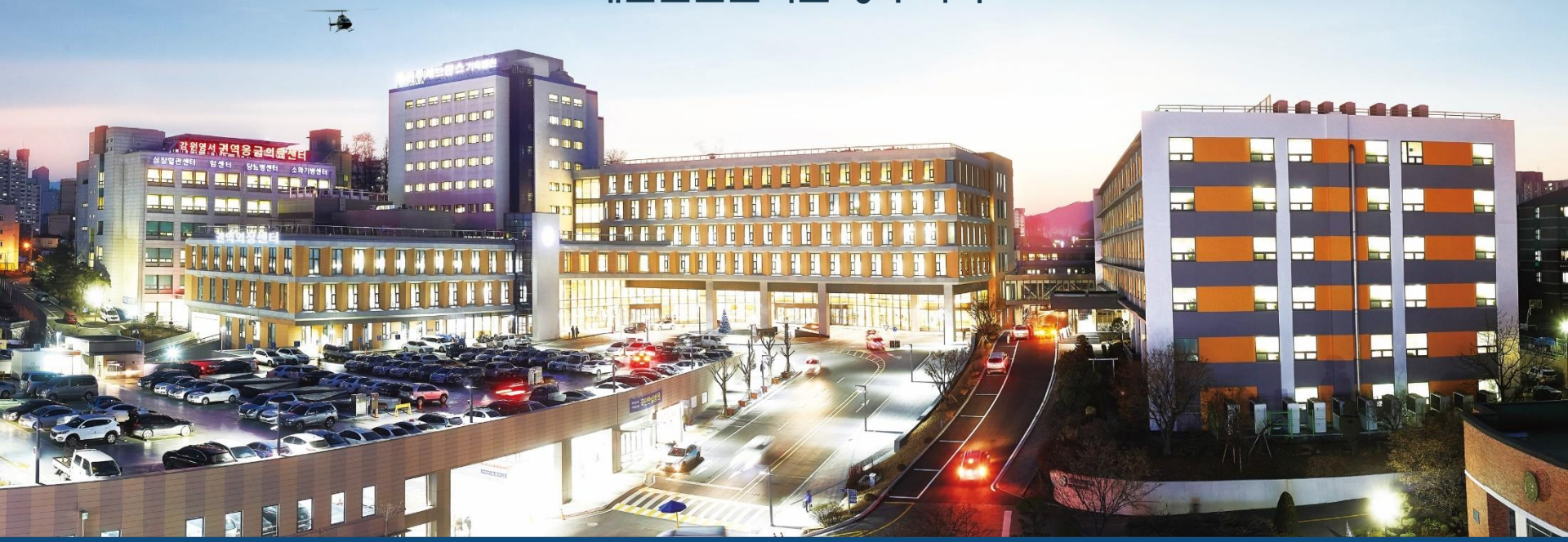
2021.10.21

-제2회 고압의학 전공의 기초교육과정 연수강좌-

Acute carbon monoxide poisoning

연세원주의대 응급의학과 차용성

대한고압의학회 총무이사



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1. 발병률(prevalence)

미국

- 미국에서는 연간 5만명 이상의 환자가 급성일산화탄소(carbon monoxide, CO) 중독으로 응급실을 내원
- 매년 1,500명 정도의 환자가 사망
- 2000년대 중반의 연간 2,700명의 사망률에서 2010년대 중반에는 연간 1,319명정도로 사망률은 감소
- 하지만 매년 15,000명 정도의 intentional poisoning 환자가 발생하고 보고되는 사망환자의 2/3이상을 차지

미국

사고로 인한 CO 중독으로 인한 병원비와 소득손실이 연간 1조 2천억원

한국

2019년 국가응급의료진료정보망 (NEDIS) 데이터

2. 원인과 병태생리

원인

- CO는 무색, 무취, 무미한 가스로 일반적으로 탄소성분의 incomplete combustion에 의해 발생

- 흔한 원인
  - 화재
  - 엔진 배기가스
  - 결함이 있는 화구(faulty furnaces)
  - 번개탄, 연탄 (charcoal)

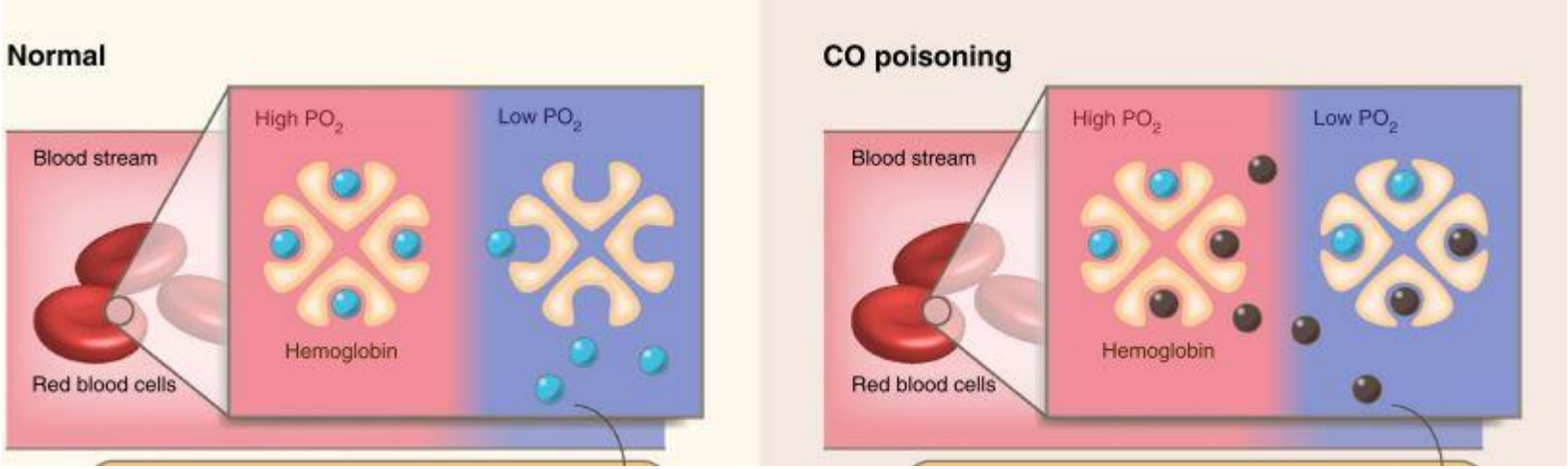
- 10ppm정도의 낮은 CO 노출에도 CO-Hb은 약 2%까지 나올 수 있음

- WHO에서는 6ppm이상의 CO에 장기간 노출 시 독성을 가질 수 있다고 이야기

- CO-Hb 진단기준
  - 비흡연자: 2%이상
  - 흡연자: 10%이상
  - Heavy smoke의 경우 3.0%-7.7%까지 정상적으로 CO-Hb이 나올 수 있음

- The injuries caused by CO
  - A hypoxic stress brought on by an elevated COHb level
  - Left shift of the oxyhemoglobin curve

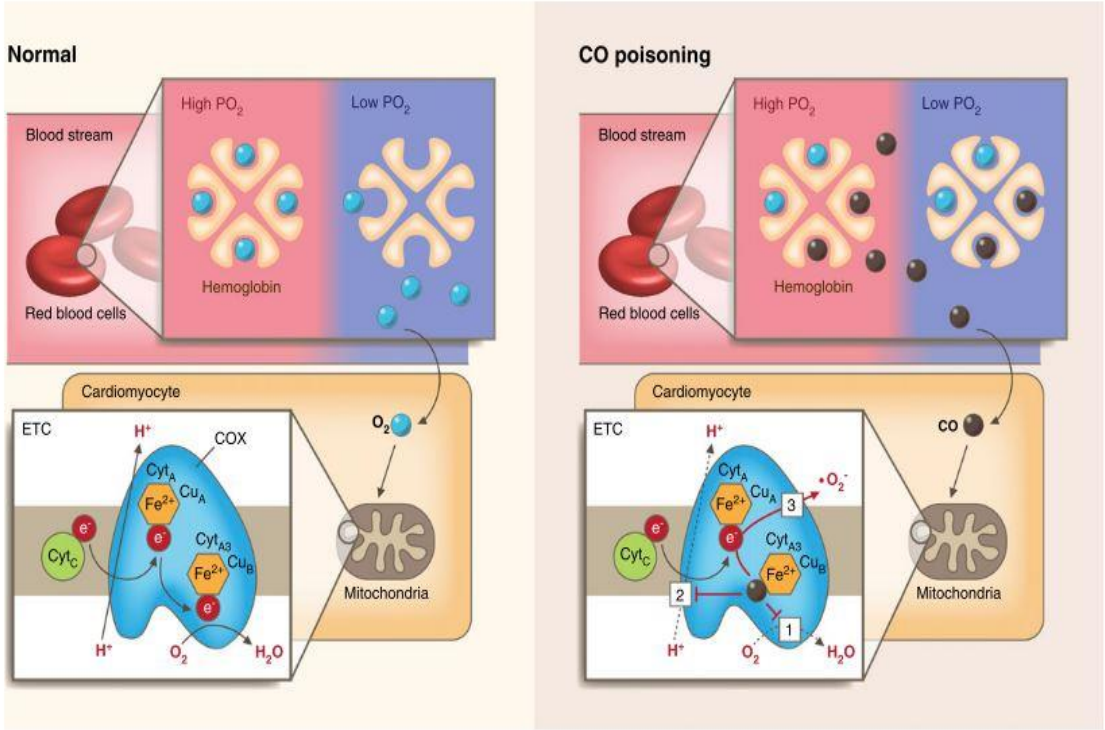
Roughton F, et al. Am J Physi. 1944



Rose JJ, et al. Am J Respir Crit Care Med 2017

Neuropathology is due to a complex cascade of biochemical events
- Several immunological and inflammatory pathophysiologic processes
- Many independent of pure hypoxic stress

