Hyperbaric Oxygen: Outpatient Applications

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Medical Director
Fort Healthcare Wound and Edema Center
Background: RJ Goldman, MD

- MD University of Texas, Galveston
- Rehabilitation Medicine Residency (Albert Einstein, Bronx, NY)
- NIH Fellow (University of Pennsylvania)
- Associate Professor, Rehabilitation Medicine (U of PA)
Training as a Hyperbaricist

- Visiting Faculty, University of Texas, Houston (2006)
- Wound care and Hyperbaric Oxygen Center
- Memorial Hermann Hospital
- Caroline Fife, MD, Director
- Supervised 1000 HBO treatments, wound care.
Undersea Hyperbaric Medicine

- Private practice, then FMG and additional 250 dives.
- Supervised HBOT on >100 patients
- Board certification: Subspecialty of American Board of Preventive Medicine: 2010
Hyperbaric Chambers
Multiplace chamber
Multiplace chamber: Hyperbaric Air.
“Wet” vs “Dry” diving.

Diving
- Air
- 21% Oxygen
- 78% Nitrogen

High pressure chamber (twice pressure of air)
- 100% Oxygen (mono)
- 21% Oxygen (multi)
Oxygen as Drug

- **Benefits**
  - Reduce inflammation
  - Reduce edema
  - Improve killing of bacteria.
  - Promote neoangiogenesis

- **Risks**
  - Oxygen seizures.
  - Pulmonary fibrosis.
HBO “Dive” Profile

Descent

1 ATA

Air Break

90 minutes

Air Break

Ascent

2.5 ATA

45 FSW
Decompression sickness

- Dissolved nitrogen forms bubbles on rapid ascent
- CNS symptoms.
- Rapid improvement with HBOT
- HBOT 100% O2, 2.8 ATA re-dissolves Nitrogen
Critical care and HBOT.

- Decompression sickness: “bends”
- CO poisoning.
- Necrotizing Fasciitis
- Clostridia infection: “gas gangrene”
- Intracranial abscess.
- Compartment syndrome.
- Exceptional anemia.
Critical Care and HBOT

- 2-3 treatments/day
- Usually less than 20 treatments
- Compression to 3 ATM
- Require 24 hour “on call” staffing.
- Ventilator-capability
- Inside “tender”.
Outpatient HBOT Indications

- Late effects of cancer radiation therapy
- Diabetic Foot Ulcers (DFU) healing and limb preservation.
- Ischemic ulcers
- Compromomised flaps or grafts
- Refractory osteomyelitis.
- One treatment/day, 90 minutes, 30-40 total treatments.
Mechanism: Hyperoxia enhances healing

- Infection control (leukocyte killing, direct effect)
- Reduce ischemia reperfusion.
- Edema reduction
- Neo-vascularization.
- Enhanced collagen synthesis
- Wound repair.
- Promote release of stem cells from marrow which migrate to wound site: Endothelial precursor cells.
It's taking a lot longer for my leg to grow back than I thought it would.
Hyperbaric Oxygen Therapy for Wound Healing and Limb Salvage: A Systematic Review

