

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

2021.09.09.

소 속 : 연세대학교 원주의과대학

이 름 : 김 현 교수

Korean Academy of
Undersea and Hyperbaric Medicine



대한고압의학회
Korean Academy of Undersea and Hyperbaric Medicine

1st Generation (1986 - 2015)



2nd Generation (2015 - 2018)



3rd Generation (2018 -)

다인용 챔버



1인용 챔버



동물용 챔버



HBOT CENTER

연세대학교 원주의과대학 고암의과학연구소

세포용 챔버





고압산소치료란? (HBOT: hyperbaric oxygen therapy)

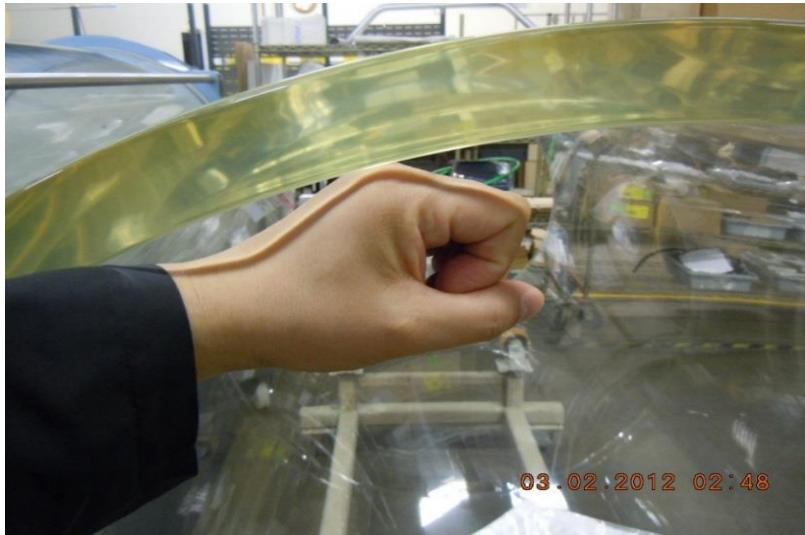
- 정의: 챔버를 이용하여 1.4기압 이상으로 100%산소를 호흡시킴으로 의학적 효과를 나타내는 치료법
(의학적 압력은 2.0 – 3.0 기압)
- 원리와 효과 – 고농도 산소 유지(hyperoxygenation)

Topical Oxygen Therapy

- 100% O₂
- 1 atmosphere of pressure



Soft vs hard chamber

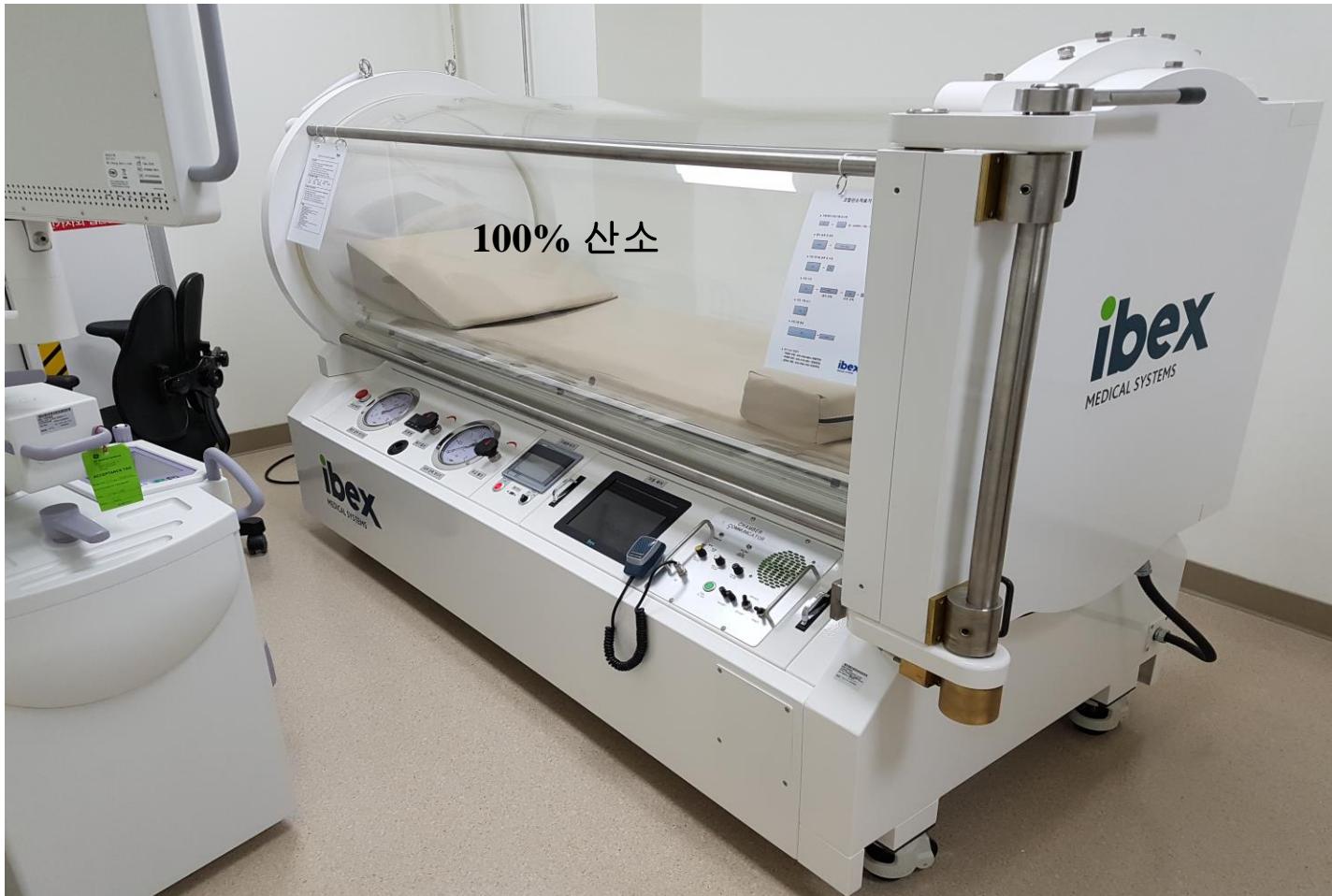


강화 PVC
철(다인용챔버)
고강도
(고압산소치료)



천
플라스틱
저강도
(고압산소치료 불가능)

고압산소치료란?

