급성 일산화탄소 중독과 합병증의 치료

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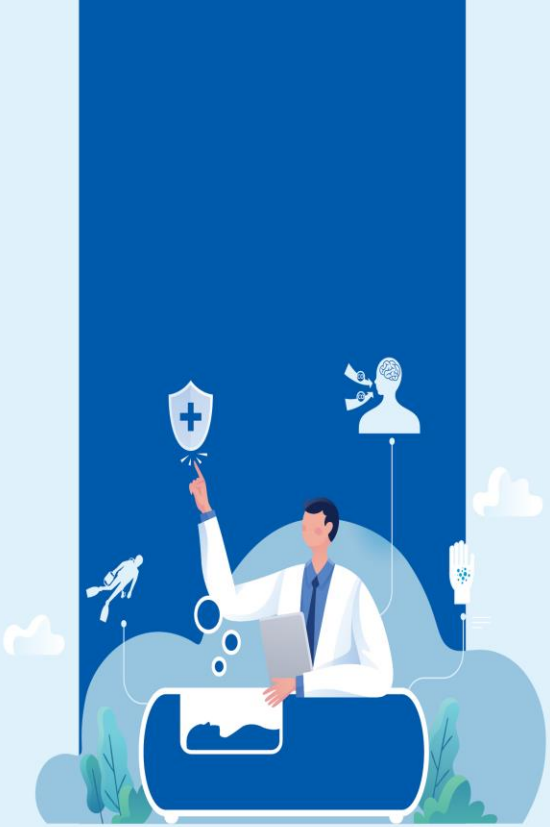
대한고압의학회
Korean Academy of Undersea and Hyperbaric Medicine

Now, first things first !

I have got no conflict of interest to declare.



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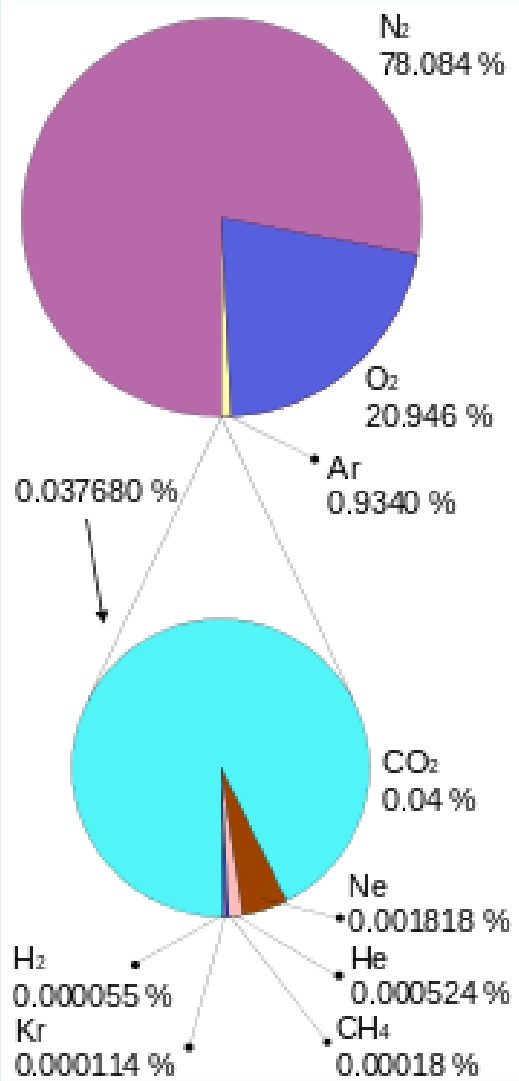
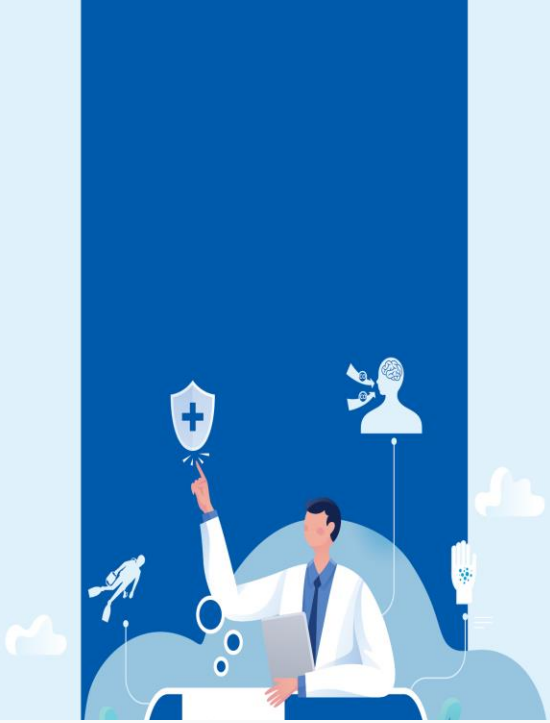
Carbon Monoxide (CO)?





Concentration	Source
0.1 ppmv	Natural atmosphere level (MOPITT)[37]
0.5–5 ppmv	Average level in homes[38]
5–15 ppmv	Near-properly adjusted gas stoves in homes, modern vehicle exhaust emissions[39]
17 ppmv	Atmosphere of Venus
100–200 ppmv	Exhaust from automobiles in the Mexico City central area[40]
700 ppmv	Atmosphere of Mars
5,000 ppmv	Exhaust from a home wood fire[41]
7,000 ppmv	Undiluted warm car exhaust without a catalytic converter[39]

PPM (parts per million): 1 / 10^{-7} (백만분의 일)

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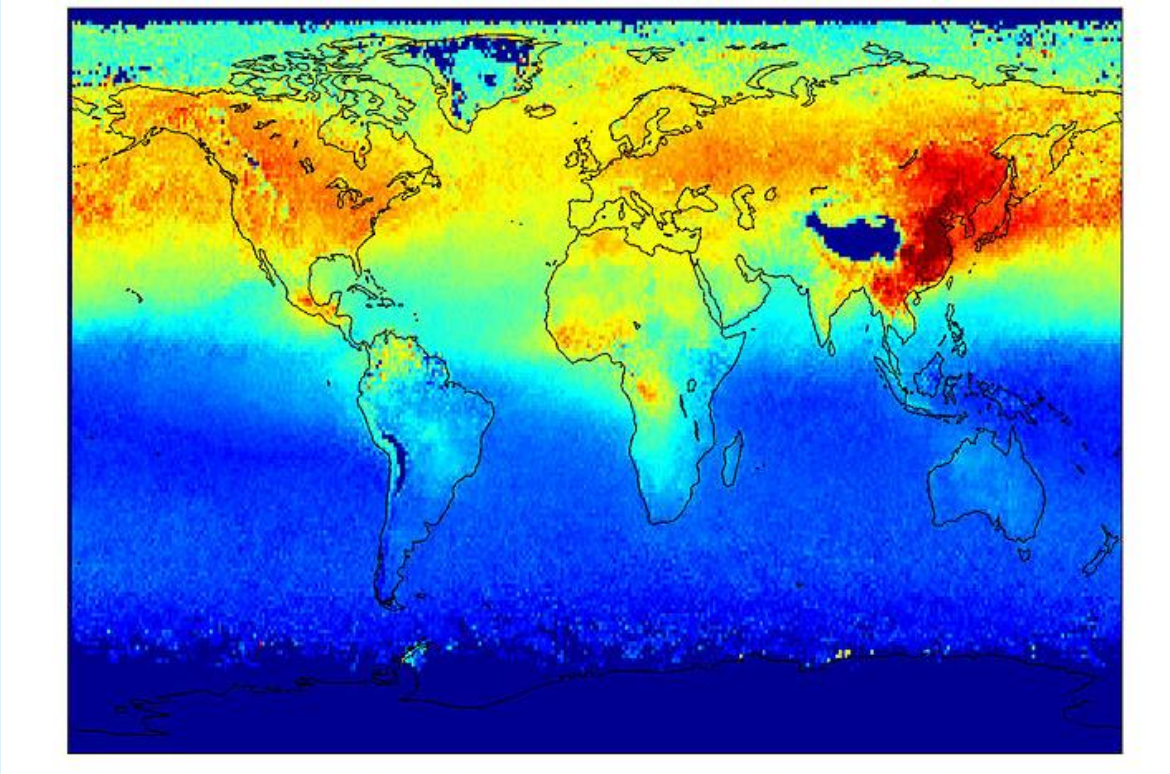
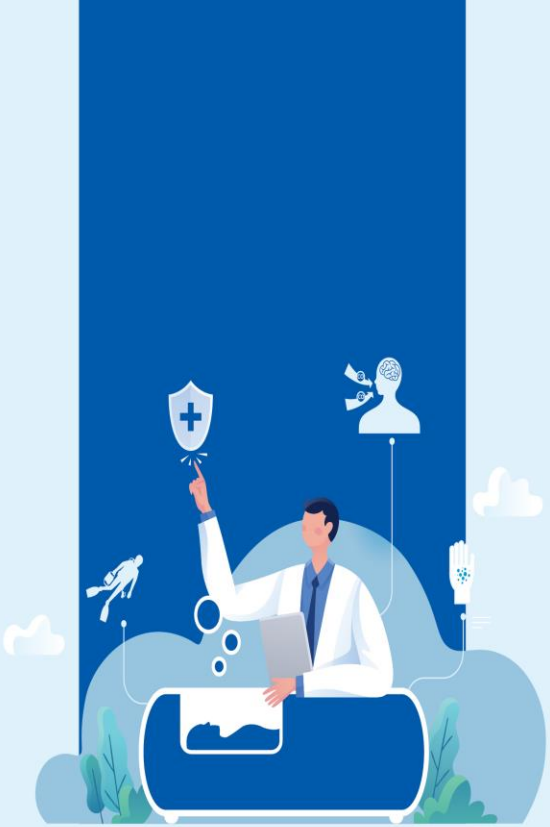
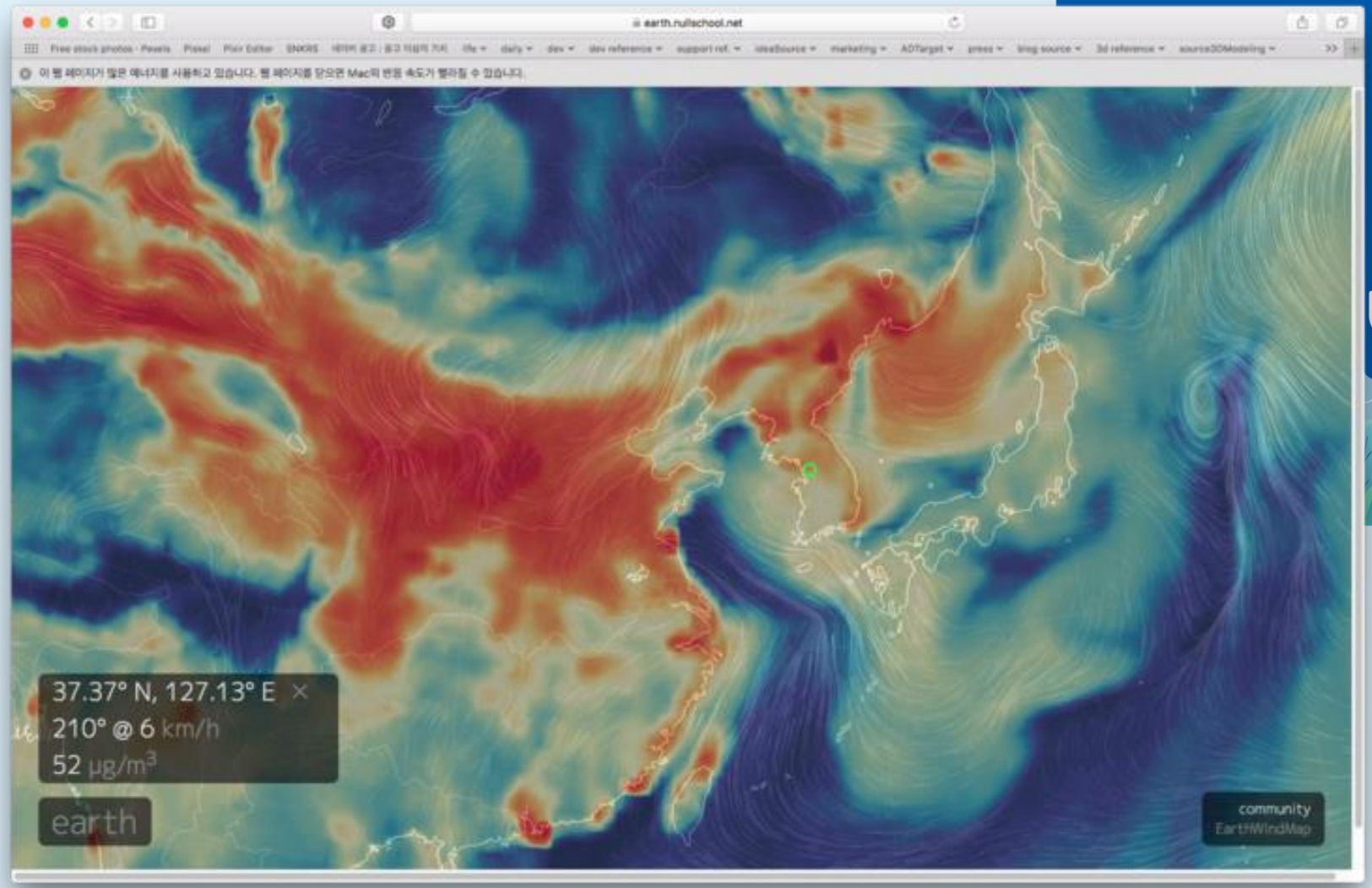


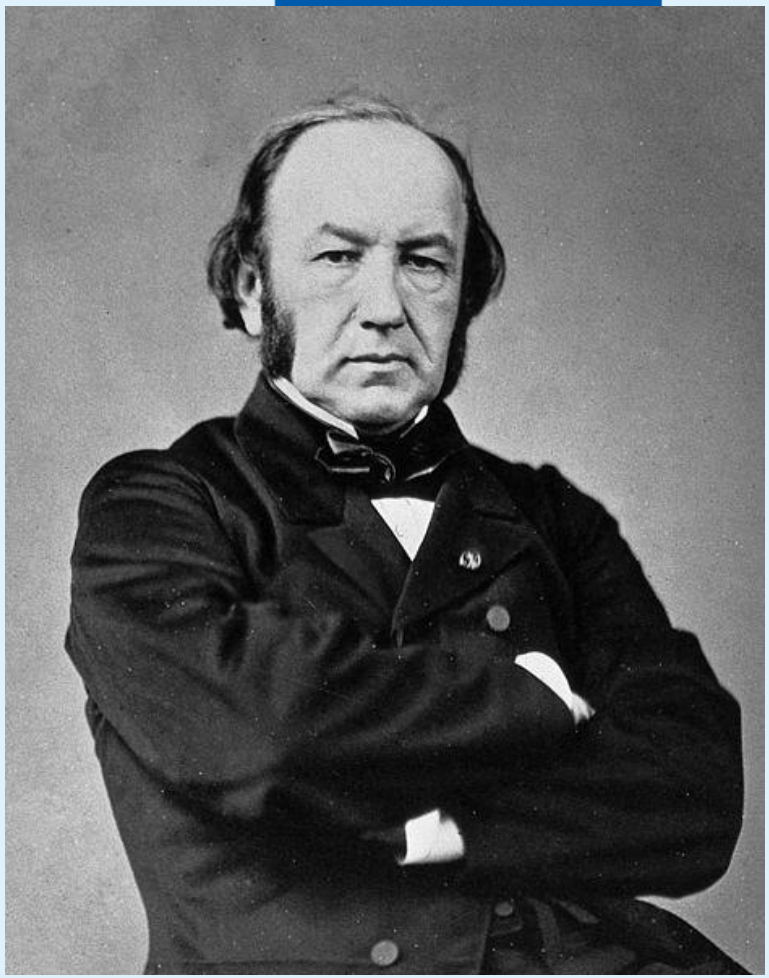


- North hemisphere: 0.1 ~ 0.2 ppm (0.00001 ~ 0.00002 %)
- South hemisphere: 0.04 ~ 0.06 ppm


earth.nullschool.net
37.37° N, 127.13° E
210° @ 6 km/h
52 μg/m³
earth
community
EarthWindMap

