Arterial & Venous Ulcerations:
What Role HBO?

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Arterial & Venous Ulcerations: What Role for HBO?

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NO FINANCIAL CONFLICT OF INTEREST TO DISCLOSE

HBO in Lower Extremity Ulcers:

- Main mechanism by which HBO is effective in lower extremity ulcers:
  - Improves hypoxia
    - Amount of oxygen dissolved in plasma & readily available for cellular metabolism proportionally increased
    - Increased availability of substrate for oxygen dependent enzymatic reactions critical to repair and resistance to infection
  - Decreases edema

Lecture Objectives

- Etiology and diagnosis of these type wounds.
- What evidence does basic science & clinical research provide?
- How is hyperbaric oxygen applied?

Evolution of Underlying Mechanisms

- HBO initially employed for its antimicrobial properties (1960's)
- Predominately diabetic gangrene/advanced infections
- Basis was bacteriostasis for anaerobes, enhanced neutrophil activity for aerobes
- Pts invariably admitted for aggressive multimodal care

Evolution of Underlying Mechanisms: A Biological Plausibility

- Evident that disrupted circulation in wounds was problematic in terms of healing
- Key role of oxygen not yet apparent
  - *"First requirement for wounds to progress along anticipated timelines is healthy vascular tissue"*
  - *Suggests one or more vascular-derived substrates drives wound repair*

Hunt TK, *et al.* 1969
Amer. J. Surgery 118

Evolution of Underlying Mechanisms: A Biological Plausibility

- Commonly used rabbit acute wound model
- Wound fluid measured over time transcutaneously
- Eventually used implanted tonometer
  - Began to recognize:

"Oxygen tensions are low in the area of injury"

Hunt TK, *et al*. 1969
Amer. J. Surgery 118

Evolution of Underlying Mechanisms

- If inspired oxygen levels are increased, actively healing wound dead space pO_2 increases by a fraction of increase in paO_2
  - As more O_2 becomes available, more appears consumed during wound repair

Zederfeldt B, Hunt TK 1969
Curr Topics Surg Research

Evolution of Underlying Mechanisms

- Basis for HBO for lower extremity ulcers; overcomes presumed local hypoxia
  - *non-healing wounds commonly considered ischemic*
  - *O_2 would 'nourish' under-oxygenated tissue*
- Counter argument – HBO only delivered 90 minutes every 24 hours

Oxygen & Wound Repair

- O_2 identified as **THE** rate dependent variable in moving wounds through healing time lines
- Local *hypoxia* normal response/inevitable consequence of tissue injury
  - As injury profoundly disrupts oxygen supply to local environment
- Local ***ischemia***, however, imposes vulnerability to healing and infection.
  - due to critical requirement for O_2 in several phases of healing cycle
  - Infected wounds have increased O_2 demand
  - Decreased blood flow compounds hypoxic response

Phases of Healing

- 4 overlapping phases:
  - Hemostasis (Some recognize as the first of two inflammatory phases)
  - Inflammatory
  - Proliferative/Migratory
  - Maturation/Remodeling
- Phases can move forward & backward based upon intrinsic & extrinsic factors

Wound Healing Sequence

Hemostasis ~ sets the stage for healing by vessel retraction, platelet aggregation and fibrin deposition

Inflammation ~ Vascular & cellular response focused on cleaning up debris (microorganisms, foreign matter, dying tissue)

- Triggers events that have implications for the entire healing process
- Macrophages release cytokines (angiogenesis factor & various growth factors)
- These cytokines direct the next stage of healing

Wound Healing Sequence

Fibroplasia ~ slowed by ischemia
- Good cell growth at 38 mmHg
- Best at 80 mmHg

Collagen production ~ extremely sensitive to ischemia
- Increasing paO2 from 82 to 200 increases transport by 1%
- Increases deposition by 50%

Angiogenesis ~ an oxygen-dependent process
- First visible evidence of granulation tissue

Epithelialization ~ slowed or halted by ischemia
- proportional to O2 availability

Wound Healing Paradox: Lactate and Oxygen

Hypoxia & high lactate are characteristic of wound healing and both are known to stimulate angiogenesis

Conversely, considerable evidence that oxygen pressure governs rate of wound repair

what appears contradictory best explained as two independent mechanisms'

