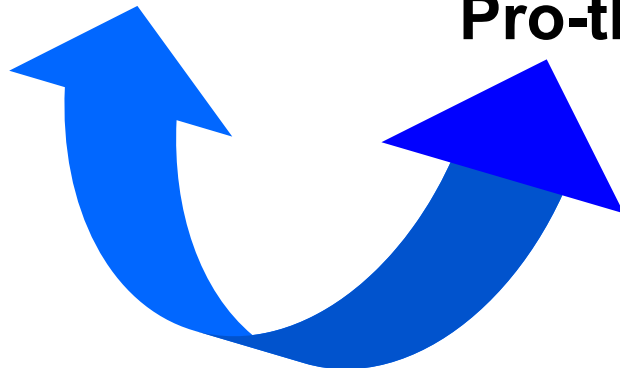
**Myocardial stress, injury,  
Contractile dysfunction**



**Oxidative Stress**



**Inflammatory cell activation,  
Pro-thrombotic changes**



# Inflammatory changes in the vessel / atrial wall?



# Clinical risk factors for Thromboembolism in AF

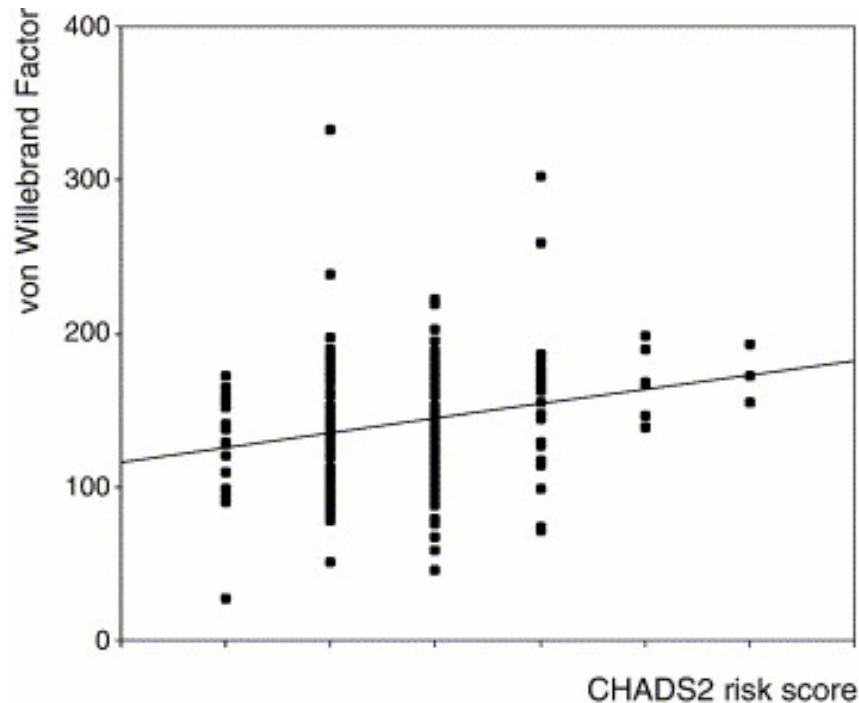
- Congestive heart failure
- Hypertension
- Advanced age
- Diabetes mellitus
- Prior TIA or stroke

CHADS<sub>2</sub>

**Endothelial injury / dysfunction may be a common theme linking these risk factors**



# Increased plasma vWF levels are associated with increased stroke risk

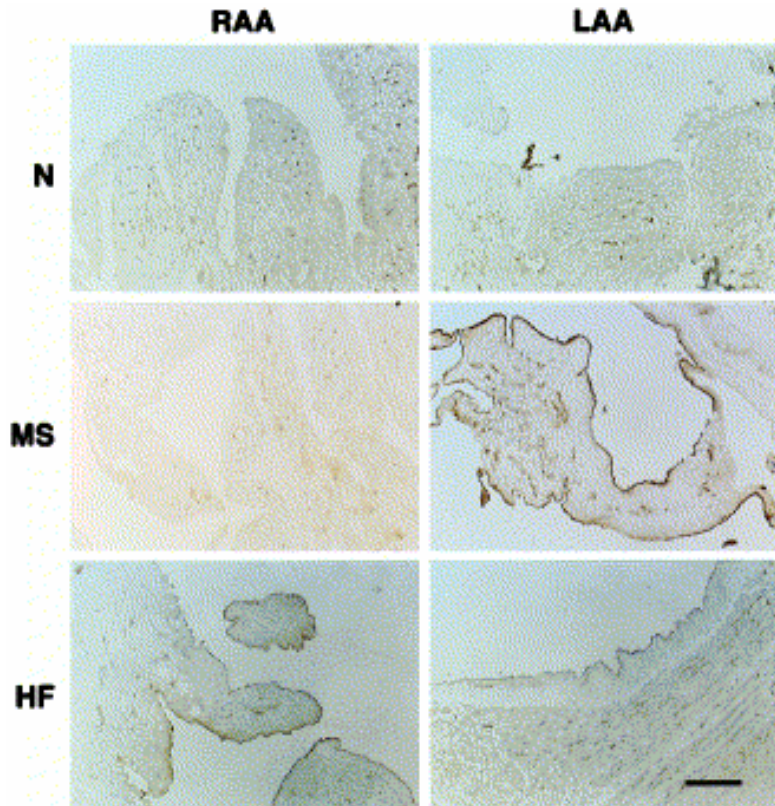


V. Roldán et al.,  
**Thrombosis Research**  
116:321-325, 2005

- Is produced in response to endothelial injury, and is required for platelet adherence
- In a study of 200 pts with AF, WF levels were strongly correlated with CHADS<sub>2</sub> risk score
- Plasma assessment of vWF levels likely provides a reflection of vascular and atrial endothelial status



