

Atrial fibrillation and oxidative stress

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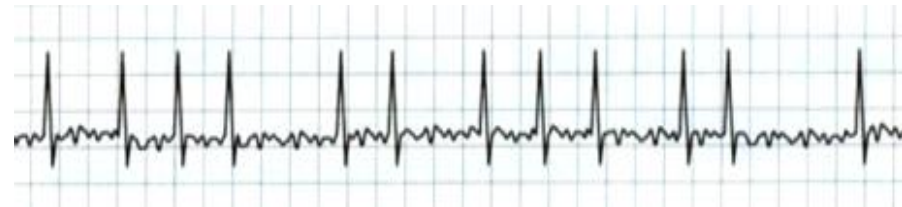
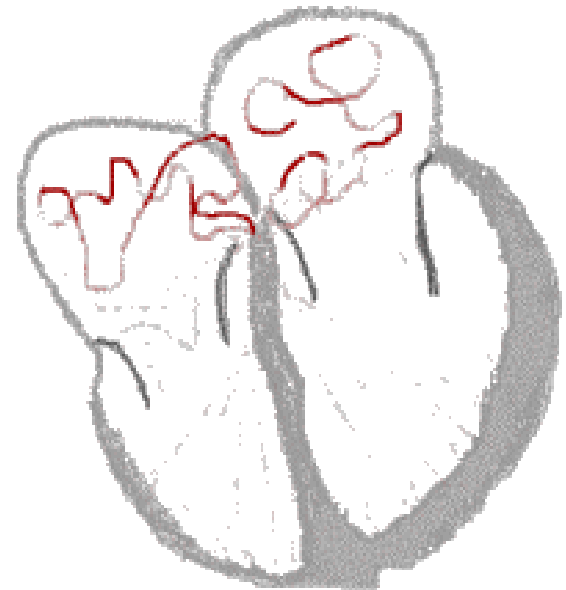


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Sinus Rhythm



Atrial Fibrillation



AF: epidemiology & treatment

- Most common sustained clinical arrhythmia (1:4 lifetime risk)

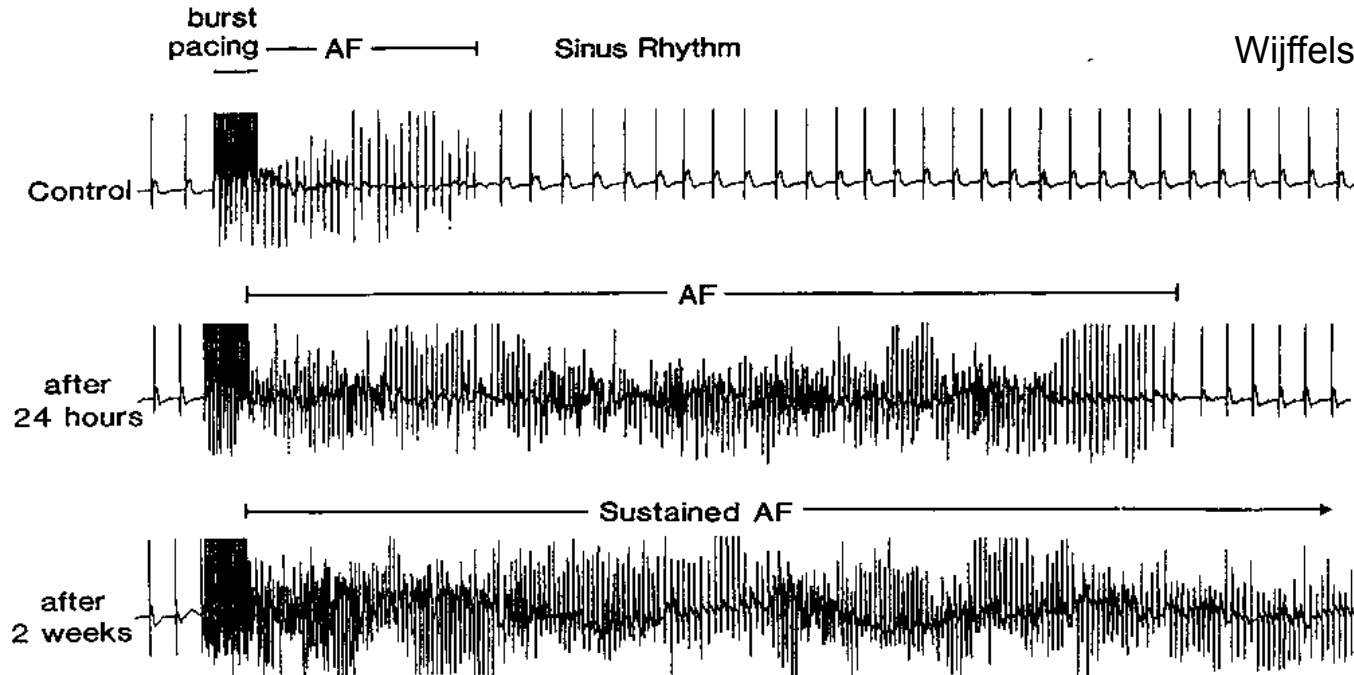
AF: epidemiology & treatment

- Most common sustained clinical arrhythmia (1:4 lifetime risk)
- AF is associated with a significantly increased morbidity and mortality and high medical costs

