Hyperbaric Medicine for Hound Healing

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Hyperbaric Medicine and Wound Care Clinic
Objectives

By the end of this lecture, attendees should be able to:

- Describe the history of hyperbaric medicine
- Describe conditions where hyperbaric oxygen therapy can improve patient outcomes
- Associate the mechanisms of hyperbaric oxygen therapy with the conditions for which hyperbaric oxygen therapy has been shown to improve patient outcomes
- Identify patients for whom hyperbaric oxygen therapy may be helpful

I have no relevant financial relationships to disclose
A BRIEF HISTORY OF HBO
Henshaw 1662

- First recorded attempt to use changes in atmospheric pressure for a therapeutic effect
- Inspired by salutary effects associated with changes in climate (elevation)
Henshaw 1662

- “Domicilium”
  - Sealed room attached to a pair of organ bellows
  - Atmosphere could be “condensed” or “rarified” by compressing or decompressing the room

- Condensed atmosphere used to treat “acute” conditions
- Rarified atmosphere used to treat “chronic” conditions

“In times of good health this domicilium is proposed as a good expedient to help digestion, to promote insensible respiration, to facilitate breathing and expectoration and consequently, of excellent use for prevention of most affections of the lungs”
Late 19th Century

- Available in most European cities
- Advertised like health spas
Forlanini 1875

- Specialized in the treatment of tuberculosis and other respiratory disorders
- Started a “pneumatic institute” in Milan, Italy
- Credited with the creation of the first horizontal hyperbaric chamber
The Industrial Revolution

- Coal replaced wood as the primary fuel source
- The search for coal led miners to deposits beneath the Loire River and quicksand
- Mine shafts rapidly filled with water
Caisson Work

- French for “box”
- Some caissons were pressurized to as high as 4.25 atm abs (107 fsw equivalent)
- Typical work shifts were 4 hours (240 min)
Triger c. 1850

- French paleontologist and mining engineer
- Designed inter-connecting 5-foot diameter circular steel rings
- Weight of the steel rings forced its way deeper into the soft bottom of the riverbed as sand and earth was excavated
- Additional rings added until the shaft reached the coal deposits
- Air lock installed at the top
- Compressed air introduced into shaft to force water and moist sand out
Triger’s notes after exposure

“Knee pain appeared in the left side, and we felt a rather severe painful discomfort for several days… After we were quite free of these pains, we were anxious to try the experiment again. At the same hour, this is, 20 hours our exit from compressed air, we felt in the right side pains just like the former ones, which kept us numb for four or five days”
Eads Bridge 1869

- Designed and built by Captain James B. Eads
- World’s first steel arch bridge span built in St. Louis, MO to cross the Mississippi river
- First bridge to span a body of water using caissons
SECTION OF CONSTRUCTION WORKS AND MACHINERY FOR SINKING CAISSON AND LAYING MASONRY OF EAST PIER.
SECTION OF EAST PIER AND CAISSON
SHOWING THE INTERIOR OF MAIN ENTRANCE SHAFT AND
AIR CHAMBER AND WORKING OF ONE OF THE RAIN PUMPS

BED ROCK OF RIVER
Eads Bridge 1869

- Exposures within the caissons reached 4.45 atm abs (114 fsw)
- 352 workers
  - 5% died
  - 10% suffered serious symptoms of decompression sickness
Brooklyn Bridge 1870

- Spans the East River in New York
- Work began in 1870 and lasted 13 years
- Construction was supervised by Washington Roebling, who engaged an on-site physician – Dr. Andrew Smith
10.3 THE WORKING CHAMBER.

Point de Brooklyn, 1870
INSIDE CAISSON PIER II 60 FT BELOW WATER LINE
2500 LBS AIR PRESSURE TAKEN SEPT 14-88
During the 5 months of his tenure, Smith saw 110 cases of what he coined “caisson disease.”

Bedrock first encountered at 33 psig (3.24 atm abs)

At 34 psig (3.31 atm abs) there were 2 fatalities after exiting the caisson

At 35 psig (3.38 atm abs) there was a 3rd fatality

Roebling decided to halt further digging even though bedrock was not uniformly exposed across the bottom of the caisson
Brooklyn Bridge 1870

- Smith recommended that a recompression chamber be made available on site, but this recommendation was not followed.
- Roebling suffered permanent paralysis after repeated visits to the caissons and supervised the construction from his bedroom, which overlooked the construction site.
Fontaine 1879

- Created the first mobile hyperbaric chamber and surgical suite capable of holding 12 people
- Realized that nitrous oxide was more effective during pressurized surgeries
  > Fewer side effects and faster recovery times
- Died during construction of a hyperbaric surgical amphitheater designed to hold 300 people
Cunningham c. 1918

- Chairman of the Dept. of Anesthesiology at Kansas University Medical School
- Noted that the Spanish Flu pandemic’s highest morbidity and mortality were in areas of higher elevation than in coastal regions
- Borrowed a hyperbaric chamber and began treating influenza patients with promising results
The Cunningham Sanitarium