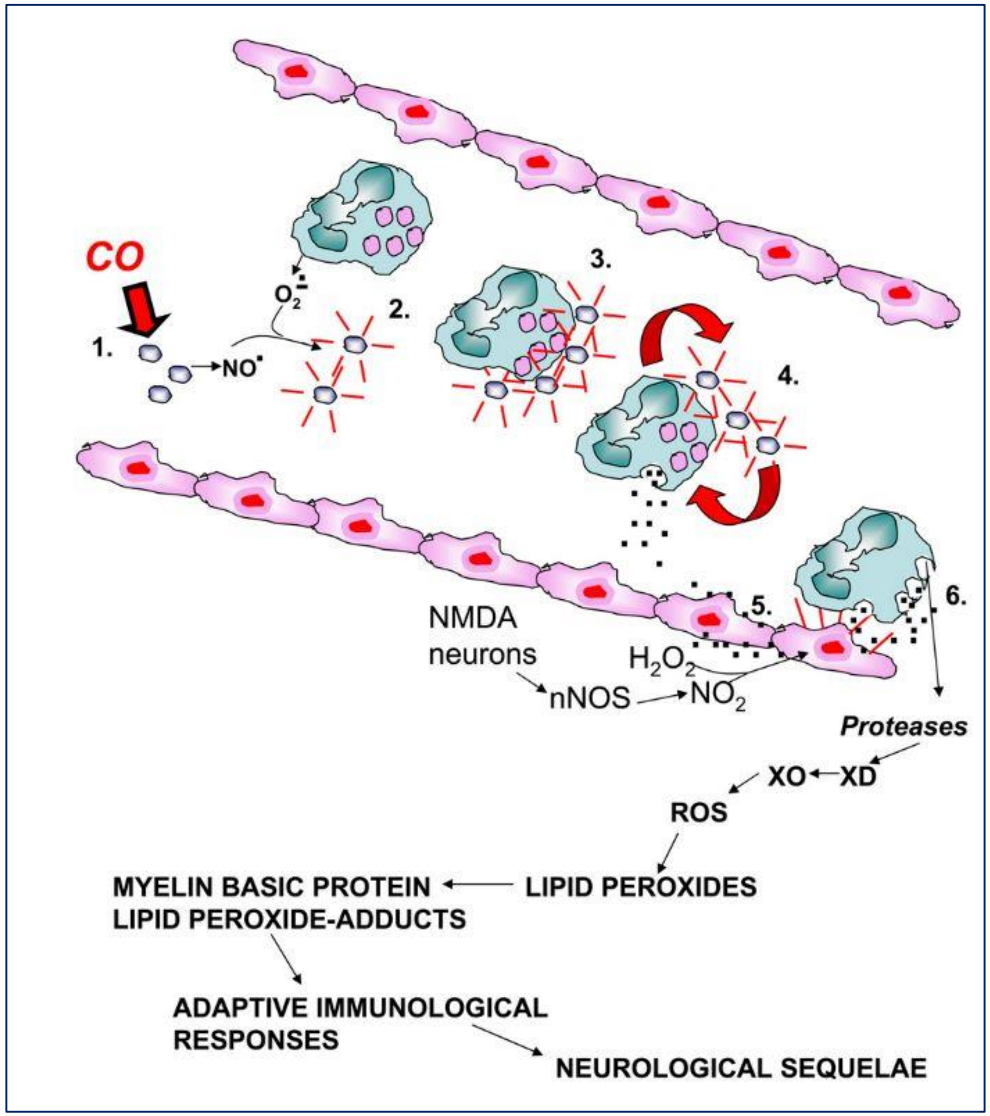
- Mitochondria 효과



- CO는 cytochrome c oxidase (COX)에 산소보다 3배 이상 더 잘 결합하는 특성

- CO가 COX에 결합하여 mitochondria respiration을 억제
  - Oxidative phosphorylation 억제
  - Oxidative stress 발생 (superoxide)

- 혈소판과 염증 효과



1. CO가 platelet의 heme protein과 결합하면서 platelet에 있던 NO (nitric oxide)가 release

2 & 3. NO와 neutrophil에서 release된 superoxide가 결합하여 platelet-neutrophil을 비정상적으로 결집시킴

4 & 5. 비정상적으로 neutrophil에서 degranulation이 발생하면서 myeloperoxidase (MPO)를 미세혈관의 endothelial에 침착시키고 neutrophil을 혈관 endothelium에 부착시킴

6. Neutrophil에서 나오는 protease들이 혈관 내피세포에 있는 xanthine dehydrogenase를 xanthine oxidase로 변형시키면서 많은 ROS 생성됨

Activation of platelet adhesion molecules and platelet-neutrophil aggregation ⇒neutrophil degranulation, release of myeloperoxidase, and endothelial cell oxidative stress

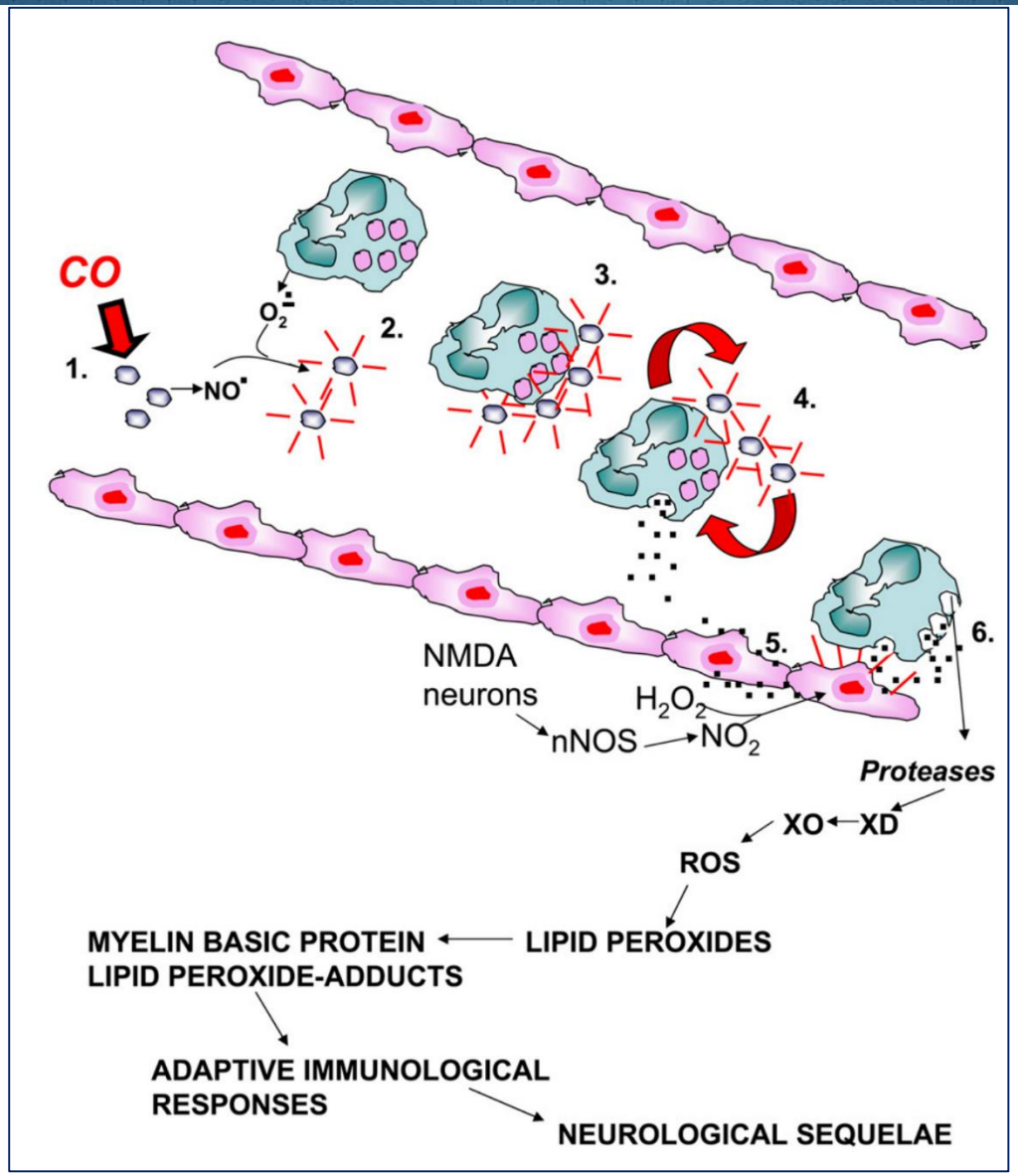
Intravascular Neutrophil Activation Due to Carbon Monoxide Poisoning

Stephen R. Thom, Veena M. Bhopale, Shih-Tsung Han, James M. Clark, and Kevin R. Hardy

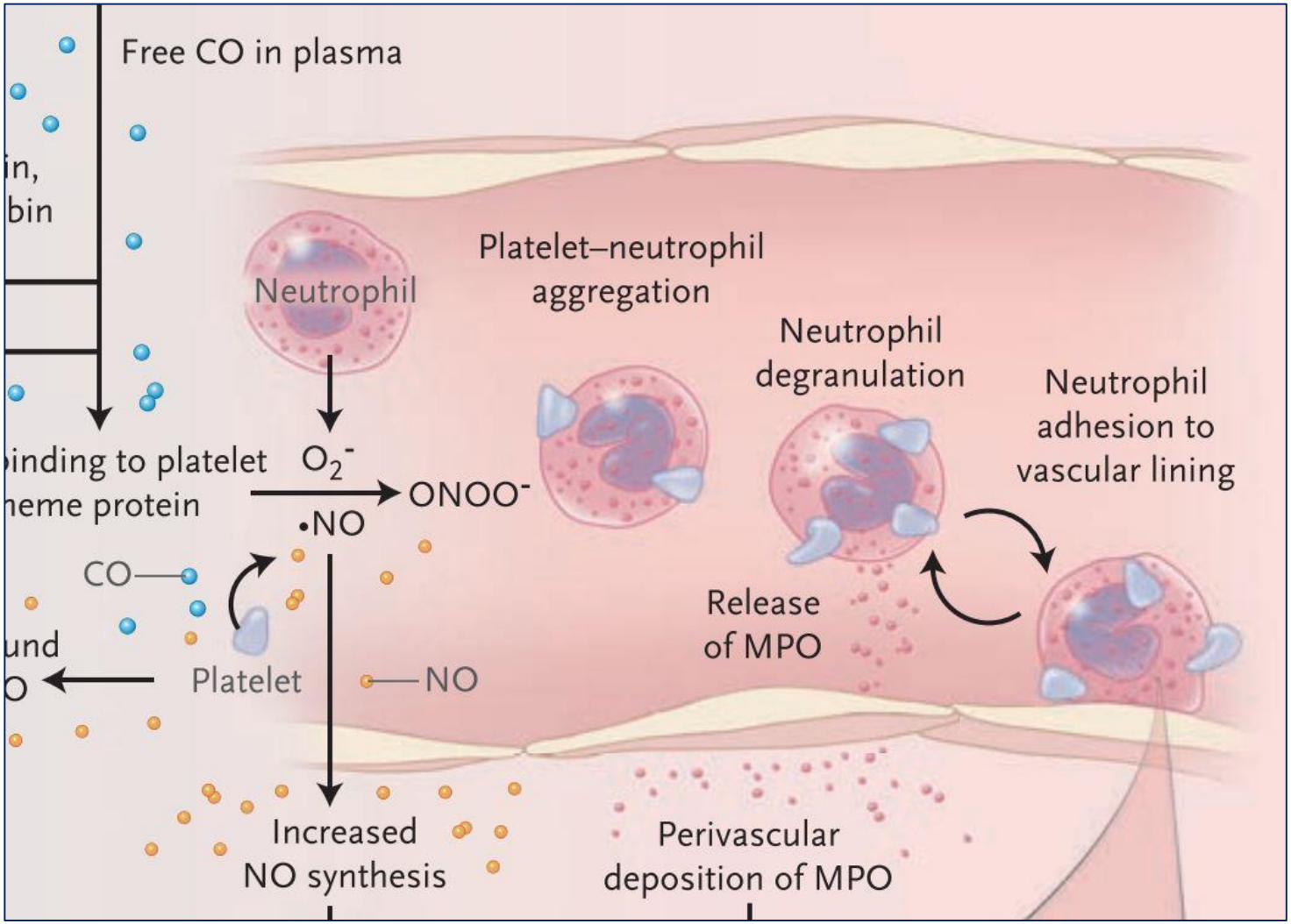
Institute for Environmental Medicine, and Department of Emergency Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; and Emergency Department, Chang-Gung Memorial Hospital, Taoyuan, Taiwan, Republic of China

