On the potential increase of the oxidative stress status in patients with abdominal aortic aneurysm
(Redox Report 17: 139-144, 2012)


University of Liège – CHU. Depts of Cardiovascular Surgery and Biostatistics. Sart Tilman, 4000 Liège, Belgium.

Email: J.Pincemail@chu.ulg.ac.be
OXIDATIVE STRESS (OS)

imbalance between oxidants (reactive oxygen species or ROS derived from oxygen) and antioxidants in favour of the oxidants, leading to a disruption of redox signalling and/or molecular damage.
O$_2$ (fundamental oxygen)

**Superoxide anion**
- SOD, Vit C

**Hydrogen peroxide**
- Catalase
- Fe,Cu
- Ferritin, transferrin, chelating agents

**OH$^-$ (hydroxyl radical)**
- Uric acid, Vit C, GSH

**ROOH (lipoperoxides)**
- Vit E, Se-GPx, ubiquinone

**Singlet oxygen**
- Uroetoids, lycopene

**Singlet oxygen**

**H$_2$O$_2$ (hydrogen peroxide)**
- Cl$^-$, MPO

**O$_2^*$ (hypochlorous acid)**
- «eau de Javel»
The development of oxidative stress can potentially contribute to the pathologic features of AAA.

Increased ROS production

Iron: Fenton reaction

Endothelial dysfunction

could the local OS in AAA tissues be detected in the systemic circulation of the patients?

only a few number of studies available

Sakalihasan et al

first report of decreased vitamin E level in AAA

Martinez – Pinna R et al,

peroxiredoxin-1 as a novel biomarker of AAA.
<table>
<thead>
<tr>
<th>variable</th>
<th>Control group (n = 18; 67 years)</th>
<th>AAA patients (n = 27; 70 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>Women</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Fruit and vegetables</td>
<td>3.5 servings</td>
<td>3.76 servings</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>statins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>yes</td>
<td>3</td>
<td>18</td>
</tr>
</tbody>
</table>
fasted for at least 12 hours before blood sampling

not allowed to drink fruit juice and
to perform physical activity

not under antioxidant medication

blood immediately centrifuged after sampling and
plasma or serum kept at – 80°C until analysis
investigated blood OS biomarkers

1° antioxidants
  vitamin C
  $\alpha$ and $\gamma$ - tocopherol (vitamin E)
  $\beta$-carotene
  reduced glutathione /oxidized glutathione
  ubiquinone (CoQ10)
  glutathione peroxidase (GPx)
  thiol proteins

2° trace elements
  Se, Cu, Zn, ratio Cu/Zn
  Cu : prooxidant (« Fenton like reaction »)
  Zn : inhibition of Cu prooxidant effect
investigated OS parameters

3° markers of oxidative damages to lipids
lipid peroxides (not MDA or TBAR’s)
oxidized LDL (ox-LDL)
antibodies against ox-LDL
isoprostanes (gold standard)

4° marker of neutrophils activation
myeloperoxidase (MPO)
<table>
<thead>
<tr>
<th>Variable</th>
<th>control group (n = 18)</th>
<th>AAA patients (n = 27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>vitamin C (µg/mL)</td>
<td>10.9 ± 3.85</td>
<td>8.43 ± 2.98</td>
<td>0.035</td>
</tr>
<tr>
<td>α - tocopherol (µg/mL)</td>
<td>14.5 ± 3.34</td>
<td>12.1 ± 3.01</td>
<td>0.021</td>
</tr>
<tr>
<td>γ - tocopherol (µg/mL)</td>
<td>0.81 ± 0.38</td>
<td>0.80 ± 0.43</td>
<td>0.97</td>
</tr>
<tr>
<td>β - carotene (mg/L)</td>
<td>0.29 ± 0.17</td>
<td>0.16 ± 0.14</td>
<td>0.032</td>
</tr>
<tr>
<td>thiol proteins (µM)</td>
<td>311 ± 38</td>
<td>328 ± 44.7</td>
<td>0.19</td>
</tr>
<tr>
<td>ubiquinone (mg/L)</td>
<td>0.84 ± 0.32</td>
<td>0.64 ± 0.22</td>
<td>0.037</td>
</tr>
<tr>
<td>copper (mg/L)</td>
<td>0.88 ± 0.12</td>
<td>0.90 ± 0.28</td>
<td>0.78</td>
</tr>
<tr>
<td>zinc (mg/L)</td>
<td>0.79 ± 0.14</td>
<td>0.69 ± 0.13</td>
<td>0.022</td>
</tr>
<tr>
<td>copper/zinc ratio</td>
<td>1.14 ± 0.21</td>
<td>1.33 ± 0.40</td>
<td>0.093</td>
</tr>
<tr>
<td>selenium (µg/L)</td>
<td>92.7 ± 16.4</td>
<td>77.8 ± 20.3</td>
<td>0.022</td>
</tr>
</tbody>
</table>