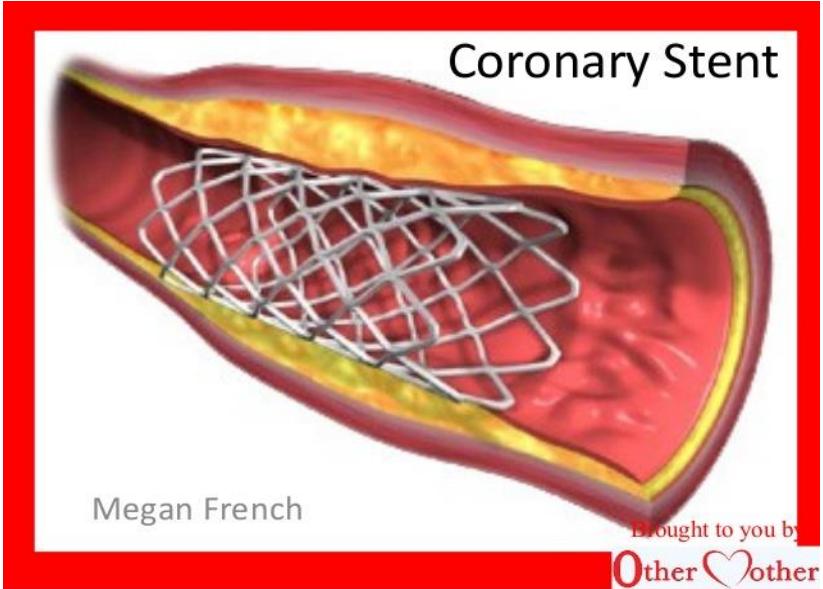


치료 프로토콜

- 100% 산소
- 2~2.8 기압
- 90~120분

고압산소치료란?





Macrocirculation

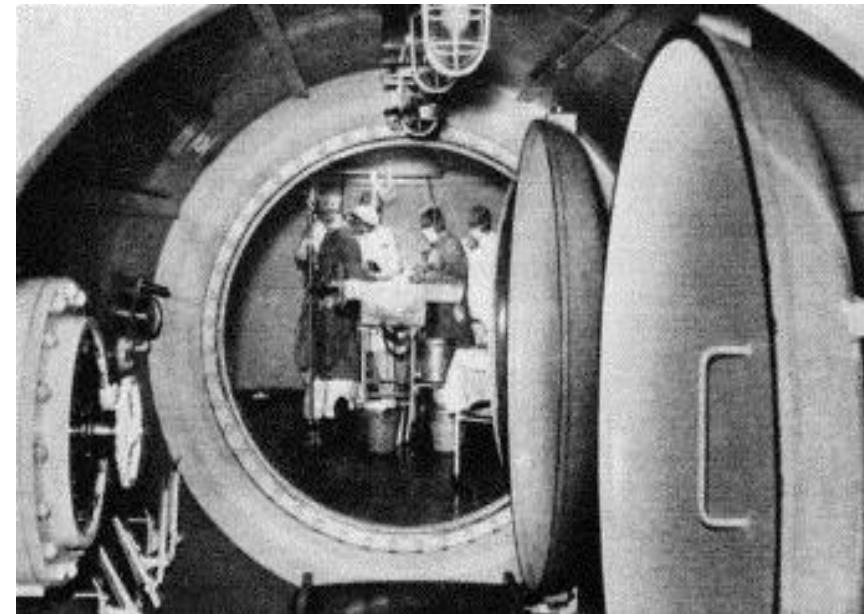
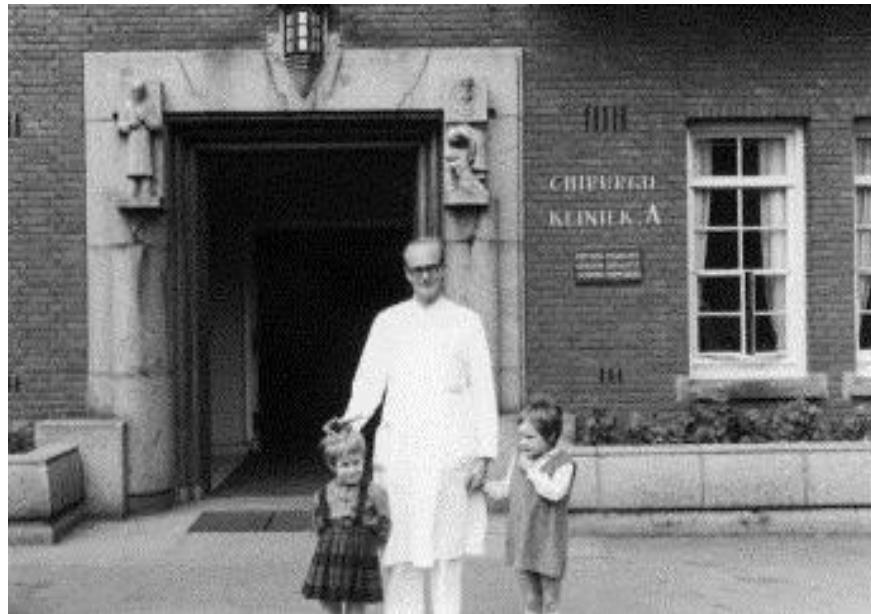


Microcirculation

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. BROKHEMMA ^{1,2}, N. G. MEYNE, W. K. DRUMMELICAMP,
K. INOMATA, H. H. MHNSCHE, P. KAMERMANS, M. STIBER HANSE
and W. VAN AALSTHUIS
(from the Surgical Department of the University of Amsterdam)

When in 1948 we (first of research) started our experiments 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 to 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 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 20°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 1966 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 22°C.^{1,2} 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.