Thom SR, et al. Am J Respir Crit Care Med 2006

Conclusion: Acute CO poisoning causes intravascular neutrophil activation due to interactions with platelets. MPO liberated by neutrophils mediates perivascular oxidative stress, which is linked to immune-mediated neurologic sequelae.

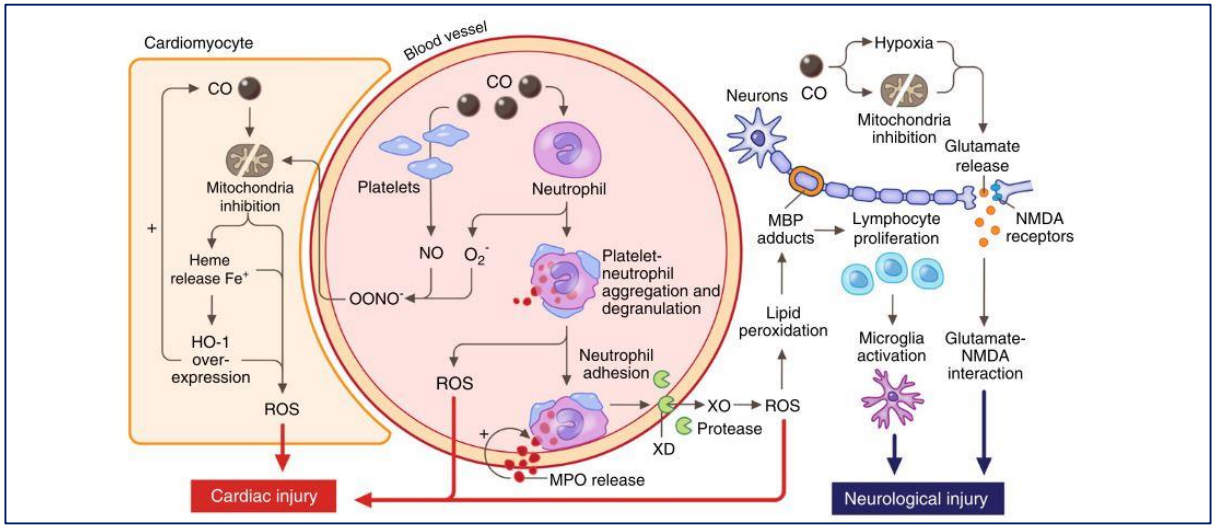


Thom SR, et al. Am J Respir Crit Care Med 2006

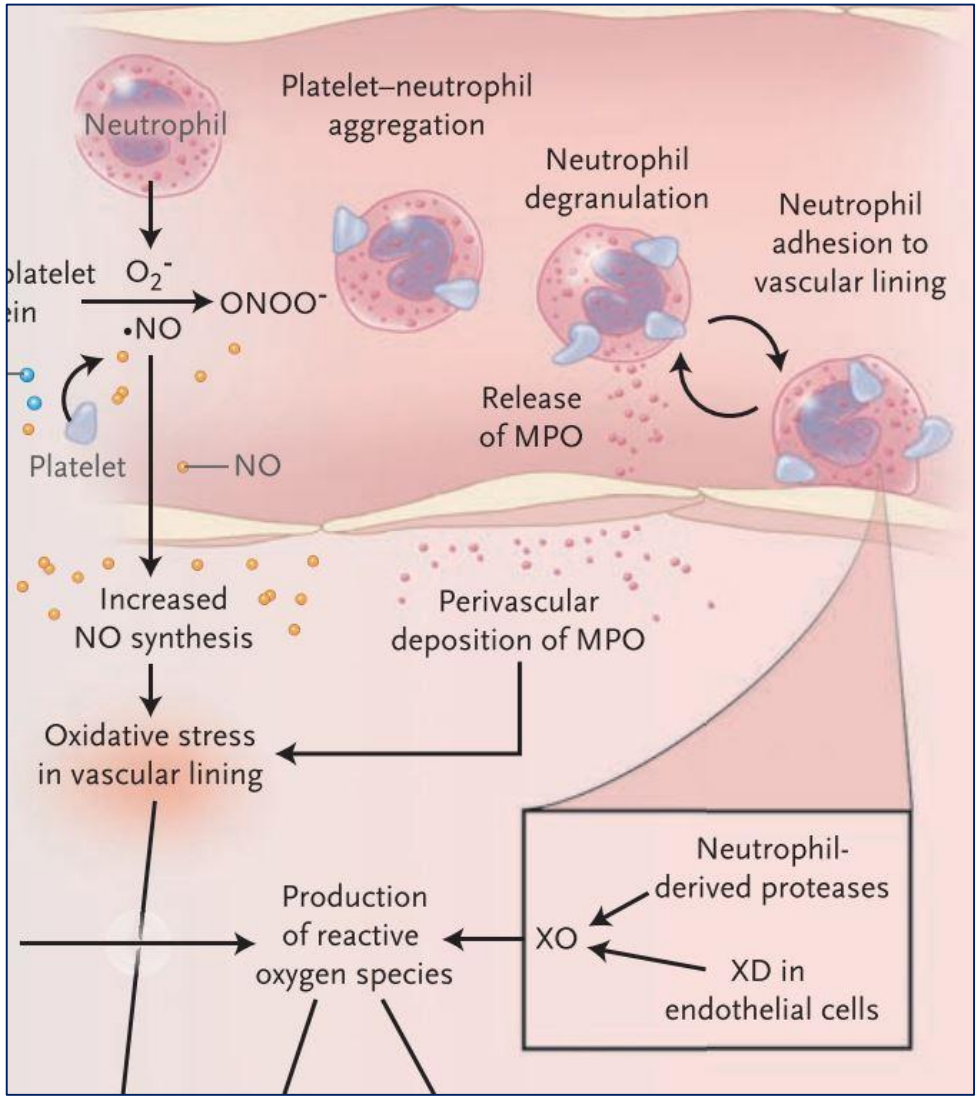


Weaver LK, et al. N Engl J Med 2009

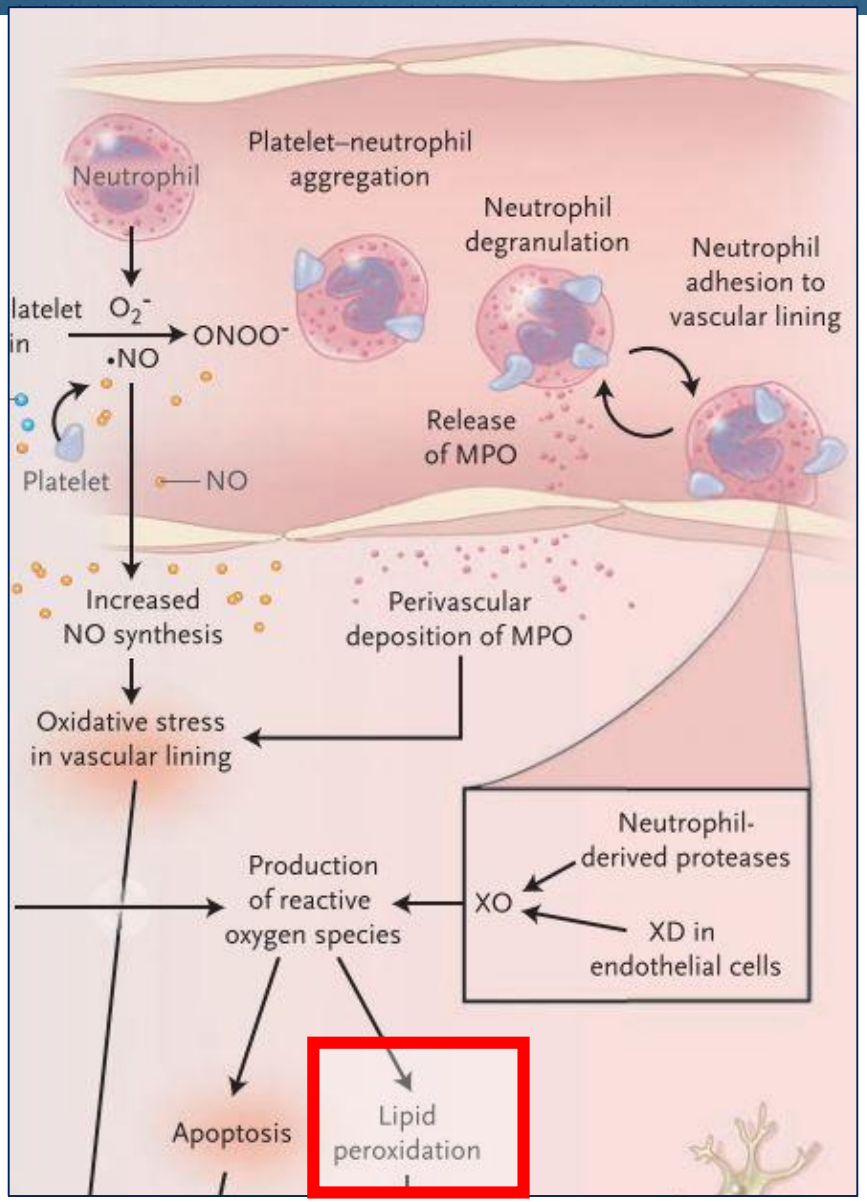
- Inflammatory 및 immunologic 효과



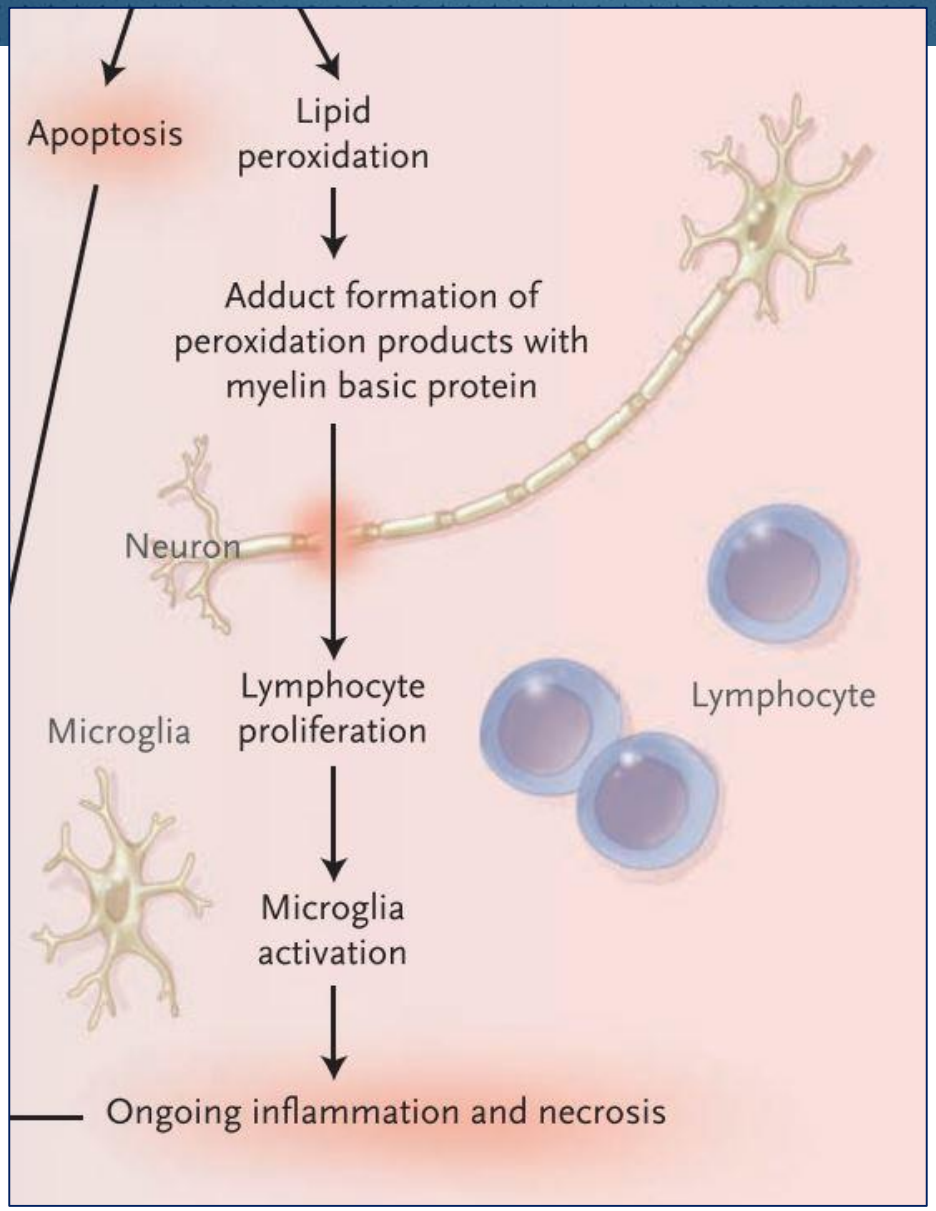
- Lipid peroxidation
- Myelin basic protein adduct 형성
- Lymphocyte 활성화
- Microglia 활성화



Weaver LK, et al. N Engl J Med 2009