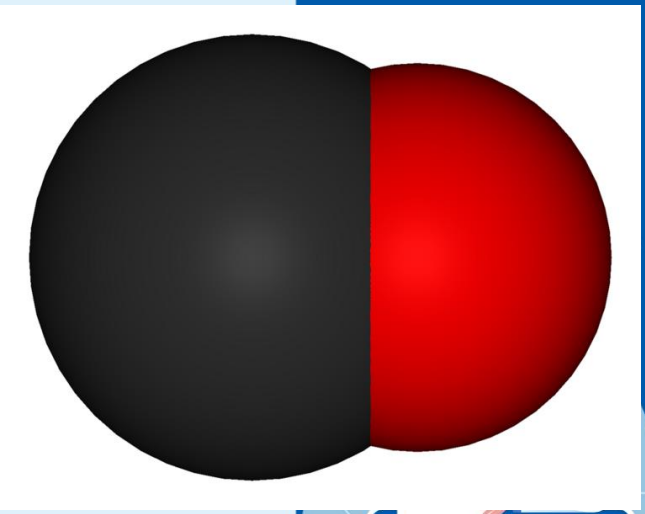
Carbon Monoxide

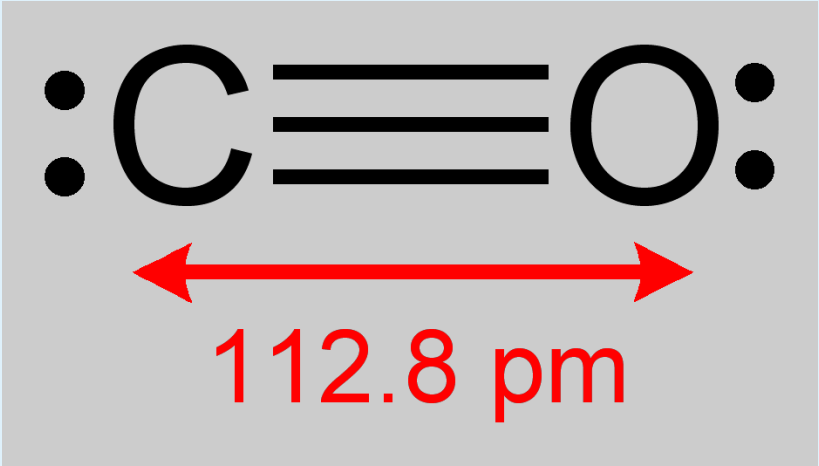
- Significantly more is known ab out CO poisoning since Claude Bernard described it in 1857.
  - Bernard C. *Lecons sur les Effe ts des Substaces Toxiques et Medicamenteuses*. (Lectures on the effects of toxic and medicinal substances) Paris: J-B Bailliere et Fils, 1857



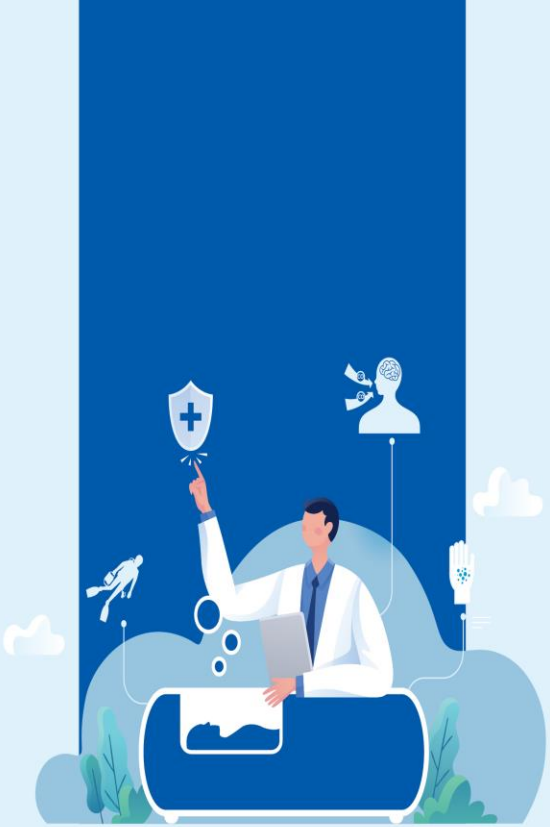
Chemistry

- M/C cause of fatal poisonings in USA
- Gas
- Odorless
- Colorless
- Tasteless
- Relative vapor density = 0.97
- Extremely stable

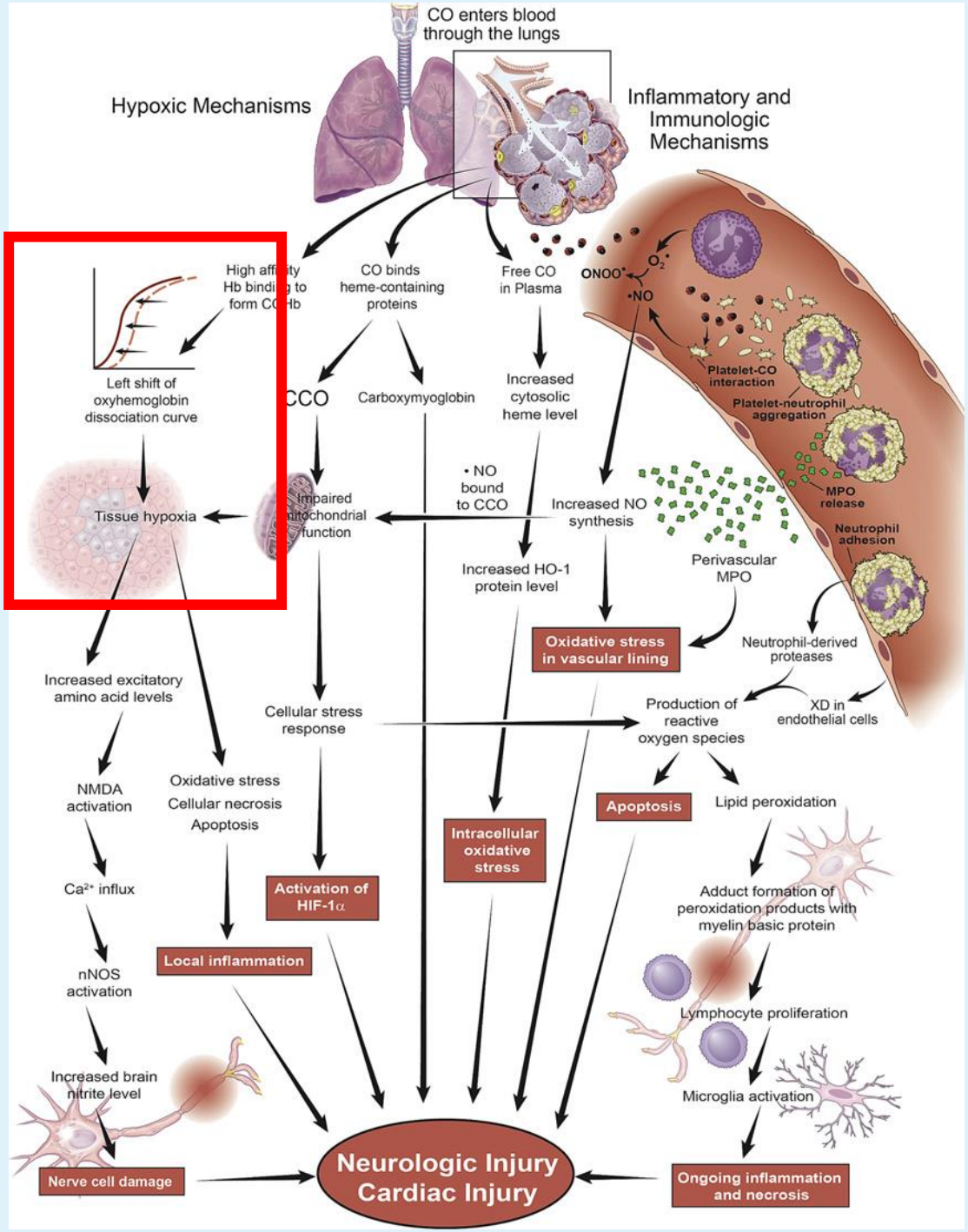


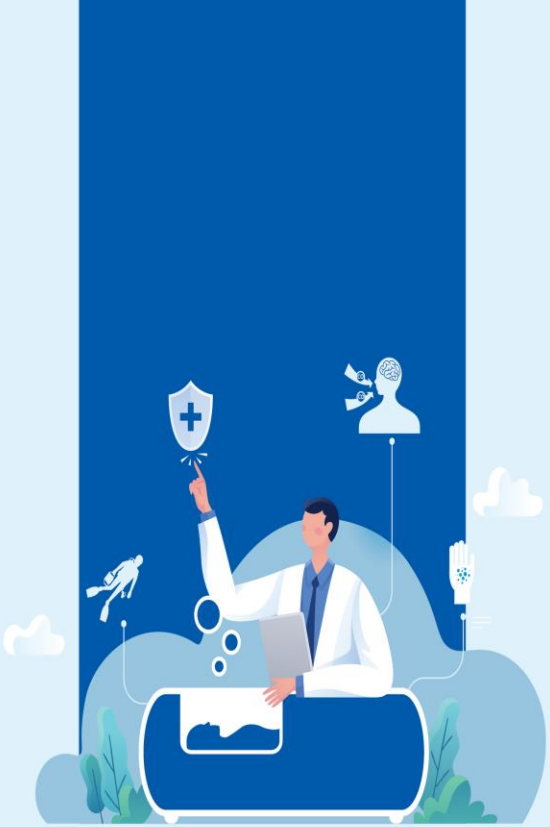


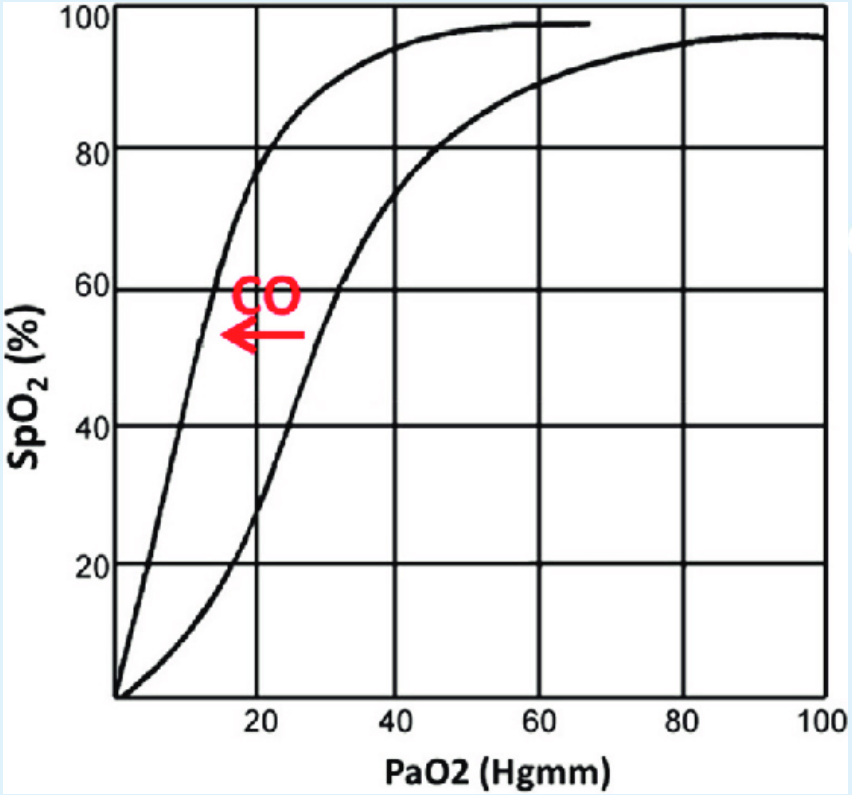
Carbon Monoxide (CO)