Courtesy of Stuart Miller, MD
The end of an era

- Cunningham was challenged by the American Medical Association’s Bureau of Investigation and was eventually censured in 1928
- He retired in 1935
- The “steel ball hospital” was converted to a conventional hospital but closed in 1940 and scrapped for metal in the war effort
Hyperbaric Medicine Facilities in the US

![Graph showing the increase in hyperbaric medicine facilities in the US from 1971 to 2015. The number of facilities increased significantly over time, particularly after 2000. The data is courtesy of Tom Workman.]
Monoplace hyperbaric chamber
Air break system
What is NOT hyperbaric medicine
Hybrid Chambers
Deck Diving Support Chambers

Santa Barbara City College

(photos by J. Holm)
University of Pennsylvania
Intermountain Regional Medical Center – Rectangular Chamber

Courtesy of Jim Holm, MD
St. Luke’s Medical Center, WI

Courtesy of Laurie Gesell, MD
Virginia Mason Medical Center, WA
Legacy Emanuel Medical Center
Legacy Emanuel Medical Center
Part 2

MECHANISMS OF HBO₂
## Pressure Effects

<table>
<thead>
<tr>
<th>Depth (fsw)</th>
<th>Pressure (ATA)</th>
<th>Volume (% change)</th>
<th>Diameter (% change)</th>
<th>Bubble Size</th>
<th>Bubble Length</th>
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<td>66</td>
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<td>25</td>
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<td>132</td>
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<td>165</td>
<td>6</td>
<td>17</td>
<td>55.0</td>
<td>●</td>
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</tbody>
</table>
Hyperoxygenation

- Higher amounts of oxygen are dissolved in the body
  - Hyperbaric oxygen therapy allows enough oxygen to be carried in the plasma to maintain tissue oxygenation in the absence of blood (ischemia)
OXYGEN TENSIONS WITH HBO

( mmHg )

Time (Hours)

Start HBO

Stop HBO

Blood

Muscle Subq

1 2 1 1
Hydroxygengenation

- Higher amounts of oxygen are dissolved in the body
  > Hyperbaric oxygen therapy allows enough oxygen to be carried in the plasma to maintain tissue oxygenation in the absence of blood (ischemia)

- Carbon Monoxide poisoning first treated in 1962
  > CO binds to hemoglobin 200 times stronger than oxygen, but hyperbaric oxygen can force it off of the hemoglobin

- Acute blood loss anemia
  > Patients who cannot get a transfusion right away can be kept alive with repeated treatments
Angiogenesis with $\text{HBO}_2$

- Angiogenesis is assumed based on Marx’s research on CRTI
  - Increase in capillary density as measured by TCOM
  - This mechanism has been extrapolated to other tissue locations and disease conditions
Angiogenesis in Irradiated Tissue

Effect of hyperbaric oxygen treatment on oxygen tension and vascular capacity in irradiated skin and mucosa

Effect of hyperbaric oxygen treatment on irradiated oral mucosa: microvessel density

Angiogenesis in Irradiated Tissue

Gingival Blood Flow (via LDF)  Skin Blood Flow (via LDF)

Angiogenesis in Irradiated Tissue

Enhanced Antibacterial Effects

- **White Blood Cell function**
  - WBCs bind to bacteria
  - They use oxygen based mechanisms to kill the bacteria
  - Less effective in areas with low oxygen

- **Gas Gangrene first treated in 1961**
  - Solders in WWI were treated by injecting oxygen directly into gangrenous limbs
  - Bacteria are anaerobic, so oxygen suppresses them
  - Toxin production is inhibited at high oxygen concentrations
HUMAN STEM CELL MOBILIZATION BY HBO$_2$

Am. J. Physiology 290: H1378, 2006

% CD 34+ IN GATED CELL POPULATION

n=26

2 X

8 X

- PATIENTS PREVIOUSLY EXPOSED TO RADIATION -

Slide Courtesy of Stephen Thom, MD
HBOT CAN MOBILIZE STEM CELLS:

**Slide Courtesy of Stephen Thom, MD**
Ischemia-Reperfusion Injury

- Conditions where there is period of low or no blood flow then a period where blood flow is restored
- Results in paradoxical tissue swelling and damage
  - Compromised surgical flaps and grafts
  - Carbon monoxide poisoning
- Reduces inflammation
  - Hyperbaric oxygen prevents WBCs from “sticking” to blood vessel walls after a period of low blood flow
  - “Sticky” WBCs release inflammatory factors that cause leaky blood vessels and swelling and damage
  - Has shown decreased morbidity and mortality in sepsis models
Attenuation of I-R injury

http://www.acssurgery.com/acssurgery/secured/figTabPopup.action?bookId=ACS&linkId=part08_ch27_fig2&type=fig
Binding of human neutrophils (in vitro)

![Graph showing percent adherence vs. PO2 (ATA) with data from Thom SR Am J Physiol 1997]
HBO$_2$ mechanisms for Wound Healing