AF: epidemiology & treatment

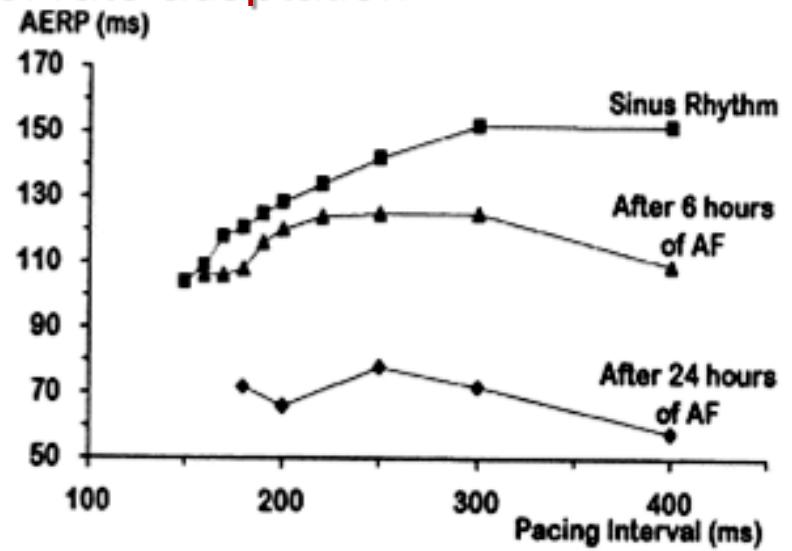
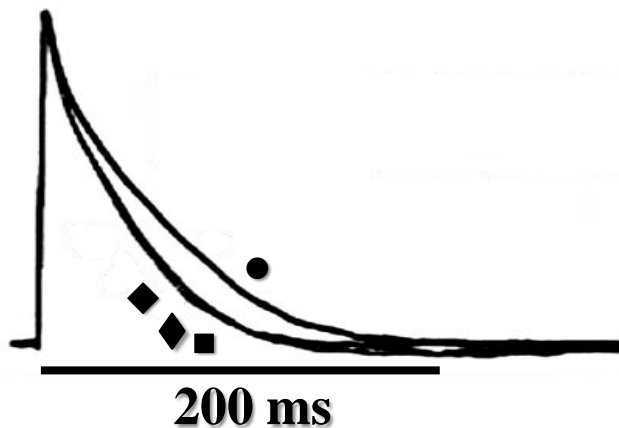
- Most common sustained clinical arrhythmia (1:4 lifetime risk)
- AF is associated with a significantly increased morbidity and mortality and high medical costs
- Available treatment is suboptimal (targeted to symptoms and prevention of thromboembolism)

'AF begets AF'



Shorter APD & loss of rate adaptation

● 0.5Hz ■ 1Hz ◆ 2Hz ◆ 4Hz

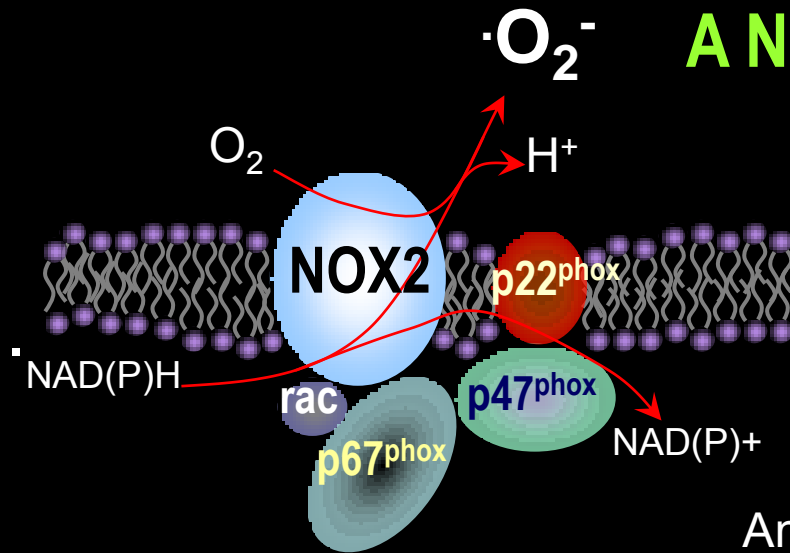


Atrial oxidative stress and AF

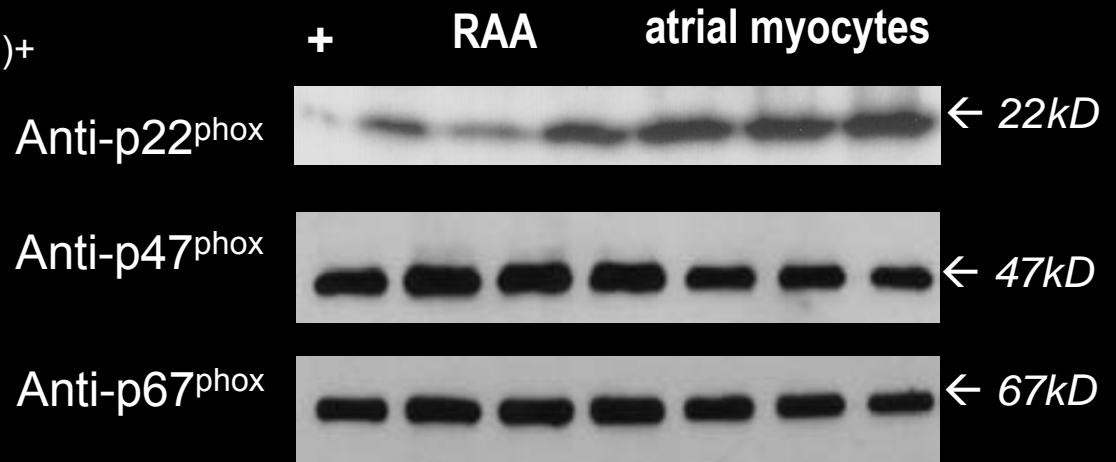
- **There is evidence of oxidative injury in atrial samples from patients with AF** (Mihm *et al.* Circ 2001)
- **There is a correlation between oxidative stress and atrial ERP shortening in animal models** (Carnes *et al.* Circ Res 2004)
- **Treatment with anti-oxidant/anti-inflammatory agents prevents atrial electrical remodelling and AF induction in a dog model of atrial tachypacing** (Carnes *et al.* Circ Res 2001, Shiroshita-Takeshita *et al.* Circ Res 2004)

