
Hyperbaric Oxygen for Delayed Effects of Therapeutic Radiation
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My Background
• Education
– UNMC, 1987
– Naval Undersea Medical Institute 1988
– Toledo, OH
• Residency in EM 1996
• Board Certified
– Emergency Medicine
• Medical Practice
– Emergency Medicine for 21 years
– Diving and Hyperbaric Medicine for 6 years
• Medical Director, HMC, TNMC 2 years
LIFE FLIGHT

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Hyperbaric Oxygen (HBO)

"That's for SCUBA divers with the bends…right?"

Still a bit wet behind the ears

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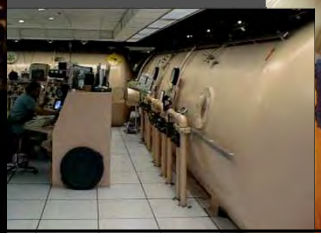
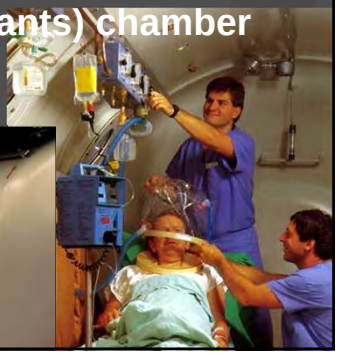
Hyperbaric Oxygen

- What it is?
  - What it is not. How it is done.
- What is it good for?
- How does it work??
- Delayed Effects of Therapeutic Radiation
  - Soft Tissue Radionecroses
  - Osteoradionecrosis
    - Prophylaxis
- Contraindications & Complications***

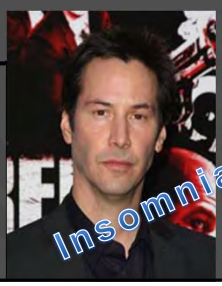
Definition of Hyperbaric Oxygen

- Breathing 100% O_2 at pressure of greater than one atmosphere absolute (1 ATA)
  - Usually between 2 and 3 ATA (roughly 33 fsw to 66 fsw)
- Delivered via monoplace (single occupant) or multiplace (multiple occupants) chamber

HBO Does Not:

- Increase IQ
- Increase visual acuity and hearing
- Increase memory
- Increase hair growth
- Increase sexual potential



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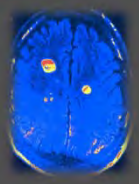
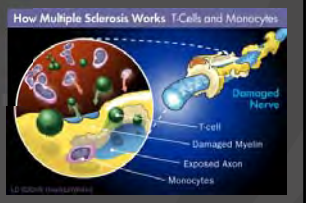
"Off Label" HBO Therapy





The Internet is full of HBO indications that are not approved by CMS/UHMS which includes "cures" for Stroke, Traumatic Brain Injury, Cerebral Palsy, Multiple Sclerosis, Lyme's Disease, Chronic Fatigue, etc. These are delivered in non hospital settings on a cash basis.

We only treat the "approved Indications" (CMS/UHMS) unless it is part of an IRB approved research protocol.

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Topical Hyperbaric Oxygen

Actually: Uses very low pressures (<1.1 ATA) and no significant oxygen is absorbed into the wound or thru skin.

** Not Approved by Medicare**

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Hyperbaric Oxygen is useful in a number of emergent conditions:

- Infectious
  - Clostridial gas gangrene
  - Necrotizing soft tissue infections
  - Intracranial abscess
  - Mucormycosis
  - Life threatening Osteomyelitis
- Hypoxemia
  - Carbon Monoxide Poisoning
  - Acute Blood Loss Anemia
- Bubble Disease
  - Decompression Sickness
  - Arterial Gas Emolism
- Acute Peripheral Arterial Insufficiency
  - Compromised Flaps and Grafts
  - Central retinal Artery Occlusion
  - Idiopathic Sudden Sensorineural Hearing Loss
  - Purpura fulminans
- Traumatic Ischemias
  - Burns
  - Frostbite
  - Compartment Syndrome
  - Crush Injury
  - Reimplantation of digits & limbs

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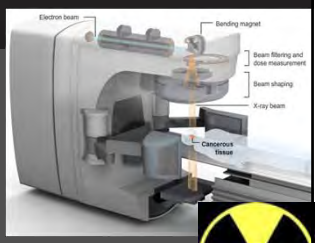
HBO Does:

Chronic Issues



- Delayed Radiation Injury
  - Progressive Obliterative Endarteritis
  - Osteoradionecrosis
  - Soft Tissue Radiation Effects
- Problem Wounds
  - Diabetic Foot Ulcers
- Chronic Refractory Osteomyelitis

Diagnosis	2008-2012 data TNMC			
	Patients/year	Treatments/year	RX %	Pt %
Delayed Radiation Injury	34	1038	65%	40%
Diabetic foot wound	8	185	12%	10%
Osteomyelitis (Refractory)	2	70		2
Skin Grafts/Flaps	5	75		6
CHRONIC totals	52	1417	89%	62%
Necrotizing Infection	10	98	6%	12%
CO Poisoning	18	47	3%	21%
Air/Gas Embolism	2	18		
DCS	2	2		
Compartment Syndrome & Other Acute Ischemias	1	10		
Osteomyelitis (Acute)	1	2		
ACUTE totals	32	180	11%	38%
Totals (per year)	84	1597		

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Therapeutic Mechanisms of HBO

