MHIF FEATURED STUDY:

EV ICD (Extravascular Implantable Cardioverter Defibrillator Pivotal Study)

OPEN AND ENROLLING

EPIC message: *Research MHIF Patient Referral*

CONDITION:	PI:	RESEARCH CONTACT:	SPONSOR:
life-threatening ventricular tachyarrhythmias	Charles Gornick, MD	Jessica Whalen Jessica.whelan@allina.com | 612-863-1661	Medtronic

DESCRIPTION:

The EV ICD system is designed to deliver lifesaving defibrillation and pacing therapy via a device the same size as traditional, transvenous ICDs, but with a lead (thin wire) placed outside the heart and veins. The EV ICD device is implanted below the left armpit (in the left mid-axillary region), and the lead is placed under the sternum (breastbone).

Purpose: to demonstrate safety and efficacy of the EV ICD System.

CRITERIA LIST/ QUALIFICATIONS:

Inclusion:

1. Class I or IIa indication for implantation of an ICD according to the ACC/AHA/HRS Guidelines, or ESC guidelines
2. Geographically stable and willing and able to complete the study procedures and visits for the duration of the follow-up

Exclusion:

1. Indications for bradycardia pacing or Cardiac Resynchronization Therapy (CRT) Class I, IIa, or Iib indication
2. Existing pacemaker, ICD, or CRT device implant or leads
3. History of these medical interventions: sternotomy, any medical condition or procedure that leads to adhesions in the anterior mediastinal space (i.e., prior mediastinal instrumentation, mediastinitis), abdominal surgery in the epigastric region, planned sternotomy, chest radiotherapy
4. Previous pericarditis that was chronic and recurrent, **or** resulted in pericardial effusion, **or** resulted in pericardial thickening or calcification
5. History of these medical conditions or anatomies: hiatal hernia that distorts mediastinal anatomy, marked sternal abnormality (e.g., pectus excavatum), decompensated heart failure, COPD with oxygen dependence, gross hepatosplenomegaly

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Hyperbaric Oxygen Therapy

Senthil Jayarajan, MD, MS, FACS
Director, Hyperbaric Medicine
Vascular Surgery
Minneapolis Heart Institute @ Abbott Northwestern Hospital

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Overview

- History of Hyperbaric Medicine
- Mechanism of Action
- Process of Treatment
- Indications
- Future Directions

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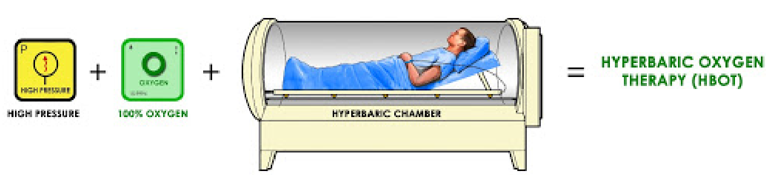
What is Hyperbaric Oxygen Therapy?

- The use of high pressure and oxygen as a drug to treat basic pathophysiologic processes and their diseases



- Administrated by placing the entire patient inside a pressured vessel
- Duration of therapy and pressure vary based on indication

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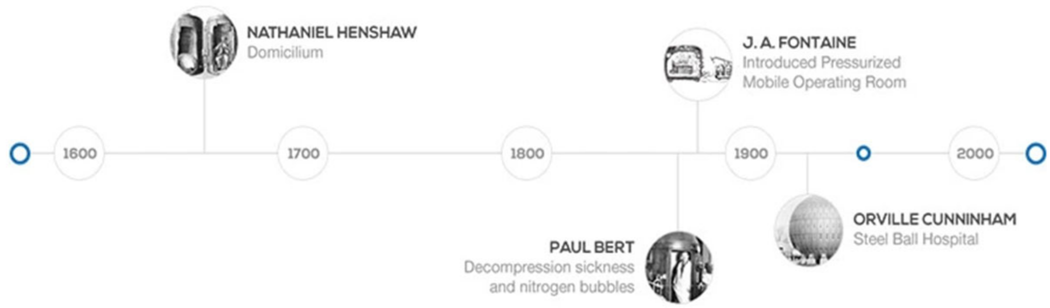
HBOT is not new…



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Modern Investigations of HBOT

- 1937 – Behnke and Shaw first used hyperbaric oxygen successfully for treatment of decompression sickness suffered by deep sea divers
- In 1950's – Modern clinical application of HBOT began with increased understanding of blood gas analysis and gas exchange physiology
- In 1960's –
  - First treatment of **gas gangrene** at University of Amsterdam
  - First used to **assist wound healing** of burns sustained in coalmine explosions
- Since 1970's, research for new indications for HBOT and testing of efficacy has accelerated

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So how does HBOT work?