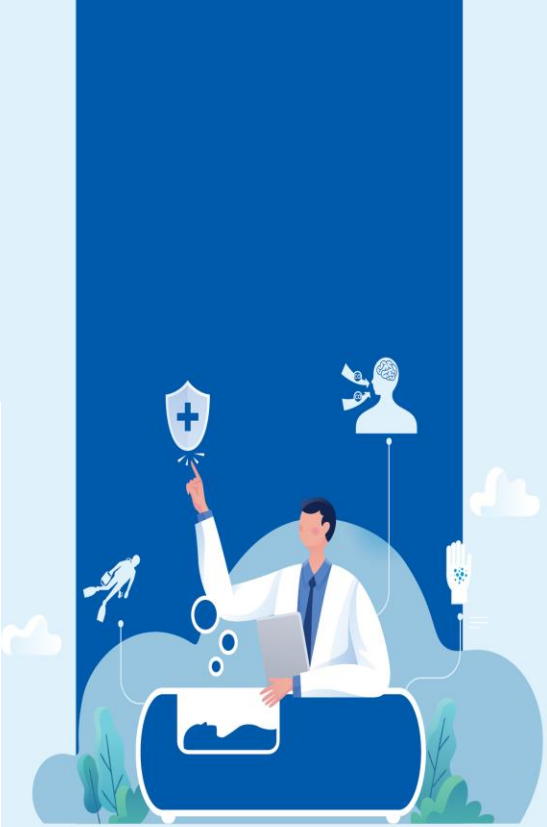


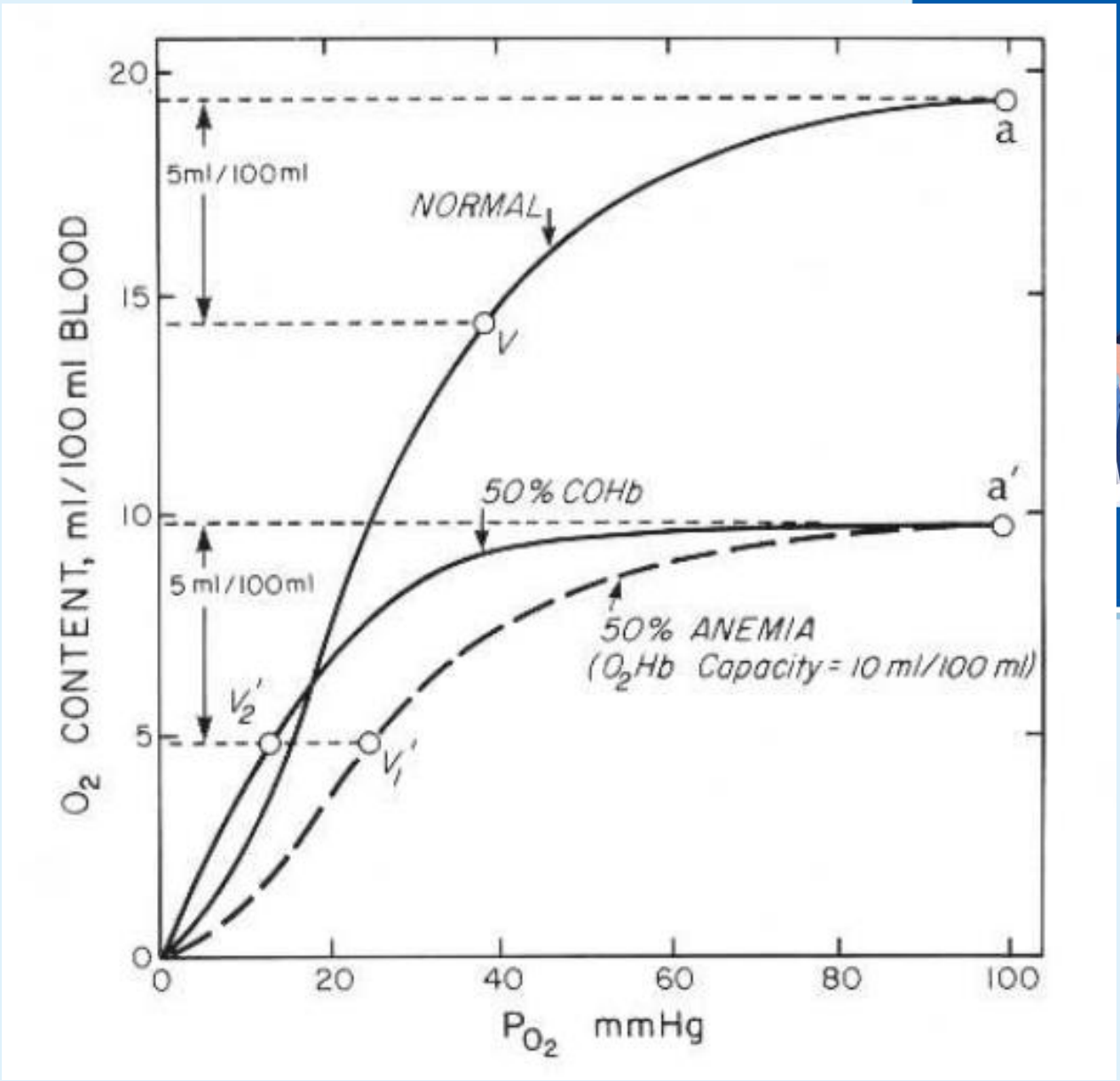
- CO from incomplete combustion
- CO + Hb → COHb (affinity 200-250x)
- **LEFT** shift of oxy-Hb curve (Haldane effect)
- CO binding to intracellular cytochromes and metalloproteins **(myoglobin)**


CO enters blood through the lungs
Hypoxic Mechanisms
Inflammatory and Immunologic Mechanisms
High affinity Hb binding to form COHb
CO binds heme-containing proteins
Free CO in Plasma
ONOO⁻
$O_2^{\bullet}$
•NO
Left shift of oxyhemoglobin dissociation curve
CCO
Carboxymyoglobin
Increased cytosolic heme level
Platelet-CO interaction
Platelet-neutrophil aggregation
MPO release
Neutrophil adhesion
Tissue hypoxia
Impaired mitochondrial function
• NO bound to CCO
Increased NO synthesis
Perivascular MPO
Increased HO-1 protein level
Oxidative stress in vascular lining
Neutrophil-derived proteases
Increased excitatory amino acid levels
Cellular stress response
Production of reactive oxygen species
XD in endothelial cells
NMDA activation
Oxidative stress
Cellular necrosis
Apoptosis
Apoptosis
Lipid peroxidation
Intracellular oxidative stress
Activation of HIF-1α
Ca²⁺ influx
Adduct formation of peroxidation products with myelin basic protein
Local inflammation
nNOS activation
Lymphocyte proliferation
Increased brain nitrite level
Microglia activation
Nerve cell damage
Neurologic Injury
Cardiac Injury
Ongoing inflammation and necrosis

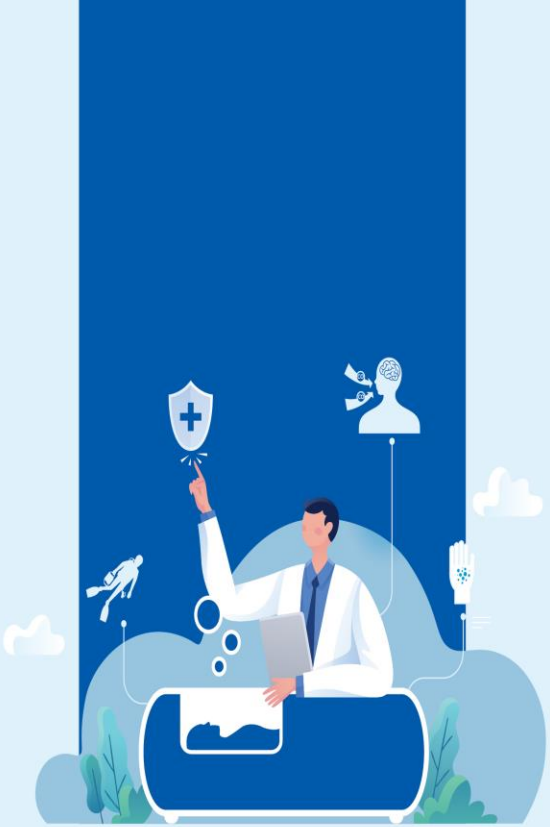



100
80
60
40
20
SpO2 (%)
CO
20
40
60
80
100
PaO2 (Hgmm)



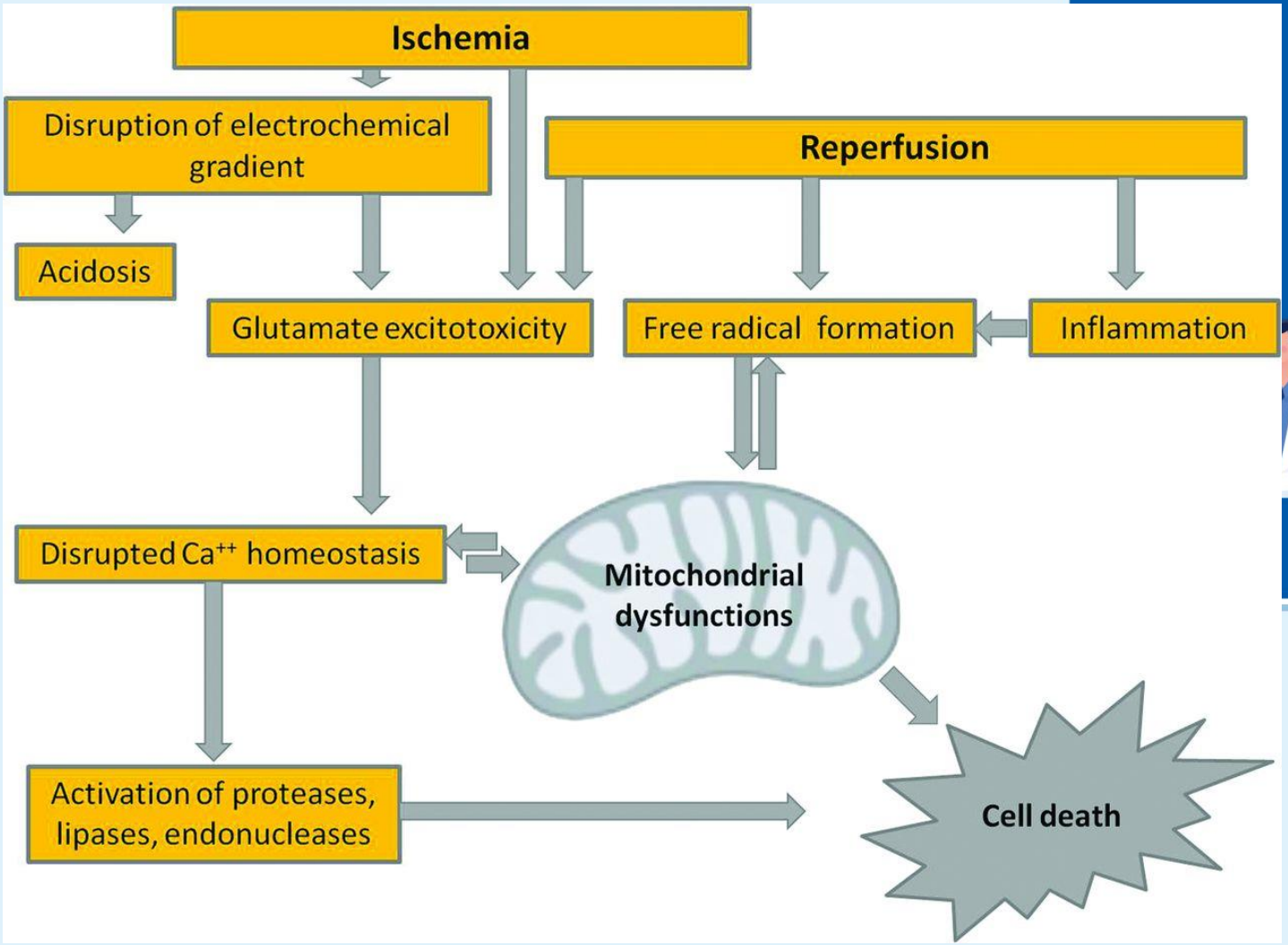

20
15
10
5
0
5ml/100ml
NORMAL
V
a
50% COHb
a'
5 ml/100ml
50% ANEMIA
(O_2Hb Capacity = 10 ml/100 ml)
V_2'
V_1'
0
20
40
60
80
100
O_2 CONTENT, ml/100 ml BLOOD
P_{O_2} mmHg

Mechanisms of CO toxicity



- Hemoglobin
- Myoglobin
- Cytochrome oxidase
- Cytochrome P450-dependent mechanisms
- Veiled others

Hemoglobin (Hb) and mitochondrial effects of CO

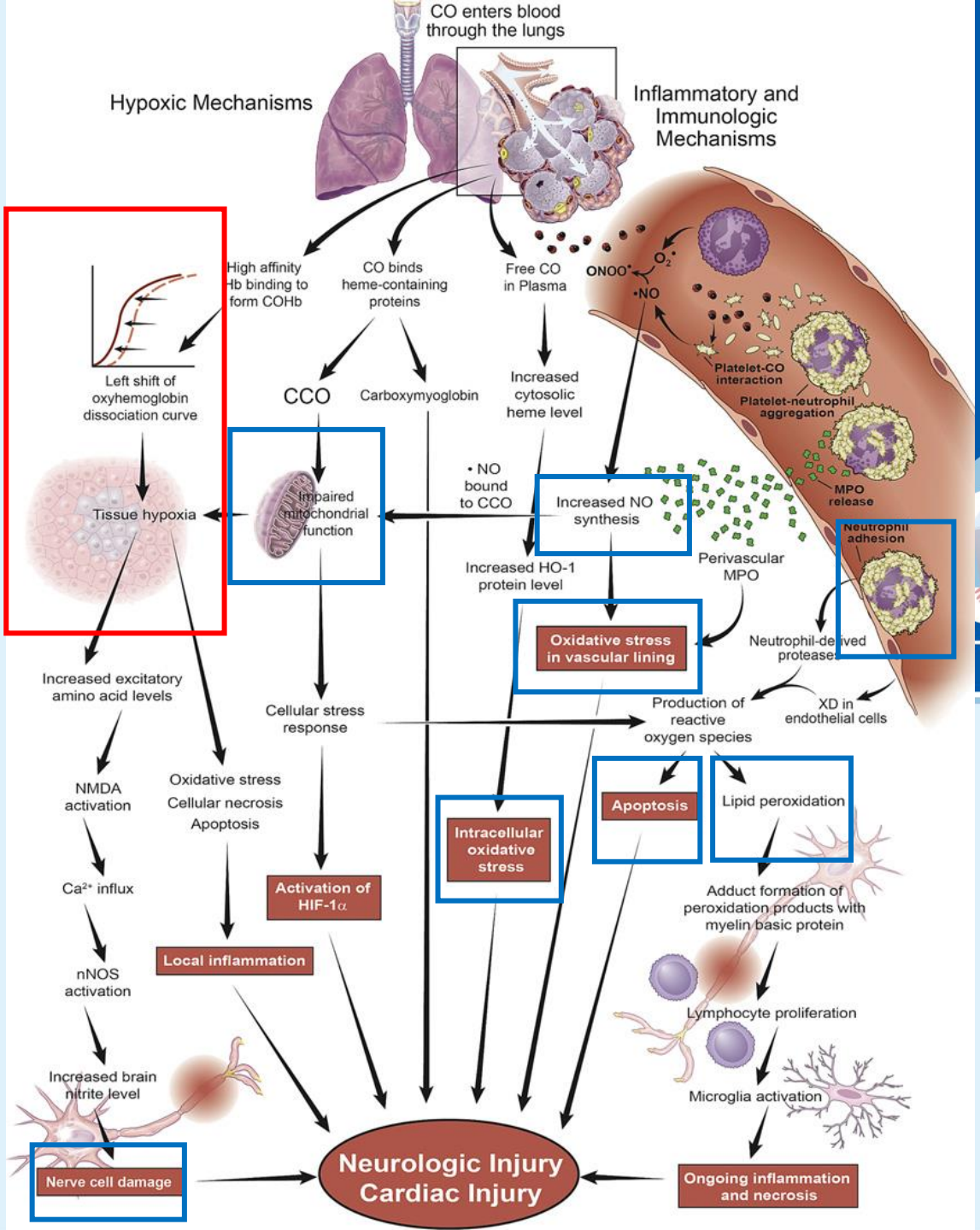

Ischemia
Disruption of electrochemical gradient
Reperfusion
Acidosis
Glutamate excitotoxicity
Free radical formation
Inflammation
Disrupted Ca++ homeostasis
Mitochondrial dysfunctions
Activation of proteases, lipases, endonucleases
Cell death

