Oxygen toxicity

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Runtime: 30 min
Slides: 31
Video clips: 2
Oxygen toxicity

Symptoms of Oxygen toxicity

- Eyes
  - Visual field loss
  - Near-sightedness
  - Cataract formation
  - Bleeding
  - Fibrosis
- Muscular
  - Twitching
- Central
  - Seizures
- Respiratory
  - Jerky breathing
  - Irritation
  - Coughing
  - Pain
  - Shortness of breath
  - Tracheobronchitis
  - Acute respiratory distress syndrome
What is a radical?

Atom or molecule with one or more unpaired electrons in its outer shell

\[
\begin{align*}
\text{O}_2 & \rightarrow e^- \rightarrow 2\cdot\text{O}_2^- \\
2\cdot\text{O}_2^- & \rightarrow 2e^- + 2\text{H}^+ \rightarrow 2\text{H}_2\text{O}_2 \\
\text{H}_2\text{O}_2 & \rightarrow e^- + \text{H}^+ \rightarrow 2\cdot\text{OH}
\end{align*}
\]

- Superoxide anion
- Hydrogen peroxide
- Hydroxyl radical

Oxygen and other Reactive Oxygen Species

- Oxygen
- Superoxide anion
- Peroxide
- Hydroxyl radical

\[
\begin{align*}
\text{O}_2 & \\
2\cdot\text{O}_2^- & \\
2\text{H}_2\text{O}_2 & \\
2\cdot\text{OH} &
\end{align*}
\]
A leaky chain!
1-2% of electrons, prematurely and only partly, reduce $O_2$

Other sources of ROS:
- **enzymetic:**
  - NADPH oxidase
  - $P_{450}$ system liver
- **non enzymatic:**
  - OXPHOS
- **External:**
  - ionizing radiation
  - metals
  - chemicals
  - drugs
Superoxide anion ($O_2^-\cdot$)

- OXPHOS spill
- It has one unpaired electron
- precursor of most other ROS
  - peroxynitrite
  - hydroxyl radical
  - hydrogen peroxide

\[
\begin{align*}
\text{HO}^- \text{ (hydroxyl free radical)} \\
\end{align*}
\]
Oxidative damage
Oxygen toxicity in diving

- neurological oxygen toxicity
  - Paul Bert effect
  - > 1.6 bar, on/off, unpredictable
- pulmonary oxygen toxicity
  - Lorraine Smith effect
  - > 0.5 bar, cumulative
- ocular toxicity
  - cumulative

Also relevant for:
- astronauts
- hyperbaric oxygen treatment (HBO)
- neonates
- ventilated ICU patients
- post CPR
- during ACS
Neurological oxygen toxicity

A convulsion during diving is almost always fatal!
The problem.....

- inter individual variation in susceptibility
- intra individual variation in susceptibility
- screening on susceptibility not useful
- warning signs are unreliable
- many risk factors
- lethal
Day to day variation

- 1942-43 (Donald 1947)
- single diver 20 x
- in 3 months
- 100% $O_2$ @ 3.7 bar
- time to convulsion

$O_2$ induced twitching & convulsions
Oxygen limits in diving

- Symptoms may occur \( \text{PO}_2 > 1.4 \)
- No convulsions \( < \text{PO}_2 1.3 \)
- 4 hours 100% \( \text{O}_2 \) at 7 meter = \( \text{PO}_2 1.7 = \) safe
- Limit depends on situation:
  - 1.4 rec scuba diving
  - 1.6 Tec, deco stops
  - 2.5 short periods under operational circumstances (military)

\[ \text{MOD} = (14 : \text{fiO}_2) - 10 \]


### NOAA Oxygen Exposure Limits

<table>
<thead>
<tr>
<th>PO2 (atm)</th>
<th>Maximum Single Exposure (minutes)</th>
<th>Maximum per 24 hr (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.60</td>
<td>45</td>
<td>150</td>
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<tr>
<td>1.55</td>
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<td>1.40</td>
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<td>1.35</td>
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<tr>
<td>1.30</td>
<td>180</td>
<td>210</td>
</tr>
<tr>
<td>1.25</td>
<td>195</td>
<td>225</td>
</tr>
<tr>
<td>1.20</td>
<td>210</td>
<td>240</td>
</tr>
<tr>
<td>1.10</td>
<td>240</td>
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<td>1.00</td>
<td>300</td>
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<td>0.90</td>
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<td>0.80</td>
<td>450</td>
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<tr>
<td>0.70</td>
<td>570</td>
<td>570</td>
</tr>
<tr>
<td>0.60</td>
<td>720</td>
<td>720</td>
</tr>
</tbody>
</table>

Source: NOAA

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Exact mechanism of NOTOX is not well understood but...