Hunt TK Hussain Z, 1992
Wound Heal. Biochem. Clin. 16

Wound Healing Paradox: Lactate and Oxygen

- Zhang and colleagues from UT Medical branch
- Dug very deep into molecular mechanisms of HBO in ischemic wound healing
- Confirmed hypoxia as cell signaling mediator

" hypoxia an essential cell signal during normal wound healing, but appears detrimental when wounds are ischemic"

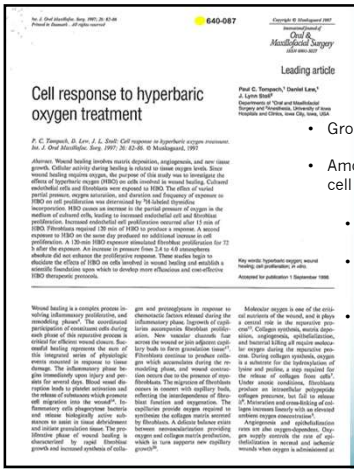
Zhang Q, *et al.* 2008
J Invest. Dermatol; Online pub.

Hyperbaric Oxygen Therapy: What Mechanism?

- Proponents first believed it acted as a respiratory metabolite
  - However, hyper-oxygenation is only achieved for 1.5-2.0 hours daily in an otherwise constantly hypoxic tissue
- Subsequently proposed that HBO increases wound oxygen gradients
  - This remained controversial because of a paucity of analytically supportive data

Hyperbaric Oxygen Therapy: What Mechanism?

- Recently apparent that HBO therapy acts by a signal transduction pathway
  - Stimulating growth factors and/or their receptor sites through nitric oxide dependent and other cell signaling processes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Leading article

Cell response to hyperbaric oxygen treatment

Tompach PR, *et al.* 1997
Int J Oral Max Surg 26

- Group from University of Iowa
- Among first to identify highly specific cell response to HBO
  - Knew wound healing requires O2
- Cellular activity during healing relates to tissue oxygen levels
- Studied effects of HBO on endothelial cells & fibroblasts

Cell Response to Hyperbaric Oxygen

Single HBO Exposure:

Increased endothelial cell proliferation within 15 mins

Fibroblasts required 120 mins.

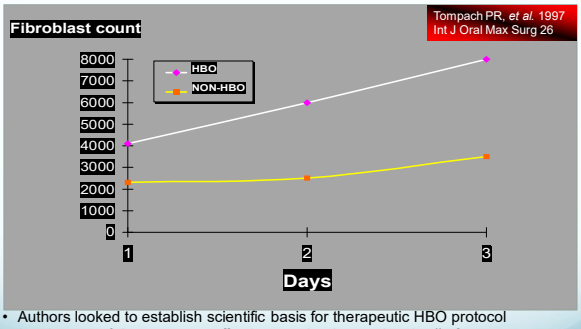
A 120-min HBO exposure stimulated fibroblast proliferation for 72 hours after exposure

A second same day exposure produced no further increase

An increase from 2.4 to 4.0 ATA O_2 did not enhance response

Tompach PR, *et al.* 1997
Int J Oral Max Surg 26

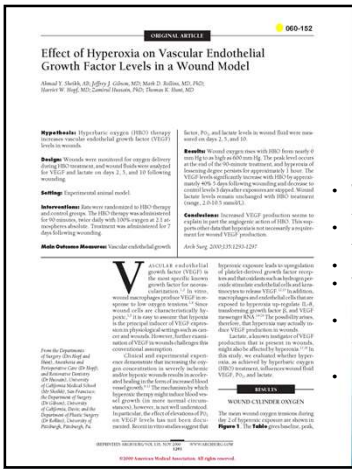
Fibroblast Response to Single HBO Exposure



- Authors looked to establish scientific basis for therapeutic HBO protocol development & improve cost effectiveness by decreasing the # of treatments
- Mechanism of how effects are stimulated were identified as next important steps

Vascular Endothelial Growth Factor (VEGF)

- Angiogenic growth factors promote closure of chronic wounds with hypoxia & compromised vascularity
- Research confirmed VEGF as high specific growth factor for neovascularization and an essential angiogenic regulator
- It functions as:
  - An endothelial cell mitogen
  - Chemotactic agent
  - Inducer of vascular permeability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ORIGINAL ARTICLE