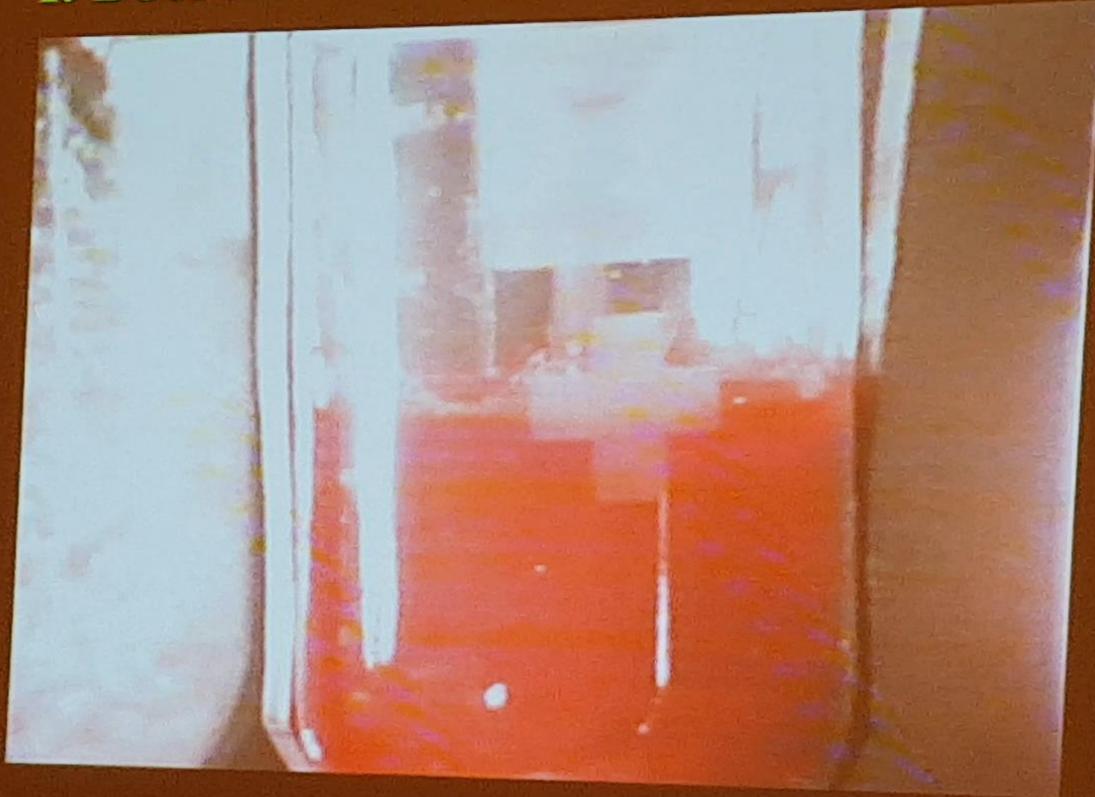
^{1,2} Professor of Surgery.

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



Life without blood

I. Boerema 1960: "Life Without Blood"



일차기전

고압산소치료의 기전

(일차 & 이차기전)

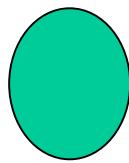
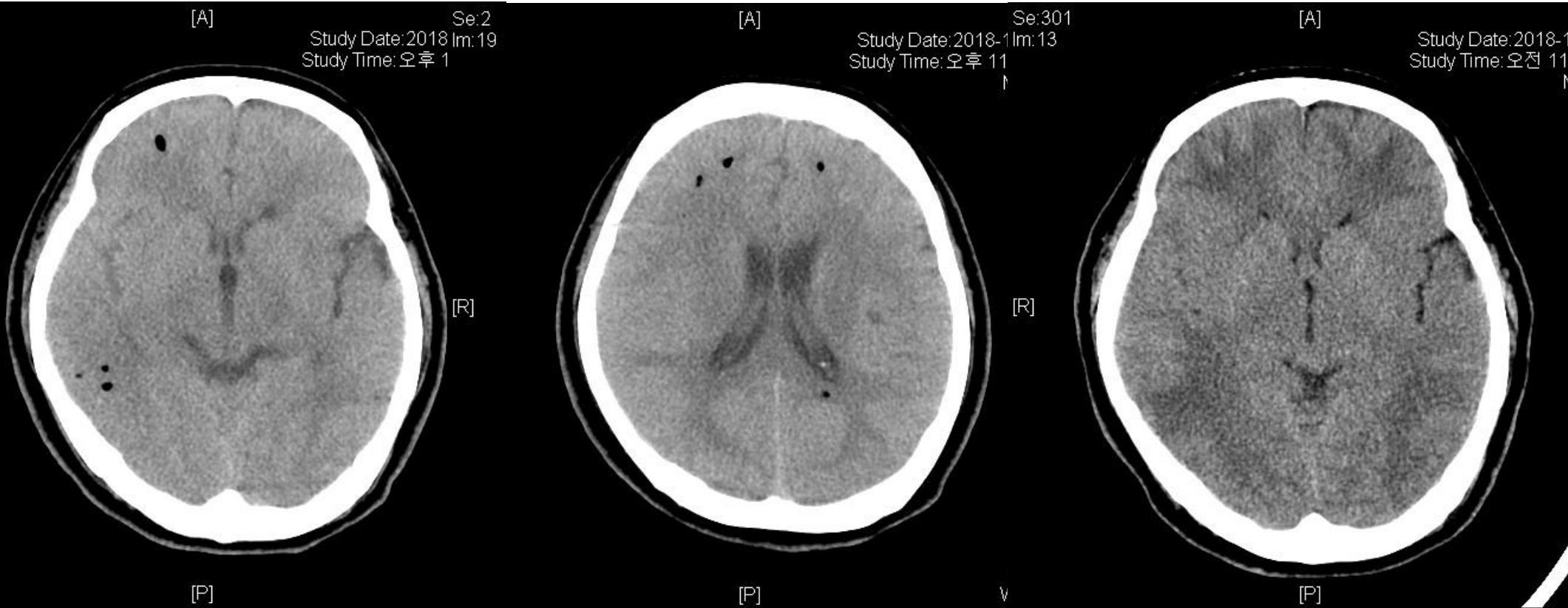
일차