- **Hyperoxygenation**
  - Decreases bubble size
- **Peripheral vasoconstriction**
- **Angiogenesis**
- **Stem cell mobilization**
- **Fibroblast proliferation/Collagen Synthesis**
- **Reduced leukocyte adhesion**
- **Reduced lipid peroxidation**
- **Edema reduction**
- **Enhanced leukocyte antimicrobial activity**
- **Antibiotic synergy**
- **Toxin inhibition**
Part 3

INDICATIONS FOR HYPERBARIC OXYGEN THERAPY
Indications for Hyperbaric Oxygen

- Decompression Sickness
- Arterial Gas Embolism
- Carbon Monoxide Poisoning
- Chronic Radiation Tissue Injury
- Selected Non-healing Wounds
  - Diabetic Wounds of the Lower Extremities
- Traumatic Peripheral Ischemia
- Chronic Osteomyelitis
- Thermal Burns
- Exceptional Blood Loss Anemia

- Gas Gangrene, Myonecrosis, Necrotizing Soft Tissue Infections
- Compromised Skin Flaps
- Acute Peripheral Arterial Insufficiency
- Intracranial Abscess

Primary Therapy

Adjunctive Therapy
Elective Indications

- These indications are usually performed on an outpatient basis
- Patients are hemodynamically stable and are often carrying out their activities of daily living
  - Treatment typically interrupts their day to day schedule
  - Many patients complain about the need to come so frequently
  - Referring physicians often undermine the treatment plan because they give in to the patient’s sense of inconvenience
- Bread and butter for hyperbaric facilities
- Evidence for some indications is stronger than for others
Elective Indications for Hyperbaric Oxygen

- Decompression Sickness
- Arterial Gas Embolism
- Carbon Monoxide Poisoning
- Chronic Radiation Tissue Injury
- Selected Non-healing Wounds
  - Diabetic Wounds of the Lower Extremities
- Traumatic Peripheral Ischemia
- Chronic Osteomyelitis
- Thermal Burns
- Exceptional Blood Loss Anemia
- Gas Gangrene, Myonecrosis, Necrotizing Soft Tissue Infections
- Compromised Skin Flaps
- Acute Peripheral Arterial Insufficiency
- Intracranial Abscess
Urgent Indications for Hyperbaric Oxygen

- Decompression Sickness
- Arterial Gas Embolism
- Carbon Monoxide Poisoning
- Chronic Radiation Tissue Injury
- Selected Non-healing Wounds
  > Diabetic Wounds of the Lower Extremities
- Traumatic Peripheral Ischemia
- Chronic Osteomyelitis
- Thermal Burns
- Exceptional Blood Loss Anemia
- Gas Gangrene, Myonecrosis, Necrotizing Soft Tissue Infections
- Compromised Skin Flaps
- Acute Peripheral Arterial Insufficiency
- Intracranial Abscess
SELECTED NON-HEALING WOUNDS (DIABETIC FOOT ULCERS)

Part 3
Diabetic Foot Ulcers

- Diabetes has a constellation of pathologies
  - Autonomic neuropathy
    - Mechanical Deformities (e.g., clawfoot and hammertoe)
  - Sensory neuropathy
    - Loss of protective sensation
  - Hyperglycemia
    - Osmotic diuresis
    - Limits neutrophil functioning
    - Increased catabolism
  - Microvascular disease
    - Lack of hyperemic response to injury
    - Decrease oxygen diffusion across basement membrane
  - Macrovascular disease
    - Increased atherosclerosis of lower extremity vessels
Timeline of Studies

RCT
- Goldman 2009
- Cochrane 2012
- Bishop-Mudge 2012
- Tiaka 2012
- Game 2012
- Wunderlich 2000
- Bakker 2000
- Senior 2000
- Cianci 1994
- Williams 1997
- Neal 2001
- Neal 2001
- Abidin 2003
- Kessler 2003
- Duzgun 2008
- Londahl 2010 (2011)
- Ma 2013
- Fedorko 2016

non-RCT
- Hart & Strauss 1979
- Barr 1984
- Emhof 1984
- Pedicini 1984
- Orlani 1992
- Wattei 1991
- Orlani 1990
- Fadila 1996
- Zamboni 1997
- Lee 1997
- Fife 2002
- Kelani 2002
- Albuquerque 2002
- Fife 2007
- Ong 2008
- Kaya 2008
- Margolis 2013
- Williams 1997
- Cianci 2004
- Cochrane 2004
- Goldman 2009
- Cochrane 2012
- Bishop-Mudge 2012
- Tiaka 2012
- Game 2012
- Liu 2013
- Londahl 2013