A NOX2 oxidase in human atrial cells

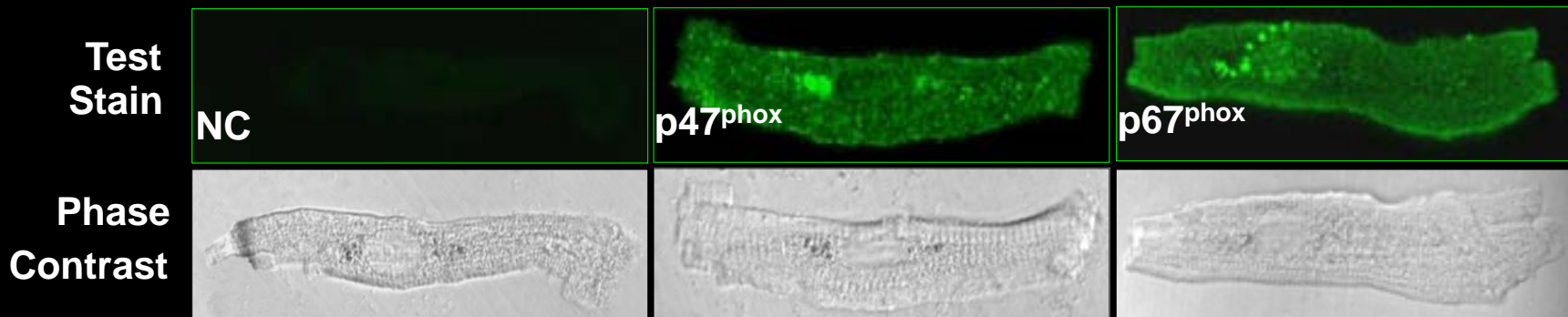
Kim et al, Circ Res 2005



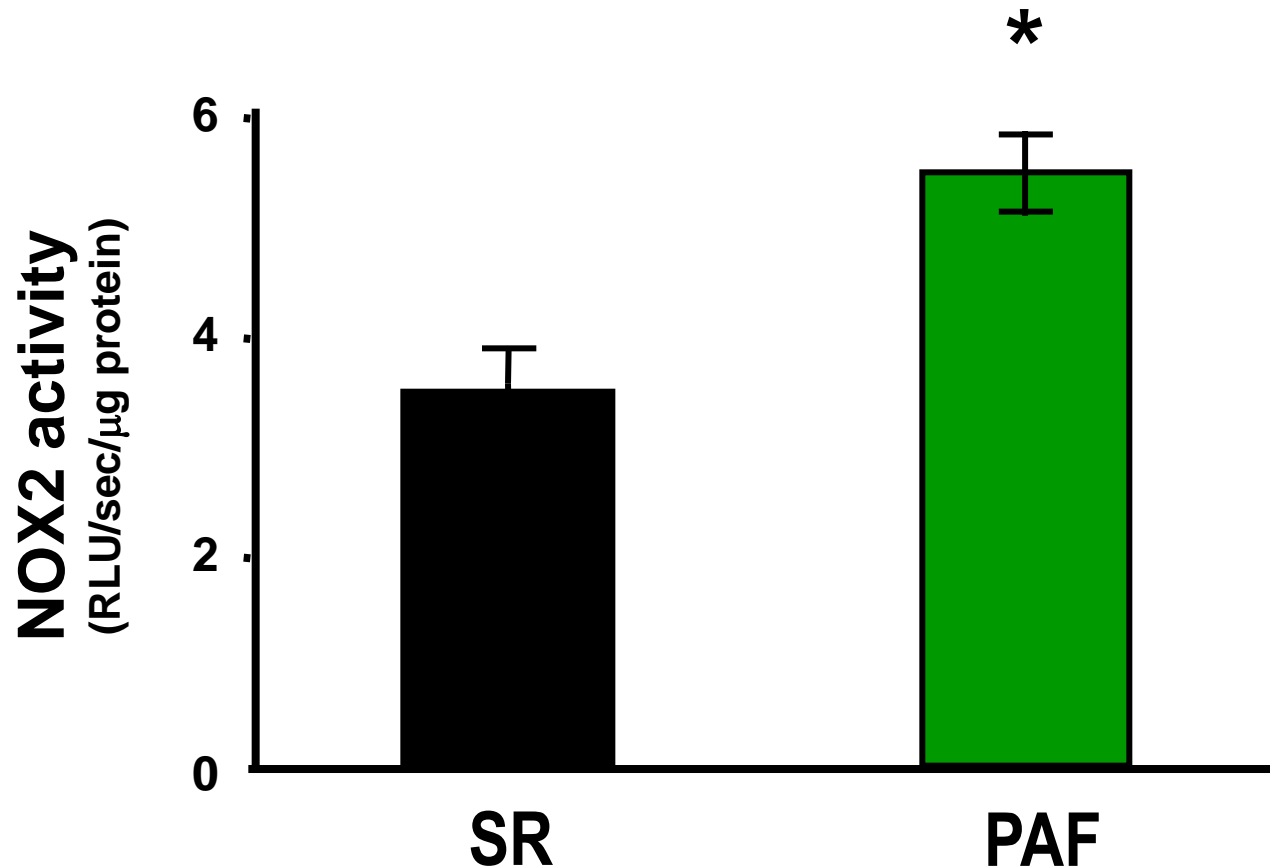
Immunoblotting



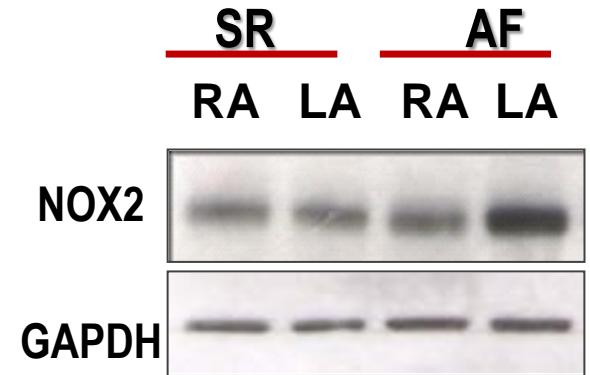
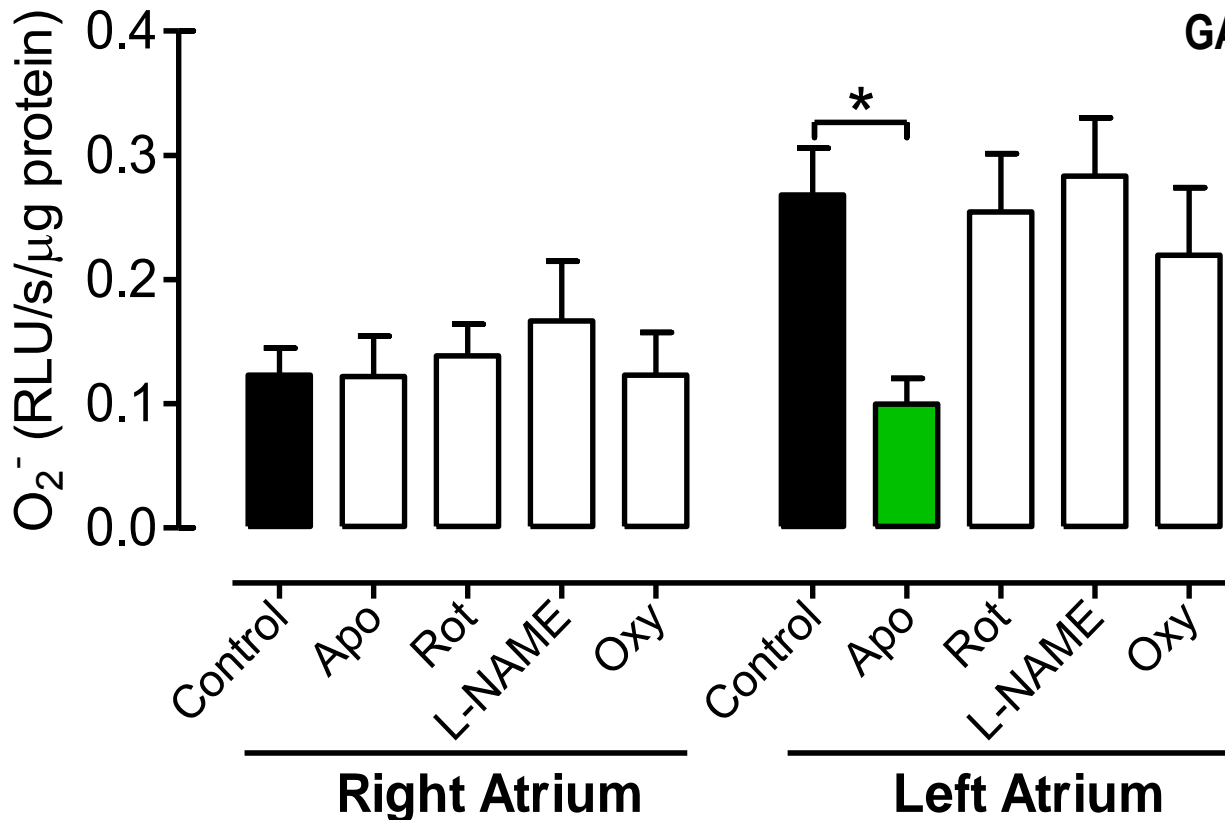
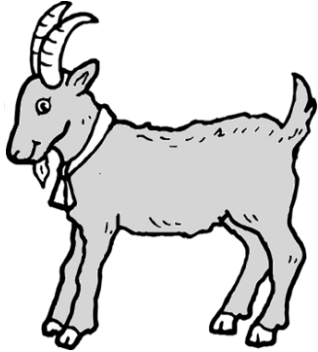
Immunolocalization in human atrial myocytes



Atrial NOX2 activity is increased in patients with (mostly) PAF



NOX2 activity is increased in the LA of goats after 2 weeks of AF



Atrial NOX2 activity and AF: cause or effect?

- NOX2 oxidases are present in the human atrial myocardium
- Atrial NOX2 activity is increased in AF and correlated with the extent of the AF-induced atrial electrical remodelling
- Does an increase in atrial NOX2 activity precede AF?