Effect of Hyperoxia on Vascular Endothelial Growth Factor Levels in a Wound Model

Sheikh A, *et al.* 2000
Arch Surg 2000;135:1293-1297

- Randomized HBO rat study
- 90 min. HBO·2.1 ATA·2x/day
- Measured VEGF in wound fluids

- Wound O_2 increased from nearly zero to as high as 600 mmHg
- Peak levels at end of 90 minute tx
- Hyperoxia persists for approx.1 hr
- VEGF levels ⇧ by 40% with HBO

- Explains in part the angiogenic action of HBO

- Supports other data that hypoxia not necessary for wound VEGF production

Hyperbaric Oxygen-Induced Angiogenesis

HBO observed to induce angiogenesis via VEGF production

VEGF critical to new vessel formation

- *its activity only initiates formation of immature vessels*
- *for mature functioning vessels, VEGF must work in concert with angiopoietins*

HBO selectively enhanced Ang2 gene expression

- *Via endothelial nitric oxide synthase*
- *inhibition of eNOS blocked this process*

They termed HBOT as the oxygen donor that facilitates production of nitric oxide

Lin S, *et al.* 2002
Biochem Biophys Res Comm; 296


ORIGINAL INVESTIGATION

060-232

Hyperbaric Oxygen Therapy Mediates Increased Nitric Oxide Production Associated With Wound Healing: A Preliminary Study

Boykin J, *et al.* 2007
Adv Skin Wound Care 2007;20:382-8

- 6 chronic wound patients
- Measured wound fluid nitric oxide levels during HBO treatments
- Significantly elevated at 1 and 4 weeks after therapy
- Correlated with reductions in wound area


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CALL FOR PAPERS | Regulation and Function of Stem Cells in the Cardiovascular System

Stem cell mobilization by hyperbaric oxygen

Thom SR, *et al*. 2006
Am J Physiol Heart Circ;290C

- 3 reports from team at UPENN
- Researched stem cell side of wound healing
- Specifically, bone marrow derived stem progenitor cells to damaged vasculature

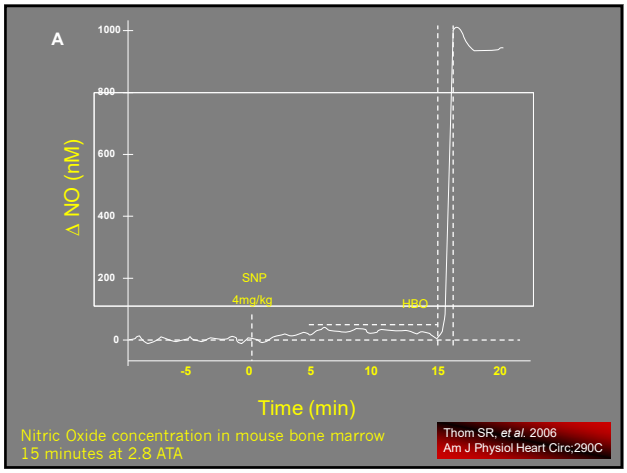
Stem Cell Mobilization by Hyperbaric Oxygen

Stem cells (SPC's) mobilized by peripheral ischemia, vigorous exercise, hematopoietic growth factors

Nitric oxide plays a key role in triggering SPC mobilization

~ can HBO also activate this process?