Review
- Liu 2013
- Londahl 2013
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>N</th>
<th>Study Population</th>
<th>Co-Morbidities Addressed</th>
<th>HBO2 Protocol</th>
<th>Strength of Evidence</th>
<th>Generalizable Results</th>
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<td>RCaS</td>
<td>11</td>
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<td>PCoT</td>
<td>18 vs 10</td>
<td>2 3 4</td>
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<td>Oriani 1990</td>
<td>RCoT</td>
<td>62 vs 18</td>
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<td>RCT</td>
<td>15 vs 15</td>
<td>3 4</td>
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<td>Atypical</td>
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<td>Low</td>
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<td>Faglia 1996</td>
<td>RCT</td>
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<td>2 3 4</td>
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<td>Zamboni 1997</td>
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<td>2.0 Daily</td>
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<td>Lin 2001</td>
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<td>Ma 2013</td>
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<td></td>
<td>2.5 BID</td>
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RCT - Randomized Controlled Trial   PCoT - Prospective Cohort Trial   PCaS - Prospective Case Series   RCoT - Retrospective Cohort Trial   RCoS - Retrospective Case Series
### Baroni 1988

<table>
<thead>
<tr>
<th>The Question</th>
<th>Does HBO₂ improve healing in DFU?</th>
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<tbody>
<tr>
<td>Study Design</td>
<td>Prospective Cohort Trial (N=28)</td>
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<td>Study Population</td>
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<td>Comparison</td>
<td>18 HBO₂ vs. 10 ∅HBO₂</td>
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<td>Co-Morbidities Addressed</td>
<td>V O I D</td>
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<td>HBO₂ Protocol</td>
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<tr>
<td></td>
<td>2.5-2.8 ATA x90 min 6/7 days (34±21 Tx)</td>
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<tr>
<td>Strength of Evidence</td>
<td>Low</td>
</tr>
<tr>
<td>Generalizability</td>
<td>Moderate - all patients hospitalized</td>
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<tr>
<td>The Answer</td>
<td>HBO₂ significantly improved healing rate (89% vs. 10%, p=.001) and decreased amputation rate (11% vs. 40%, p=.001). It suggests faster healing as decreased hospital LOS (62 days vs 82 days, NS)</td>
</tr>
</tbody>
</table>

- **V** - Vascular
- **O** - Offloading
- **I** - Infection
- **D** - Diabetes Control

- ★ Well Addressed
- ★★ Moderately Addressed
- ★★☆ Poorly Addressed
- ☆☆☆☆ Not Addressed
<table>
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<tr>
<th>Time Period</th>
<th>AKA Rate</th>
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<tr>
<td>1979-1981 (∅ HBO₂)</td>
<td>17/42 (40%)</td>
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<tr>
<td>1982-1984 (HBO₂)</td>
<td>8/71 (8.4%)</td>
</tr>
<tr>
<td>1982-1984 (∅ HBO₂)</td>
<td>4/10 (40%)</td>
</tr>
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</table>
Baroni 1987

- Patients in both arms had improved HbA$_{1c}$ by the end of the study

- **All patients were admitted** throughout the study (62 days vs. 82 days, $p=NS$)

- None of the 16 patients healed in the HBO$_2$ group relapsed in the follow-up period

- No demographic details about vascular status, but they recognized that macroangiopathy could adversely affect healing
<table>
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<tr>
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<td>V - Vascular</td>
<td>O - Offloading</td>
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<tr>
<td>Well Addressed</td>
<td>Moderately Addressed</td>
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<tr>
<td>HBO₂ Protocol</td>
<td>2.5-2.8 ATA x 90 min 5-6 days/wk (72±29 Tx)</td>
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<td>Strength of Evidence</td>
<td>Low</td>
</tr>
<tr>
<td>The Answer</td>
<td>HBO₂ significantly improved healing rate (96% vs. 67%, p&lt;.001) and decreased amputation rate (5% vs. 33%, p&lt;.001).</td>
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## Orian 1990

<table>
<thead>
<tr>
<th>Time Period</th>
<th>AKA Rate</th>
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<tr>
<td>1979-1982 (ØHBO₂)</td>
<td>19/49 (38.8%)</td>
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<tr>
<td>1983-1987 (HBO₂)</td>
<td>3/62 (4.8%)</td>
</tr>
<tr>
<td>1983-1987 (ØHBO₂)</td>
<td>6/18 (33%)</td>
</tr>
</tbody>
</table>
Oriani 1990

- Daily debridement
- Aggressive glycemic control
- Culture driven antibiotics eliminated 70% of infections in both groups
- Treatment protocol - 2.5 or 2.8 ATA initially 6 days/week until beginning of granulation then 5 days/week
<table>
<thead>
<tr>
<th>The Question</th>
<th>Does HBO\textsubscript{2} improve healing and decrease amputation rate in DFU?</th>
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<tbody>
<tr>
<td>Study Design</td>
<td>Randomized Controlled Unblinded Trial (N=68)</td>
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<tr>
<td>Study Population</td>
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<tr>
<td>Comparison</td>
<td>35 HBO\textsubscript{2} vs 35 ∅HBO\textsubscript{2}</td>
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<td>Co-Morbidities Addressed</td>
<td>V  O  I  D</td>
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<tr>
<td>HBO\textsubscript{2} Protocol</td>
<td>2.2-2.5 ATA x 90 min 5-7 days/wk (38±8 Tx)</td>
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<td>Strength of Evidence</td>
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<tr>
<td>Generalizability</td>
<td>Moderate - all patients hospitalized</td>
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<tr>
<td>The Answer</td>
<td>HBO\textsubscript{2} group had less major amputations (9% vs 33%, p=.002) and greater increase in $P_{tcO_2}$ (14 mm Hg vs. 5 mm Hg, p=.00002) than the control group</td>
</tr>
</tbody>
</table>

