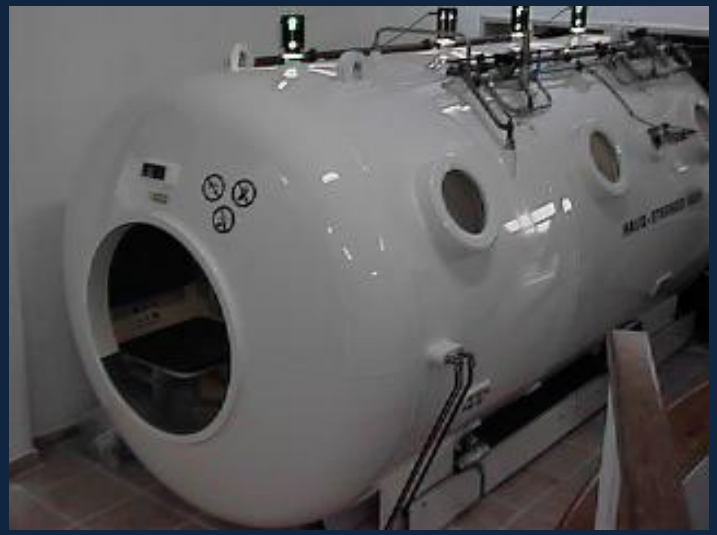
HİPERBARİK OKSİJEN TEDAVİSİ

DOÇ.DR.GÜNALP UZUN
GATA HAYDARPAŞA EĞİTİM HASTANESİ
SUALTI HEKİMLİĞİ VE HİPERBARİK TIP SERVİSİ

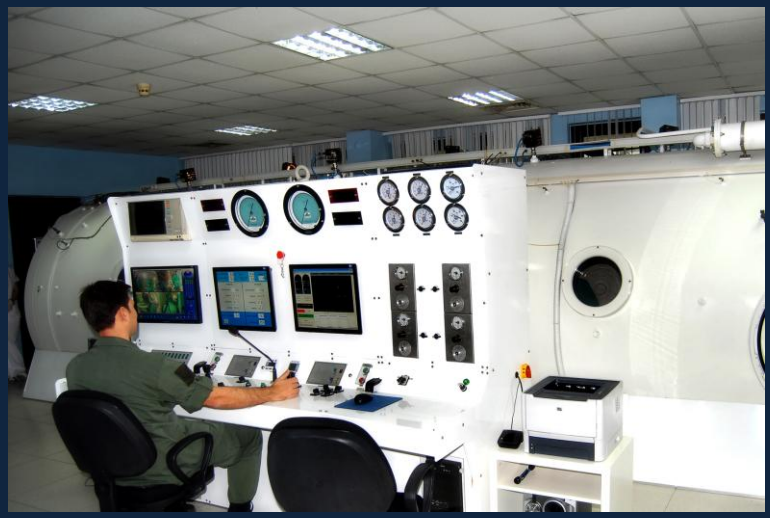
UDAİS

II. Ulusal Diyabetik Ayak İnfeksiyonları Simpozyumu

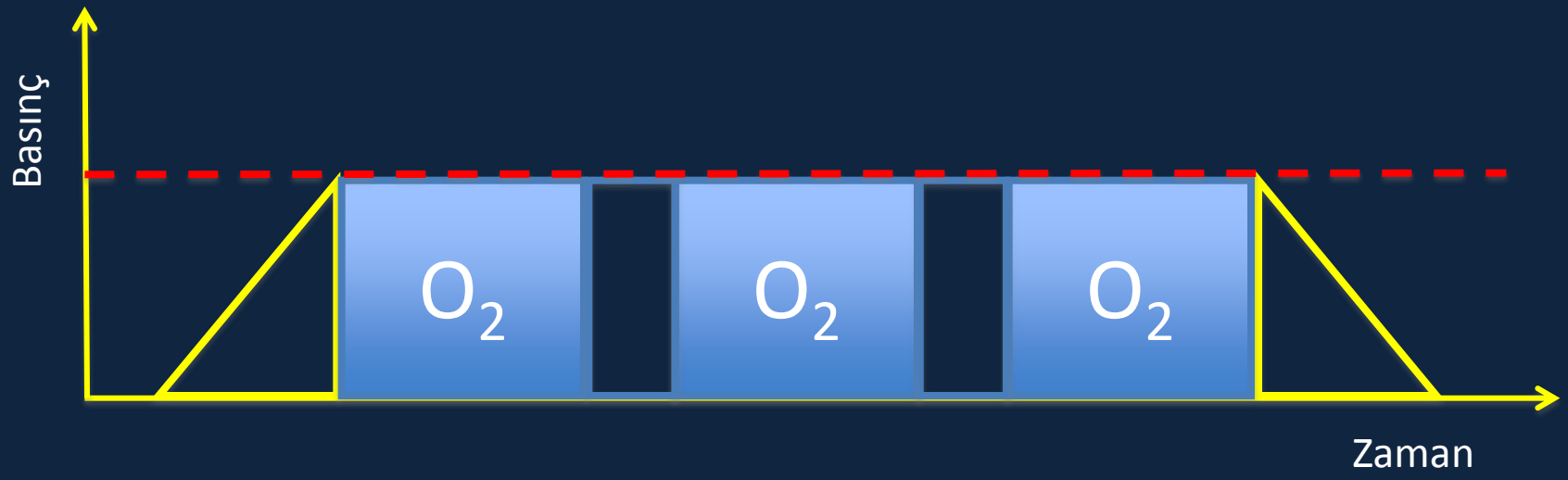
Hiperbarik oksijen tedavisi; hastalara *yüksek basınç* altında *%100 oksijen* solutulmasıdır.



Hiperbarik oksijen tedavisi; hastalara *yüksek basınç* altında *%100 oksijen* solutulmasıdır.



HBO tedavisi sırasında pO_2 seviyeleri



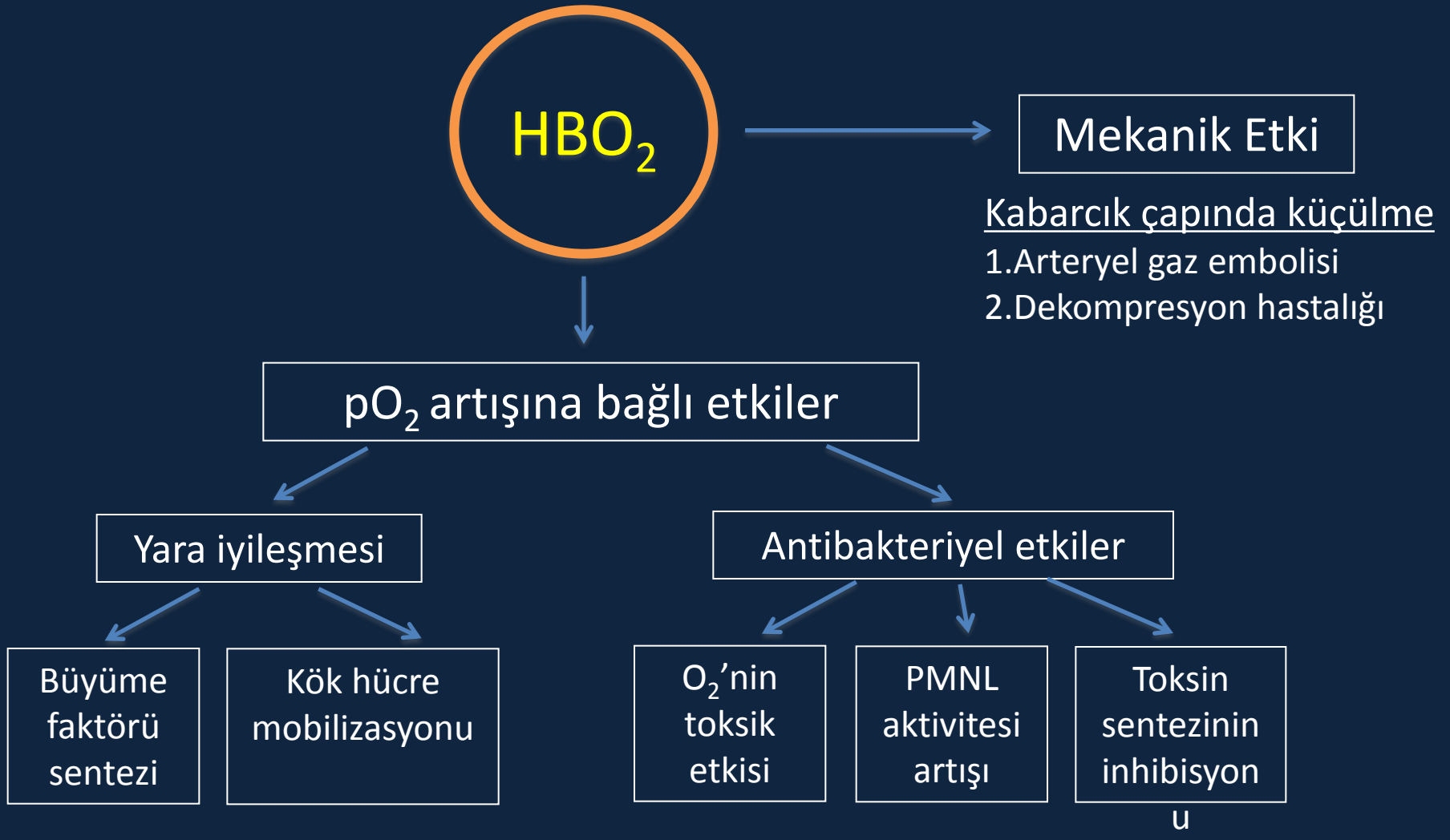
Solunan Oksijen Basıncı (atm)	Arteryel pO_2 (mmHg)	Doku pO_2 (mmHg)
0.21	90 ± 9	41 ± 10
1.0	625 ± 23	76 ± 45
2.0	1356 ± 28	280 ± 50
2.5	1700	348

J Appl Physiol 1963;8:869. J Infect Dis. 1980;142:915. Ann NY Acad Sci 1965;117;688. JAMA 1966;198:1280. Plast Reconstr Surg 1970;45:25.

Oksijen difüzyonu

- Hiperoksi plazmada yüksek miktarda oksijen çözünmesine ve dokularda oksijen difüzyon mesafesinin etkin bir şekilde artmasına neden olur.
- Diabette kapiller bazal membran anormallikleri nedeni ile doku oksijenasyonu bozulmuştur. Artan diffüzyon mesafesi sayesinde iskemik yara dokusunda tekrar oksijen seviyesi yükseltilebilir.

pO_2	Etkin diffüzyon mesafesi
100 mmHg	64 µm
2000 mmHg	246 µm



Plast.Reconstr. Surg. 2011; 127(Suppl.):131S-141S.