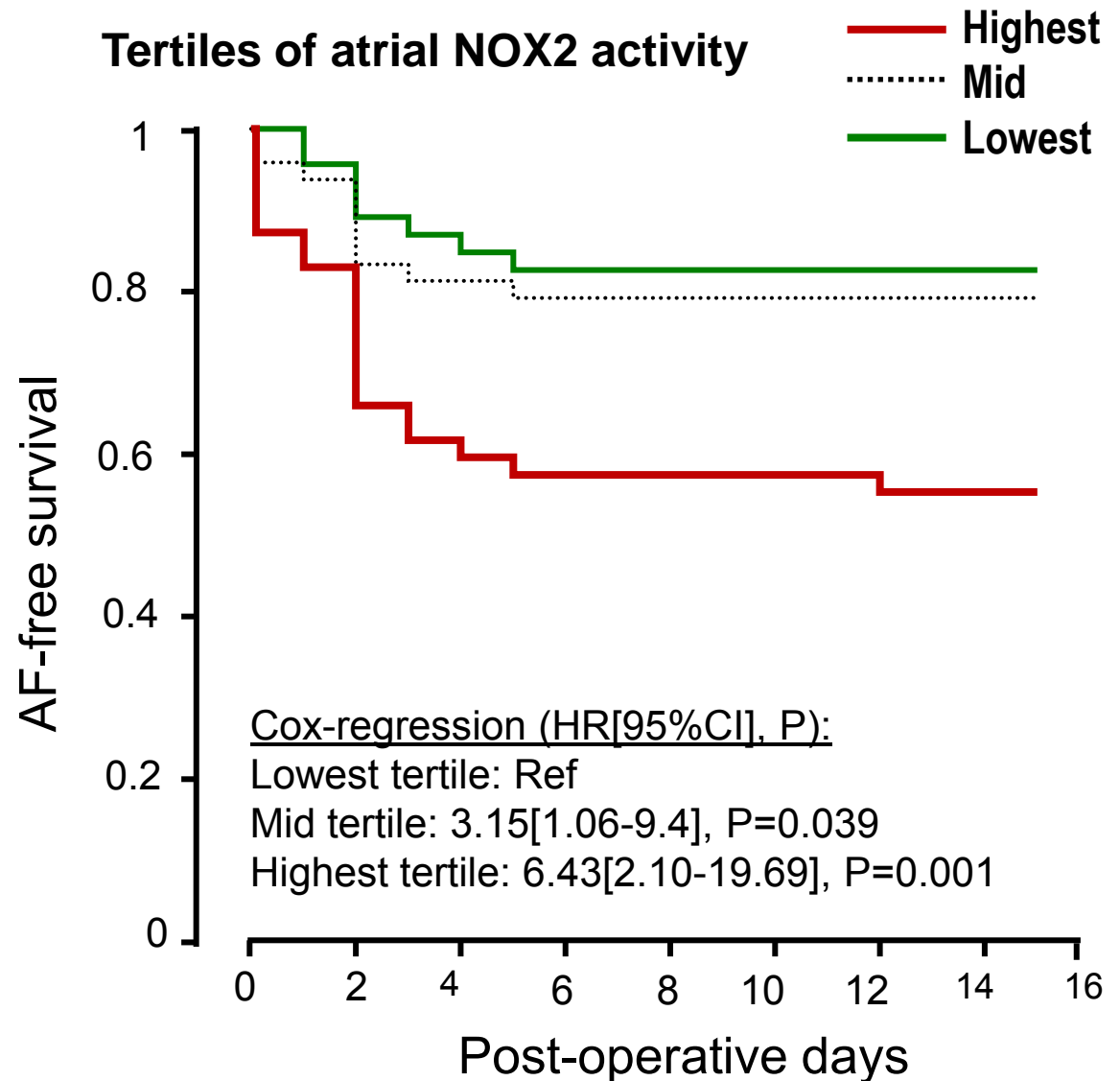


Post-operative atrial fibrillation

- AF is a frequent complication of cardiac surgery
- The inflammatory reaction associated with cardiac surgery and cardiopulmonary bypass has been implicated in the genesis of this arrhythmia

Hypothesis: *Atrial NOX2 oxidases can “sense” systemic inflammation and translate it into a local increase in oxidative stress leading to arrhythmogenesis*

Atrial NOX2 activity is an independent predictor of new-onset AF after cardiac surgery (n=281)



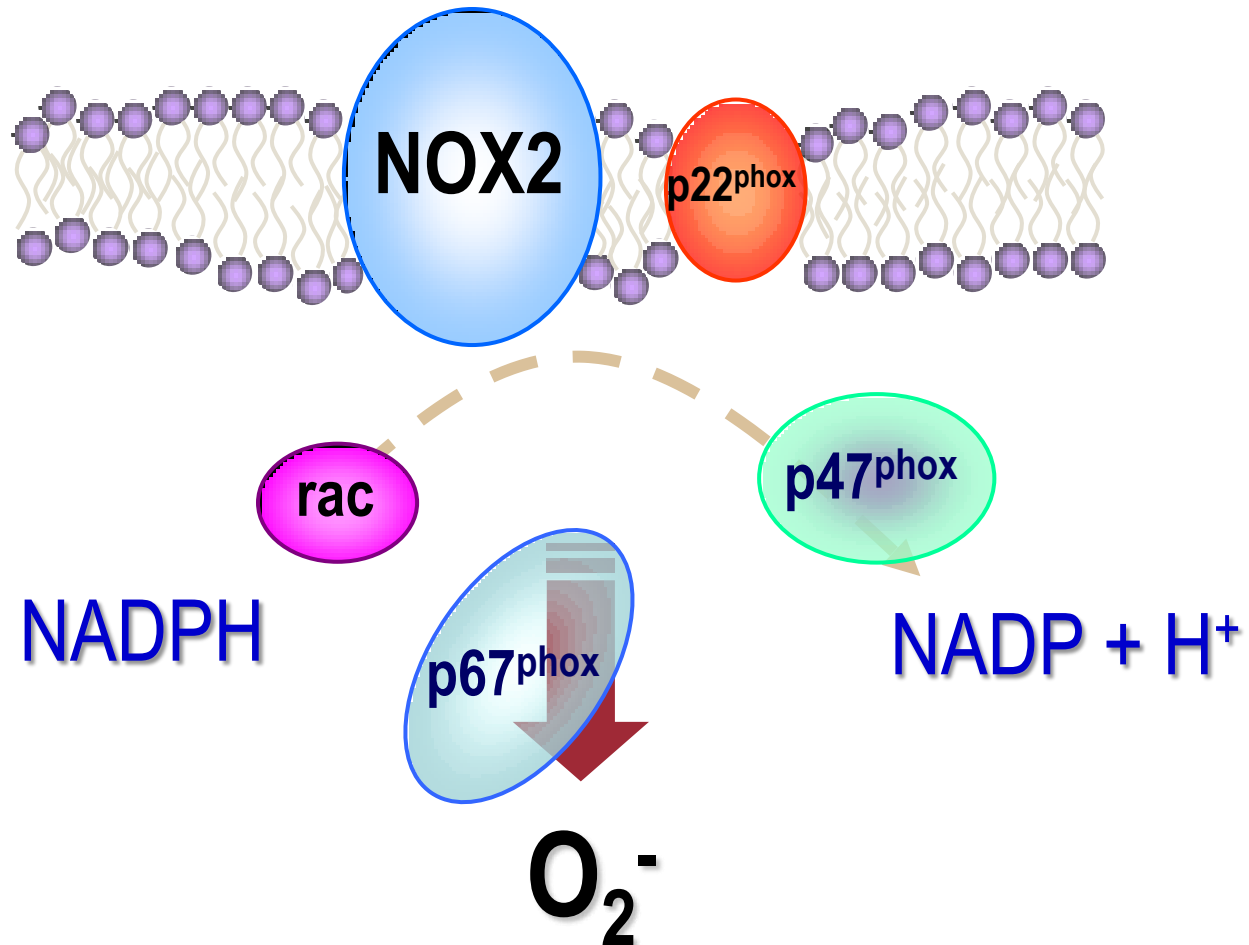
Atrial NOX2 activity and AF: cause or effect?

- NOX2 oxidases are present in the human atrial myocardium ✓
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- An increase in atrial NOX2 activity precedes AF ✓
- **Is increased atrial NOX2 activity sufficient to create a substrate for AF?**