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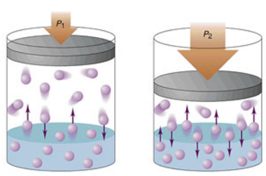
Mechanism of Action

- Physics
  - Henry's Law – solubility of a gas is directly proportional to partial pressure of gas above the liquid



  - Increasing the atmospheric pressure increases amount of gas dissolved into a fluid
    - Oxygen into blood plasma
- Physiology
  - What is getting hyper oxygentated?
    - Blood Plasma
    - Cerebrospinal Fluid
    - Lymph Fluid
  - At clinical hyperbaric pressures
    - 10-15 x normal amount of oxygen
    - Allows bypass of body's normal system of transporting oxygen

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Mechanism of Action

100cc of blood
1 ata, 21% FIO_2 → 19cc O_2 in Hb
0.32cc in plasma

100cc of blood
1 ata, 100% FIO_2 → 20cc O_2 in Hb
2.09cc in plasma ↑

The higher pressure during HBOT pushes more oxygen into plasma

100cc of blood, 2 ata, 100% FIO_2 → 20cc O_2 in Hb, **4.4cc** in plasma
100cc of blood, 3 ata, 100% FIO_2 → 20cc O_2 in Hb, **6.8cc** in plasma

This additional O_2 in plasma is sufficient to meet tissue needs **without** contribution from O_2 bound to hemoglobin and is responsible for most of the beneficial effects of this therapy

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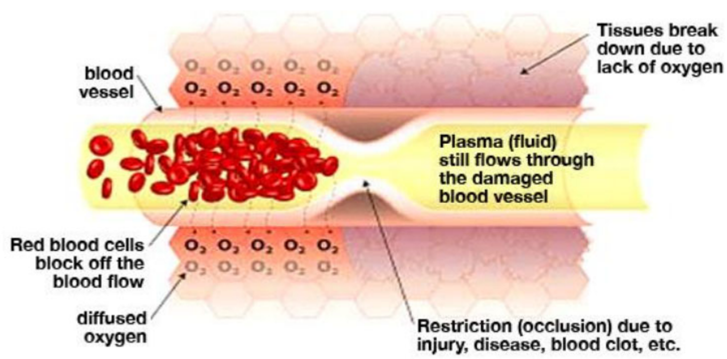
Mechanism of Action

POOR BLOOD FLOW
=
POOR OXYGENATION
=
TISSUE DAMAGE



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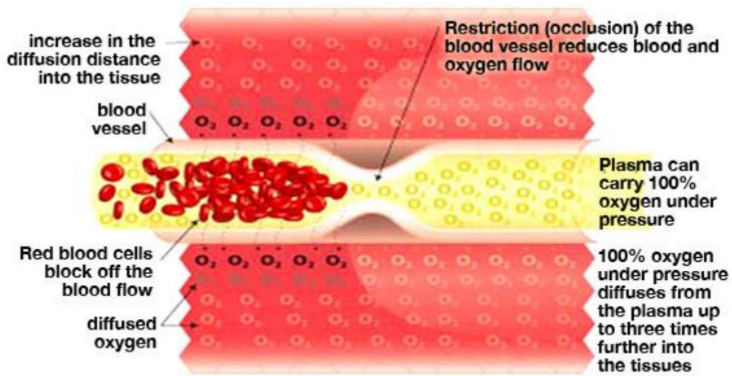
Mechanism of Action

HYPERBARIC CONDITIONS



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Mechanism of Action

- Limits ischemia damage, cell death, inflammation
- Promotes collagen synthesis (fibroblast stimulation)
- Decreases lactate production and tissue acidosis
- Aids in oxygen dependent killing of bacteria
- Limits leukocyte adhesion and degranulation
- Decreases tissue edema

- Stem Cell Mobilization
  - Causes mobilization of CD34+ progenitor cells from bone marrow
- Angiogenesis
  - Promotes neovascularization of poorly perfused tissue
- Oxygen is more than a metabolite
  - Initiates signal transduction and activating wound healing pathways