Weaver LK, et al. N Engl J Med 2009



Weaver LK, et al. N Engl J Med 2009

Alteration in the structure of myelin basic protein and subsequent lymphocyte proliferation

PNAS

Delayed neuropathology after carbon monoxide poisoning is immune-mediated

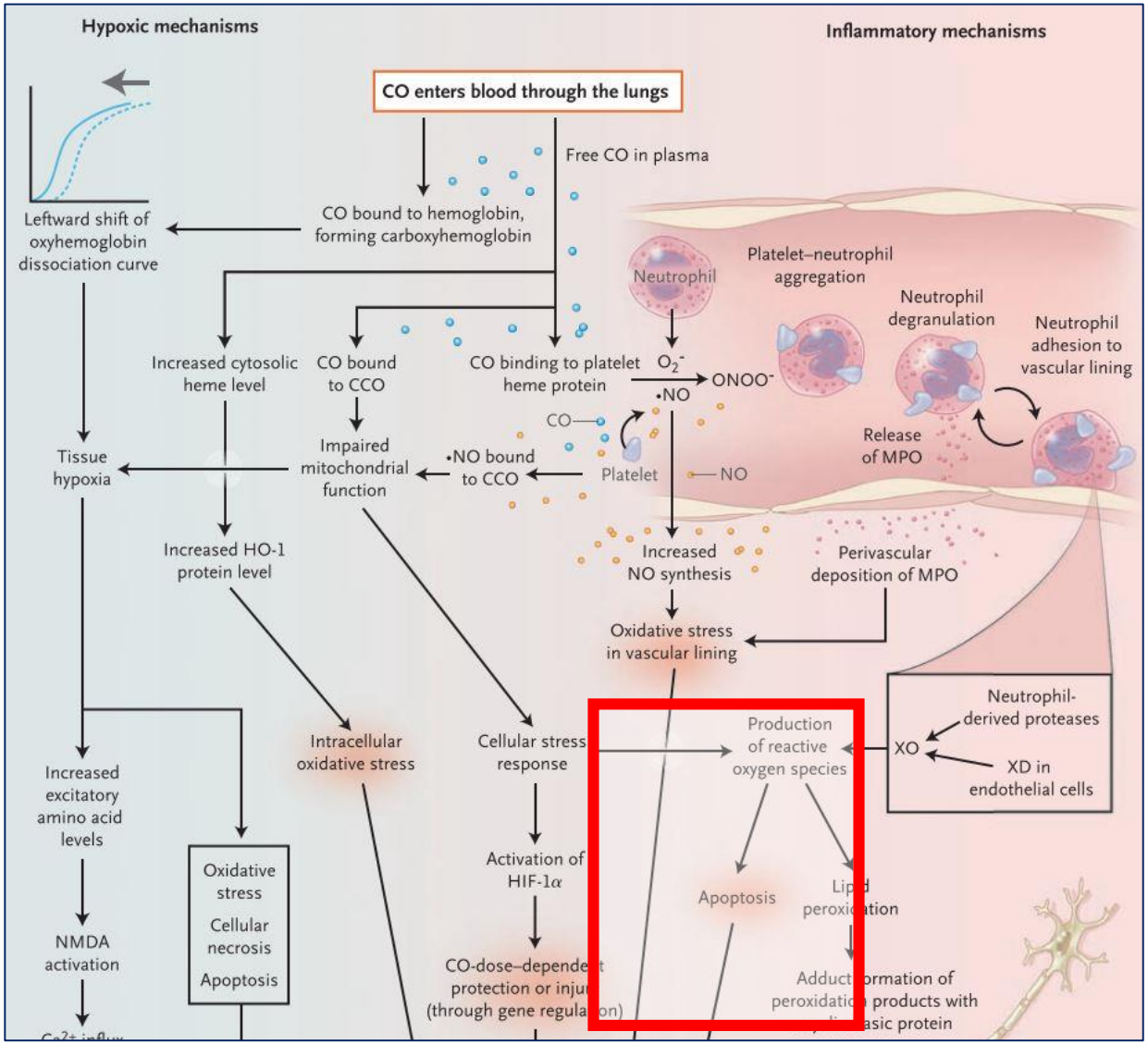
Stephen R. Thom*†‡, Veena M. Bhopale*, Donald Fisher*, Jie Zhang*, and Phyllis Gimotty§

*Institute for Environmental Medicine, †Department of Emergency Medicine, and §Department of Biostatistics and Epidemiology, University of Pennsylvania Medical Center, Philadelphia, PA 19104-6068

Communicated by Robert E. Forster, University of Pennsylvania School of Medicine, Philadelphia, PA, August 3, 2004 (received for review February 4, 2004)

