Atrial fibrillation and oxidative stress

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ESC Summer School 2013

British Heart Foundation
AF: epidemiology & treatment

- Most common sustained clinical arrhythmia (1:4 lifetime risk)
AF: epidemiology & treatment

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- 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’

Wijffels et al, 1995

Shorter APD & loss of rate adaptation
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)

A NOX2 oxidase in human atrial cells

Kim et al, Circ Res 2005

Immunoblotting

+ RAA atrial myocytes

Anti-p22phox

< 22kD

Anti-p47phox

< 47kD

Anti-p67phox

< 67kD

Immunolocalization in human atrial myocytes
Atrial NOX2 activity is increased in patients with (mostly) PAF

Kim et al, *Circ Res* 2005
NOX2 activity is increased in the LA of goats after 2 weeks of AF

Reilly et al. Circulation 2011
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)

Cox-regression (HR[95%CI], P):
- Lowest tertile: Ref
- Mid tertile: 3.15[1.06-9.4], P=0.039
- Highest tertile: 6.43[2.10-19.69], P=0.001

AF-free survival

Tertiles of atrial NOX2 activity
- Highest
- Mid
- Lowest

Post-operative days

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Antoniades et al. JACC 2011
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- 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
- An increase in atrial NOX2 activity precedes AF
- Is increased atrial NOX2 activity sufficient to create a substrate for AF?
Atrial NOX2 activity and AF: cause or effect?

- NOX2 oxidases are present in the human atrial myocardium
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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.
Effect of peri-operative statin treatment on post-operative AF

Chen et al. J Thorac Cardiovasc Surg. 2010

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin (n/N)</th>
<th>Control (n/N)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannaclo, 2008</td>
<td>18/100</td>
<td>35/100</td>
<td>0.51 (0.31, 0.84)</td>
</tr>
<tr>
<td>Song, 2008</td>
<td>8/62</td>
<td>17/62</td>
<td>0.47 (0.22, 1.01)</td>
</tr>
<tr>
<td>Caorsi, 2008</td>
<td>5/21</td>
<td>8/22</td>
<td>0.65 (0.25, 1.68)</td>
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<tr>
<td>Tamayo, 2008</td>
<td>0/22</td>
<td>1/22</td>
<td>0.33 (0.01, 7.75)</td>
</tr>
<tr>
<td>Patti, 2006</td>
<td>35/101</td>
<td>56/99</td>
<td>0.61 (0.45, 0.84)</td>
</tr>
<tr>
<td>Chello, 2006</td>
<td>2/20</td>
<td>5/20</td>
<td>0.40 (0.09, 1.83)</td>
</tr>
<tr>
<td>Combined [random]</td>
<td>68/326</td>
<td>122/325</td>
<td>0.57 (0.45, 0.72)</td>
</tr>
</tbody>
</table>
A double-blind, randomised, placebo-controlled trial of perioperative Rosuvastatin (20 mg od)

Treatment is started 3 days before surgery and continued until the 5\textsuperscript{th} 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

Atrial NOX2 Activity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Activity (RLU/sec/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3d-Placebo</td>
<td><strong>8x10^4</strong></td>
</tr>
<tr>
<td>3d-Atorva</td>
<td><strong>4x10^4</strong></td>
</tr>
</tbody>
</table>

Antoniades et al. JACC 2011; Antoniades et al. Circulation 2011

Arterial NOX2 Activity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Activity (RLU/sec/mg tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3d-Placebo</td>
<td>10**^5**</td>
</tr>
<tr>
<td>3d-Atorva</td>
<td><strong>5x10^4</strong></td>
</tr>
</tbody>
</table>

Pre-op

Post-op

FMD (%)

<table>
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<th>Treatment</th>
<th>FMD (%)</th>
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<tbody>
<tr>
<td>3d-Placebo</td>
<td>0</td>
</tr>
<tr>
<td>3d-Atorva</td>
<td><strong>5</strong></td>
</tr>
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LDL-C (mg/dl)

<table>
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<th>Treatment</th>
<th>LDL-C (mg/dl)</th>
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<tbody>
<tr>
<td>3d-Placebo</td>
<td>100</td>
</tr>
<tr>
<td>3d-Atorva</td>
<td><strong>150</strong></td>
</tr>
</tbody>
</table>

**Pre-op**

**Post-op**
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?