Robert Goldman, MD

A systematic review evaluating published clinical evidence of the efficacy of hyperbaric oxygen therapy (HBOT) for wound healing and limb salvage. PubMed/Medscape database for key word “Hyperbaric Oxygenation” with search limits (human studies, 1978-2009). Results combined by Boolean AND with 1 of the 3 following searches: (a) wound healing (10 permutations); (b) compartment (3); and (c) osteomyelitis (3). The authors evaluated 620 citations, of which 64 reported original observational studies and randomized controlled trials (RCTs) on HBOT and healing outcomes. All citations with 3 subjects were selected for full text review (44 articles) and evaluated according to GRADE criteria for high, medium, low, or very low level of evidence. A Cochrane review identified 1 additional study with a low level of evidence. This systematic review discusses and tabulates every article of high or moderate level of evidence. For patients with diabetic foot ulcers (DFUs) complicated by surgical infection, HBOT reduces chance of amputation (odds ratio [OR] 0.242, 95% CI 0.137-0.428 [7 studies] and improves chance of healing (OR 9.992, 95% CI 3.972-25.132 [6 studies]). Positive efficacy corresponds to HBOT-induced hyperoxygenation of at-risk tissue (7 studies) as measured by transcutaneous oximetry. HBOT is associated with remission of about 85% of cases of refractory lower extremity osteomyelitis, but an RCT is lacking to clarify extent of effect. There is high level of evidence that HBOT reduces risk of amputation in the DFU population by promoting partial and full healing of problem wounds. There is moderate level of evidence that HBOT promotes healing of arterial ulcers, calciphylactic and refractory vascular ulcers, as well as refractory osteomyelitis. There is a low to moderate level of evidence that HBOT promotes successful “take” of compromised flaps and grafts.

INTRODUCTION

Wound care practice is traditionally an important role for physicians [1]. The practice continues today as treatment of pressure ulcers of patients with spinal cord injury. Physicians can also participate in wound care of potential amputees with “tissue at risk” because of improved wound healing techniques limb salvage is increasingly an option for this patient population [2].

Outpatient wound centers currently number 1000 (compared with about 100 15 years ago) and a sizable number of these are for-profit wound management organizations. Such outpatient settings offer new opportunities to physicians to focus on wound care. In addition, teaching and research opportunities for such wound care specialists have recently expanded. A notable example is the Physical Medicine and Rehabilitation Department at East Carolina University, which launched the first academic-based psychiatry-directed wound center in 2007 [3].

Because so many of these wound care centers also offer hyperbaric oxygen therapy (HBOT), an increasing number of Physical Medicine and Rehabilitation physicians are becoming certified in or practice HBOT. HBOT (unlike wound care) is also an American Board of Medical Specialties recognized subspecialty, offered by the Board of Preventive Medicine. Physicians in HBOT practice, with 2 years of post-time experience, may sit for the Undersea and Hyperbaric Medicine Board Examination until 2010. After 2010, an HBOT Fellowship will be required [4].

HBOT is defined as compression of the whole body with at least 1.4 atmospheres absolute pressure (ATA) of pure oxygen [5]. Since the 19th century, HBOT has been
Systematic review: Goldman (2009)

- Original observational studies and RCT
- 1978-2008
- Wound healing and limb salvage
- Late effects of radiation (not included in manuscript)
- Ovid/Medline: 8500 citations on HBOT
Systematic review

- **GRADE scale:**
  - High: Randomized Controlled Trials (RCT)
  - Moderate
  - Low: Case series, cohort studies
  - Very low (n<5 subjects)

- **Advantages:**
  - Simplicity
  - Accommodates HBOT well.

Wound healing and HBOT

- DFU
- Venous ulcers
- Arterial ulcers
- Compromised flap
- Refractory osteomyelitis
Wagner IV
DFU: Falgia (1996)

- **RCT:** Un-blinded
- **N=68** (48M, 20F)
- **Setting:** Milan Italy.
- **ABI:** = 0.64, **26 revasc. Procedures.**
- **90% neuropathy.**
- **Wagner III, IV (abcess, gangrene)**
- **Comprehensive DM management**
- **HBOT 2.4 ATM, 90 min, 38 +/- 8 sessions.**
Standard of care

- Peripheral arterial disease, With or without diabetes:
- Revascularization.
Falgia (1996) Results.