- Enhanced fibroblast proliferation
- Collagen maturation
- Angiogenesis
- Attenuation of the inflammatory cascade
  - **Decreased WBC Adhesion**
- Enhanced host immune competency
  - **Enhanced WBC Killing**
  - **Increase in growth factors and receptors**
  - **Mobilization of stem cells**
- Antibiotic synergism
- Bubble size and gas volume reduction
  - Direct compression
  - Enhanced oxygen diffusion
  - Laplace's Law
- Hyperoxygenation
- Enhanced oxygen diffusion
- Vasoconstriction and edema reduction
- Enhanced elimination of Carbon Monoxide
- Toxin inhibition and inactivation
- Direct bacteriocidal activity

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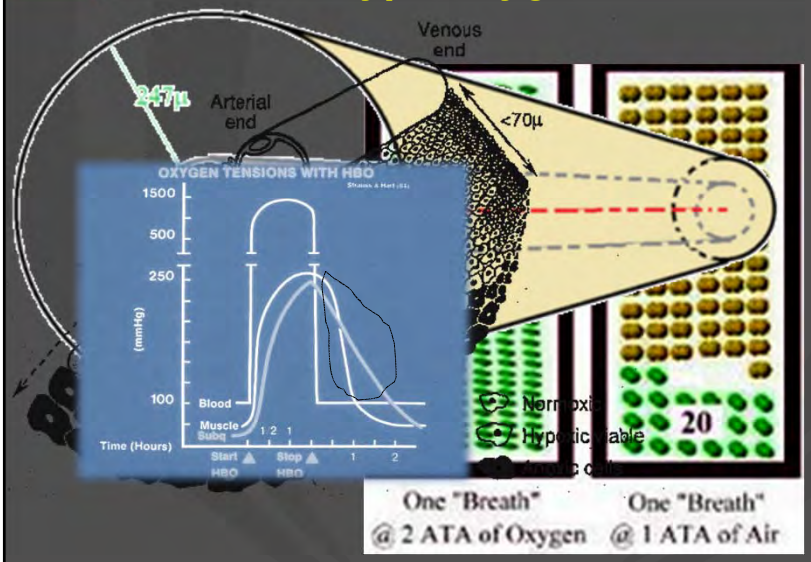
Hyperoxygenation



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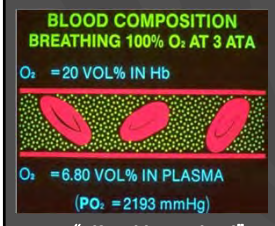
Oxygen Content

(Hgb = 12 g/dl)

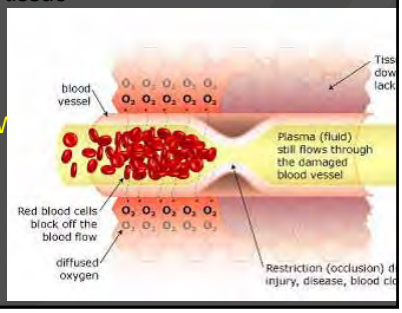
Pressure (ml/dl)(ATA)	FiO_2	PaO_2 (mmHg)	Hgb Bound	O_2 Dissolved	Content Total
1	0.21	120	15.8	0.4	16.2
1	1.0	720	16.1	2.2	18.3
2	1.0	1480	16.1	4.6	20.7
3	***1.0***	***2240***	***16.1***	***6.9***	***23.0***

5.8 vol% is extracted by tissue



"Life Without Blood"
Boerema: J Cardiovasc Surg. 1960:1:133-146

Exceptional Anemia
Jehovah's W
Massive Hemolysis
CO poisoning



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Hyperoxygenation

- **Clinical applications of hyperoxygenation**
  - **Acute traumatic and peripheral ischemias**
  - **Carbon monoxide poisoning**
  - **Compromised skin flaps and grafts**
  - **Thermal burns**
  - **Severe anemia / Exceptional blood loss**
  - **Crush injury and Compartment Syndrome**
- **For radionecrosis:**
  - Enhanced fibroblast proliferation
  - Collagen maturation
  - Enhanced host immune competency
    - **Enhanced WBC Killing**
    - **Increase in growth factors and receptors**
    - **Mobilization of stem cells**
  - Antibiotic synergism

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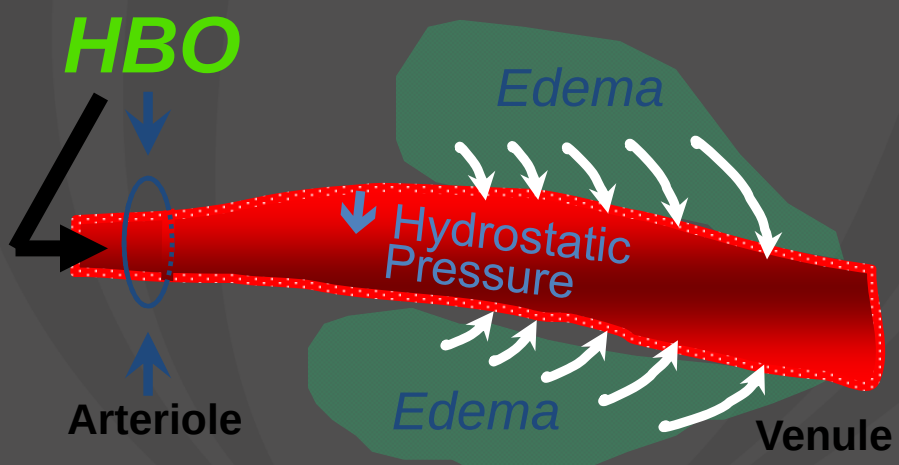
Vasoconstriction



Burns, crush and compartment syndromes, etc

Inflammatory complications of radiation injury and in particular radiation induced cerebral edema

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The Problem

- Radiation is needed to treat cancer
- Radiation can cause Delayed Radiation Injury
  - 5-10% estimated
  - Decreasing with improved treatment strategies

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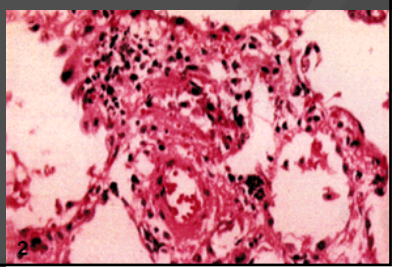
Delayed Radiation Injury

Pathophysiology

- Formerly attributed to trauma and infection
- Tissue biopsies demonstrate progressive, **obliterative endarteritis**
- Subsequent reduction in blood flow results in tissue that is:
  - **Hypovascular**
  - **Hypoxic**
  - **Hypocellular**



Marx RE. *J Oral Maxillofac Surg* 1983;41:283-288.