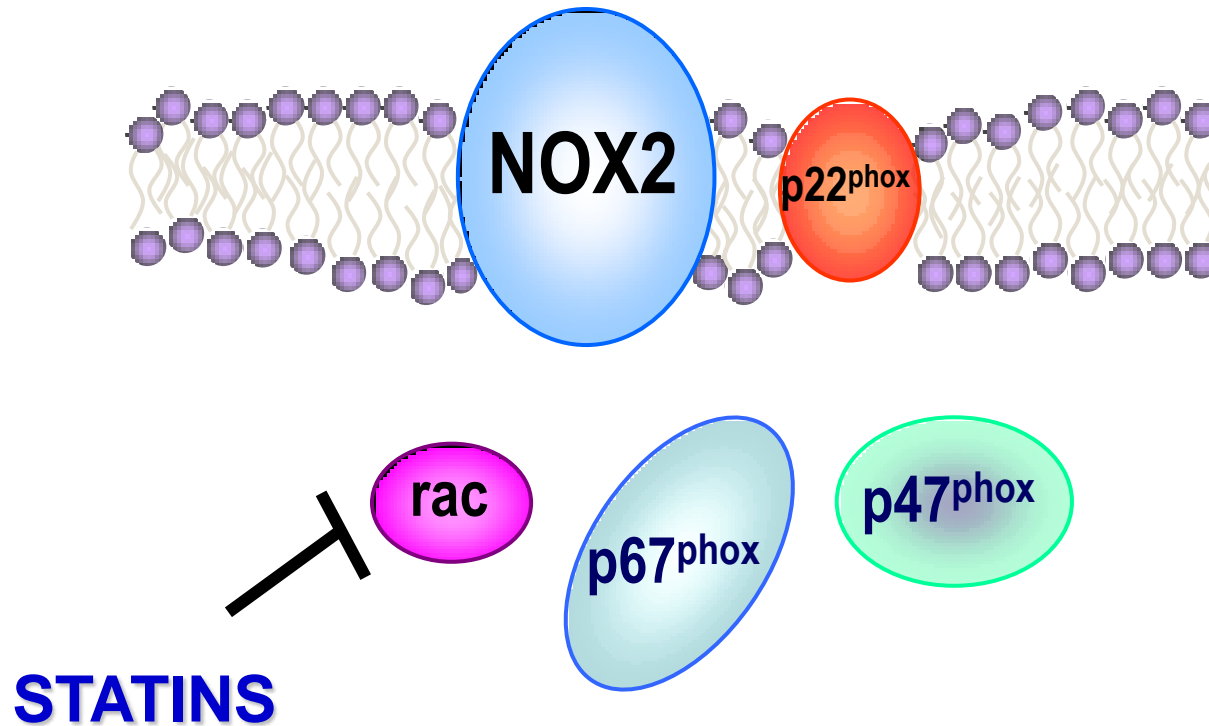
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- Increased atrial NOX2 activity is sufficient to create a substrate for AF ✓
- **Do pharmacological interventions that inhibit NOX2 activity prevent AF?**

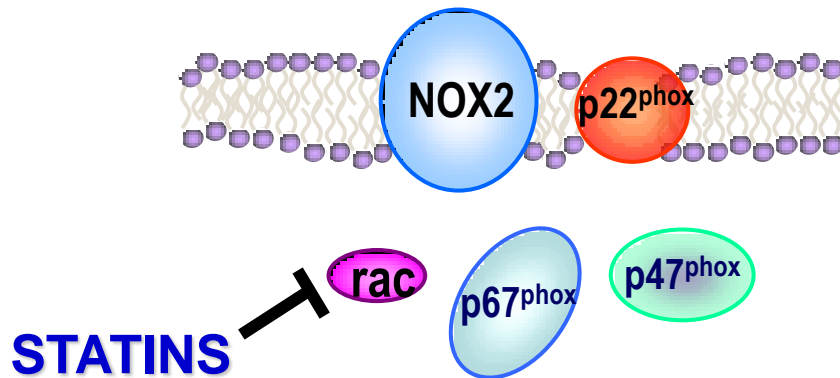
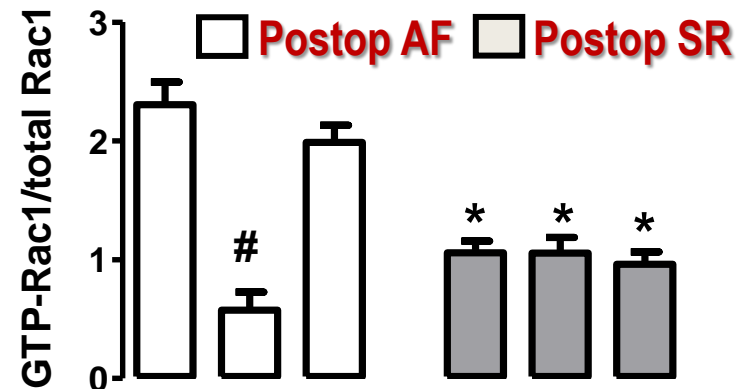
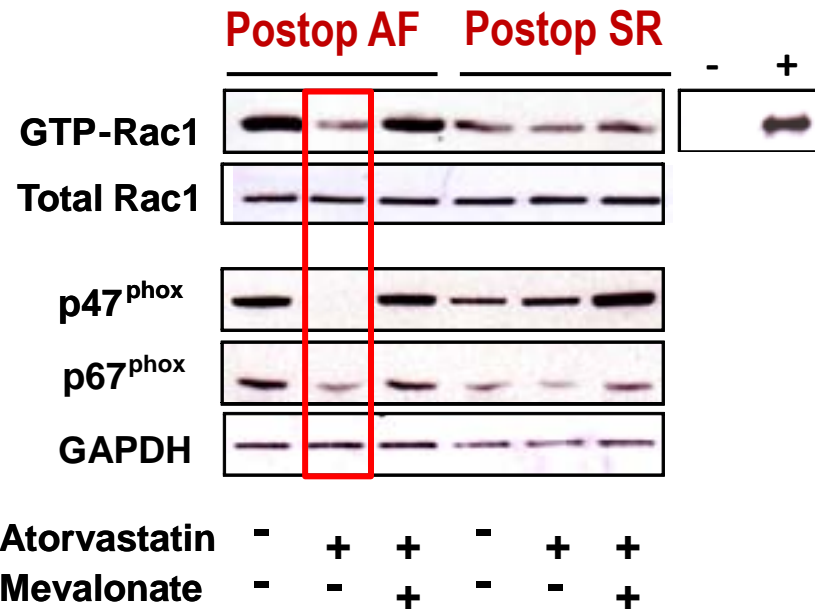
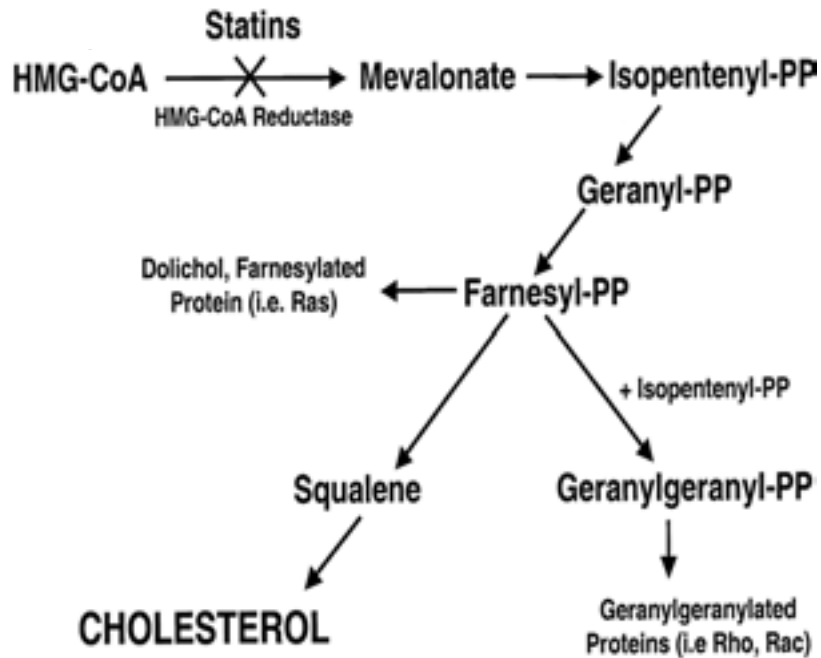
NOX2 NADPH oxidases: activated by cytokines and AngII