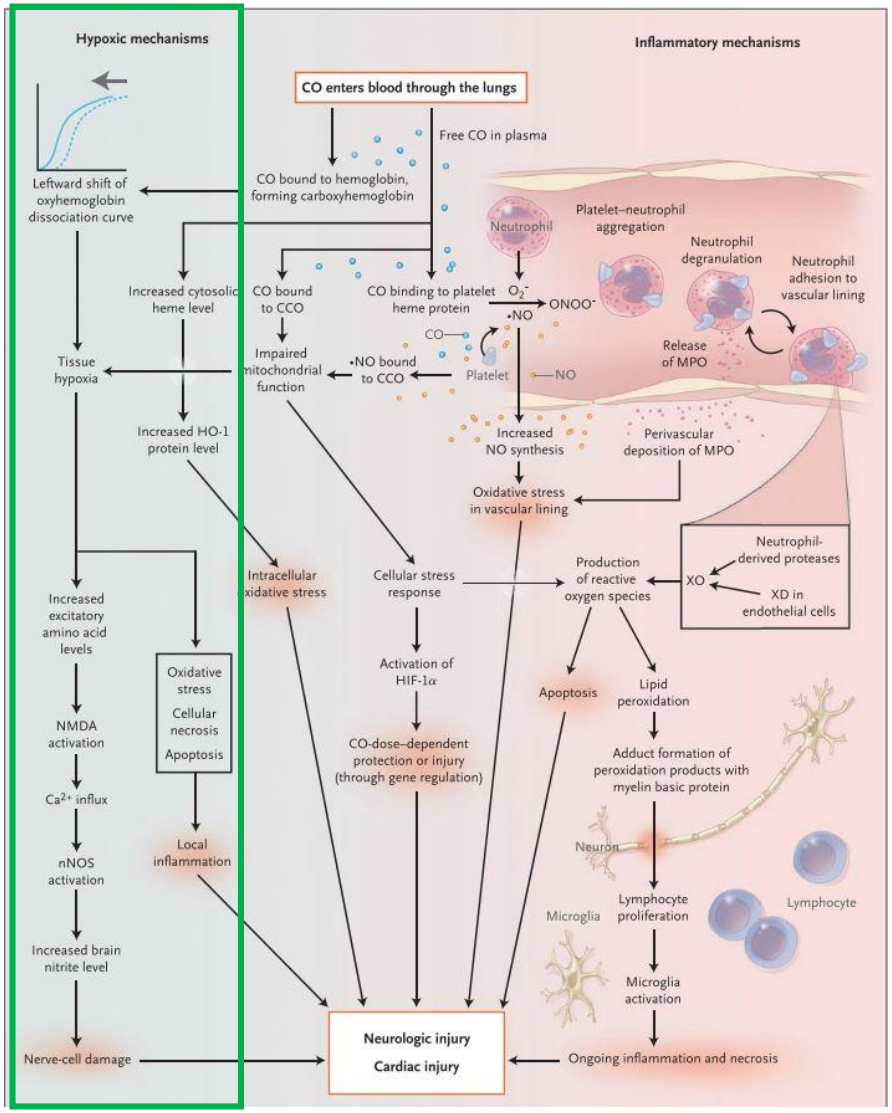
Thom SR, et al. Proc Natl Acad Sci U S A 2004

Conclusion: These results demonstrate that delayed CO-mediated neuropathology is linked to an adaptive immunological response to chemically modified MBP.

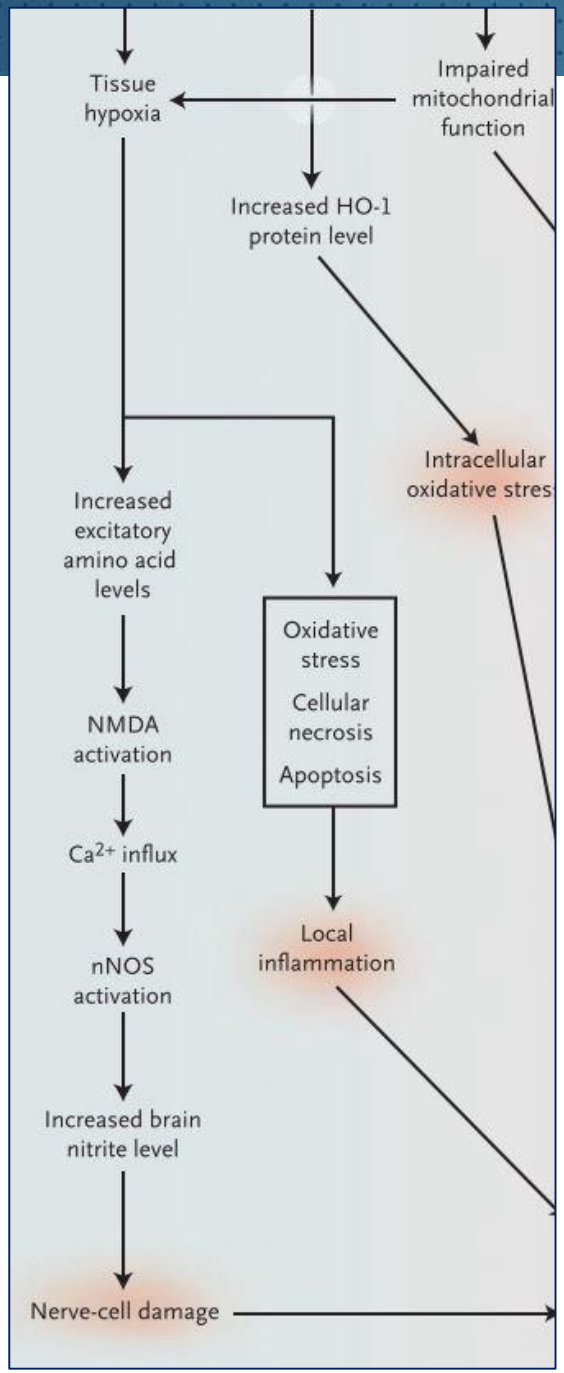


Weaver LK, et al. N Engl J Med 2009

- Brain ischemia 효과



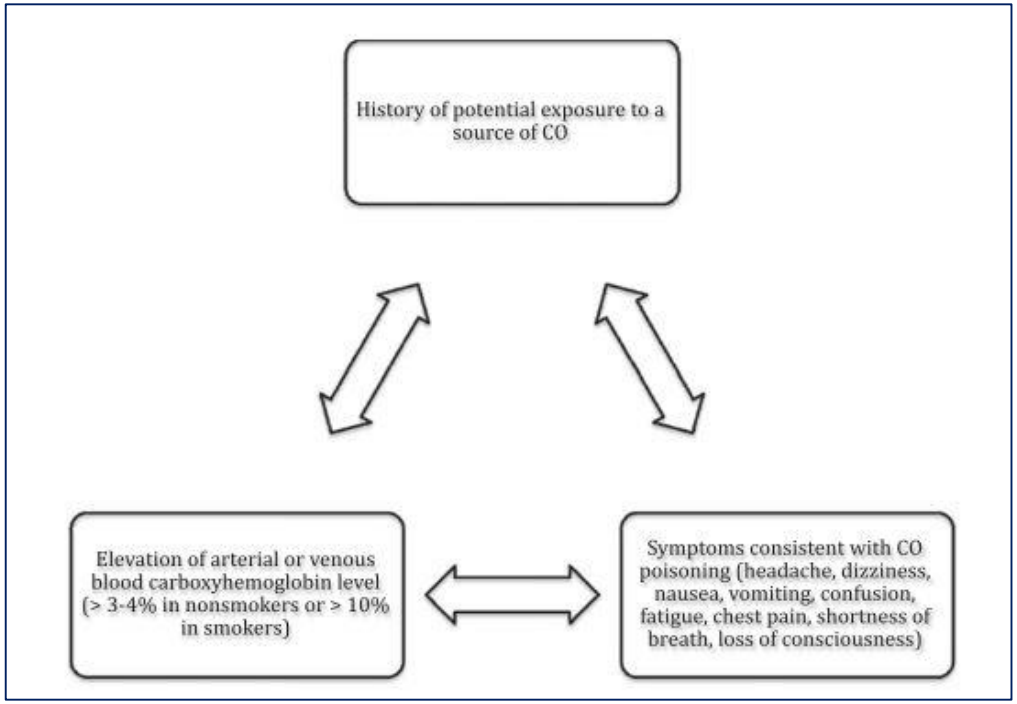
- Glutamate 분비 및 NMDA receptor 활성화
- Calcium influx
- nNOS 활성화
- 신경세포 파괴



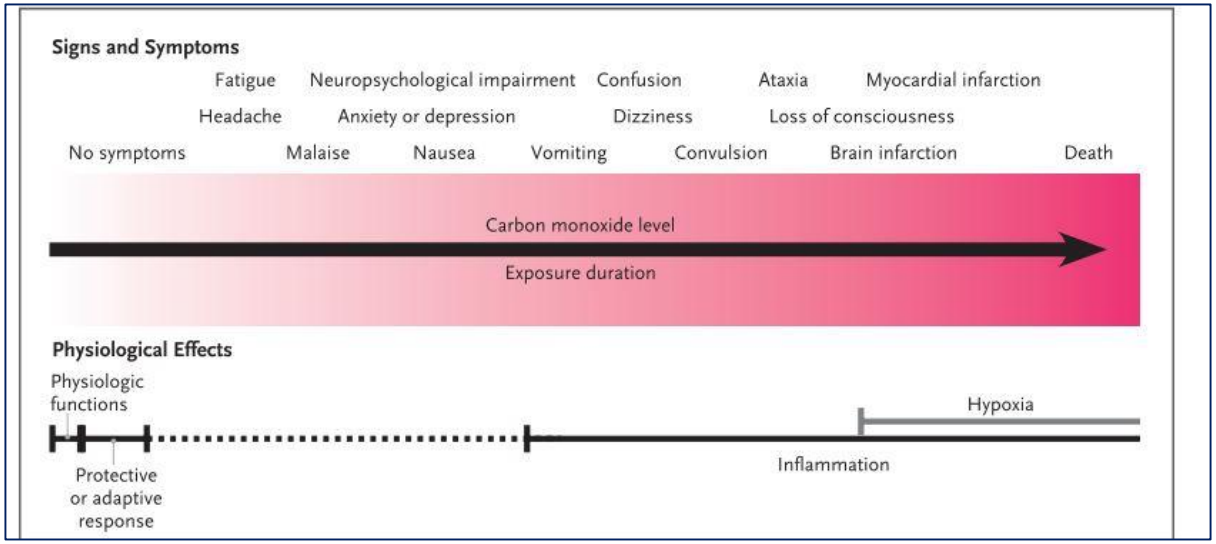
Weaver LK, et al. N Engl J Med 2009

3. 진단

- 최근 CO 노출 history
- CO 중독과 관련된 증상
- CO-Hb의 상승



증상



- 비특이적
- 경증
  - 두통, 근육통, 어지러움, neuropsycholoical 장애
- 중증
  - Confusion, 의식소실, 사망…

CO-Hb

- 절대적이지 않다.
  - 시간이 지나면서 ventilation에 의해 감소
  - 많은 산소를 줄 수록 더 빨리 감소
  - 이 부분을 반드시 감안

- Laboratory CO oximeter로 확인
  - 4 wavelength

- Fingertip pulse CO oximeter
  - 이 결과로 CO 중독을 rule-out하지 마라.
  - 아직까지 정확도에 대한 검증이 약함
  - 보조적으로 만 사용고려