Thom SR, *et al*. 2006
Am J Physiol Heart Circ;290C

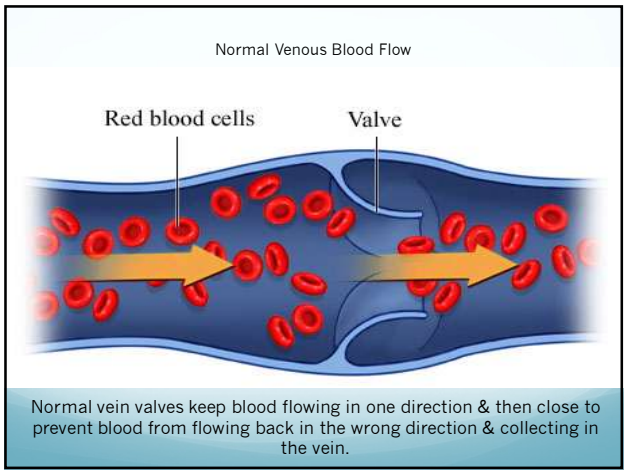


Nitric Oxide concentration in mouse bone marrow
15 minutes at 2.8 ATA

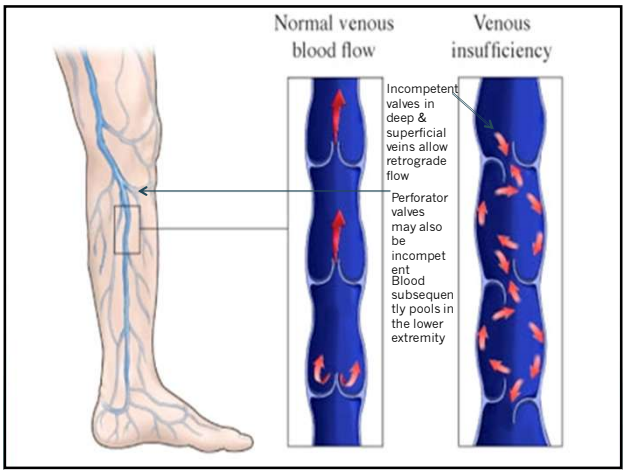
Thom SR, *et al*. 2006
Am J Physiol Heart Circ;290C

Venous Stasis Ulcers

- **Represent 76% of all lower extremity ulcers**
- 61% are on the medial malleolus
- Rarely on the foot
- Irregular border
- Little or no undermining
- Granulating bed (may have eschar)
- 54% present greater than 1 year
- 72% have recurrence



Normal vein valves keep blood flowing in one direction & then close to prevent blood from flowing back in the wrong direction & collecting in the vein.



Etiology of Chronic Venous Insufficiency

- **DVT (1/3 patients)**
- Obesity
- Elderly
- Pregnancy
- Mechanical Obstruction IVC (Clot/Tumor/Filter)
- CHF
- Abnormal Muscle Pump (muscular dysfunction)
- Limited Mobility/Sedentary Lifestyle
- Injection drug use

Cause of Ulceration of Skin in Chronic Venous Insufficiency

- Increased venous pressure (hypertension) with incompetent valves causes:
  - pressure to be transmitted to the superficial venous system
  - then to skin capillaries
- Sustained pressure results in
  - dermal changes
  - subcutaneous fibrosis
  - eventual ulceration

Clinical Diagnosis

Extremity Assessment:

- Frequently initiated with trauma
- Edema may be soft (early) or "woody" (late)
- Hyperpigmentation of surrounding skin
- Ankle flaring (cluster of reticular/spider veins)

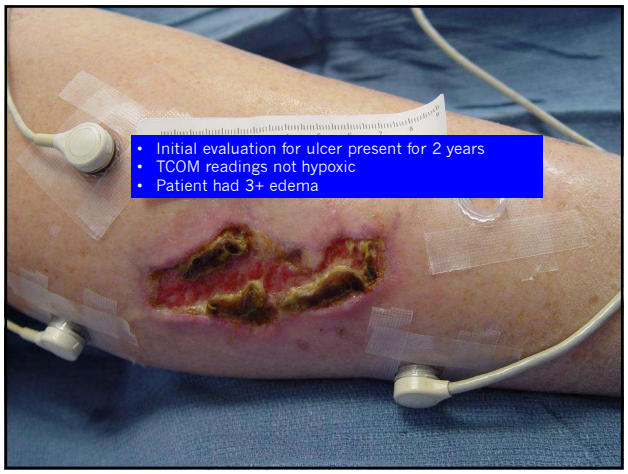
Treatment of Venous Stasis Ulcers

- Generally not appropriate for HBO
- Literature suggests HBO may promote healing, but is not required
- May be due to treatment of edema related hypoxia
  - Should resolve with compression, elevation – edema resolution
- Standard treatment adequate for healing

Hyperbaric Oxygen Therapy

- **Presence of venous ulcer alone <u>is not</u> an indication recognized by CMS, or most payors.**
- UHMS found insufficient evidence for support of HBO use
- May be used to prepare wound bed for graft, or support failing or compromised graft
- Skin substitutes don't count as failed graft for HBO
- May be <u>adjunctive</u> in growth factor use
- Cell cultures have shown HBO to increase growth factor receptor sites on cell membranes,
  - acts as facilitating agent rather than respiratory one

Compression is the Gold Standard of Venous Ulcer Treatment!!