Statin-mediated inhibition of NOX2

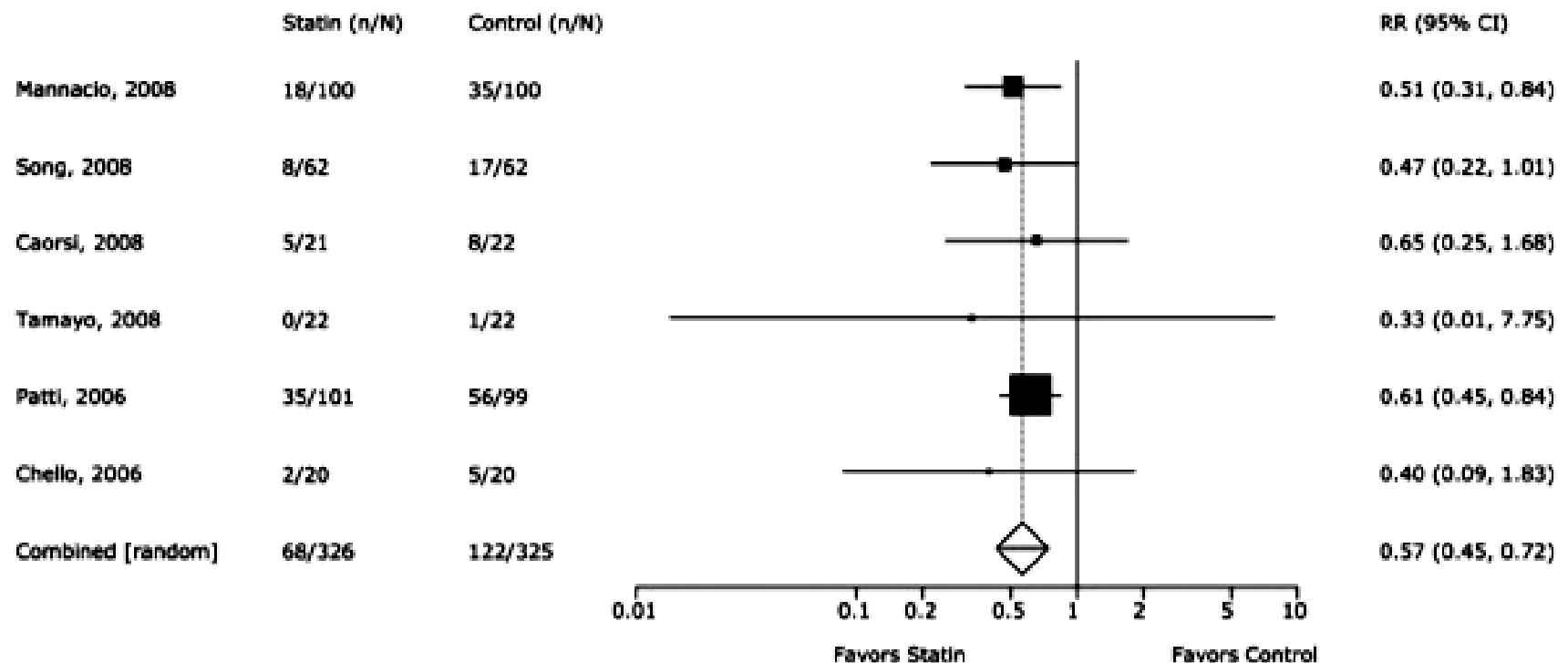


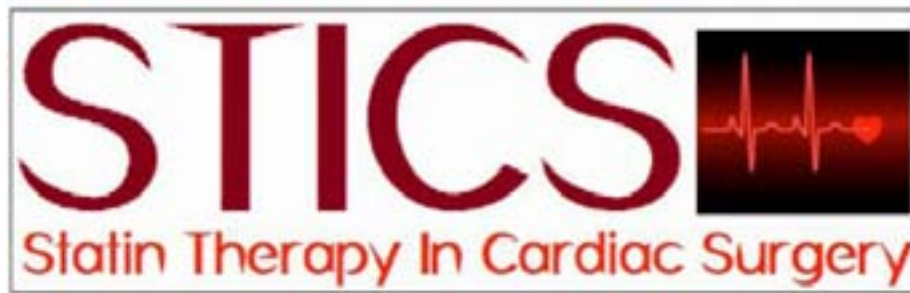
Atrial Rac1 activity is increased in patients who develop post-operative AF and is inhibited by atorvastatin