Pathophysiology of CO toxicity

- HbCO associated with hypoxia

+

- Increased free radical-mediated injury
- ROS mediated neuronal and/or cellular (e.g. erythrocytes) injury
- Apoptosis
- Abnormal inflammatory responses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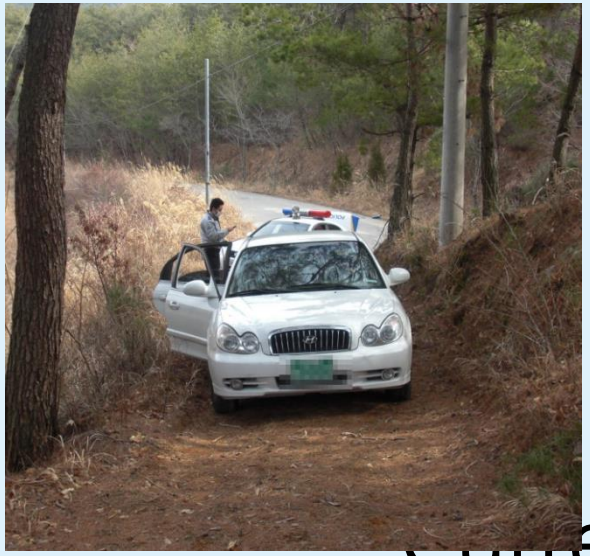
MPO release
Neutrophil adhesion
Tissue hypoxia
Impaired mitochondrial function
• NO bound to CCO
Increased NO synthesis
Perivascular MPO
Increased HO-1 protein level
Oxidative stress in vascular lining
Neutrophil-derived protease
Increased excitatory amino acid levels
Cellular stress response
Production of reactive oxygen species
XD in endothelial cells
NMDA activation
Oxidative stress
Cellular necrosis
Apoptosis
Intracellular oxidative stress
Apoptosis
Lipid peroxidation
Ca²⁺ influx
Activation of HIF-1α
Adduct formation of peroxidation products with myelin basic protein
Local inflammation
nNOS activation
Lymphocyte proliferation
Increased brain nitrite level
Microglia activation
Nerve cell damage
Neurologic Injury
Cardiac Injury
Ongoing inflammation and necrosis

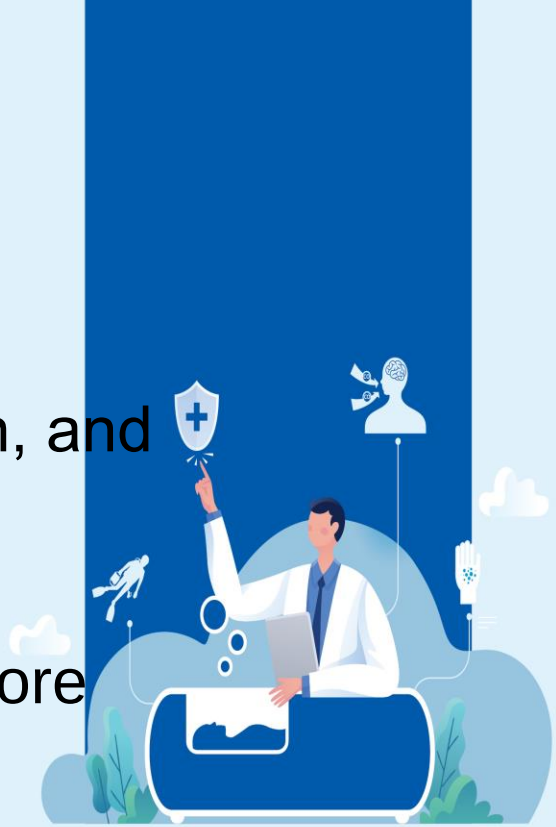
Current Prob



Symptoms and Signs

Dangerous CO Levels

- Depending on level of CO, patient’s health, and length of exposure.
- Above 70 ~ 80 ppm symptoms become more apparent.
- Above 150 to 200 ppm, disorientation, unconsciousness, and death are possible.



Toxic Symptoms

- "Cherry-red lips, cyanosis, retinal hemorrhage – rare
- **CNS** and **Cardiovascular**
  - ↑ RR, ↑HR, dysrhythmias, MI, ↓BP, coma, seizures, cardiomyopathy
- **Delayed neuropsychiatric syndrome** (3-240d)
  - Cognitive / personality changes / Parkinsonism
  - Spontaneous resolution posssible

Signs and Symptoms

- Malaise
- Flu-like symptoms
- Fatigue
- Dyspnea on exertion
- Chest pain
- Palpitations
- Lethargy
- Confusion
- Depression
- Impulsiveness
- Distractibility
- Hallucination
- Confabulation
- Agitation
- Nausea
- Vomiting
- Diarrhea
- Abdominal pain

Signs and Symptoms 2

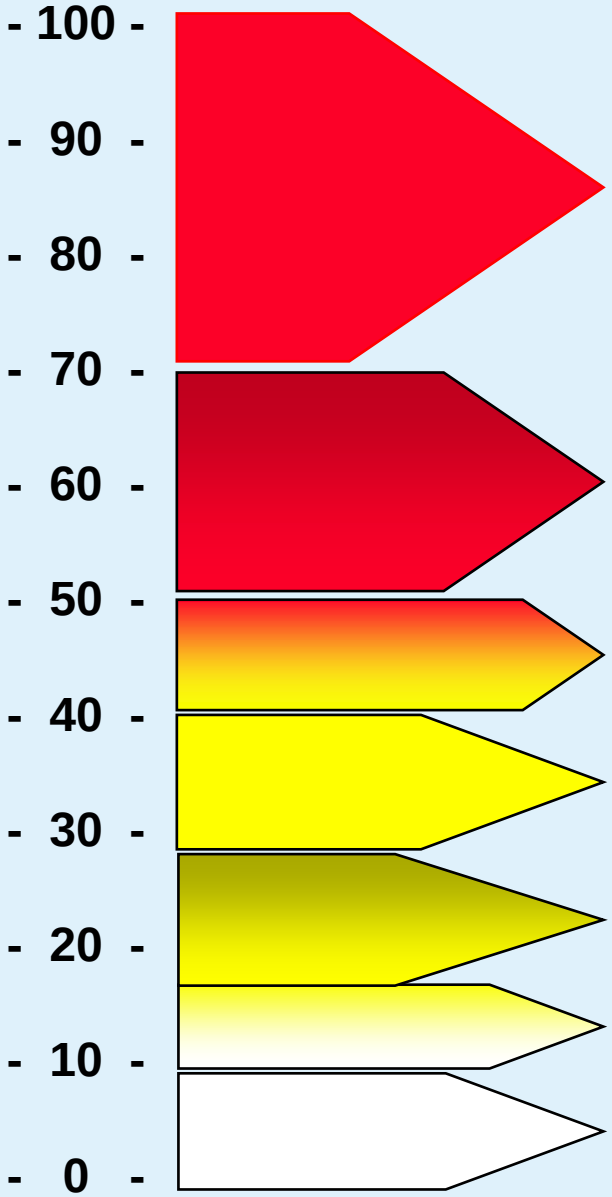
- Headache
- Drowsiness
- Dizziness
- Weakness
- Confusion
- Visual disturbances
- Syncope
- Seizures
- Fecal incontinence
- Urinary incontinence
- Memory disturbances
- Gait disturbances
- Bizarre neurologic sympt oms
- Coma
- Death

- **COHb levels do not always correlate with symptoms nor predict severity and sequelae !**
- **Cherry red skin color is not always present and, when present, is often a late finding !**

Severity by CO level

Severity	CO-Hb Level	Signs & Symptoms
Mild	< 15 - 20%	Headache, nausea, vomiting, dizziness, blurred vision.
Moderate	21 - 40%	Confusion, syncope, chest pain, dyspnea, weakness, tachycardia, tachypnea, rhabdomyolysis.
Severe	41 - 59%	Palpitations, dysrhythmias, hypotension, myocardial ischemia, cardiac arrest, respiratory arrest, pulmonary edema, seizures, coma.
Fatal	> 60%	Death

Signs and Symptoms



Death

Unconsciousness, Respiratory Failure, Death in Long Exposures

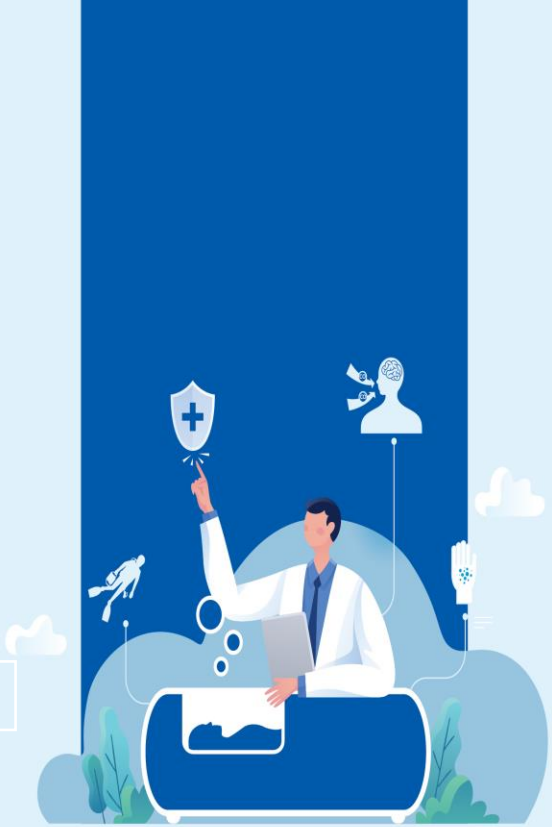
Headache, Disorientation, Fainting, Collapse

Pronounced Headache, Fatigue, Irritability, **Impaired Judgment,** blurred vision

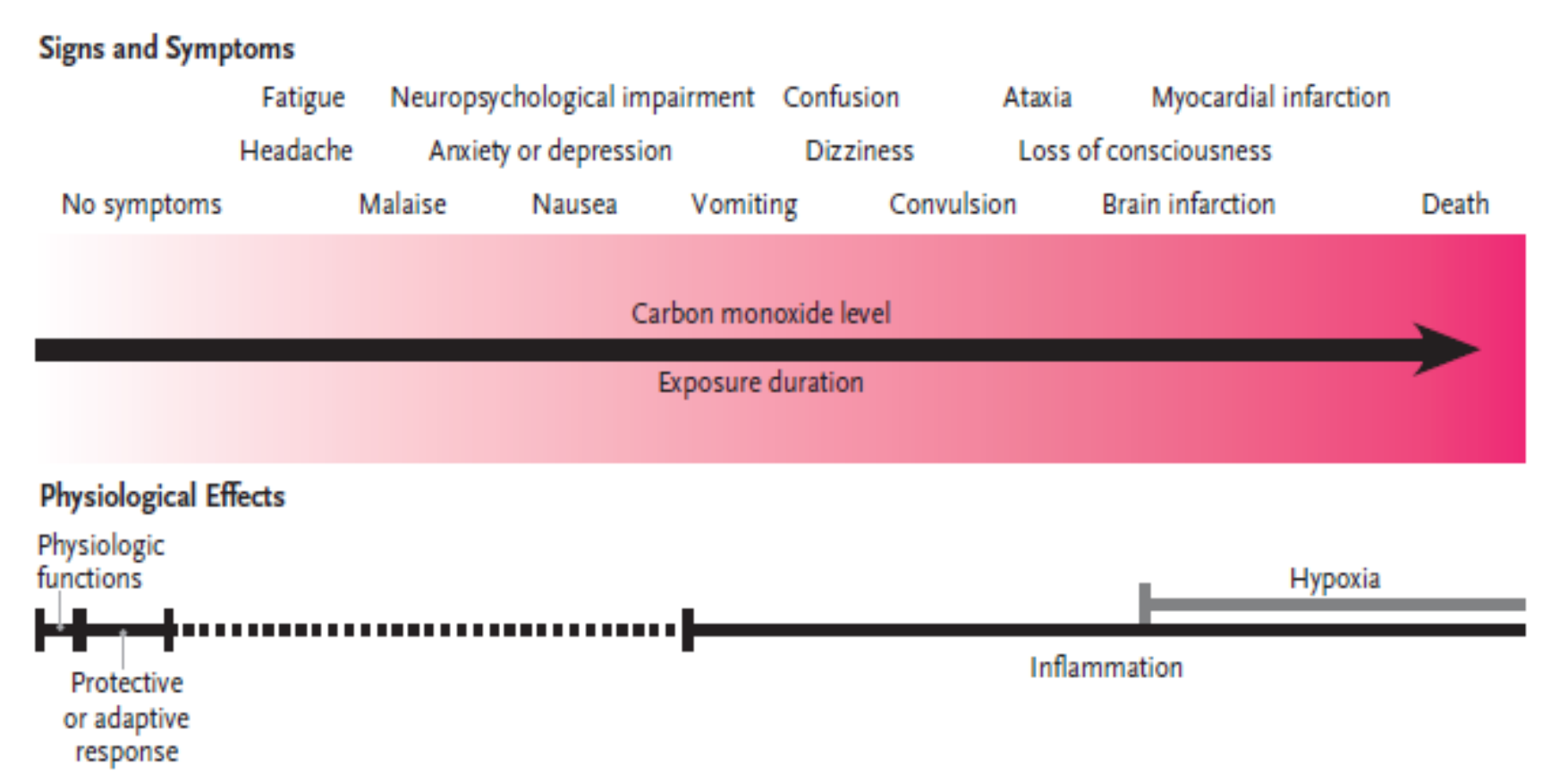
Extreme Shortness of Breath during Moderate Exertion, Minor Headache

No major effect except for Shortness of Breath on Extreme Physical Activity

No effect



Signs and Symptoms



Weaver LK. N Engl J Med 2009;360:1217-25.

CO-Induced Cardiomyopathy

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Myocardial Disease

Carbon Monoxide-Induced Cardiomyopathy

– Epidemiology, Clinical Characteristics and Prognosis –

Yoon-seok Jung, MD; Ji-sook Lee, MD; Young-gi Min, MD; Jin-sun Park, MD; Woo-chan Jeon, MD; Eun-jung Park, MD; Joon-han Shin, MD; Sungho Oh, PhD; Sang-Cheon Choi, MD

Background: Previous reports demonstrated mechanisms of cardiac toxicity in acute carbon monoxide (CO) poisoning. Still, none established CO-induced cardiomyopathy (CMP) as a clinical entity. The aim of this study is to investigate CO-induced CMP in patients with acute CO poisoning in terms of its epidemiology, clinical characteristics, and prognosis.

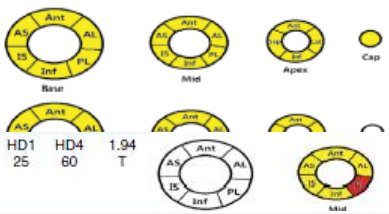
Methods and Results: A retrospective study was conducted on consecutive patients who were diagnosed with acute CO poisoning at the emergency department of Ajou University Hospital during the period of 62 month. Six hundred and twenty-six patients were diagnosed with acute CO poisoning. During the initial echocardiography, 19 patients were abnormal: (1) global hypokinesia/akinesia (n=7), (2) regional wall hypokinesia/akinesia [n=12; takotsubo type (n=6), reverse takotsubo type (n=2), non-specific type (n=4)]. The ejection fraction (EF) was 36.3±13.5% (from 15% to 55%) and less than 45% for 14 patients. In the follow-up echocardiography performed within 12 days after the initial performance, most patients were found to have cardiac wall motion abnormalities, and their EF had returned to normal (ie, EF ≥50%).