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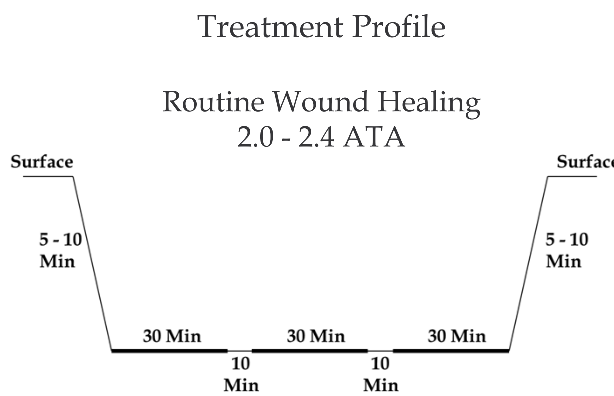
Process of Treatment

- 100% oxygen at 2-2.4 ATA
- Airbreaks are used to reduce oxygen toxicity
- Treatment time – 90-120 minutes
- Usually once daily x 5 days x 2-8 weeks, depending on indication



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Multiplace Chamber

- Large room that is pressurized with 100% oxygen provided via mask
- Multiple people (6-8) can be treated at same time
- Allows for critically ill patients to be treated

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Monoplace Chamber

- One patient per chamber
- Allows for individualized treatment protocol
- More commonly available

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Adverse Effects of HBOT

- Otic barotrauma: usually mild (2-10%)
- Reversible myopia: incidence (2%)
- CNS oxygen toxicity: seizure (1:10,000-1:80,000) - No long term sequelae
- Pulmonary barotrauma: pneumothorax (very rare <1:1,000,000)
- May exacerbate congestive heart failure (run at lower pressure)

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Contraindications

- Untreated tension pneumothorax
- Recent or current use of:
  - Doxorubicin (Adriamycin) - cardiotoxicity
  - Cisplatin – impaired wound healing
  - Bleomycin – interstitial pneumonitis
  - Disulfiram (Antabuse) – blocks superoxide dismutase, which is protective against oxygen toxicity
  - Mafenide acetate (Sulfamylon) – impaired wound healing

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Relative Contraindications

- Decompensated CHF
- Severe upper respiratory infections
- High fevers –should be lowered before HBOT
- Emphysema with CO_2 retention
- History of thoracic surgery
- Malignant disease: highly vascular cancers
- Patients at risk for middle ear barotrauma
- Hypertension, low blood sugars

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When can we use HBOT?

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Indications

- Acute CO intoxication
- Decompression illness
- Gas embolism
- Acute traumatic peripheral ischemia
- Crush injury
- Actinomycosis
- Cyanide poisoning
- Soft tissue radiation injury
- Diabetic lower extremity wounds
- Arterial insufficiencies
- Preparation/preservation of compromised skin/muscle grafts/flaps
- Osteoradionecrosis
- Chronic refractory osteomyelitis
- Progressive necrotizing infections/Gas gangrene

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"Off Label" Uses - Worldwide

- Aging
- Sports injury and recovery
- Lyme disease
- Cerebral palsy
- Autism
- Bells Palsy
- Crohn's Disease/IBD
- Chronic Fatigue Syndrome
- CRPS/RSD
- Arthritis
- Diabetic Retinopathy
- Post Surgery Recovery/ Healing from laser and cosmetic surgery
- Migraine and cluster headaches
- Multiple Sclerosis (acute, relapsing, remitting, chronic)
- Osteonecrosis – avascular, aseptic, ischemia bone necrosis
- Non-healing Fractures – Nonunion
- Peripheral Neuropathy
- Psoriasis
- Lupus
- Immune System Support
- Cancer
- Macular Degeneration

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Cases

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Indication: Skin Flap Necrosis

- 82M Russian speaking only developed a left toe diabetic foot ulcer that developed osteomyelitis 4-6 months prior to consultation.
- He had undergone multiple arterial revascularization procedures at OSH with little success
- Left TMA performed one month prior to hospitalization during which he was evaluated for Hyperbaric Oxygen Therapy
- He had been told that the TMA was failing and that he would likely need below knee amputation, which he was adamantly against.

