Thomas Serena

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The role of Hyperbaric Oxygen Wound Management

The Mechanism of Action of Hyperbaric Oxygen in Wound Healing.

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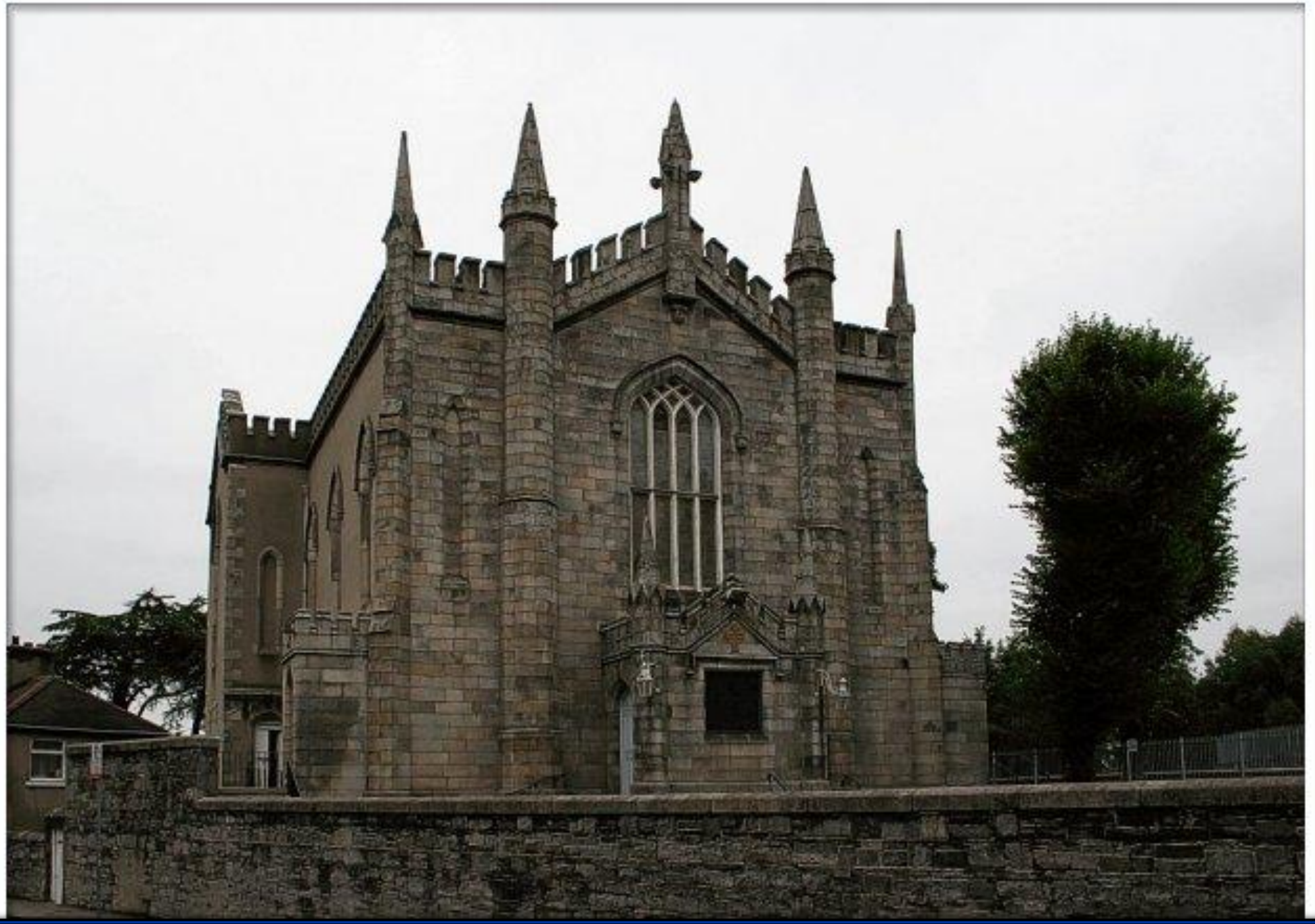
Founder & Medical Director – SerenaGroup™

Scientific Director – SerenaGroup Research

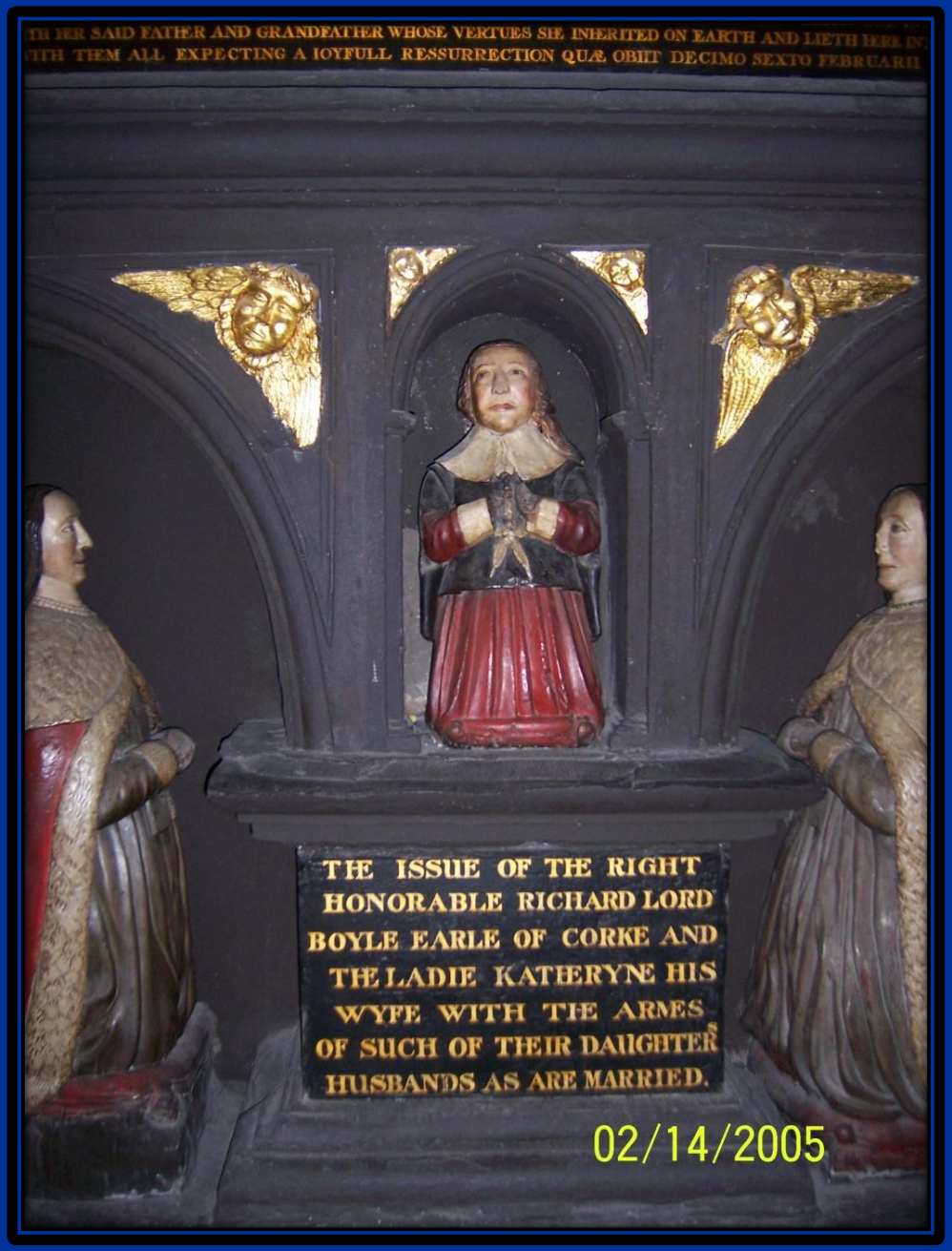
Vice President - American College of Hyperbaric Medicine

