Hyperbaric Medicine in Neurological Disease

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No Disclosures!
“The bends” caused annual mortality of 25% of caisson workers on the East Hudson tunnel.
78 y/o male with aortic valvular dysfunction and atrial fibrillation underwent AoVR with root replacement and MAZE procedure with left atrial ligation. Postoperatively found to have flaccid left hemiparesis with myoclonic jerking. CT perfusion study showed decrease in cerebral blood flow in the right hemispheric white matter c/w watershed pattern. Neurological consultation: Course c/w arterial gas embolism.

Patient currently three months after event with residual left hemiparesis with dysphagia requiring tube feeds, pressure ulcers, indwelling urinary catheter, atrial fibrillation, orthostatic hypotension and inability to transfer.
Gas Embolus Epidemiology

- May occur autochthonously from decompression injury or externally from iatrogenic introduction
- May be venous, or arterial if shunt or pulmonary filtration overwhelmed
- Incidence of macrovascular CAGE during cardiac bypass surgery ~ 0.1%
- 2.65/100,000 hospitalizations, with 1-year mortality 21%

Bessereau J et al Intensive Care Med 2010; 36: 1180-7
Iatrogenic Gas Embolus Causes

- **Highest risk surgeries:**
  - Seated craniotomy
  - C-section
  - Hip replacement
  - Cardiac bypass

- **Other causes:**
  - Central or peripheral IV leak
  - Pulmonary/ventilator barotrauma
  - Insufflation
  - TURP/prostatectomy
  - Upper airway laser YAG laser
  - Lung biopsy
  - Contrast injection
  - Carotid endarterectomy
### Iatrogenic Causes of Gas Embolization

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Hennepin County</th>
<th>Marseille</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVC leak or removal</td>
<td>9</td>
<td>56</td>
</tr>
<tr>
<td>Cardiac bypass</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Carotid injection</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Lung biopsy</td>
<td>2</td>
<td>other = 11</td>
</tr>
<tr>
<td>Pulmonary barotrauma</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

- 8 of 9 with venous AGE source had CXR changes c/w pulmonary edema vs 0 of 9 with arterial source
- Only 26% of head CTs or TTEs showed intravascular gas
- All patients with GCS = 3 before HBO2 died

Bubble Injury in Gas Embolus

• Threshold for venous-to-arterial air to cerebral circulation without PFO:
  • > 20 ml bolus or
  • 11 ml/min infusion
Bubble Injury

- Mechanical occlusion with downstream hypoxia
- PMN adhesion and degranulation with vessel injury and activation of inflammation with resultant edema

Areas of bubble migration reflect cardiac output to end organs.
Cerebral emboli typically involves 30-60 micron dia small arteries

From: Muth CM, Shank ES. NEJM 2000;342:476-82
## Causes and Treatment of Gas Embolism

<table>
<thead>
<tr>
<th>Cause</th>
<th>Venous gas embolism</th>
<th>Paradoxical embolism</th>
<th>Arterial gas embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Central line manipulation&lt;br&gt;Seated craniotomy&lt;br&gt;Barotrauma&lt;br&gt;Laparoscopy</td>
<td>Right → Left Shunting</td>
<td>Paradoxical embolism Injection of air during imaging procedures&lt;br&gt;Surgery&lt;br&gt;Lung biopsy&lt;br&gt;Cardiac bypass&lt;br&gt;Hemodialysis&lt;br&gt;Central line introduction&lt;br&gt;Others</td>
</tr>
<tr>
<td>Treatment</td>
<td>100% Oxygen</td>
<td>Hyperbaric Oxygen</td>
<td>Hyperbaric Oxygen</td>
</tr>
</tbody>
</table>

Immediate effect:

Reduces bubble size and decreases vascular occlusion
Effect of Pressure on Bubble Size

Percent

Atmospheres Absolute

- Surface Area
- Volume
Non-immediate effects:

