Vascular Aspects of Wound Healing

Sandra Wainwright, MD
Medical Director, Hyperbaric and Wound Healing
Greenwich Hospital
Yale New Haven Health
Disclosures

- I have nothing to disclose
Objectives

• To understand the role the arterial and venous systems play in wound healing

• To review the physiologic aspects of hypoxemia and how impediments to Oxygen delivery impact wound healing

• To understand the mechanism behind hyperbaric therapy in ischemic wounds

• To take a deeper look at the venous system and current concepts in managing venous hypertension
Why Physiology?

- A word on evidence based medicine...
- New technologies, new therapeutics, new diagnostics, new procedures, targeted molecular therapy
- Human Body still has the original design
- When you understand physiology, you can think yourself out of a difficult situation
There are 3 reasons a wound won’t heal

- Arterial
- Venous
- Something else
There are 4 phases of wound healing:

- Hemostasis
- Inflammation
- Proliferation
- Remodeling
Hemostasis

- Duration = minutes
- Platelets aggregate around exposed collagen
- Platelet derived growth factors facilitate clot formation creating a hemostatic “plug”
- Platelets release α-granules which release growth factors which recruit inflammatory cells to the wound site
Inflammation

- Duration = Days
- Inflammatory cells – secrete enzymes that lyse collagen in ECM
- Creates chemotactic effect on macrophages
- Macs secrete TNF-α → IL-1β
- Inflammatory cytokines influence synthesis of collagen via fibroblast formation
- Inflammatory cells secrete growth factors
  - Continue to stimulate migration of fibroblasts, epithelial cells and vascular endothelial cells into the wound
Proliferation

- Duration = Weeks
- Collagen degradation stimulates fibroblast, vascular endothelial cell, and keratinocyte proliferation
- Secreted GF’s (VEGF, PDGF) promoting angiogenesis which guide formation of the ECM
- Vascularized ECM, granulation tissue forms
- Keratinocytes migrate from the edge of the wound and re-epithelization is achieved
Remodeling

- Duration = 1 year
- Balance between new tissue synthesis and degradation of scar matrix is reached
- Capillary density decreases as the scar matures
- This results in greater tensile strength of the tissue
- After 12 months the site will only be 75% of its former strength
Three Vascular Systems

- Arterial
- Venous
- Everything else
  - Venules
  - Capillaries
  - Lymphatics
  - Cellular
  - Autoimmune
Plumbing
Plumbing Analogy
Arterial – why and how?

- Distribution of oxygenated blood to end organs
- Cardiac pump
- Large vessel distribution
- Medium vessel
- Small vessel
- Capillary
- RBC’s
Cardiac Pump

- Cardiac output
- \( \text{CO} = \text{SV} \times \text{HR} \)
- Variables include EF, preload and afterload
- If we’re talking about wounds, what’s the question?

To increase cardiac output
- Increase stroke volume or
- Increase heart rate or
- Increase both
What pressure is needed to perfuse skin?

- We don’t really know...

- **Optimizing mean arterial pressure in septic shock: a critical reappraisal of the literature**


- 2000 to 2014, 12 studies on MAP goals and the effects on tissue perfusion

- MAP = \( \frac{(2 \times \text{diastolic}) + \text{systolic}}{3} \)

- Surrogate for end organ perfusion
MAP and Macrocirculation


Oxygen exchange measured in 5 studies

Increase in cardiac output was associated with an increase in oxygen delivery

The effects of increasing MAP on mixed venous oxygen saturation or central venous oxygen saturation were inconsistent

The magnitude of change in oxygen variables did not appear to be clinically relevant
In patients with septic shock, increasing MAP improved microcirculatory variables in the patients with impaired microcirculation at baseline.

- Jhanji et al found that increase in MAP was accompanied by a significant increase in cutaneous oxygen partial pressure and red blood cell flow.
Clinical Application

- A decent cardiac output, in the setting of a decent MAP generates adequate tissue perfusion and oxygenation via the arterial, capillary to RBC conduit
Clinical Application

- 82y WM with CHF, systolic and diastolic dysfunciton, EF of 35%, known PAD, s/p revascularization
- “allergic to lasix” – caused bullous pemphigoid
- Spends 24 hours a day in a chair with legs dependent
- You’re consulted to see him because of cold swollen legs, blisters and mottling
- Meds – bumex, cefepime, prednisone 20mg and prn dilaudid for dressing changes and back pain
Why are the legs like this?

- Poor pump function
- Poor perfusion pressure
- Impingement on arteriolar and capillary perfusion pressures due to peripheral edema from CHF, overload of the venous and lymphatic systems
- Exacerbated by positioning, meds, skin integrity
What to do?

- Optimization of cardiac output with diuresis – improving CO through Starling curve
- Mild compression (ace wraps)
- Leg elevation
- Infection control, pain management, establish goals of care
Ulcerated Toe Tip

- 72y WM with necrotic toe x1 year, probes to bone
- s/p angioplasty and stenting of the SFA 3 months ago
- Getting IV antibiotics at out patient infusion center
- Sent to me for nonhealing wound
Work Up?