- V - Vascular
- O - Offloading
- I - Infection
- D - Diabetes Control
- Well Addressed
- Moderately Addressed
- Poorly Addressed
- Not Addressed

**Faglia 1996**
Faglia 1996

- All patients in the study were admitted to the hospital at the start of the study period
  - Wagner IV (Full-thickness gangrene)
  - Wagner III (Abscess)
  - Wagner II (if ulcer was large and infected and showed a defective healing in 30 days of outpatient therapy)
Faglia 1996

- Aggressive and radical debridement
- Dressing changes with debridement carried out not less than twice a day when necrosis or exudate were present, daily when ulcer was clean, and every 2 days during granulation period
Faglia 1996

- Offloading in hospital was addressed with an orthotic insert in an extra deep shoe
- Empirical broad-spectrum antibiotics were started and then adjusted based on culture results
- Diabetes was controlled with oral hypoglycemic agents or SQ insulin based on blood glucose checks (7 times/day)
  - Blood glucose of >22 mmol (396 mg/dL) started on IV insulin until blood glucose < 9.9 mmol (178 mg/dL)
  - Hb\textsubscript{a1c} checked at time of admission and at discharge
Faglia 1996

- If ABI <0.9 and/or $P_{tcO_2} < 50$ mmHg, therapy with prostacyclin was established and angiography performed.
- If arteriography showed >50% focal stenosis, then PTA or BPG.
- If arteriography showed occlusion of >10cm then BPG if a patent vessel in continuity with the foot was present.
- 26 subjects had revascularization during the study (13 in each arm).
Faglia 1996

- Limb considered salvaged when plantar support was preserved and the ulcer healed despite minor amputation
  
  - Reduction in major amputations in Wagner IV DFU (9.1% vs. 55%, \( p=0.002 \))
  
  - No difference in major amputations in Wagner III DFU (25% vs. 0%, \( p=0.33 \)) or Wagner II DFU (0% vs. 0%)

- Pivotal Study for CMS approval of HBO\(_2\) for DFU
Wagner Grades

- Grade 0: No open lesion
- Grade 1: Superficial ulcer
- Grade 2: Deep ulcer
- Grade 3: Abscess osteitis
- Grade 4: Gangrene forefoot
- Grade 5: Gangrene entire foot

Wagner, FW The Dysvascular Foot, Foot & Ankle 2(2) 1981
CMS requirements

- Diabetic wounds of the lower extremities in patients who meet the following three criteria:
  - Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes;
  - Patient has a wound classified as Wagner grade III or higher; and
  - Patient has failed an adequate course of standard wound therapy.

- The use of HBO therapy is covered as adjunctive therapy only after there are no measurable signs of healing for at least 30 – days of treatment with standard wound therapy and must be used in addition to standard wound care... Failure to respond to standard wound care occurs when there are no measurable signs of healing for at least 30 consecutive days. Wounds must be evaluated at least every 30 days during administration of HBO therapy. Continued treatment with HBO therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment.
Hyperbaric Medicine Facilities in the US

![Graph showing the number of hyperbaric medicine facilities in the US from 1971 to 2015. The graph shows a significant increase in facilities over time.](image-url)
<table>
<thead>
<tr>
<th>The Question</th>
<th>What is the effect of HBO$_2$ on healing of DFU?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Randomized, Double-Blinded, Placebo-Controlled Trial (N=75)</td>
</tr>
<tr>
<td>Study Population</td>
<td>Study Population</td>
</tr>
<tr>
<td>Comparison</td>
<td>Comparison</td>
</tr>
<tr>
<td>Co-Morbidities Addressed</td>
<td>Co-Morbidities Addressed</td>
</tr>
<tr>
<td>HBO$_2$ Protocol</td>
<td>HBO$_2$ Protocol</td>
</tr>
<tr>
<td>Strength of Evidence</td>
<td>Strength of Evidence</td>
</tr>
<tr>
<td>Generalizability</td>
<td>Generalizability</td>
</tr>
<tr>
<td>The Answer</td>
<td>The HBO$_2$ group had significantly better healing at 1 year than the control group (52% vs. 29%, p=0.03) using intention-to-treat (ITT) analysis. Per protocol analysis showed even stronger results (61% vs 27%, p=.009).</td>
</tr>
</tbody>
</table>

- **V** - Vascular
- **O** - Offloading
- **I** - Infection
- **D** - Diabetes Control

- ★ Well Addressed
- ★★ Moderately Addressed
- ★☆ Poorly Addressed
- ★★☆ Not Addressed