Literature Review

- *"Hyperbaric Oxygen Reduced Size of Chronic Leg Ulcers: A Randomized Double-Blind Study"*
- Small, but very important footnote for HBO specialty
- First sham-controlled, randomized double-blinded clinical trial in HBO history

Hammarlaud C et al 1994

Plastic Reconst. Surg: 93

Randomized Double-Blind Study on Leg Ulcers

- Tx. Group: *2.5 ATA O_2 X 90 min. Once daily x 30 txs*
- Controls: *2.5 ATA Air X 90 min. Once daily x 30 txs*
- Inclusion:
  - Min. 1 yr. Chronically
  - No change in last 2 months
- Exclusion:
  - Diabetes
  - Smoking
  - Collagen vascular diseases
  - Large vessel disease

Hammarlaud C et al 1994

Plastic Reconst. Surg: 93

Results Randomized Double-Blind Study on Leg Ulcers

- Tx. Group: *2.5 ATA O_2 X 90 min. Once daily x 30 txs*
- Controls: *2.5 ATA Air X 90 min. Once daily x 30 txs*

Mean Decrease in Wound Size (%)

Week	Air	Oxygen	P.
2	2.8%	6%	
4	3.7%	22%	<0.05
6	2.7%	35.7%	<0.001

Hammarlaud C et al 1994

Plastic Reconst. Surg: 93

Additional Literature Review

- *Cochrane review*
- 18 patients with venous ulcers
  - Failed other treatments for 1 year or >
- Conclusion:
  - Insufficient evidence of increased effectiveness with HBO vs sham

Kranke et al 2005

Additional Literature Review

- 42 patients with venous ulcers
  - Avg. 29.7 HBO treatments
- Conclusion:
  - No statistically significant results for wound healing as a direct result of HBO

Andrade et al 2016

Additional Literature Review

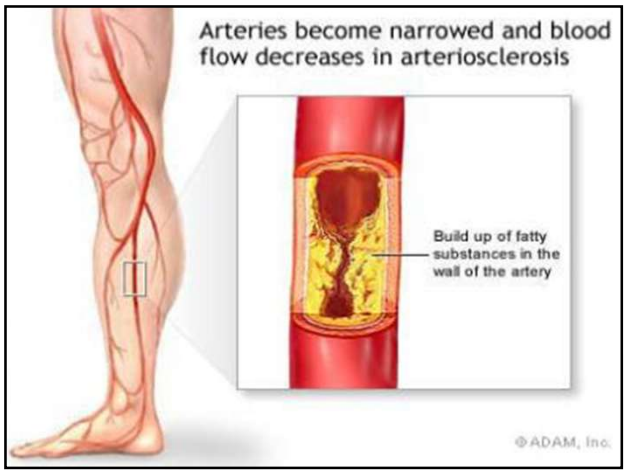
- Randomized, double-blind, placedo-controlled trial
  - Involved 3 hyperbaric medicine centers
  - 31 adult patients
  - TCOM measurements demonstrated wound hypoxia
  - All were responsive to oxygen challenge
  - No contraindications
  - Randomized to either 30 HBO or sham treatments
- Conclusion:
  - No difference in primary outcome of patients with complete healing at 12 weeks

Thistlethwaite 2018

Arterial Insufficiency Ulcers

Prevalence of Peripheral Arterial Disease

- Approximately 10 million people in the U.S. have PAD
- LEAD is under-diagnosed, under-appreciated & under-treated
- Approximately 50% of patients with LEAD are asymptomatic or unaware of the condition because of atypical leg symptoms
- Disease often silent until a limb or life threatening event occurs
- 10 year mortality rate is 60%



PAD Risk Factors

- **Smoking** (#1 risk factor)
- Diabetes
- Hypertension
- Hyperhomocysteinemia
- Hypercholesterolemia
- Obesity
- Hypothyroidism
- Chronic renal insufficiency
- Family history of cardiovascular disease
- African American Ethnicity
- > 70 y.o.
- 50-69 y.o. plus history of smoking or diabetes
- <50 y.o. with diabetes & one other risk factor