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Vascular Surgery Consult

- ABI demonstrated noncompressible PT/DP, no flow in digits
- Taken for an angiogram to try and improve arterial circulation. However, no revascularization options for either endovascular techniques or bypass.
- TCPO2 - significant reduction in readings but improved with oxygen challenge
  - Baseline (supine): 26-33 mmHg (need >40 mmHg for wound healing)
  - O_2 challenge: increased to 83 mmHg

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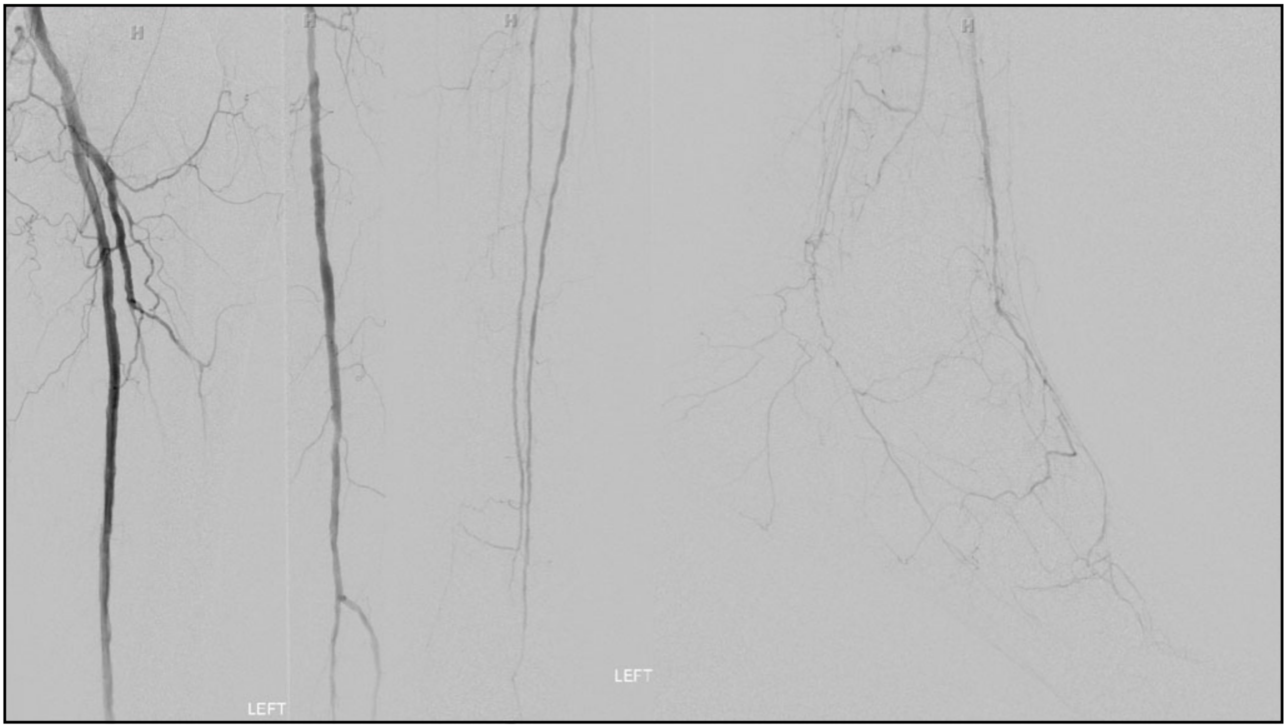

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Treatment

- He was started on HBOT at 2.4ATA for 90 minutes with airbreaks

Session 1, Day 1

Session 14, Day 25

Session 30, Day 37

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Outcome

- Poor wound healing potential of TMA flap given diabetes and poor arterial revascularization options
- But had a favorable TCPO2 with good response to oxygen challenge
- HBOT as an adjunct to good wound care principles applied at ANW wound clinic was able to encourage a wound healing response and avoid major amputation

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Indication: Crush Injury/Chronic Osteomyelitis

- 69-year-old gentleman who had sustained a traumatic right leg fracture during a boating accident status post open reduction internal fixation.
- He had a right ankle ulceration for the past 6 months that was resistant to healing. He was found to have underlying osteomyelitis on bone biopsy and bone scan. Bactrim was prescribed for the osteomyelitis
- He had been wheelchair bound due to pain with weightbearing at wound for nearly a year and on disability at the time of presentation.