- Increases $O_2$ – bubble gradient, leading to exchange of metabolically active $O_2$ for $N_2$
- Increases $O_2$ to ischemic tissue
- Decreases PMN adhesion and vascular damage by down-regulating ICAM-1/beta-integrin receptors
- Decreases cerebral edema and ICP
Diagnosis of CAGE

- Imaging insensitive
- Clinically
  - Prolonged anesthesia recovery
  - Cardiac arrest
  - Hemiparesis, especially left–sided
  - Decreased LOC
  - Hypotension
  - Chest pain/dyspnea/Cheyne-Stoke breathing
  - “Mill wheel” splashing murmur
  - ?Transcranial doppler
Time to Hyperbaric Oxygen Treatment of Gas Embolus and Outcome: Conventional Wisdom

Full recovery or minor sequelae in 83% of gas emboli treated within 6 hours vs 53% with greater delay.

No difference in outcome with delay in arterial gas embolization.

[N = 86; Recovery = 67% venous, 35% arterial]

But:

<table>
<thead>
<tr>
<th>Delay</th>
<th>&lt;6 Hours</th>
<th>&gt;6 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Venous</td>
<td>84%</td>
<td>16%</td>
</tr>
<tr>
<td>% Arterial</td>
<td>53%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Ref: Blanc P. Intensive Care Med 2002; 28: 559
### Time to Hyperbaric Oxygen Treatment of Gas Embolus and Outcome

<table>
<thead>
<tr>
<th>REF</th>
<th>N=</th>
<th>Clinical / Diver</th>
<th>Average Delay</th>
<th>% Fully Recovered</th>
<th>% Mortality/Severe Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leitch &amp; Green, 1986</td>
<td>89</td>
<td>D</td>
<td>&lt;10 min</td>
<td>65%</td>
<td>1% / 16%</td>
</tr>
<tr>
<td>Pearson &amp; Goad, 1982</td>
<td>5</td>
<td>D</td>
<td>20 min</td>
<td>80%</td>
<td>20% / 0</td>
</tr>
<tr>
<td>Kol et al 1993</td>
<td>6</td>
<td>C</td>
<td>3 h [2-20]</td>
<td>50%</td>
<td>33% / 17%</td>
</tr>
<tr>
<td>Blanc et al 2002</td>
<td>86</td>
<td>C</td>
<td>3.5 h [2-8]</td>
<td>58%</td>
<td>8% / 9%</td>
</tr>
<tr>
<td>Murphy et al 1985</td>
<td>16</td>
<td>C</td>
<td>8 h [0.2-25]</td>
<td>50%</td>
<td>12% / 6%</td>
</tr>
<tr>
<td>Neuman % Hallenbeck, 1987</td>
<td>4</td>
<td>D</td>
<td>9 h [1-15]</td>
<td>75%</td>
<td>0 / 0</td>
</tr>
<tr>
<td>Ziser et al, 1999</td>
<td>17</td>
<td>C</td>
<td>9.6 h [1-20]</td>
<td>47%</td>
<td>18% / 35%</td>
</tr>
<tr>
<td>Takahashi et al, 1987</td>
<td>34</td>
<td>C</td>
<td>13 h [0.5-40]</td>
<td>62%</td>
<td>24% / 0</td>
</tr>
<tr>
<td>Massey et al, 1990</td>
<td>14</td>
<td>C</td>
<td>17.5 h [1-48]</td>
<td>50%</td>
<td>22% / 14%</td>
</tr>
<tr>
<td>Betterman &amp; Melamed, 1988</td>
<td>6</td>
<td>C</td>
<td>24 h [11-60]</td>
<td>33%</td>
<td>33% / 0</td>
</tr>
<tr>
<td>Muskat et al, 1995</td>
<td>4</td>
<td>C</td>
<td>26 h [3-48]</td>
<td>75%</td>
<td>25% / 0</td>
</tr>
</tbody>
</table>

Ref: Van Hulst RA, Klein J, Lachmann B.  
Clin Physiol Funct Imaging 2003; 23:237
Adjunctive Treatment of CAGE