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Delayed Radiation Injury

Pathophysiology - continued

- Loss of vascularity is progressive
  - Time does not heal *all* wounds
- Tissue breakdown may be spontaneous or follow <u>minor</u> trauma/surgery
- Subsequent hypovascular lesions are frequently **non-healing**
- Grafts or flaps into an irradiated field are frequently unsuccessful

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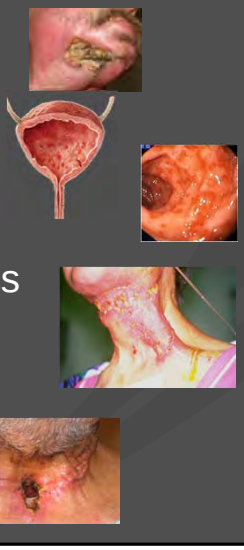
Many areas at risk

- Osteoradionecrosis
- Radiation Cystitis
- Radiation Enteritis/Colitis
- Radiated Bowel Syndrome
- Radiation Mucositis/Stomatitis
- Soft Tissue Radionecrosis
- Radiation Dermatitis
- Laryngeal Radionecrosis



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Therapeutic Mechanisms of Delayed Radiation Effects HBO

- Enhanced fibroblast proliferation
- Collagen maturation
- Angiogenesis
- Attenuation of the inflammatory cascade
  - **Decreased WBC Adhesion**
- Enhanced host immune competency
  - **Enhanced WBC Killing**
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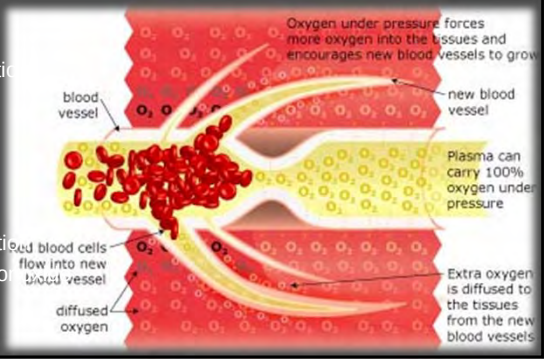

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Neovascularization (Angiogenesis)

- **Adequate oxygen tension is a prerequisite for the formation of collagen matrix by fibroblasts**
- **The collagen matrix provides a framework on which neovascularization can take place**
- **Clinical applications**
  - **Radiation necrosis of bone and soft tissue**
    - **Prophylaxis**
  - **Wound healing in areas of impaired circulation**
    - **Radiation damaged tissue**
    - **Diabetic wounds**
    - **Connective tissue disease**
    - **Peripheral vascular disease (but no substitute for correction of macrovascular disease)**

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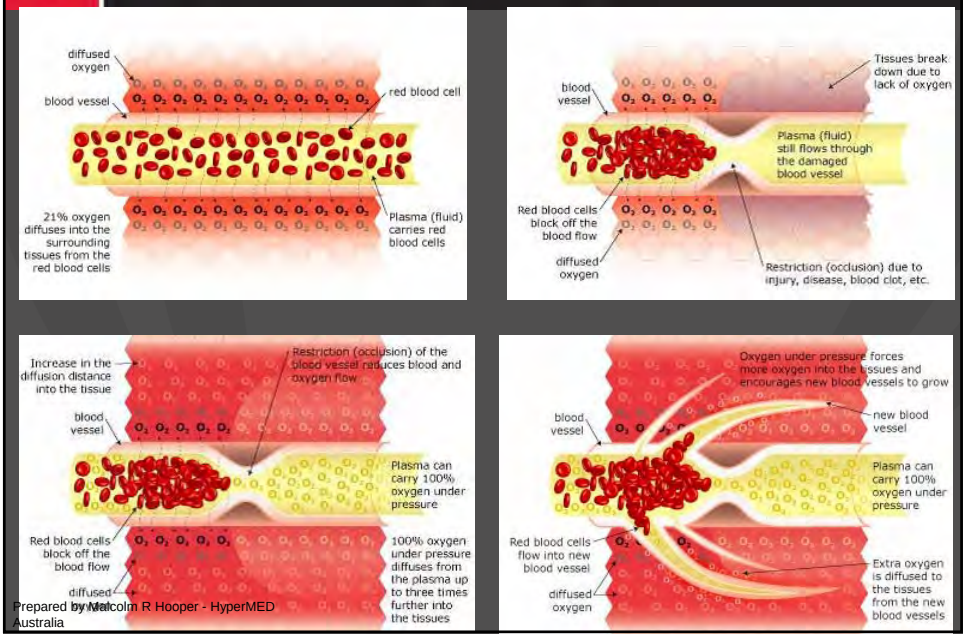
Neovascularization