# Atrial von Willebrand's Factor

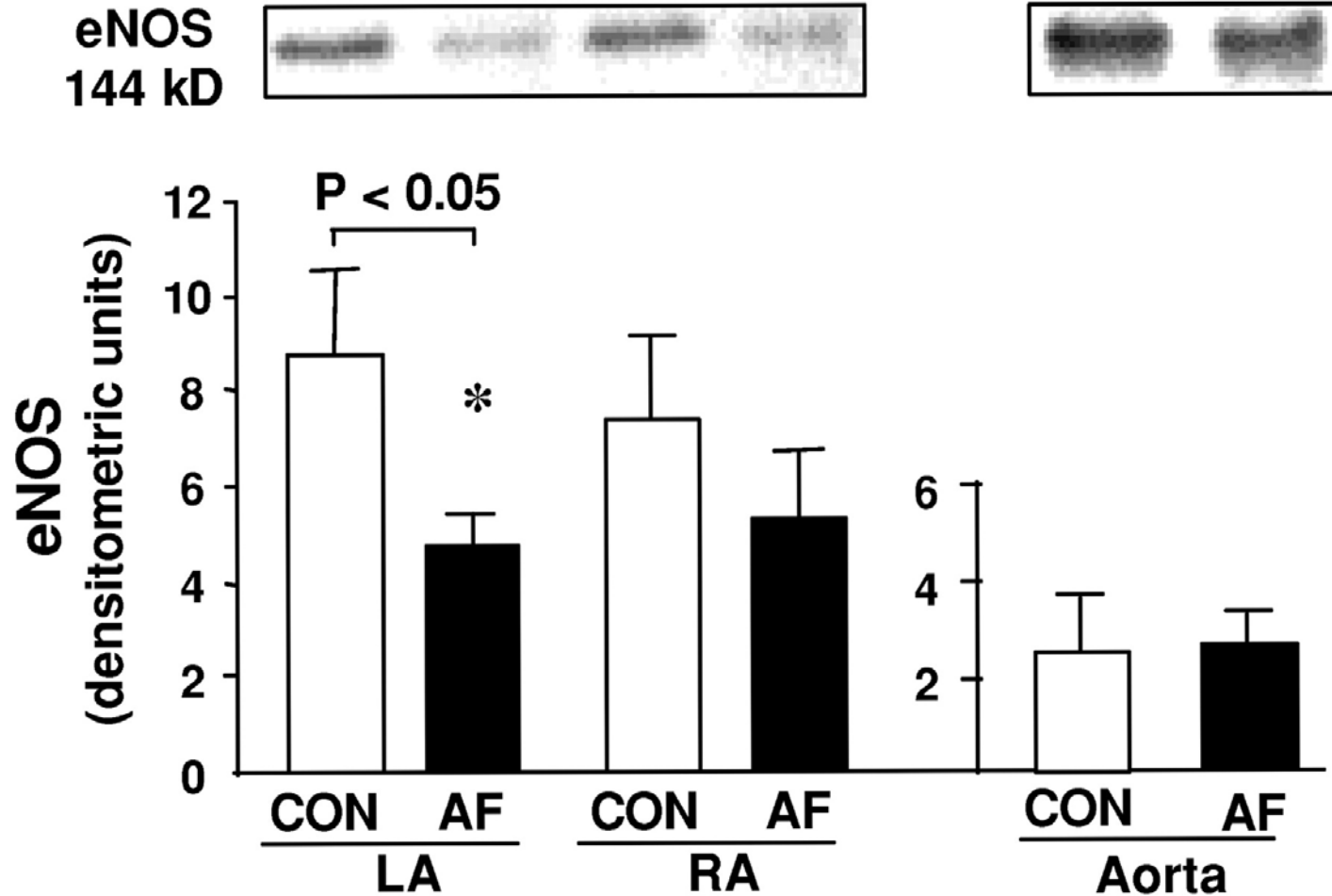


Fukuchi et al., JACC 37:1436, 2001

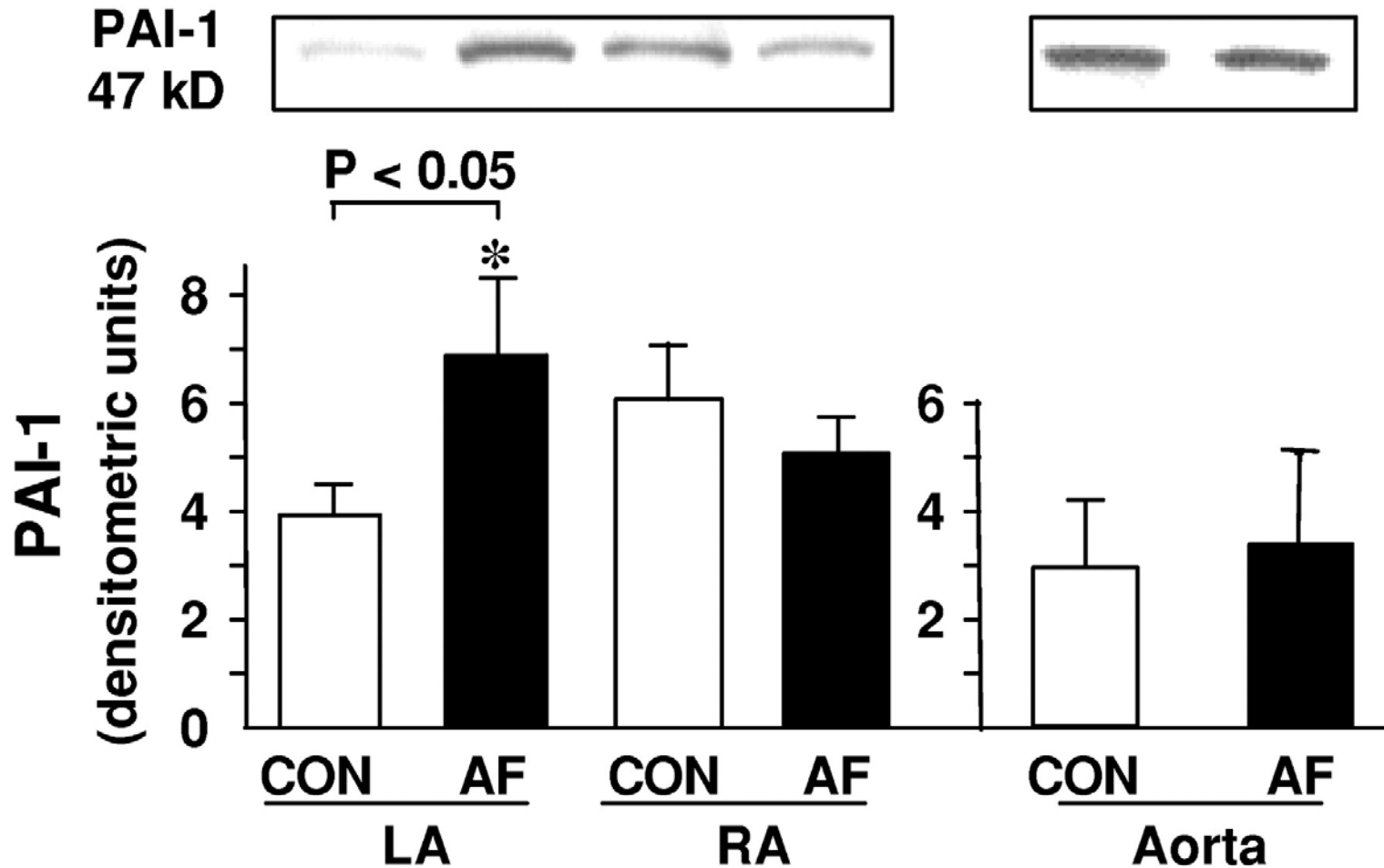
- Immunoreactive vWF was **more abundant in LAA** than RAA in patients with valvular disease;
- Bi-atrial vWF expression was increased in heart failure patients
- Platelet adhesion correlated with increased vWF staining and **decreased eNOS expression**



