고압의학의 세포/조직 치료기전 (Oxygen transport & mitochondria as a target for HBOT)

Korean Academy of
Undersea and Hyperbaric Medicine

2021.09.09.

소 속 : 연세대학교 원주의과대학

이 름 : 김 현 교수

대한고압의학회
Korean Academy of Undersea and Hyperbaric Medicine

1st Generation (1986 - 2015)

2nd Generation (2015 - 2018)

3rd Generation (2018 -)

"Hyperbaric oxygen therapy course for Nurse, EMT, and Technicians"
제4회 고압산소치료 및 챔버운영 교육과정(non-MD HBOT course)
일시 19. 3. 29(금) 09:00 ~ 19. 3. 30(토) 17:00
장소 원주세브란스기독병원 권역외상센터 2층 컨퍼런스룸
주최
주관 대한고압의학회

EPSON
Flap

"Hyperbaric medicine: introductory course for a physician"
제3회 임상의 기초교육과정 연수강좌
일시 2019.5.18.(토) 09:00 ~ 19:10
장소 원주세브란스기독병원 권역외상센터 2층 컨퍼런스룸
주최 대한응급의학회
주관 대한고압의학회

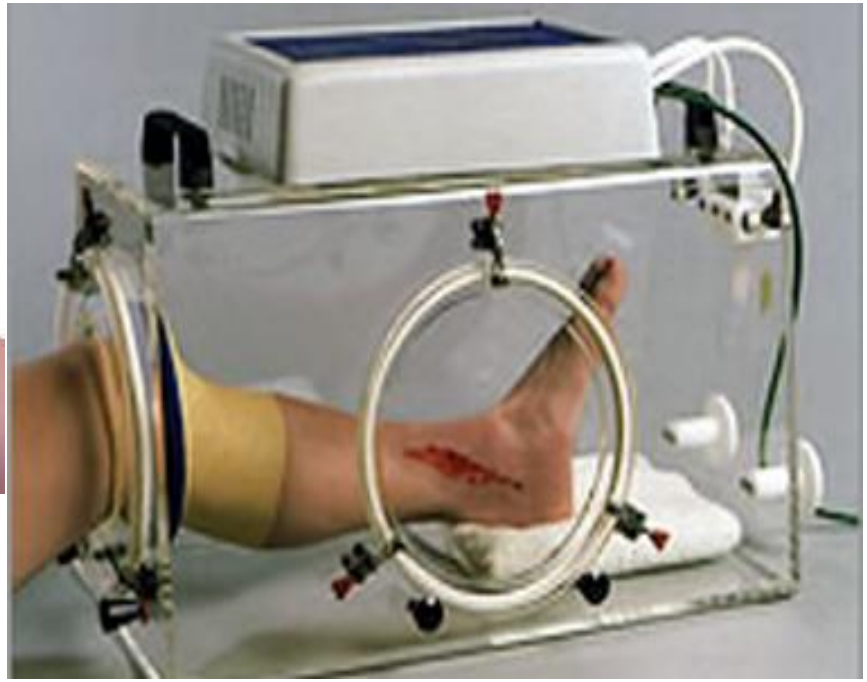
고압산소치료란?
(HBOT: hyperbaric oxygen therapy)

- 정의: 챔버를 이용하여 **1.4**기압 이상으로 **100%산소를** 호흡시킴으로 의학적 효과를 나타내는 치료법 (의학적 압력은 **2.0 – 3.0** 기압)

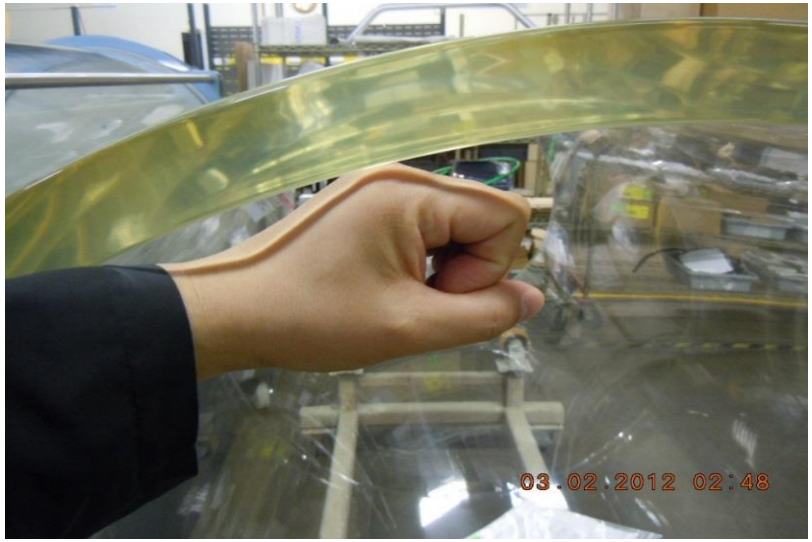
- 원리와 효과 – 고농도 산소 유지(**hyperoxygenation**)

Topical Oxygen Therapy

- 100% O_2
- 1 atmosphere of pressure



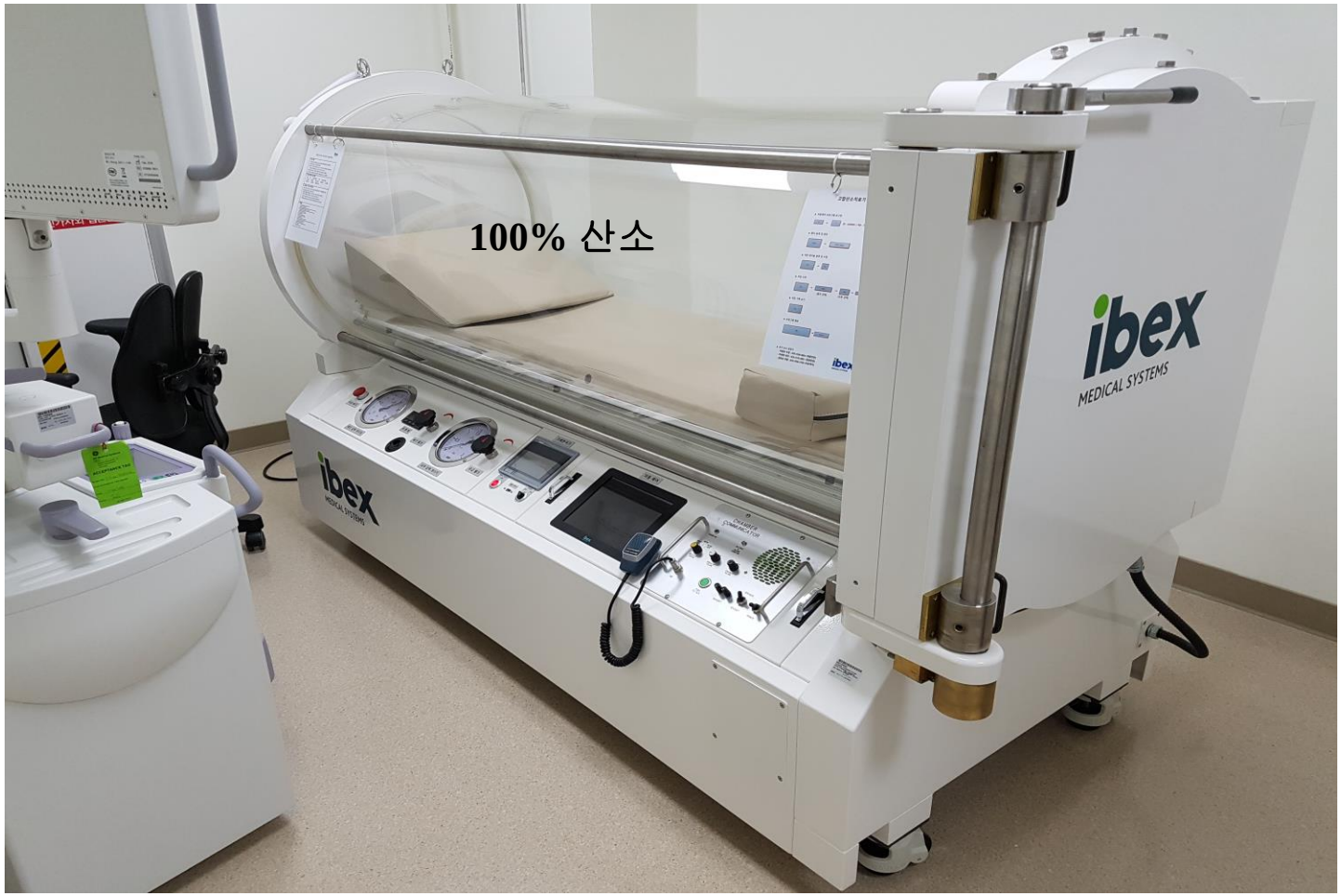
Soft vs hard chamber



강화 PVC
철(다인용챔버)
고강도
(고압산소치료)

천
플라스틱
저강도
(고압산소치료 불가능)

고압산소치료란?



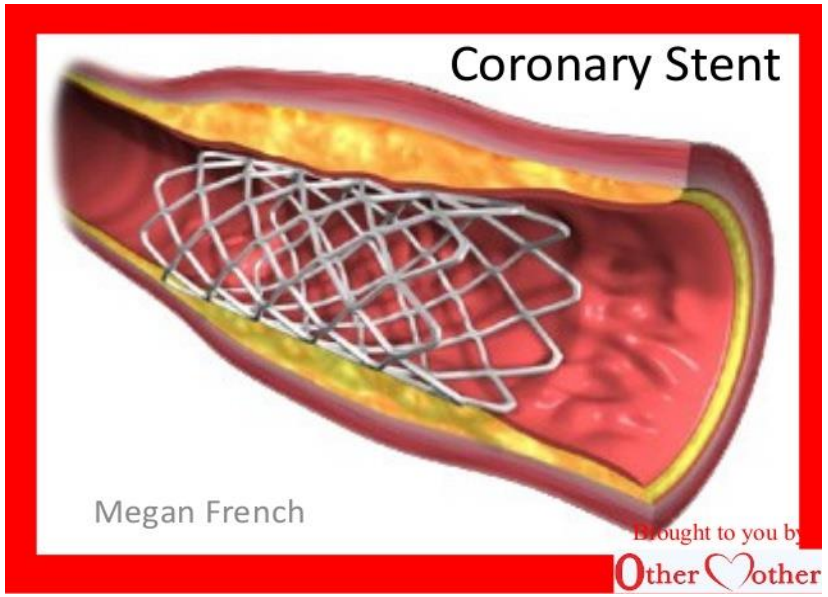
치료 프로토콜

- **100% 산소**
- **2~2.8 기압**
- **90~120분**

고압산소치료란?

O_2 transport

- The first concern in any life-threatening to maintain an adequate supply of oxygen to sustain oxidation metabolism.
- The delivery of O_2 and its utilization: integration of the respiratory, cardiovascular, and **microvascular systems**.



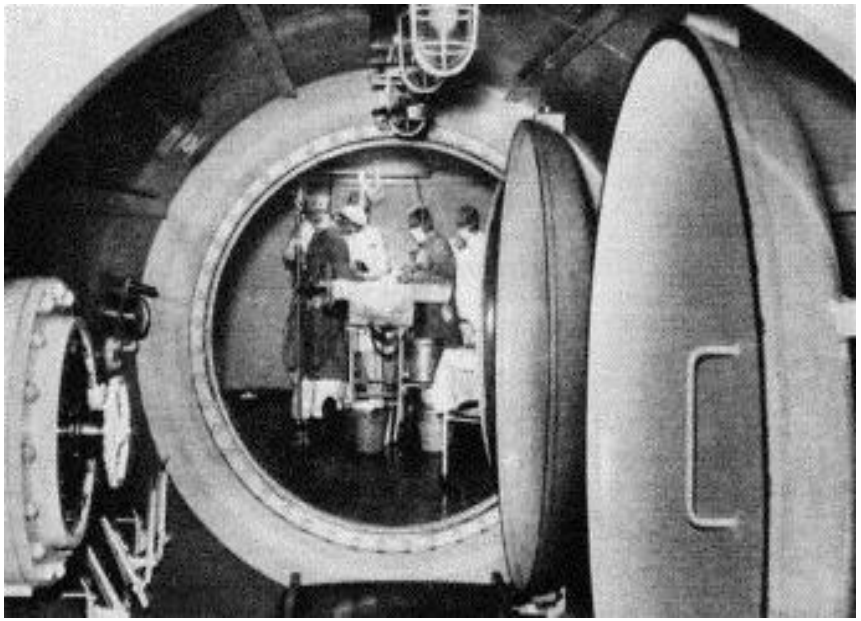
Macrocirculation

Microcirculation

Major contributions (legacy)

Dr. Ite Boerema

- 1902-1978, professor of surgery at the university of Amsterdam
- Surgeon and engineer with a double-Dutch legacy to medical technology
- Gas gangrene: sudden decline in mortality rate (from 66% to 23%)



Life without blood (1959)

Life without blood

(A study of the influence of high atmospheric pressure and hypothermia on dilution of the blood)

by

J. BOEKEMA (*), N. G. MEYNE, W. K. DRUMMELKAMP
S. BOUMA, M. H. MONSICH, F. KAMERMANS, M. STORM HANF
and W. VAN AALDEREN
(from the Surgical Department of the University of Amsterdam)

When in 1948 we (first at research) started our experiment on hypothermia[1] [2] our ultimate aim was to reduce the metabolism of a warm-blooded animal to such an extent that all the physiological processes would almost come to a standstill.