Prepared by Malcolm R Hooper - HyperMED Australia

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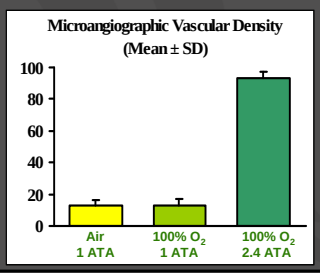
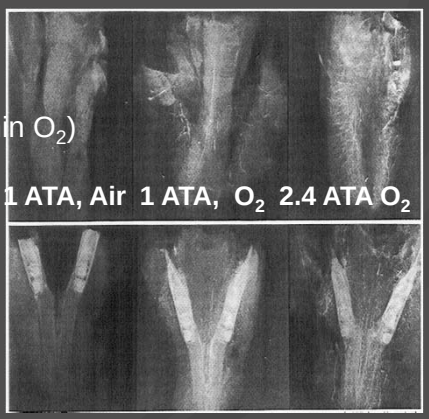
Angiogenesis in Irradiated Tissue

Oxygen Dose Relationship

- 35 rabbits: mandibular radiation
- Dose equal to 60 Gy
- 6 months for injury to develop
- Randomized to:
  - HBO (20 rx, 2.4 atm abs, 90 min O_2)
  - NBO_2 (90 min per day)
  - Air breathing controls





Marx RE. *Am J Surg* 1990;160:519-524

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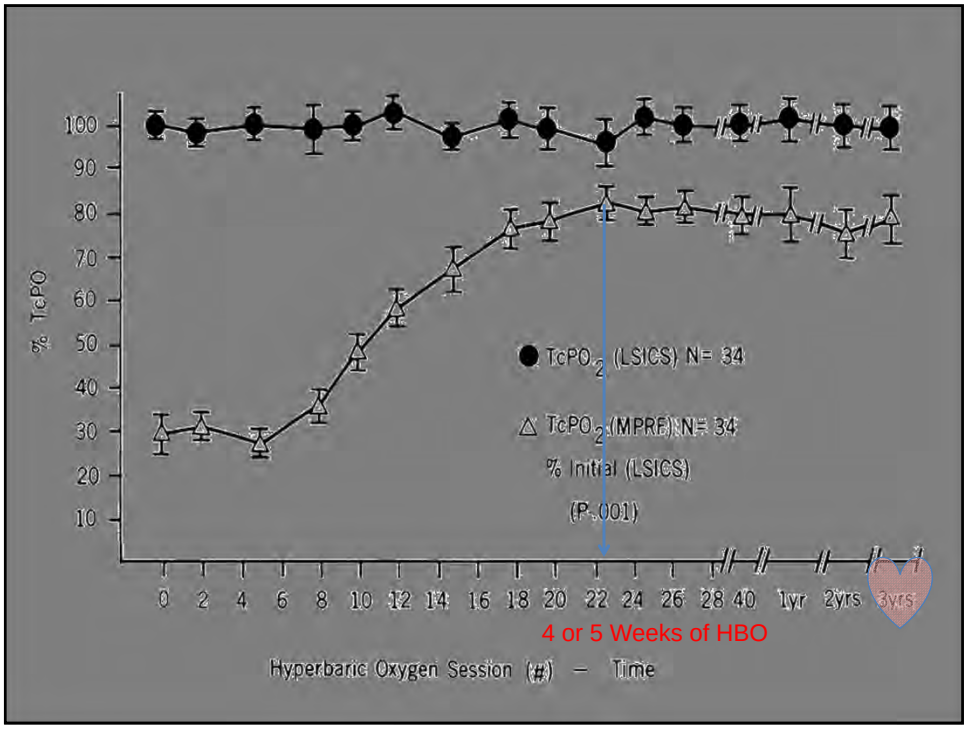
% TcPO
100
90
80
70
60
50
40
30
20
10
TcPO2 (LSICS) N= 34
TcPO2 (MPRF) N= 34
% Initial (LSICS)
(P<.001)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 40 1yr 2yrs 3yrs
4 or 5 Weeks of HBO
Hyperbaric Oxygen Session (#) – Time

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Delayed Radiation Injury and HBO_2
UHMS Committee Recommendations

- Osteoradionecrosis
  - Usually Mandibular
- Soft tissue radionecrosis
- Surgical wounding in radiation-damaged tissue

Hyperbaric Oxygen Therapy Committee 2008 Report.

Mandibular Osteoradionecrosis
Pathophysiology

- Bacterial infection is not typically a part of the process
- Primarily related to vascular damage
- Paucity of nutrient vessels and fibroblasts

Marx RE. *J Oral Maxillofacial Surg* 1983.

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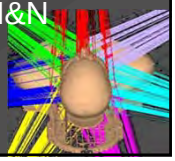
Osteoradionecrosis

- Damage to osteocytes from radiotherapy
  - Weakens bone, predisposing to fracture
  - Often painful, broken down mucosal coverage
  - Decreased blood flow, difficulty fighting infection
- Body of the mandible most affected
  - Least redundant blood supply & muscle coverage
  - Incidence decreased significantly in last 30 years
    - Lower radiation doses, more targeted fields
    - Currently less than 5% of patients receiving H&N radiotherapy



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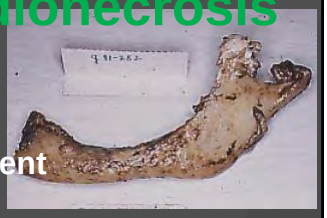
Mandibular Osteoradionecrosis



- **Etiology**
  - **Avascular aseptic necrosis**
  - **Infection is not a major component**
- **Incidence of ORN**
  - **0% with < 6000 cGy**
  - **1.8% with 6000 to 7000 cGy**
  - **9% with >7000 cGy**
- **Occurs > 6 months after radiotherapy**
- **Progressive over time**
- **Maybe precipitated by trauma or surgery**

Bedwinek JM. *Radiology* 1976;119:665

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Mandibular Osteoradionecrosis

HBO Treatment – Evidence for Efficacy

- From 1975-2001, 14 case series using HBO and surgery were reported
- 13/14 studies found benefit from HBO
- From combined reported series, 368 of 429 patients (86%) improved

Feldmeier JJ, Hampson NB. *Undersea Hyperbaric Med* 2002.