Secondary

- 고농도산소화 (O_2 tensions)
- 고압

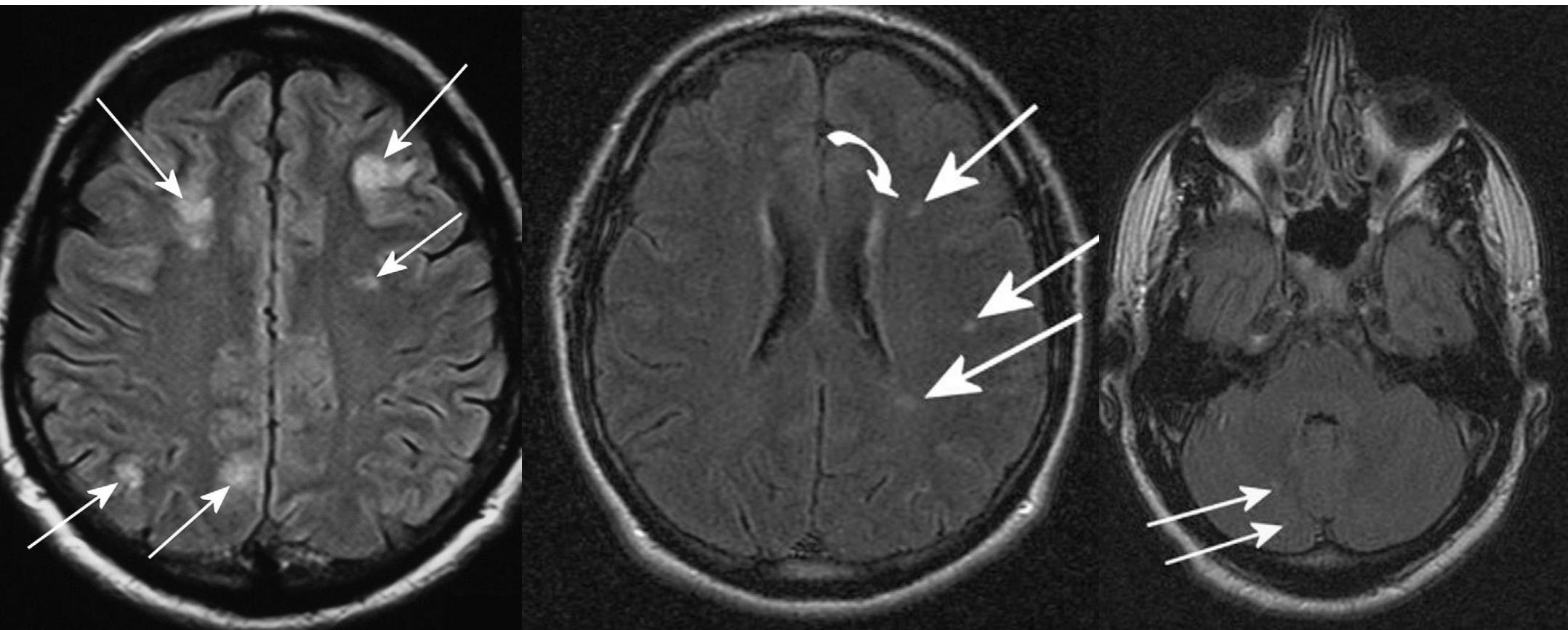
Oxygen delivery/uptake
Bubble size reduction

HBOT: primary mechanism (AGE)