- **Endpoint:** Major amputation
- **HBOT group:** 3 (8.6%)
- **Control:** 11 (31%)
  - (p=.004)
- **Wagner IV (gangrene)**
  - 9% vs 55% (p=.002).
- **Note:** Patients hospitalized average 46 days.
Odds ratio: Amputation reduction

Meta-analysis

Faglia (1996)
Abidia (2003)
Doctor (1992)
Faglia (1998)
Kalani (2002)
Baroni (1987)
Oriani (1990)

Total (fixed effects)
Total (random effects)

Favors HBOT

Odds ratio
Odds ratio: Healing

Meta-analysis

Albida (2003)
Kessler (2003)
Hammerlung (1994)
Kalani (2002)
Baroni (1987)
Zamboni (1997)
Total (fixed effects)
Total (random effects)

Favors HBOT
HBOT improves healing of DFU

- Randomized, double blinded, sham-controlled trial
- N=94 patients with Wagner 2, 3, 4 for >3 months; Most Wagner 3.
- Intent to treat
- At one year: 52% healed in HBOT group and 29% in sham control group.
- For >35 treatments: 61%/27%

Level “A” evidence: Improved diabetic healing with HBOT
I’m confused, oh wait, maybe I’m not
Dose of Oxygen = Effectiveness!

- Oxygen measured as mm Hg (Mercury).
- Manometer.
- Pressure of oxygen in
  - Air.
  - Hyperbaric chamber.
  - Blood.
  - Skin (target tissue)
  - Ischemic skin (target tissue)
“Dose” of Oxygen: Transcutaneous Oxygen Monitor
Transcutaneous Oximetry (TcPO2) adds to vascular workup

- Room air = 21% (760 mm Hg) = 157 mm O2
- TcPO2 > 40 mm Hg normal: GOOD PX
- TcPO2 < 20 mm Hg ischemic: BAD PX

Tissue Hypoxia

- Leads to the following alterations in normal healing:
  - ↓ phagocytic capacity of PMNs.
  - ↓ fibroblast proliferation and collagen production.
  - ↓ neovascularization.
  - ↓ osseous repair.
DFU: Fife (2002)

Dose response predicts healing.

- Retrospective case series.
- Very large: N=641
- Setting: Five TX wound HBO centers
- DFU Wagner II-V;
- Positive response (granulation) as function of:
  - Oxygen Challenge (HBO)
  - Wagner grade.
Fife (2002) HBO-challenge TCOM
response: Positive wound change.
Case Study: MW

- 54 year old female with Type I DM age 10
- DM neuropathy, vasculopathy. HbA1c=8
- Non-reconstructable RLE arterial disease.
- Pain moderate to severe: Percocet.
- Failed angioplasty
- Failed vascular growth factor study (Madison).
Case Study: MW

- Underwent 40 dives start at 2.0 ATA.
- No otic barotrauma.
- Blood sugar modified, drops 120 mg/dl in chamber, usually start at 250 mg/dl.
- Fifth treatment: Increased to 2.5 ATA. Post treatment, much less pain and livido.
- Completed 40 treatments.
Case Study: MW

- Underwent Ray amputation
- Healed!
- HBOT helped preserve limb:
- Alternative, major amputation.
Arterial ulcers: Grolman (2001)

- Retrospective case series
- N=36 with arterial ulcers (20 bypass)
- Face mask Oxygen challenge:
- Peri-wound change TCOM > 10 mm Hg: 70% healed
- Change TCOM < 10, 11% healed (p<.01).
- Moderate strength of evidence:

- Prospective case series
- N=15
- HBOT twice per day, 2.5 ATM, 14 sessions.
- Success >90% salvage.
- Hyperbaric Oxygen challenge
- TCOM>50 mm Hg, all healed.
- TCOM<50 mm HG, all failed.
Refractory osteomyelitis: Davis (1986)

- Retrospective time series.
- Fail previous surgery, duration >6 months, actively draining wounds
- Surgery plus AB standard of care
- Endpoint: Complete healing
- HBOT 2.4 ATM, 90 minutes, 40 sessions
- Successful outcome 89% (follow up 34 months)
- Outcome similar to 15 other observational studies
Late Effects of Radiation: Head and Neck Cancer
Histology

- 5000 plus rads (50 Grey)
- Hyperemia and endarteritis up to 6 months.
- Thrombosis: blood clots then fibrous thrombi.
- Cellular loss and microvascular content progressive after 6 months.
- Hypovascularity and fibrosis in the "end stage".
- TGF-beta mechanism

Osteoradionecrosis of the mandible
HBOT improves oxygenation of irradiated tissue
Declared Osteoradionecrosis

- Marx Protocol
  - 30 compressions followed by ablative surgery, then 10 compressions
  - Ablative surgery to remove “dead” bone critical to success.