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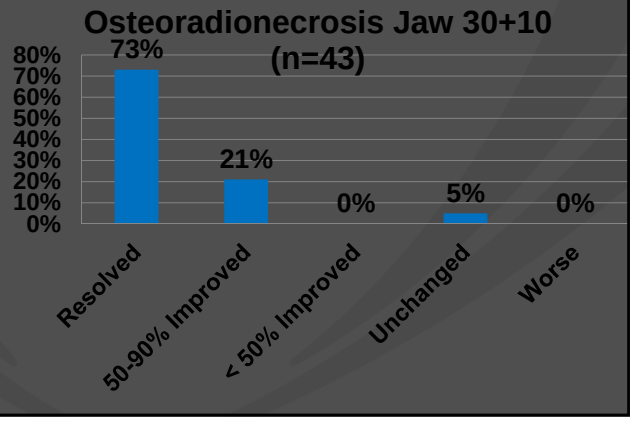
Mandibular Osteoradionecrosis

Robert Marx Success Rates

Treatment	# Pts.	Resolution Rate
Non-HBO	65	8%
HBO alone	51	17%
WHMC-UM Protocol	130	100%



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Osteoradionecrosis

- Cochrane review 2005
  - Outcome measures
    - Primary: Survival, resolution of disease
    - Secondary: Mucosal coverage, bony continuity, pain (poor data)
  - Identified 6 trials that met rigorous evidence standards
    - Treatment algorithms differed slightly
    - Pooled data for mandible
    - 92% resolution with HBO, 65% in control group NNT < 4
    - Improved mucosal coverage (93% v. 67%)
      - RR 1.4 (95%CI 1.2-1.6, p< 0.001); NNT < 4
    - Improved bony continuity (92% v. 65%)
      - RR 1.4 (95%CI 1.1-1.7; p=0.009); NNT < 4
  - Conclusion: HBO is safe and likely effective for ORN

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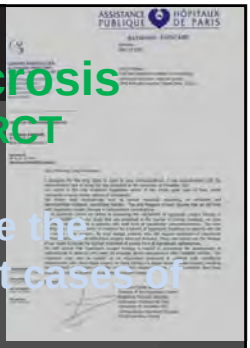
Mandibular Osteoradionecrosis

HBO Treatment – One Negative RCT



- **Study was designed to determine the effect of HBO on the very earliest cases of mandibular ORN (Marx Stage 0)**
- **Attempted to investigate HBO as a solo modality, hoping to avoid surgery**
- **Findings have limited application because advanced cases of ORN were not included**
- **Marx had already published that HBO was adjunctive NOT a stand alone therapy**

J Clin Oncol 2004; 22:1-8.

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Mandibular Osteoradionecrosis

Cost Effectiveness of HBO Treatment

- Cost of ORN management in 2006 US dollars:

  $168,000 without HBO

  $53,000 with HBO

Marx RE. 1999.
www.westegg.com/inflation

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Marx Protocol (Prophylaxis)

- **Prophylaxis**
  - **For oral surgery / tooth extractions in a previously irradiated field**
  - **Mandible… maxilla not a problem**
  - **> 5000 cGy**
- **Treatment Protocol**
  - **20 pre-op HBO (2.0 to 2.5 ATA x 90 minutes)**
  - **Surgery/Tooth Extractions**
  - **10 post-op HBO**
- **If repeated surgery … only post-op HBO is needed (up to 3 to 5 years minimum)**

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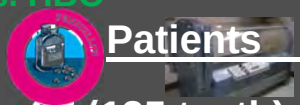
Osteoradionecrosis Prophylaxis

Penicillin vs. HBO



	Patients	ORN
Penicillin	37 (135 teeth)	11 (29.9%)
HBO	37 (156 teeth)	2 (5.4%)

1:3 →1:20

- 74 patients requiring tooth extraction from previously irradiated mandible
- 6000 cGy or greater
- Randomized to perioperative penicillin or prophylactic hyperbaric oxygen treatments (20 + 10)

Marx RE. *JADA* 1985;111:49-54.

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Osteoradionecrosis Prophylaxis

HBO Treatment – Evidence for Efficacy

- From 1985-2001, 3 studies (1 RCT and 2 case series) using HBO have been reported
- 3/3 studies found benefit from HBO therapy
- From combined reported series, 86 of 90 patients (96%) have been successfully treated with HBO

Feldmeier JJ, Hampson NB. *Undersea Hyperbaric Med* 2002

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Soft Tissue Radionecrosis

Role of Hyperbaric Oxygen

- Daily outpatient treatments to stimulate angiogenesis
- Goal is primary healing or promotion of granulation tissue to support grafting
- When healing is underway, HBO can be stopped
- Post-operative treatment may be of value