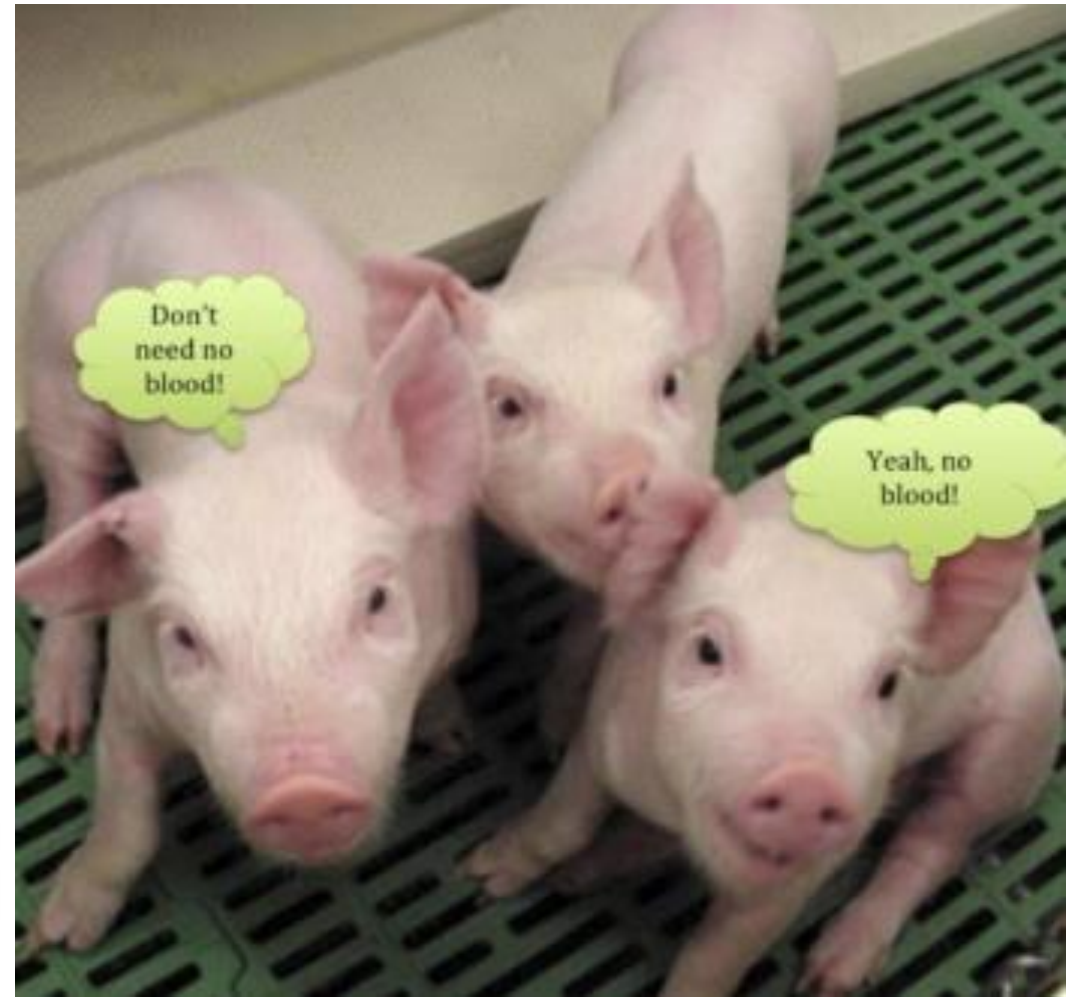
If successful, this would enable the heart to be clamped off for a period long enough to allow for a major intracardiac operation to take place. When, however, we presented our results in the Netherlands Society of Surgeons in 1950 this aim had not been achieved by any means. In a hypothermic animal at about 27° C., the circulation could be stopped with good chances of survival for about twice as long as in a normothermic animal. The gain in time, about 100 per cent, was relatively great, but absolutely it was very modest, amounting to about five minutes; the reason for this was that below 28° C. the physiology was altered too much and the normal harmony of life processes disturbed too much to allow for continuation of life or normal recovery by warming up.

Efforts to achieve safe conditions at a lower level of hypothermia so as to gain a greater period of time for clamping off the heart failed until recently, at any rate for animals with the same weight as human patients. So in 1956 we presented a series of experiments which showed that it was possible to clamp off the circulation for a greater length of time without lowering the temperature further than 27° C.[3] [4] We operated on the animal in a pressure chamber at an absolute pressure of three atmospheres. The animal breathed pure oxygen, the investigators naturally breathed air.

Through the combination of inhaling pure oxygen and being under three atmospheres of pressure, the whole body was supersaturated with oxygen in physical solution.

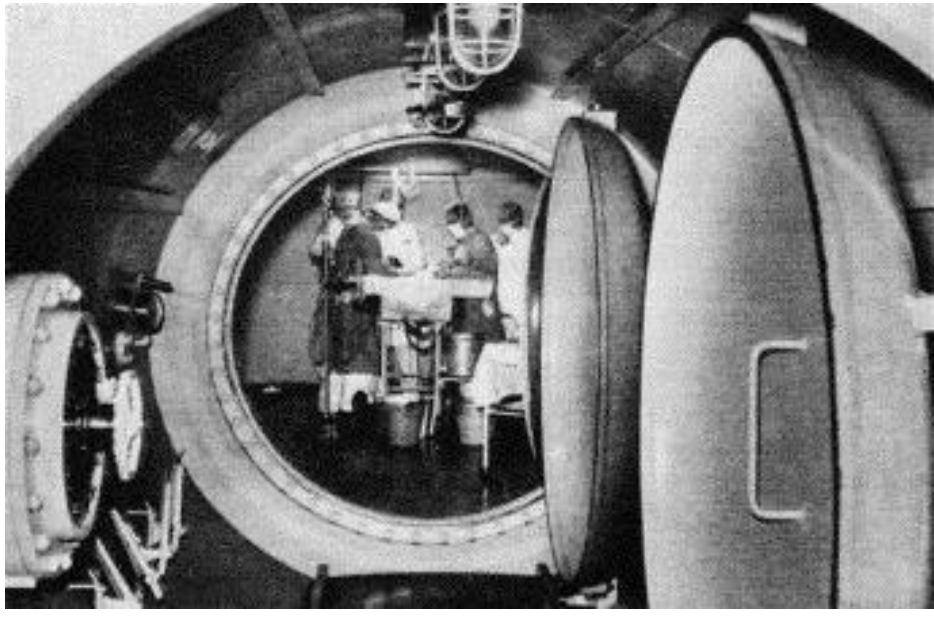
(*) Professor of Surgery.

Again we are much indebted to T.N.O. (Institute for Applied Physical Research) for financial aid, to the staff of the Mijnsectional of the Royal Dutch Navy at Den Helder and to our adviser on technical matters, F. Bouma.

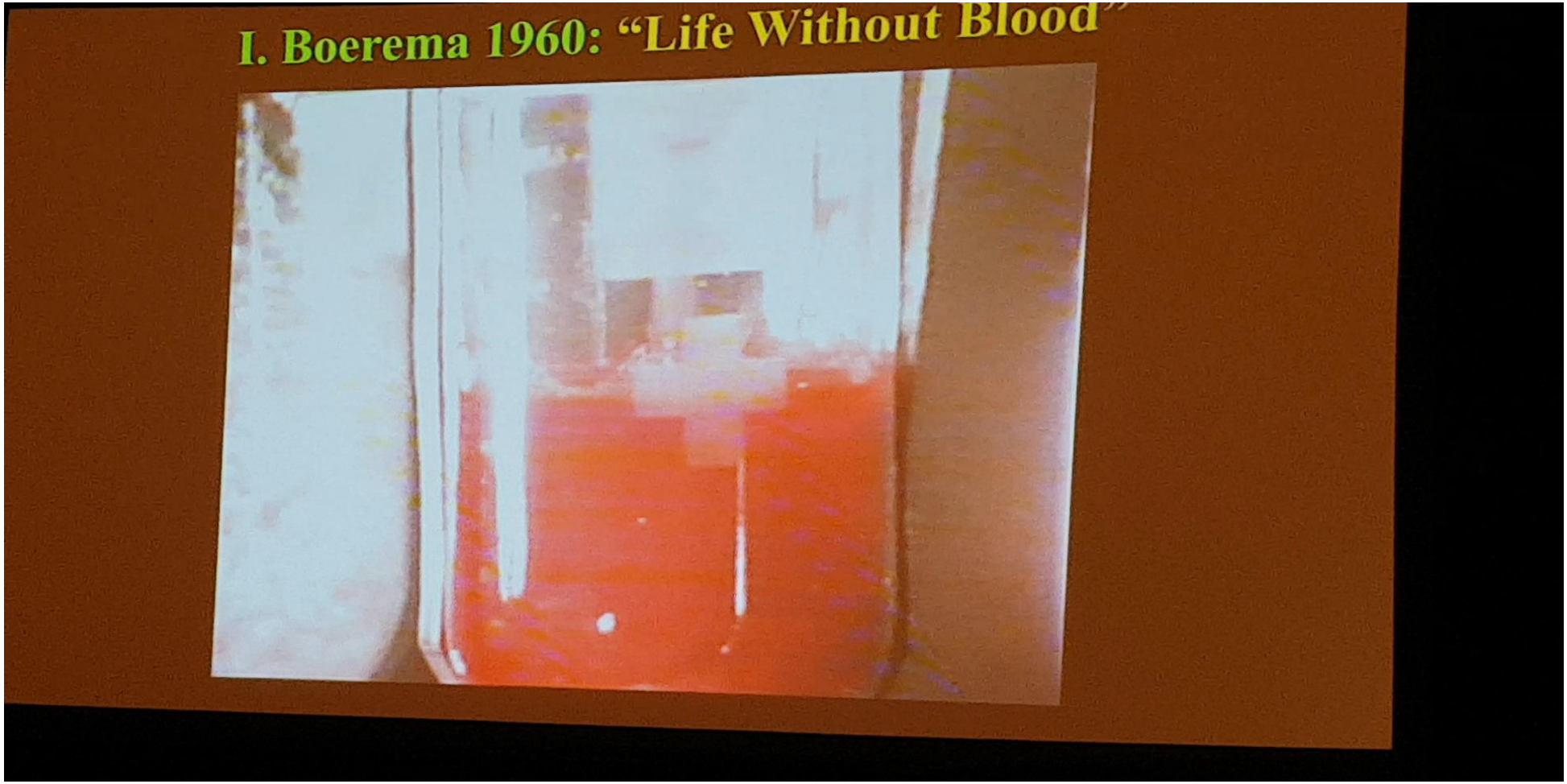


Life without blood

- A study of the influence of **high atmospheric pressure** and **hypothermia** on dilution of the blood (J Cardiovasc Surg 1959;13:133-146)
- 1948: hypothermia (27도)
- Hg: 0.4%, plasma solution, 3 ATA (45 mins)
- EEG: no pathologic changes
- Recovery: reinfusion of normal blood



Life without blood



Primary mechanism

Mechanisms of HBOT

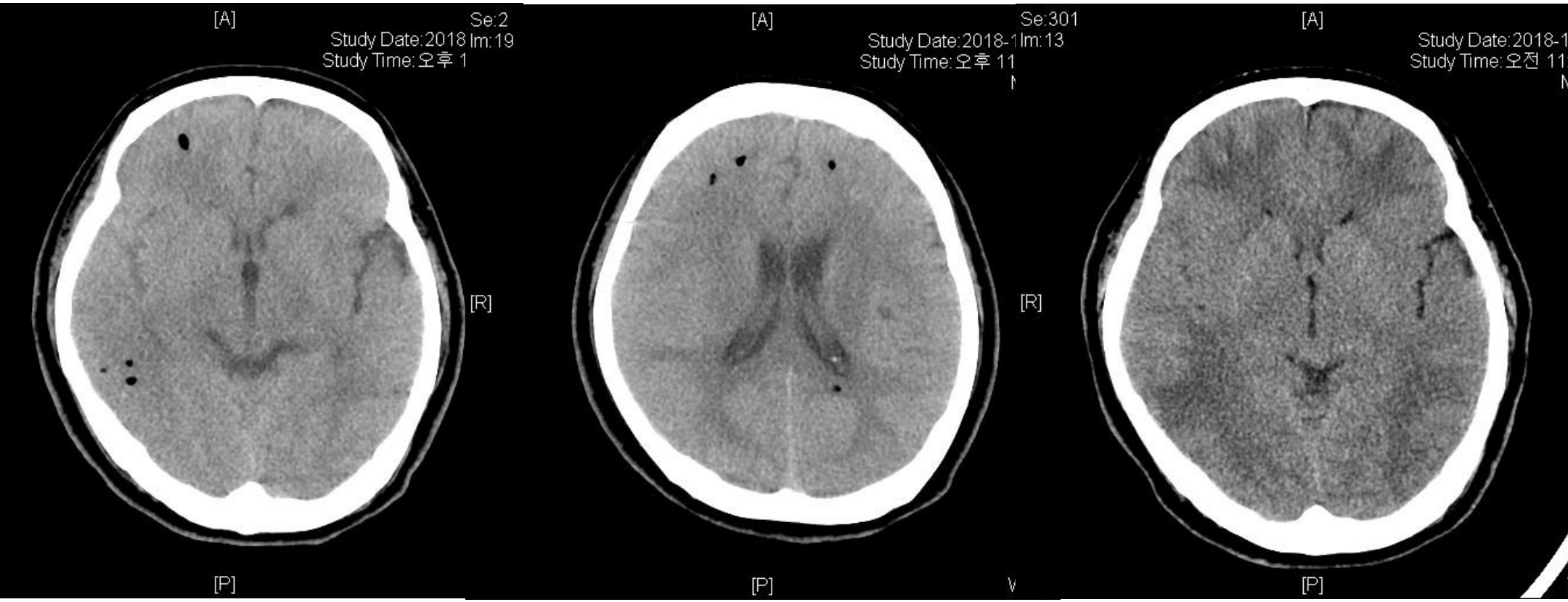
(Primary & Secondary)