- Study where dead bone was not removed, HBOT was not effective
ORN prophylaxis: Marx (1985)

- RCT, unblinded
- N = 74
- HBOT 20 sessions pre-extraction, 10 post.
- Outcome was ORN post extraction
- ORN defined as socket unable to cover bone 6 months post extraction.

Marx (1985) Results

- HBOT group: 2 patents (5%) developed ORN post extraction
- Control group: 11 (29.9%) developed ORN post extraction.
- Difference $p=0.005$.
- ORN 4 sockets HBOT group.
- 31 sockets control group.
- High level of evidence: ORN Prophylaxis.
Other reports by Marx stated as RCT by Cochrain Review

- hemimandibular jaw reconstruction
- High level of evidence.

- patients requiring major flaps into reconstructed area
- High level of evidence.
Patient PG: ORN prophylaxis

- PG, 50 year old male s/p Squamous CA R tonsil, 7/2005 Stage III (T2, N1).
- Received 64 Grey, end Oct, 2007;
- May, 2010, referred to JC wound center with fractured crown for extraction.
- For HBOT 30 treatments pre extraction, 10 post: 2.5 ATA, 90 minutes
- HTN fair control
Patient PG: ORN prophylaxis

- Underwent 30 “dives”
- Dive 2: Teed 2 right TM (old scaring) Otic barotrauma: Underwent myringotomy tubes
- 11th dive, decreased visual acuity 20/70, advised to have a driver.
- After excision, good healing of socket.
Late Effects of Radiation: Soft tissue Radionecrosis
Soft tissue radionecrosis

- Proctitis.
- Hemoragic Cystitis.
- Soft tissue pelvic “late effects of XRT”.
- Level of evidence moderate to high.
Radiation Proctitis

- Pain
- Tenesmus
- Bleeding
- Objective evidence per direct visualization.
Proctitis: Clarke (2008)

- Double blinded multi-center RCT.
- N = 150 (75/group)
- Controls: Treated with “sham” HBOT at 1.1 ATA
- Endpoint: Validated SOMA-LENT score (14-0)
- 30-40 HBOT sessions at 2.0 ATM

Clarke (2008) Results:

- Initial SOMA-LENT equivalent 12.5-12.8
- After HBOT
  - HBO group: 7.5
  - Sham Control: 10.2
  - p-=.0019
  - Followed by crossover, and controls=HBO thereafter (F/U 5 years).
  - SOMA-LENT: 4 in “outyears”.
  - Significant improvement in QOL.
- High strength of evidence.
Patient RU

- 76 year old male with history of prostate CA hormonal treatments and XRT 40 treatments.
- After one year, onset of rectal bleeding, passing clots.
- Current: Five BM/day, urge to stool up to 12 times per day, lower abdominal pain 5/10, clots every 3-4 days.
- Three colonoscopies which revealed multiple telangectasias c/w radiation proctitis. 10/2009 Argon laser ablation of ¼ circumference.
- Hx chronic otitis media; Placement myringotomy tubes 2001. Negative cardio-pulmonary history.
Patient RU

- Generalized anxiety dive #2: Valium 2 mg pre-dive (later increased to 4 mg).
- By dive #5 “75% improvement in symptoms”. Also myringotomy tubes bilateral.
- By dive #15 abdominal discomfort and tenesmus mostly resolved.
- By dive #40: complete resolution of symptoms.
- Urology follow-up: No return to bleeding, Hb stabilized, off iron.
Hemorrhagic Cystitis

- Retrospective cohort study.
- N=62; 56 M
- Failed conservative measures
  - One or more cystoscopy with cauterization.
- Endpoint: Resolution of macroscopic hematuria.
- HBOT 2.4 ATM, average 33 sessions.