HBO & Büyüme faktörleri

- İskemik yarada VEGF (vascular endothelial growth factor) sentezini arttırır
  - [Arch Surg. 2000;135(11):1293-7]
- İnsan dermal fibroblastlarından BFGF (basic fibroblast growth factor) ve TGF-β1 (transforming growth factor-β1) salınımını
  - [Arch Facial Plast Surg. 2004;6(1):31-5.]
- İnsan umblikal ven endotel hücrelerinden anjiopoietin-2 salınımını artırır
  - [Biochem Biophys Res Commun. 2002;296(3):710-5.]

HBO & Büyüme faktörleri

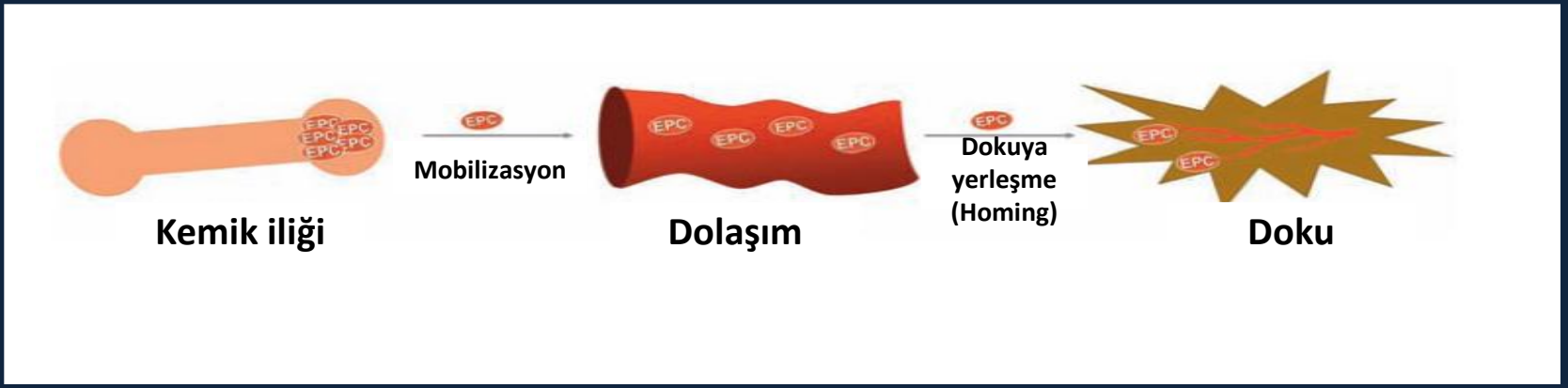
- Deneysel yaralarda PDGF (platelet derived growth factor) reseptör sayısını arttırır
  - [Undersea Hyperb Med. 1998;25(4):211-6.]
- İnsan mezenkimal kök hücrelerinden PGF (plasental growth factor) sentezini arttırır
  - [Life Sci 83;65:2008]
- İskemik bacaklarda BFGF ve HGF ekspresyonunu ve damar dolaşımını arttırır
  - [Circ J 2007:71:405-11]
- Deneysel yanık yarasında kollajen sentezini arttırır
  - [Burns 2008:34;467-73]

pO_2 ve prolil hidroksilaz aktivitesi

pO_2	
20 mmHg	Enzim maksimum enzimatik hızın yarısı hızda çalışır.
150 mmHg	Maksimum enzimatik hızın %90'ında çalışır.

Epidermal öncül hücreler ve yara iyileşmesi

- Kemik iliği önemli bir kök hücre rezervidir.
- Uyarı sonrası hızlı olarak perifere çıkabilirler ancak bazıları önce prolifere olur ve geç dönemde dolaşıma çıkarlar
- Mobilizasyonu uyaran faktörler
  - Egzersiz
  - Periferal iskemi
  - Hematopoetik uyarıcı faktör



Antioxid Redox Signal. 2008 Nov;10(11):1869-82.

Epidermal öncül hücreler ve yara iyileşmesi

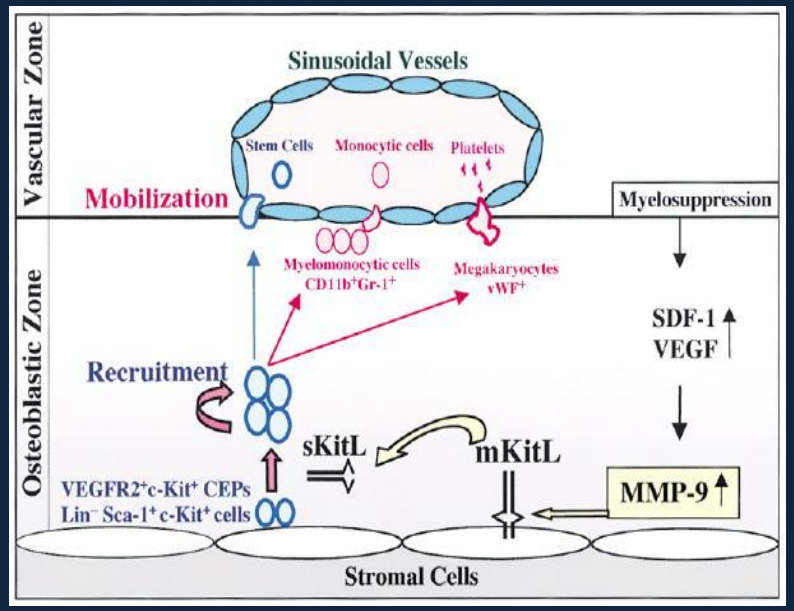
- Dolaşımda çok az miktarda bulunur (~ % 0,01)
- Yüzey belirteçleri (CD34,VEGFR2,CD133)
- Hasarlanan damar duvarında endotele katılır
  - Yara iyileşmesi, MI sonrası, damar greftlerinin endotelizasyonu
- Patolojik neovaskülarizasyon
  - Retinal neovas., tümör büyümesi, ateroskleroz

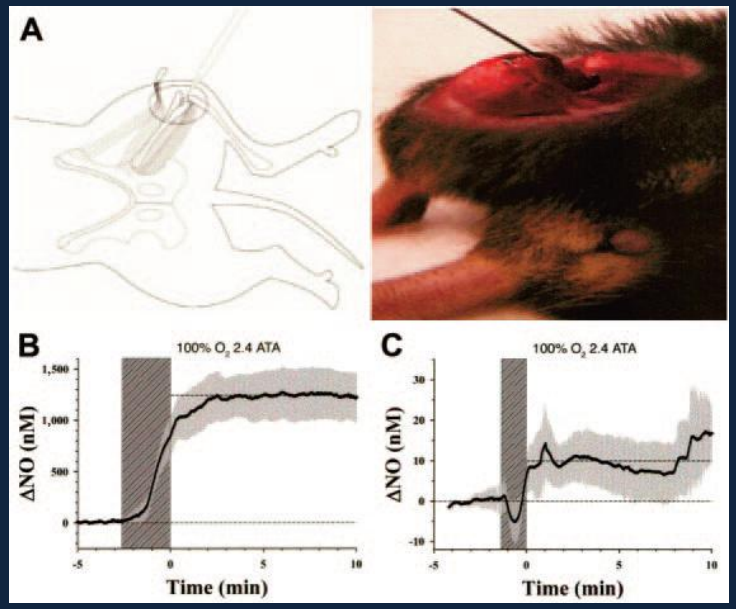
Antioxid Redox Signal. 2008 Nov;10(11):1869-82.

EPC & diyabet

- Diyabetik hastalarda dolaşımdaki EPC oranı azalır
  - [Fadini et al. J Am Coll Cardiol. 2005 May 3;45(9):1449-57.]
- Proliferasyon, adezyon, damar duvarına yerleşme fonksiyonları daha düşüktür
  - [Tepper OM, et al. Circulation 2*002;*106: 2781–2786.]
- Yara dokusuna yerleşimi daha az
  - [Gallagher et al. J Clin Invest 117: 1249–1259, 2007.]

HBO & EPC mobilizasyonu





Stem cell mobilization by hyperbaric oxygen

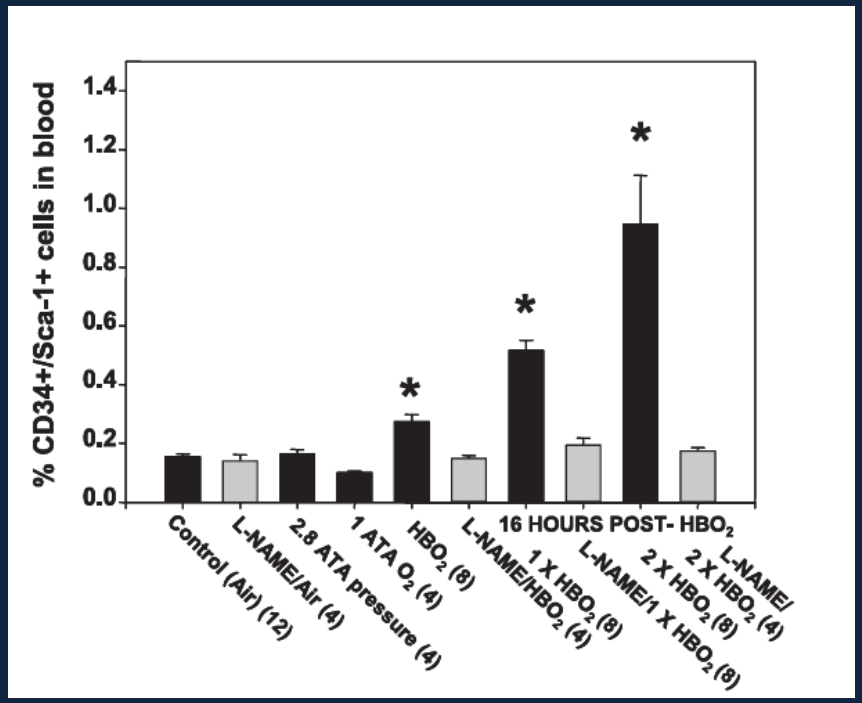
Am J Physiol Heart Circ Physiol 290: H1378–H1386, 2006.