Löndahl 2010/2011
Löndahl 2010

- All patients had ulcers >3 months duration and had been treated at a diabetic foot clinic for >2 months
- Foot infections included when acute phase of infection was resolved (no breakdown of osteomyelitis vs. cellulitis)
- HBO2 group had non-significant increase in major amputations (5% vs. 2%) vs. control group
- Number needed to treat was 4.2 and 3.1, for ITT and PP analysis respectively
Hyperbaric Oxygen Therapy Does Not Reduce Indications for Amputation in Patients With Diabetes With Nonhealing Ulcers of the Lower Limb: A Prospective, Double-Blind, Randomized Controlled Clinical Trial
Design

- Wagner 2-4 DFU were randomized to HBO$_2$ (n=51) vs. Sham (n=56)
  - 244 kPa O$_2$ x 90 min
  - 125 kPa air x 90 min (~27% O$_2$)
Primary Outcome

- Meeting criteria of need for amputation or undergoing amputation
  > Lack of significant progress in wound healing
  > Persistent deep infection involving bone/tendon
  > Inability to bear weight on affected limb
  > Pain causing significant disability
Secondary Outcome

- Wound healing

  > At 12 weeks, wounds classified as Wagner grade 0 or 1 were considered healed
  > Patients with a TMA were considered a Major amputation
Results

Only one patient in the sham group had an actual amputation (great toe) during the study period.
Strengths of Paper

- Randomized, double-blinded study design
- Sham control group
- Allocation concealment
- Intention to treat analysis
To amputate or not to amputate…

- “The primary goal of the trial was to assess the efficacy of HBOT in reducing indications for amputation (rather than reducing amputation events themselves)…”
- “That we did not use actual amputation rates in this placebo-controlled trial may be considered a limitation…”
Is a picture worth a thousand words?

- “Blind” vascular surgeon determined whether amputation (major or minor) was indicated using digital photographs.
- The surgeon had full discretion on a case-by-case basis about whether the... wound could be assessed through the digital photography and clinical information alone...
COMMENT ON LEDORSKO ET AL.

Hyperbaric Oxygen Therapy Does Not Reduce Indications for Amputation in Patients With Diabetes With Nonhealing Ulcers of the Lower Limb: A Prospective, Double-Blind, Randomized Controlled Clinical Trial. Diabetes Care 2016;39:392–399

Enoch T. Huang
A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers

**CPG Authors:** Enoch T. Huang, Jaleh Mansouri, M. Hassan Murad, Warren S. Joseph, Michael B. Strauss, William Tettelbach, Eugene R. Worth

**UHMS CPG Oversight Committee:** Enoch T. Huang, John Feldmeier, Ken LeDez, Phi-Nga Jeannie Le, Jaleh Mansouri, Richard Moon, M. Hassan Murad

**CORRESPONDING AUTHOR:** Dr. Enoch T. Huang – enoch.huang@mac.com

**ABSTRACT**

**BACKGROUND:** The role of hyperbaric oxygen (HBO2) for the treatment of diabetic foot ulcers (DFUs) has been examined in the medical literature for decades. There are more systematic reviews of the HBO2 / DFU literature than there have been randomized controlled trials (RCTs), but none of these reviews has resulted in a clinical practice guideline (CPG) that clinicians, patients and policy-makers can use to guide decision-making in everyday practice.

**METHODS:** The Undersea and Hyperbaric Medical Society (UHMS), following the methodology of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, undertook this systematic review of the HBO2 literature in order to rate the quality of evidence and generate practice recommendations for the treatment of DFUs. We selected four clinical questions for review regarding the role of HBO2 in the treatment of DFUs and analyzed the literature using patient populations based on Wagner wound classification and age of the wound (i.e., acute post-operative wound vs. non-healing wound of 30 or more days). Major amputation and incomplete healing were selected as critical outcomes of interest.

**RESULTS:** This analysis showed that HBO2 is beneficial in preventing amputation and promoting complete healing in patients with Wagner Grade 3 or greater DFUs who have just undergone surgical debridement of the foot as well as in patients with Wagner Grade 3 or greater DFUs that have shown no significant improvement after 30 or more days of treatment. In patients with Wagner Grade 2 or lower DFUs, there was inadequate evidence to justify the use of HBO2 as an adjunctive treatment.

**CONCLUSIONS:** Clinicians, patients, and policy-makers should engage in shared decision-making and consider HBO2 as an adjunctive treatment of DFUs that fit the criteria outlined in this guideline. The current body of evidence provides a moderate level of evidence supporting the use of HBO2 for DFUs. Future research should be directed at improving methods for patient selection, testing various treatment protocols and improving our confidence in the existing estimates.
Diabetic Foot Ulcers

- Adjunctive Treatment only after:
  > Vascular intervention
  > Offloading
  > Infection Control
  > Debridement
Recommendation 1

- In patients with Wagner Grade 2 or lower diabetic foot ulcers, we **suggest against** using hyperbaric oxygen therapy (very low-level evidence in support of HBO2, conditional recommendation)
Recommendation 2

- In patients with Wagner Grade 3 or higher diabetic foot ulcers that have not shown significant improvement after 30 days of treatment, we suggest adding hyperbaric oxygen therapy to the standard of care to reduce the risk of major amputation and incomplete healing (moderate-level evidence, conditional recommendation)
# Effects of HBO$_2$