- Avoid glucose-containing IV fluids
  (Lanier WL et al Anesthesiology 1987; 66:39)

- Avoid steroids *(may increase ischemic injury)*

- Avoid heparin *(? Decreases injury in animal models, but fear of ICH)*

- Use phenobarbital *(Decreased O2 demand, decreases ICP, decreases catecholamine release)* and phenytoin

- Consider lidocaine 1.5 mg/kg load then gtt
  *(Reduces infarct size in animal models with decreased cognitive loss if give for 48 h after valve replacement surgery (Mitchell, 1999))*
Case #1: 78 y/o diabetic woman presents with fever, facial paralysis and right retroorbital pain two weeks after right-sided otalgia and otorrhea. A small cholesteotoma and a large amount of granulation tissue were observed in the EAC. She had received several short “courses” of antibiotics, but continued to be febrile. Two months after first noticing the fever and pain, she was transferred to a referral center and in early August a CT showed A/F level in the mastoid with “thickening” of the middle ear space. No bony erosion was noted. She underwent a surgical debridement, with negative bacterial cultures. When 8 weeks of treatment with Unasyn did not improve her pain and fever, she was transferred to VMMC.
Temporal bone CT 10/02/04 showed right OE and OM, marked sclerosis of the mastoid remnant, medial inferior temporal and sphenoid bone, erosion of the right mandibular head, and cortical thinning of the clivus.

$^{99}$Tc scan 10/05/04 showed increased uptake in right mastoid region and clivus, but SPECT not done due to patient movement. Findings similar found on $^{67}$Ga citrate scan at the same time.
Otogenic Skull Base Osteomyelitis

- Usually in elderly diabetics
- Male:female ratio 1:1
- Trivial trauma such as hearing aids lead to portal (?)
- Usually occurs weeks to months after NEO treatment
- *Pseudomonas aeruginosa* is such a predominate pathogen that empirical treatment is justified
- No standard duration for therapy, but is no longer a surgical disease
Otogenic Skull Base Osteomyelitis: Presentation

- Follows NEO by weeks to months
- Spreads not through aerated bone, but by septic venous thrombosis and along subfascial planes, so cranial nerve presentation can be early
- Persistent pain, usually headache, is most frequent symptom. Residual otalgia, otorrhea, hearing loss may be present, along with new CN deficits
- Fever, like in NEO, usually absent
- Tenderness may be less than in NEO
- WBC infrequently elevated, ESR elevated in majority
**Otogenic Skull Base Osteomyelitis**

<table>
<thead>
<tr>
<th>Cranial Nerve</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII NEO local effect</td>
<td>Facial paresis</td>
</tr>
<tr>
<td>X Foraminal effect</td>
<td>Dysphonia, dysphagia</td>
</tr>
<tr>
<td>XI</td>
<td>Shoulder weakness</td>
</tr>
<tr>
<td>IX</td>
<td>Choking, aspiration, vocal weakness</td>
</tr>
<tr>
<td>V</td>
<td>Sensory effects/neuralgia</td>
</tr>
<tr>
<td>III, IV, VI</td>
<td>Diplopia</td>
</tr>
</tbody>
</table>
Cerumen pH is increased to ~7.0

PMNs exhibit impaired chemotaxis and phagocytosis

Monocytes and macrophages have decreased phagocytosis

Decreased oxidative burst and killing

Defects are not reversed by tight glycemic control
Skull Base Osteomyelitis: Etiology

• Malignant otitis externa
• Bacteremia/sphenoiditis/tuberculous petrositis
• Penetrating (usually) trauma
• Fungal otic invasion
• Paranasal sinus contiguous spread
Non-otogenic Skull Base Osteomyelitis

- No pathognomonic signs or imaging; surgery to r/o neoplasm is the rule
- Staph aureus the most common bacterial agent. Coag – Staph, Candida, and Pseudomonas next in frequency
- Patient often bacteremic and toxic, with prominent fever and early CN signs (particularly VI)
- IDU is frequently reported in bacteremic sphenoiditis