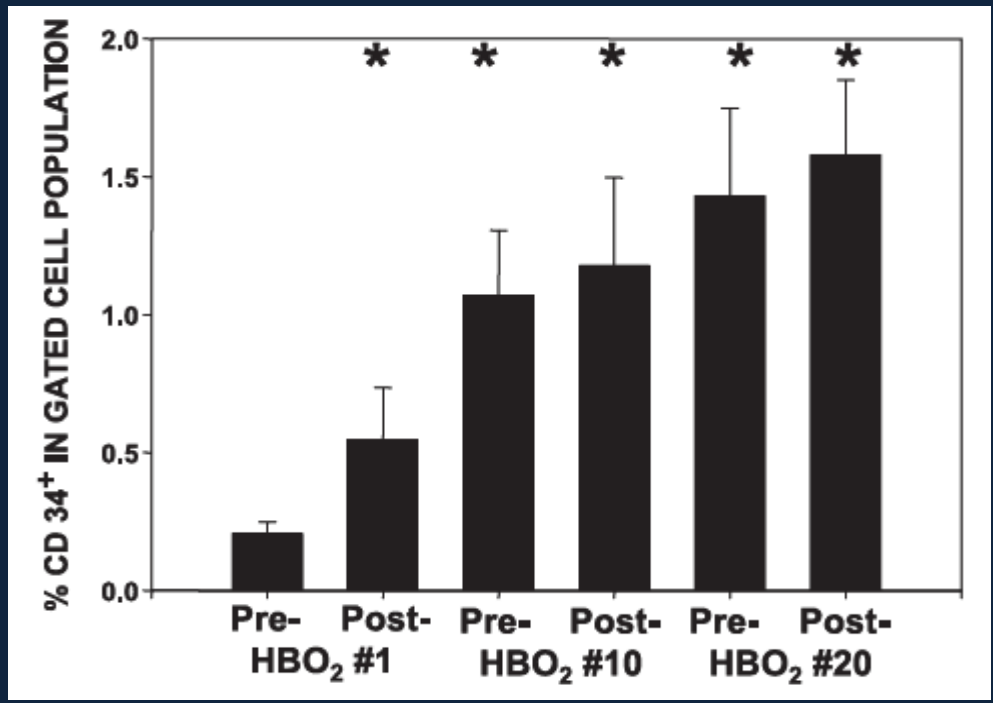
Stem cell mobilization by hyperbaric oxygen

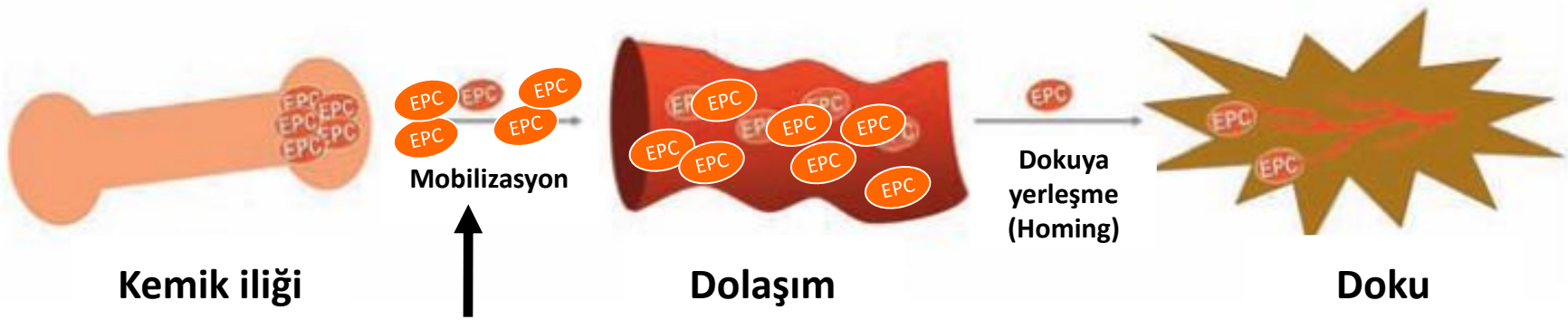
Stephen R. Thom,[1,2] Veena M. Bhopale,[1] Omaida C. Velazquez,[3] Lee J. Goldstein,[3] Lynne H. Thom,[1] and Donald G. Buerk[4]

[1]Institute for Environmental Medicine and Departments of [2]Emergency Medicine, [3]Surgery, and [4]Physiology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

Am J Physiol Heart Circ Physiol 290: H1378–H1386, 2006.







NO

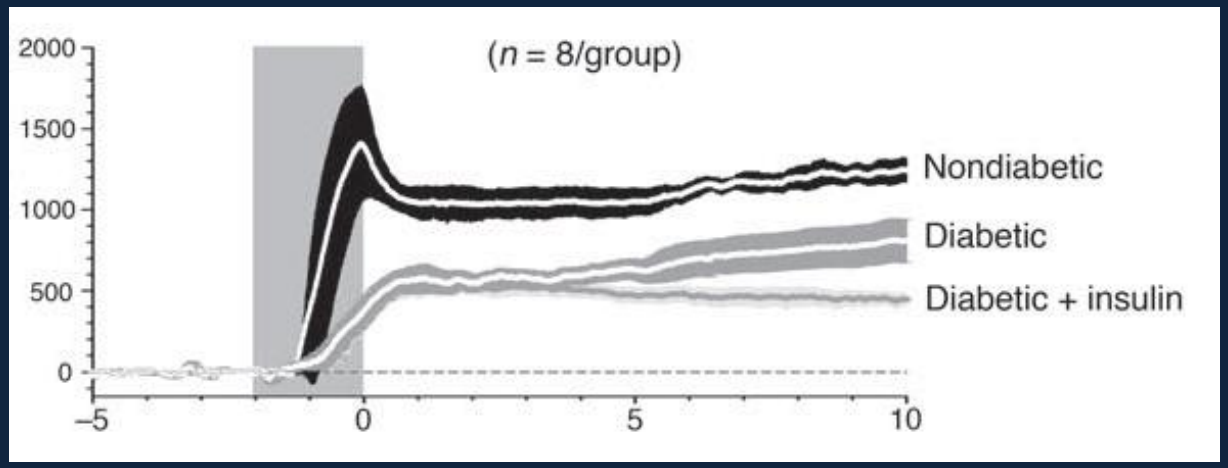
HBO

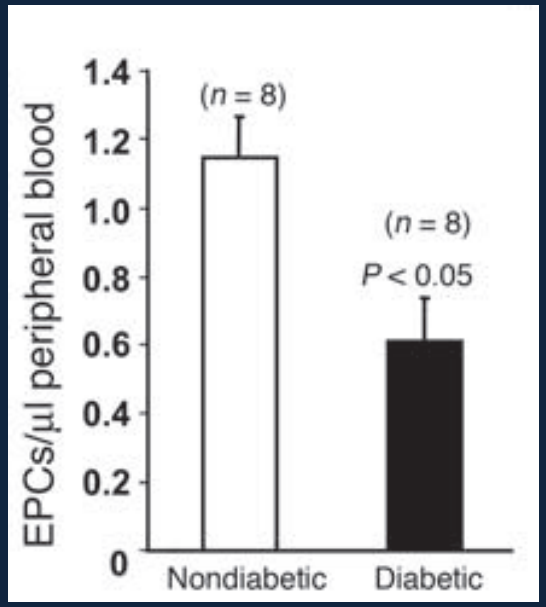
Diyabetik yara iyileşmesi

Diabetic impairments in NO-mediated endothelial progenitor cell mobilization and homing are reversed by hyperoxia and SDF-1α

Katherine A. Gallagher,[1] Zhao-Jun Liu,[1] Min Xiao,[1] Haiying Chen,[1] Lee J. Goldstein,[1] Donald G. Buerk,[2] April Nedeau,[1] Stephen R. Thom,[3] and Omaida C. Velazquez[1]

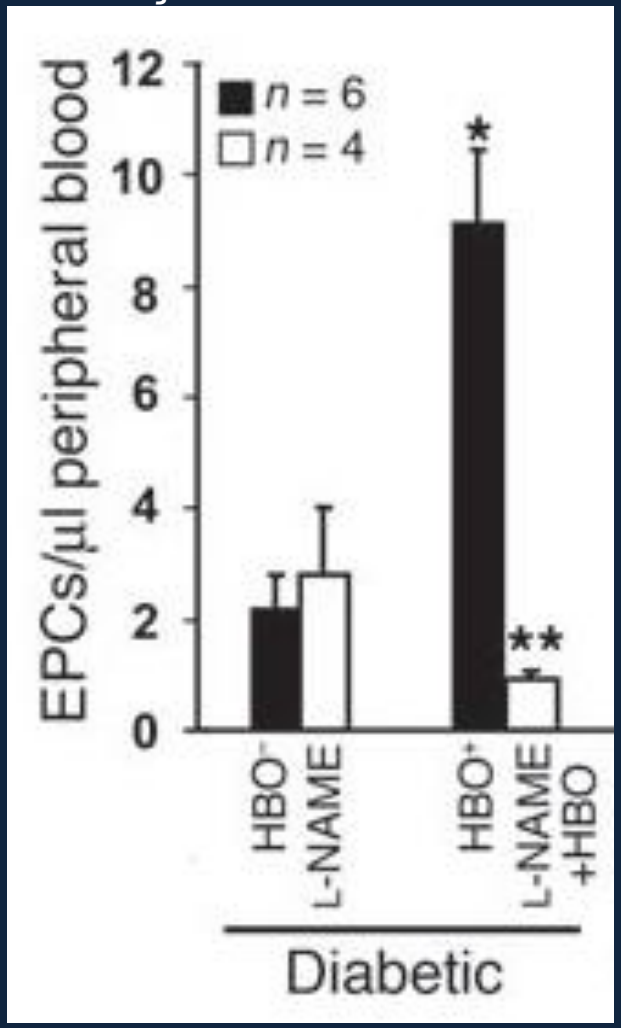
J. Clin. Invest. **117**:1249–1259 (2007). doi:10.1172/JCI29710.