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>% Healed Ø Major Amp</th>
<th>Delay before HBO$_2$?</th>
<th>Increases Healing Percentage</th>
<th>Decreases Major Amputations</th>
<th>Increases Rate of Healing</th>
<th>Increases Durability of Healing</th>
<th>↑ p$_\text{tO}_2$ after HBO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baroni 1987</td>
<td>PCoT</td>
<td>89 vs 10</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>n/a</td>
<td>Maybe</td>
<td>n/a</td>
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<tr>
<td>Oriani 1990</td>
<td>RCoT</td>
<td>96 vs 67</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>n/a</td>
<td>n/a</td>
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<td>Doctor 1992</td>
<td>RCT</td>
<td>87 vs 53</td>
<td>NS</td>
<td>Yes</td>
<td>Yes</td>
<td>Maybe</td>
<td>n/a</td>
<td>n/a</td>
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<td>Faglia 1996</td>
<td>RCT</td>
<td>91 vs 67</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<td>Zamboni 1997</td>
<td>PCoS</td>
<td>80 vs 20</td>
<td>Yes &gt; 6mo</td>
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<td>n/a</td>
<td>n/a</td>
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<tr>
<td>Faglia 1998</td>
<td>RCoT</td>
<td>86 vs 69</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>n/a</td>
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<td>Lin 2001</td>
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<tr>
<td>Kalani 2002</td>
<td>PCoT</td>
<td>76 vs 48</td>
<td>Yes &gt; 8 wks</td>
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<td>n/a</td>
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<tr>
<td>Abidia 2003</td>
<td>RCT</td>
<td>63$^b$ vs 0</td>
<td>Yes &gt; 6 wks</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Kessler 2003</td>
<td>RCT</td>
<td>14$^c$ vs 0</td>
<td>Yes &gt; 3 mos</td>
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<td>Duzgun 2008</td>
<td>RCT</td>
<td>74 vs 18</td>
<td>Yes &gt; 4 wks</td>
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<td>Löndahl 2010</td>
<td>RCT</td>
<td>52 vs 29</td>
<td>Yes &gt; 3 mos</td>
<td>Yes</td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>Ma 2013</td>
<td>RCT</td>
<td>n/a</td>
<td>Yes &gt; 8 wks</td>
<td>n/a</td>
<td>n/a</td>
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<td>n/a</td>
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<tr>
<td>Margolis 2013</td>
<td>RCoT</td>
<td>43 vs 50</td>
<td>Yes &gt; 8 wks</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*Reported improvement, not healing  
$^b$only at 1 year follow-up  
$^c$4 week follow-up
Recommendation 3

- In patients with Wagner Grade 3 or higher diabetic foot ulcers who have just had a surgical debridement of an infected foot (e.g., partial toe or ray amputation; debridement of ulcer with underlying bursa, cicatrix or bone; foot amputation; incision and drainage [I&D] of deep space abscess; or necrotizing soft tissue infection), we suggest adding acute post-operative hyperbaric oxygen therapy to the standard of care to reduce the risk of major amputation (moderate level evidence, conditional recommendation).
Variance from LCD

- CMS NCD states
  
  *The use of HBO therapy is covered as adjunctive therapy only after there are no measurable signs of healing for at least 30 days of treatment with standard wound therapy and must be used in addition to standard wound care*

- Faglia 1996
  
  > Wagner 3 and 4 DFU were immediately admitted, had revascularization, foot surgery, and had HBO immediately
  > Only Wagner 2 DFUs that had not healed with 30 days of therapy were included in study
Objectives

- By the end of this lecture, attendees should be able to:
  > Describe conditions where hyperbaric oxygen therapy can improve patient outcomes
  > Associate the mechanisms of hyperbaric oxygen therapy with the conditions for which hyperbaric oxygen therapy has been shown to improve patient outcomes
  > Identify patients for whom hyperbaric oxygen therapy may be helpful
Part 4

COMPROMISED FLAPS AND GRAFTS
Graft vs. Flap

- **Graft** – a tissue that is completely separated from any blood supply.
  > Non-vascularized.

- **Flap** – a tissue that retains some form of blood supply.
  > May be vascularized locally or by a distant blood supply via microsurgical techniques.
Graft Physiology

- Simple Grafts
  - Composed of a single tissue type (skin)

- Composite Grafts
  - Composed of multiple tissue types (skin, muscle, cartilage, bone)

- Grafts rely on the wound bed for survival and “take”.
  - Thicker and larger grafts (full thickness skin graft) have a higher requirement than smaller and thinner grafts (split thickness skin graft).
  - Composite grafts have an even higher metabolic requirement due to the multiple tissue types
Random Flaps

- Blood supply comes from un-named subcutaneous vessels
Axial Flap

- Blood supply is still attached to its source but tissue is relocated

http://www.plasticsurgerynow.com/breast-procedures-washington-dc/breast-reconstruction/
Free Flap

- Blood supply is separated from its source and has to be re-stored in a new location

http://www.plasticsurgerynow.com/breast-procedures-washington-dc/breast-reconstruction/
Why do flaps fail?