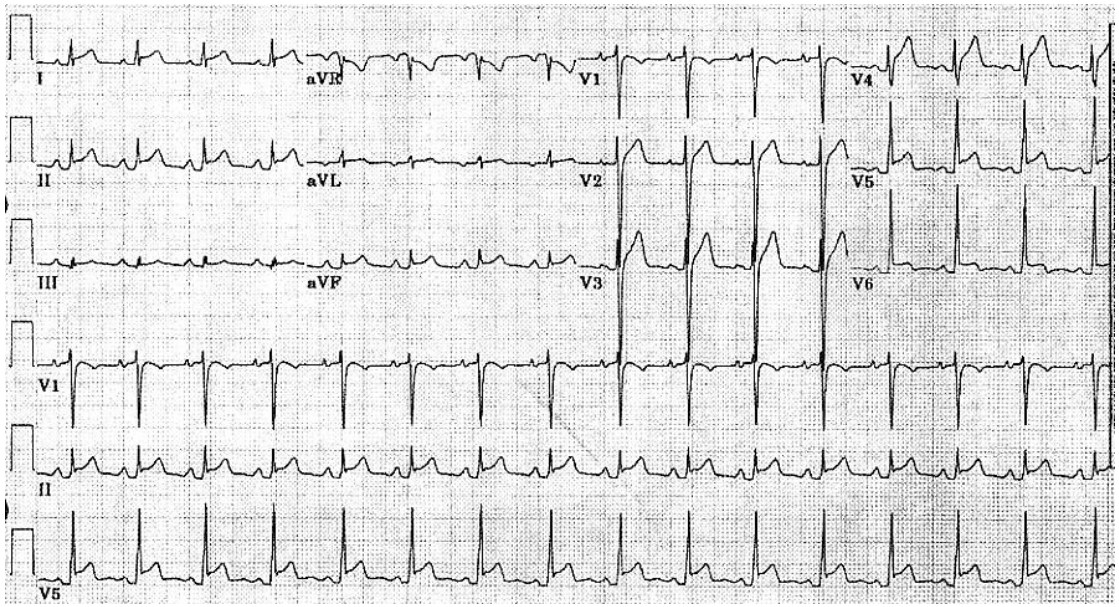
4. 임상적 발현

(clinical manifestation)

Critical illness

- 단기 사망률 (High short-term mortality) 관련 인자
  - pH < 7.20
  - 화재
  - 의식소실
  - CO-Hb 상승
  - 고압산소치료시 기도삽관의 필요

CO-mediated cardiac death



Neurologic/affective 후유증

- CO 중독 이후 생존자들은 long-term 후유증으로 고통 받는다.

- 증상
  - Impaired memory, cognitive dysfunction, depression, anxiety, and/or vestibular and motor deficits (굉장히 다양)

- 일반적으로 6주 이내 발생(12-47%)
  - 발생 후 50% 정도에서 일부 호전 (1년 정도)

- 6주 cognitive impairment 위험인자
  - 36세 이상
  - 24시간 이상 CO 노출

- 초기 증상의 중증도가 long-term neurological 후유증과 꼭 연관된 건 아니다.

심혈관 영향

- 고압산소치료가 필요한 moderate to severe CO 중독환자의 2/3에서 myocardial injury가 발생하고 left ventricle의 기능이 떨어짐
  - 이 환자들은 long-term mortality가 myocardial injury가 없던 환자보다 의미있게 높음

- The clinical spectrum of heart involvement in patients with CO intoxication is rather broad
  - Typically encompass cardiomyopathy, angina attack, myocardial infarction, arrhythmias and heart failure up to myocardial stunning, cardiogenic shock and sudden death

- In autopsy samples, the pathological features of CO intoxication are variegated and may include scattered and punctiform necrotic areas, subendocardial hemorrhages in the left ventricle, degenerative involvement of papillary and other muscles, as well as focal myocardial necrosis

New report

NEW RESEARCH PAPER

Myocardial Injury and Fibrosis From Acute Carbon Monoxide Poisoning

A Prospective Observational Study

Dong-Hyuk Cho, MD, PhD,[a,*] Sung Min Ko, MD, PhD,[b,*] Jung-Woo Son, MD,[a] Eung Joo Park, MS,[c] Yong Sung Cha, MD[d]

ABSTRACT

OBJECTIVES This study sought to evaluate the prevalence and patterns of late gadolinium enhancement (LGE) after carbon monoxide (CO) poisoning using cardiac magnetic resonance (CMR) imaging (CMRI) and transthoracic echocardiography (TTE).

BACKGROUND In acute CO poisoning, cardiac injury can predict mortality. However, it remains unclear why increased mortality and cardiovascular events occur despite normalization of CO-induced elevated troponin I (TnI) and cardiac dysfunction.

METHODS Patients with acute CO poisoning with elevated TnI were evaluated. CMRI was performed within 7 days of CO exposure and after 4 to 5 months. Patients were divided into LGE (n = 72; 69.2%) and no-LGE (n = 32; 30.8%) groups.

RESULTS In the LGE group, 39.4%, 4.8%, and 25.0% of patients exhibited midwall, subendocardial, and right ventricular insertion point injury, respectively. Diffuse injury was observed in 22.1% of patients, and 67.6% of the 37 patients who underwent follow-up CMRI showed no interval change. On TTE, baseline left ventricular ejection fraction and global longitudinal strain were significantly deteriorated in the LGE group; serial TTE within 7 days indicated that only left ventricular global longitudinal strain remained significantly deteriorated. Three cases of mortality occurred in the LGE group during the 1-year follow-up.

CONCLUSIONS The LGE prevalence in patients with acute CO poisoning with elevated TnI levels, with no underlying cardiovascular diseases and eligible for CMRI, was 69.2%; this proportion primarily comprised patients with a midwall injury. Of the 37 patients who underwent follow-up CMRI, most chronic phase images showed no interval change. Myocardial fibrosis detected on CMR images was related to acute myocardial dysfunction and subacute deterioration of myocardial strain on TTE. (Cardiac Magnetic Resonance Image in Acute Carbon Monoxide Poisoning; NCT04419298) (J Am Coll Cardiol Img 2021;■:■–■) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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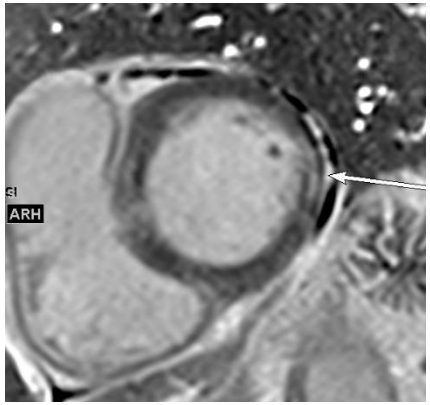
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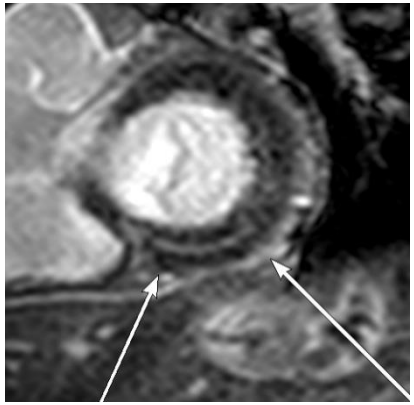