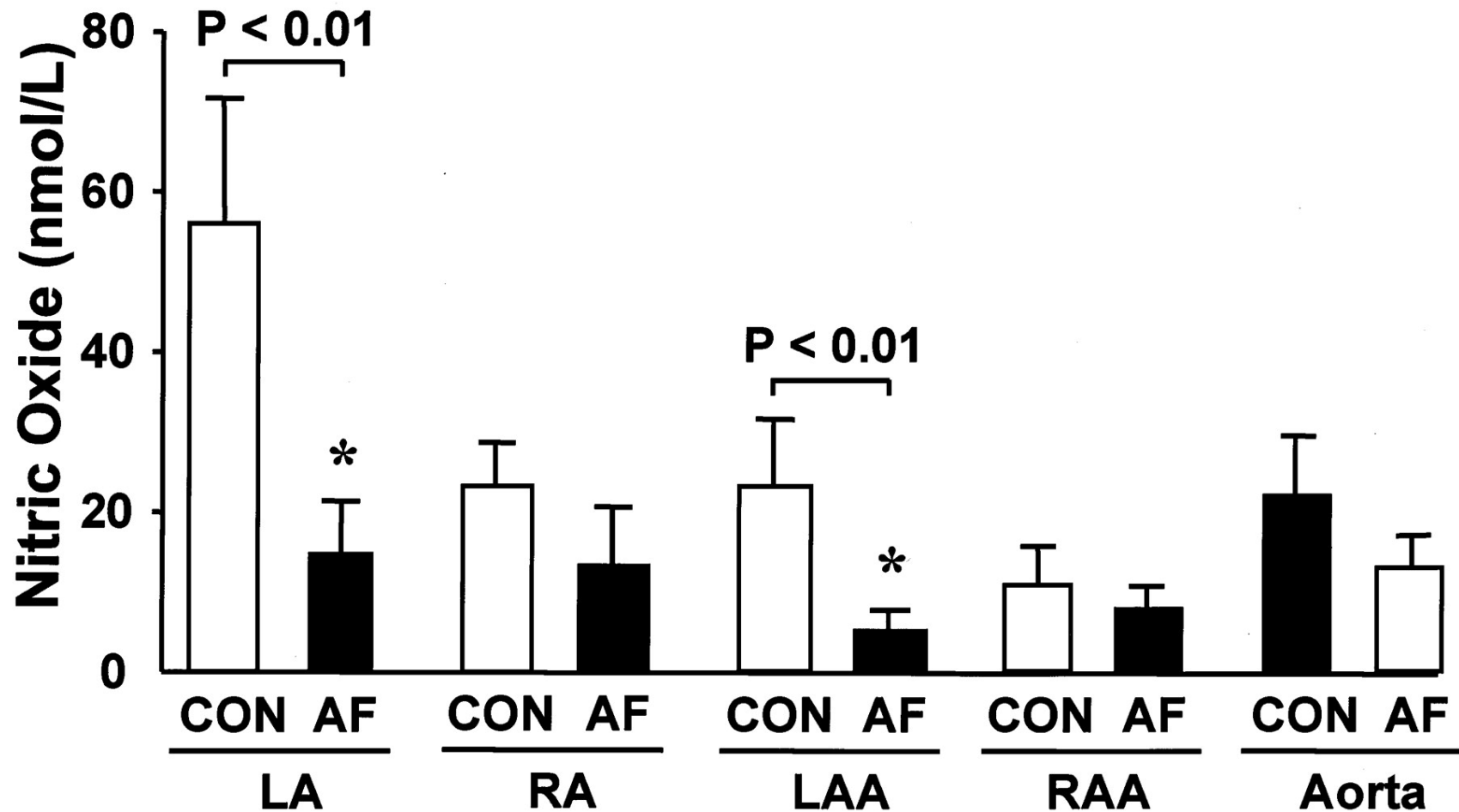
# ↓ eNOS protein in *paced* AF



# And ↑ left atrial PAI-1 ...



# ↓ NO<sup>•</sup> with rapid atrial pacing



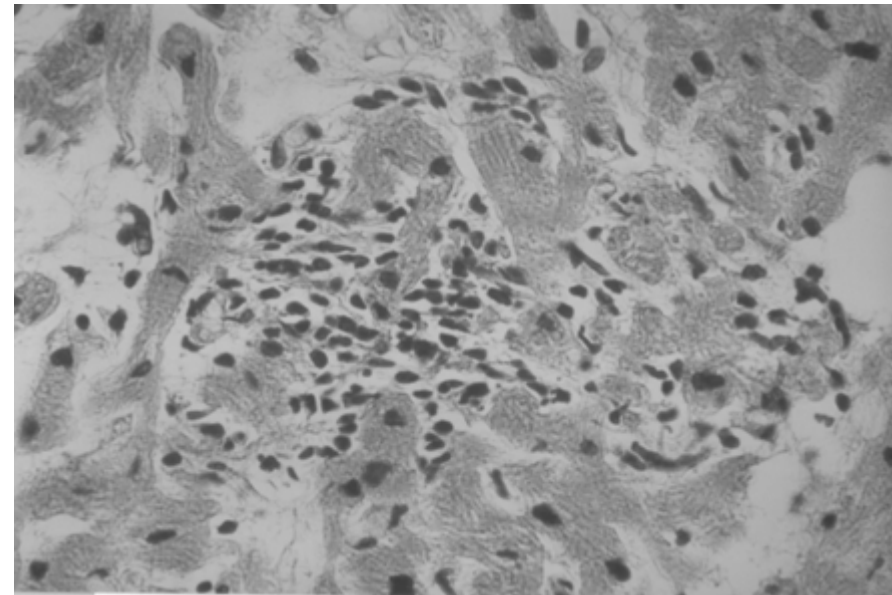
# NO<sup>•</sup> availability...