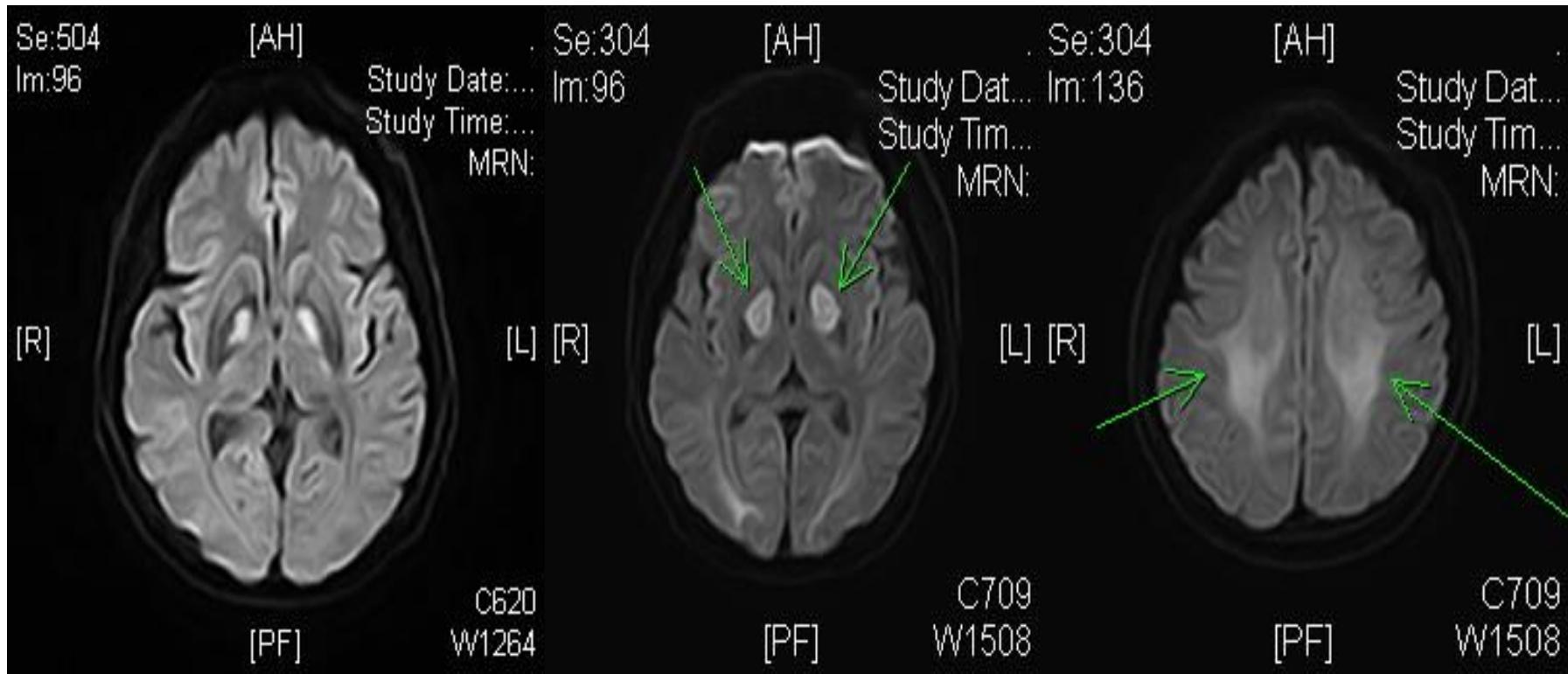


• Bubble size reduction

HBOT: primary mechanism (DCS)



HBOT: primary mechanism (CO)

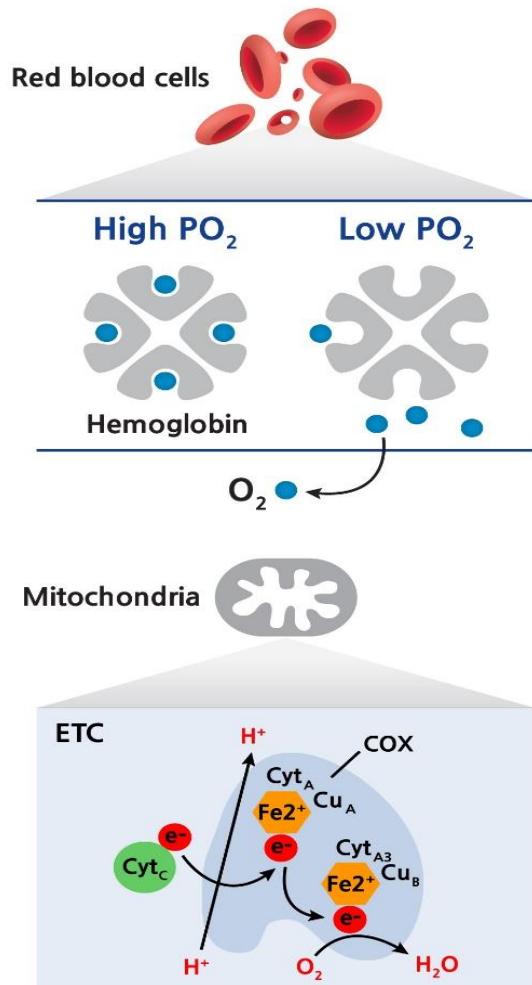


HBOT: primary mechanism

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

세포내로의 산소운반

산소의 운반



두 개의 형태

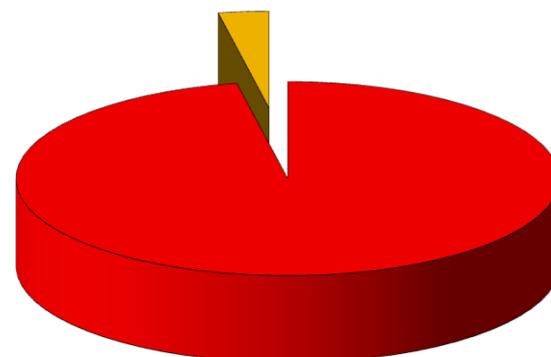
1. 적혈구

Bound to Hb

97-98%

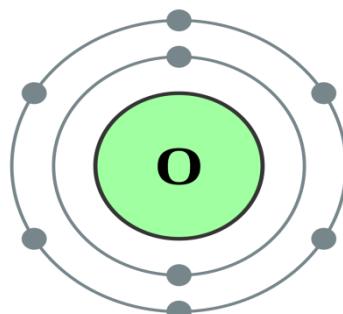
2. 혈장

S



O₂ content (CaO₂)

- $\text{CaO}_2 = \boxed{1.34 \times \text{Hb} \times \text{SaO}_2} + \boxed{0.003 \times \text{PaO}_2}$
 Hg-bound dissolved
- NL CaO₂ = $1.34 \times 15 \times 0.98 (19.7) + 0.003 \times 100 (0.3)$
 $= 20.0 \text{ ml}/100 \text{ ml} (\text{ or } 200 \text{ ml/L})$
- Solubility of O₂: 0.028 ml O₂/L/mm Hg
- Hb can bind 1.34 ml O₂/g when fully saturated