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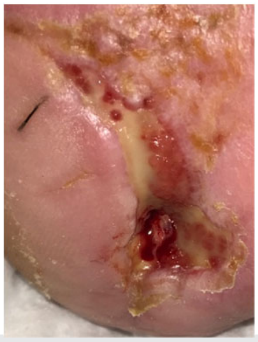
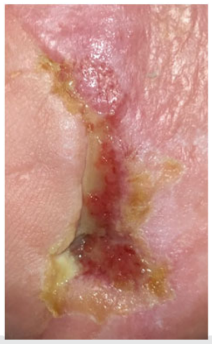
Treatment

- He was started on 2.4 ATA for 90 minutes with 2 ten minute air breaks

Day 1, Dive 1

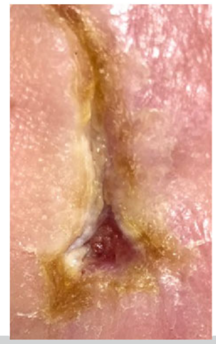


Day 17, Dive 12



Day 31, Dive 22

Day 41, Dive 30



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Outcome

- Nonhealing crush injury with open ulceration and chronic osteomyelitis
- HBOT as an adjunct to good wound care principles and appropriate treatment of osteomyelitis was able to encourage a wound healing response and avoid above knee amputation
- He began HBOT confined to a wheelchair, but by the end he was back to walking with a cane for assistance.

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Indication: Necrotizing Soft Tissue Infection

- 53 year old Spanish only speaking man undergoing chemotherapy for acute promyelocytic leukemia, developed MRSA bacteremia and left hip and thigh necrotizing soft tissue infection.
- Underwent multiple debridements at an outside hospital, transferred to Abbott Northwestern for consideration for Hyperbaric Oxygen Therapy
- Alternative would have been left hip disarticulation, which may have failed due to burden of infection

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Initial CT Scan at ANW

- Large complex lobulated peripherally enhancing fluid collection in the medial left hip and posteromedial left thigh nearly the entire length compatible with complex abscess.
- Likely myositis combined with myonecrosis left adductors and posterior compartment left thigh musculature.
- Multiple small pelvic wall abscesses noted along left pelvic brim

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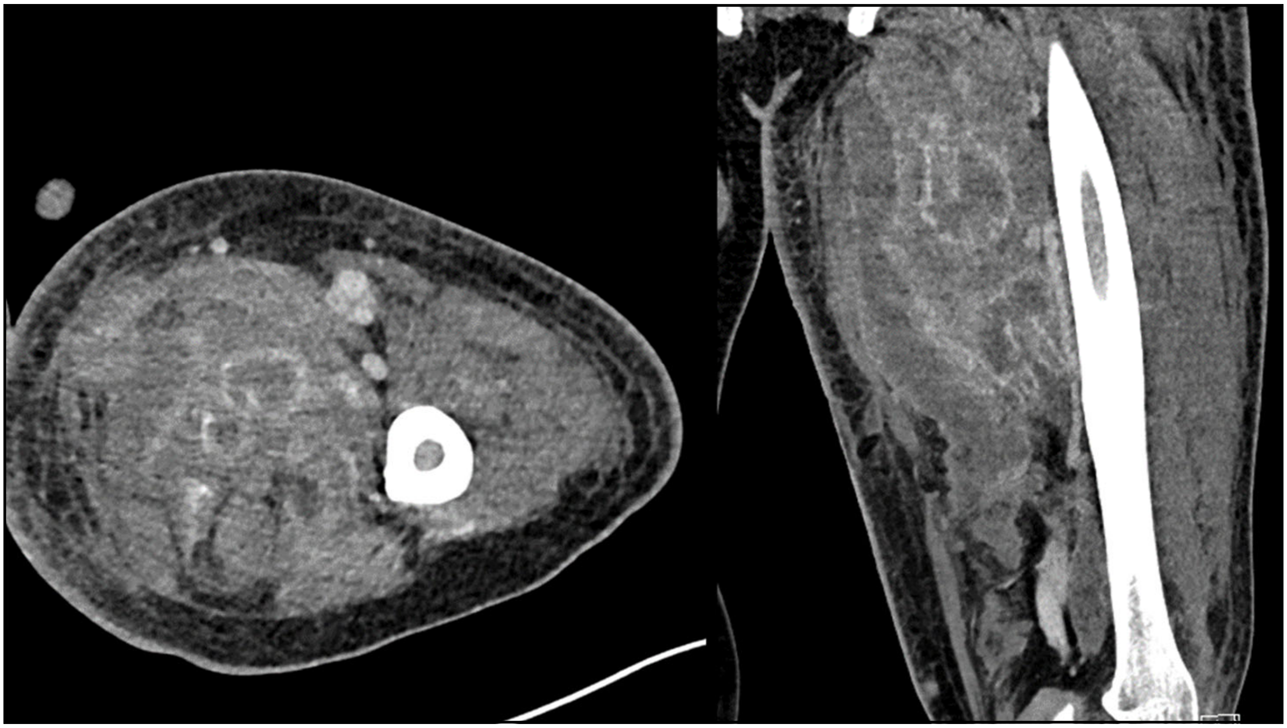

