Adjunctive Hyperbaric Oxygen Therapy in the Lower Extremity

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Who has been in a hyperbaric chamber?
Everyone in this room has been in a hyperbaric chamber.... compressed to 8000 ft
The Delivery Systems

Monoplace Chamber
Single patient

Multiplace Chamber
Accommodates 12 patients
What is Hyperbaric Oxygen?

- In order for Hyperbaric Oxygen to be effective, it must be **inhaled**
- The patient is entirely enclosed in a pressure chamber, breathing oxygen at greater than one atmosphere (1.3 ATA)

- Therefore, sleeves and the like do not work
- Oxygen does not diffuse into the tissues enough to provide the necessary oxygen for wound healing
  - In order for that to happen even marginally, the patient’s extremity must be compressed with so much pressure that it would tourniquet the extremity, impeding blood flow to an already critical limb
Oxygen Transport

- Plasma
  - 2% Oxygen is carried in plasma and the water of the RBC

- Red blood cells
  - 98% is reversibly bound to hemoglobin
Direct effect of pressure and oxygen = hyperoxygenation

- Oxygen content of the blood is comprised of oxygen carried by hemoglobin + oxygen carried in plasma
  - Arterial oxygen content = 1.34 (Hg)(%saturation) + 0.003(PaO2)
- Oxygen is bound to hemoglobin and physically dissolved into plasma
- The O2 carrying capacity in the blood from hemoglobin is only increased by addition more hemoglobin, that is a blood transfusion
- Under normobaric conditions the arterial oxygen content is 20.4 vol%
- Under normal metabolic extraction, venous oxygen content is 14 vol%

6 vol% is extracted
Under normal conditions resting tissues extract 50 mL O₂ /L blood (or 6 vol%) 

Under hyperbaric conditions 3 ATA plasma levels reach 72 mL O₂ /L blood (or 26 vol%) 

Therefore, after one pass the oxygen needed can be extracted from the plasma, hence.....Ite Boerema, MD in 1956 published “life without Blood” J Cardiovascular Surgery
## Relationship Between Respiratory Gas and Blood PO2

<table>
<thead>
<tr>
<th>Atmospheric Pressure (ATA)</th>
<th>Breathing Gas</th>
<th>FiO2 (mmHg)</th>
<th>Theoretical Alveolar &amp; Arterial PO2 (mmHg)</th>
<th>Measured Arterial PO2 (mmHg)</th>
<th>Measured Venous PO2 (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>Air</td>
<td>160</td>
<td>110</td>
<td>89 +/- 3.2*</td>
<td>41 +/- .9*</td>
</tr>
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<tr>
<td>1.0</td>
<td>100% O2</td>
<td>760</td>
<td>673</td>
<td>507 +/- 13.9</td>
<td>57 +/- 3.5</td>
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</tr>
<tr>
<td>3.0</td>
<td>100% O2</td>
<td>2280</td>
<td>2193</td>
<td>1721 +/- 33.5</td>
<td>424 +/- 77.8</td>
</tr>
</tbody>
</table>

* +/- one standard error

Mean blood levels measured in 10 normal subjects (modified from Saltzman, Smith et al, 1965)
Important to remember this concept with disease processes that have narrowed vessels, or have flaws in the autonomic regulatory process.
Graham’s Law describes the result of hyperoxygenation at the tissue level being that the physically dissolved O2 in the plasma equilibrates with the O2 tensions in the tissue fluids to provide an O2 rich environment for tissue metabolism.
Applications of Hyperoxygenation

- Improved oxygen delivery in low flow states
  - Peripheral arterial disease
    - Improved oxygen delivery across relative barriers by mass effect, down a concentration gradient
      - drive O2 across relative barriers such as cicatrix and edema

http://lucytomkinson.blogspot.com/2011/03/capillary-action-further-tests.html
Secondary Mechanisms

- Vasoconstriction
- Host Cellular Responses
  - Fibroblast function
  - White blood Cell oxidative killing
  - Microbiological Effects, static and cidal
    - Toxin effect
  - Angiogenesis/Vasculogenesis
  - Osteogenesis
- Reperfusion Injury Mitigation
- Stem Cell Recruitment
HBO Secondary Mechanisms

- **30-40 mmHg O2** tensions are required for appropriate fibroblastic function.
- When wound healing is considered, the concept of gradient is fundamental.
- Often the center of a wound is anoxic, the margins are normally oxygenated.
- Within those margins fibroblastic activity continues.
In an ACUTE wound the gradient is steep.