- Blood supply is insufficient to maintain viability of the flap
  - Arterial supply
  - Venous congestion
  - Poor recipient bed
    - Irradiated tissue
    - Peripheral arterial disease
  - Bad technique (excessive size of flap/graft)
  - Long ischemic times

- Excessive external forces
  - Shear
  - Pressure
  - Trauma
    - Degloving injuries
Rationale for Hyperbaric Oxygen

- Not recommended for the support of normal, uncompromised flaps or grafts
- Indicated for flaps in compromised tissue
  - Previous radiation
  - Decreased perfusion/hypoxia
  - Traumatic amputations/degloving injury
- Hyperbaric oxygen can
  - Maximize viability of the compromised tissue
  - Reduce the need for re-grafting or repeat flap procedures
  - Decrease patient morbidity
History

- 68 yo female s/p bilateral mastectomy with immediate TRAM reconstruction
- 15 hour procedure complicated by clotting of end-to-end anastomoses
- Flap reassessed the next day and HBO₂ initiated
  > Thursday evening at 11 pm
History

- 9 year-old male who ran into a non-tempered sliding glass door in Clarkston, WA over the New Year holiday.
- He sustained a severe laceration of the nose, nearly severing the nose and splitting his upper lip.
- He had surgical repair of this by OMFS.
  - The repaired nose did well for a few days but then became ecchymotic and ischemic.
  - HBO$_2$ consulted at Post-operative Day #3:
    - Referral source was not the facial surgeon.
    - Referral source was the mother of the host family, who happened to be friends with the hyperbaric physician.
36 hours post injury
- After 6 HBO\textsubscript{2} treatments
- No debridement of wound was performed
History

- Patient received 20 HBO$_2$ treatments and then returned home to Vancouver, WA
- Referral to HBO$_2$ in Portland for follow-up evaluation
Evidence for Hyperbaric Oxygen

- Multiple studies
  - Majority are animal experimental studies
- Multiple animal models
  - Rats, rabbits, pigs, guinea pigs and cats
  - Composite grafts and multiple flap types
- The animal experiments overall indicate a small, but significant, improvement with the use of HBO$_2$ to salvage compromised grafts and flaps.
Perrins (1967)

- Prospective, blinded, randomized controlled trial of 48 patients undergoing split-thickness skin grafting.
  - 24 HBOT and 24 Controls
    - HBOT: 2.0ATA for 120 min. BID x 3 days
  - Complete graft take defined as >95% total surface area survival.

- A significant 29% improvement in graft survival was seen in the HBOT group vs. controls.

- 64% of the HBOT group achieved complete take.
  - Only 17% of control group achieved complete take.

- 100% of HBOT patients achieved >60% take.
- Only 64% of controls achieved at least 60% take.

- Although the etiology of graft compromise is unclear, the patients in this study clearly manifest some reason for graft compromise given the low success rate in controls.

Zhou (2014)

- Largest review of randomized controlled clinical studies (all from China)
  - 957 HBOT patients
  - 583 control patients
- 23 total clinical trials
  - 16 controlled trials
  - 12 randomized-controlled trials
- Overwhelmingly positive results
  - 62.5% - 100% healing/survival rate in those treated with HBOT
- Positive results associated with initiation of treatment < 72 hours after surgery
  - Treatment planned, not for salvage
  - All literature reviewed in Chinese
- One study found success rates of 96%, 56% and 14% when HBOT was initiated immediately, 10 hours and 48 hours after surgery, respectively.
- Another found wound healing to be 100%, 71% and 50% when HBOT was used for skin grafts @ <12hrs, 12-48hrs and >48hrs, respectively.

Patient selection for HBO$_2$

- Referral is time critical
- Optimal treatment within 24 hours
- BID treatments in first 48 hours, then daily
- Treatments should be stopped when flap declares itself
HBO₂ mechanisms for Wound Healing

- Hyperoxygenation
  - Decreases bubble size
- Peripheral vasoconstriction
- Angiogenesis
- Stem cell mobilization
- Fibroblast proliferation/Collagen Synthesis
- Reduced leukocyte adhesion
- Reduced lipid peroxidation
- Edema reduction
- Enhanced leukocyte antimicrobial activity
- Antibiotic synergy
- Toxin inhibition
Indications for Hyperbaric Oxygen

- Decompression Sickness
- Arterial Gas Embolism
- Carbon Monoxide Poisoning
- Chronic Radiation Tissue Injury
- Selected Non-healing Wounds
  - Diabetic Wounds of the Lower Extremities
- Traumatic Peripheral Ischemia
- Chronic Osteomyelitis
- Thermal Burns
- Exceptional Blood Loss Anemia

- Gas Gangrene, Myonecrosis, Necrotizing Soft Tissue Infections
- Compromised Skin Flaps
- Acute Peripheral Arterial Insufficiency
- Intracranial Abscess

Primary Therapy
Adjunctive Therapy
References

Thank you!