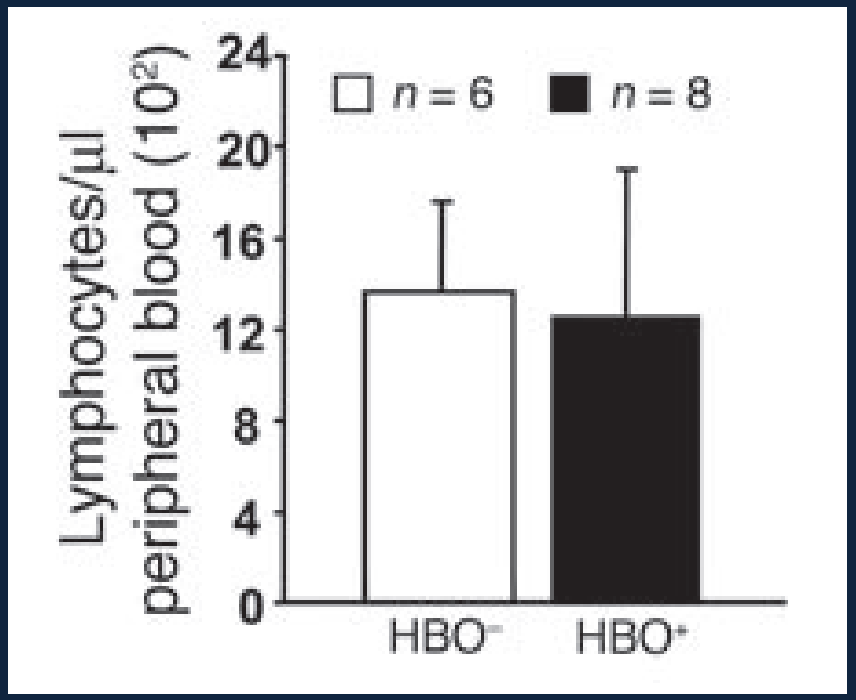


J. Clin. Invest. **117**:1249–1259 (2007). doi:10.1172/JCI29710.

Dolaşımdaki EPC miktarı

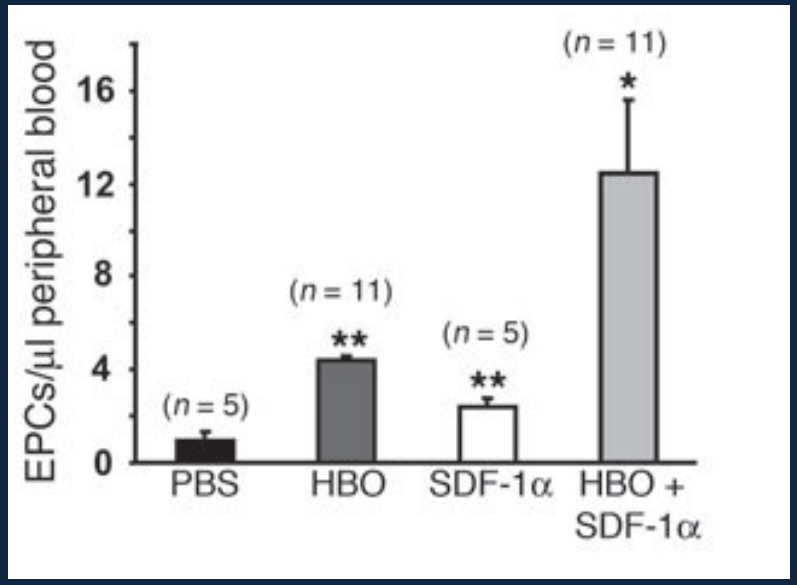


Dolaşımdaki lenfosit miktarı

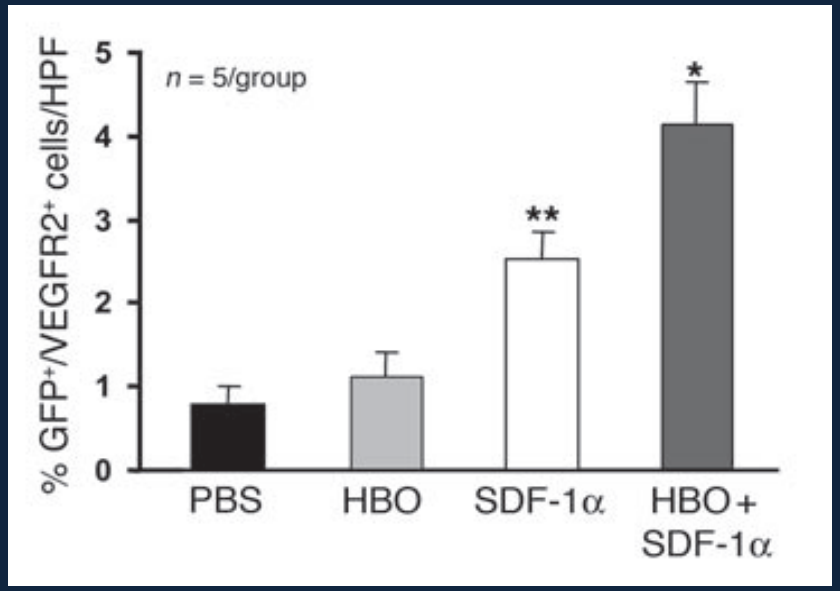


J. Clin. Invest. **117**:1249–1259 (2007). doi:10.1172/JCI29710.

Dolaşımdaki EPC miktarı

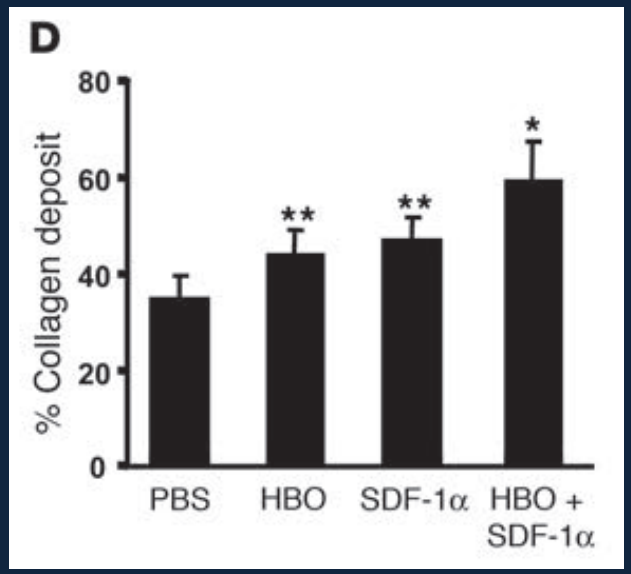


Yara dokusunda EPC miktarı

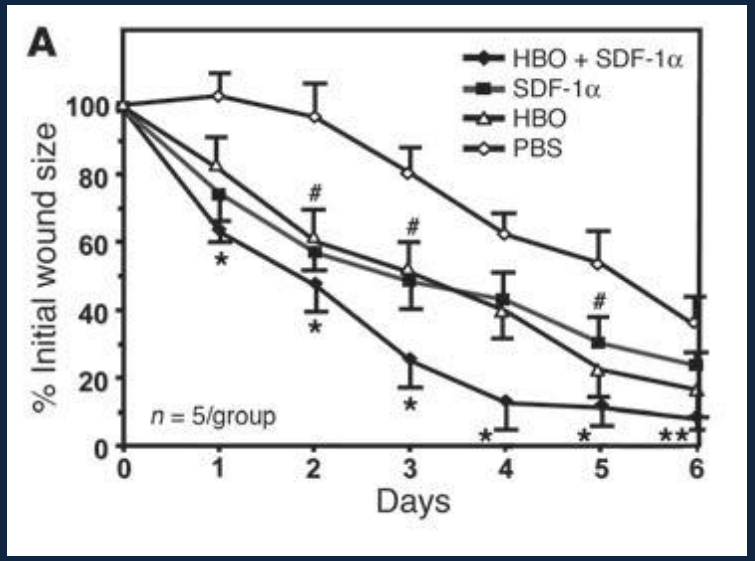


J. Clin. Invest. **117**:1249–1259 (2007). doi:10.1172/JCI29710.

Kollajen depolanması



Yara alanı

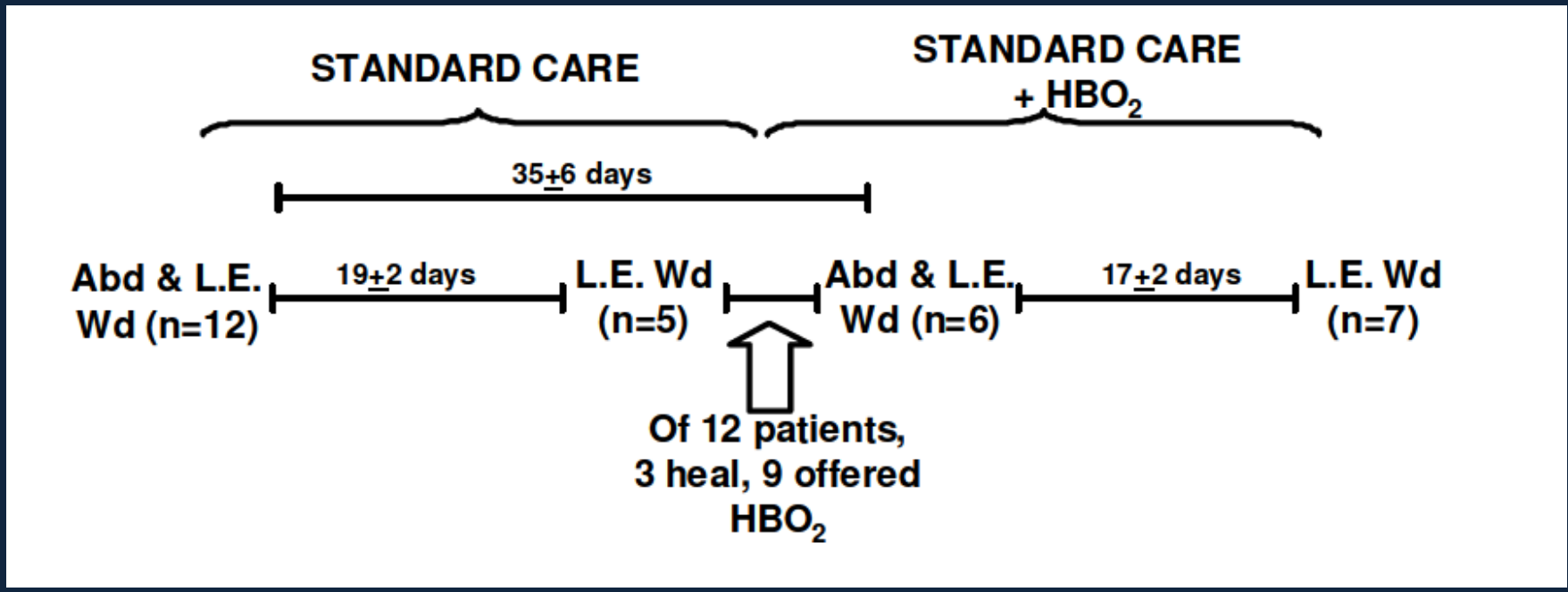


ORIGINAL RESEARCH – CLINICAL SCIENCE

Wound Rep Reg (2011) 19 149–161

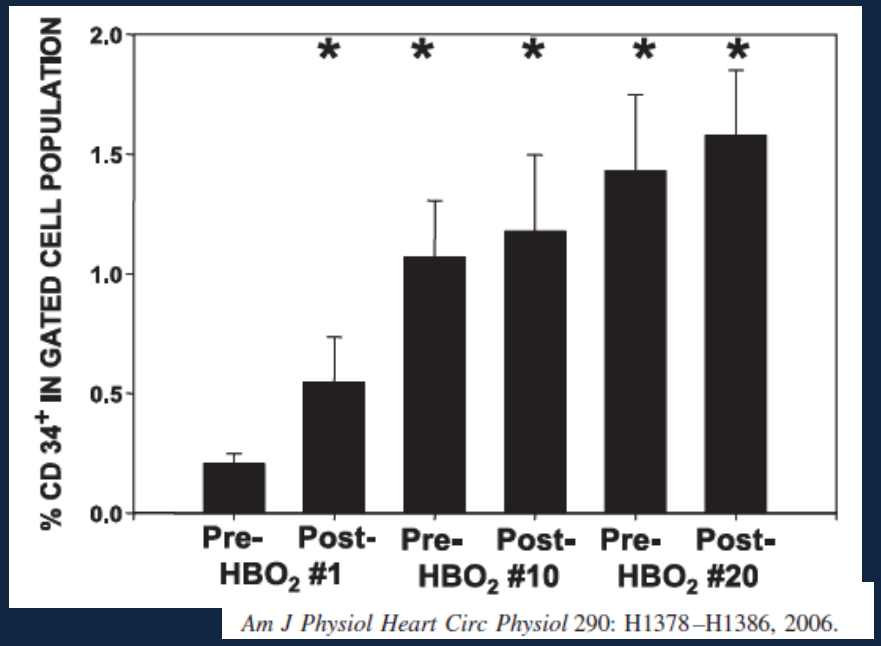