Founder – S.T.R.O.N.G. cooperative group



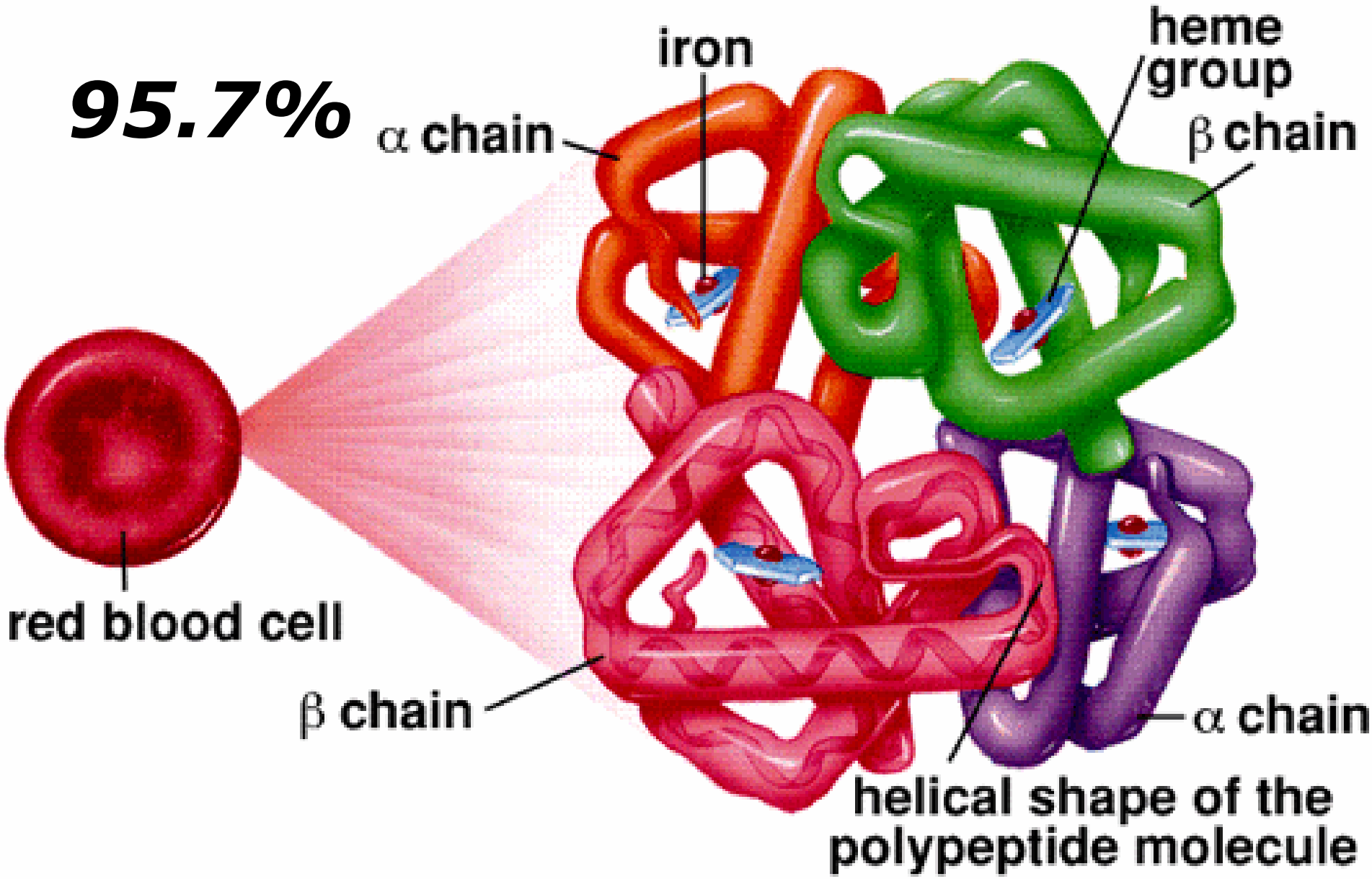
Robert Boyle

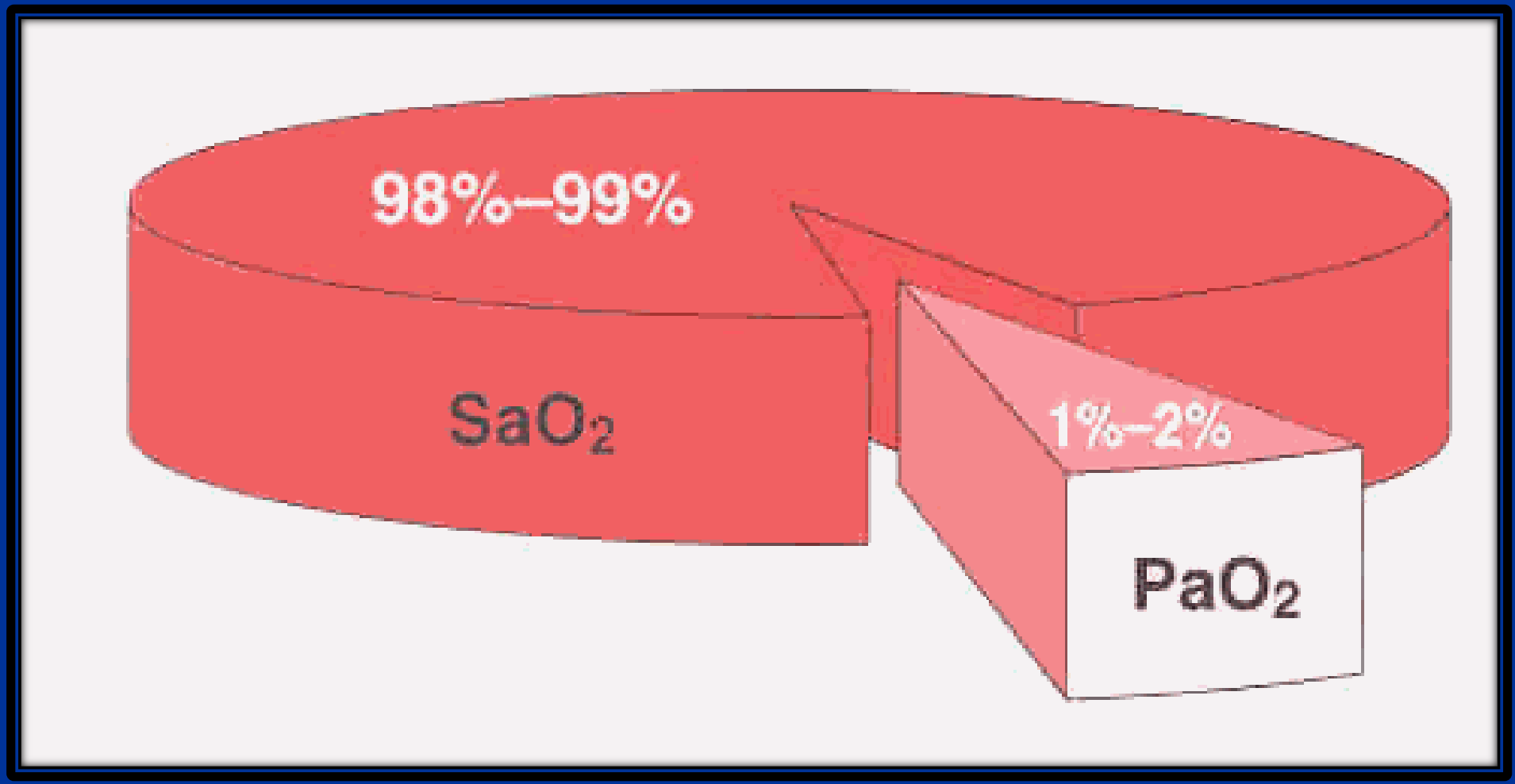
"At constant temperature, the pressure and volume of a gas are inversely proportional to each other."

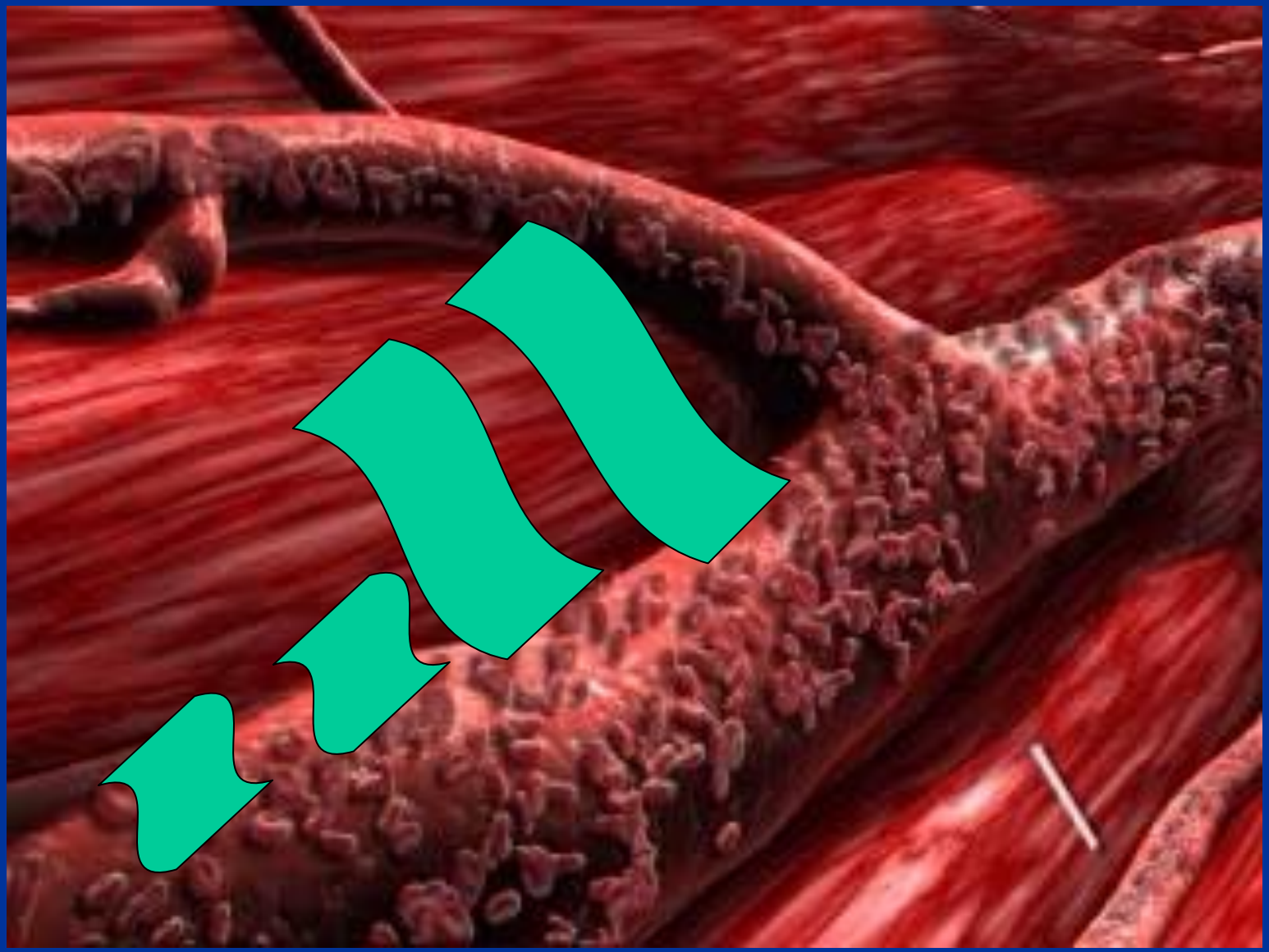



Two Oceans
AQUARIUM
reef
SOUTH AFRICA

Hemoglobin Molecule




98%–99%
SaO_2
1%–2%
PaO_2



Mechanisms: Cellular & Immunologic – from J.Rozikowski MD, 2004

Oxygen plays an important role in each phase of wound healing.