*after adjustment for smoking and diet*
<table>
<thead>
<tr>
<th>Variable</th>
<th>control group</th>
<th>AAA patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 18)</td>
<td>(n = 27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lipid peroxides (µM)</td>
<td>520 ± 228</td>
<td>570 ± 331</td>
<td>0.79</td>
</tr>
<tr>
<td>oxidized LDL (ng/mL)</td>
<td>756 ± 964</td>
<td>231 ± 231</td>
<td>0.019</td>
</tr>
<tr>
<td>antibodies against oxidized LDL (UI/L)</td>
<td>263 ± 283</td>
<td>208 ± 240</td>
<td>0.42</td>
</tr>
<tr>
<td>isoprostanes (ng/mL)</td>
<td>1.01 ± 0.66</td>
<td>1.40 ± 0.77</td>
<td>0.18</td>
</tr>
<tr>
<td>total glutathione (µM)</td>
<td>852 ± 203</td>
<td>943 ± 175</td>
<td>0.1</td>
</tr>
<tr>
<td>oxidized glutathione (µM)</td>
<td>1.01 ± 0.67</td>
<td>4.73 ± 11.8</td>
<td>0.17</td>
</tr>
<tr>
<td>glutathione peroxidase (UI/g Hb)</td>
<td>51.5 ± 9.97</td>
<td>51.3 ± 10.9</td>
<td>0.93</td>
</tr>
<tr>
<td>myeloperoxidase (ng/mL)</td>
<td>22.0 ± 24.4</td>
<td>51.4 ± 83.8</td>
<td>0.11</td>
</tr>
</tbody>
</table>

after adjustment for smoking and diet
is there a relationship between the alteration of OS status and the aneurysm diameter?

only a few number of studies available
vitamin C

CHU reference values: 6.2 – 18.8 µg/mL

values associated with increased cardiovascular risks

P = 0.011

<table>
<thead>
<tr>
<th></th>
<th>µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>control group</td>
<td>10.0</td>
</tr>
<tr>
<td>AAA &lt; 50 mm</td>
<td>8.5</td>
</tr>
<tr>
<td>AAA &gt; 50 mm</td>
<td>7.0</td>
</tr>
</tbody>
</table>

(n = 18) (n= 15) (n= 12)
vitamin E (α – tocopherol)

CHU reference values: 8.6 – 19.2 µg/mL

* not significant after standardization to cholesterol
β-carotene

CHU reference values: 0.05 – 0.68 mg/L

Values associated with increased cancer risks

P = 0.0096
ubiquinone or CoQ10 (implicated in energy production)

CHU reference values: 0.3 – 1.39 mg/L

Effect of statins?

P = 0.014
Zinc

**CHU reference values**: 0.7 – 1.20 mg/L

<table>
<thead>
<tr>
<th>Group</th>
<th>mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>control</strong></td>
<td>0.8</td>
</tr>
<tr>
<td>AAA &lt; 50 mm</td>
<td>0.6</td>
</tr>
<tr>
<td>AAA &gt; 50 mm</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*P = 0.0035*
copper/zinc (prooxidant marker)

CHU reference values: 1 – 1.17

P = 0.046
relationship between Cu/Zn ratio and blood lipid peroxides in AAA patients

\[
y = 675.21x - 325.26
\]
\[
R^2 = 0.6698
\]
selenium

CHU reference values: 94 – 130 µg/L

P = 0.0038
isoprostanes

P = 0.052
ruptured AAA on arrival at hospital

Lindsay et al. J Vas Surg 30:219-228, 1999

elective AAA

F2-isoprostanes (pg/ml)

0 40 80 120 160 200

PI  PR  15 MIN  1 HR  D1  D3  D5

EAAA  RAAA
## Correlation between Aneurysm Diameter and OS Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C (µg/mL)</td>
<td>-0.45</td>
<td>0.01</td>
</tr>
<tr>
<td>β-carotene (mg/L)</td>
<td>-0.41</td>
<td>0.01</td>
</tr>
<tr>
<td>Zinc (mg/L)</td>
<td>-0.57</td>
<td>0.01</td>
</tr>
<tr>
<td>Copper/zinc ratio</td>
<td>0.43</td>
<td>0.01</td>
</tr>
<tr>
<td>Selenium (µg/mL)*</td>
<td>-0.44*</td>
<td>0.01</td>
</tr>
</tbody>
</table>

No correlation for the other investigated parameters


\[ r = -0.382 \]
conclusions (I)

1° when compared to control group, the blood concentration of some important actors (vitamin C, β- carotene, selenium, zinc, ubiquinone) implicated in the antioxidant network is significantly reduced in AAA patients

2° the antioxidant network is more affected in patients having a AAA size > 50 mm than those with an AAA size < 50 mm
conclusions (II)

3° there is a significant negative correlation between these parameters and the AAA size
   → monitoring of these biomarkers to identify AAA prone to rupture?
   → more patients to be studied

4° more attention must be given to the measurement of isoprostanes as a specific marker of lipid peroxidation, a process involved in the aneurysm development.
conclusions (III)

5° the weakening of the antioxidant defences may suggest that an antioxidant therapy could be beneficial to AAA patients.

- in angiotensin II-infused apolipoprotein E-deficient mice, vitamin E inhibits AAA formation (Gavrilla et al. 2005)

- in a rat model, vitamin E reduces 8-isoprostane content and aortic macrophage infiltration in AAA tissues (Nakahashi et al. 2002)
conclusions (III)

5° the weakening of the antioxidant defences may suggest that an antioxidant therapy could be beneficial to AAA patients.

- by contrast, in a controlled trial, vitamin E or β-carotene supplementation did not have a preventive effect for large sized AAAs among male smokers.

(Törnwall et al. 2001)