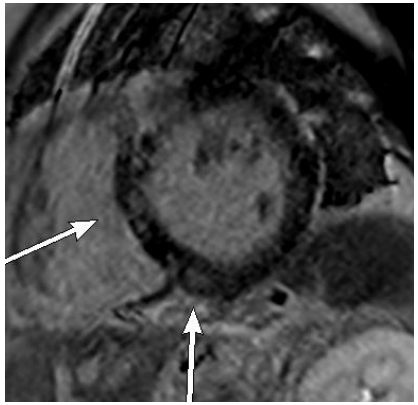

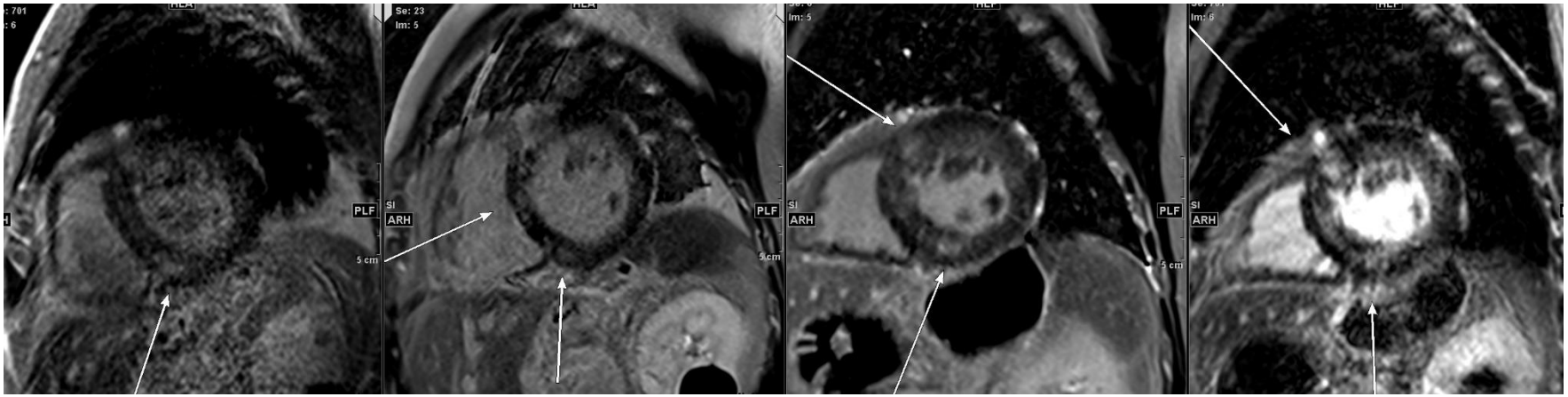
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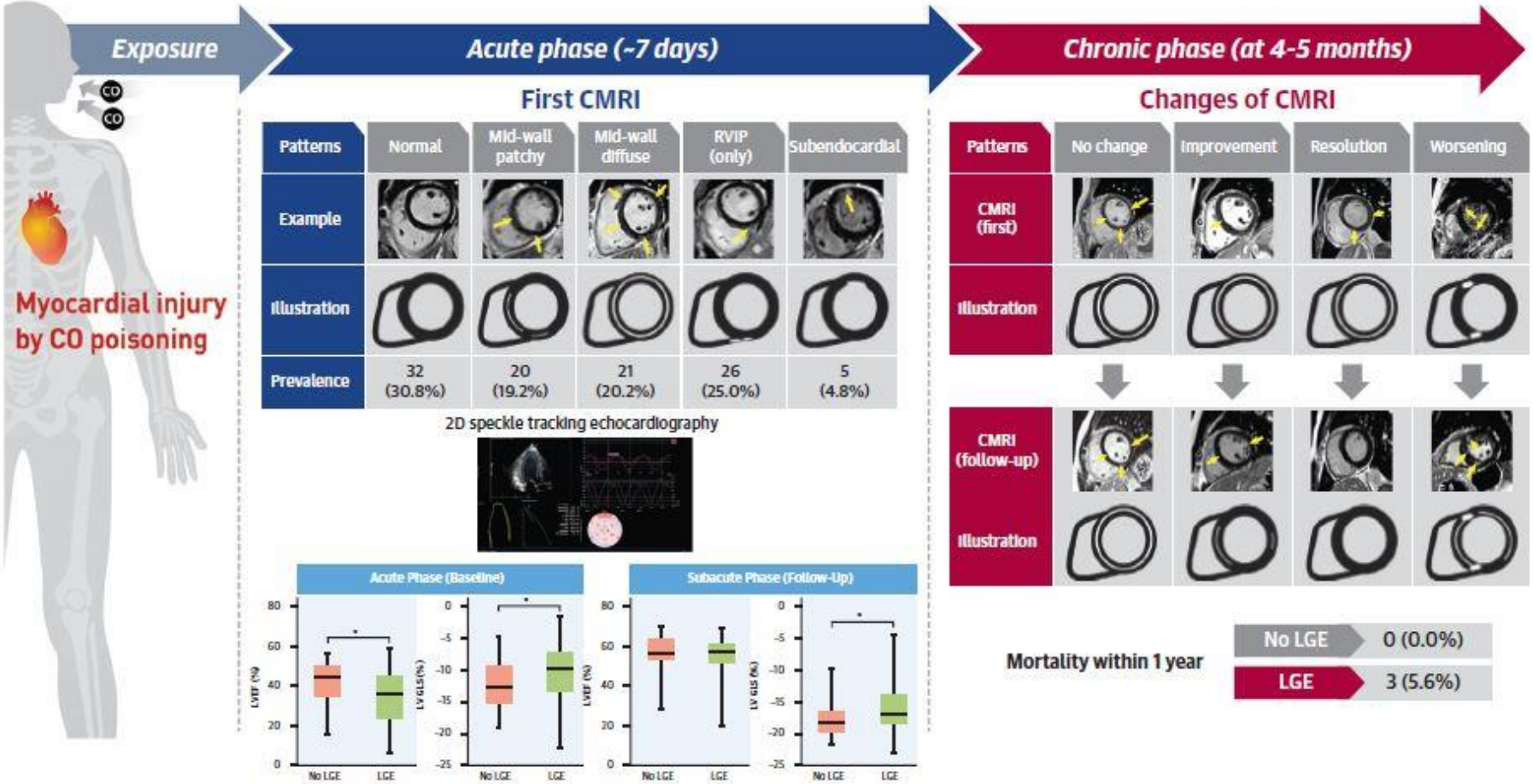
CENTRAL ILLUSTRATION **Myocardial Injury Detected by Cardiac Magnetic Resonance Imaging in Carbon Monoxide Poisoning**



Cho, D.-H. et al. J Am Coll Cardiol Img. 2021;■(■):■-■.

The prevalence of late gadolinium enhancement positivity in patients with acute carbon monoxide poisoning with elevated troponin I levels was 69.2%, and the midwall was the most commonly affected (39.4%). Of the 37 patients (35.6%) who underwent follow-up CMRI, chronic phase CMRI results showed no interval changes from the acute phase CMRI results for most (67.6%) patients. Myocardial fibrosis on CMRI was related to acute myocardial dysfunction and subacute deterioration of myocardial strain on transthoracic echocardiography. CMRI = cardiac magnetic resonance imaging.

5. 치료

Short-term management

- Normobaric oxygen therapy (NBOT)
  - Nonrebreather reservoir face mask
  - CO washout을 빠르게
  - 하지만 환자의 cognitive sequelae를 줄인다는 evidence는 없다...
  - 하지만 안전하고 쉽게 사용할 수 있고 싸니까 사용한다.
  - CO-Hb 5% 미만까지
  - 보통 6시간이내

고압산소치료(HBOT)

- Rapid clearance of CO from blood and tissues
- Sufficient dissolved oxygen in blood that O_2Hb is unnecessary
- Normalization of tissue oxygenation

어떻게 좋아지는 것인가?

Reversal of cytochrome binding

Recovery of Energy Metabolism in Rat Brain after Carbon Monoxide Hypoxia

Steven D. Brown and Claude A. Piantadosi
Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710

Brown SD, et al. J Clin Invest 1992

- Cytochrome oxidation state가 NBOT 90분 후에 80%정도 호전을 보였고 HBOT를 실시한 경우는 완전히 회복되었다. ($P < 0.05$).

Preservation of adenosine triphosphate production

ELSEVIER

Brain Research Bulletin 69 (2006) 109–116

BRAIN RESEARCH BULLETIN

www.elsevier.com/locate/brainresbull

Involvement of the mitochondrial ATP-sensitive potassium channel in the neuroprotective effect of hyperbaric oxygenation after cerebral ischemia

Min Lou [a,*], Yizhang Chen [b], Meiping Ding [a], Christoph C. Eschenfelder [c], Günther Deuschl [c]

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[c] *Department of Neurology, Christian-Albrechts-University of Kiel, Schittenhelmstrasse 10, D-24105 Kiel, Germany*

Received 9 October 2005; received in revised form 19 November 2005; accepted 19 November 2005
Available online 15 December 2005

Lou M, et al. Brain Res Bull 2006

- 초기 HBOT가 apoptosis도 예방하고 신경학적 기능회복도 증진시켰다. 이것은 mitochondrial ATP-sensitive K channel의 improvement를 가져와서 neuroprotective 효과를 보였다.

Adaptive/protective oxidative stress response through increased heme oxygenase-1

Carcinogenesis vol.22 no.12 pp.1979–1985, 2001

Involvement of heme oxygenase-1 (HO-1) in the adaptive protection of human lymphocytes after hyperbaric oxygen (HBO) treatment

Rothfuss A, et al. Carcinogenesis 2001

Upregulation and modulation of various antioxidant enzymes

Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Aging, Cancer, and Age-Related Diseases*

Hyperbaric oxygen treatment induces antioxidant gene expression

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Godman CA, et al. Ann N Y Acad Sci 2010

Induction of heat shock protein, which protects against oxidative stress

Dennog C, Radermacher P, Barnett YA, Speit G. Antioxidant status in humans after exposure to hyperbaric oxygen. Mutat Res 1999;428:83-9.

Shyu WC, Lin SZ, Saeki K, Kubosaki A, Matsumoto Y, Onodera T, et al. Hyperbaric oxygen enhances the expression of prion protein and heat shock protein 70 in a mouse neuroblastoma cell line. Cell Mol Neurobiol 2004;24:257-68.

Globus MY, Busto R, Lin B, Schnippering H, Ginsberg MD. Detection of free radical activity during transient global ischemia and recirculation: effects of intraischemic brain temperature modulation. J Neurochem 1995;65:1250-6.

Reduced myeloperoxidase activity

Zhang Y, Lv Y, Liu YJ, Yang C, Hu HJ, Meng XE, et al. Hyperbaric oxygen therapy in rats attenuates ischemia-reperfusion testicular injury through blockade of oxidative stress, suppression of inflammation, and reduction of nitric oxide formation. Urology 2013;82:489.e9-.e15.

Ayvaz S, Kanter M, Aksu B, Sahin SH, Uzun H, Erboga M, et al. The effects of hyperbaric oxygen application against cholestatic oxidative stress and hepatic damage after bile duct ligation in rats. J Surg Res 2013;183:146-55.

Miljkovic-Lolic M, Silbergleit R, Fiskum G, Rosenthal RE. Neuroprotective effects of hyperbaric oxygen treatment in experimental focal cerebral ischemia are associated with reduced brain leukocyte myeloperoxidase activity. Brain Res 2003;971:90-4.

Decrease in hypoxia-inducible factor-1 expression

Calvert JW, Cahill J, Yamaguchi-Okada M, Zhang JH. Oxygen treatment after experimental hypoxia-ischemia in neonatal rats alters the expression of HIF-1alpha and its downstream target genes. J Appl Physiol (1985) 2006;101:853-65.

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Calvert JW, Zhou C, Nanda A, Zhang JH. Effect of hyperbaric oxygen on apoptosis in neonatal hypoxia-ischemia rat model. J Appl Physiol (1985) 2003;95:2072-80.

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Prevention of brain lipid peroxidation

TOXICOLOGY AND APPLIED PHARMACOLOGY **105,** 340–344 (1990)

SHORT COMMUNICATIONS

Antagonism of Carbon Monoxide-Mediated Brain Lipid Peroxidation by Hyperbaric Oxygen[1]

Thom, S. R. 1990 Toxicol Appl Pharmacol

Reduced leukocyte adhesion & Blocking XD conversion to XO & Inhibition of immune response!!!