**NEO vs SBO**

<table>
<thead>
<tr>
<th>NEO</th>
<th>SBO</th>
</tr>
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<tbody>
<tr>
<td>Otalgia</td>
<td>Headache</td>
</tr>
<tr>
<td>Otorrhea</td>
<td>Worsened hearing loss</td>
</tr>
<tr>
<td>Swelling</td>
<td>Afebrile</td>
</tr>
<tr>
<td>Afebrile</td>
<td></td>
</tr>
<tr>
<td>Point tenderness</td>
<td></td>
</tr>
</tbody>
</table>

Chandler: “Marked tenderness is invariably present on palpation between the mastoid process and the ascending ramus of the mandible just beneath the external auditory canal.”
Skull Base Osteomyelitis: Complications

- Foraminal syndromes and CN paresis
- Sigmoid/cavernous sinus thrombosis
- Meningitis/brain abscess

Relapses can occur over a year after treatment

Ref: Amedee RG, Mann WJ. Am J Otolaryngol 1989; 10(5): 402-4
Otogenic Skull Base Osteomyelitis

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- Male:female ratio 1:1
- Trivial trauma such as hearing aids lead to portal (?)
- Usually occurs weeks to months after NEO treatment
- Pseudomonas aeruginosa is such a predominate pathogen that empirical treatment is justified
- No standard duration for therapy, but is no longer a surgical disease
**Pseudomonas aeruginosa**

- Predominant, but not exclusive, agent in otogenic SBO
- Gram-negative, facultative aerobe
- Only species of 25 human Pseudomonas pathogens to produce SBO
- Produces elastase, collagenase and (like Staph aureus) can run through cartilage
- Can produce mucoid capsule which inhibits phagocytosis
- Highly aggressive in neutropenia
- Like Staph aureus, produces ecthyma gangrenosum
- Has multiple mechanisms of antimicrobial resistance
- Can develop quinolone resistance during therapy
McRipley and Sbarra showed that phagocytic killing of Ps. aeruginosa is reduced in hypoxic conditions [J Bacteriol 1967; 94: 1417-24]

Produces several toxins, one of which may have clinically significant neurotoxic activity
Quinolones in NEO/SBO

- Achieve 7-9x concentration in bone
- High post-antibiotic effect
- Ciprofloxacin > levofloxacin ~ gatifloxacin, moxifloxacin
- Increasing proportion of Pseudomonas aeruginosa now resistant

<table>
<thead>
<tr>
<th>High Resistance Potential</th>
<th>Low Resistance Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
<td>Piperacillin</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Cefepime</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Meropenem</td>
</tr>
<tr>
<td>Imipenem</td>
<td>Polymixin B</td>
</tr>
</tbody>
</table>

Ref: Cunha B. *Pseudomonas aeruginosa* resistance and therapy. Semin Respir Infect 2002; 17(3): 231-9
Theoretical Rationale for Adjunctive HBO2 in Osteomyelitis

- Direct killing of superoxide dismutase-deficient (anaerobic) organisms by higher intra- and extracellular oxygen radicals/superoxide
- Enhanced phagocytic killing
- Enhances antimicrobial activity of aminoglycosides and possibly vancomycin
- Increases fibroblast activity
### Effects of Tobramycin and Hyperbaric Oxygen on Experimental Pseudomonas aeruginosa Osteomyelitis

Log of quantitative bacterial counts in rabbit tibia model

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.24±0.19</td>
<td>5.40±0.22</td>
<td>6.00±0.19</td>
</tr>
<tr>
<td>HBO2</td>
<td>5.74±0.29</td>
<td>5.81±0.31</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>4.89±0.34</td>
<td>4.27±0.31</td>
<td></td>
</tr>
<tr>
<td>Tobramycin + HBO2</td>
<td>3.92±0.50</td>
<td>3.38±0.27</td>
<td></td>
</tr>
</tbody>
</table>