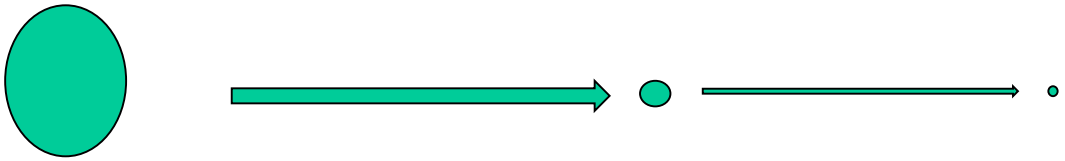
Primary **Secondary**

- Hyperoxygenation (O_2 tensions)
- Direct effects of pressure

Oxygen delivery/uptake
Bubble size reduction

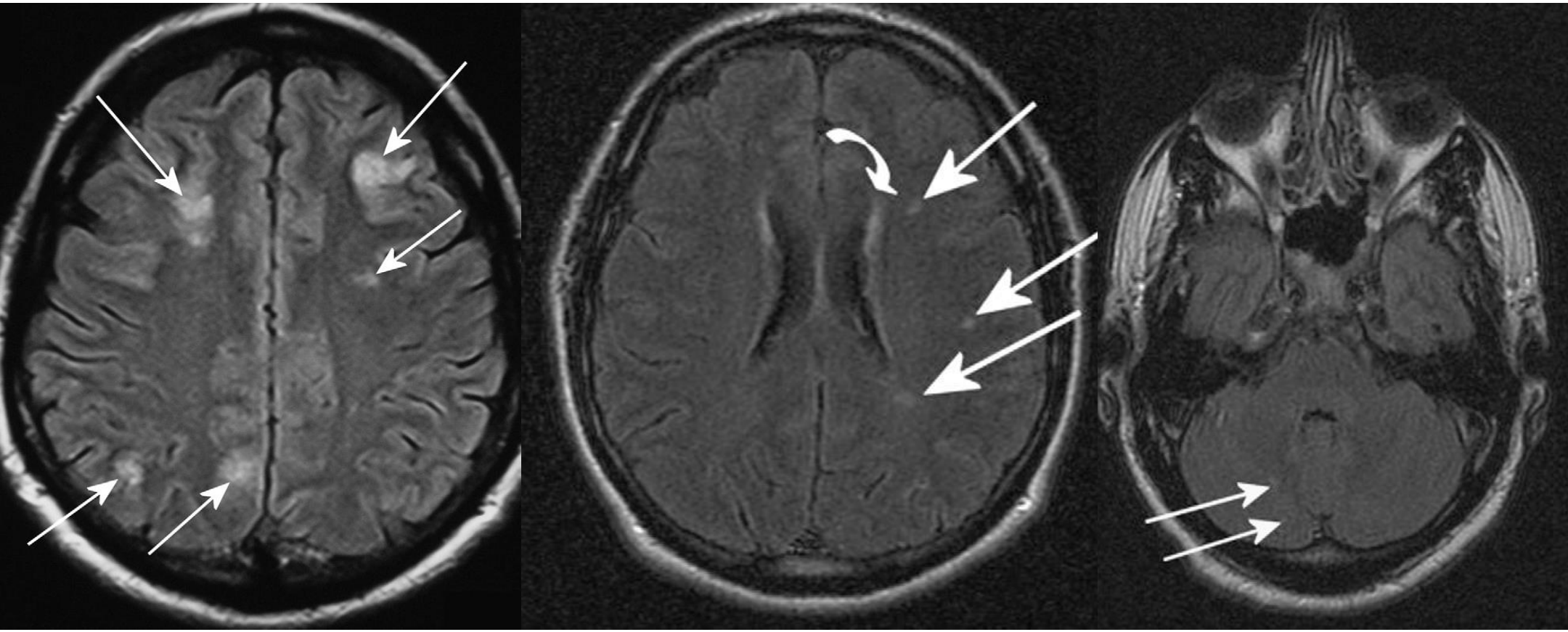
HBOT: primary mechanism (AGE)

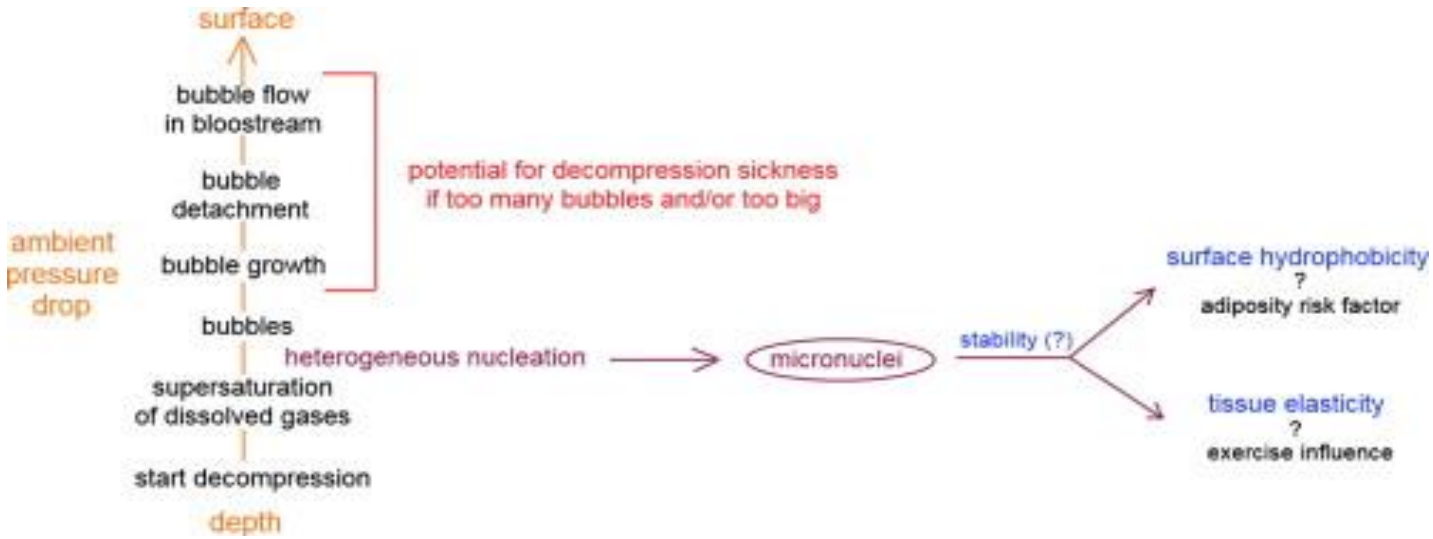




Bubble size reduction

HBOT: primary mechanism (DCS)

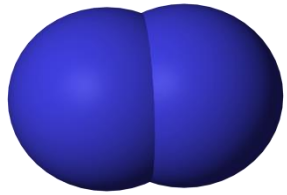


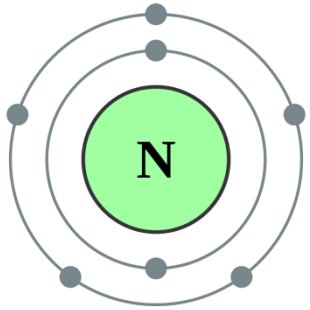


(*Papadopoulou et al (2013)A critical review of physiological bubble formation in hyperbaric decompression Advances in Colloid and Interface Science. Elsevier. 191–192 (191–192): 22–30*)

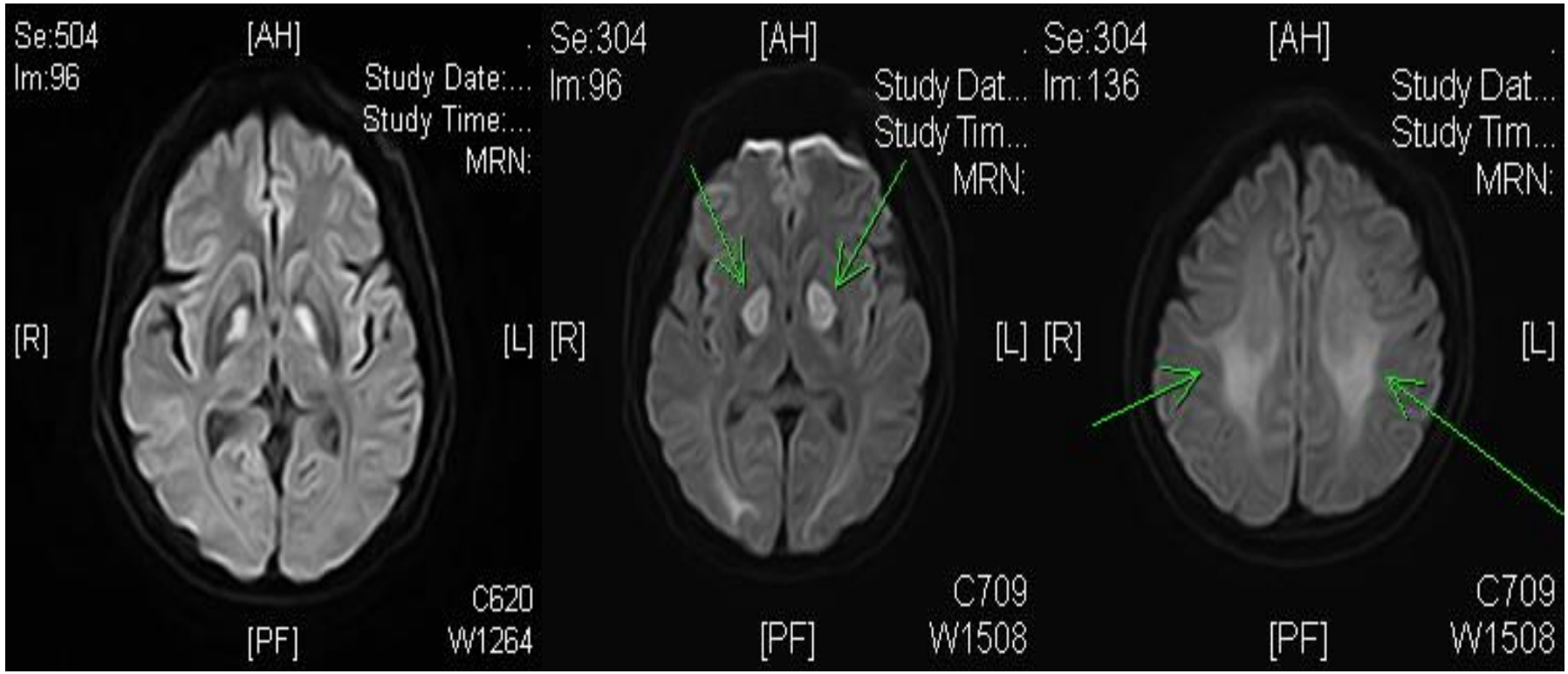
Nitrogen

- N_2 solubility in blood: 0.0138 to 0.0148, dissolved by whole blood under nitrogen pressures varying from 1 to 6 atmospheres (absolute) has been found directly proportional (1.3 -> 7.9)
- 단백질(아미노산), 알칼로이드





HBOT: primary mechanism (CO)