- Determined by the balance of production (via NOS isoforms) and consumption
- Endocardial and endovascular NO<sup>•</sup> generation (via eNOS) is shear dependent
- AF results in a loss of endocardial shear.  
↓ Shear → ↓ NO<sup>•</sup> production.
- Modulates endothelial/endocardial adhesion of platelets and leucocytes (pro-inflammatory changes that can initiate thrombus formation)



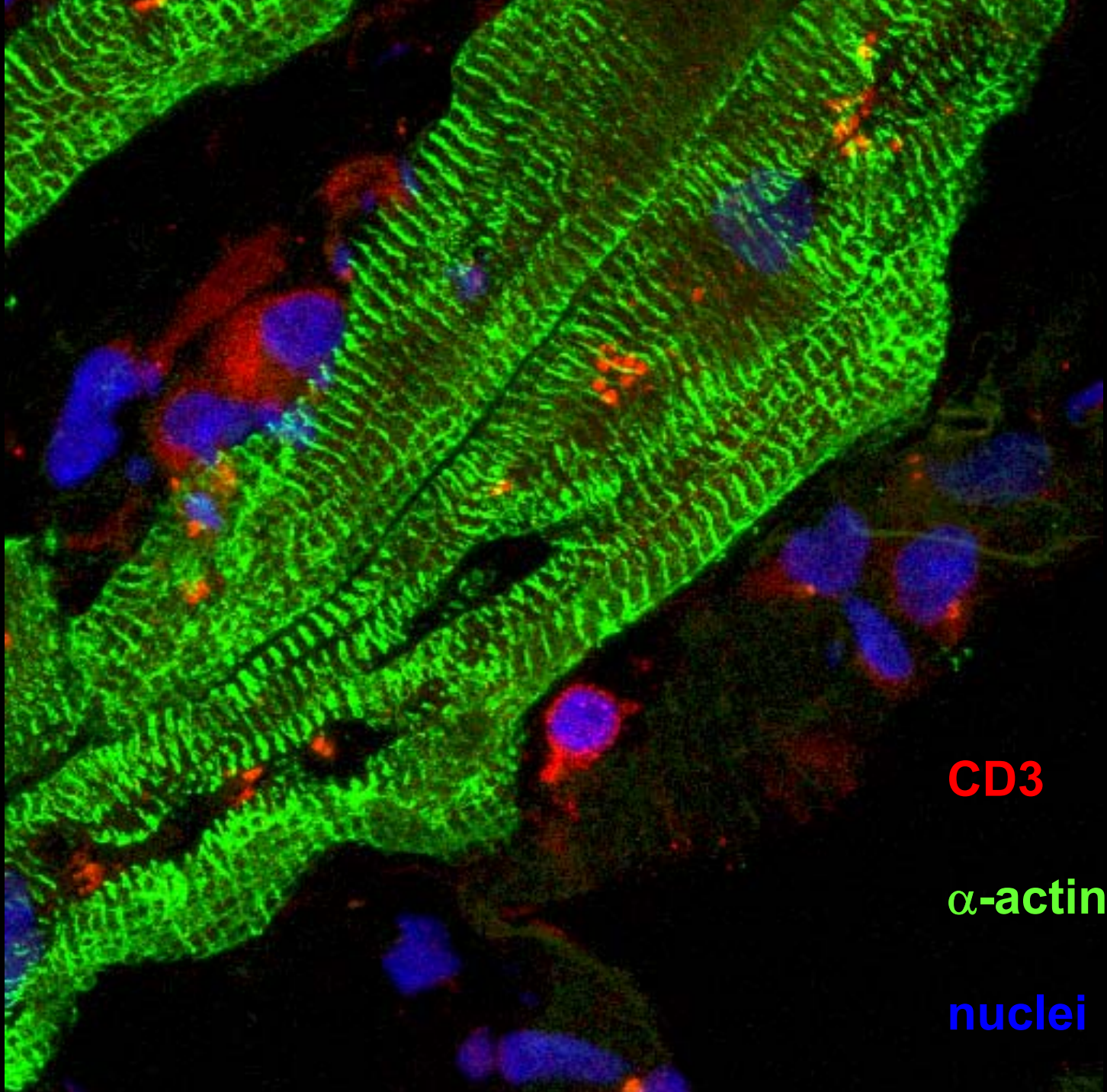
# Inflammatory structural remodeling in AF

- Frustaci evaluated atrial septal biopsies from 12 pts w/ lone pAF
- All biopsies showed structural abnormalities (fibrosis, hypertrophy)
- 8 had lymphomononuclear infiltrates with necrosis of the adjacent myocytes
- Results were compatible with myocarditis in 66% of pts, with significant fibrosis in the remainder