Vasculogenic stem cell mobilization and wound recruitment in diabetic patients: Increased cell number and intracellular regulatory protein content associated with hyperbaric oxygen therapy

Stephen R. Thom, MD, PhD[1,2]; Tatyana N. Milovanova, MD, PhD[1]; Ming Yang, MD[1]; Veena M. Bhopale, PhD[1]; Elena M. Sorokina, PhD[1]; Günalp Uzun, MD[3], D. Scot Malay, DPM, MSCE[4]; Michael A. Troiano, DPM[4]; Kevin R. Hardy, MD[1,2]; David S. Lambert, MD[1,2]; Christopher J. Logue, MD[1,2]; David J. Margolis, MD, PhD[5]



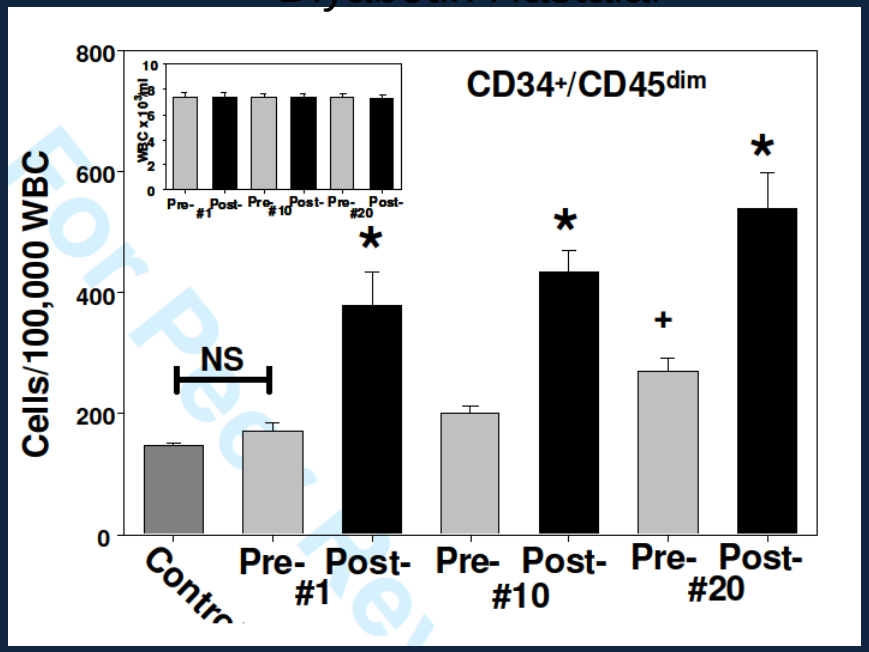
Diyabetik hastalarda EPC mobilizasyonu

Diyabetik Olmayan Hastalar

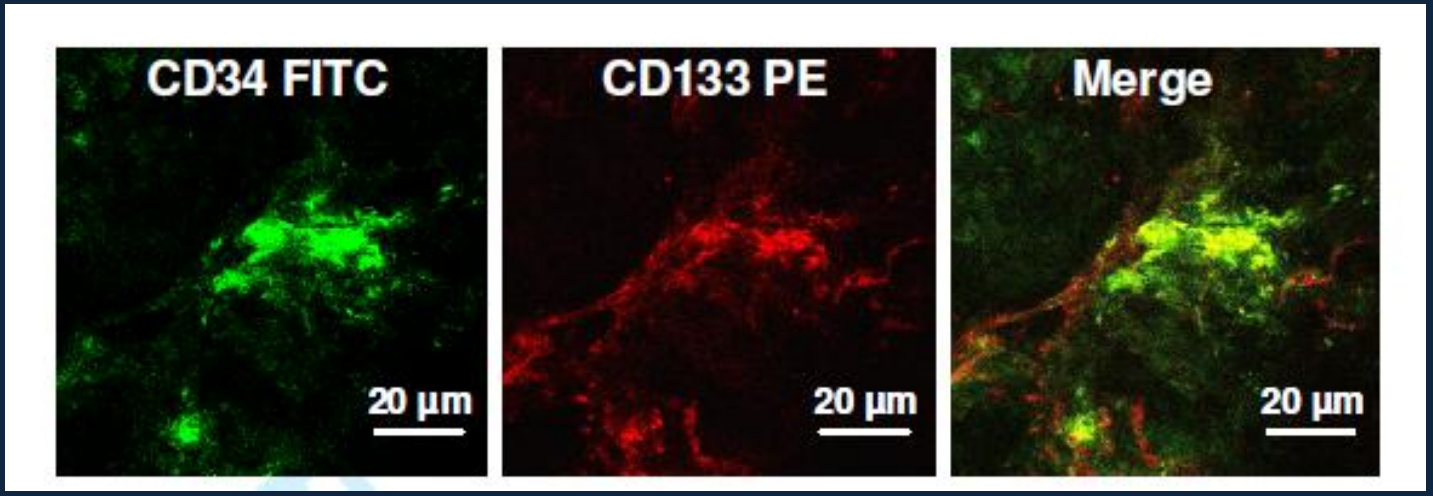


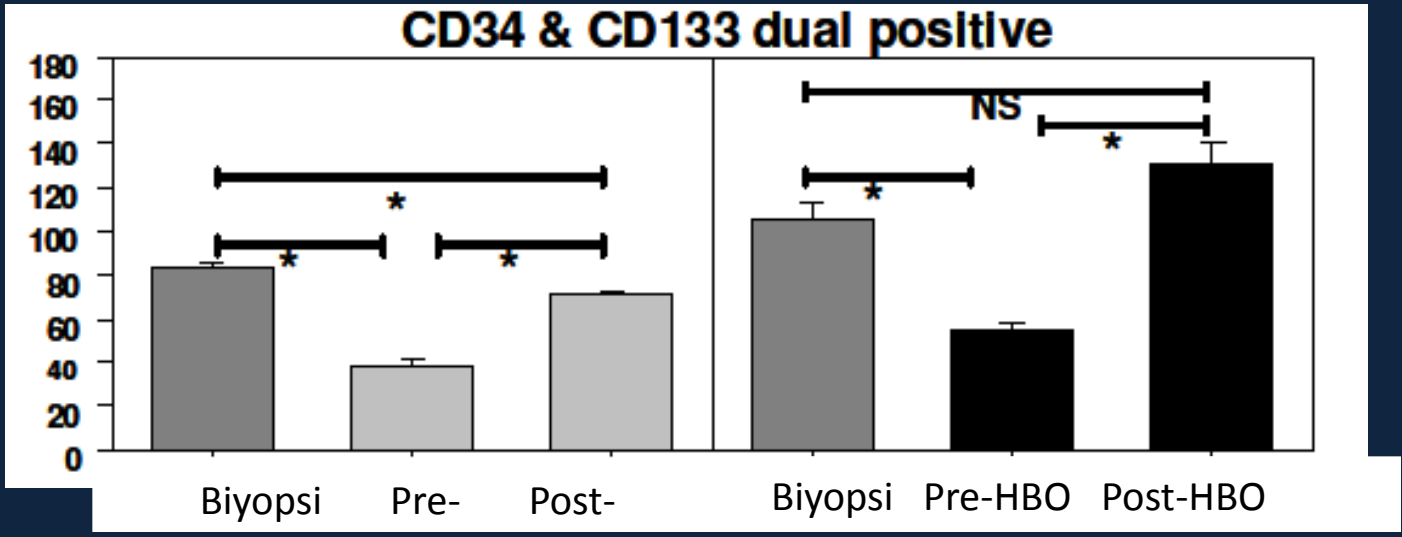
Am J Physiol Heart Circ Physiol 290: H1378–H1386, 2006.