Solubility of O₂ & CO₂ 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

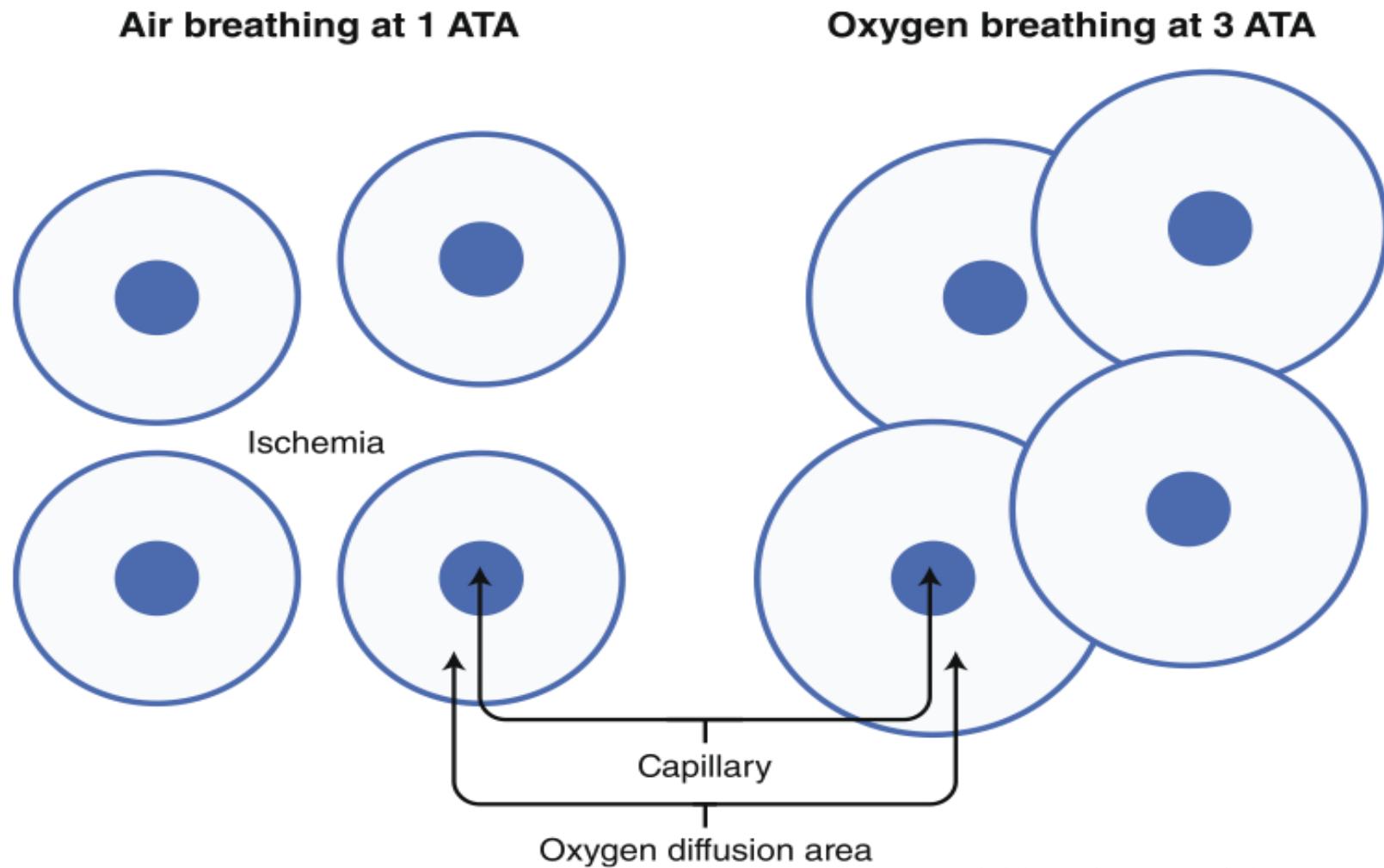
Different scenarios

	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

고농도 산소화의 효과

	헤모글로빈과 결합 Hemoglobin carried O ₂ (Vol%)	혈장내에 녹아있는 형태 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 diffusion area



Londahl et al, Curr Diab Res 2011

이차기전

Mechanisms of HBOT (Primary & Secondary)

Primary

- Hyperoxygenation (O_2 tensions)
- Direct effects of pressure

Oxygen delivery/uptake
Bubble size reduction

Secondary

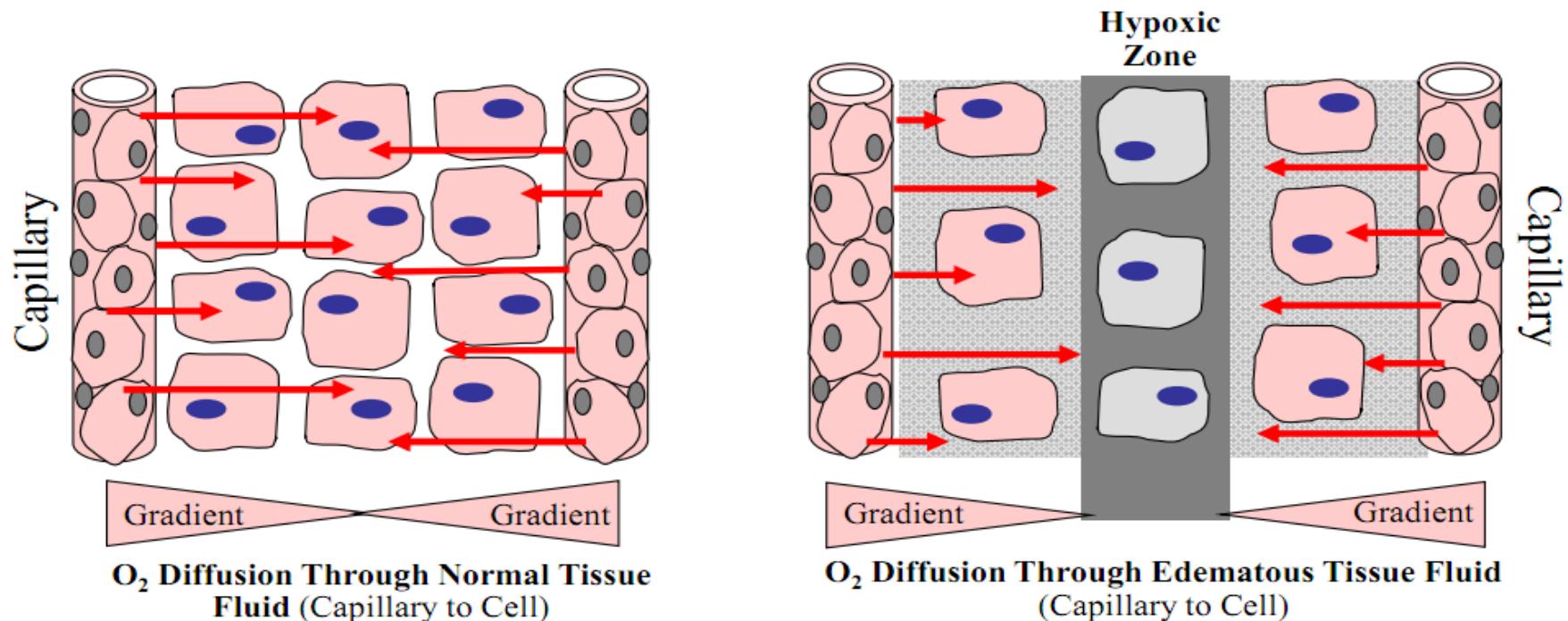
- Hyperoxygenation (enriched $O_2 \rightarrow$ cellular functions)