A. Frustaci et al.,  
Circulation. 1997;96:1180-1184



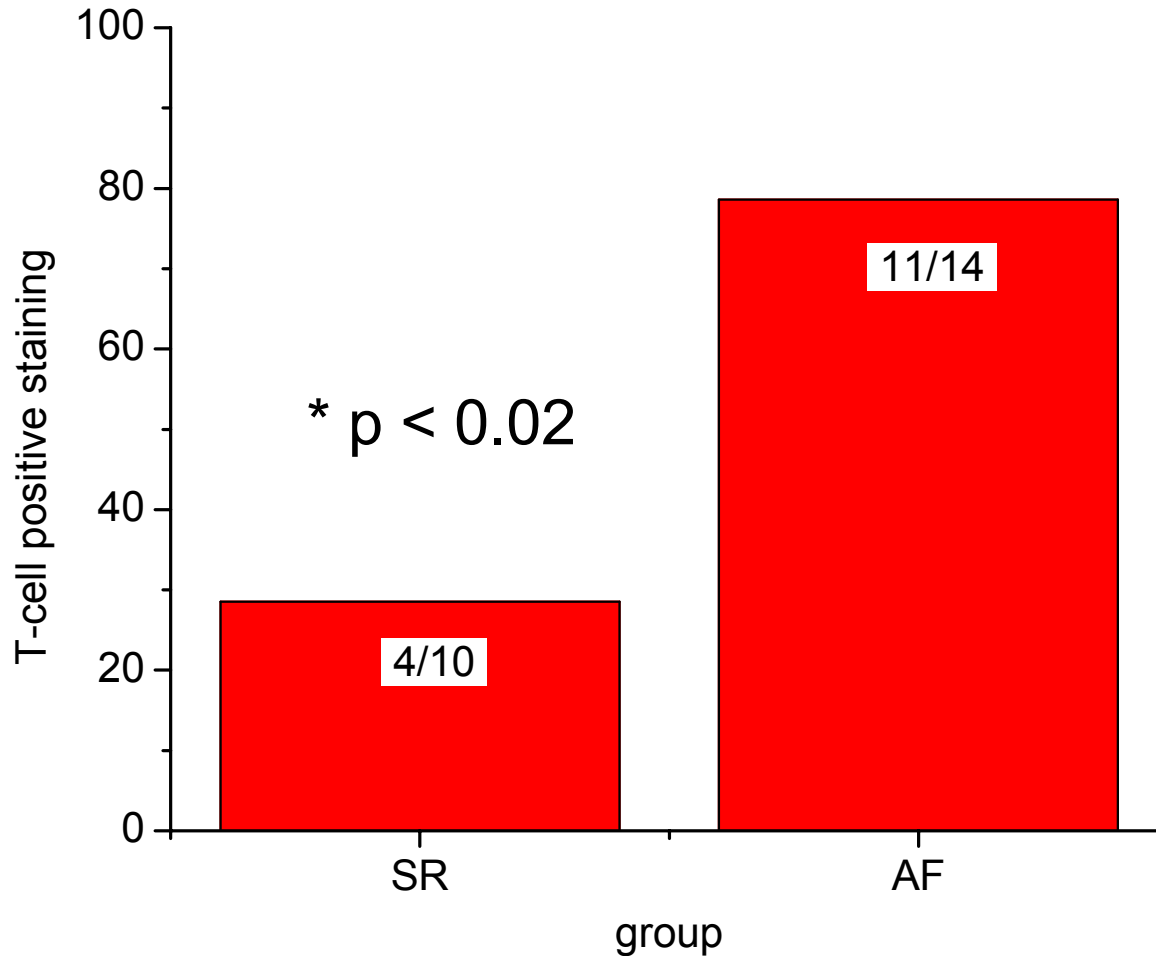


**CD3**

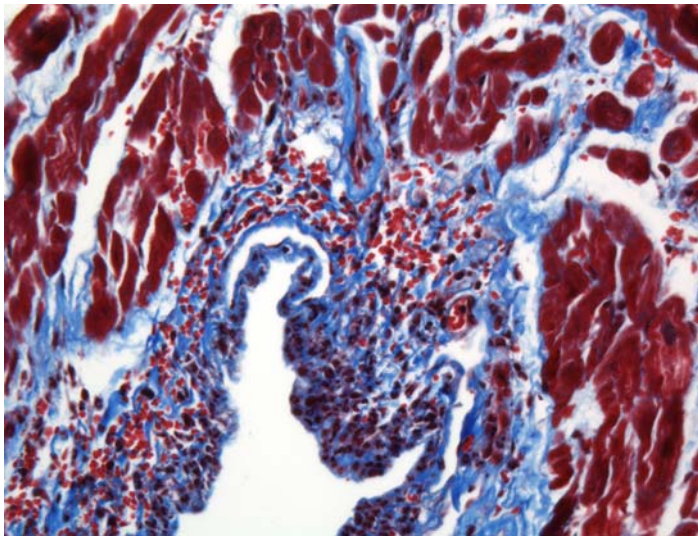
**$\alpha$ -actinin**

**nuclei**

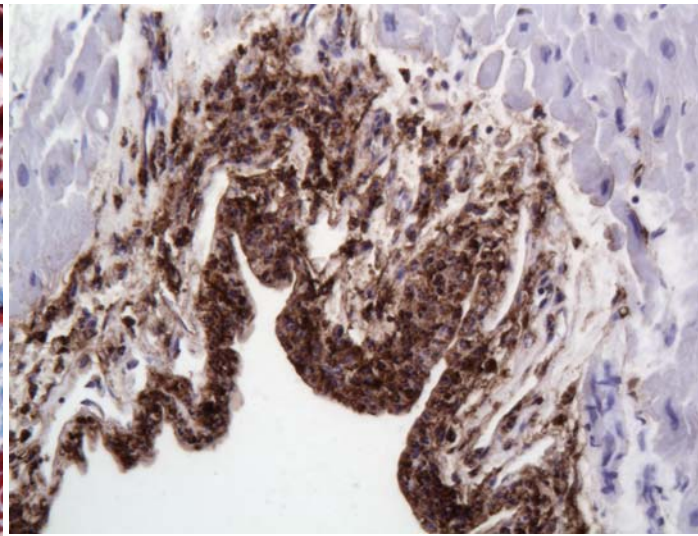
# T-lymphocytes were more frequently found and more abundant in AF tissues



Myeloperoxidase (in neutrophils, macrophages) consumes  $\text{NO}^{\cdot}$ , is associated with atrial fibrosis