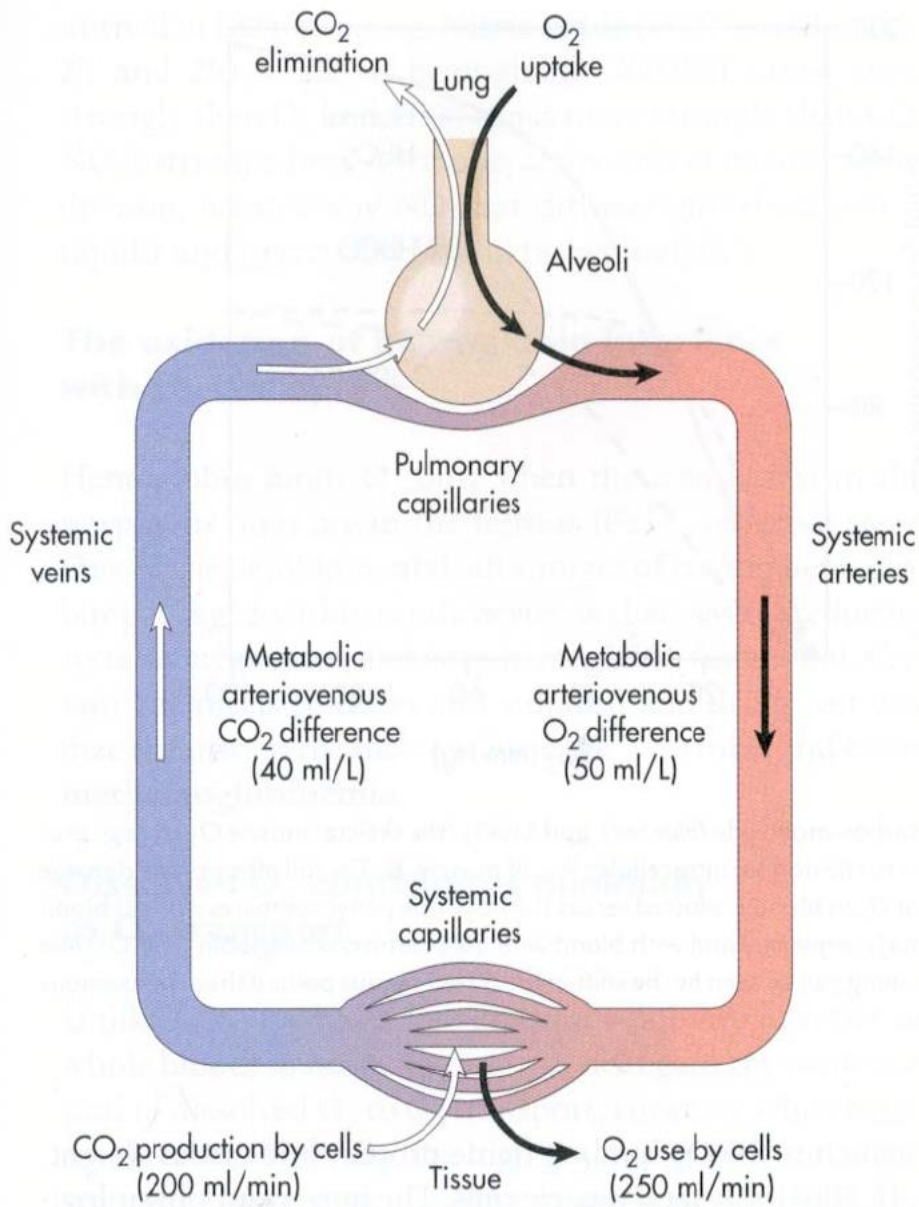


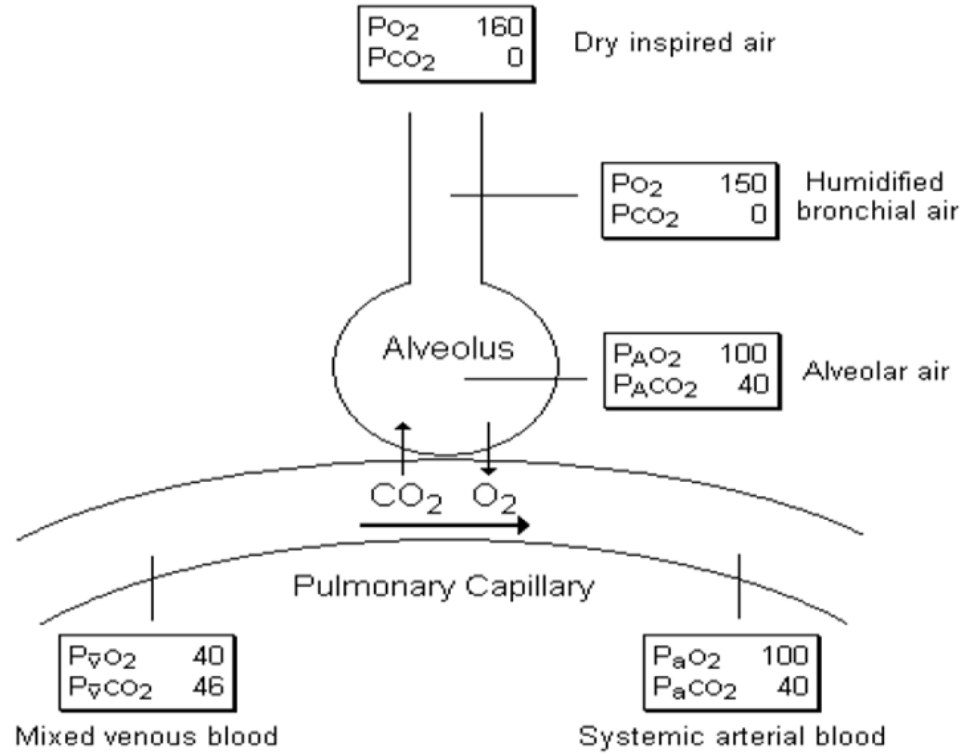
HBOT: primary mechanism

- Emergent condition (time dependent)
- Direct bubble size reduction: AGE, DCS
- Hyperoxygenation: CO, cyanide, toxic gases

O_2 transport (cellular level)

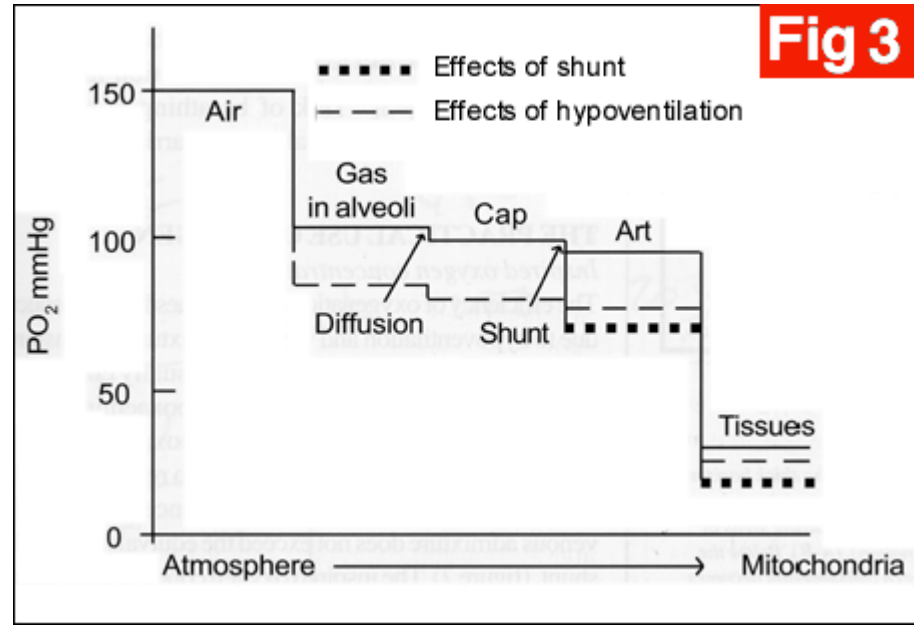
Movement of O_2 down





Movement of O_2 down

- Oxygen concentration: down (air -> cell)
- $P0_2$: the lowest level (4-20 mmHg)
  in the mitochondria

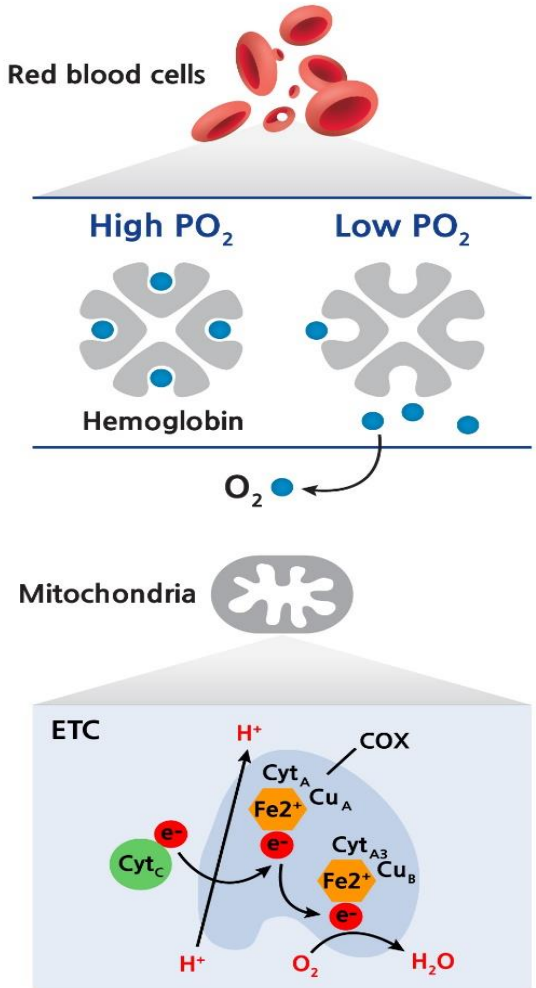


Oxygen transport

- 4 factors:

  - O_2 content of whole blood (CaO_2)
  - O_2 delivery (DO_2)
  - O_2 uptake
  - Fractional extraction of O_2 from capillary blood

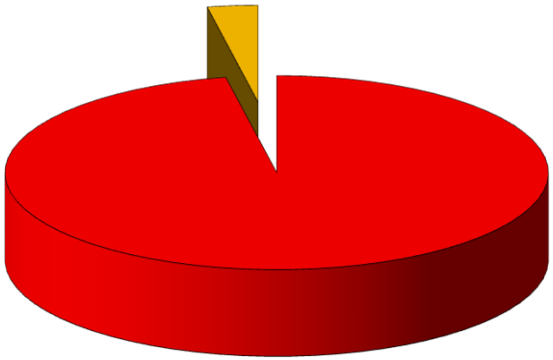
O_2 transport



Carried in blood in 2 forms:

1. by red blood cells
   Bound to Hb
   97-98%
2. Dissolved O_2 in plasma

S



O_2 content (CaO_2)

- CaO_2= $\boxed{1.34 \times Hb \times SaO_2}$ + $\boxed{0.003 \times PaO_2}$

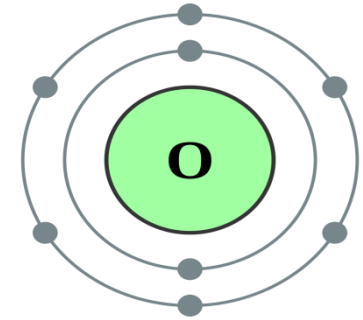
  Hg-bound dissolved

- NL CaO_2= 1.34 x 15 x 0.98 (19.7) + 0.003 x 100 (0.3)

  = 20.0 ml/100 ml (or 200 ml/L)

- Solubility of O_2: 0.028 ml O_2/L/mm Hg
- Hb can bind 1.34 ml O_2/g when fully saturated

Solubility of O_2 & CO_2 in plasma



Temp	ml O_2/L/mm Hg	ml CO_2/L/mm Hg
25	0.033	0.892
30	0.031	0.802
35	0.028	0.713
37	0.028	0.686
40	0.027	0.624

Christoforites C et al. J Appl Physiol 1969;26:56
Severinghaus JW et al. J Appl Physiol 1956;9:189

Different scenarios

	PaO_2	$\%O_2$ Sat	Hg	Hct	Dissolved oxygen	Hg-bound O_2	CaO_2
Normal	100	100	14	42	0.3	19.6	19.9
Low Hg	100	100	7	21	0.3	9.8	10.1
Low PaO_2	25	50	14	42	0.1	9.8	9.9
MetHg (50%)	100	50	14	42	0.3	9.8	10.1
Very low Hg	100	100	2	6	0.3	2.8	3.1
3 ATA	2200	100	3	6	6.6	2.8	9.4

Effects of hyperoxygenation

(O_2 content of blood)

	Hemoglobin carried O_2 (Vol%)	Plasma dissolved O_2 (Vol%)	Total O_2 content (Vol%)
1 ATA air	19.7	0.3	20.0
2 ATA HBOT	19.7	3.0	22.7
3 ATA HBOT	19.7	4.5	24.2

Oxygen delivery (DO_2)

- DO_2 = cardiac output(Q) x CaO_2

  = Q (mL/min/m^2) x 1.34 x Hb x SaO_2 x 10

  = NL (520 - 570 mL/min/m^2)

Oxygen uptake (VO_2)

- $VO_2 = Q \times (CaO_2 - CvO_2)$

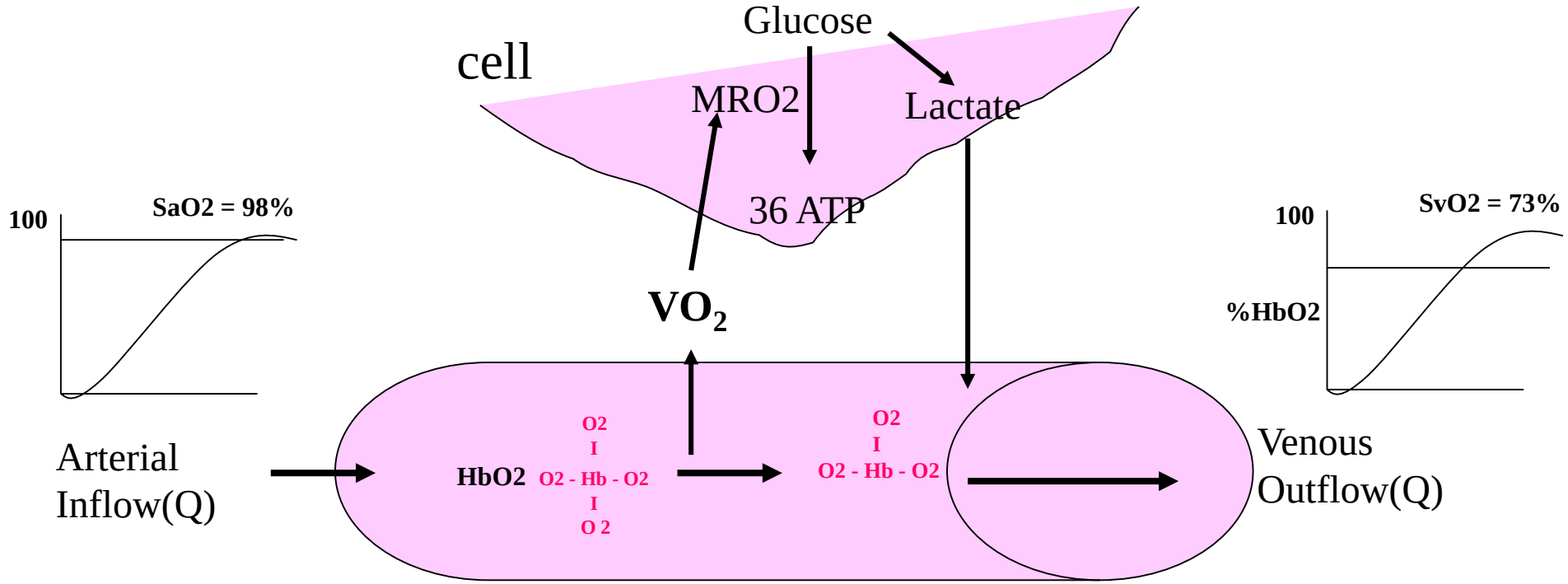
  $= Q(mL/min/m^2) \times 1.34 \times Hb \times SaO_2 \times 10$