Clinical Diagnosis

- Located between toes, tips of toes, lateral malleolus, or where there is trauma and/or friction from walking
- Deep punched out hole in appearance
- Poor granulation tissue
- Well defined edges
- Extremely painful, worse at night, improves with dangling
- History for any risk factors & physical exam

Diagnostic Evaluation

- **Pure arterial ulcers are unusual**
- Often complicated by DM, venous insufficiency, or other diseases
- In ischemic appearing ulcers, look for contributing factors other than atherosclerosis involving the arterial system:
  - Thromboangiitis
  - Vasculitis
  - Raynaud's
  - Pyoderma Gangrenosum
  - Thalassemia
  - Sickle Cell Disease

Diagnostic Evaluation

- **All patients with lower extremity ulcers should be assessed for arterial disease**
- Decreased or absent palpable pedal pulses (presence of pulses does not rule out LEAD)
- Delayed capillary refill response
- $TcPO_2$ better test for tissue oxygenation
- 10-15 second delay in return of color when raising the leg 45 degrees for 1 minute, dependent rubor (Buerger's test)
- Assess for complications (cellulitis, gangrene, osteomyelitis)

Diagnostic Evaluation: ABI

- Should be performed on all patients with lower extremity ulcers to determine large vessel PAD
- Values of <0.9 or > 1.2 are abnormal & warrant referral to vascular specialist
- Not all patients will require or qualify for surgery, but referral should still occur

Diagnostic Evaluation: ABI

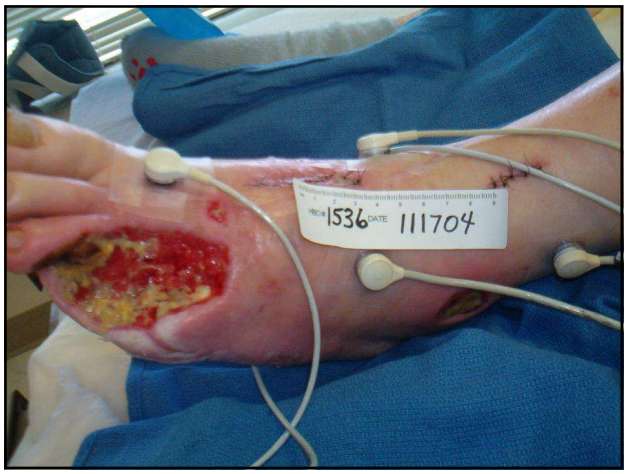
- > 50% of patients with PAD due to abnormal ABI may not have limb ischemia, but will have a decrease in their functional activity limiting their quality of life
  - Assess functional ability
    - Walking aids
    - Frequent stops when walking
    - Neuropathy & LOPS

Diagnostic Evaluation: ABI

- ABI should be rechecked every 3 months for nonhealing LEU
- Toe Brachial Index (TBI) should be checked for ABI > 1.3
- If performed by properly trained professional, with proper equipment, use of pocket doppler is interchangeable with vascular lab test to detect LEAD [3]
- Pulse palpation or automated blood pressure devices are not considered reliable to use for ABI test
- The exact location of stenosis or occlusion cannot be determined by ABI alone

Diagnostic Evaluation: $TcPO_2$

- **Should be considered in all patients with lower extremity ulcers**
- Tissue oxygen tension is most effective test for predicting failure to heal without intervention.
- Periwound tissue oxygen tissue < 40mmHg is a good predictor of impaired healing due to inadequate oxygen supply.
- O_2 challenge can provide anticipated response to HBO.
- $TcPO_2$ readings < 40mmHg should initiate a vascular referral.
- $TcPO_2$ readings < 20mmHg indicate critical ischemia and should initiate an urgent vascular referral.



"In the presence of an arterial ulceration, the natural history is one of disease progression and eventual limb loss, and the treatment options are revascularization or amputation."

Arterial Disease Ulcers, Part 1: Clinical Diagnosis and Investigation
Weir, Gregory Ralph et al
Advances in Skin & Wound Care
September 2014
Vol. 27 – Issue 9: p 421-428

Restoration of blood flow by revascularization is the intervention that will most likely lead to healing.