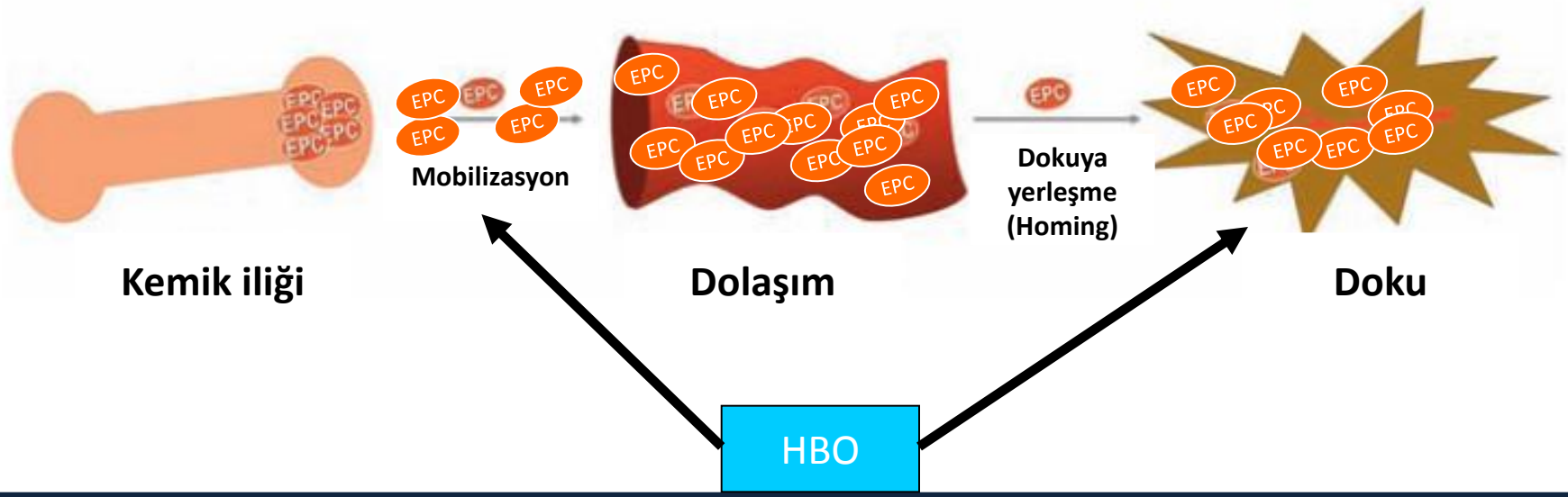
Diyabetik Hastalar



Doku örneklerinde EPC miktarı





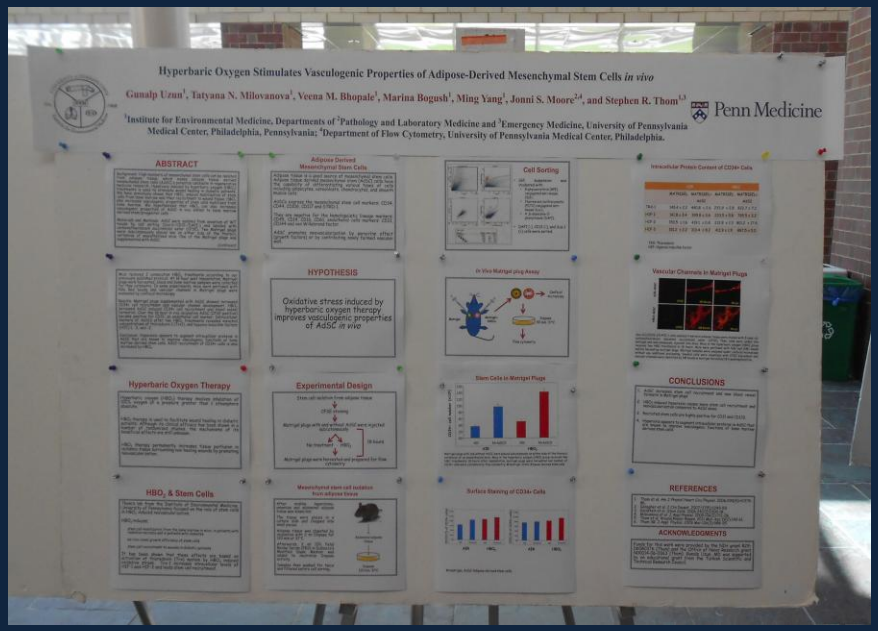


- Diyabetik hastalarda EPC mobilizasyonu HBO ile artar.
- EPC'lerin yara dokusuna yerleşimi HBO tarafından arttırılır.

Hyperbaric oxygen stimulates vasculogenic properties of adipose derived stem cells in vivo.

Gunalp Uzun, Tatyana Milovanova, Veena Bhopale, Marina Bogush, Ming Yang, Jonnie Moore, Stephen R.Thom

PennFlow Annual Scientiflc Meeting on Adipose-derived Stem Cells 2011 Philadelphia, PA

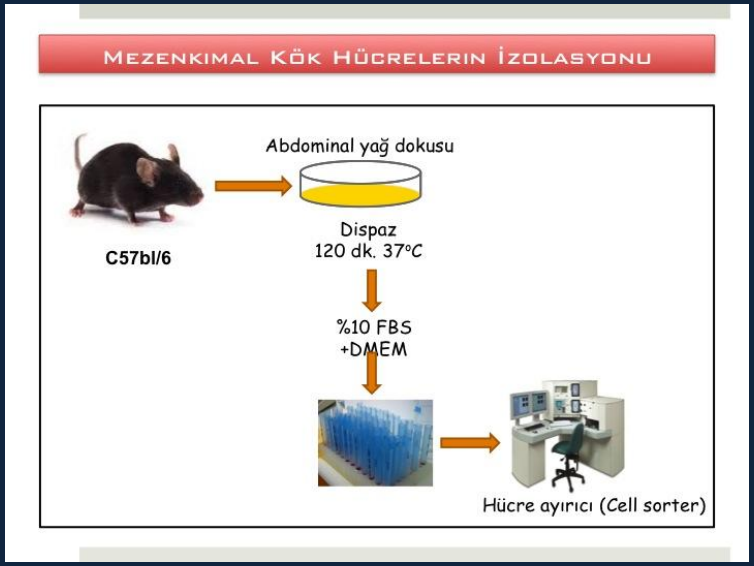


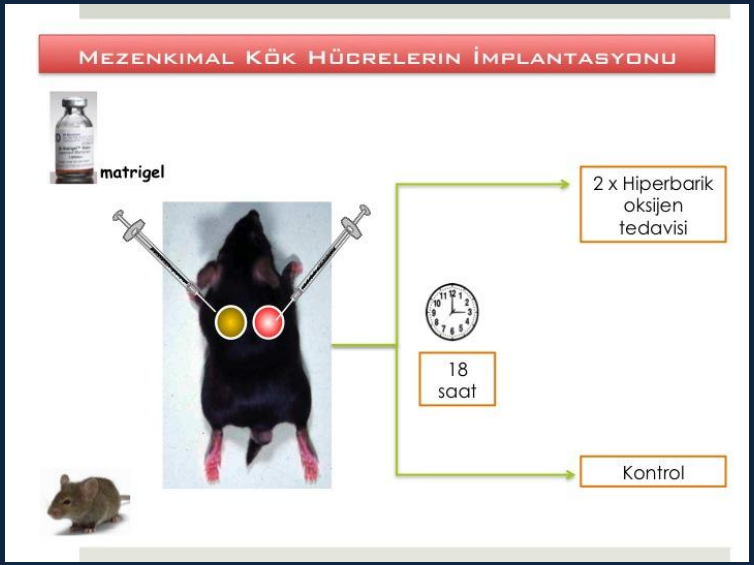
DESTEKLER

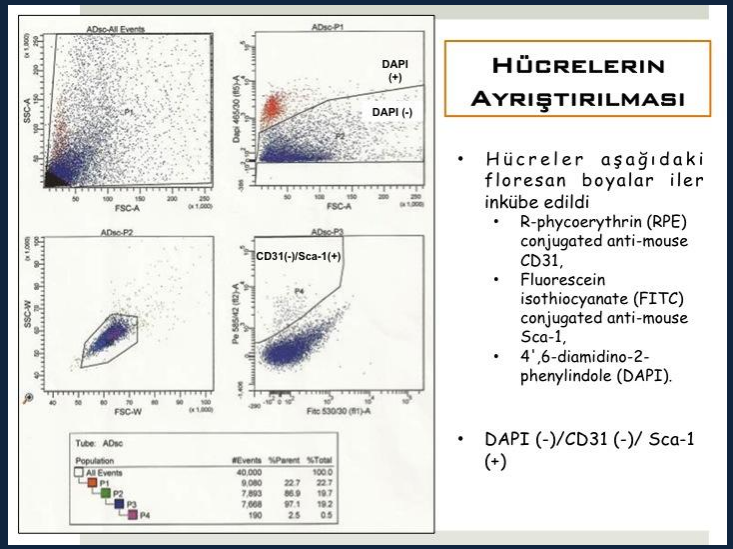
NIH R29-DK080376 (Stephen R. Thom)
ONR N00014-06-0363 (Stephen R. Thom)
TUBİTAK BIDEP 2219 (Günalp Uzun)

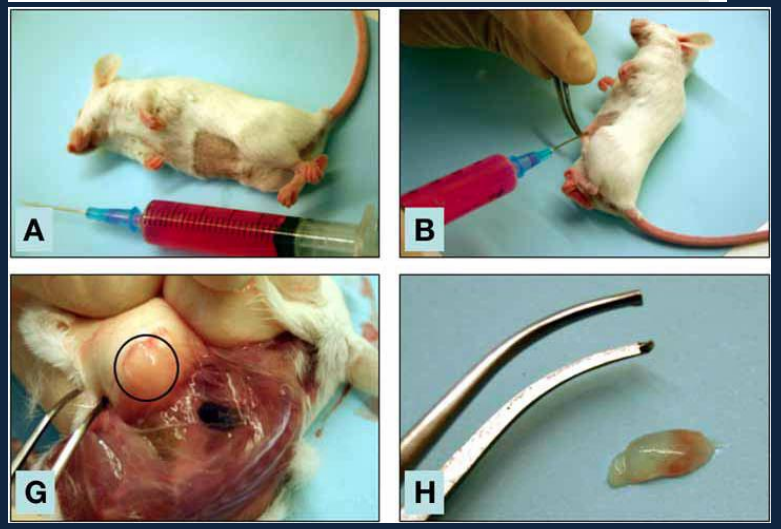
Hyperbaric oxygen stimulates vasculogenic properties of adipose derived stem cells in vivo.