Masson's trichrome



MPO / hematoxylin



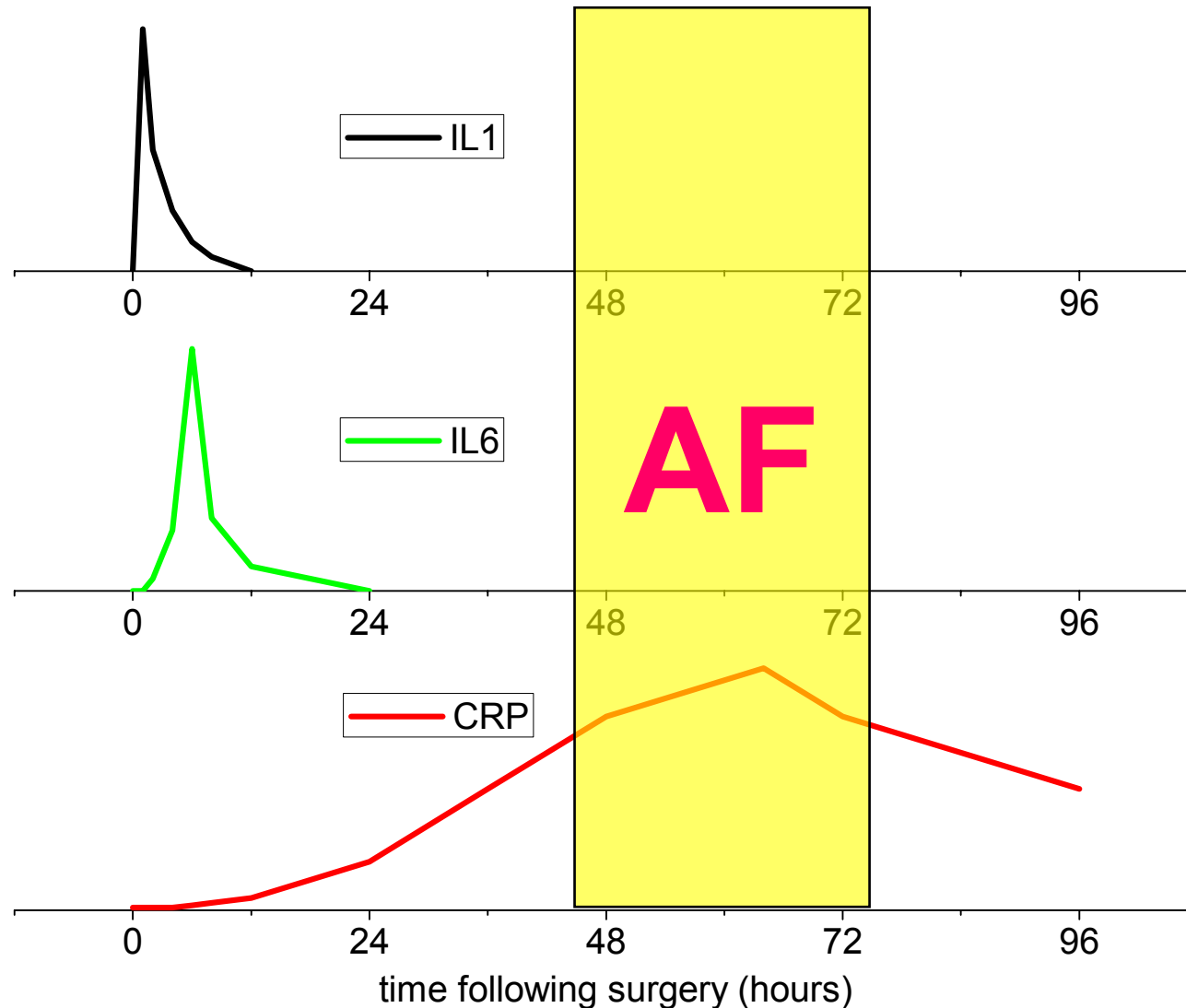


# Systemic inflammation in AF

Inflammation may affect both  
atrial and vascular  
thrombogenesis...



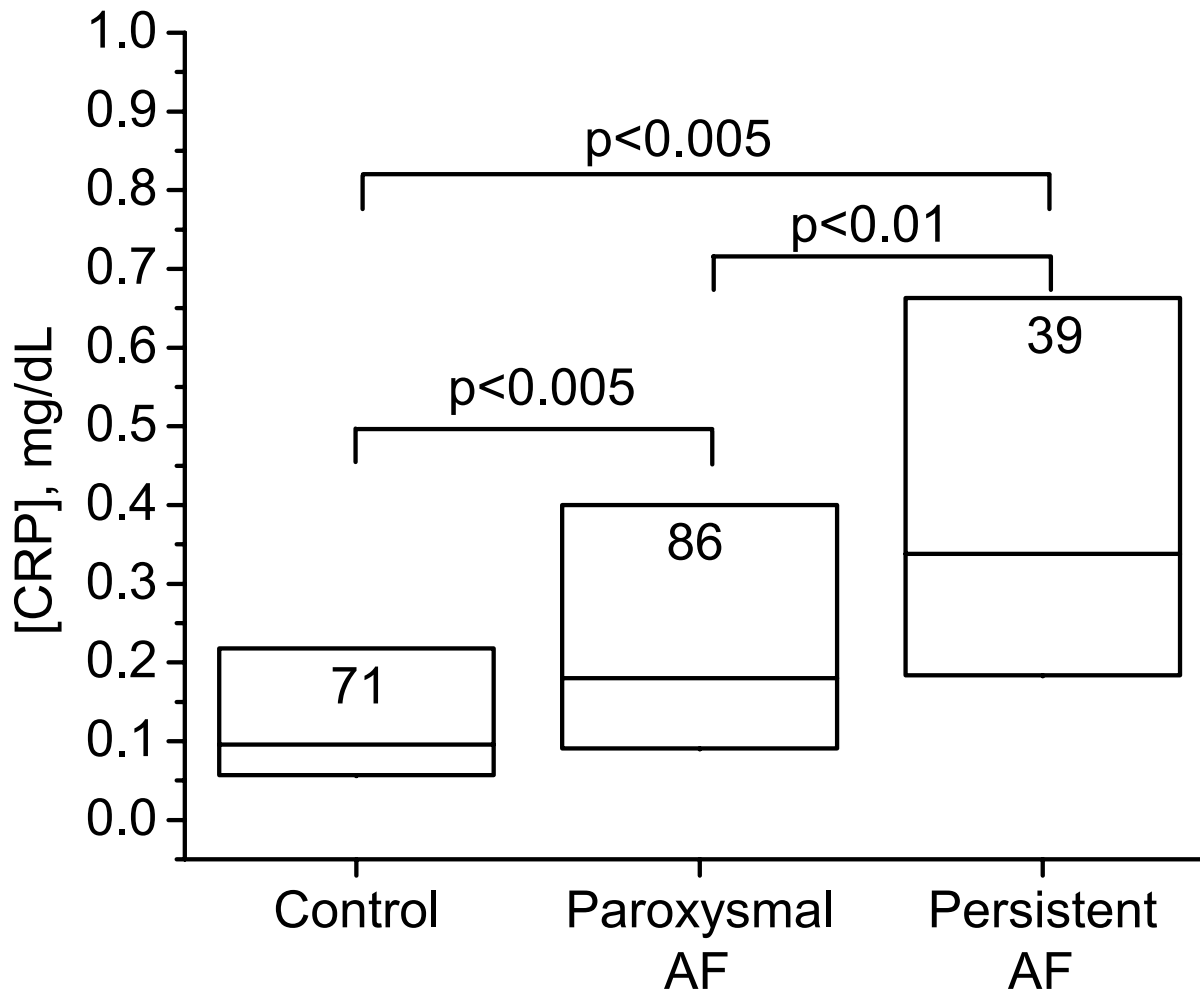
# Cytokine changes following cardiac surgery