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



부종의 해로움

HBO effect in Edema

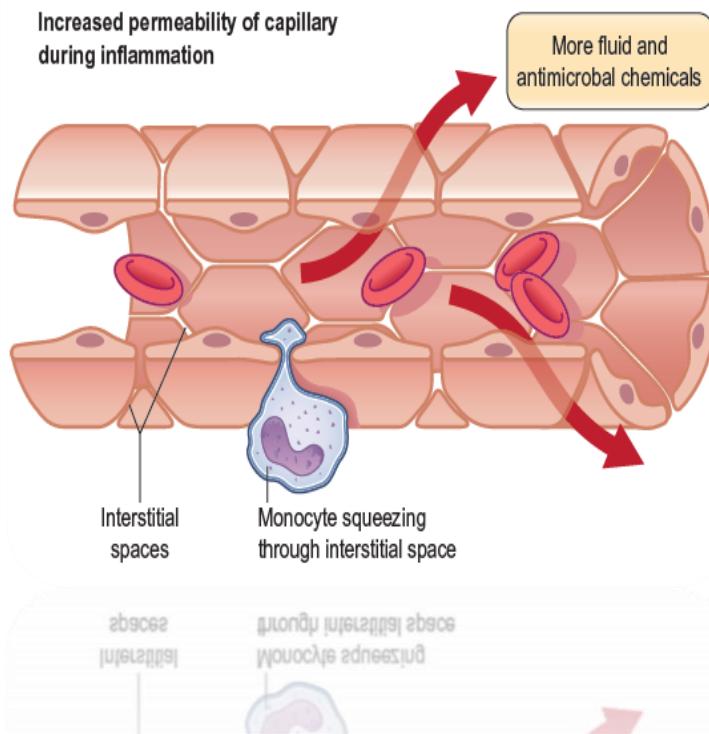
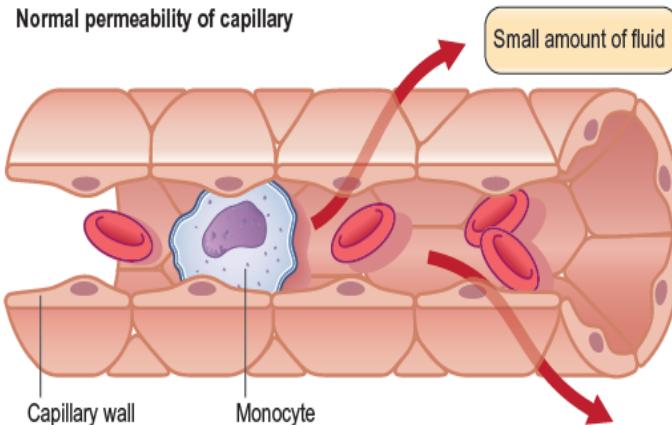
Vasoconstriction: defense mechanism against hyperoxia

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



HBO₂ also inhibits leukocyte pro-inflammatory cytokine production

Human, Mouse, Rat

Macrophage:

BBRC 179: 886, '91

Clin Exp Immunol 102: 665, '95 J Appl Physiol Feb. 2019

J Clin Immunol 17: 154, '97

Clin Exp Immunol. 134: 57, '03

PMN:

Dig Dis Sci 51: 1426, 2006

Microglia & Astrocytes

Brain Res 1627: 21, 2015

Molecular Pain 14: 1, 201

Oncotarget 9: 7513, 2018

Decreases IL-1 β , IL-6, TNF α , NF- κ B

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

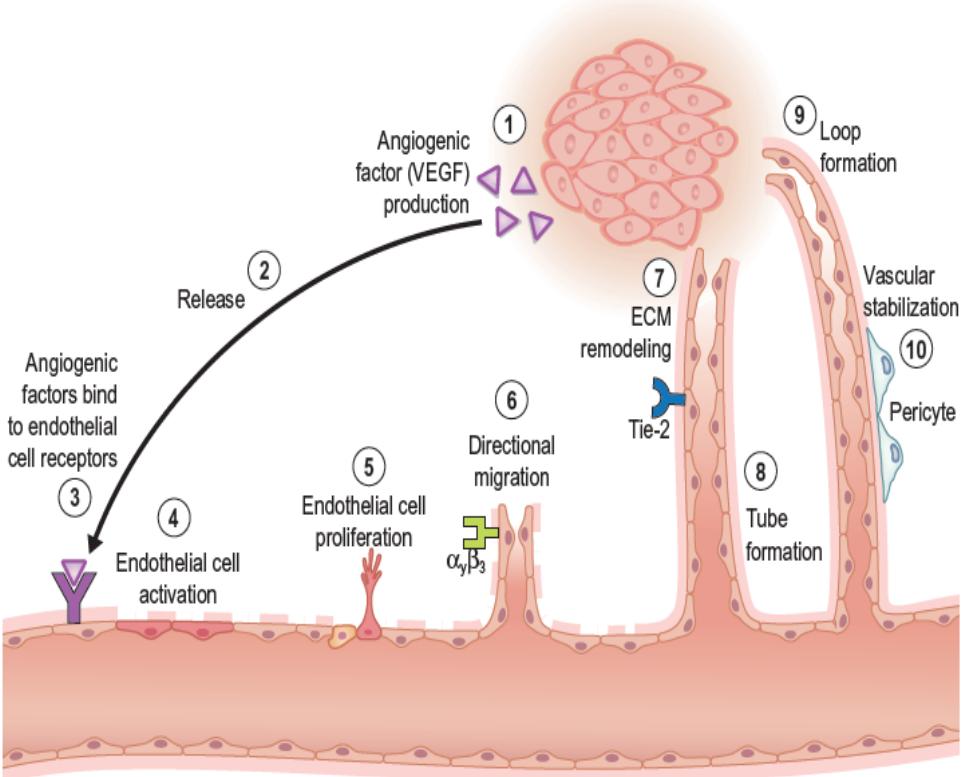
Med Sci Monitor 22:284, 2016

Oncotarget 8: 111522, 2017

Molecular Pain 14: 1, 2018

Oncotarget 9: 7513, 2018

HBO effect in Neovascularization



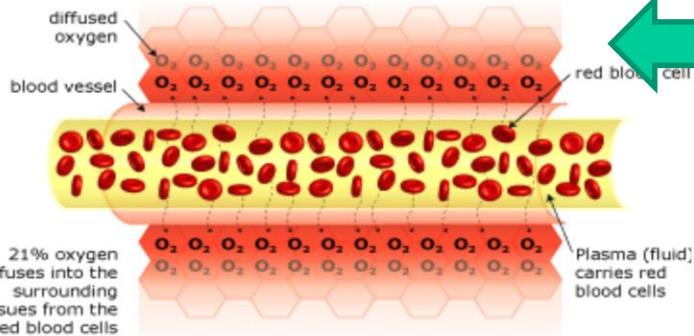
>2ATA : collagen synthesis

Both hypoxia & O₂: VEGF release

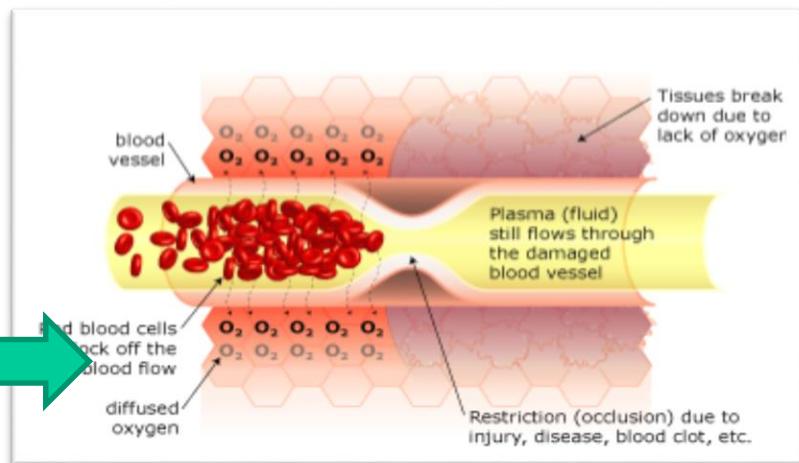
Li, J., Brown,L. et al. VEGF, Flk-1 and Flt-1 expression in rat myocardial infarction model of angiogenesis. *Am. J. Physiol.* ;210:1803-1811, 1996.

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

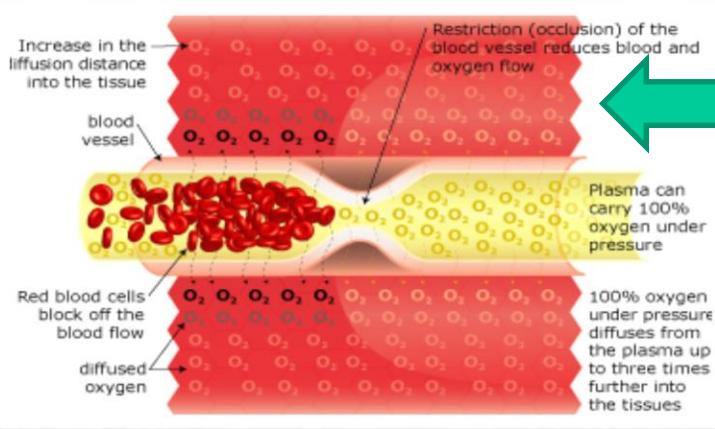
Lin, S. et al. Hyperbaric oxygen selectively induces angiopoietin-2 in human umbilical vein endothelial cells. *Biochem. Biophys. Res. Comm.*;296:710-715, 2002.



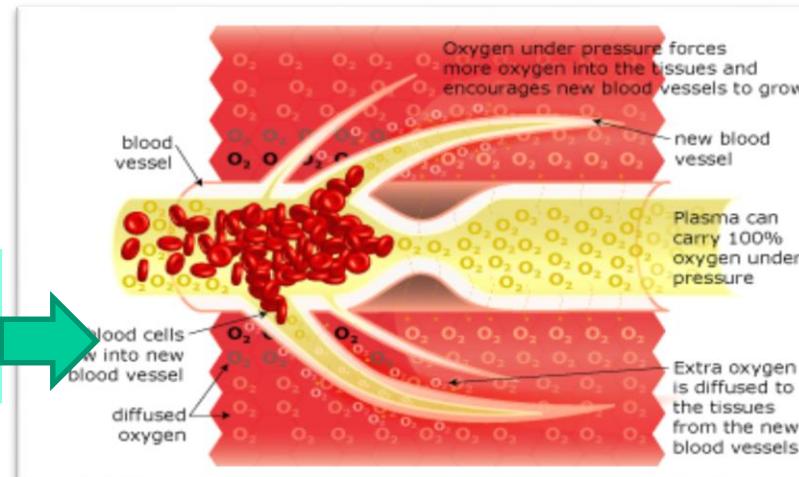
normal
blood flow



restricted
blood flow



pressurised
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 개재)



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

결론

Trauma center

PS, OS

CS, Endo

Infection

Oncology

Urology

Gyn

Dental

- Compromised skin grafts and flaps
- Non-Healing
- Traumatic
- Infections
- Burns

- Air or Gas embolism
- Decompression sickness
- Carbon monoxide poisoning and smoke inhalation

Wounds

Primary Treatment

HBOT

Oncology

Others

- Radiation tissue damage
- Osteoradionecrosis
- Radiosensitiser
- Prophalactically in irradiated tissues

- Acute sensorineural hearing loss
- Intracranial abscess
- Bells palsy
- Neurorehabilitation (CP, head injury, stroke etc.)

EM

ENT

Eye

NS

Korean Academy of
Undersea and Hyperbaric Medicine

Thank you



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