Conclusions: CO-induced CMP was identified in 3.04% (n=19) of all patients (n=626). It might not be too critical in acute clinical courses of acute CO poisoning because the prognosis seems favorable. Considering the common factors between CO-induced CMP and takotsubo CMP, myocardial stunning subject to a catecholamine surge most likely plays a central role in the development of CO-induced CMP. (*Circ J* 2014; **78:** 1437–1444)

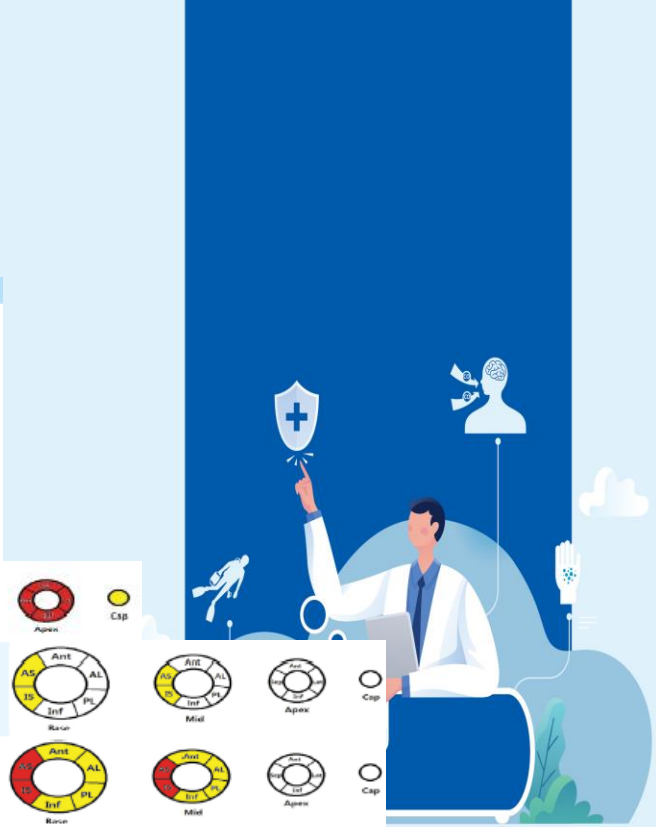
Key Words: Carbon monoxide (poisoning); Cardiomyopathy; Catecholamine; Myocardial stunning; Prognosis

Table. Clinical Characteristics and Echocardiography Results in Patients With CO-Induced Cardiomyopathy

Wall Motion Abnormality

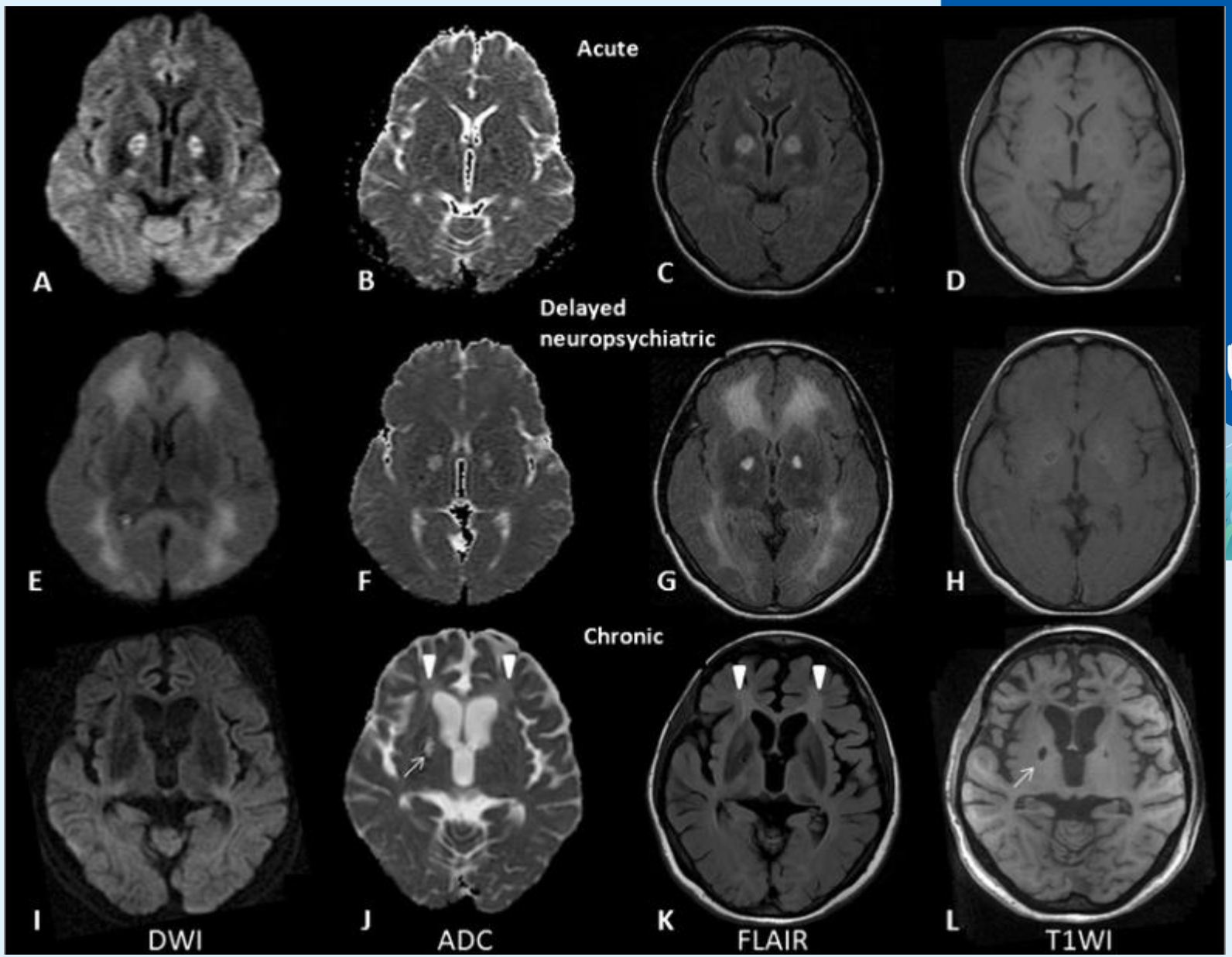


	Age (years)	Gender	EKG Changes	Enzyme Elevation Tro I or T / CK-MB (S-100b)	LVEF (%) Initial	LVEF (%) F/U	WMSI Type
1	44	M	Bifascicular B	0.09/ >500 (1.720)	HD2 44		2 G
2	31	M	ST Change QTc ↑	0.16/8.2 (0.18)	HD1 20	HD12 60	2 G
3	34	M	ST Change QTc ↑	0.44/10.2	HD1 25	HD4 60	1.94 T
8	18	F	ST Change QTc ↑	0.25/14.2 (0.352)	HD1 53		1.25 RT
9	26	F	ST Change QTc ↑	30.04/169.0 (0.86)	HD2 25		2 RT
10	37	F	ST Change QTc ↑	0.09/58.5	HD1 40		1.81 NS
11	33	F	ST Change	0.12/247.9 (0.09)	HD1 45		1.44 NS
12	75	F	ST Change QTc ↑	0.32/25.2 (0.06)	HD1 55	HD4 64	1.12 NS
14	42	M	ST Change QTc ↑	0.39/40.8	HD2 55		1.12 NS
15	22	M	ST Change QTc ↑				
16	83	F	ST Change QTc ↑				
17	69	M	QTc ↑				
18	43	F	NSR QTc ↑				
19	79	M	QTc ↑				



Type of brain injury

- Acute / Persistent
  - Ischemia /reperfusion injury
  - Posterior Reversible Encephalopathy Syndrome (PRES)
- Delayed
  - Delayed neurological sequelae (DNS)
  - PSH
- Chronic


Acute
Delayed
neuropsychiatric
Chronic
A
B
C
D
E
F
G
H
I
J
K
L
DWI
ADC
FLAIR
T1WI

Delayed Neurologic Sequelae

- Memory loss
- Confusion
- Ataxia
- Seizures
- Urinary incontinence
- Fecal incontinence
- Emotional lability
- Disorientation
- Hallucinations
- Parkinsonism
- Mutism
- Cortical blindness
- Psychosis
- Gait disturbances
- Other motor disturbances

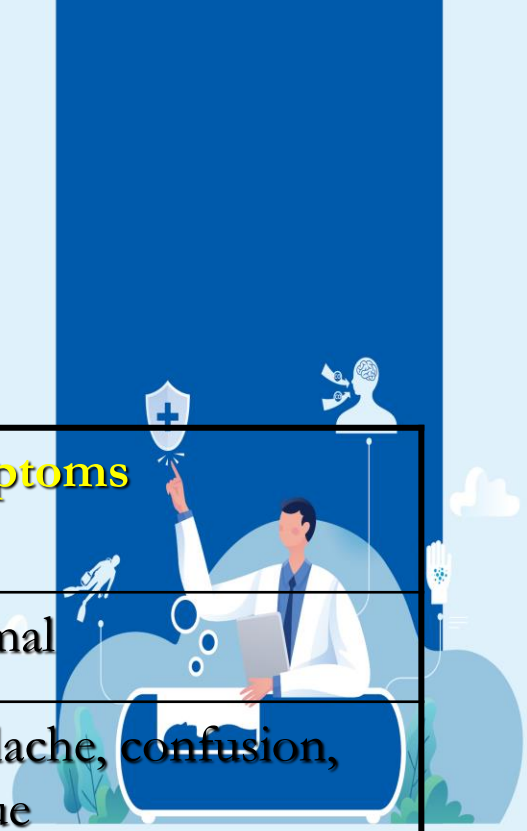
주의사항
Dns.wmv

DNS AND PSH

Diagnosis

- Pulse oximetry false HIGH SpO_2
- Need <u>cooximetry</u> direct measurement of COHb
  - Older ABG analyzers (estimate off dissolved PO_2)
- MRI – lesions in globus pallidus/basal ganglia/deep white matter

COHb%	Symptoms
0-5	Normal
15-20	Headache, confusion, fatigue
20-40	Hallucination, vision Δ's
40-60	Combative, coma
60 +	Cardiopulmonary arrest



Treatment

Treatment

- 100% oxygen
  - Reducing half-life CO-Hb 4~6hr to 60~ 90 minutes
- Assess for pregnancy
- Note that pulse oximetry is inadequate
  - Oxygen saturation may appear artificially high
- Assess for end organ damage
  - VS, ECG, symptomatology, neurological examination

Treatment

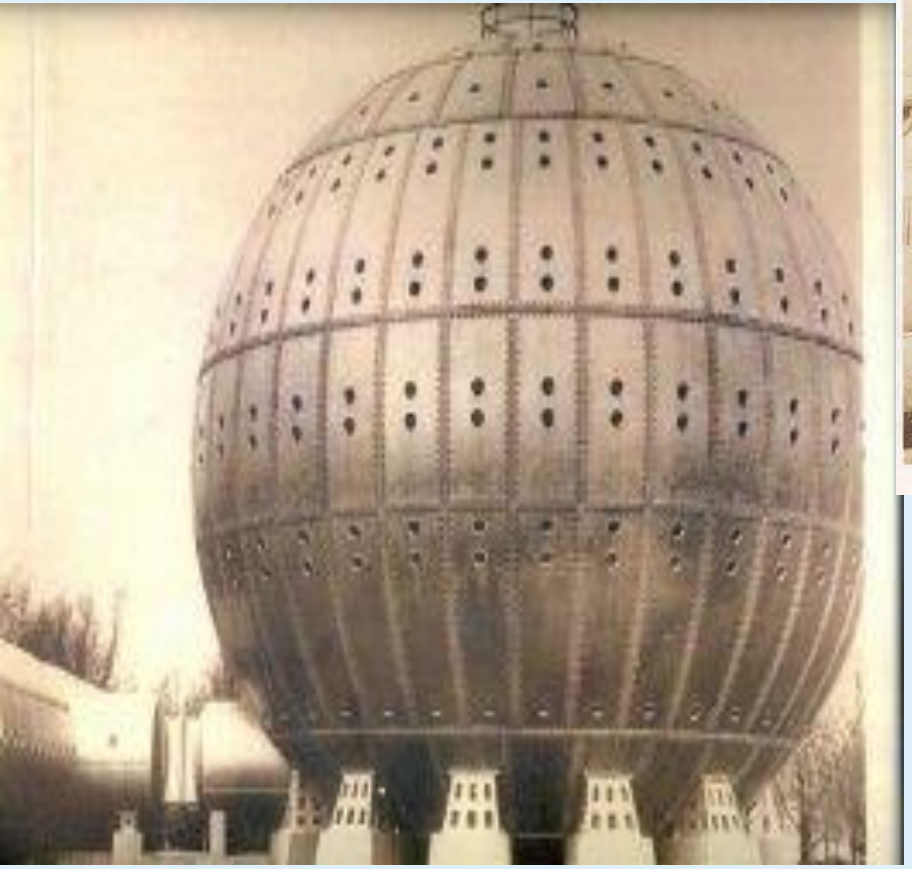
- **OXYGEN**
  - Half-life COHb (min)

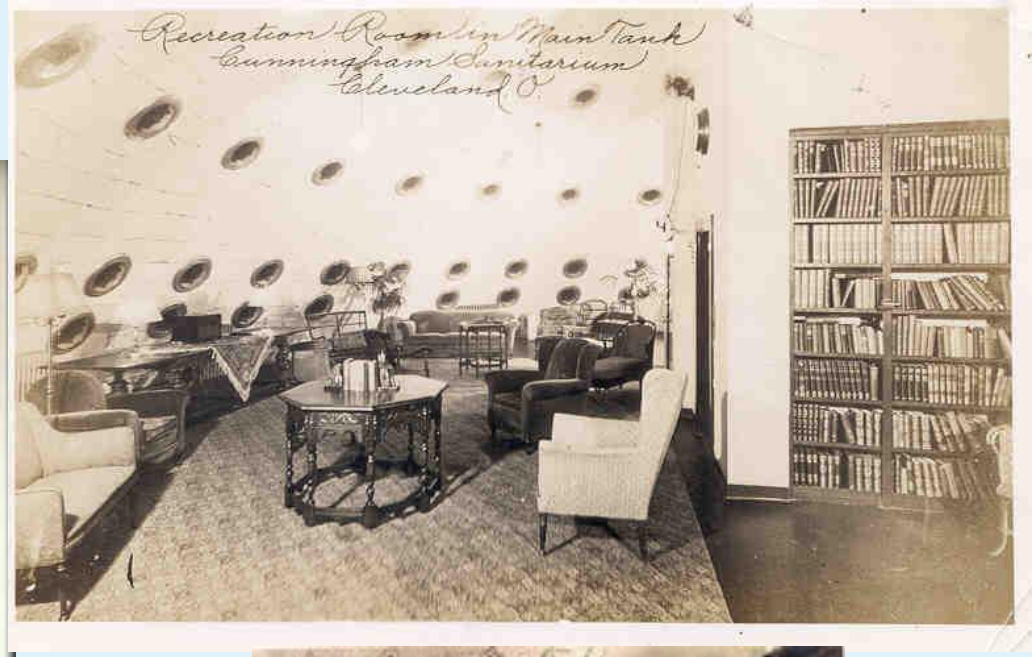
	RA 1ATM	100% O_2	100% O_2 2.5 ATM
Male	240	47	22