Cystitis:  (Corman, 2003)
Corman 2003 Results

- On intent to treat basis, 82% complete or marked improvement.

- Related to duration of RN:
  - HBOT therapy <6 months post-onset: 96% Improvement
  - HBOT >6 months post-onset: 66% (p=.0003).

- Level of evidence: Moderate.
Corman 2003 Results

- On intent to treat basis, 82% complete or marked improvement.

- Related to duration of RN:
  - HBOT therapy <6 months post-onset: 96% Improvement
  - HBOT >6 months post-onset: 66% (p=.0003).

- Level of evidence: Moderate.
HBOT complications
HBOT Complications

- Cardiovascular effects.
- Oxygen Toxicity (CNS, pulmonary, ocular).
- Barotrauma (middle ear, inner ear, sinus, dental pulmonary).
- Hypoglycemia (diabetes)
- Confinement Anxiety
Cardiovascular effects

- Oxygen is a vasoconstrictor.
- Increases cardiac afterload.
- CHF should be well compensated.
- Guideline: Avoid HBOT for those with EF<30%.
- More relevant to monoplace chambers.
Oxygen Toxicity: Neurologic

- Oxygen seizure 1:200 patients.
- Seizure disorder: Watch therapeutic level.
- Watch medications that lower seizure threshold.
  - Chantix.
  - Glucophage
  - Digoxin
  - Steroids
  - Opiates.
Oxygen Toxicity: Neurologic

- Dose dependent: O2 pressure and duration.
- More likely at 2.5 ATA than 2.0 ATA.
- At normal dose for ORN is 2.5 ATA, two, 5 minute “air breaks”.
- Increase number and time of “air breaks” (e.g., 3 air breaks).
Oxygen toxicity

- **Pulmonary**
  - Pulmonary fibrosis (restrictive disease).
  - May decrease vital capacity.
  - Usually not seen below <60 dives.

- **Ophthalmologic**
  - Cataracts mature more quickly.
  - No risk of new cataract formation.
Barotrauma

Otic: Occurs on descent.

- 1:6 patients.
- Equilibrated by Eustachian tubes.
- Distraction of TM leads to barotrauma.

- Elective myringotomy: 1:60 patients.
  - Probably higher for head and neck patients
Plate 1  Middle-ear barotrauma of descent: grades 0–5, graded by otoscopy
Pulmonary Barotrauma: Occurs on Ascent

- Mechanism: “Bleb” or one-way valve.
- Ruptures on ascent.
- Could lead to pneumothorax.
- Absolute contraindication: untreated lung CA.
- Relative contraindications.
  - TB history
  - Bronchitis, Emphysema.
- Very rare: Not reported in series of 9000 patients.
Other complications

- Claustrophobia.
- Hypoglycemia (Diabetes).
- Note: Active cancer not an absolute contraindication (theoretical risk of spread of CA not seen in practice).
Conclusion: Strength of evidence

- ORN prophylaxis: High
- Declared ORN: moderate.
- Proctitis: High
- Cystitis: moderate to high
- Other soft tissue radionecrosis (moderate)
Wound healing:

- DFU Wagner III-IV:  Limb salvage High
- Wound healing:  high
- Arterial ulcers moderate.
- Calciphyaxis, vasculitis moderate
- Compromised Flaps and grafts:  Low to moderate
- Refractory osteomyelitis:  moderate.
Thank you!!

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Mechanism of ORN (Marx 1987)

- TCOM shows decreased relative vascularity
- More severe with time (years post irradiation).
- Skin at center of the XRT field
- Improved vascularity after 20 sessions of HBOT.
- Neovascularization
DFU: Definition of Wagner scale

- **Wagner I**: Superficial
- **Wagner II**: Tendon or bone
- **Wagner III**: Abscess cellulitis or osteomyelitis
- **Wagner IV**: Local gangrene
- **Wagner V**: Extensive gangrene