- Xray

- Vascular study
  - ABI/Doppler
  - Transcutaneous Oximetry Measurement
    - 6mm Hg at the foot
    - 13mm Hg at the calf
    - 26mm Hg at popliteal level
Tcom or TcPO2

- A transcutaneous oxygen measurement assesses the oxygen level of tissue beneath the skin.
- Another way to say this is, it measures the density of capillaries beneath the skin – microvascular disease.
- This an indirect measure of blood flow because the blood supply carries oxygen and the TcPO2 is a useful test for predicting wound healing and whether the patient would benefit from hyperbaric oxygen therapy (HBOT).
Understanding the Impact of Tissue Hypoxia

- Final common denominator is tissue hypoxia
- Tissues with oxygen levels below 40mmHg signify impaired healing
- If a TcPO2 value is less than 20mm Hg, the risk of amputation is 161 times greater
- A tissue level of at least 30 mm of Hg is required for adequate endogenous antimicrobial activity to occur
Hypoxia

- Only 5 causes for hypoxemia
  - Shunt
  - V/Q mismatch
  - Low FiO2
  - Alveolar Hypoventilation

- O2 delivery
  - \( \text{DO}_2 = \text{CO} \times \text{CaO}_2 \times 10 \)
  - \( \text{CaO}_2 = (\text{Hb} \times 1.39 \times \text{SaO}_2) + (\text{PaO}_2 \times 0.003) \)
Back to Our Patient

- Based on his Tcom he had now flow to the popliteal vessels
- I told him to prepare for BKA or AKA
- Sent back to vascular
- SFA stent occluded, was patent at 1 month post-stent, by month 3 was occluded
- Was revascularized, flow restored to leg, now he can get and amputation and heal the wound
- ...With hyperbaric therapy
What Role Does HBOT Have?

- Not a substitute for revascularization when possible
- Hyperbaric therapy is a modality of treatment that enhances wound healing by overcoming ischemic conditions
Is there a role for HBO in Limb Salvage?

- Physiologically O₂ is driven into the plasma through gas exchange at the alveolar capillary level
- A base line PaO₂ of 80mm Hg can be increased to a PaO₂ of >2000mm Hg under pressure
  - 3ATA with FiO₂ 100%
Why breathe O2 under pressure?

Capillary network near the surface of the skin. Gases are exchanged in and from the capillaries, through the thin epidermal layer.
Physiology of Respiration

O2 enters the lungs where it interacts with the blood

Binds to RBC’s forming oxyHb that is distributed to tissues throughout the body

O2 is bound to hemoglobin (99%) and dissolved in plasma (0.003%)

Some is bound to intracellular proteins (myoglobin, cytochrome c, and others)
O2 Transport

- Oxygen is transported by 2 mechanisms
  - Reversible binding to hemoglobin subunits
  - Physical dissolution in plasma
Hypoxia

- Only 5 causes for hypoxemia
  - Shunt
  - V/Q mismatch
  - Low FiO2
  - Alveolar Hypoventilation

- O2 delivery
  - DO2 = CO x CaO2 x 10
  - CaO2 = (Hb x 1.39 x SaO2) + (PaO2 x 0.003)
• Arterial Oxygen Content

\[(\text{CaO}_2) = 1.36 \times \text{Hgb} \times \text{SaO}_2 + (0.003 \times \text{PaO}_2)\]

1ATA = 760mmHG

2ATA = 1520mmHg

3ATA = 2280 mmHg
Closer Look at the Effects of HBO

- Gains of an additional 2 vol% of oxygen carrying capacity for every ATA of added pressure.

- HBO up regulates growth factors and the activation of growth factor receptors control excess inflammation.

- Thus achieving better control of infection and increased angiogenesis.

**HBO2 increases EGFR expression *in vivo***

Before HBO₂  24 hrs after HBO₂

Oxygen Diffusion

Model for Oxygen Diffusion in Tissues

1 ATA of air, concurrent blood flow

3 ATA of oxygen, concurrent blood flow
Hyperbaric Treatment is a Drug

- Cyclical hypoxia and hyperoxia activates HIF-1 alpha which leads to an increase in VEGF which increases neovascularization.
Objectives

- To understand the role the arterial and vascular systems play in wound healing.
- To review the physiologic aspects of hypoxemia and how impediments to oxygen delivery impact wound healing.
- To understand the mechanism behind hyperbaric therapy in ischemic wounds.
- To take a deeper look at the venous system and current concepts in managing venous hypertension.
Chronic Venous Hypertension
Above and Beyond Compression
Scope of Problem
United States

- 40% Americans (124 million) w/ Vein Dx.
- 24 million Varicose Veins
- 6 million Skin Changes with CVI
- 500,000 Venous stasis Ulcers
Risk Factors

- Age, sex, family history, obesity
- Pregnancy phlebitis, previous leg injury
- Prolonged standing or sitting posture at work
Normal Venous Anatomy and Function

- Vascular system is analogous to plumbing
- Arteries are high pressure system = pipes
- Veins are the low pressure passive system = drains
Venous System

- Relies on calf muscle pump to increase pressure on the system that is greater than the forces of gravity
- This is an intermittent but continuous process that is assisted by the valvular system
Valve Picture