3 Phases of Wound Healing:

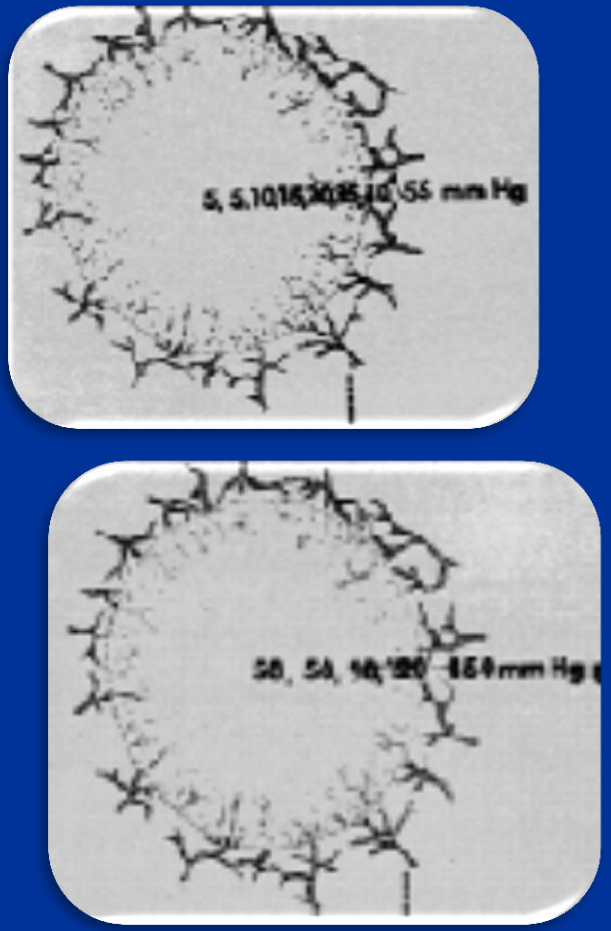
Inflammation	→	Repair	→	Maturation
Superoxide radicals reduce bacterial load		Superoxide radicals reduce bacterial load Hydroxylated proline and lysine form procollagen Hypoxia-upregulated VEGF stimulates angiogenesis (Acute-Phase)		Superoxide radicals reduce bacterial load Oxygen-dependent hydroxylases form mature collagen fibers Keratinocyte rate of migration and reepithelization are proportional to pO_2
Profound hypoxia inhibits all wound healing		Profound hypoxia inhibits all wound healing		Profound hypoxia inhibits all wound healing

Mechanism of Action, Direct

Mechanism	Effect	Clinical Application
Hyper-oxygenation	•Greater oxygen carrying capacity •Increased oxygen diffusion in tissue fluid. •Diffusion distance proportional to the square root of dissolved oxygen	Severe blood loss anemia (unable to carry oxygen) Crush injury, compartment syndrome graft, and flap salvage (decreased perfusion) Edema (increased diffusion barrier)
Decrease Bubble size	Gas law	Air Embolism Decompression sickness

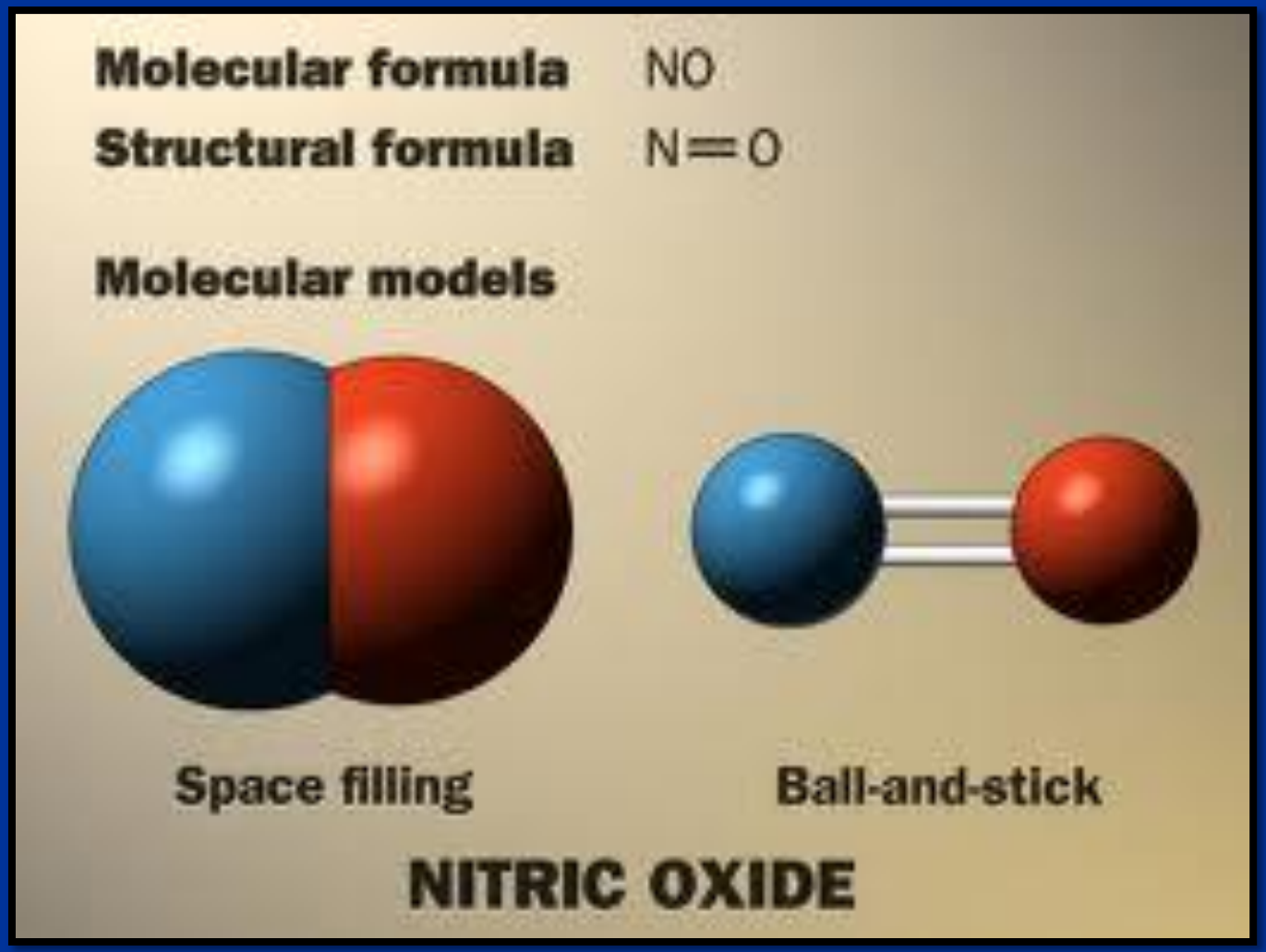
Angiogenesis dependent on Oxygen gradient

- In irradiated tissue oxygen gradient 10-20mmHg
- Under hyperbaric conditions increases to 230mm Hg.



From Marx, Problem Wounds
(Davis & Hunt, eds. 1988)

Nitric Oxide



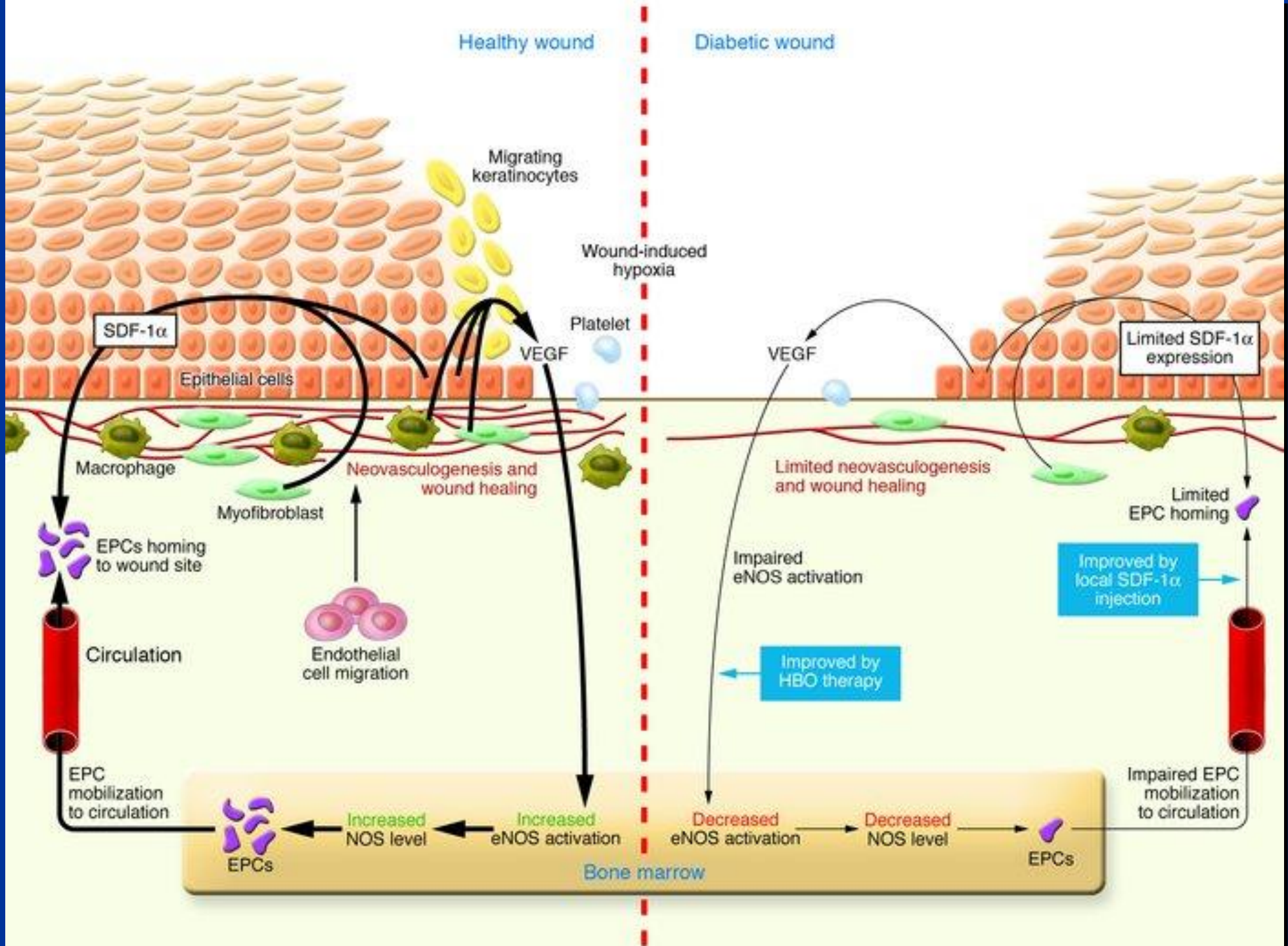
HBO stimulates stem cell release

Hyperbaric oxygen stimulates vasculogenic stem cell growth and differentiation in vivo. *Milovanova TN, , Velazquez OC, Thom SR. J Appl Physiol. 2009 Feb;106(2):711-28.*

We hypothesized that oxidative stress from hyperbaric oxygen HBO, exerts a trophic effect on vasculogenic stem cells. In a mouse model, circulating stem/progenitor cell (SPC) recruitment and differentiation in subcutaneous Matrigel were stimulated by HBO and by a physiological oxidative stressor, lactate. In combination, HBO and lactate had additive effects. Vascular channels lined by SPCs were identified. HBO and lactate accelerated channel development, cell differentiation based on surface marker expression, and cell cycle entry. SPCs exhibited increases in thioredoxin-1 (Trx1), Trx reductase, hypoxia-inducible factors (HIF), phosphorylated mitogen-activated protein kinases, vascular endothelial growth factor, and stromal cell-derived factor-1. Cell recruitment to Matrigel and protein synthesis responses were abrogated by N-acetyl cysteine, dithioerythritol, oxamate, apocynin, and several other agents as well as mice conditionally null for HIF-1 in myeloid cells. By causing an oxidative stress, HBO activates a physiological redox-active autocrine loop in SPCs that stimulates vasculogenesis. Thioredoxin system activation leads to elevations in HIF-1 and -2, followed by synthesis of HIF-dependent growth factors. HIF-3 has a negative impact on SPCs.