  - Hyperbaric Oxygen Therapy (HBOT)

- Carbogen – normobaric, normocapnic, hyperventilation (4.5-4.8% CO_2)

The Steel Ball

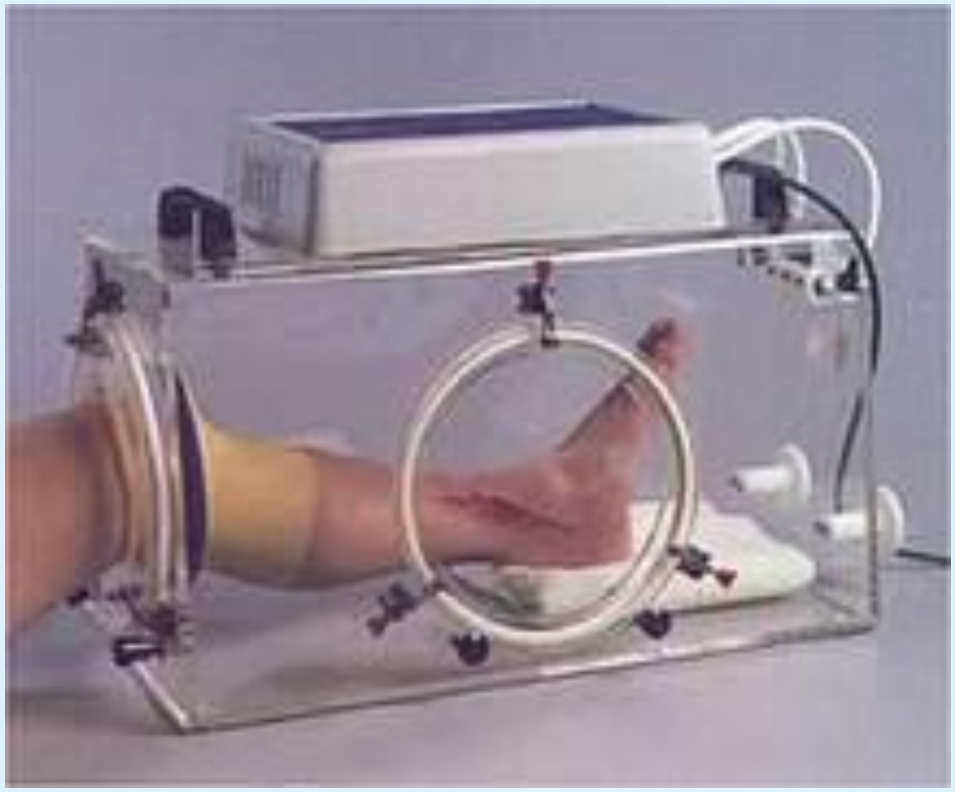




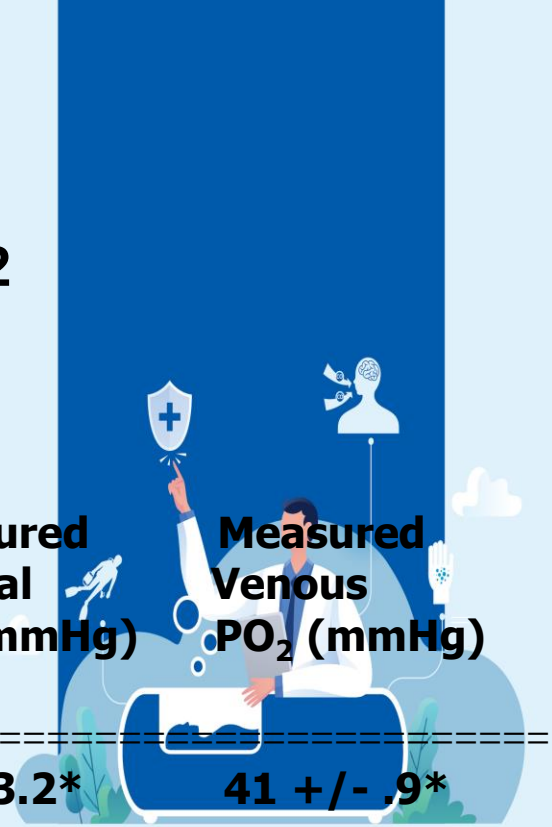
ibex
MEDICAL SYSTEMS

Multiplace Chambers

Not Hyperbaric Therapy!!!



Relationship Between Respiratory Gas and Blood PO_2

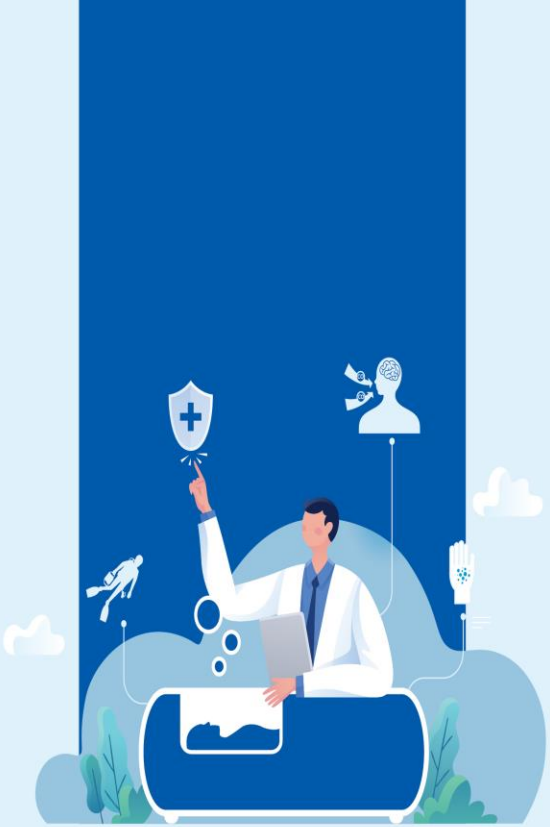


Atmospheric Pressure (ATA)	Breathing Gas	FiO_2 (mmHg)	Theoretical Alveolar & Arterial PO_2 (mmHg)	Measured Arterial PO_2 (mmHg)	Measured Venous PO_2 (mmHg)
1.0	Air	160	110	89 +/- 3.2*	41 +/- .9*
1.0	100% O2	760	673	507 +/- 13.9	57 +/- 3.5
3.0	100% O2	2280	2193	1721 +/- 33.5	424 +/- 77.8

Mean blood levels measured in 10 normal subjects (modified from Saltzman, Smith et al, 1965)

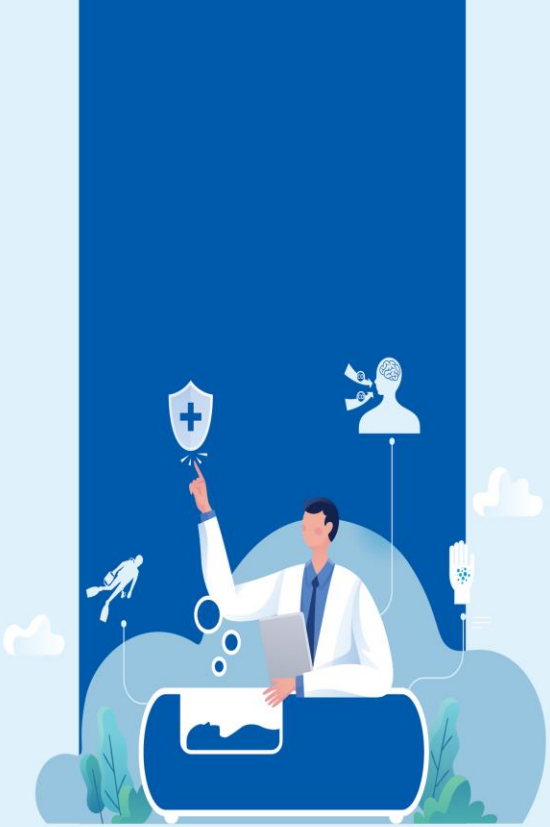
Mode of Action

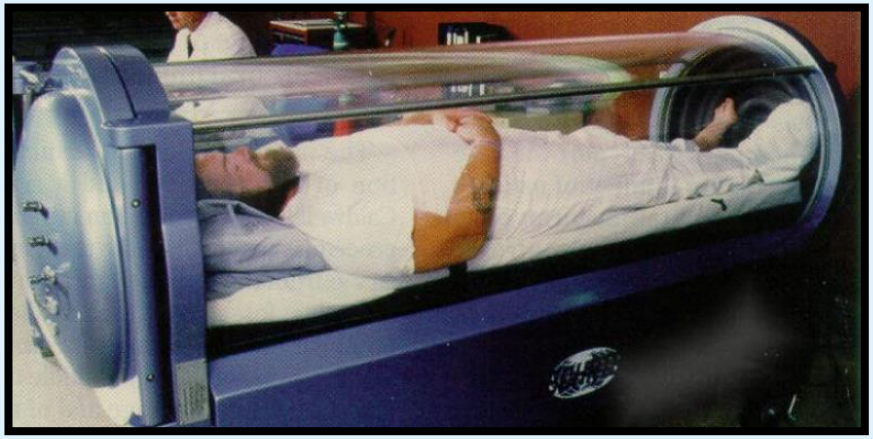
- Decreasing COHb half life
- Displacing CO from tissues
- Improving oxygen carrying capacity
- Limiting lipid peroxidation
- Improving dissolved oxygen

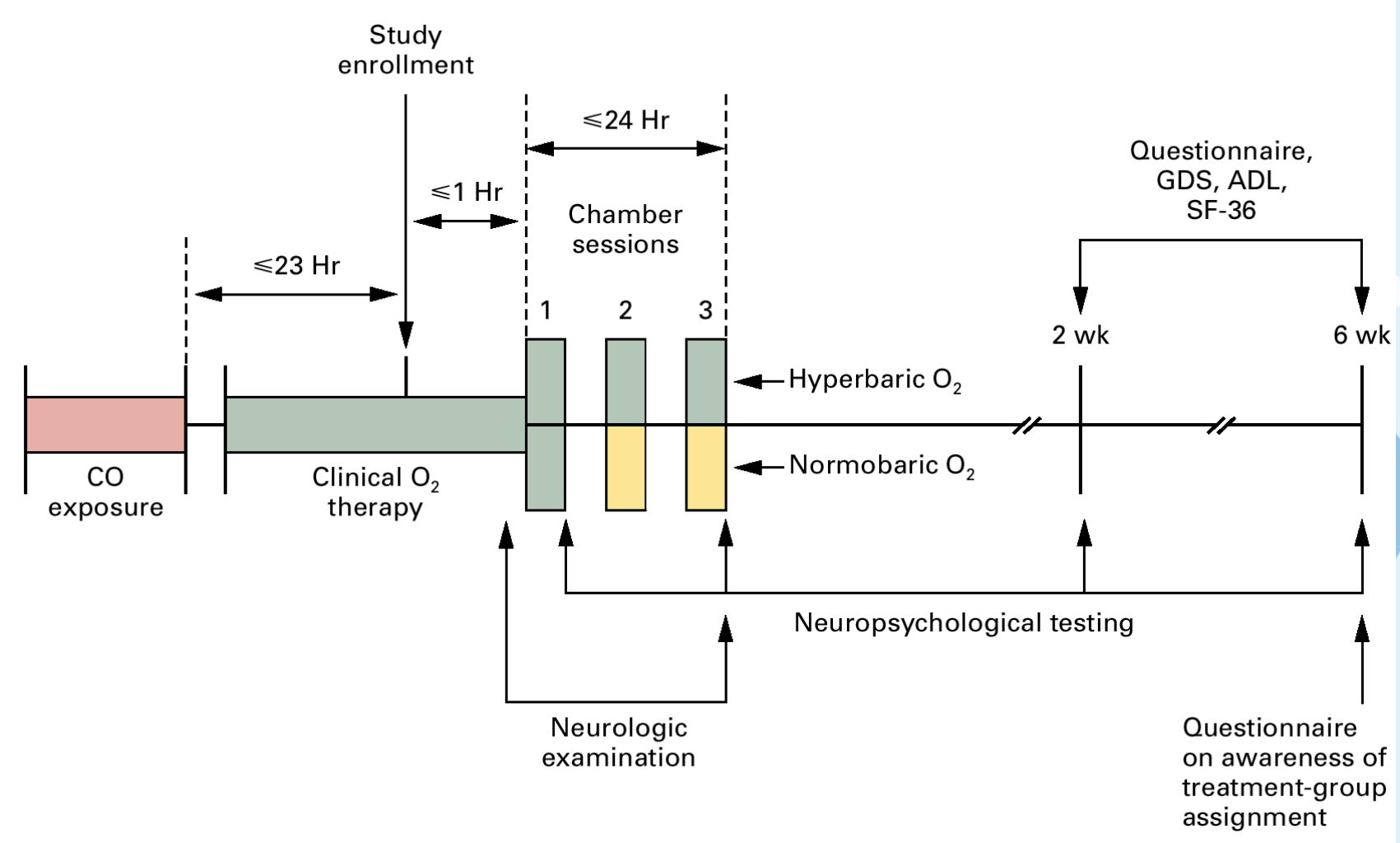


Indications

- Neurological damage
- Cardiovascular events
- Loss of Consciousness
- Persistent symptoms
- COHb > 25% (some centers use >40%)
- COHb > 15% in pregnant woman
- Ideally within 6 hours of exposure
- S100 & NSE level







Weaver LK, et al: Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 2002; 347:1057-67