- rise in free radical levels in the blood during hyperoxia.
- free radical generation in the brain precedes hyperoxia induced convulsion
- directly by affecting cell membrane (especially PUFA’s), ion channels, membrane transporters and receptors
- affecting both inhibitory and excitatory neurotransmitters
Neurotransmitters

• increased spontaneous neurotransmitter release
• disbalance between inhibitory and excitatory neurotransmitters
• affects:
  – GABA
  – acetylcholine
  – glutamate
  – dopamine
  – ammonia
  – norepinephrine
  – aspartate
• Protection!

• Almost all vascular beds:
  – brain, heart, skeletal muscle, retina, skin, kidney
  – linear effect

• 2 exceptions:
  – hypoxic pulmonary vasoconstriction
  – maternal – placental circulation
Cerebral vasoconstriction

(b) Change in CBF in response to transient hyperoxia

Percentage decrease in CBF

Minutes

FiO₂ = 1.0

Radicals and NO

L-Arg → NOS → NO → O2⁻ → ONOO⁻ → cGMP

Superoxide anion scavenges NO


CBF biphasic response

- initial vasoconstriction due to decreased NO levels
  - NO scavenging
- secondary increase (hyperemic phase)
  - upregulation of cNOS & eNOS

Cerebral vasoconstriction breakthrough

- hyperoxia causes general vasoconstriction
- cerebral vasoconstriction protects the brain against free radicals and excitatory neurotransmitters
- breakthrough (vasodilation) explains sudden onset of convulsions
  - upregulation cNOS & eNOS
  - local depletion antioxidants
  - hypercapnia/ exertion

The big picture

Hyperoxia

- radicals

NO scavenging

- cerebral vasoconstriction
- cerebral vasodilation

brain radicals

- damage:
  - lipid bilayer
  - receptors
  - channels

- disbalance inhibitory/excitatory neurotransmitters

- convulsion
- ventid

eNOS & cNOS upregulation

hypercapnia exercise

antioxidant depletion
• variation in incidence of symptoms of NOTOX
• PADI: VENTID
• progression to convulsion may be halted by decreasing $PO_2$

probable symptoms:
• nausea (N)
• dizziness (D)
• headache
• disorientation
• Irritability (I)
• light-headedness
• apprehension

definite symptoms:
• blurred vision (V)
• tunnel vision (V)
• tinnitus (ringing ears) (E)
• irregular breathing
• twitching; lip, mouth, eye (T)
• convulsions

Bitterman N. CNS toxicity. UHM 2004;34: 63-71
Convulsion

• generalize tonic-clonic (grand mal)
• disappear upon reducing $PiO_2$
• no neurological damage (hyper oxygenation)
• probably focal origin due to local variations in:
  – cerebral bloodflow
  – amino acids levels
  – lipid peroxide distribution
  – anti oxidant levels
Risk factors

- hypercapnia
- exercise
- darkness
- circadian rhythm
- drugs

Theoretical!
Protective (GABA):
benzo’s, C₂H₅OH
A seizure during diving

• is usually fatal!
• problem technical + military divers
• traditional teaching:
  – wait for convulsion to die down and then ascend
  – ascend during convulsion > lung rupture + CAGE
  – US Navy manual advice: wait
• control buoyancy with the victims BCD
• don’t go up yourself if you have a deco obligation!
Maximum operating depth (MOD)

active: max $pO_2 = 1.4$

passive: max $pO_2 = 1.6$

<table>
<thead>
<tr>
<th>Maximum Operating Depth</th>
<th>$PO_2 = 1.4$</th>
<th>$PO_2 = 1.6$</th>
</tr>
</thead>
<tbody>
<tr>
<td>21%</td>
<td>56 m</td>
<td>66 m</td>
</tr>
<tr>
<td>32%</td>
<td>33 m</td>
<td>40 m</td>
</tr>
<tr>
<td>50%</td>
<td>18 m</td>
<td>22 m</td>
</tr>
<tr>
<td>80%</td>
<td>7 m</td>
<td>10 m</td>
</tr>
<tr>
<td>100%</td>
<td>4 m</td>
<td>6 m</td>
</tr>
</tbody>
</table>
• less $N_2$ to decrease nitrogen narcosis
• less $O_2$ to minimize risk $O_2$ toxicity

• Example: dive to 110 m!
  – $O_2$ 10% > $pO_2 = 1.2$ bar
  – He 50%
  – $N_2$ 40% > $pN_2 = 3$ bar (EAD 28 m)
Deco gasses for a 100 msw dive
Yes.... personal record!
oxygen affects the whole body
in diving we look at CNS & pulmonary toxicity
neurological toxicity is lethal during diving!
toxicity can be avoided by proper dive planning (depth, mix and time)
Thank you for listening