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Treatment

- Patient began HBOT at 2.4 ATA with 10 minute airbreaks on day of transfer
- Continued HBOT for 5 days a week for 3 weeks for 15 sessions
- Did have a few debridements by Orthopedic surgery via lateral and medial thigh incisions with reduction in purulence and necrotic tissue over the course of therapy. Unable to reach the pelvic abscesses via open or percutaneous approach safely
- After necrosis controlled, the patient underwent closure with Primatrix graft application over medial wound

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Outcome

2 months after discharge:

- He was able to ambulate with minor assistance
- He had resumed oncologic treatments
- The thigh wounds had completely healed and off antibiotics

Conclusion:

Successful treatment of necrotizing soft tissue infection and return to decent functional status with serial debridements, veriflow vac dressing, and antibiotics with hyperbaric oxygen therapy as an adjunct to potentially reduce loss of muscle.

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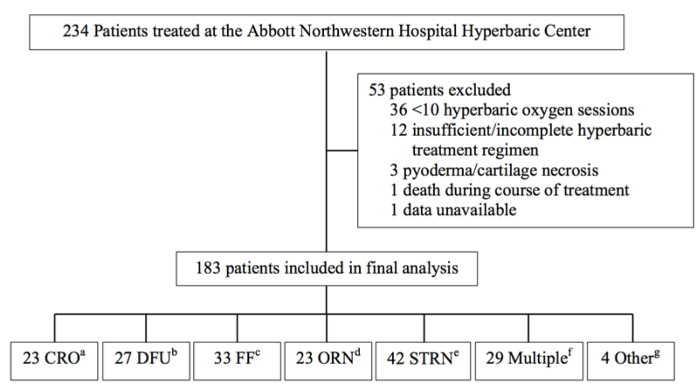
MHI/ANW HBOT Experience

- The Hyperbaric Oxygen Treatment center here at Minneapolis Heart Institute/Abbott Northwestern Hospital was opened in 2006.
- Correlates well with other published series
- Skeik N et al. Hyperbaric oxygen treatment outcome for different indications from a single center. Ann Vasc Surg. 2015

Figure 1. Selection of Study Population with Exclusion Criteria



[a] Chronic refractory osteomyelitis
[b] Diabetic foot ulcer
[c] Failed flap or skin graft
[d] Osteoradionecrosis
[e] Soft tissue radiation necrosis
[f] Multiple: 21 CRO+DFU, 4 FF+STRN, 2 DFU+FF, 1 CRO+FF, 1 CRO+FF+STRN
[g] Other: 2 necrotizing faciitis, 1 toe ulcers due to peripheral arterial disease, 1 crush injury

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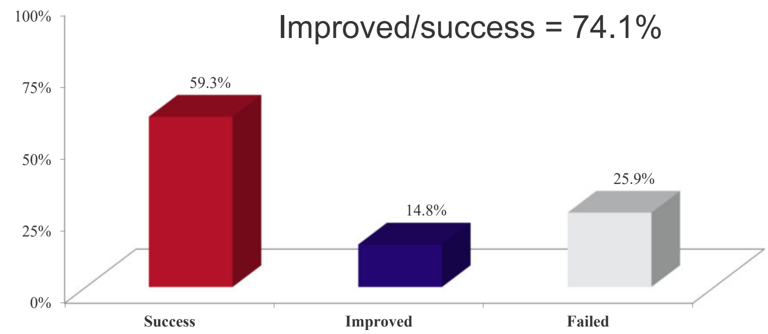
Diabetic Foot Ulcer