CO poisoning, acute

Mechanisms

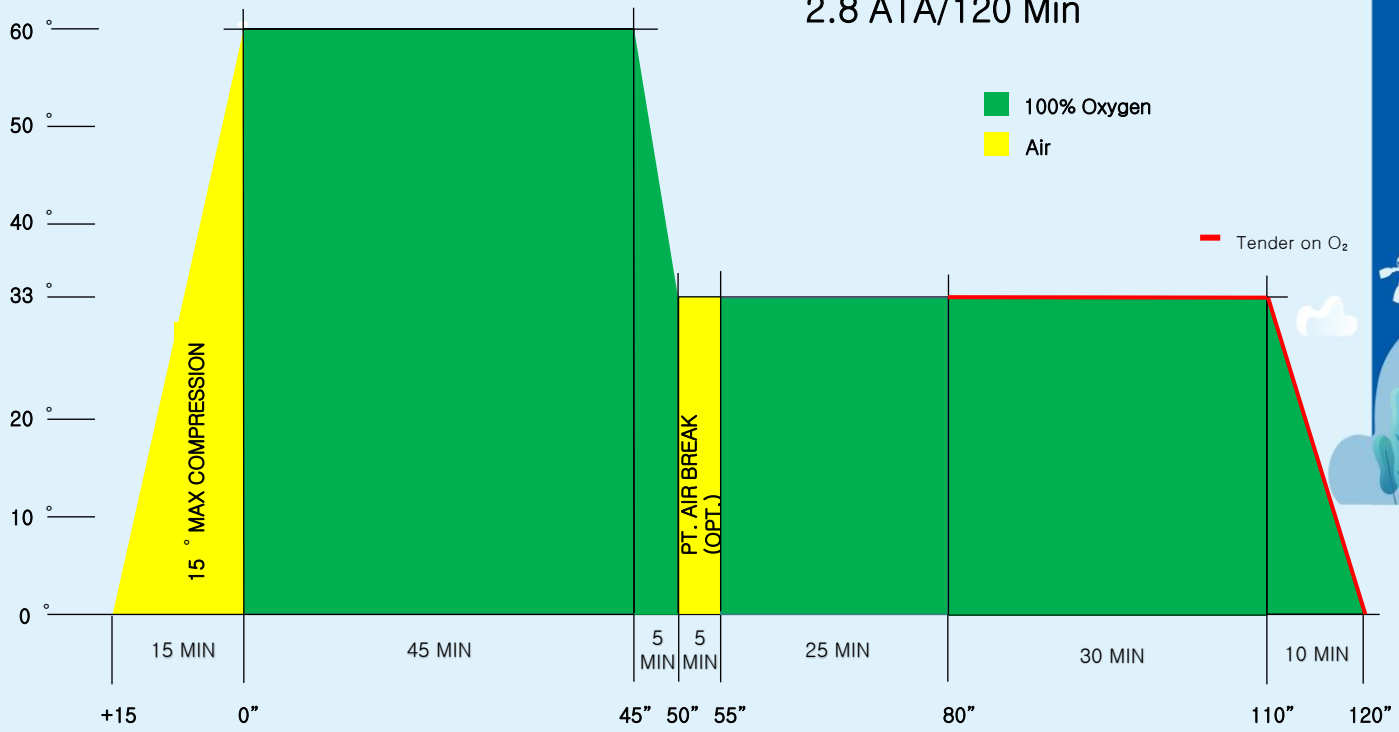
- CO washout
- Treatment of ischemia
- Modulation of ischemia-reperfusion injury and inflammation

Typical Dose

- Up to 3 ATA
- 1~3 sessions

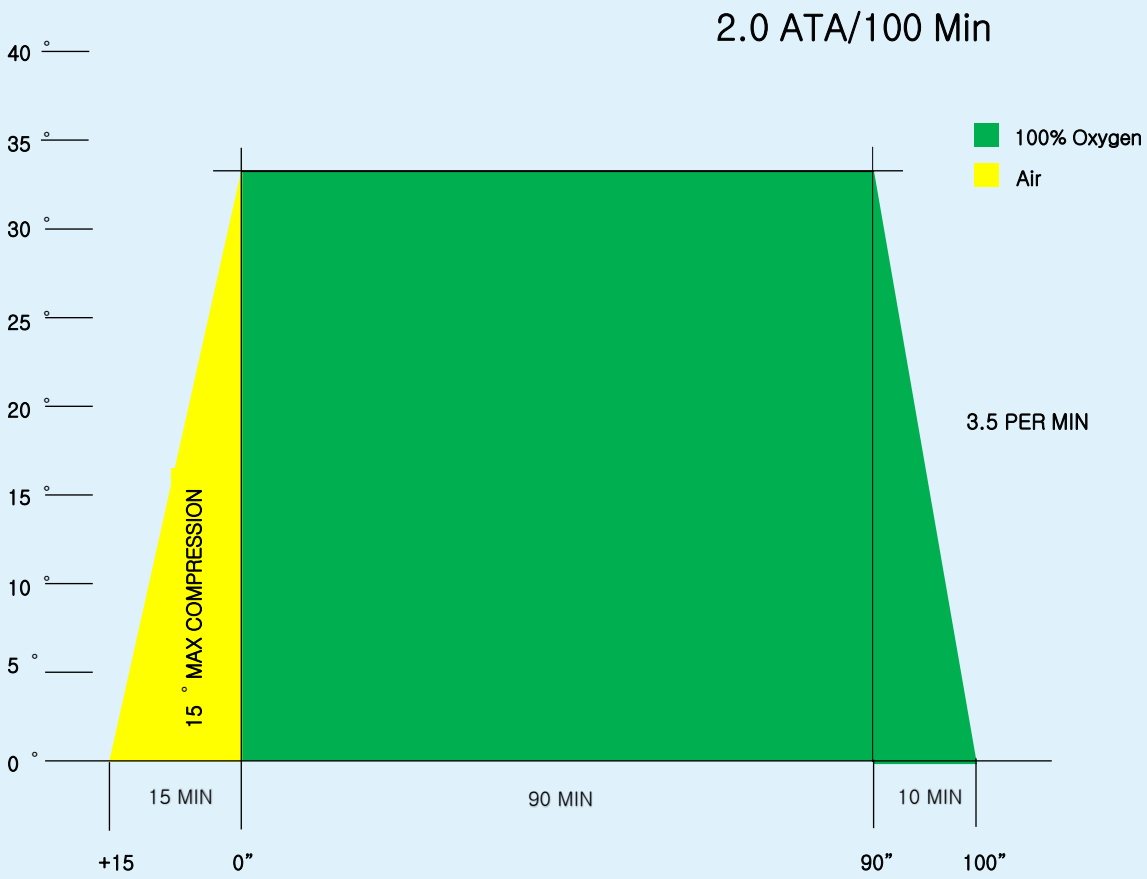
WSCH HBOT treatment protocol #1

2.8 ATA/120 Min



NOTE: 33fsw에서의 air break는 의사의 재량으로 시행유무를 판단할 수 있다.

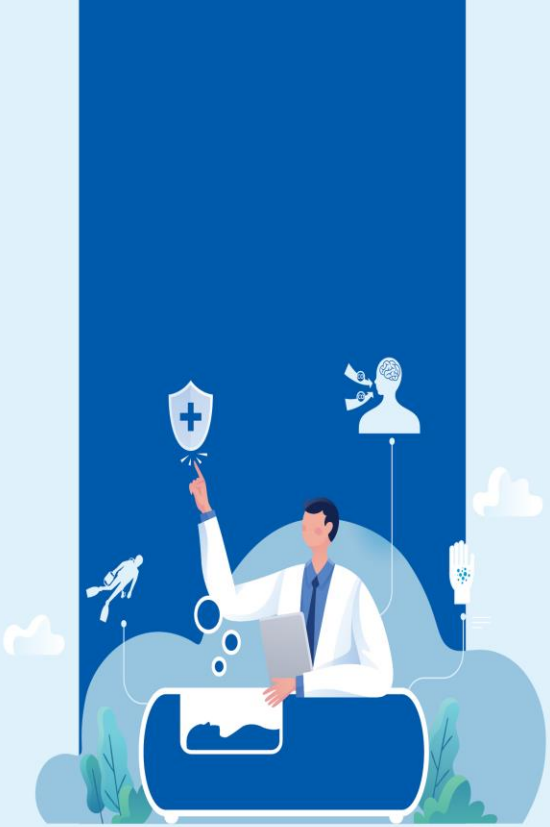
WSCH HBOT treatment protocol #2



적응증

1. 급성일산화탄소중독(1st treatment 이외 모두)

2. Wound 관련
- Problem wound[DM포함]
- Crushing injury
- Compartment syndrome.
- Acute traumatic ischemia
- Necrotizing soft tissue infection
- Chronic refractory osteomyelitis
- Delayed radiation injury
- Compromised grafts/flaps
- Thermal burns



Potential adjunctive therapy

CEEM Clinical and Experimental Emergency Medicine

Clin Exp Emerg Med 2016;3(2):100-104
http://dx.doi.org/10.15441/ceem.15.034

CrossMark

eISSN: 2383-4625

Original Article

Treatment of acute carbon monoxide poisoning with induced hypothermia

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Received: 6 January 2016

> Crit Care Med. 2020 Aug;48(8):e706-e714. doi: 10.1097/CCM.0000000000004419.

Effects of Adjunctive Therapeutic Hypothermia Combined With Hyperbaric Oxygen Therapy in Acute Severe Carbon Monoxide Poisoning

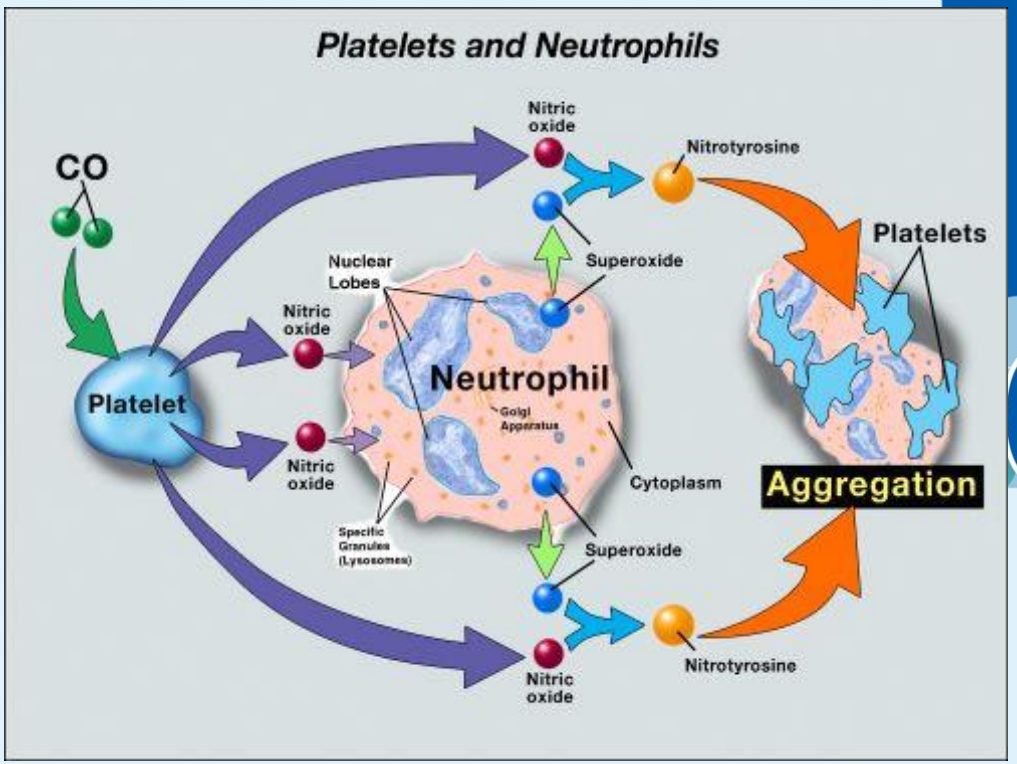
Sun Ju Kim [1], Stephen R Thom [2], Hyun Kim [1 3], Sung Oh Hwang [1], Yoonsuk Lee [1 3], Eung Joo Park [4], Seok Jeong Lee [5], Yong Sung Cha [1 3]

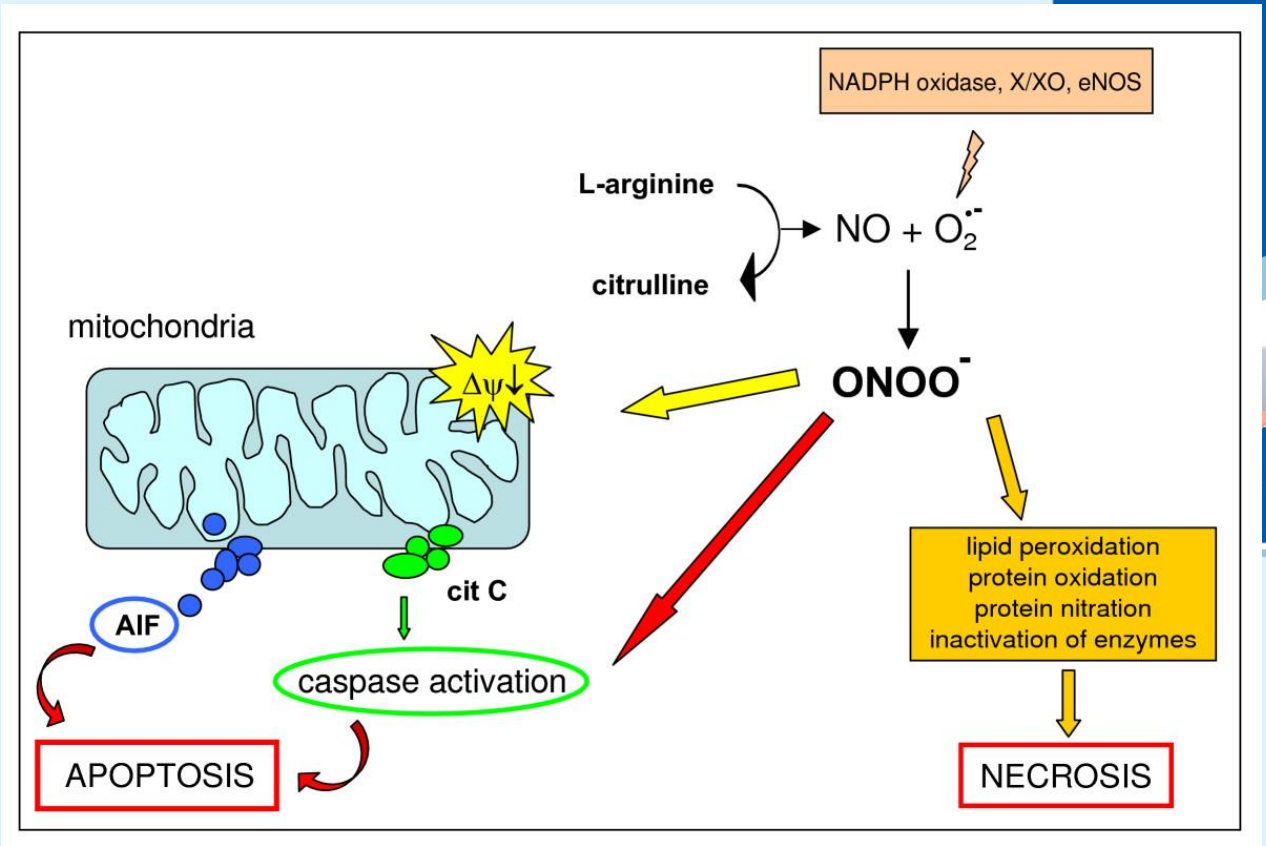
Case no.	Sex/age	MS/GCS at ED	Serum S100B (μ/L)	FU S100B (μ/L, hr)	CO Hb (%)	Lactic acid (mg/dL)	Epinephrine (ng/mL)	Norepinephrine (ng/mL)	Dopamine (ng/mL)	HBOT application	IT duration (hr)
1	F/36	3/4	0.71	0.14 (58)	2.3	1.2	NP	NP	NP	○	32
2	M/29	3/5	0.44	0.10 (23)	16.6	5.2	0.05	0.18	0.02	×	48
3	M/78	3/6	0.49	NP	1.2	1.9	0.18	2.05	0.15	×	36
4	F/31	3/4	0.46	0.10 (37)	12.3	4.2	0.02	0.36	0.02	×	48
5	M/41	3/5	0.84	0.18 (86)	14.5	10.3	0.48	1.24	0.17	×	51
6	M/67	3/7	0.10	0.09 (24)	34	9.0	NP	NP	NP	×	5
7	M/32	3/4	0.47	7.65 (24)	27.9	5.9	0.24	24.54	0.03	×	46
8	M/32	2/8	0.11	0.06 (24)	4.1	1.4	0.05	0.37	0.03	×	48
9	M/48	3/11	0.08	0.04 (23)	33	2.2	NP	NP	NP	×	67
10	M/31	2/14	0.05	0.03 (22)	50.2	4.1	0.04	0.27	0.02	×	24
11	M/30	3/5	0.53	0.10 (23)	46.6	17.8	2.03	2.55	0.48	×	32
12	M/66	3/7	0.11	0.05 (25)	36.8	2.0	0.05	3.2	9.76	×	53
13	M/51	4/3	4.84	6.39 (24)	41.7	13.4	7.02	0.32	0.29	×	48
14	M/54	2/13	0.54	0.37 (24)	2.2	19.5	0.07	0.45	0.152	×	48
15	M/35	3/7	0.72	0.37 (25)	16	7.5	0.42	1.37	0.09	×	59