Gunalp Uzun, Tatyana Milovanova, Veena Bhopale, Marina Bogush, Ming Yang, Jonnie Moore, Stephen R.Thom



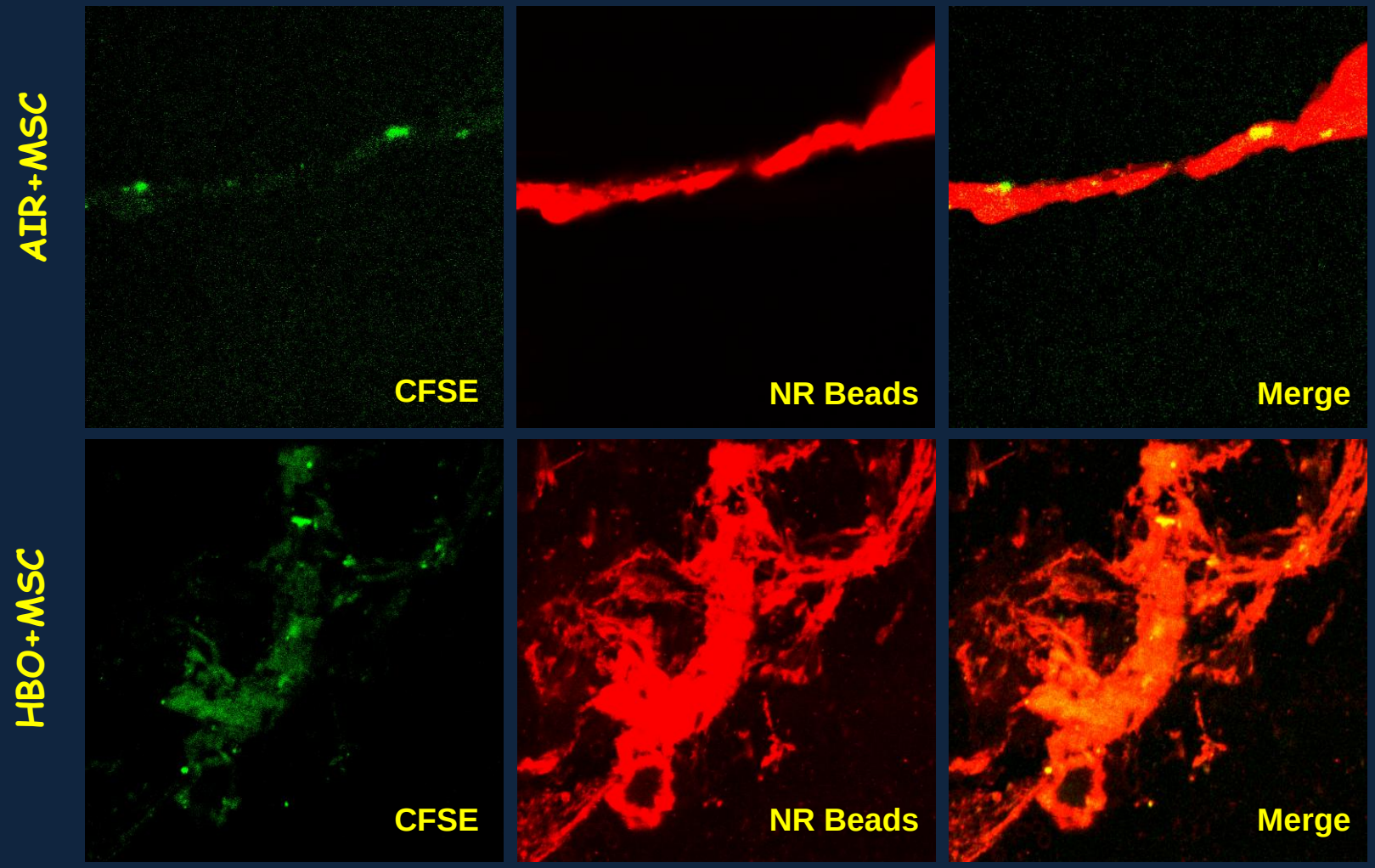






Skovseth DK, Küchler AM, and Haraldsen G. The HUVEC/Matrigel Assay. Methods in Molecular Biology 360:253-62.

HBO & yeni damar oluşumu



Plast.Reconstr. Surg. 2011; 127(Suppl.):131S-141S.

Oksijenin toksik etkisi

- Oksijen tüm organizmalara toksiktir
  - Ancak hassasiyet oranları değişir (oksijen kısmı basıncı ve zaman bağımlıdır)
  - HBO serbest oksijen radikalleri (süperoksit, hidroksil radikali, peroksitler, aldehit hipoklorit, hipoklorit) üretimini artırarak bunlara karşı savunma sistemleri olmayan anaerob bakterilere karşı bakterisidal etkinlik gösterir.
  - HBO aerobik ve fakültatif anaerobik bakterilere karşı bakteriostatik etkinlik gösterir. HBO bakterilerde protein sentezi, nükleik asitler, mebran transport fonksiyonlarını etkiler.

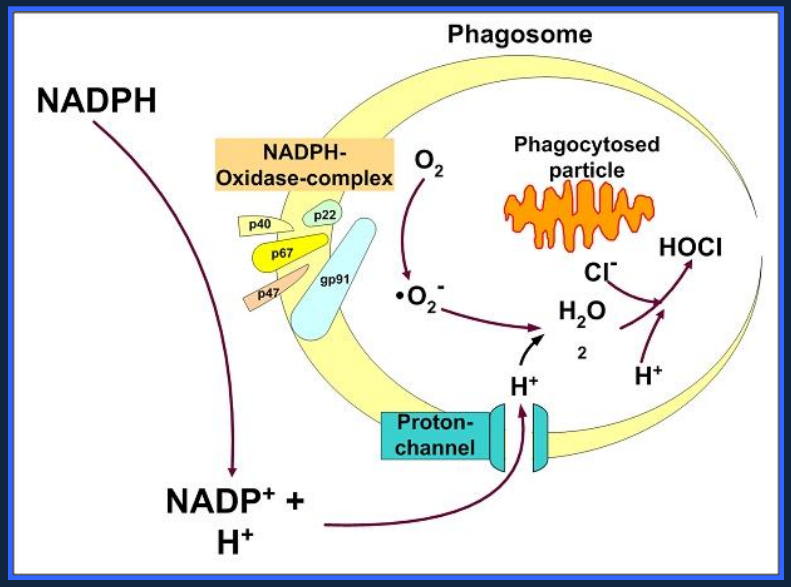
j clin microbiol 1975;1:161

Nötrofil aracılıklı bakteri öldürme mekanizması

- Nötrofillerin bakterisidal etkinliği hipoksik ortamda azalır.
- Hiperoksi bakterisidal reaktif ürünleri arttırır.

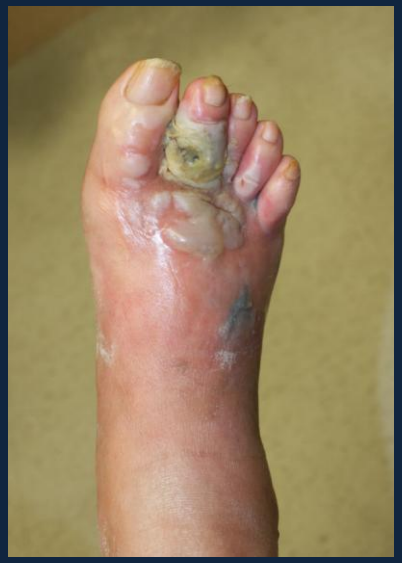
J Infect Dis 1980;142:915.

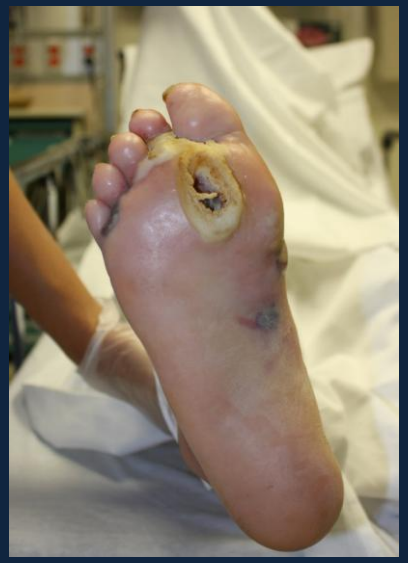
pO_2 ve NADPH oksidaz aktivitesi

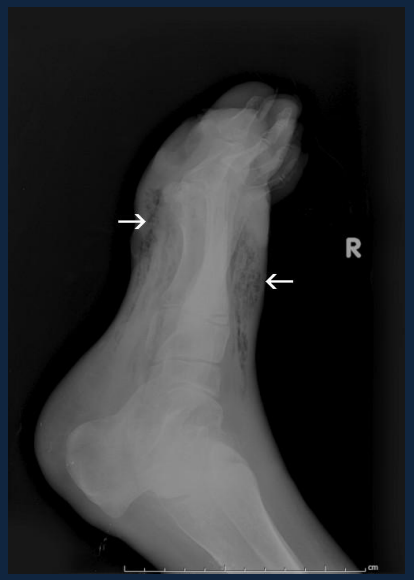


< 30 mmHg	Bakteriyel öldürme kapasitesinde ciddi kayıp olur.
45-80 mmHg	Enzim maksimum enzimatik hızın yarısı hızda çalışır.
300 mmHg	Maksimum enzimatik hızın %90'ında çalışır.

Toksin sentezinin inhibisyonu







International Journal of Emergency Medicine 2011, 4:14

- pO_2 330 mmHg *C. perfringens* alpha-toxin (oxygen-stabile) üretimini durur.

- *C. perfringens* theta-toxinini (oxygen-labile) detoksifiye eder.

Ann NY Acad Sci 1965:117;688

HBO ve antibiyotikler

1. Antibakteriyel ajanların etkinlik gösterebilmeleri için gerekli doku pO_2 değerlerinin sağlanması:
   - Aminoglikozidler,
   - Sülfonamidler,
   - Florokinolonlar,
   - Vankomisin,
   - Trimetoprim

HBO ve antibiyotikler

2. Bakteriyel biosentetik reaksiyonların inhibisyonu:
   - Pseudomonas enfeksiyonlarında sülfonamid aktivitesinin potansiyalizasyonu,
   - Aminoglikozidlerin postantibiyotik etkinliğinin uzatılması.