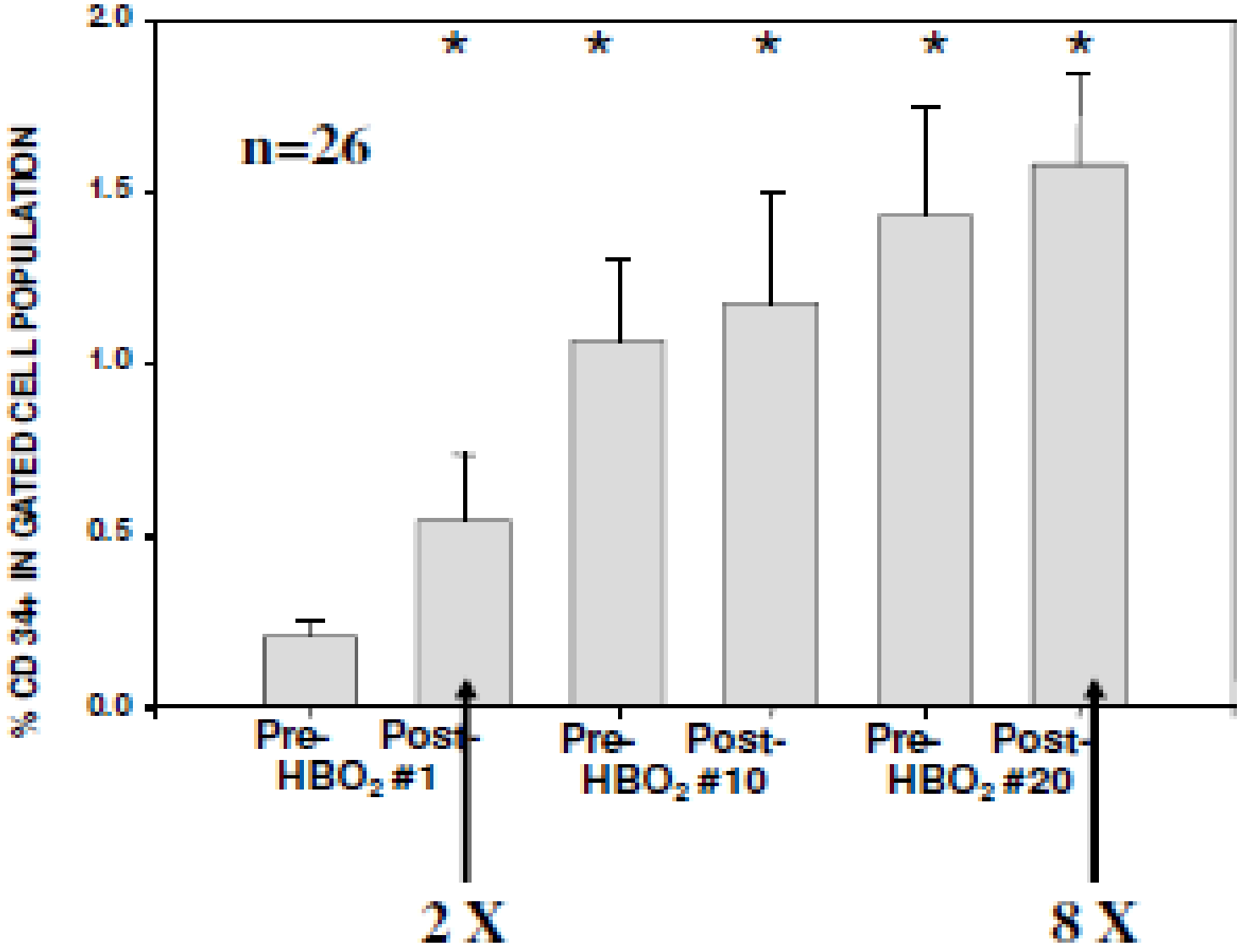
Diabetic impairments in NO-mediated endothelial progenitor cell mobilization and homing are reversed by hyperoxia and SDF-1 alpha. *Gallagher KA, Thom SR, Velazquez OC, J Clin Invest. 2007 May;117(5):1249-59.*

Endothelial progenitor cells (EPCs) are essential in vasculogenesis and wound healing, but their circulating and wound level numbers are decreased in diabetes. This study aimed to determine mechanisms responsible for the diabetic defect in circulating and wound EPCs. Since mobilization of BM EPCs occurs via eNOS activation, we hypothesized that eNOS activation is impaired in diabetes, which results in reduced EPC mobilization. Since hyperoxia activates NOS in other tissues, we investigated whether hyperoxia restores EPC mobilization in diabetic mice through BM NOS activation. Additionally, we studied the hypothesis that impaired EPC homing in diabetes is due to decreased wound level stromal cell-derived factor-1alpha (SDF-1alpha), a chemokine that mediates EPC recruitment in ischemia. Diabetic mice showed impaired phosphorylation of BM eNOS, decreased circulating EPCs, and diminished SDF-1alpha expression in cutaneous wounds. Hyperoxia increased BM NO and circulating EPCs, effects inhibited by the NOS inhibitor N-nitro-L-arginine-methyl ester. Administration of SDF-1alpha into wounds reversed the EPC homing impairment and, with hyperoxia, synergistically enhanced EPC mobilization, homing, and wound healing. Both hyperoxia and SDF-1alpha reversed the diabetic defect in EPC homing. The targets identified, which we believe to be novel, can significantly advance the field of diabetic wound healing.

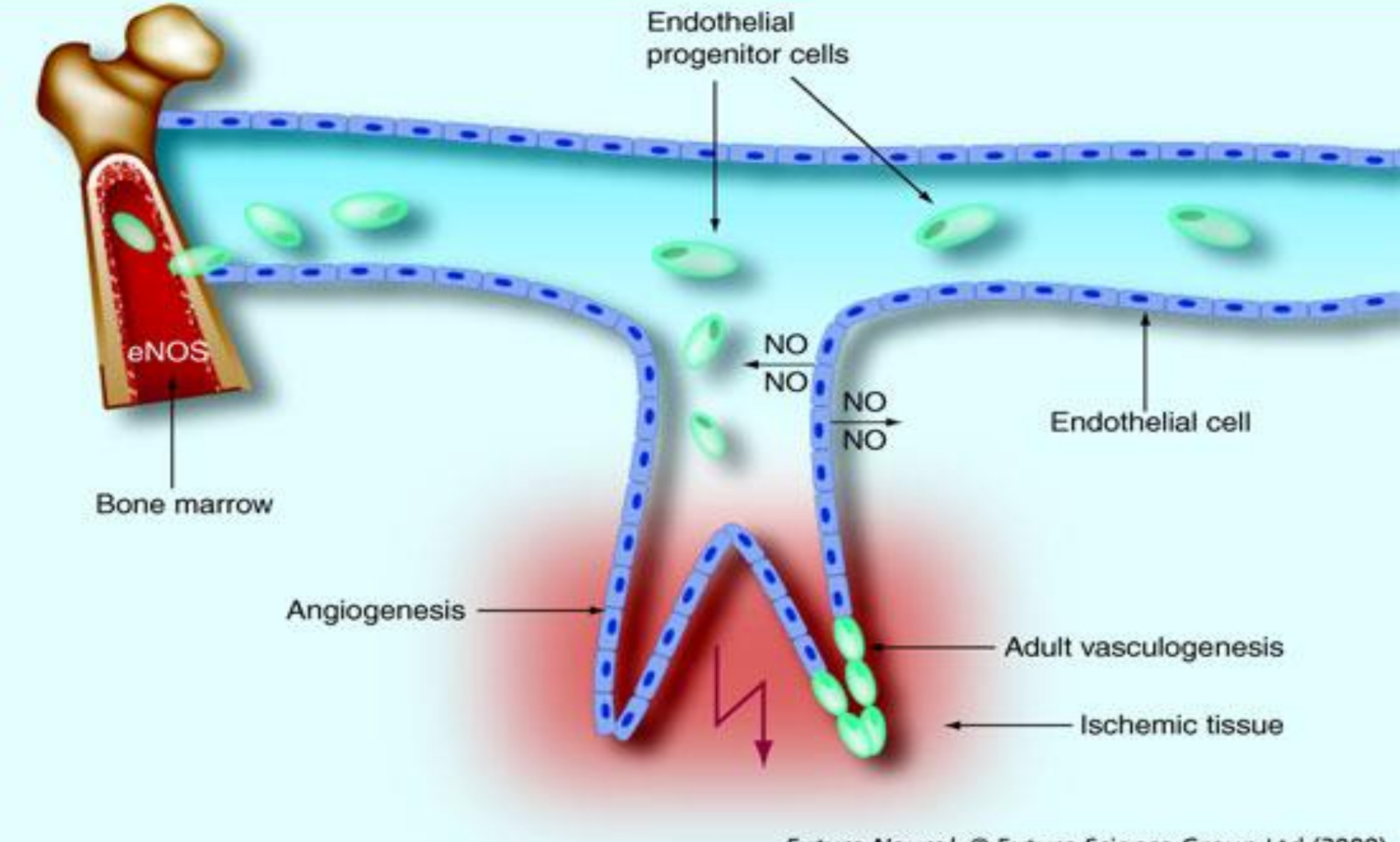

Healthy wound
Diabetic wound
Migrating keratinocytes
Wound-induced hypoxia
Platelet
SDF-1α
VEGF
VEGF
Limited SDF-1α expression
Epithelial cells
Macrophage
Myofibroblast
Neovasculogenesis and wound healing
Limited neovasculogenesis and wound healing
Limited EPC homing
EPCs homing to wound site
Impaired eNOS activation
Improved by local SDF-1α injection
Circulation
Endothelial cell migration
Improved by HBO therapy
EPC mobilization to circulation
Impaired EPC mobilization to circulation
EPCs
Increased NOS level
Increased eNOS activation
Decreased eNOS activation
Decreased NOS level
EPCs
Bone marrow