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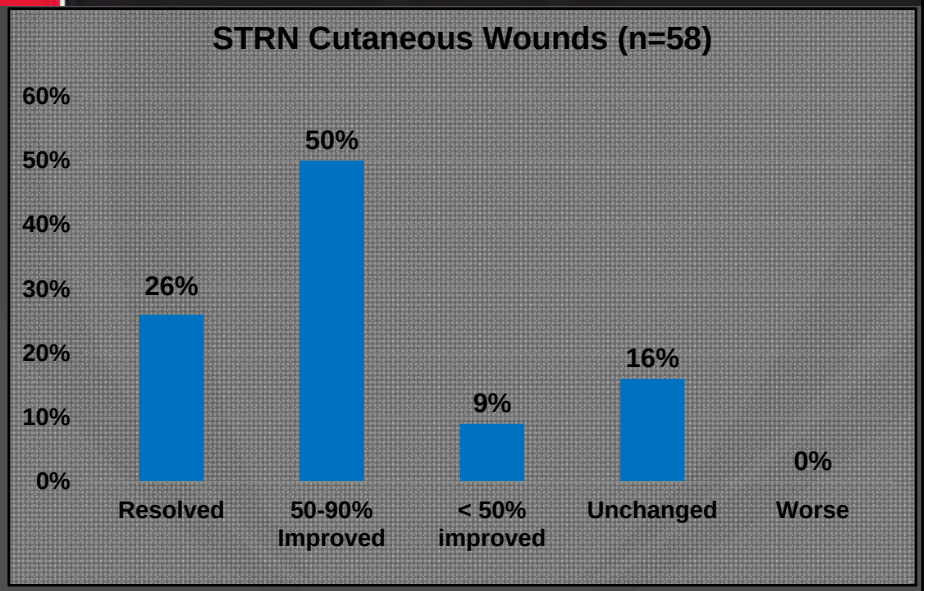

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STRN of the Head and Neck

HBO Treatment – Evidence for Efficacy

- From 1979-2001, 6 studies (1 PCT and 5 case series) using HBO ± surgery were reported
- 6/6 studies found benefit from HBO_2
- From combined reported series, 117 of 133 patients (88%) were successfully treated with HBO_2

Feldmeier JJ, Hampson NB. *Undersea Hyperbaric Med* 2002.

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Laryngeal Radionecrosis

Treatment with HBO

- 18 patients unimproved for at least 3 months
- Mean radiation dose 6600 cGY
- Chandler Grade:
  III - 2 patients; IV - 16 patients
- Treated with an average of 41 HBO treatments
- 13 patients (72%) had major improvement
  - None required laryngectomy
  - All maintained voice and deglutition in good or normal condition
- 5 patients (28%) failed to respond and underwent total laryngectomy

Filntisis GA. *Ann Otol Rhinol Laryngol* 2000

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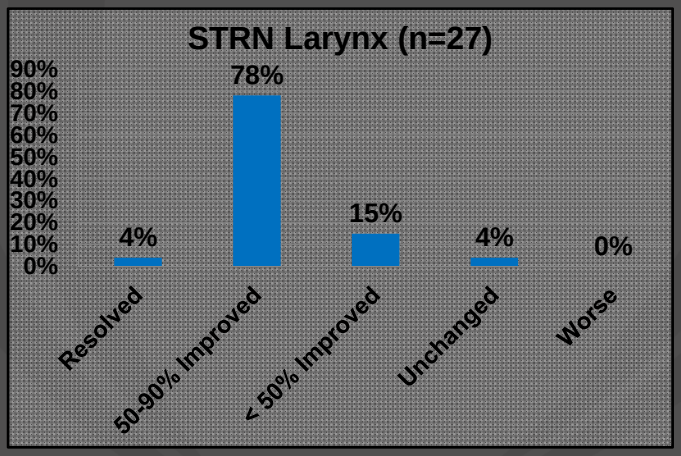
Laryngeal Radionecrosis

Treatment with HBO - Results



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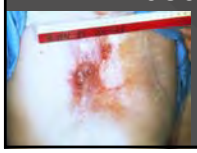
Chest Wall Radionecrosis

Feldmeier JJ. *Undersea Hyperbaric Med* 1995.

- 23 patients with chest wall radionecrosis
  - 8 soft tissue only
  - 15 bony and soft tissue necrosis
- Treated with HBO (av. 36 treatments; 2.4 ATA x 90')
- Soft tissue only:
  6 of 8 (75%) healed (4 required flaps or grafts)
- Soft tissue and bony involvement:
  8 of 15 (53%) resolved (all required aggressive debridment and 4 flaps)



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Breast Surgery and Radiation Injury

Treatment with HBO

- 44 patients with persisting symptoms after breast-conservation surgery and radiation (50 Gy in 25 fractions)
- 32 received HBO (2.4 ATA x 90' median 25 treatments)
- 12 refused HBO_2 and served as controls

Carl UM. *Int J Radiation Oncology Biol Phys*, 2001.

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Breast Surgery and Radiation Injury

Treatment with HBO - Results

SOMA LENT Score	Control*	HBO_2*	p-value
Pain (1-4)	3 → 3	3 → 0	<0.001
Edema (1-3)	2 → 2	3 → 1	<0.001
Erythema (1-3)	3 → 2	2 → 0	<0.001
Sum Score (3-10)	8 → 7	8 → 1	<0.001

*Results are medians for each group.

Carl UM. *Int J Radiation Biol Phys*, 2001.