- Success = More than 50% healed
  "complete or significant healing"
- Improvement = <50% healed
  "partially healed"
- Failed = Amputation



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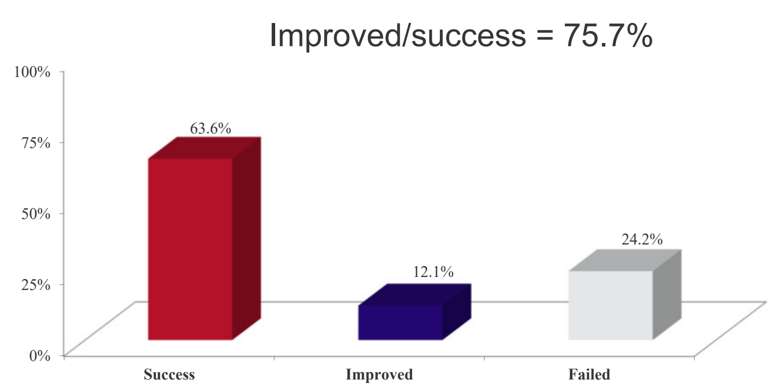
Failing Flap

- Success = graft significant or completely taken (75%-100%)
- Improvement = graft 50%-75% taken, partially taken
- Failed = graft <50% taken, or new graft needed



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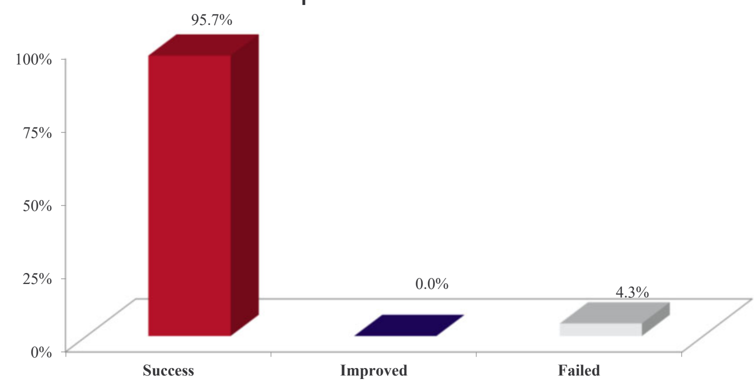
Osteoradionecrosis

- Generally, relates to mandibular osteoradionecrosis after XRT for head and neck cancers
  - Prior to HBOT – success rates ~40-50%
  - Marx protocol – 95+%
- Failure = no improvement of original problem

Improved/success = 95.7%



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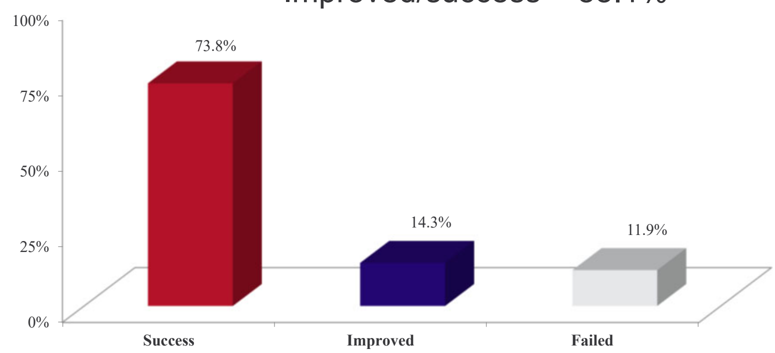
Soft Tissue Radiation Necrosis

- Often need more sessions than other indications
- Includes radiation cystitis, laryngeal radionecrosis, nonhealing wounds in radiated tissue beds

Improved/success = 88.1%



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Future Directions

- Myocardial Infarction
  - Reverse hypoxia in marginally perfused areas
  - Modulation of tissue repair
    - Reduce effects of ischemia reperfusion injury
  - Increase antioxidant enzyme expression in tissues and plasma
  - Mobilize stem cells from bone marrow; aid revascularization of healing tissue