HUMAN STEM CELL MOBILIZATION BY HBO_2

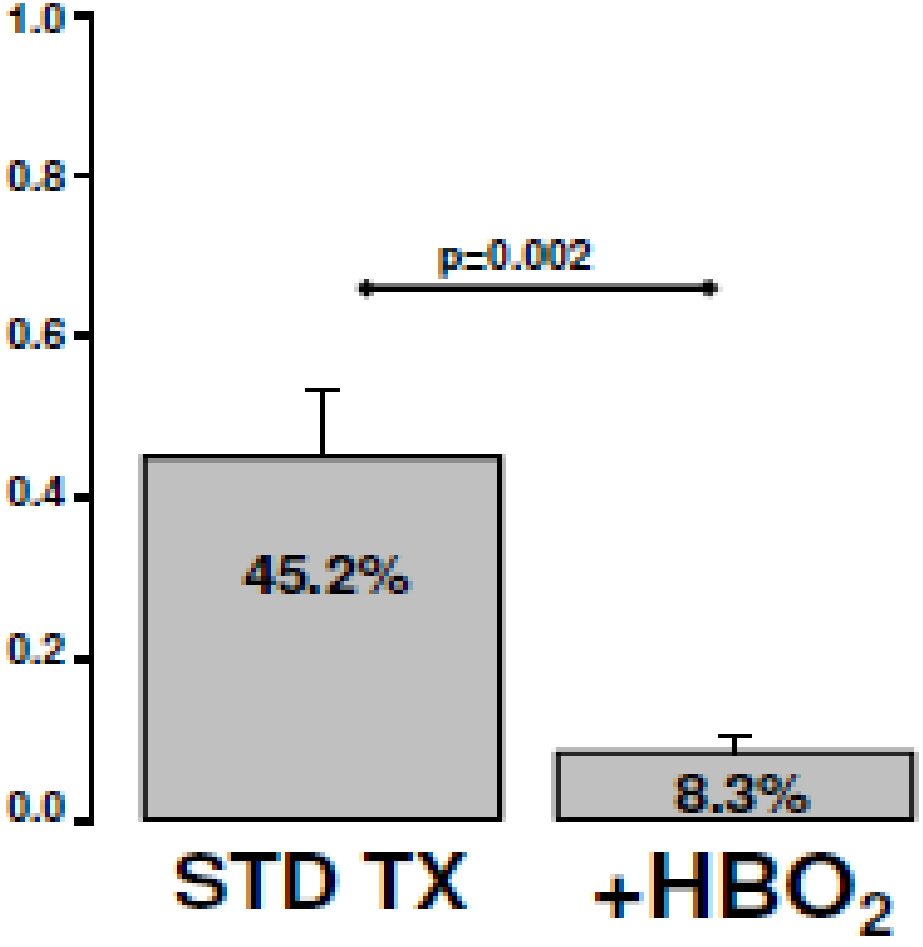
Am. J. Physiology 290: H1378, 2006



- PATIENTS PREVIOUSLY EXPOSED TO RADIATION -

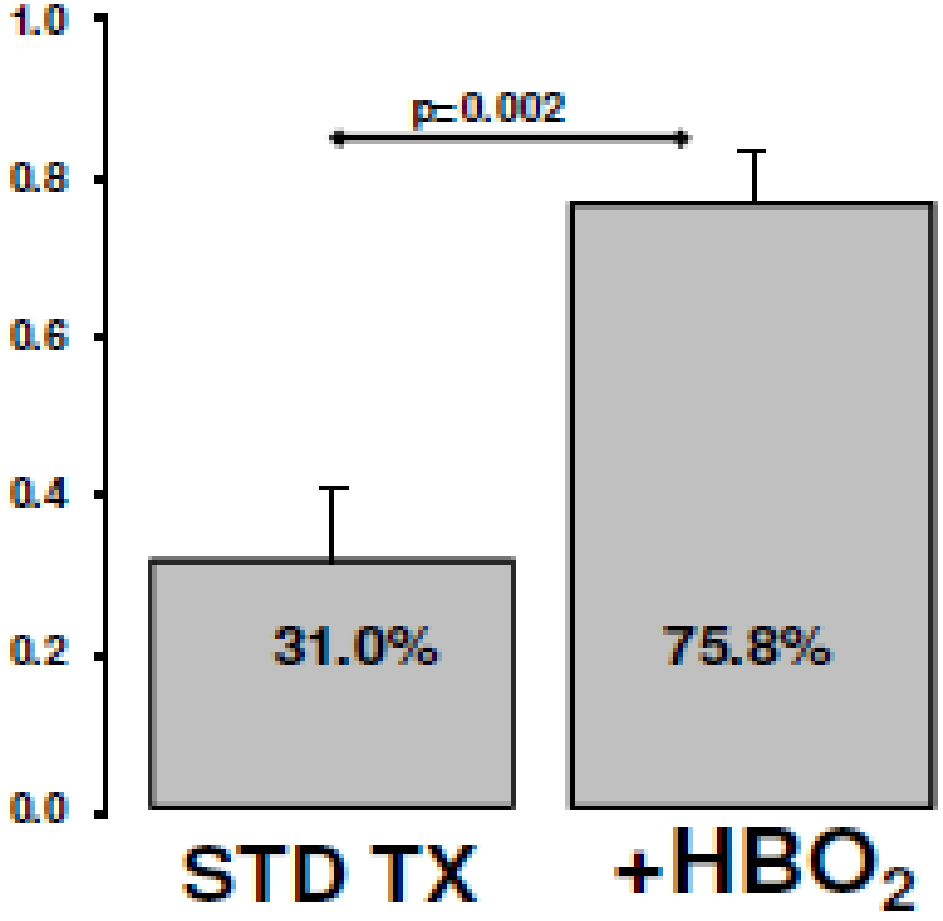


MAJOR AMPUTATIONS

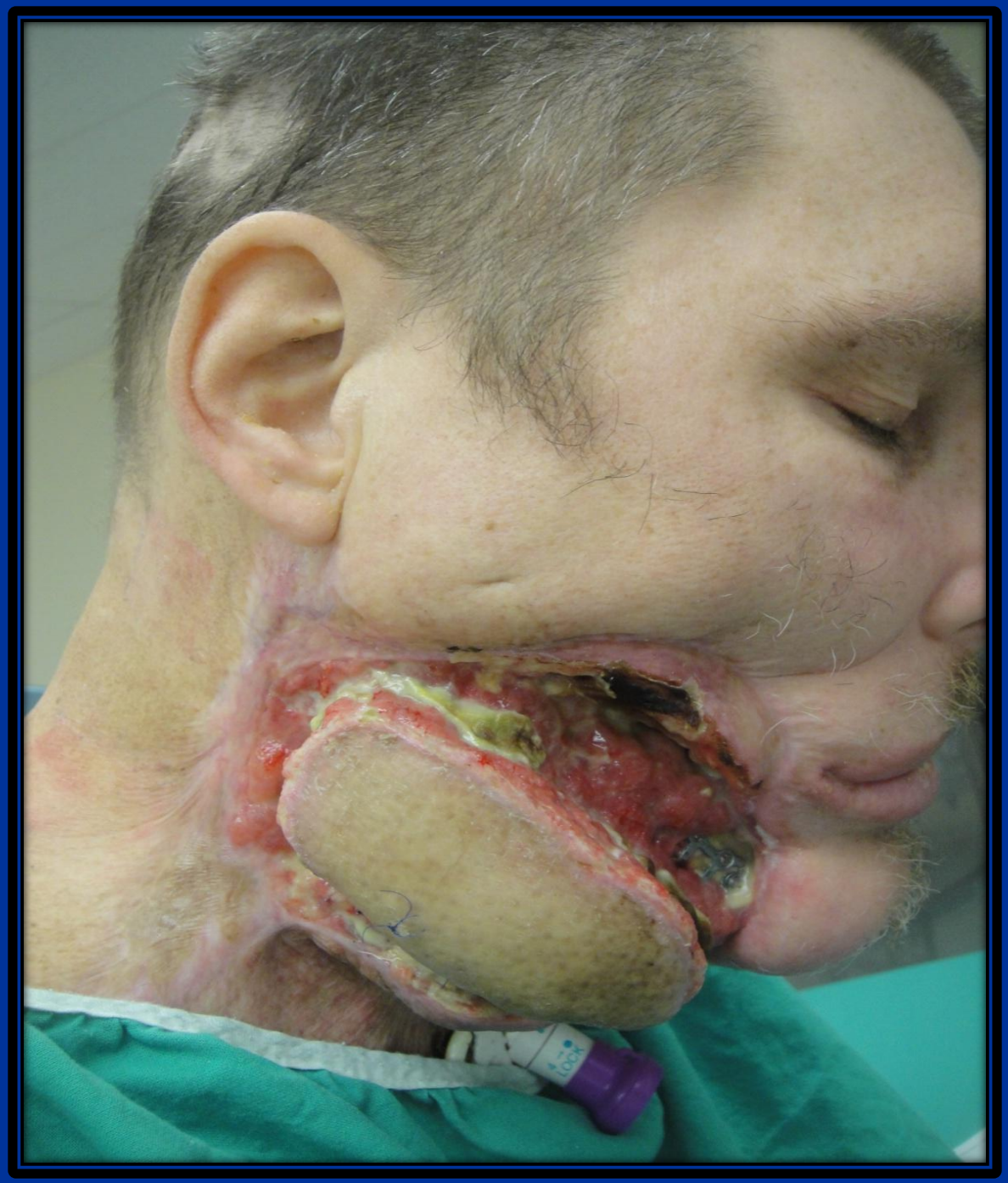


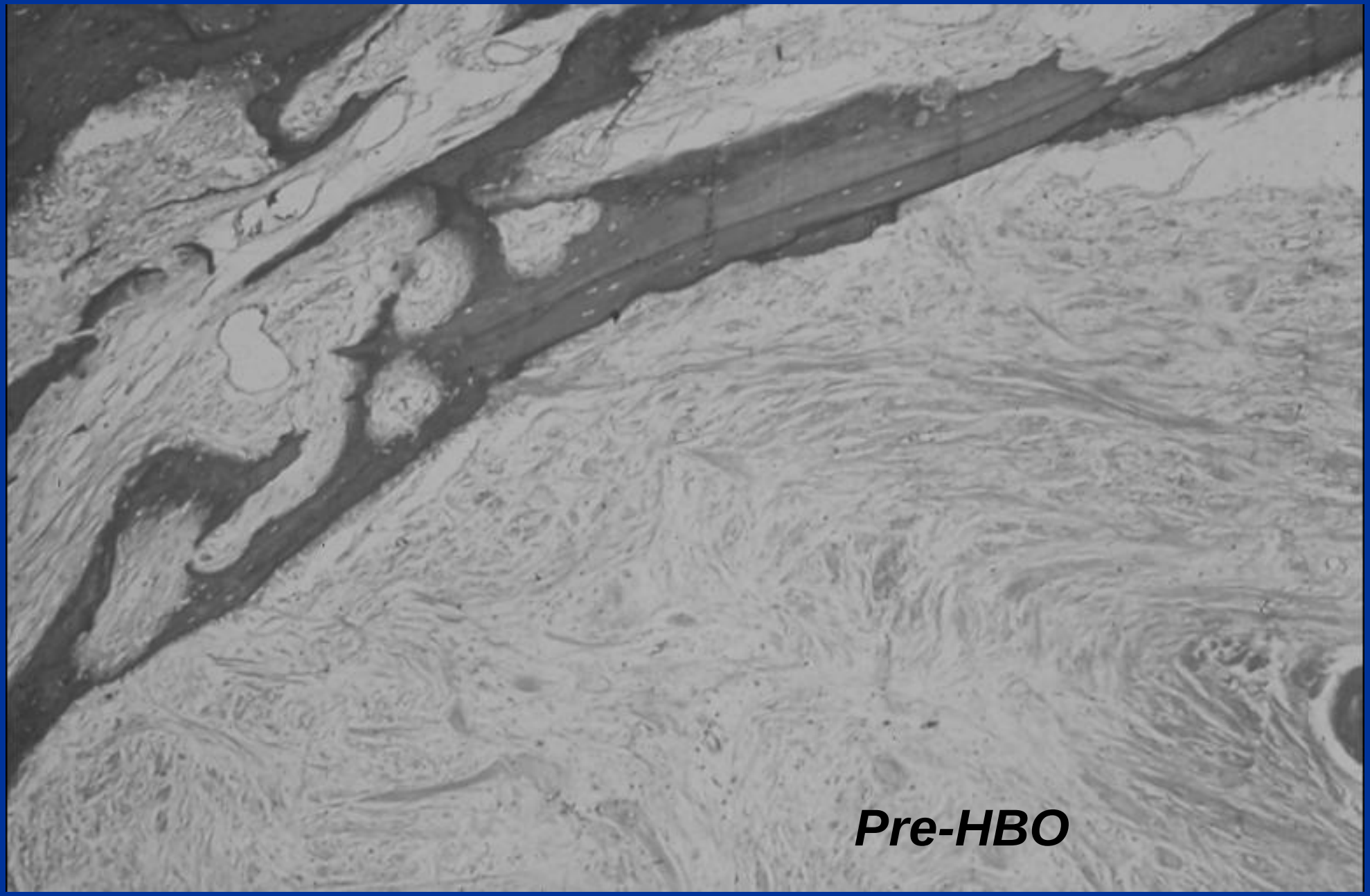
Doctor (Postgrad Med 49: 54,'92) – RCT - Mod
Faglia (Diab Care 19: 1338,'96) – RCT - High
Kalani (J Diab Comp 16: 153,'02) – Prosp Cohort -Mod
Baroni (Diab Care 10: 81,'87) – Prosp Cohort -Mod
Oriani (J Hyperb Med 5: 171,'90) – Retro Cohort -Mod