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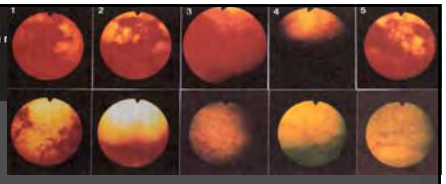

Radiation Cystitis

Clinical Aspects

- Incidence of 1.0-2.5% in pelvic irradiation
- Bladder biopsies demonstrate obliterative endarteritis
- Frequency, urgency, pain, hematuria
- Conventional therapy - fulguration or installation of alum, formalin, silver nitrate

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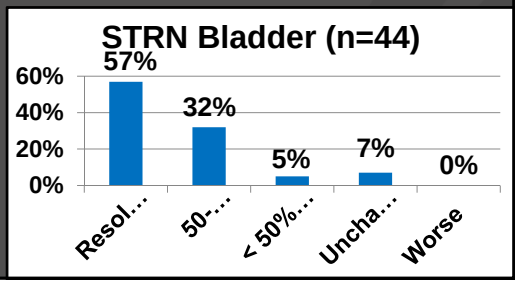
Radiation Cystitis

HBO Treatment – Evidence for Efficacy

- From 1985 to 2001, case series from 14 institutions using HBO_2 were reported
- 13/14 studies found benefit from HBO_2
- Of 177 patients reported, 145 (82%) have had improvement or resolution of hematuria with HBO_2



Feldmeier JJ, Hampson NB. *Undersea Hyperbaric Med* 2002.

EFFECTIVENESS OF HYPERBARIC OXYGEN THERAPY ON RADIATION INDUCED HEMORRHAGIC CYSTITIS.

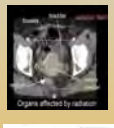
Justin Johnson MD, Jeffrey Cooper MD, Lon Keim MD, Larry Siref MD
University of Nebraska Medical Center and The Nebraska Medical Center's Hyperbaric Medicine Clinic

Study Type: Case Series

Introduction:
Hemorrhagic cystitis is an unfortunate complication of radiation therapy (XRT) for pelvic malignancies occurring in 3-5% of treated patients. It occurs 2 months to 15 years post XRT. XRT leads to progressive obliteration of small blood vessels in bladder mucosa, leading to hypoxia and tissue damage. Symptoms range from frequency and urgency to bleeding with clot retention. Palliative treatments (cystoscopy with fulguration, instillation of alum, silver nitrate, or formalin) may be ineffective at improving the patient's symptoms and do not treat the disease's pathogenesis. Hyperbaric oxygen therapy (HBO) has been used for treatment of radiation−induced tissue injury and poorly healing wounds. Studies have shown that HBO can promote angiogenesis and collagen deposition. We assess the short and long−term efficacy of HBO for radiation−induced hemorrhagic cystitis (RIHC).

Methods:
A retrospective, chart−review was performed on 20 patients, with RIHC refractory to palliative treatments, treated with HBO at our institution in eleven years. Mean age was 70.9 years (41−90). Primary pathologic conditions were prostate (80%), colorectal (10%), and cervical (10%) cancers. Mean time between radiation treatment and HBO was 4.75 years (.25 - 17).

Results:
17/20 patients (85%) had marked improvement or complete resolution of symptoms with HBO. Of the remaining three patients, 2 were considered treatment failures and 1 patient had treatment terminated due to medical co -morbidities. In long term follow−up 14/17 continued to have marked improvement or complete resolution of symptoms, 1 patient had persistent/recurrent hematuria and had an angioembolization procedure and 2 patients were lost to follow up. These results are consistent with previous reports.

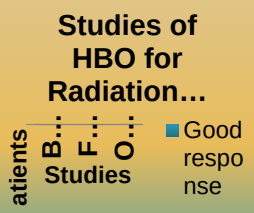


Review of the Literature
Feldmeier and Hampson reviewed published case series reports (there are no randomized controlled studies) of HBO for radiation cystitis. 16 of the 17 studies from 14 institutions (1985 to 2001) found benefit from HBO. Of 190 patients reported on, 145 (76%) have had improvement or resolution of hematuria with HBO.

Bevers published the largest of these case series (n=40) and the only one done prospectively although not randomized or controlled. He found a 75% response rate with about 17% moderate response and 8% failure rates.

A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. Feldmeier JJ, Hampson NB. Undersea Hyperb Med. 2002 Spring;29(1):4-30

Hyperbaric oxygen treatment for haemorrhagic radiation cystitis. Bevers RF, Bakker DJ, Kurth KH. Lancet. 1995 Sep 23;346(8978):803-5.



Conclusion
Hyperbaric Oxygen Therapy for Radiation Induced Radiation Cystitis is an efficacious treatment option, both short and long−term, for patients that have failed other treatment options.

Recent advances in radiation therapy. Gerber DE, Chan TA. Am Fam Physician. 2008 Dec 1;78(11):1254-62.

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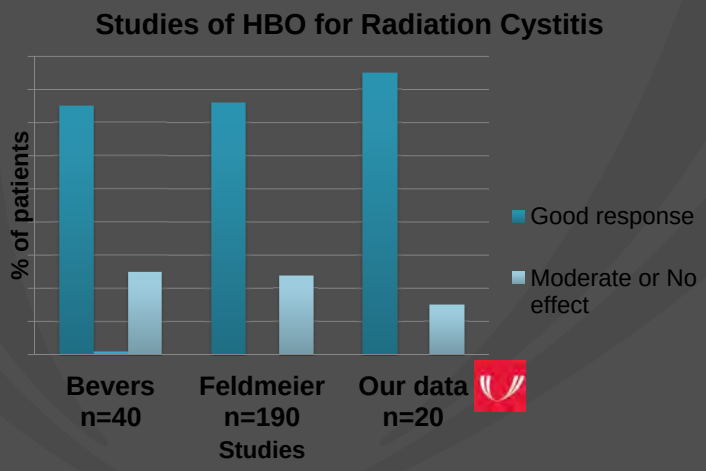
Radiation Cystitis

HBO Treatment – Evidence for Efficacy



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HBO for Radiation Cystitis

Is Early Treatment Better?

- 60 patients treated for hemorrhagic radiation cystitis at VMMC in Seattle
- 80% overall response rate
- When treated < 6 months after onset of hematuria, 96% response
- When treated > 6 months, 66% response

Chong KT, Hampson NB, Corman JM. *J Urol* 2005.