- When valves are competent they open with increased distal pressure and close against gravity.
- This returns the blood to the deep venous system.
- In turn, enters the systemic circulation.
Venous Pressure

- Ranges from 15-90 mm Hg
- Blood pools in the veins causing pressure to rise
- Calf muscle compresses the venous system lowering the venous pressure
- Valves prevent blood from refluxing distally with gravity
Pressure Dynamics

Circulation. 2005;111:2398-2409
Advanced Venous Disease
CEAP 3-6

Swelling / Pigment

Swelling / Dermatitis

Hemosiderin / Ulcer
Venous Pathophysiology

- Microangiopathy - pressure changes in the large LE veins are transmitted to the microcirculation
  - Elongation, dilation and tortuosity of the capillary beds
  - Thickening of basement membranes, alteration in collagen type and quantity
  - Endothelial damage, increased peri-capillary edema, accumulation of fluid abnormally rich in proteins, extravasated RBC’s
  - Fragmentation and destruction of micro-lymphatics, dysfunction of local nerve fibers - alter regulatory mechanisms
Pathophysiology

- As a result of the pathologies affecting the microcirculation
- Microscopic and macroscopic visible signs include hemosiderosis, S/Q fibrosis (lipodermatosclerosis) and can lead to ulceration
Pelvic Pathology: Surgical DDX

- Chronic deep venous obstruction is usually previous DVT (post phlebitic syndrome)
- Retroperitoneal fibrosis; trauma; congenital venous anomalies or tumors
- Primary malignant tumor such as a venous leiomyosarcoma
  - Secondary tumors invading the vena cava include adenocarcinoma or liposarcoma
  - Renal carcinoma may extend into the IVC
  - Congenital webs or caval coarctation

Gloviczki, P; Fischer’s Mastery of Surgery: Ch 248, 2436-9
Medical Differential DX

- In addition to these three things consider...
  - Vasculitides
  - Congenital and acquired thrombophilia
  - Obesity and diet
  - Muscle pump efficiency (motor function)
  - Dermal inflammation
  - Cellular and molecular derangements

Am J Transl Res 2011;3(2);149-158
May Thurner Syndrome

- Compression of the left common iliac vein by the right common iliac artery
History/PE

65 yo Caucasian Female right leg complaints

- 3 yrs reversible swelling, heaviness, ache
- No DVT, Vein Surgery, CAD, CHF, CRI
- Physical Exam
- Tense calf edema; constant weeping deep ulceration
LB Studies

- Venous Duplex Leg:
  - Mild Infrainguinal venous valvular insufficiency
  - No Deep Vein Thrombosis
  - No Scar / Chronic Post-thrombotic changes

- Laboratory:
  - Normal creatinine, ANA, RF, LFT, albumin, cryoglobulins
Iliofemoral Vein Occlusive Dx. How to Identify?

- History
  - DVT, Pelvic Surgery, RT, CHF, CRI,

- Physical Exam
  - CEAP 3-6
  - Swelling, Stasis Dermatitis, Hyperpigmentation
  - Venous Ulcers (Current or Hx.)
Iliofemoral Vein Occlusive Dx. How to Identify?

- Non-Thrombotic
  - IVUS, 90% sensitive
  - Multi-planar Venogram, 66% Sensitive

- Post-thrombotic changes
  - IVUS
  - Venous Duplex Ultrasound
  - CT/MR Venography
Venous Stenosis from Chronic DVT

Acute DVT recanalizes; Chronic stenosis in venous outflow tract remains
IVUS
IVUS Detection of Nonthrombotic Iliac Obstruction

Venography 66% sensitive
Venogram
Left Leg

CIV
EIV
CFV

IVC
CIV
Measurement images of CSA/Diameter with IVUS of Veins

EIV stenosis

Dilated Caudal EIV

75-80% stenosis
11/9/09 just before venous stent
12/28/09 after venous stent
Venogram S/P LEIV Stent
IVUS Post-Stent EIV Compression
Tx. of NonThrombotic Iliac Vein Lesions (NIVL)

- Evaluated / Stented 332 limbs in 319 pts.
- 2.5 years after stent
  - complete relief of pain 82% - 77%,
  - complete ulcer healing 67% - 76%,
  - complete relief of swelling 47% - 53%,
- Conclusions:
  - NIVL high prevalence in pts. W/ CEAP 3-6
  - Stent placement often provides relief

Raju et al, J Vasc Surg, 2006
Stenting for Venous Occlusive Disease; PTS & NIVL
Long-Term Outcomes (8 yrs)

- 1997 – 2005
- 982 chronic obstructive Iliofemoral vein lesions; IVUS / stented - 93% CEAP 3-6
- F/U 94% of pts., mean 22 mos. (1-107 mos)
- Venous stenting can be performed with low morbidity and mortality, and high long-term patency rates
- Pts. experience major symptom relief from chronic venous disease

1/11/10 (pre stent)
3/15/10 (post stent)
Medical Care of the Venous Ulcer

- Compression, compression compression
- Control of bioburden, infection
- Removal of slough
- Create an environment for healthy tissue
- Call the plumber!