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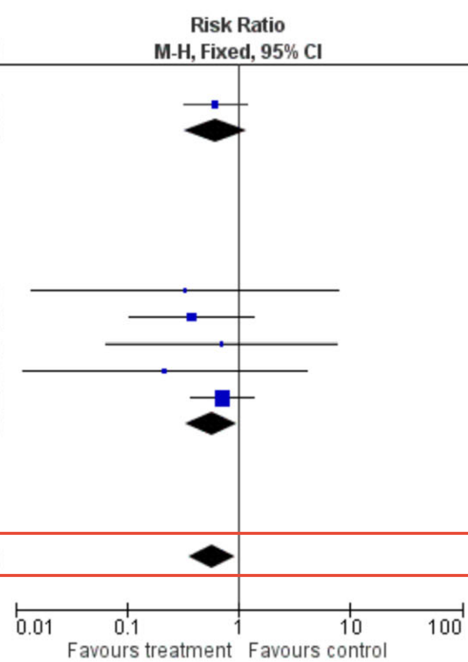
Study or Subgroup	HBOT Events	HBOT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Subjects presenting in cardiogenic shock						
Thurston 1973	4	7	5	5	16.2%	0.61 [0.32, 1.18]
Subtotal (95% CI)		**7**		**5**	**16.2%**	**0.61 [0.32, 1.18]**
Total events	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.15)						
1.1.2 Subjects presenting without cardiogenic shock						
Dekleva 2004	0	37	1	37	3.9%	0.33 [0.01, 7.93]
Dotsenko 2007	3	64	8	65	20.5%	0.38 [0.11, 1.37]
Hot MI 1998	1	59	2	83	4.3%	0.70 [0.07, 7.58]
Sharifi 2004	0	24	3	37	7.2%	0.22 [0.01, 4.03]
Thurston 1973	13	96	19	100	48.0%	0.71 [0.37, 1.36]
Subtotal (95% CI)		**280**		**322**	**83.8%**	**0.57 [0.33, 0.98]**
Total events	17		33			
Heterogeneity: Chi² = 1.40, df = 4 (P = 0.85); I² = 0%						
Test for overall effect: Z = 2.03 (P = 0.04)						
Total (95% CI)		**287**		**327**	**100.0%**	**0.58 [0.36, 0.92]**
Total events	21		38			
Heterogeneity: Chi² = 1.41, df = 5 (P = 0.92); I² = 0%						
Test for overall effect: Z = 2.32 (P = 0.02)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%						



Bennett et al. Hyperbaric oxygen therapy for acute coronary syndrome. Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD004818.

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Future Directions

- Traumatic Brain Injury
  - Improve neuroplasticity
  - Reduce ischemia reperfusion injury
  - RCTs ongoing, however 4 small RCTs did not find sustained improvement >6 months
- Aging
  - 2020 – small prospective trial demonstrated increased length of telomeres and decreased immunesenescence
    - 30 adults, average age 68 years, 60 sessions
    - Telomere length in T and B cells increased by >20%
    - Senescent T cell % reduced by 10-37%

Hachmo et al. *Aging (Albany NY)*. 2020;12(22):22445-22456.

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Conclusions

- Hyperbaric Oxygen Therapy is the administration of 100% oxygen under increased pressure conditions, which is safe and efficacious when appropriately utilized
- Hyperbaric Oxygen Therapy is proven to be beneficial for multiple indications including necrotizing fasciitis, soft tissue radiation injury, failing flaps and diabetic foot ulcers.
- Hyperbaric Oxygen Therapy is a useful adjunct to good local wound care, appropriate antibiotic administration and optimized revascularization to accelerate healing of challenging wounds

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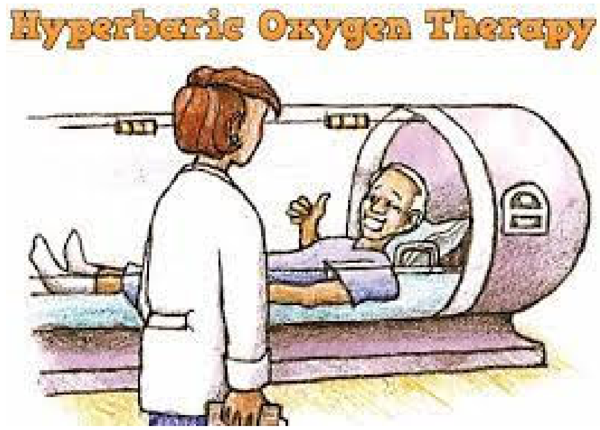
Thank you!



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