**Normal Wound**

Steep oxygen gradient from well-perfused wound margin to hypoxic wound center.
In a CHRONIC wound the gradient is shallow

**Hypoxic Wound**

Steep oxygen gradient is now a shallow one
Secondary Mechanisms
Fibroblast Function

- The fibroblast forms collagen, which provides a substrate for the keratinocytes to epithelialize the wound healing.
  - This is oxygen dependent and impacts both secretion of collagen and crosslinking of triple helix
  - Angiogenesis is dependent on the matrix secreted by the fibroblast.
  - Angiogenesis and fibroblastic migration into the oxygenated area breaks down the anoxic gradient.
Secondary Mechanisms

- Fibroblastic proliferation is both O2 dependent and age dependent. With increasing age, the rate of fibroblasts multiply decreases.
- Hyperbaric O2 mitigates the age differences in fibroblast doubling times.
- Vascular endothelial growth factor (VEGF) is O2 dependent and is an inducer and signaling device for angiogenesis
  - 40% increase with HBOT
Age associated differences in cellular proliferation (in vitro)…

![Graph showing age-related differences in cellular proliferation.](image)

- **New born (NB)**
- **Young adult (YA)**
- **Old adult (OA)**

(Renstra, UHM Supplt 25:51 #157 1998)
HBO Dramatically Increases Old Adult Fibroblast Proliferation…

(Renstra and Buras, Harvard Medical School, MGH, Boston)
Decreased cellular proliferation with diabetes…

(Reenstra and Buras, Harvard Medical School, MGH, Boston)
HBO Dramatically Increases Diabetic Fibroblast Proliferation…

(Renstra and Buras, Harvard Medical School, MGH, Boston)
Induction of PDGF receptors on cells in wound treated with HBO.
Osteoclast Function

• Bone resorption is an O2 dependent
• The osteoclast is responsible for resorption of dead and infected bone.
• The osteoclast is instrumental in the resorption and remodeling of bone as is required for fracture healing, bone strengthening in responses to mechanical stresses and managing osteomyelitis.
• The osteoclast’s metabolic activity in bone resorption is 100 times greater than that of the bone-building cell the osteoblast.
• Often, resorption of infected bone is observed only after HBO treatments are started.
Effects of HBO on fracture healing

HBO Secondary Mechanisms
Neutrophil Functions: Infection

- If O2 tensions are not **30-40mmHg** in the fluids surrounding the neutrophil, these radicals are not generated and oxidative killing of the bacteria does not occur.
- During the respiratory burst when the bacteria are killed in the phagosomes by reactive O2 species generated by these organelles, O2 consumption increases as much as 100 fold.
Trauma was the basis of most injury

- Local response to trauma
  - Stop the bleeding (clotting)
  - Clear tissue debris (gradual clearing of clot and
  - Re-establish normal function (or close to it)

- When Plan A fails (clotting), Plan B
  - Vasoconstriction

- Reperfusion injury
Polymorphonuclear Leukocytes: Reperfusion Injury

- Have inducible nitric oxide synthase (iNOS)
- PMNL CD 11/18 provide strong adhesion to the endothelial cells
- Release of destructive proteolytic enzymes
- After endothelial transmigration is source of free radicals that enhance tissue destruction
Leukocyte adhesion increases with time of reperfusion..so you have a window in which to effect attenuation of the injury

Figure 4. Representative images of leukocyte interactions in pial microcirculation of a sham-operated mouse and in mice which underwent 1-hour MCA occlusion and 12 or 24-hour reperfusion. Sham-operated animals show minimal leukocyte adhesion. Scale bar 50 μm.