Arterial Disease Ulcers, Part 1: Clinical Diagnosis and Investigation
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Adjunctive Therapies

- Revascularization is not always successful and durable
- Adjunctive therapy may augment revascularization outcomes
- **Will not correct the underlying vascular disease**
- **Cannot replace revascularization**

Hyperbaric Oxygen Therapy

- Is an adjunctive therapy
- Must have some degree of inflow
- HBO increases tissue oxygen in ischemic tissue
- Increases angiogenesis
- $TcPO_2$ values & appropriate patient selection paramount for cost-effective provision of care
- Not appropriate for chronic PVD associated ulcers

59 Year Old Male

- 2 months S/P Ray amputation great toe
- Non-healing amputation site

Pre-Op TCOMs

Lead Placement	Room Air	10 Min. O_2 Challenge
Reference	60 mmHg	----------
Mid Calf	7 mmHg	28 mmHg
Above Ankle	3 mmHg	2 mmHg
Dorsum Foot	2 mmHg	2 mmHg

Post-Op TCOMs

Lead Placement	Room Air	10 Min. O_2 Challenge
Reference	58 mmHg	----------
Mid Calf	30 mmHg	56 mmHg
Above Ankle	28 mmHg	82 mmHg
Dorsum Foot	36 mmHg	102 mmHg

Literature Review

Difficult because most studies include patients with concomitant DM

Hyperbaric oxygen for the treatment of nonhealing arterial insufficiency ulcers

Marvin Heyboer III, MD1; William D. Grant, EDD1; Joseph Byrne, MD2; Paula Pons, MD2; Monica Morgan, MD1; Bilal Iqbal, BS3; Susan M. Wojcik, PhD1

1.Department of Emergency Medicine, Division of Hyperbaric Medicine and Wound Care,
2.Center for Wound Care and Hyperbaric Medicine, St. Joseph's Hospital, Fayetteville, New York, and
3.School of Medicine, SUNY Upstate Medical University, Syracuse

Wound Repair and Regeneration
22:351, 2014

HBO –Arterial Ulcers (Hayboer, 2014)

- Retrospective Chart Review – (2005 – 2011)
- 82 Patients – Non-Healing Arterial Insufficiency Ulcers
- Designed to analyze healing rates & amputation rates in pts treated with HBO for recalcitrant arterial ulcers

HBO –Arterial Ulcers (Hayboer, 2014)

- All had vascular surgery evaluation before HBO – NO TCOMs
- Some were revascularized, others were not candidates
- All failed to heal with standard wound care (how long?)
- 15.9% diabetics (why not exclude/evaluate separately?)
- HBO 2ATA for 90 minutes – 40 Tx (5 days wk x 8 weeks)

HBO –Arterial Ulcers (Hayboer, 2014)

- Overall healed:
  - 12.2% by end of HBO txs
  - 43.9 (36/82) at 24 months
- 56% healing rate in pts who were not candidates for revascularization
  - Better than standard care alone
- Overall major amputation rate 17.1%
  - 21% major amputation rate for non-revascularized group, (better than standard care alone)

HBO –Arterial Ulcers (Hayboer, 2014)

- Results:
  - Dialysis was a strong predictor of major ampuation
  - Suggests benefit for non-healing arterial ulcers, especially patients not eligible for revascularization
  - Need for prospective study

Patient Selection

- UHMS:
  - Failure to heal following standard wound care
    - Evaluation & optimization of vascular status
    - Address systemic factors (tobacco use, glycemic control, HTN, obesity, hyperlipidemia, etc)
    - Offloading
    - Treatment of infection
    - Debridement (when tissue perfusion allows)
- Wound Healing Society:
  - Failure to heal despite revascularization, or not a candidate for vascular surgery

Treatment Protocol

- 2.0 – 2.5 ATA for 90 – 120 minutes
- 1 - 2 times per day/5-7 days per week
- 30 txs then assess for additional needs
- May consider trial of 10-15 HBO txs if amputation is the only option, even if TCOM doesn't demonstrate efficacy

Overall Considerations for Lower Extremity Wound Treatment with HBO

- Do TCOMs demonstrate tissue hypoxia?
- Have standard wound healing modalities been tried?
- Can you provide evidence to payors to support the use of HBO?
- How many treatments are planned?
- How will you objectively determine the clinical response to HBO?

Questions??