  $- Q(mL/min/m^2) \times 1.34 \times Hb \times SvO_2 \times 10$

  $= Q \times 1.34 \times Hb \times (SaO_2 - SvO_2)$

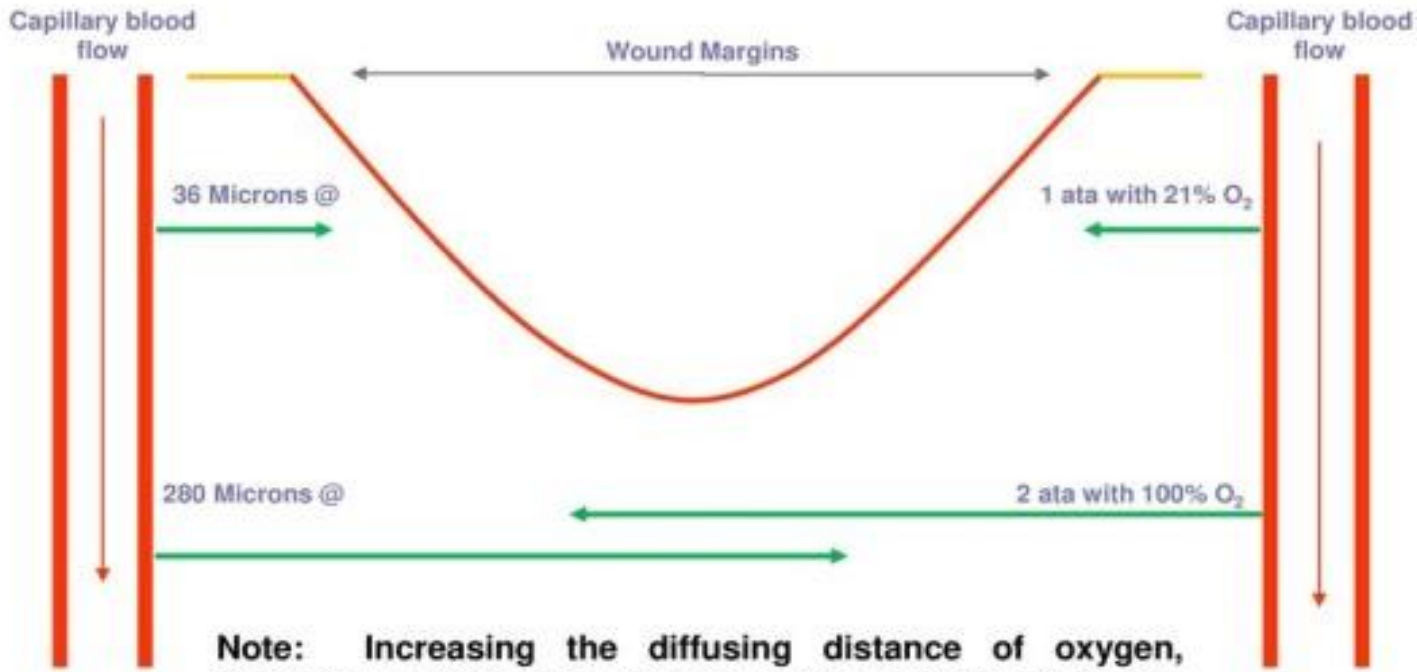
  $= NL(110 - 160\ mL/min/m^2)$

Tissue Oxygen Balance



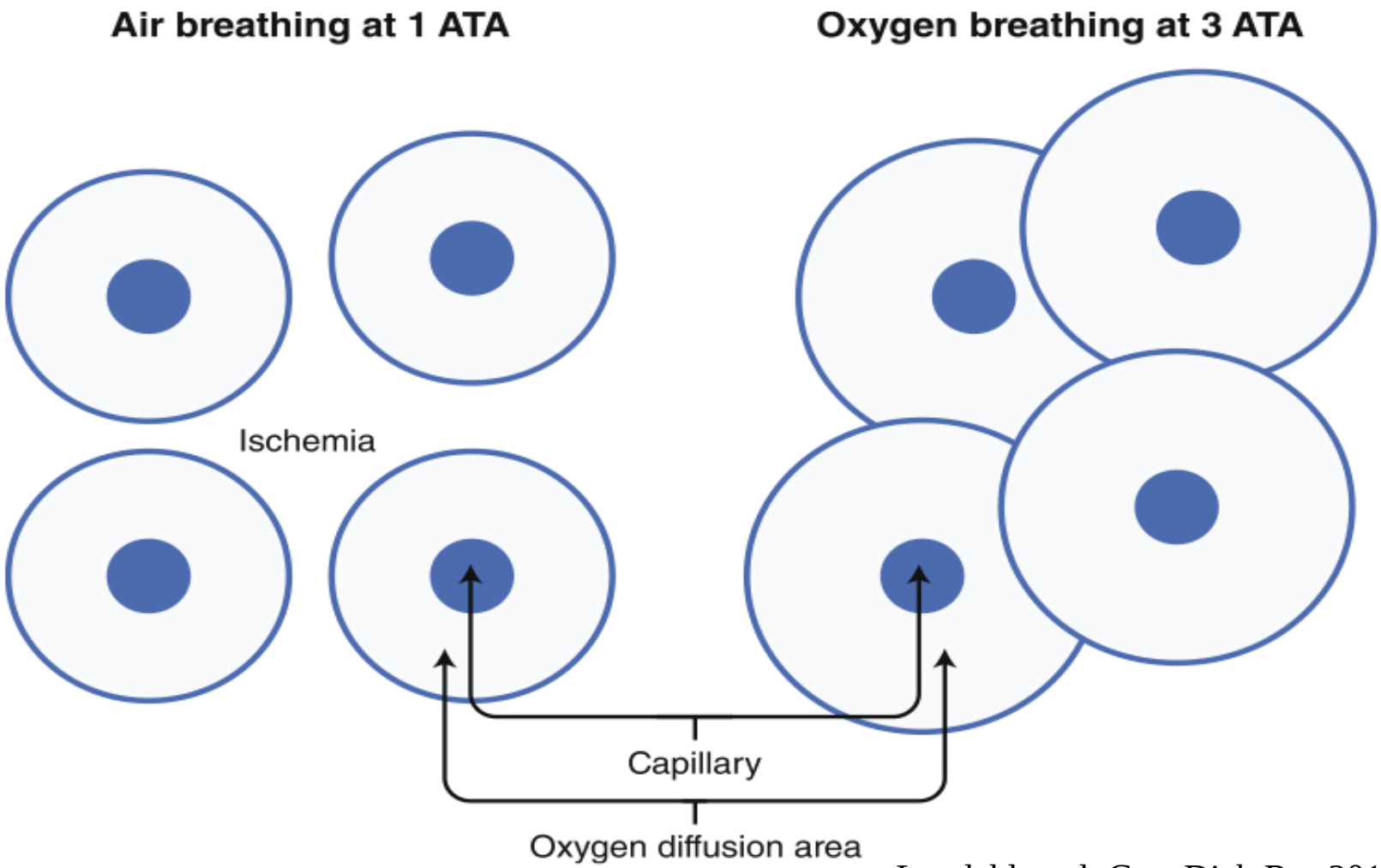
$$VO2 = Q \times 1.34 \times Hb \times (SaO_2 - SvO_2)$$

Diffusion distance of oxygen from functioning capillaries



Note: Increasing the diffusing distance of oxygen, improves oxygenation of tissue with borderline ischemia by increasing the ability of capillary beds to overlap one another.

Oxygen diffusion area



Londahl et al, Curr Diab Res 2011

Secondary mechanism

Mechanisms of HBOT
(Primary & Secondary)

Primary

- Hyperoxygenation (O_2 tensions)
- Direct effects of pressure

Oxygen delivery/uptake
Bubble size reduction

Secondary

- Hyperoxygenation
  (enriched O_2 -> cellular functions)

Edema reduction
Anti-inflammation:cytokine (leukocyte)
Neovascularization
Fibroblast GF

Accumulative effects

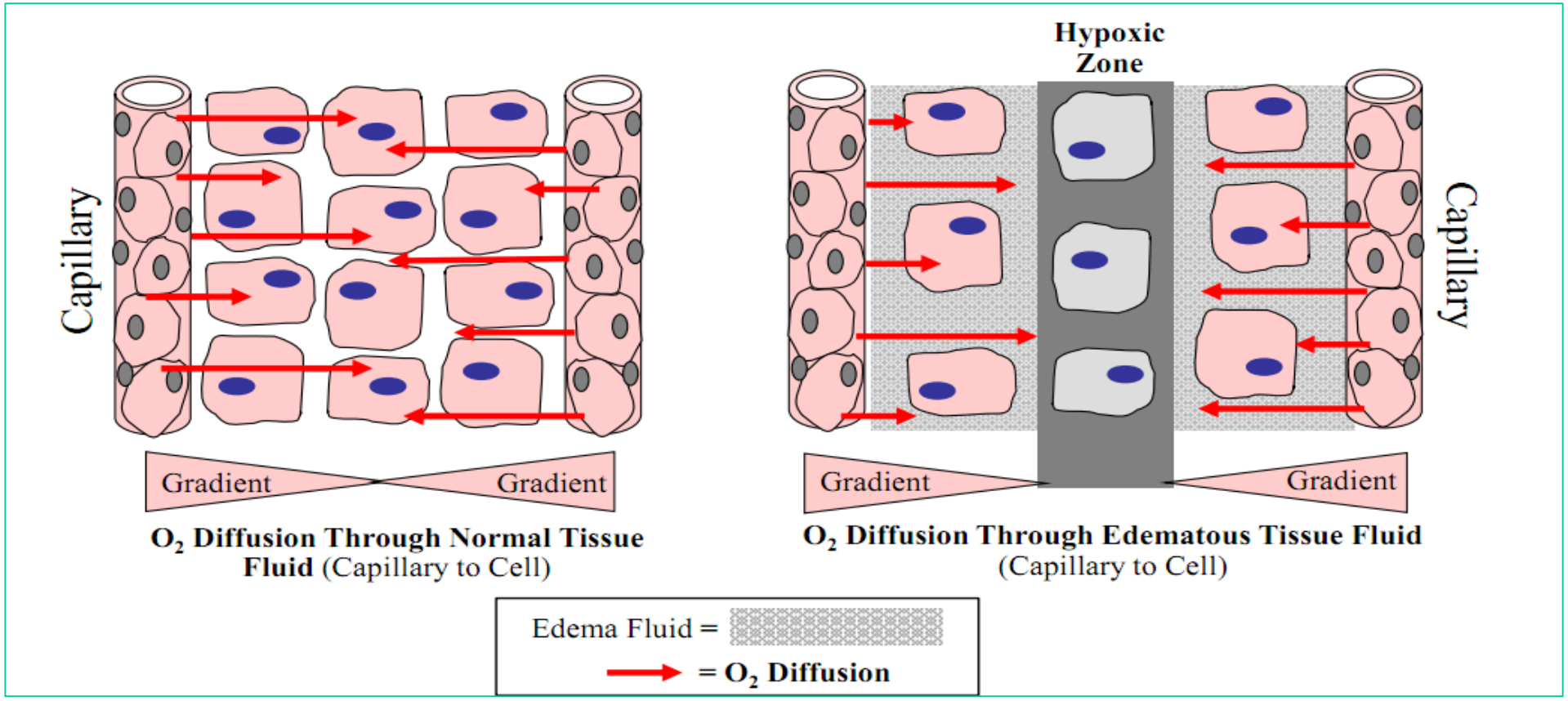
Indications

- Emergency

① **Decompression Sickness, air or gas embolism (AGE)**
② **CO, severe anemia**
③ **Arterial Insufficiencies, CRAO, ISNHL**

- Non – emergency: elective: 4 categories (wounds)

① **Chronic**: refractory diabetic wounds, arterial insufficiency ulcers
② **Radiation-induced**: delayed radiation injury, radionecrosis
③ **Infected**: gas gangrene, osteomyelitis, necrotizing soft tissue infection, brain abscess
④ **Traumatic**: crush injury, compromised skin grafts and flaps, thermal burn


Capillary
Gradient
Gradient
O_2 Diffusion Through Normal Tissue Fluid (Capillary to Cell)
Hypoxic Zone
Capillary
Gradient
Gradient
O_2 Diffusion Through Edematous Tissue Fluid (Capillary to Cell)
Edema Fluid =
= O_2 Diffusion