Duzgun (J Foot & Ankle S. 47: 545,'08) – RCT - Mod

HEALED

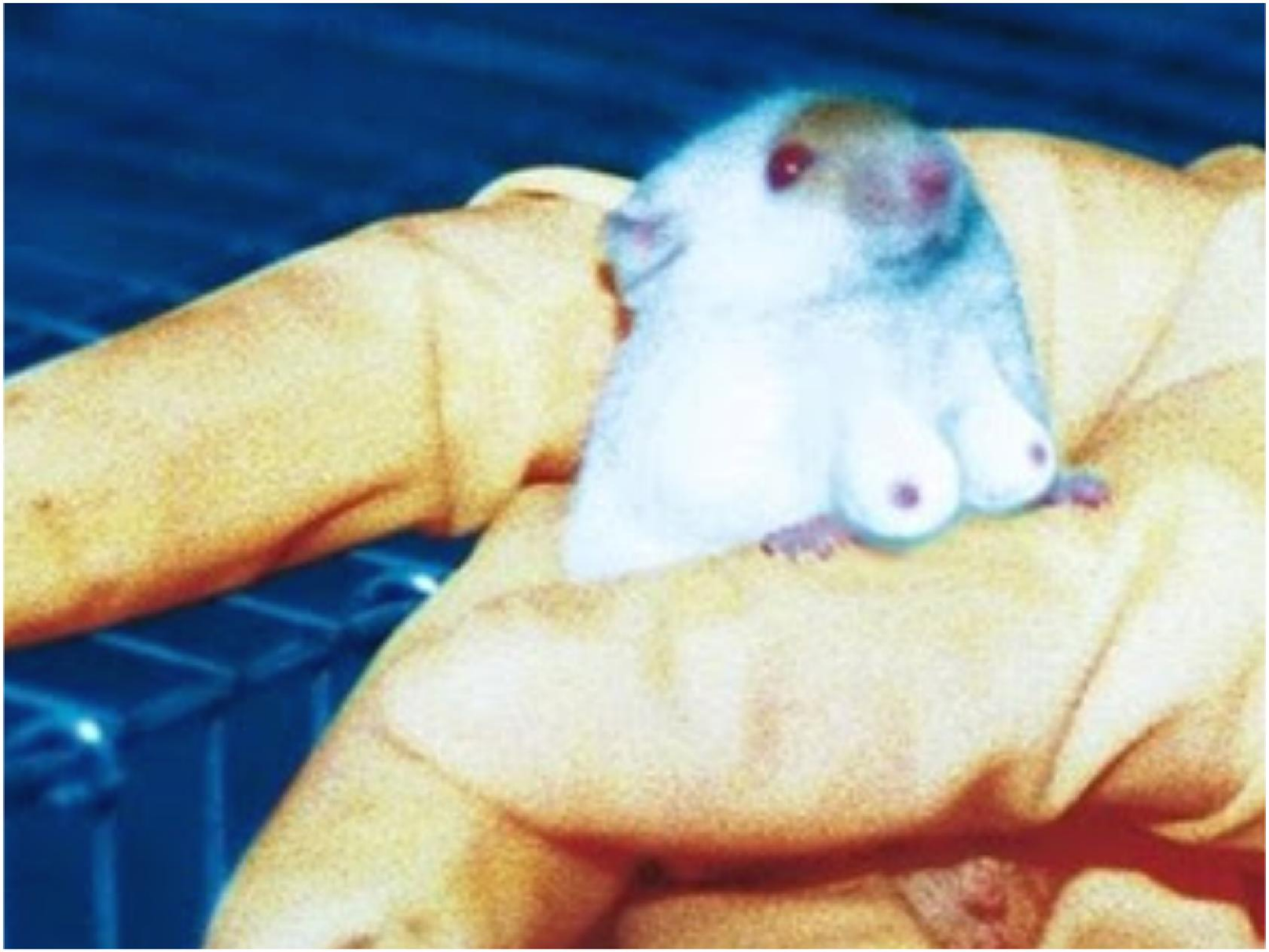


Abidia (U Hyperb Med 28: 64,'01) – RCT - High
Kalani (J Diab Comp 16: 153, '02) – Prosp Cohort - Mod
Zamboni (U Hyp Med 24: 175,'97) – Prosp Cohort - Mod
Baroni (Daib Care 10: 81, '87) – Prosp Cohort - Low
Oriani (J Hyperb Med 5: 171,'90) – Prosp Cohort - Low
Löndahl (Diab Care 33: 998, '10) – RCT - High

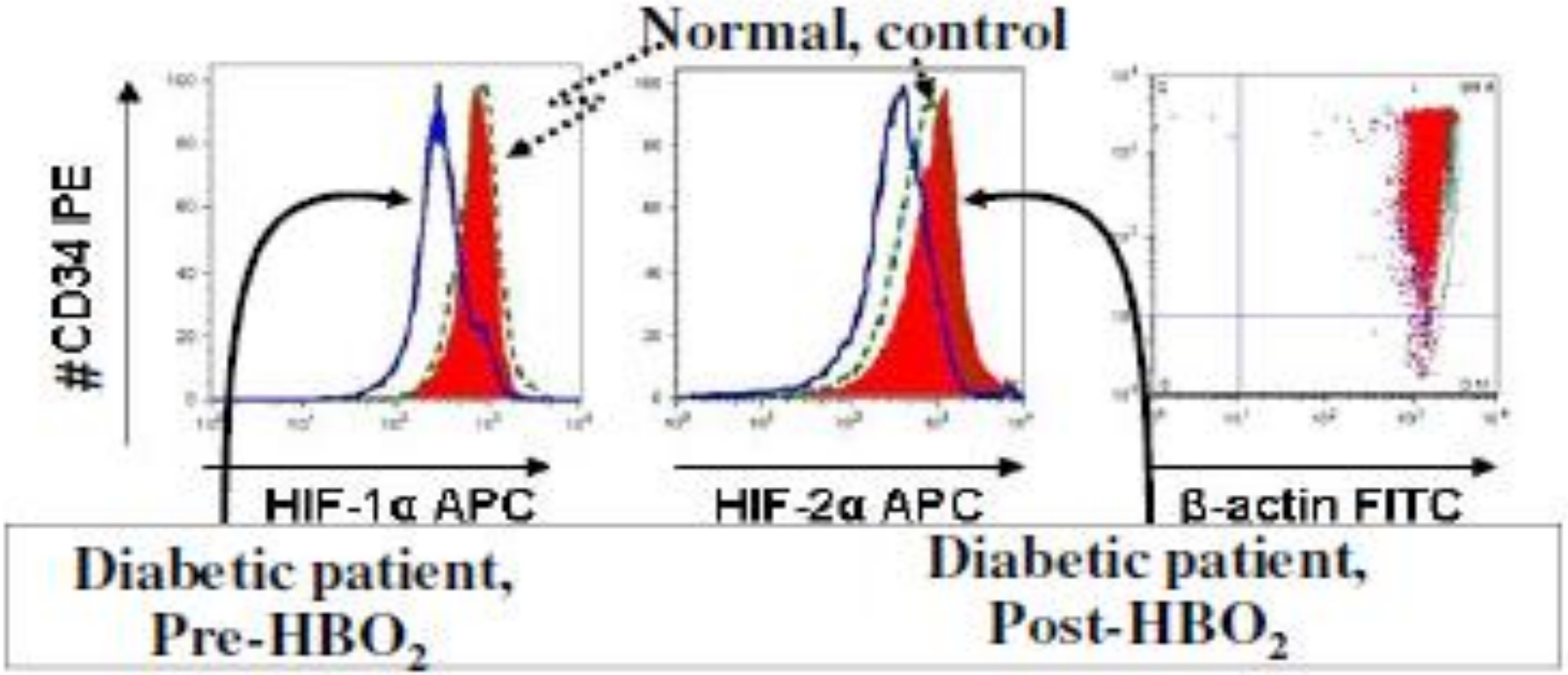



Pre-HBO

Post-HBO: There is less fibrosis and increased cellularity.