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HBO attenuates the reperfusion injury

- Reduces adhesion of CD11/18 to activated ICAM-1 on the endothelial wall
- Discrete effect, lasting about 8 hours
- HBO does not permanently inactive the PMN (monoclonal antibody therapy)
Attenuation of Reperfusion injury...rolling, rolling, rolling

http://www.acssurgery.com/acssurgery/secured/hgTabPopup.action?bookId=ACS&linkId=part08_ch27_hg2&type=fig
HBO Mechanism of Action

- HBOT stimulates stem cells to produce and release growth factors
- Vasculogenic stem cells are induced by HBOT and are mobilized to areas of wounding (vasculogenesis results from de novo generation of new vessels from circulating endothelial precursor cells)

Thom, et al., Vasculogenic stem cell mobilization and wound recruitment in diabetic patients: Increased cell number and intracellular protein content associated with hyperbaric oxygen therapy. 2011 Wound Rep Reg; 19:149-61
Stem Cells and HBO

- HBO seems to mobilize stem cells from the bone marrow
- HBO does not appear to also elevate circulating leukocyte counts - not thrombogenic
- Higher pressures seem to have more effect 2.4 ATA > 2.0 ATA

Dr. Thom "This [hyperbaric oxygen] is the safest way clinically to increase stem cell circulation, far safer than any of the pharmaceutical options."
Wound healing essentials: Let there be oxygen

- Energy metabolism
- Angiogenesis
- Collagen deposition
- Epithelialization
- Phagocytosis
- Superoxide radical production for bacterial killing
HBO under pressure is a drug

- Effect dose dependent
- Timing important
- Discrete effect, which does not render PMNL permanently inactive
DM; 52 y.o, s/p 5th Ray after trauma, developed necrotic tissue

- Had contralateral BKA
- No osteomyelitis
- Decided to start enzymatic debridement
- April 21, 2004
Enzymatic Debridement

April 21, 2004
2004

April 29, 2004
Ultrasonic debridement & Hyperbaric Oxygen
Regranex

Combination HBO, debridement, growth factors
Coaching soccer
Coaching Soccer
October 16, 2013
40 yo male with HO NIDDM stepped on a nail. Developed Osteomyelitis and required surgery with bone extraction.
IV antibiotics, HBO, Bioengineered skin equivalents and a total contact casting used.
Patient was healed in 4 weeks. Original depth of the wound was 3cm.
ACUTE ARTERIAL THROMBOSIS

40 y.o. s/p bunionectomy, three days post surgery to podiatrist office (on a Friday)
ACUTE ARTERIAL THROMBOSIS

Admitted to vascular surgery, anti-coagulated, referred for HBO, vascular surgeon was contemplating transmetatarsal amputation.
5 weeks after the injury the patient had only lost the nail on the great toe, and had an intact foot.
Acute Arterial Thrombosis...bad to

- 42 year old, no medical history, has bunionectomy and hammertoe surgery
  JANUARY 2, 2012

- Complained of pain postop but dressing remained intact until referred to vascular surgery 1/26/2012 with immediate HBO consult
30 HBO treatments with aggressive local wound management
Radiation to Toe for Wart as a child, presented at age 60 July 22, 1998, no HBO
After 30 HBO Treatments
Healed, at six months
88 yo female with HO STRN, and an open wound for 1 year ...
HBO started on 11/20...
Bioengineered skin used...
Wound healed on 2/5.
50 yo female with HO STRN and venous insufficiency with an open ulcer for 2 years.
HBO, compression therapy and bioengineered skin used.
Closed in 9 weeks.
HBO and the Lower Extremity

- Not just for Diabetic foot ulcers
- HBOT in chronic osteomyelitis
- Think about HBO in non-healing ulcers in irradiated fields
- Think about HBOT in crush injuries
- Think HBOT when the limb has been revascularized and the wound is not healing
The FOOT Book

By Dr. Seuss

Trick feet

Sick feet
Remember, Hyperbaric Oxygen is Not Voodoo Medicine
Adjunctive Hyperbaric Oxygen Therapy in the Lower Extremity

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