부종의 해로움

HBO effect in Edema

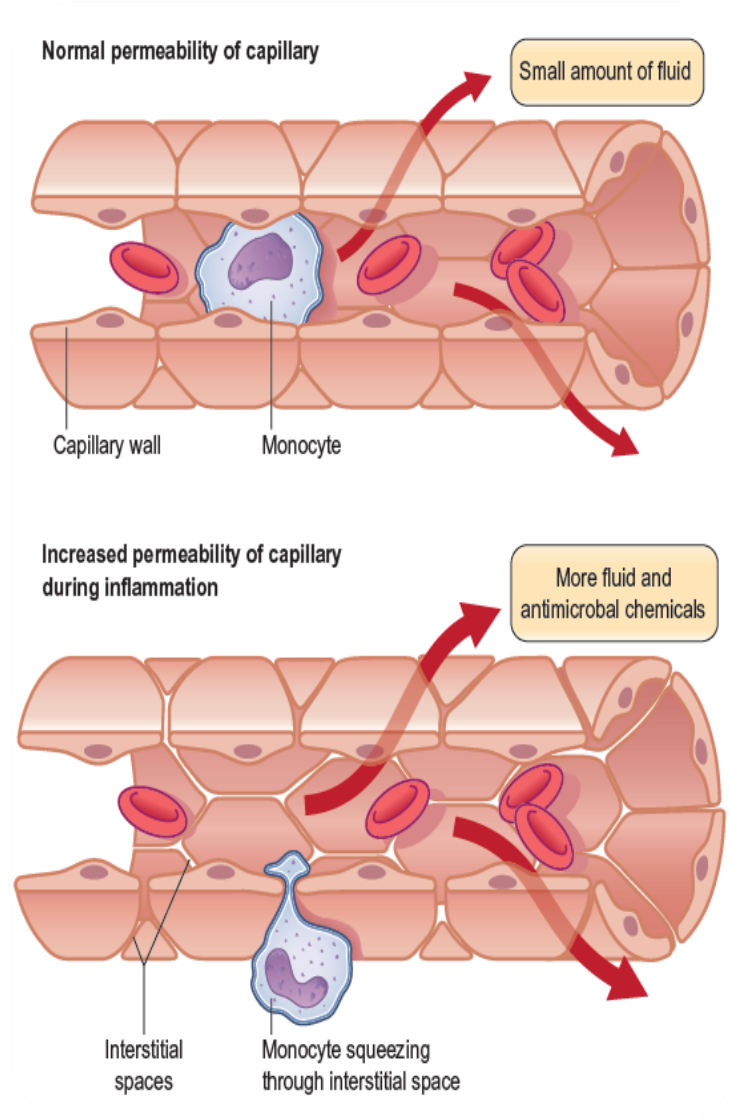
Vasoconstriction: defense mechanism against hyperoxia

Edema를 감소 ->
Edema에 의한 손상감소

HBO paradox

Villanuci, S., Di Marzio, G. et al. Cardiovascular changes induced by hyperbaric oxygen therapy. *Undersea Biomed. Res.* (Suppl.):17:117, 1990

Dooley, J., Mehm, W. Noninvasive assessment of the vasoconstrictive effects of hyperoxygenation. *J. Hyperbaric Med.*:4(4):177-187, 1990



HBO_2 also inhibits leukocyte pro-inflammatory cytokine production

Human, Mouse, Rat

Macrophage:

BBRC 179: 886,'91
Clin Exp Immunol 102: 665,'95
J Clin Immunol 17: 154,'97
Clin Exp Immunol. 134: 57,'03

PMN:

Dig Dis Sci 51: 1426, 2006
J Appl Physiol Feb. 2019

Microglia & Astrocytes

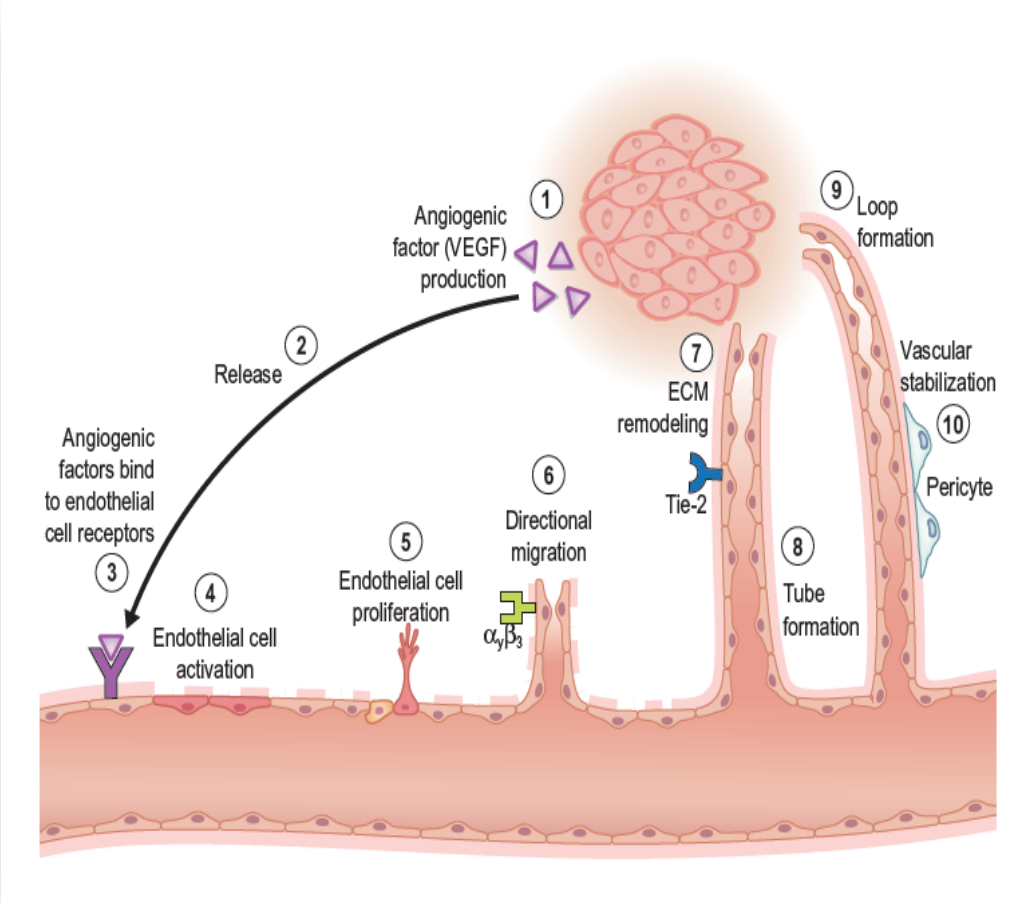
Brain Res 1627: 21, 2015
Molecular Pain 14: 1, 201
Oncotarget 9: 7513, 2018

Decreases IL-1β, IL-6, TNFα, NF- κB

Dig Dis Sci 51: 1426, 2006
Eur Surg Res. 42: 130, 2009
Anesth Analg 113: 626, 2011
Urology 82: e9, 2013
Int J Clin Exp Pathol. 7:1911, 2014
J Enzyme Inhib. Medicinal Chem. 29:297, 2014

Brain Res 1627: 21, 2015
Med Sci Monitor 22:284, 2016
Oncotarget 8: 111522, 2017
Molecular Pain 14: 1, 2018
Oncotarget 9: 7513, 2018

HBO effect in **Neovascularization**



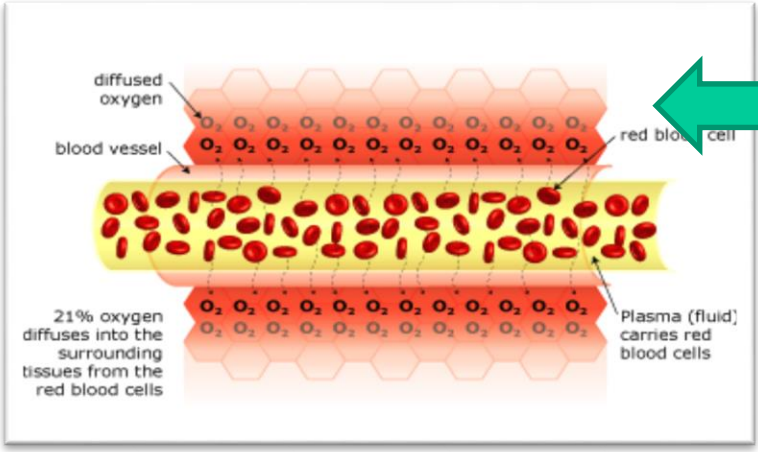
>2ATA : collagen synthesis

Both hypoxia & O_2: VEGF release

Li, J., Brown,L. et al.VEGF, Flk-1 and Flt-1 expression in rat myocardial infarction model of angiogenesis. *Am. J. Physiol.* ;210:1803-1811, 1996.

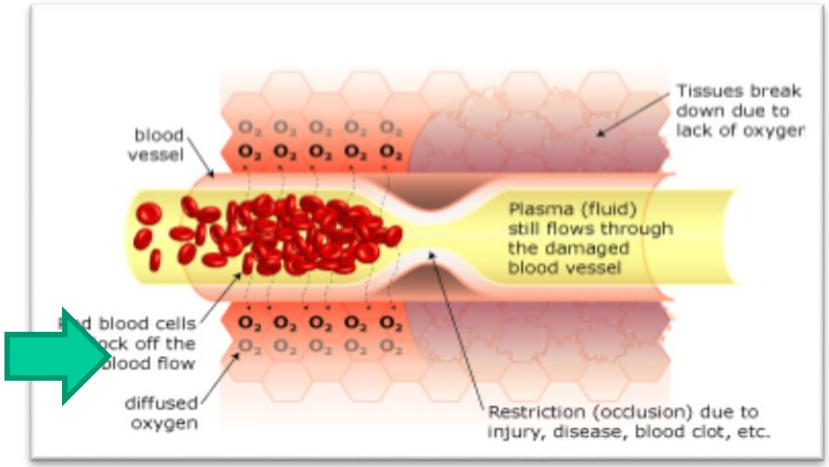
Sheikh, A., Gibson, J. et al. Effect of hyperoxia on VEGF levels in a wound model. *Arch.Surg.* ;135:1293-1297, 2000.

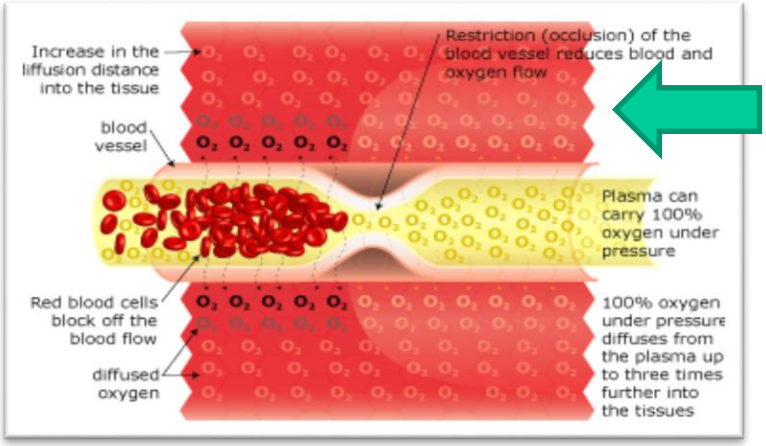
Lin, S. et al. Hyperbaric oxygen selectively induces angiopoietin-2 in human umbilical vein endothelial cells. *Biochem. Biophys. Res. Comm.*;296:710-715, 2002.



normal blood flow

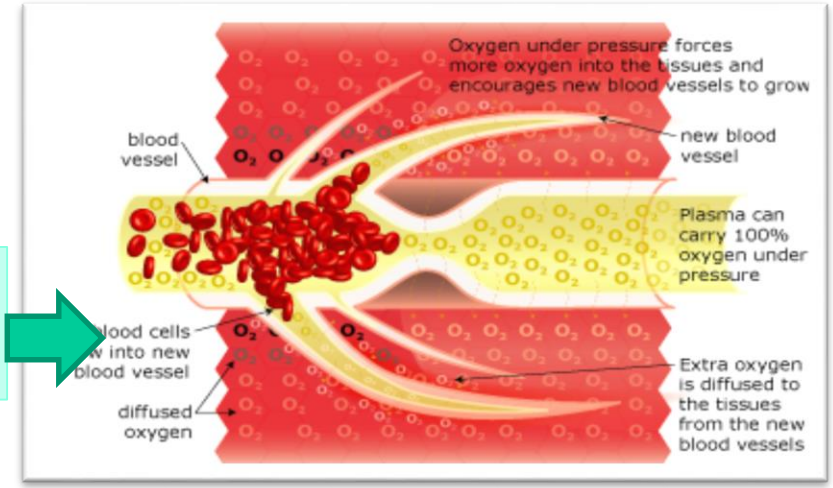
restricted blood flow





pressursed oxygenation

blood vessel regeneration



Mechanisms of action of hyperbaric oxygen therapy.
Camporesi, E M. Undersea And Hyperbaric Medicine (2014). May-Jun;41(3):247-52.

당뇨발

말초혈관 장애

심재성 2도 화상 (총 치료 횟수: 14회)

말초 혈관 장애에 의한 조직 괴사 (총 치료 횟수: 47회, SCIE 게재)

Kim YS, Youn YJ, Cha YS. Successful use of hyperbaric oxygen therapy for limb salvage of acute limb ischemia as a complication of acute carbon monoxide poisoning. Undersea Hyperb Med. 2020;47(2):235-240.