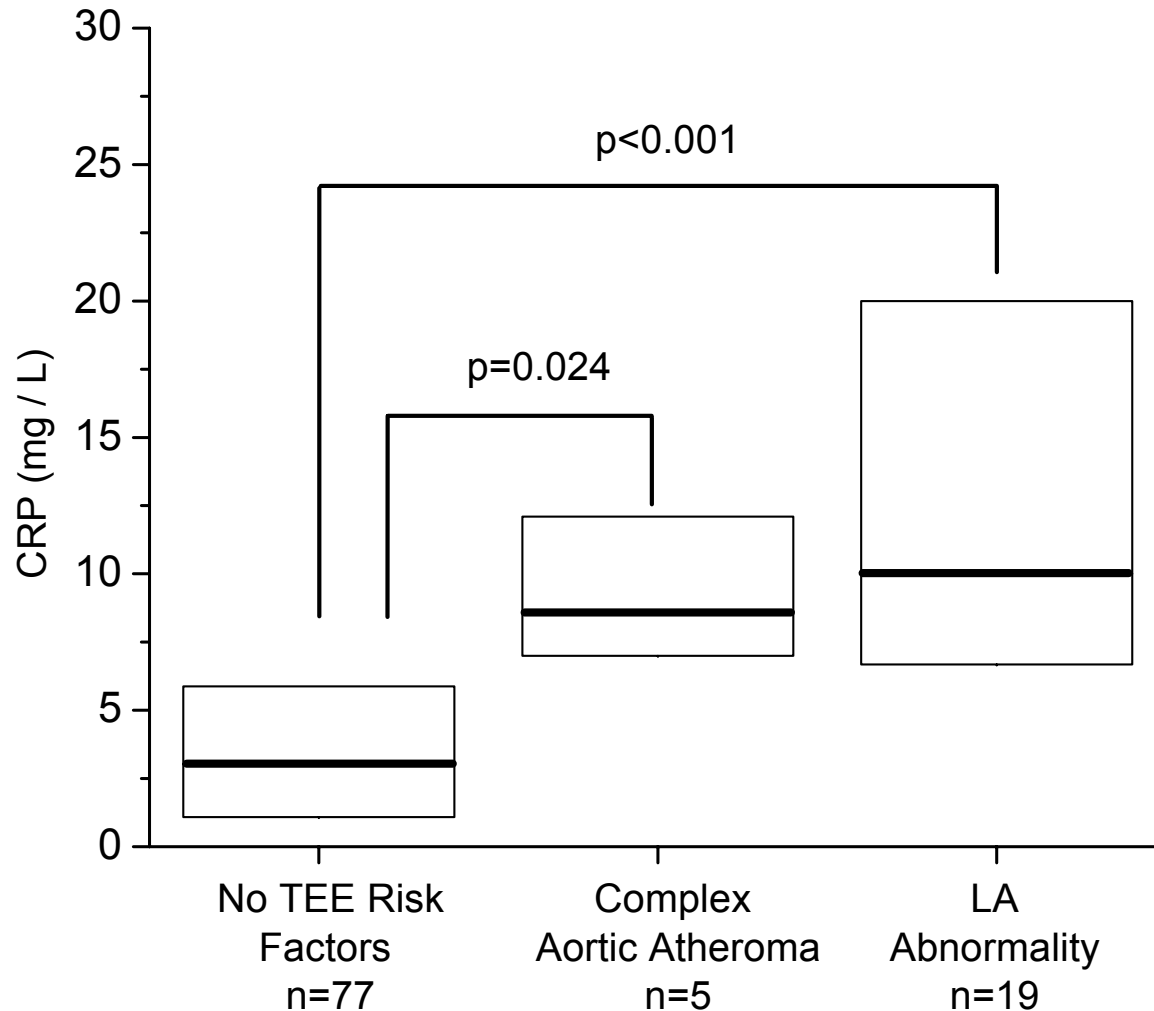
Adapted from: Bruins et al., *Circulation* 96:3542-3548, 1997



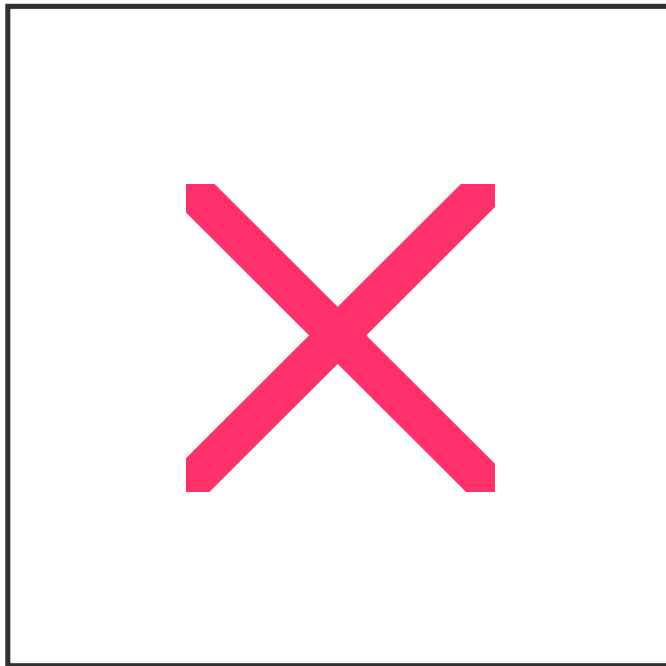
# Elevated plasma CRP is linked with increased arrhythmia persistence



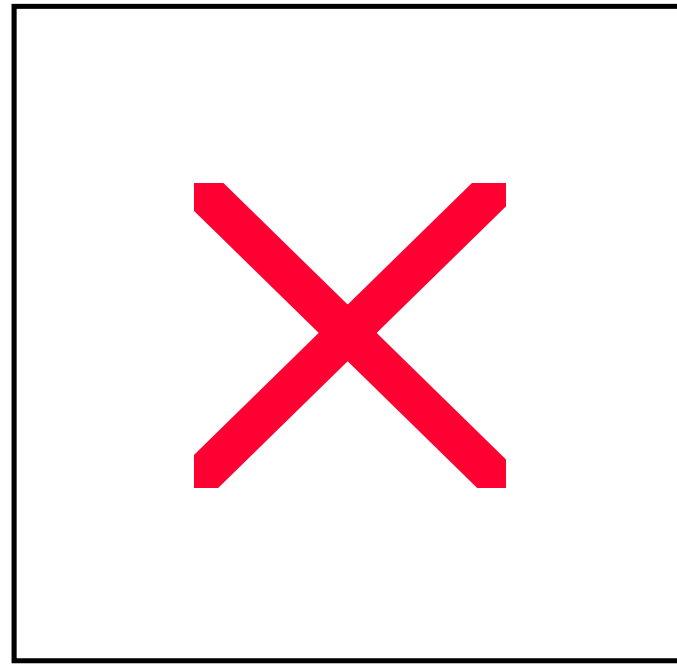
# CRP levels are VERY elevated in AF patients with TEE evidence of stroke risk