Hyperbaric Oxygen as Adjunctive Therapy in Experimental Mediastinitis

Vedat Turhan, M.D.,* Suzan Sacar, M.D.,†,[1] Gunalp Uzun, M.D.,‡ Mustafa Sacar, M.D.,§ Senol Yildiz, M.D.,‡ Nurgul Ceran, M.D.,‖ Rauf Gorur, M.D.,¶ and Oral Oncul, M.D.*

TABLE 1

Outcome Treatment of Experimental Mediastinitis

Group	Therapy	Number of culture negative/total	Bacterial count*
Group 1	No therapy	6/6	0.0
Group 2§	No therapy	0/6	5.94 ± 0.52
Group 3§,‖	HBO†	0/6	4.20 ± 0.81
Group 4§,‖	Linezolid‡	0/6	4.21 ± 0.41
Group 5§,‖	Vancomycin‡	0/6	3.62 ± 0.49
Group 6§,‖	Teicoplanin‡	0/6	3.59 ± 0.54
Group 7§,‖,¶,#	Linezolid[c] + HBO†	0/6	2.49 ± 0.85
Group 8§,‖,¶,#,$,¥	Vancomycin‡ + HBO†	2/6	1.76 ± 1.47
Group 9§,‖,¶,#,$,¥	Teicoplanin‡ + HBO†	2/6	1.75 ± 1.49

*Mean ± SD $\log_{10}$ CFU/g.
†Administered once daily.
‡Administered intraperitoneal twice daily.
§$P < 0.05$ compared with group 1.
‖$P < 0.05$ compared with group 2.
¶$P < 0.05$ compared with group 3.
#$P < 0.05$ compared with group 4.
$$P < 0.05$ compared with group 5.
¥$P < 0.05$ compared with group 6.

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Endikasyonlar

1. Dekompresyon hastalığı
2. Gaz embolisi
3. Clostridial myonekroz (gazlı gangren) ve diğer anaerobik enfeksiyonlar
4. Ciddi karbon monoksit zehirlenmesi
5. Crush injury, kompartman sendromu ve diğer akut travmatik iskemiler
6. Refrakter osteomyelit
7. Kronik yaralar (Diabetik ve non-diabetik)
8. Osteoradyonekroz ve radyoterapiye bağlı yumuşak doku nekrozları
9. Termal yanıklar
10. Problemli cilt greft ve flepleri
11. Intrakranial apse
12. Ani görme kaybı (Santral retinal arter tıkanıklığı)
13. Ani işitme kaybı (ilk bir ay içinde başlanmalı)
14. Femur başı avasküler nekrozu (erken evre)

Kontrendikasyonlar

- Mutlak
  - Tedavi edilmemiş pnömotoraks
- Diğer
  - Gebelik
  - Üst solunum yolu enfeksiyonları
  - Bilinen malignite
  - Nöbet bozukluğu
  - Yüksek ateş
  - Spontan pnömotoraks hikayesi
  - Toraks cerrahisi hikayesi
  - Konjenital sferositoz
  - İleri derece kalp yetmezliği

Yan etkiler

- Basınç değişimine bağlı yan etkiler
  - Kulak barotravması (%17)
  - Sinus sıkışması
  - Akciğer barotravması
- Oksijen toksisitesine bağlı yan etkiler
  - Geçici myopi
  - Nöbet (2.4/100000)
  - Akciğer toksisitesi

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REVIEW

Hyperbaric oxygen therapy in the management of nonhealing wounds in patients with critical limb ischemia

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Critical limb ischemia is characterized with intolerable pain at rest and nonhealing wounds and/or gangrene. The treatment of nonhealing wounds in patients with critical limb ischemia calls for an extraordinary effort. However, major amputation is required in a significant number of patients. Hyperbaric oxygen therapy is one of the adjunctive treatments used in nonhealing wounds. Hyperbaric oxygen therapy enhances collagen synthesis and maturation, fibroblast proliferation, epithelialization, increases leukocyte bacterial-killing capacity and induces angiogenesis. Hyperbaric oxygen therapy also exerts an antibacterial effect on selected microorganisms and reduces wound infection. Hyperbaric oxygen therapy is not a miraculous treatment modality. It is a good adjunctive therapy that increases the healing rate of wounds in selected patients. Hyperbaric oxygen therapy should be instituted together with conventional treatments. Antibiotherapy, strict metabolic control, daily wound care and debridement should not be overlooked during hyperbaric oxygen therapy.

Critical limb ischemia (CLI) is a severe obstruction of the arteries of the lower extremities, which markedly decreases blood flow. CLI is characterized with intolerable pain at rest and nonhealing wounds and/or gangrene. An objective criterion for CLI includes an ankle systolic blood pressure of 50 mmHg or less and a toe systolic blood pressure of 30 mmHg or less [1]. However, since the arterial wall calcification can impair compression of vessels, systolic blood pressures are measured greater than the actual levels in diabetic patients. Therefore, hemodynamic parameters of CLI are less reliable in diabetics [2].

The most frequent reason of obstructive arterial disease leading to CLI is atherosclerosis associated with hypertension, hypercholesterolemia, smoking and diabetes mellitus. Nonhealing wounds usually develop in the areas of foot trauma caused by improperly fitting shoes or an injury [3]. The treatment of nonhealing wounds in patients with CLI calls for an extraordinary effort. The goal of the treatment in patients with critical limb ischemia should be limb preservation. However, amputation is required in a significant number of patients [3].

Hyperbaric oxygen therapy (HBOT) involves the intermittent inhalation of 100% oxygen at a pressure higher than 1 atm absolute (ATA). HBOT favorably increases the amount of oxygen dissolved in arterial blood and leads to hyperoxia even in poorly perfused tissues [4–6]. The physiological effects of HBOT are related to the hyperoxia it establishes in the tissues. Oxygen in the blood is carried by two means: by binding to hemoglobin in erythrocytes and in dissolved form in plasma. People breathing room air at sea level (1 ATA) generally have a hemoglobin (Hb) oxygen saturation of approximately 97%. Assuming normal hemoglobin level (14 g/dl), Hb-bound oxygen content is 18.2 ml O_2/dl blood. At Hb 15 g/dl, it would be 19.5 ml O_2/dl blood. Dissolved oxygen content is 0.3 ml O_2/dl blood. At Hb 14 g/dl, dissolved oxygen represents 1.6% of total content; at Hb 15 g/dl, dissolved oxygen represents 1.5% of total content. Since, Hb is already 97% saturated at room air (1 ATA) it is impossible to markedly increase the amount of oxygen carried with Hb, but you can make a large difference in dissolved oxygen. HBOT leads to a favorable increase in the amount of oxygen dissolved in plasma under Henry's Law, which states that the amount of gas dissolved in a solution is directly proportional to the partial pressure of that gas. HBOT theoretically increases the dissolved oxygen content in plasma from 0.3 ml/dl to 4.4 ml/dl at 2.0 ATA and to 5.6 ml/dl at 2.5 ATA.

HBOT is used as a primary therapy in arterial-gas embolism, severe carbon monoxide poisoning, gas gangrene and decompression sickness [7]. It is also employed as an adjunctive treatment in nonhealing wounds, necrotizing soft-tissue infections, refractory osteomyelitis, osteoradionecrosis, crush injury, compromised skin grafts and flaps and thermal burns [7]. The

Keywords: chronic wound, hyperbaric oxygenation, peripheral arterial disease, transcutaneous oximetry, wound healing

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Review

EXPERT REVIEWS

Hyperbaric oxygen therapy as an anti-infective agent

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Hyperbaric oxygen therapy (HBOT) involves inhalation of 100% oxygen at supra-atmospheric ambient pressure. HBOT is used as either a primary or adjunctive treatment in the management of infections such as gas gangrene, necrotizing fasciitis, diabetic foot infections, refractory osteomyelitis, neurosurgical infections and fungal infections. HBOT acts as a bactericidal/bacteriostatic agent against anerobic bacteria by increasing the formation of free oxygen radicals. HBOT restores the bacterial-killing capacity of leukocytes in hypoxic wounds by increasing tissue oxygen tensions. In addition, HBOT acts synergistically with a number of antibiotics. This article reviews the anti-infective effects of HBOT and the use of HBOT in the treatment of certain infectious diseases.

KEYWORDS: diabetic foot infection • gas gangrene • hyperbaric oxygenation • hypoxia • necrotizing fasciitis • osteomyelitis

Hyperbaric oxygen therapy (HBOT) is used as an adjunct or main treatment in infectious diseases such as anerobic and mixed necrotizing infections, infected chronic wounds, postoperative surgical wound infections and chronic refractory osteomyelitis. Factors such as trauma, breakdown of the tissue integrity or perfusion abnormalities all are predisposing factors for an infection. A decrease in tissue and wound oxygen partial pressures and a subsequent tendency for infections as a result of perfusion impairment is a well-known entity in dehydrated postoperative patients [1,2].

The migration and functions of polymorphonuclear leukocytes (PMNLs) in a damaged tissue with limited perfusion, hence hypoxic tissue, is impaired and therefore microorganisms can easily replicate in these tissues. In addition to impaired perfusion and limited local blood supply, other causes for hypoxia are: increased oxygen consumption due to inflammation, bacterial growth, phagocyte respiratory burst, cellular exudate and tissue edema. Once the infection develops in a tissue, cure depends greatly on the oxygenation of the infected region.

The role of HBOT as an anti-infective agent stems from its antihypoxic and anti-infectious effects. Breathing 100% oxygen under high pressures increases tissue partial oxygen pressure and supplies some additive effects of oxygen that are not seen under normal atmospheric circumstances. HBOT supplies an optimal environment for the immune system by reversing tissue hypoxia and inducing bactericidal/bacteriostatic effect over microorganisms. In addition, it modifies the microbicidal effect of PMNLs and potentiates the effects of some antimicrobial drugs. HBOT dramatically improves the prognosis of infections caused by anerobic or micro-aerophilic aerobes and significantly decreases the rate of morbidity and mortality.

Moreover, the anti-edema effect of HBOT is also important. With this effect, local circulation improves, and the oxygen diffusion distance, previously decreased due to edema, increases, allowing a higher oxygenation to the tissues, improved infection control and important support for wound healing.

The aim of this article is to highlight the basic mechanisms of anti-infective affects of HBOT and to review the use of HBOT in the management of certain infectious diseases.

Principles of HBOT

Hyperbaric oxygen therapy involves the intermittent inhalation of 100% oxygen at a pressure higher than 1 atm absolute (ATA). Oxygen in the blood is carried by two means: by binding to hemoglobin in erythrocytes and in the dissolved form in plasma. Since hemoglobin is almost 100% saturated at room air (1 ATA), it is impossible to markedly increase the amount of oxygen carried with hemoglobin, but a large difference can be made in the concentration

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