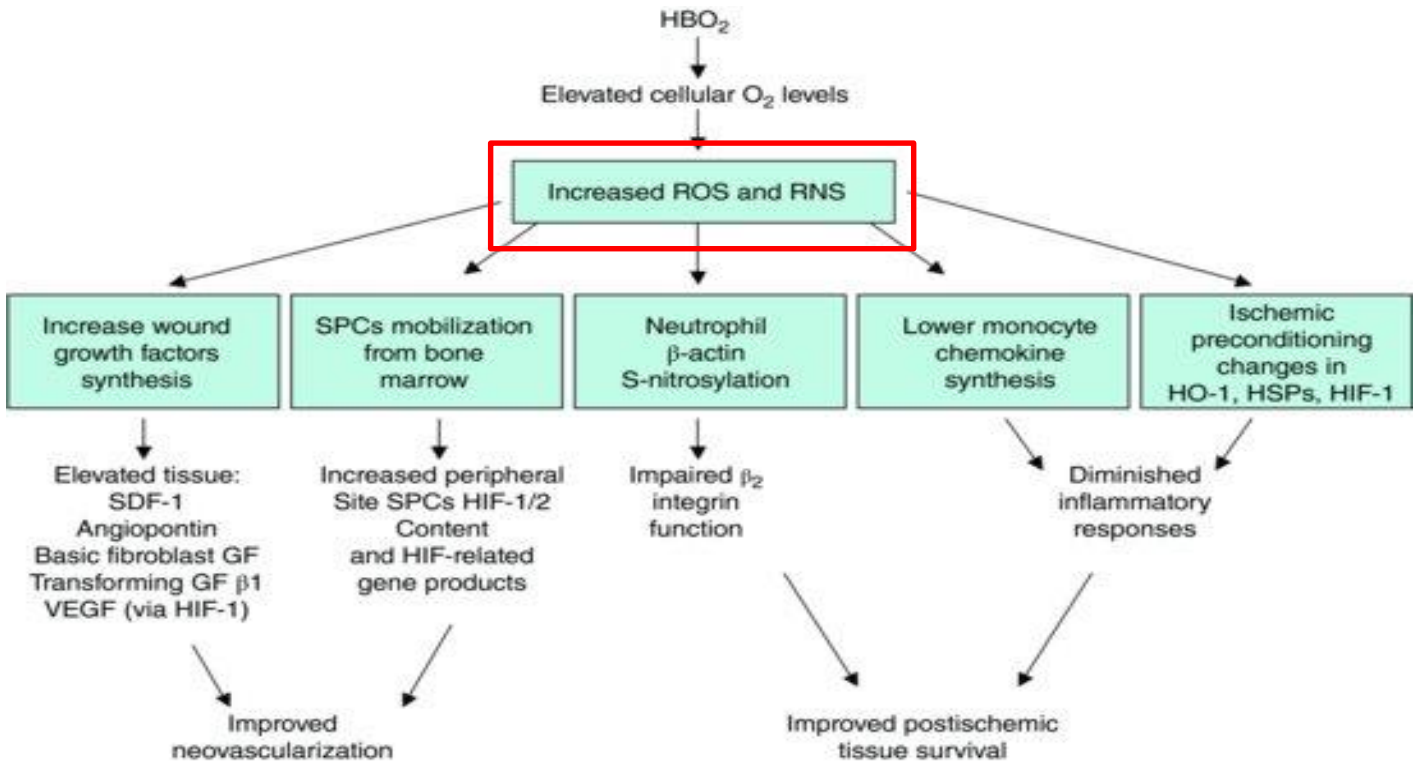
Case

고압산소치료 # 0

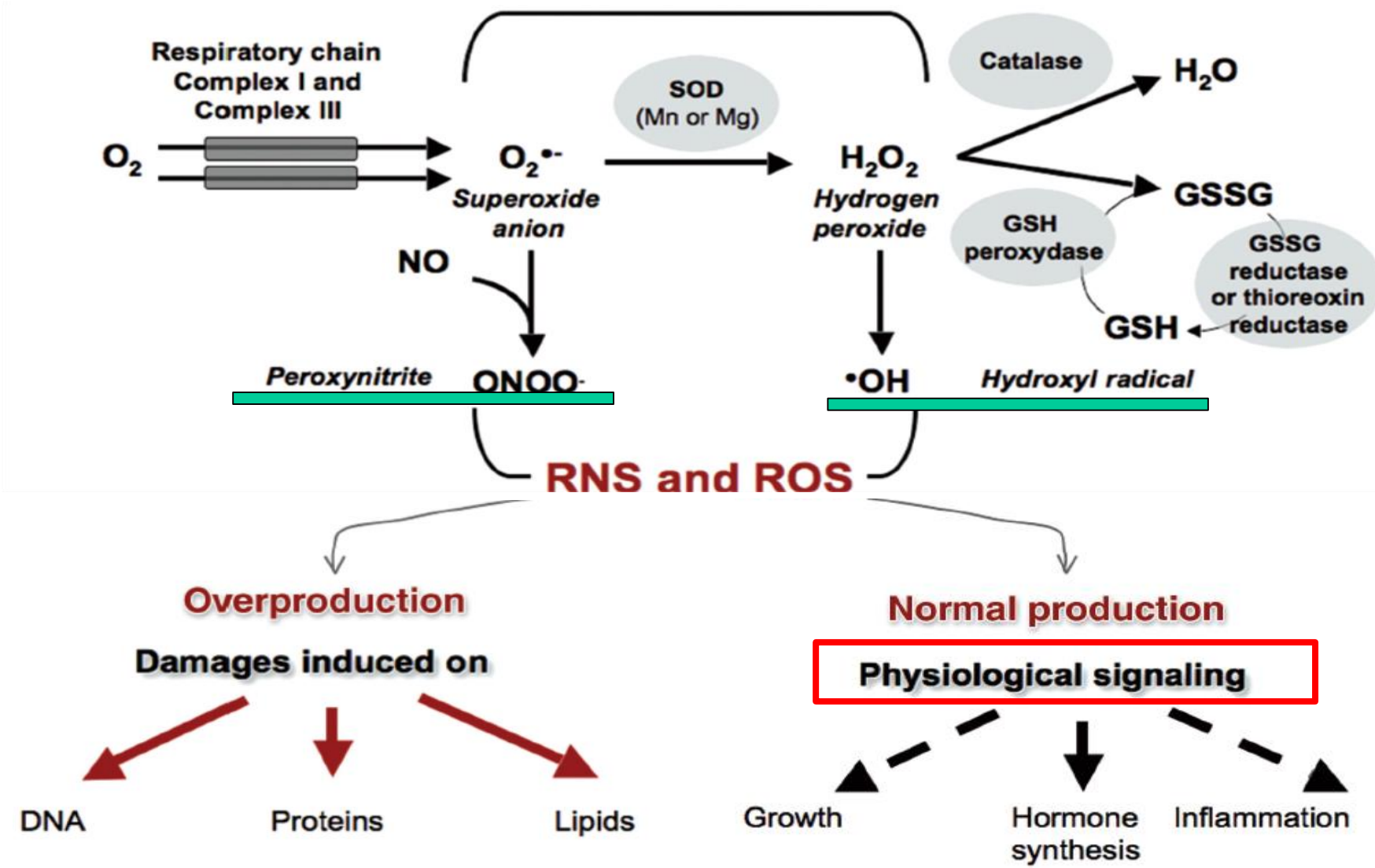
고압산소치료 # 10일

O_2 transport (intra-cellular level)

HBOT: secondary mechanism



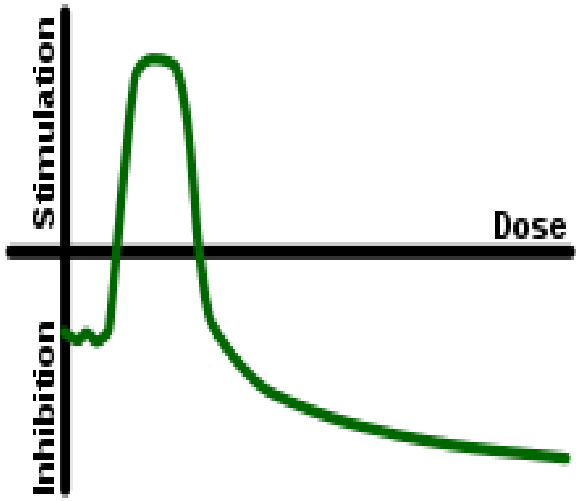
Reactive nitrogen & oxygen



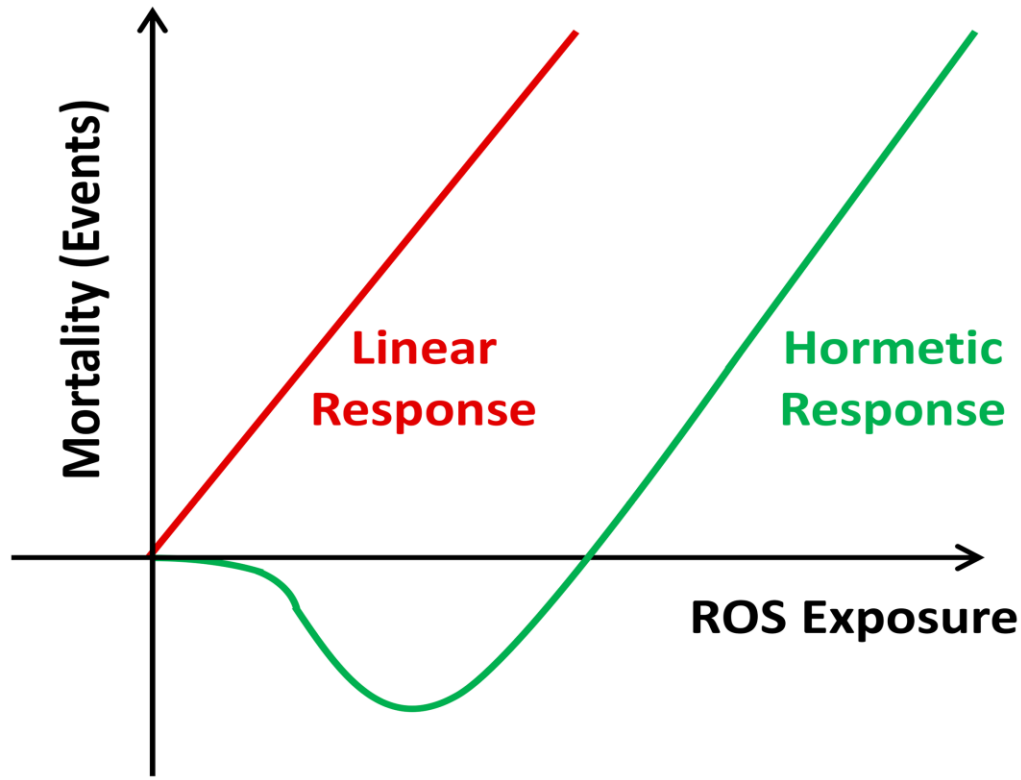
Comprehensive Physiology 2017

Hormesis

- Biphasic response: increasing amounts of a substance or condition
- Within the hormetic zone: favorable biological response to low exposures to toxins and other stressors
- Physical exercise, alcohol, mitochondria



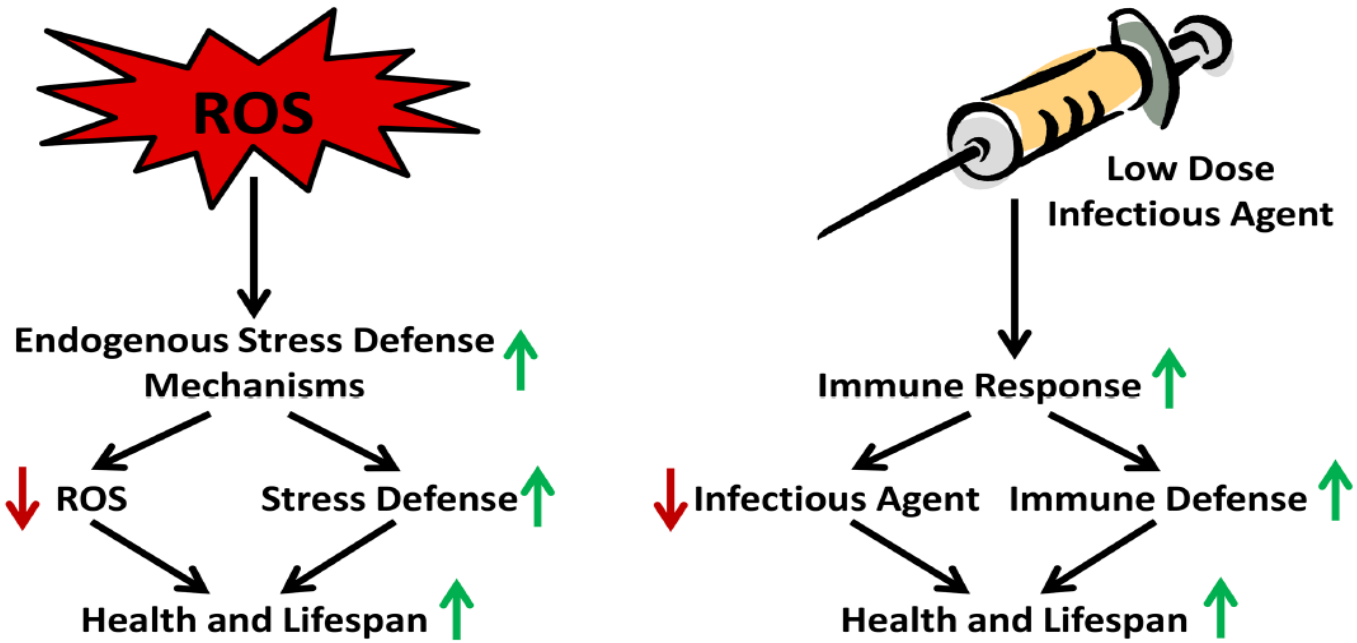
Mitochondrial hormesis (mitohormesis)



Free radical theory: linear dose-response relationship (ROS and oxidative stress and mortality)
Mitohormesis: non-linear dose-response relationship (low doses of ROS exposure decrease mortality, while higher doses promote mortality)

Dose Response. 2014 May; 12(2): 288–341

Mitochondrial hormesis (mitohormesis)



Dose Response. 2014 May; 12(2): 288–341

Possible mechanism

Low continuous
or higher intermittent
sub-lethal dose

A coordinated response to
mild mitochondrial stress

Intermittent HBOT

Mitochondrial Stress

Mitohormesis

√ **Reduce oxidative stress**

Most of O_2
in our body
is consumed
in mitochondria

√ **Recover from ischemic damage and promote wound healing**

√ **Resistant to subsequent stress**

Participation in therapeutic mechanism of HBOT

Mechanisms of HBOT

(Primary, secondary & tertiary)

Primary

- Hyperoxygenation (O_2 tensions)
- Direct effects of

Oxygen delivery/uptake
Bubble reduction

Secondary

- Enriched O_2 (cellular functions)

Anti-bacterial
Anti-inflammation (cytokine)
Ischemia-reperfusion injury
Neovascularization
Stem cell migration

Tertiary

- Oxidative stress in mitochoondria

Mitohormesis
?
?
?