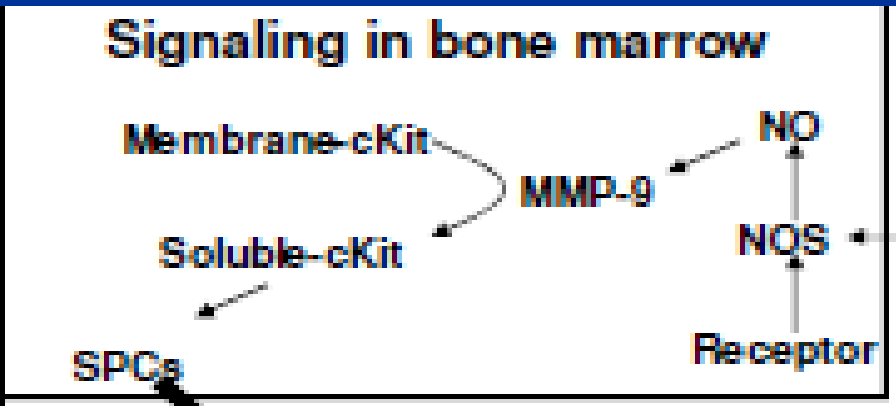


- DIABETIC PATIENTS - NEWLY MOBILIZED SPCs HAVE MORE HIFs



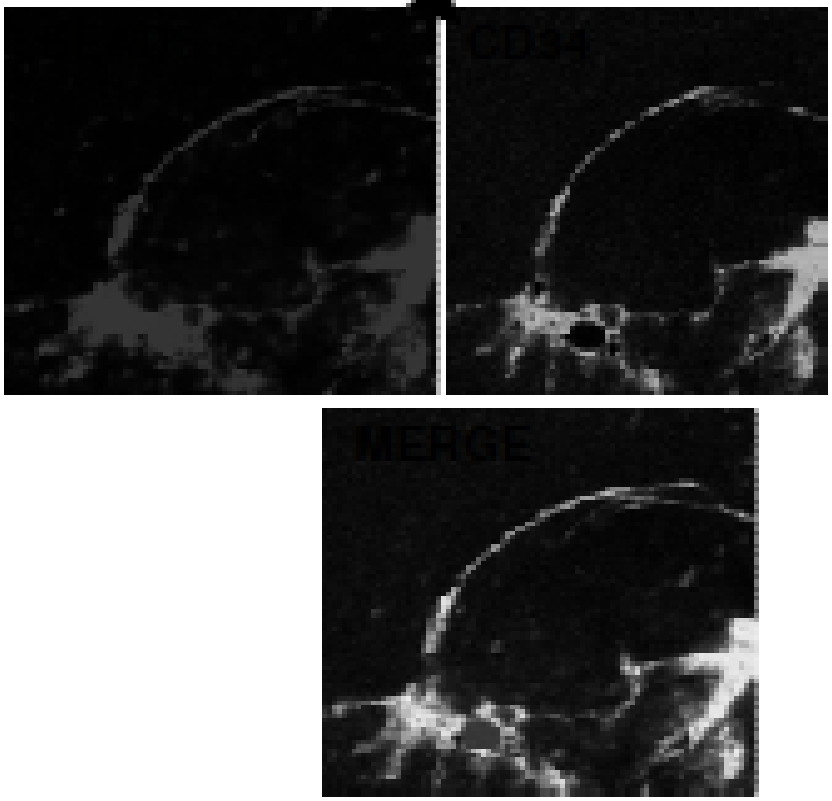
Thom, et al. Wound Repair & Regeneration – 19: 149-161, 2011

Signaling in bone marrow

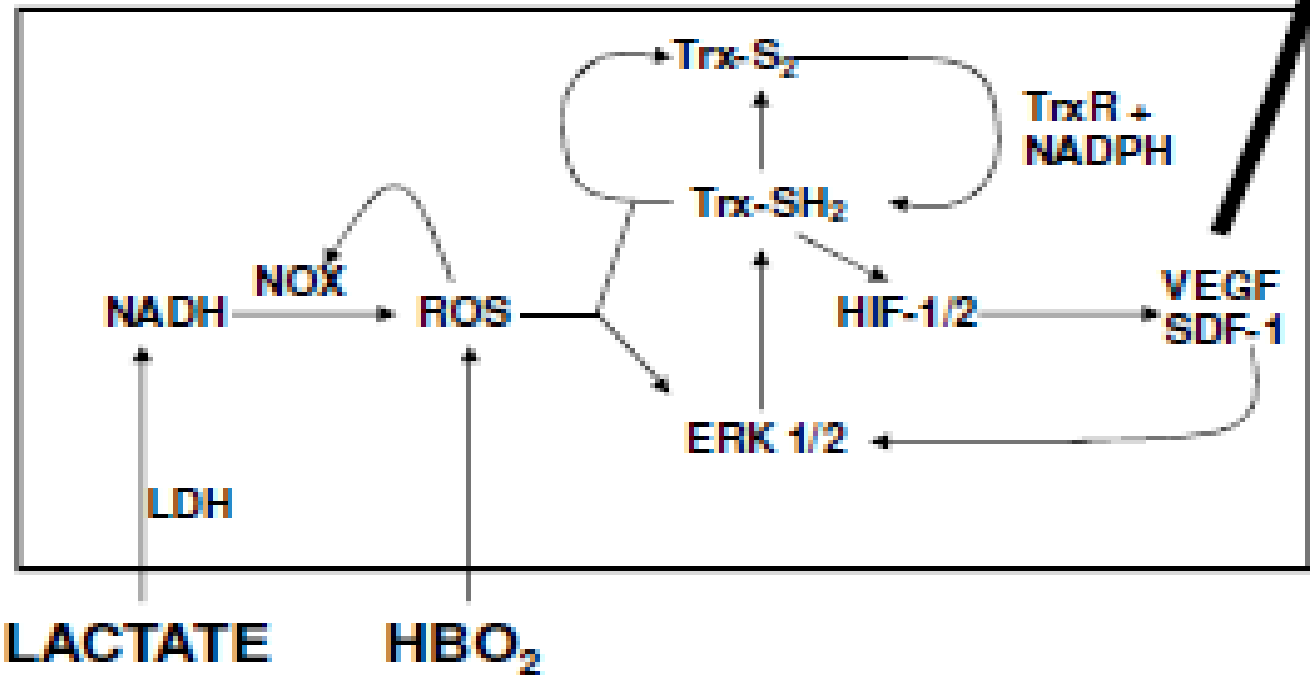


(Mol Cell Biol 28: 6248, 2008,
J Appl. Physiol 106: 711, 2009)

HBO_2



Signaling within SPCs

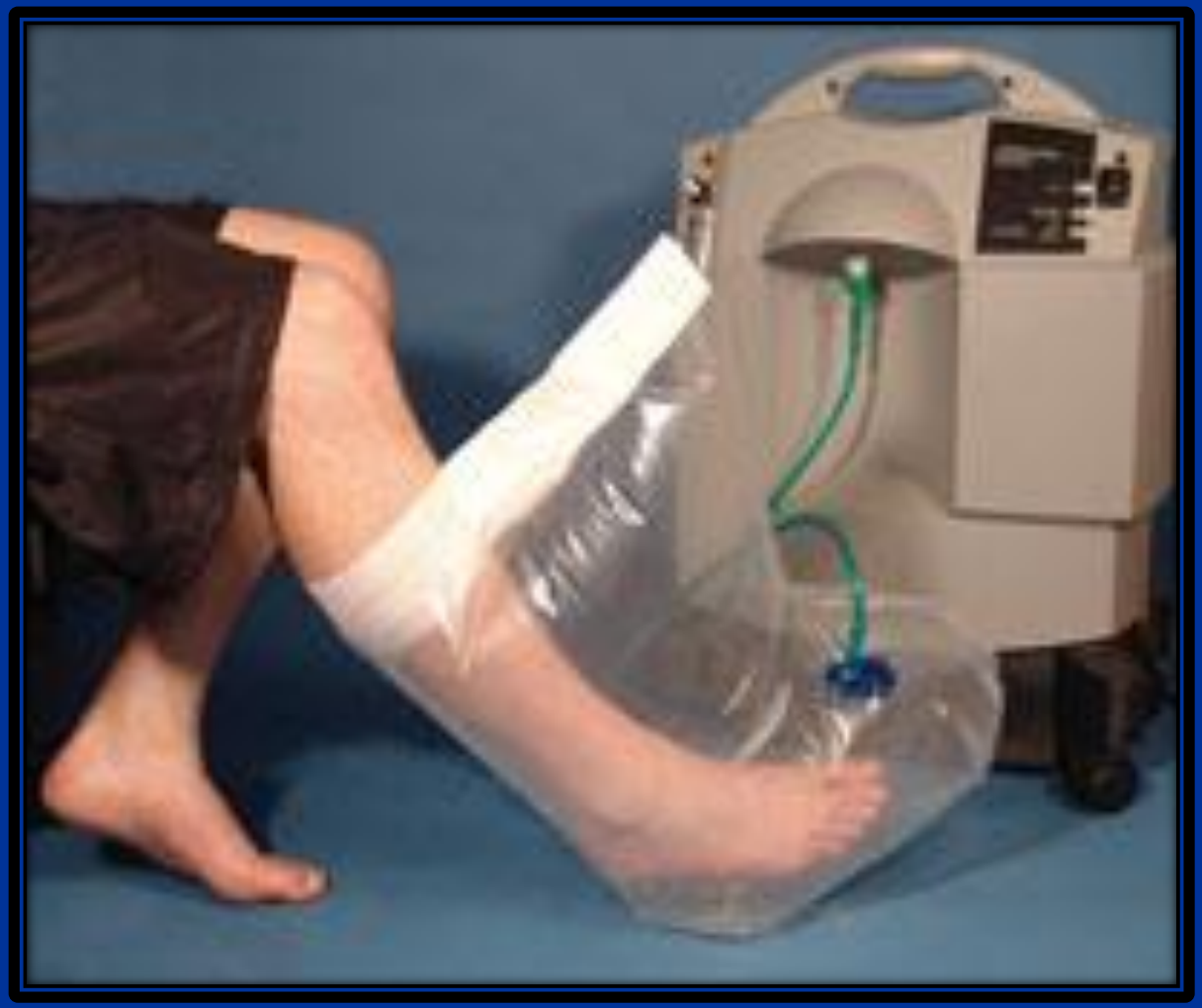


Growth Factor Production

- HBOT increases VEGF in experimental wounds (Arch Surg 135: 1293,2000).
- HBOT increases synthesis of bFGF and TGF beta-1 in human dermal fibroblasts (Arch Facial Plas Surg 6: 31, 2004).
- Increased homing molecule production. Stromal Derived Factor 1 alpha (SDF-1).
- HBOT up-regulates PDGF (UHMS 25: 211, 1998).