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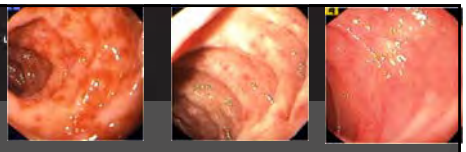

Radiation Proctitis

Treatment with HBO

- 27 men with proctitis following XRT for prostate cancer
- Average 36 HBO_2 treatments (29-60)
- Bleeding resolved in 48%, improved in 28%
- Pain improved in 75%

Dall'Era MA, Hampson NB, Corman JM. *J Urol* 2006.

Radiation Proctitis

Presence of Rectal Ulceration

- 14 of 27 had rectal ulceration
- 7 (50%) resolved or improved with HBO_2
- Failures typically had progressive ulceration requiring diverting colostomy

Dall'Era MA, Hampson NB, Corman JM. *J Urol* 2006.

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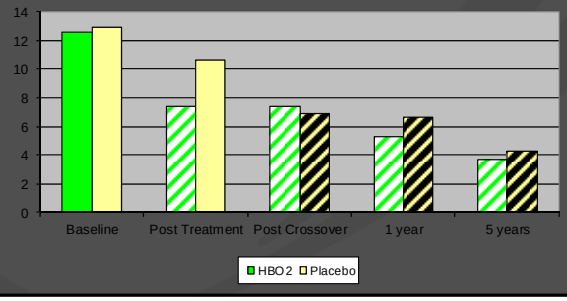
Radiation Proctitis - Double Blind RCT

Clarke RE. *Int J Radiation Oncology Biol Phys* 2008

- 150 patients randomized to 30-40 HBO_2 treatments at 2.0 ATA vs. air at 1.1 ATA
- Sham patients then crossed over to HBO_2
- 120 completed study protocol

- Healed or improved:
  - 89% HBO_2 group vs. 62% (p=0.0009)
  - Absolute risk reduction 32%, resulting in NNT=3
- Marked improvement in bowel-specific QOL in HBO_2 vs. sham group



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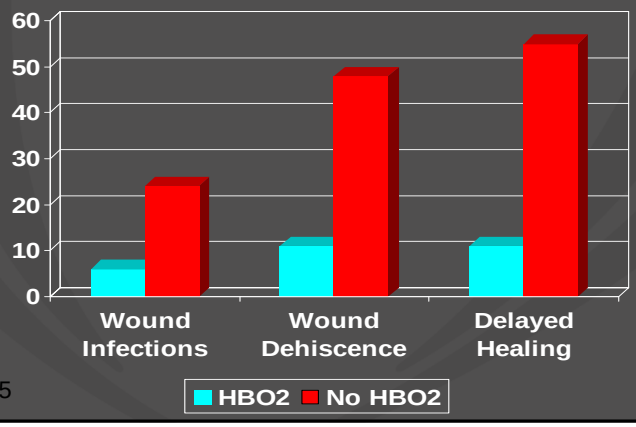
Surgery in Irradiated Tissue

Prospective Controlled Trial

- 160 patients requiring soft tissue surgery or flap introduction into irradiated tissue (>64 Gy)



Marx RE. 1995

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Radiation Encephalopathy

- Five of six patients being treated with HBO as an adjunct for Radiation encephalopathy improved by clinical and imaging criteria. (Chuba et al 1997)

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Delayed Brain Radiation Injury

Prophylaxis with HBO in Humans

- 78 patients with brain tumors treated with stereotactic radiosurgery (SRS)
- 32 received post-SRS HBO treatment
- MR evidence of radiation injury in 11% of HBO group vs. 20% controls (p=0.05)

Ohguri T. *Int J Radiation Oncology Biol Phys* 2007

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Complications of HBO Therapy

- **Claustrophobia**
- **Barotrauma**
  - **Mostly ear and sinus problems**
    - **Myringotomy**
  - **Change in refraction (reversible)**
  - **Pneumothorax (+/- tension) is very rare**
- **Oxygen toxicity seizure (1 in 10,000)**
  - **Limits depth to 3 ATA oxygen**
  - **Only seen in chamber and self limited**
    - **Does not induce Epilepsy**
  - **Chambers set up with "Air Break" masks**
- **Pulmonary Toxicity**
- **Pulmonary Edema**
  - **Rarely seen in patients except with low EF (due to inc. SVR)**
- **Fire**

Relative Contraindications

- Seizure disorder, high fevers, narcotics
- Congenital spherocytosis (very rare)
- URI/chronic sinusitis
- Otosclerosis surgery
- Spontaneous pneumothorax (diving vs. HBO)
- Emphysema and CO2 retention
- Altered mental status (aspiration risk)
- Adriamycin with HBO
- Bleomycin with HBO
- Sulfamylon
- Antabuse

Untreated Pneumothorax is the only absolute contraindication

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Hyperbaric Oxygen
Does it Cause or Promote Cancer?

- Review of 32 published studies from 1966-2001
- 15 clinical reports, 17 animal
- 10 of 15 clinical reports showed no enhancement of cancer growth
- 15 of 17 animal studies showed no cancer-enhancing effect

Feldmeier JJ. *Undersea Hyperbaric Med* 2003.

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Behold!

My Hyperb[illegible]enator

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University of Nebraska Medical Center
The Nebraska Medical Center
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- Treatment time
  - Just over 2 hours
- Treatment course
  - 5 days per week (Monday-Friday)
  - ORN prophylaxis 20+10 (4+2 weeks)
  - ORN 30+10 (6+2 weeks)
- Cost of therapy
  - Insurer dependant
  - $850-1500 per treatment (facility+profee)