임상 연구

1 정상인의 고압산소 치료에 의한 미토콘드리아 스트레스 바이오마커 변화 측정

- 건강한 정상인 자원자 10명을 대상으로 아래 프로토콜에 따라 고압산소치료 수행 후 일정 시간 간격으로 여러 혈중 지표들의 변화를 측정하였음

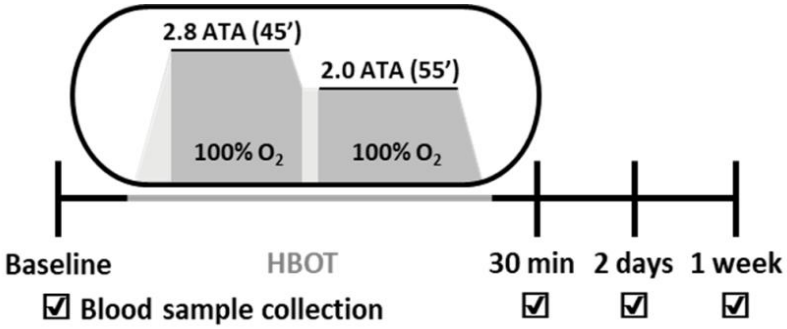


Table 1. Serum biochemical variables at baseline and following acute exposure to hyperbaric oxygen therapy (HBOT).

Variables	Baseline	1 Week Post HBOT	*p*-Value
Glucose (mg/dL)	104.4 ± 19.1	105.0 ± 35.4	0.967
TC (mg/dL)	186.5 ± 17.8	185.8 ± 24.8	0.921
TG (mg/dL) *	154.9 ± 58.4	190.4 ± 66.1	0.012
HDL-C (mg/dL)	47.2 ± 7.5	45.2 ± 7.2	0.206
LDL-C (mg/dL)	121.5 ± 23.1	116.1 ± 23.8	0.272
ALT (U/L) *	39.6 ± 21.2	36.1 ± 12.2	0.483
AST (U/L) *	29.4 ± 5.5	29.7 ± 5.3	0.812
Total protein (g/dL)	7.45 ± 0.26	7.30 ± 0.29	0.143
Albumin (g/dL) *	4.64 ± 0.25	4.58 ± 0.23	0.301
BUN (mg/dL)	12.74 ± 1.65	12.43 ± 1.76	0.599
Creatinine (mg/dL)	0.82 ± 0.05	0.81 ± 0.04	0.532
Uric acid (mg/dL)	6.37 ± 0.85	6.11 ± 0.95	0.106

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride. Statistical analyses were performed using Student's paired *t*-test or * Wilcoxon matched-pairs signed-rank test. Values represent the means ± SD.

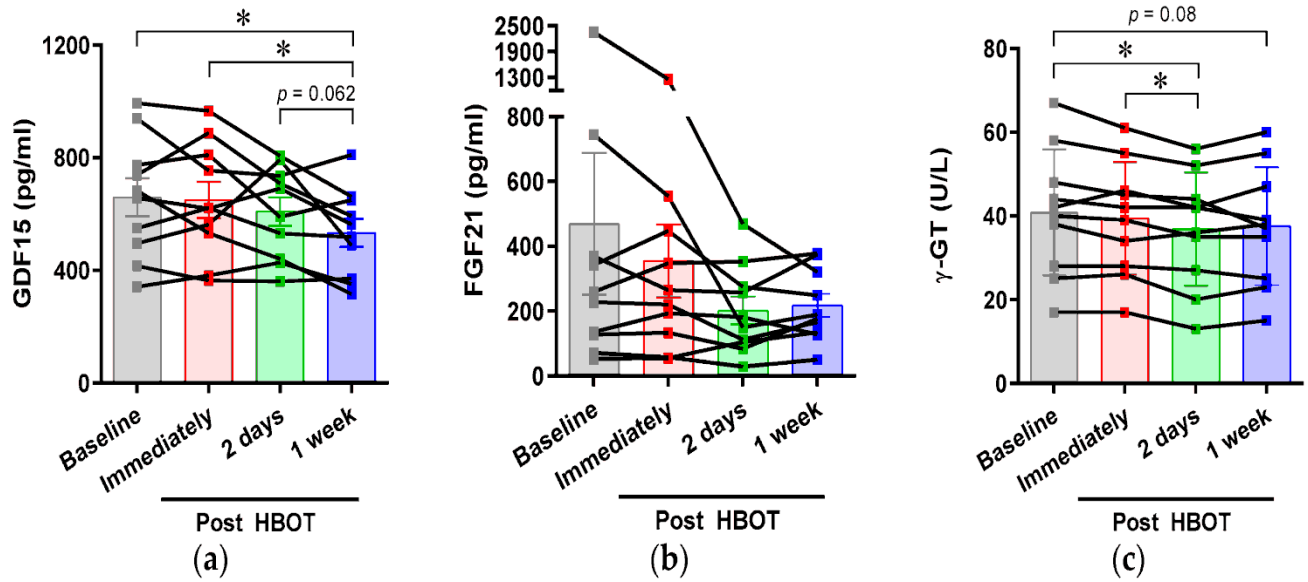
JS Jang, et al. Int. J. Environ. Res. Public Health 2020, 17, 7853

임상 연구

1 정상인의 고압산소 치료에 의한 미토콘드리아 스트레스 바이오마커 변화 측정

- 미토콘드리아 스트레스 바이오마커로 알려진 **GDF15, FGF21, γ-GT** 은 스트레스에 의해 발현 및 분비가 증가하여 이를 경감시키고 회복시키는 작용을 가짐

- 미토콘드리아 스트레스가 높은 상태에서 이들 혈중농도가 증가한다고 알려짐
- 피검자들은 고압산소치료에 의해 **GDF15, FGF21, γ-GT** 혈중 농도가 감소하였으며, 이는 미토콘드리아 스트레스가 줄어들었음을 의미함



(**a**) growth/differentiation factor 15 (GDF15), (**b**) fibroblast growth factor 21 (FGF21), and (**c**) γ-glutamyltransferase (γ-GT)

JS Jang, et al. Int. J. Environ. Res. Public Health 2020, 17, 7853

NEUMAN & THOM

PHYSIOLOGY AND MEDICINE OF HYPERBARIC OXYGEN THERAPY

SAUNDERS
ELSEVIER

Review

J Appl Physiol 106: 988–995, 2009.
First published October 9, 2008; doi:10.1152/japplphysiol.91004.2008.

HIGHLIGHTED TOPIC | *The Physiology and Pathophysiology of the Hyperbaric and Diving Environments*

Oxidative stress is fundamental to hyperbaric oxygen therapy

Stephen R. Thom
Institute for Environmental Medicine and Department of Emergency Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

Submitted 1 August 2008; accepted in final form 1 October 2008

WOUND HEALING

Hyperbaric Oxygen: Its Mechanisms and Efficacy

Stephen R. Thom, M.D., Ph.D.
Philadelphia, Pa.

Background: This article outlines therapeutic mechanisms of hyperbaric oxygen therapy and reviews data on its efficacy for clinical problems seen by plastic and reconstructive surgeons.
Methods: The information in this review was obtained from the peer-reviewed medical literature.
Results: Principal mechanisms of hyperbaric oxygen are based on intracellular generation of reactive species of oxygen and nitrogen. Reactive species are recognized to play a central role in cell signal transduction cascades, and the discussion will focus on these pathways. Systematic reviews and randomized clinical trials support clinical use of hyperbaric oxygen for refractory diabetic wound-healing and radiation injuries; treatment of compromised flaps and grafts and ischemia-reperfusion disorders is supported by animal studies and a small number of clinical trials, but further studies are warranted.
Conclusions: Clinical and mechanistic data support use of hyperbaric oxygen for a variety of disorders. Further work is needed to clarify clinical utility for some disorders and to hone patient selection criteria to improve cost efficacy. (*Plast. Reconstr. Surg.* 127 (Suppl.): 131S, 2011.)

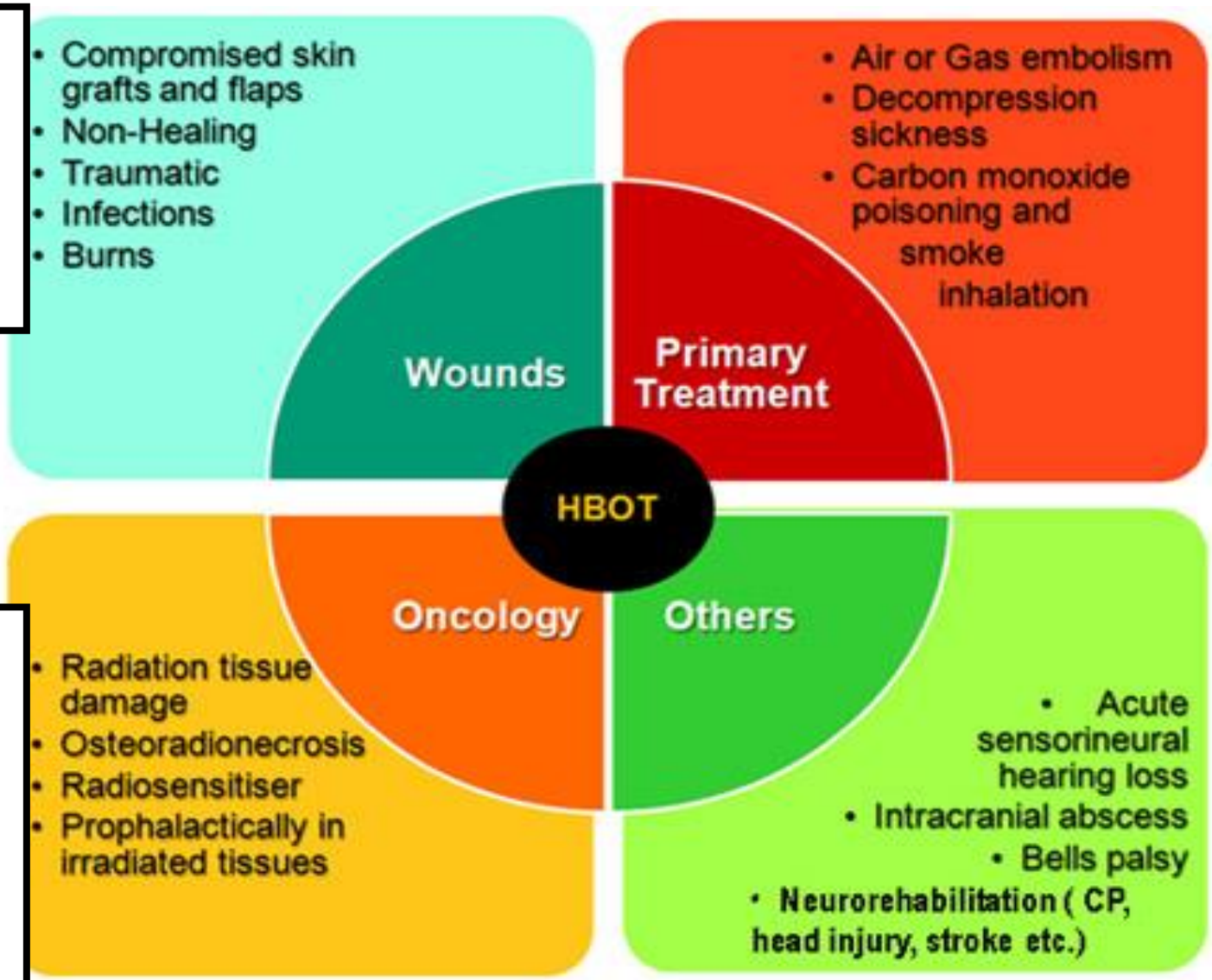
결론

Trauma center

PS, OS

CS, Endo

Infection



EM

Oncology

Urology

Gyn

Dental

ENT

Eye

NS

Korean Academy of
Undersea and Hyperbaric Medicine

Thank you

대한고압의학회
Korean Academy of Undersea and Hyperbaric Medicine