What Hyperbaric is NOT

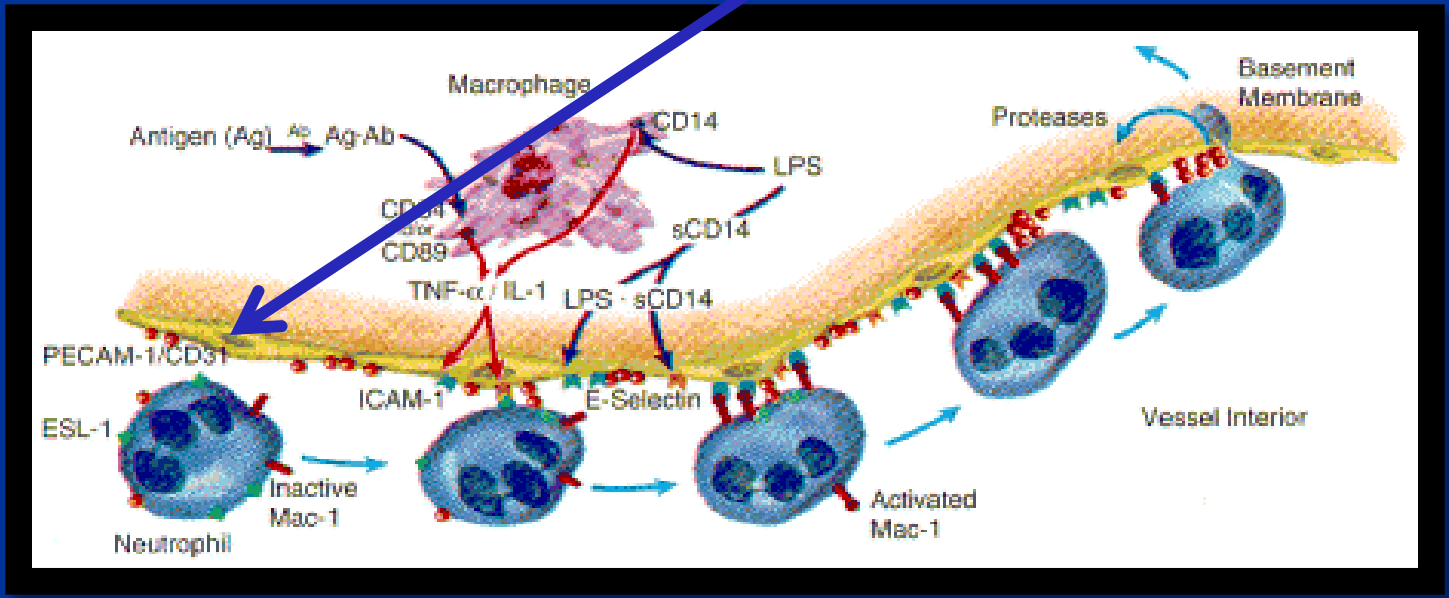
What Hyperbaric Oxygen is NOT




NEED CASH
FOR ALCOHOL
RESEARCH

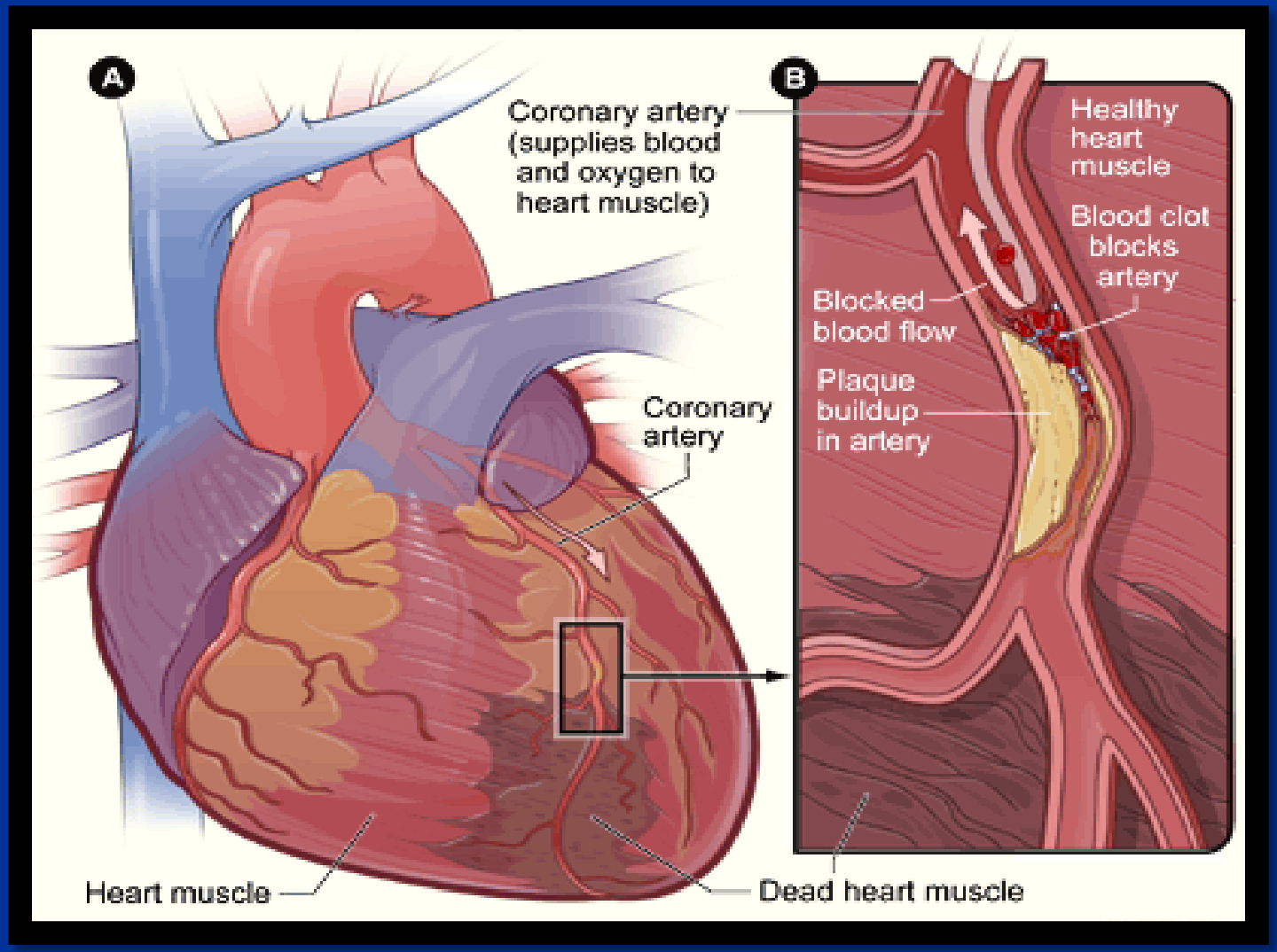
Integrin beta-2

HBOT Inhibition

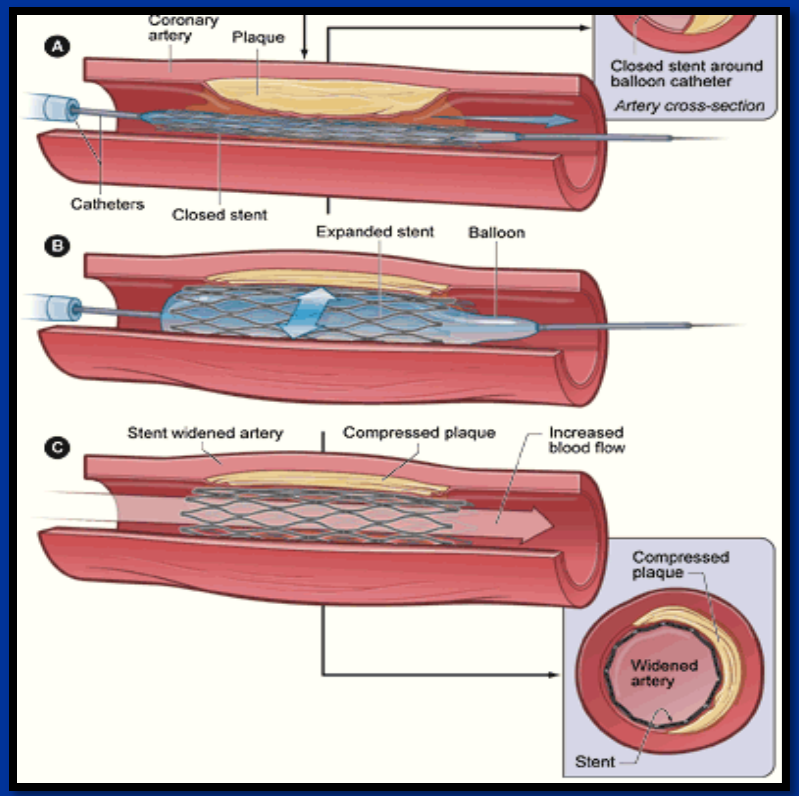


Inhibition of human neutrophil beta2-integrin-dependent adherence by hyperbaric O2

The Protective Effects Of Treatment With Hyperbaric Oxygen Prior To Bypass Heart Surgery(clinical trials.gov)



- Chronic stroke and stroke rehabilitation
- Reperfusion.
  - Pre and Post stent placement
- Cardiac indications
- Carotid Surgery and stenting.
- Critical Limb Ischemia
  - In combination with stenting
  - Non surgical candidates
  - In combination with other angiogenic modalities



Traumatic Brain Injury
Cerebrovascular Disease