Atrial CRP is evident in AF patients; at comparable plasma levels, atrial CRP abundance is greater in AF than SR



AF, CRP 13.7 mg/L



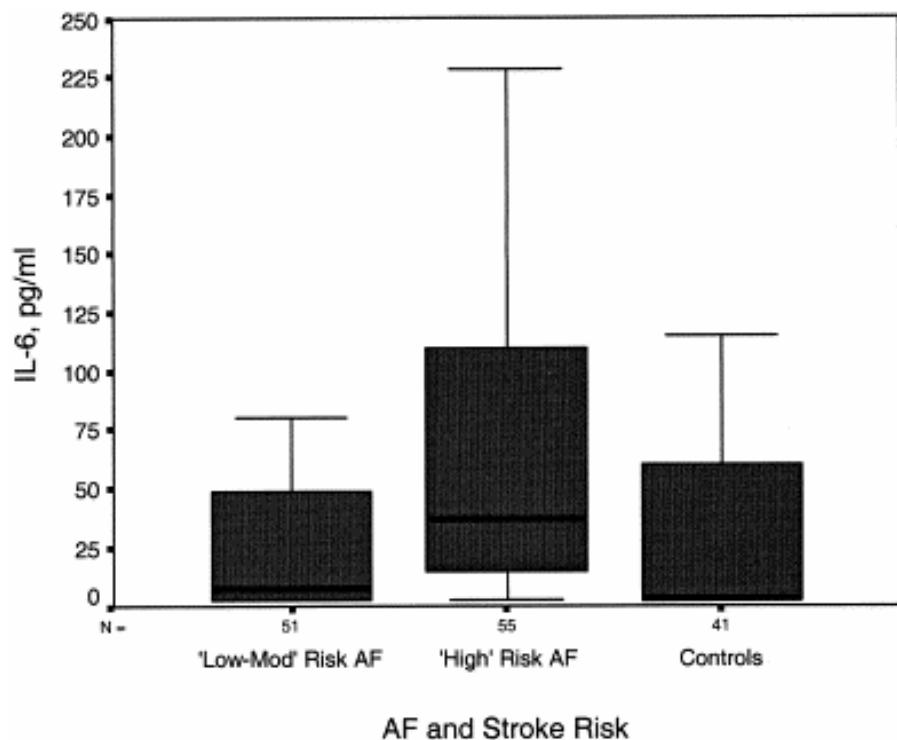
Sinus Rhythm, CRP 11.8 mg/L



# Abnormal coagulation

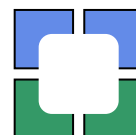


# IL-6, CRP, TF, vWF and thromboembolic risk

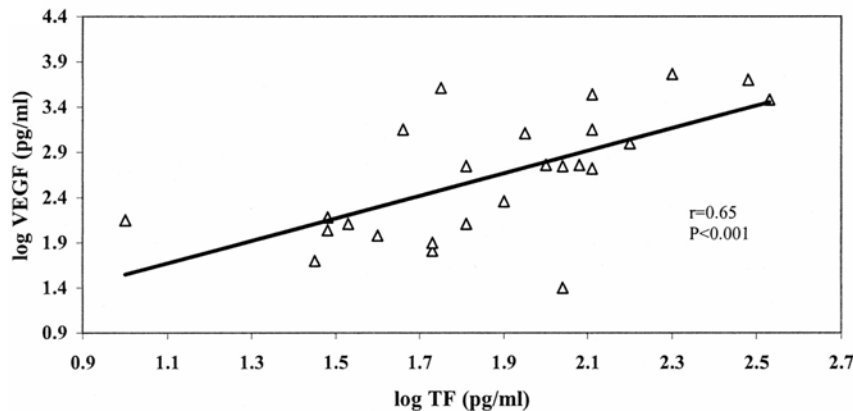
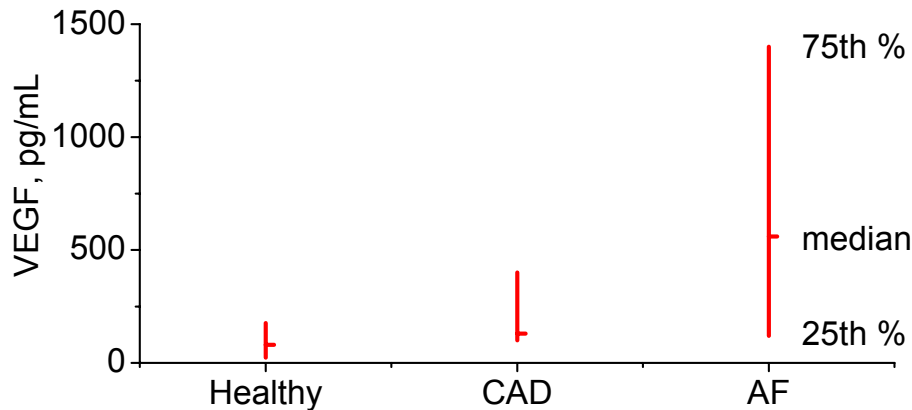


DS Conway et al.,  
JACC 43:2075-2082, 2004

- Tissue factor (initiator of the coagulation cascade) was the only thrombosis marker elevated in AF patients; TF correlated with IL-6 but not CRP levels.
- CRP levels were associated with vWF and fibrinogen levels, plasma viscosity



# Elevated plasma tissue factor levels in AF may be due to increased VEGF



- VEGF levels are increased in AF
- Increased TF levels are well correlated with increased VEGF
- Elevated tissue factor contributes to the prothrombotic state in AF





# Conclusions

- Thromboembolic risk in AF is associated with atrial contractile deficit, endothelial and endocardial injury, systemic inflammation and activation of coagulation;
- Thromboembolic changes preferentially affect the ***left atrium***, perhaps due to the increased LA hemodynamic burden in AF;
- Treatments that decrease endothelial dysfunction and inflammatory burden may lower stroke risk for patients with AF.



# Thanks to:

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