Atorvastatin	-	+	+	-	+	+
Mevalonate	-	-	+	-	-	+

Effect of peri-operative statin treatment on post-operative AF



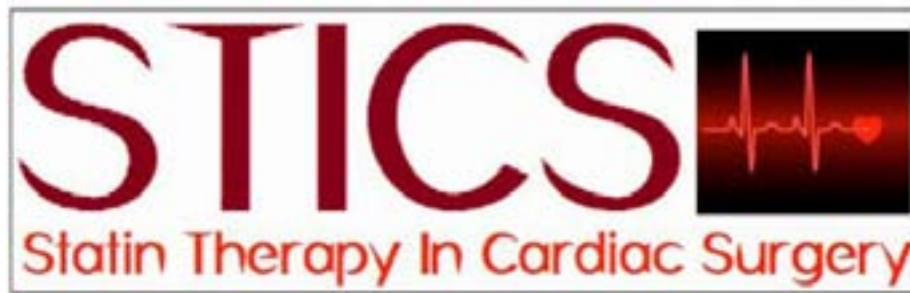


- A double-blind, randomised, placebo-controlled trial of perioperative Rosuvastatin (20 mg od)
- Treatment is started 3 days before surgery and continued until the 5th post-operative day in 1800 patients undergoing cardiac surgery (1550 randomised so far)

Primary Objectives

To establish whether perioperative administration of Rosuvastatin leads to a reduction in:

- Post-operative AF (as assessed by continuous ECG monitoring)
- Perioperative myocardial injury (as assessed by serial Troponin measurements)



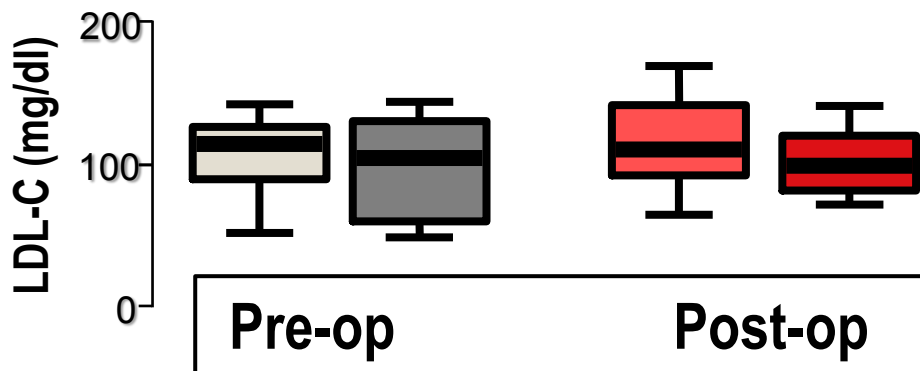
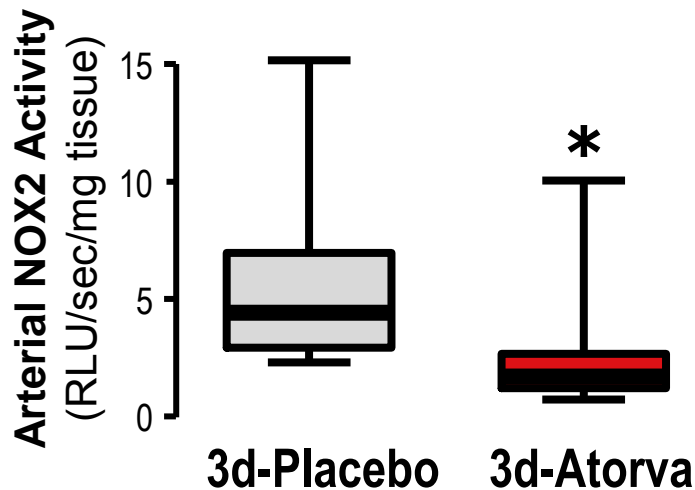
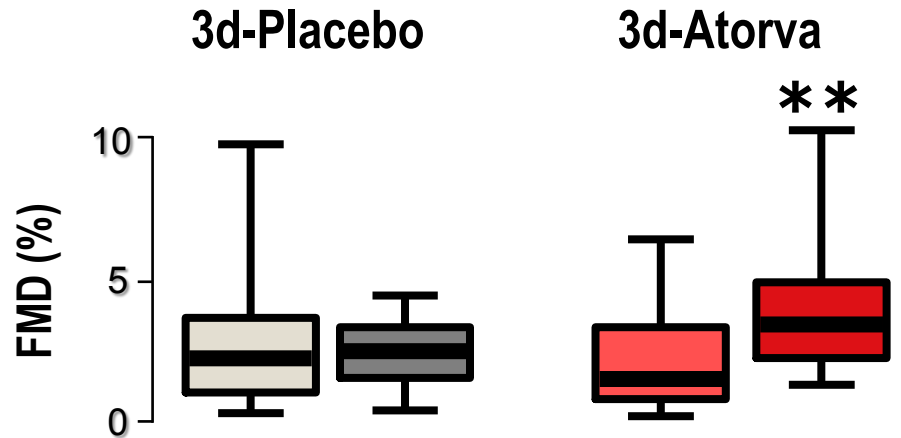
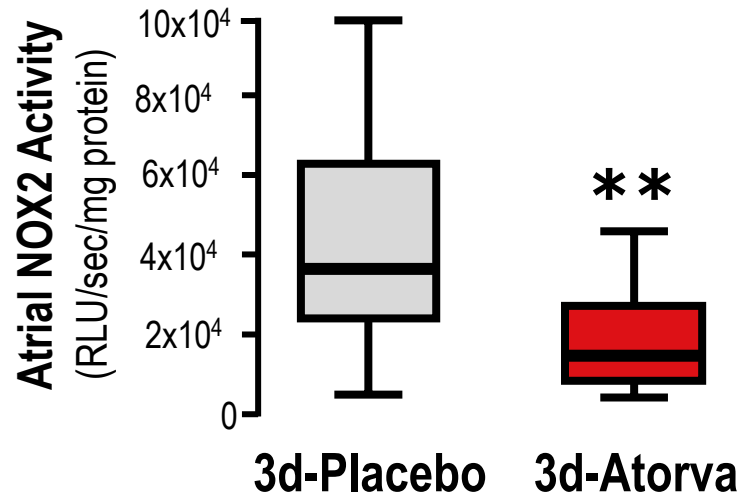
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Effect 3-day preoperative treatment with atorvastatin (20 mg od) or placebo on atrial and vascular redox state in 42 CABG patients



What will we learn?

- Is aggressive statin treatment in the perioperative period beneficial?
- Are statins cardioprotective and anti-arrhythmic in these patients?
- Are the pleiotropic effects of statins (e.g., NOX2 inhibition) clinically relevant?

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