Effects of Ginaton on nitric oxide and nitric oxide synthase in patients with delayed encephalopathy after carbon monoxide poisoning

- **Objective:** To observe the effects of Ginaton on blood nitric oxide (NO) and nitric oxide synthase (NOS) in patients with delayed encephalopathy after acute carbon monoxide poisoning (DEACMP).
- **Methods:** A total of 116 patients with DEACMP who were treated in Emergency Department of from January 2012 to April 2016 were enrolled and randomly divided into 58 patients in each group. The conventional treatment including hyperbaric oxygen, prevention and treatment of cerebral edema, and promotion of brain cell metabolism vs Ginaton in addition to the conventional treatment. The course of treatment was 2 weeks for both groups. The levels of neuron-specific enolase (NSE) , NO, NOS, and inducible nitric oxide synthase (iNOS) were measured before treatment and at 2 weeks after treatment, and the change in Mini-Mental State Examination (MMSE) score and clinical outcome were observed in both groups. The correlation between the blood NO level on admission and the MMSE score was analyzed.
- **Results:** There was a significant difference in the overall response rate between the treatment group and the control group (81.03% *vs* 62.07%, $\chi(2) = 5.124$, $P=0.024$). Before treatment, there were no significant differences in the levels of NO and NSE, the activity of NOS and iNOS, and MMSE score between the two groups ($P>0.05$). After treatment, both groups showed reductions in the levels of NO and NSE and the activity of NOS and iNOS, but the treatment group had significantly greater reductions compared with the control group ($P<0.05$). Both groups showed a significant increase in the MMSE score after treatment, while the treatment group had a significantly greater increase compared with the control group ($P<0.05$). In the patients with DEACMP, the blood NO level on admission was negatively correlated with the MMSE score ($r=-0.268$, $P=0.004$).
- **Conclusion:** In the treatment of patients with DEACMP, Ginaton can effectively reduce the levels of NO and NSE and the activity of NOS and iNOS, increase the MMSE score, and promote the recovery of neurological function.

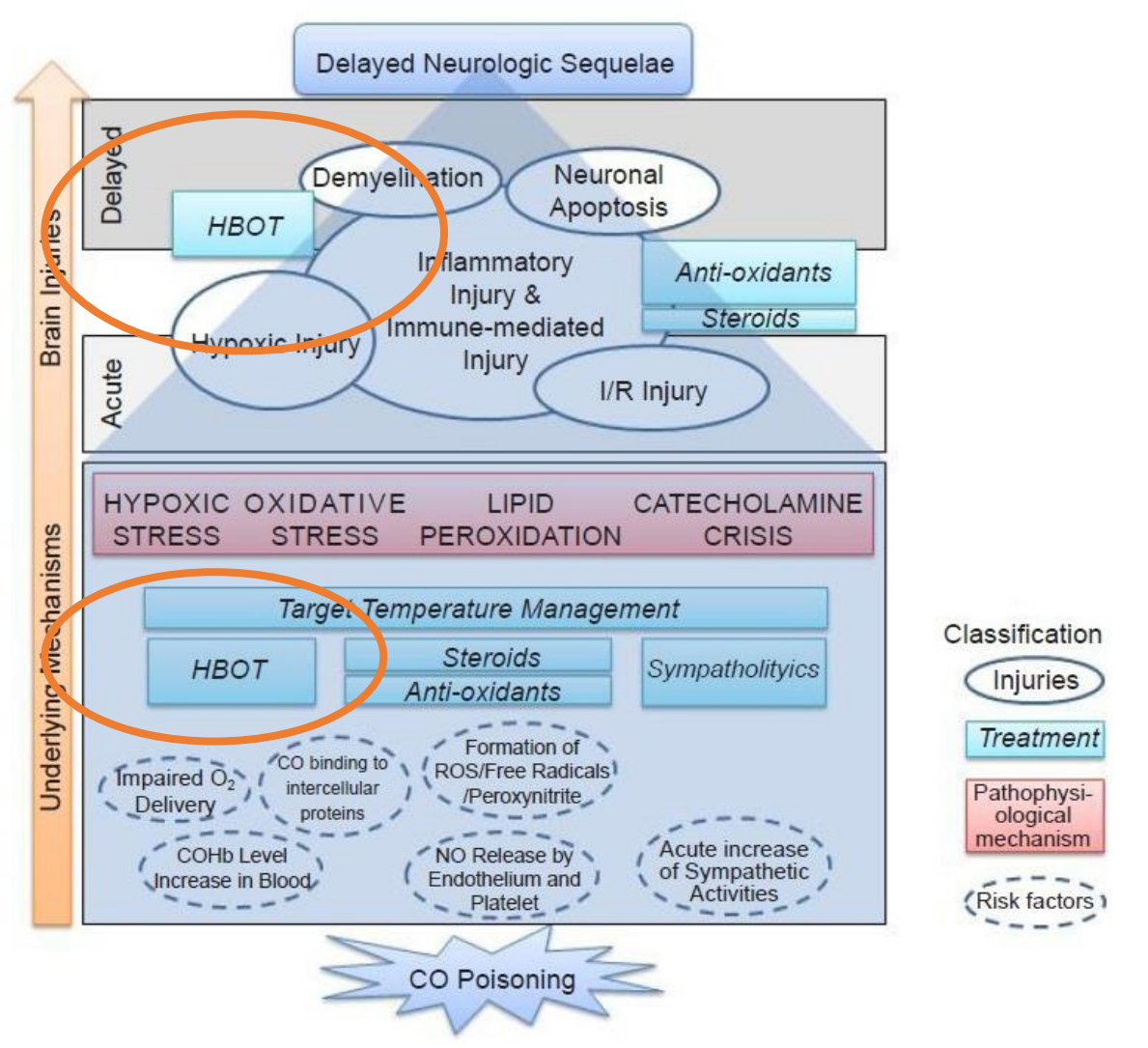
Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 2017 Jan 20;35(1):30-33.


Platelets and Neutrophils
CO
Platelet
Nitric oxide
Nitric oxide
Nitric oxide
Nitric oxide
Nuclear Lobes
Neutrophil
Golgi Apparatus
Cytoplasm
Specific Granules (Lysosomes)
Superoxide
Superoxide
Nitrotyrosine
Nitrotyrosine
Platelets
Aggregation


NADPH oxidase, X/XO, eNOS
L-arginine
citrulline
NO + $O_2^{\bullet -}$
$ONOO^-$
mitochondria
Δψ↓
cit C
AIF
caspase activation
APOPTOSIS
lipid peroxidation
protein oxidation
protein nitration
inactivation of enzymes
NECROSIS

Potential drugs as antioxidants

- *N*-acetylcysteine
- Melatonin
- Atenolol
- Edaravone
- Lactulose
- Hydrogen
- Some others such as hydrogen sulfide (H_2S)
- Other free radical blockers
- DA antagonist



NEURAL REGENERATION RESEARCH
January 2015, Volume 10, Issue 1

Int. J. Mol. Sci. **2018**, *19*(8), 2381; https://doi.org/10.3390/ijms19082381

Open Access Review

Therapeutic Aspects of Carbon Monoxide in Cardiovascular Disease

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Systematic Review and Meta-Analysis

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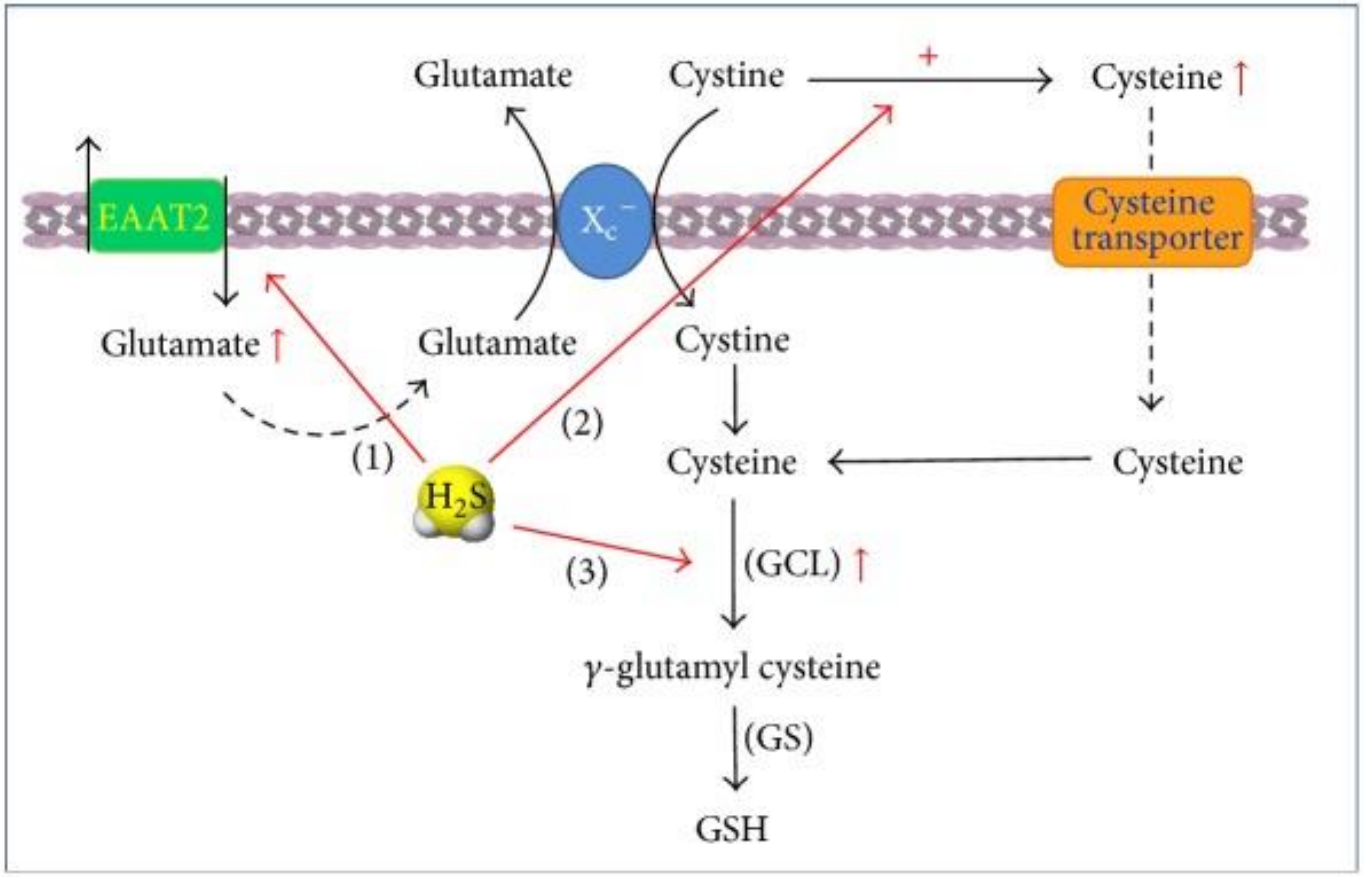
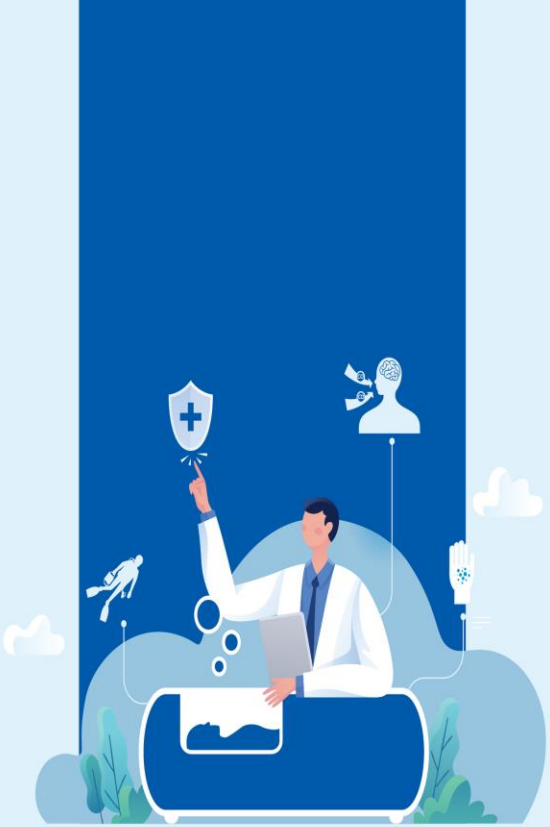
The biologic effect of hydrogen sulfide and its function in various diseases

Qing Xiao, MD, Jiayi Ying, MD, Leihong Xiang, MD, PhD, Chengfeng Zhang, MD, PhD*


Glutamate
Cystine
+
Cysteine ↑
EAAT2
X_c^-
Cysteine transporter
Glutamate ↑
Glutamate
Cystine
(1)
(2)
H_2S
Cysteine
Cysteine
(3)
(GCL) ↑
γ-glutamyl cysteine
(GS)
GSH

4주후



Take Home Message

- CO still common and under diagnosed. EPs should have a high index of suspician for screening for CO.
- There are still veiled pathophysiology regarding acute CO poisoning accordi ng to each organ.
- **HBOT is most important in current treatment options.**
- Effects of CO on hemeproteins and free-radical induction and oxidative stre ss will be probable mechanism. Therefore, bundle treatment should be nee ded !!!
- Future customized tx. should be needed for acute tx. and DNS.

Q and A ?

Korean Academy of
Undersea and Hyperbaric Medicine

Thank you

대한고압의학회
Korean Academy of Undersea and Hyperbaric Medicine