TOXICOLOGY AND APPLIED PHARMACOLOGY **123**, 248–256 (1993)

Functional Inhibition of Leukocyte B_2 Integrins by Hyperbaric Oxygen in Carbon Monoxide-Mediated Brain Injury in Rats

STEPHEN R. THOM

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Received December 22, 1992; accepted August 9, 1993

Thom, S. R. 1993 Toxicol Appl Pharmacol

Muted adduct formation and blocked inflammatory response to altered myelin basic protein & Inhibition of immune response

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Toxicology and Applied Pharmacology 213 (2006) 152 – 159

Toxicology and Applied Pharmacology

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Hyperbaric oxygen reduces delayed immune-mediated neuropathology in experimental carbon monoxide toxicity

Stephen R. Thom [a,b,*], Veena M. Bhopale [b], Donald Fisher [b]

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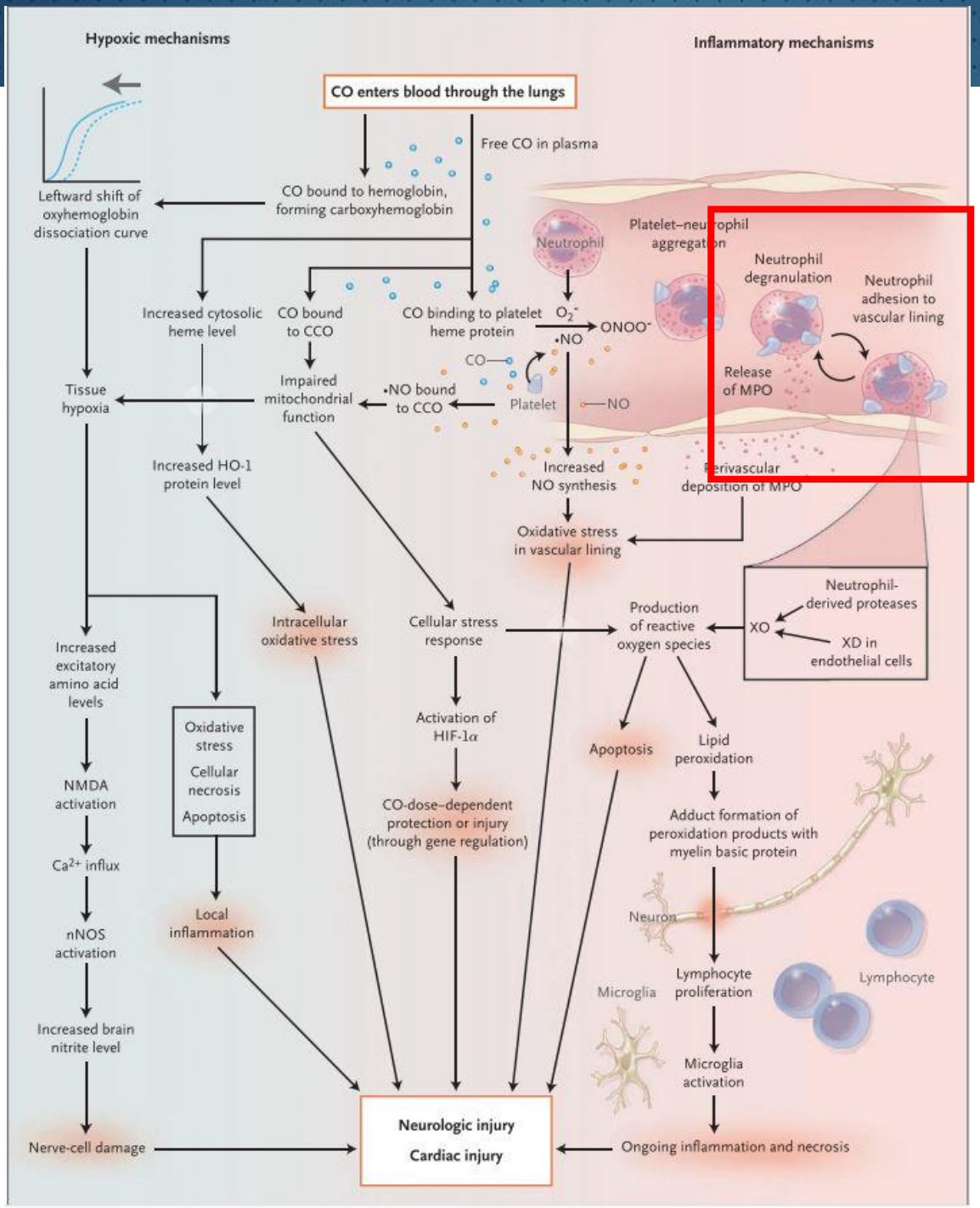
Received 28 July 2005; revised 18 October 2005; accepted 20 October 2005

Available online 1 December 2005

Thom, S. R., et al. Toxicology and applied pharmacology 2006

Conclusion: Lymphocytes from HBO2-treated and control rats do not become activated when incubated with MBP, immunohistological evidence of microglial activation is not apparent, and functional deficits did not occur, unlike untreated COexposed rats. The results indicate that HBO2 prevents immune-mediated delayed neurological dysfunction following CO poisoning.



Weaver LK, et al. N Engl J Med 2009

CO pathophysiology	Effects of HBO_2
Formation of COHb	Rapid clearance of CO from blood and tissues
Increased Hb affinity for oxygen and leftward shift of oxyhemoglobin dissociation curve	Sufficient dissolved oxygen in blood that O2Hb is unnecessary
Tissue hypoxia	Normalization of tissue oxygenation
Binding to cellular proteins [i.e., cytochromes, myoglobin] and increased steady-state concentration of nitric oxide	Reversal of cytochrome binding
Inhibition of cellular metabolism	Preservation of adenosine triphosphate production
Oxidative stress [i.e., due to mitochondrial production of reactive oxygen species and free radical production from heme degradation]	- Adaptive/protective oxidative stress response through increased heme oxygenase-1 - Upregulation and modulation of various antioxidant enzymes - Induction of heat shock protein, which protects against oxidative stress
Elevation of microparticles	
Activation of platelet adhesion molecules and platelet-neutrophil aggregation, resulting in neutrophil degranulation, release of myeloperoxidase, and endothelial cell oxidative stress	Reduced myeloperoxidase activity
Neutrophil adherence to vasculature, leukocyte immune response, and conversion of xanthine dehydrogenase [XD] to xanthine oxidase [XO]	Reduced leukocyte adhesion Inhibition of immune response Blocking XD conversion to XO
Lipid peroxidation	Prevention of brain lipid peroxidation
Alteration in the structure of myelin basic protein and subsequent lymphocyte proliferation	Muted adduct formation and blocked inflammatory response to altered myelin basic protein
Excitatory neurotransmitter toxicity	
Activation of hypoxia-inducible factor-1alpha	Decrease in hypoxia-inducible factor-1 expression
Neuronal necrosis and apoptosis	Reduction of necrosis and protection against accelerated apoptosis

현재까지 가장 중요한 기전은…

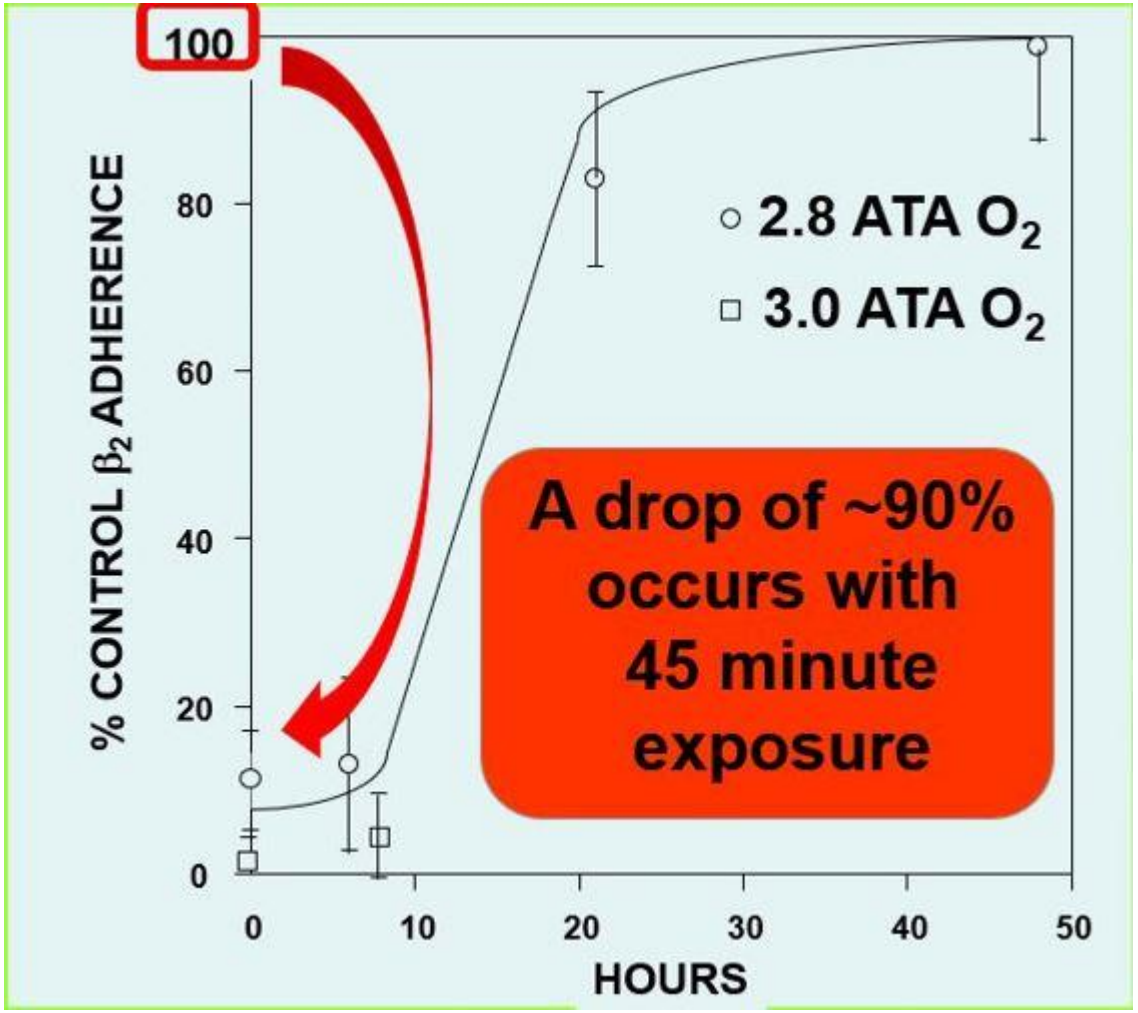
Inhibition of human neutrophil β_2-integrin-dependent adherence by hyperbaric O_2

STEPHEN R. THOM,[1,2] IGNACIO MENDIGUREN,[1,3] KEVIN HARDY,[1,2] TODD BOLOTIN,[1,2] DONALD FISHER,[1] MONIQUE NEBOLON,[1] AND LAURIE KILPATRICK[4]

[1]*Institute for Environmental Medicine,* [2]*Department of Emergency Medicine, and* [3]*Division of Pulmonary and Critical Care Medicine, University of Pennsylvania and* [4]*Department of Immunology, Childrens' Hospital of Philadelphia, Philadelphia, Pennsylvania 19104-7037*

Thom SR, et al. Am J Physiol. 1997;272

KEY POINT!!!


100
80
60
40
20
0
% CONTROL β2 ADHERENCE
0
10
20
30
40
50
HOURS
2.8 ATA O2
3.0 ATA O2
A drop of ~90% occurs with 45 minute exposure

또한 중요한 기전…

- 고압산소치료는 human, mouse, rat 모두에서 pro-inflammatory cytokine 생성을 줄인다.
  - 그 증거는 너무 많다…

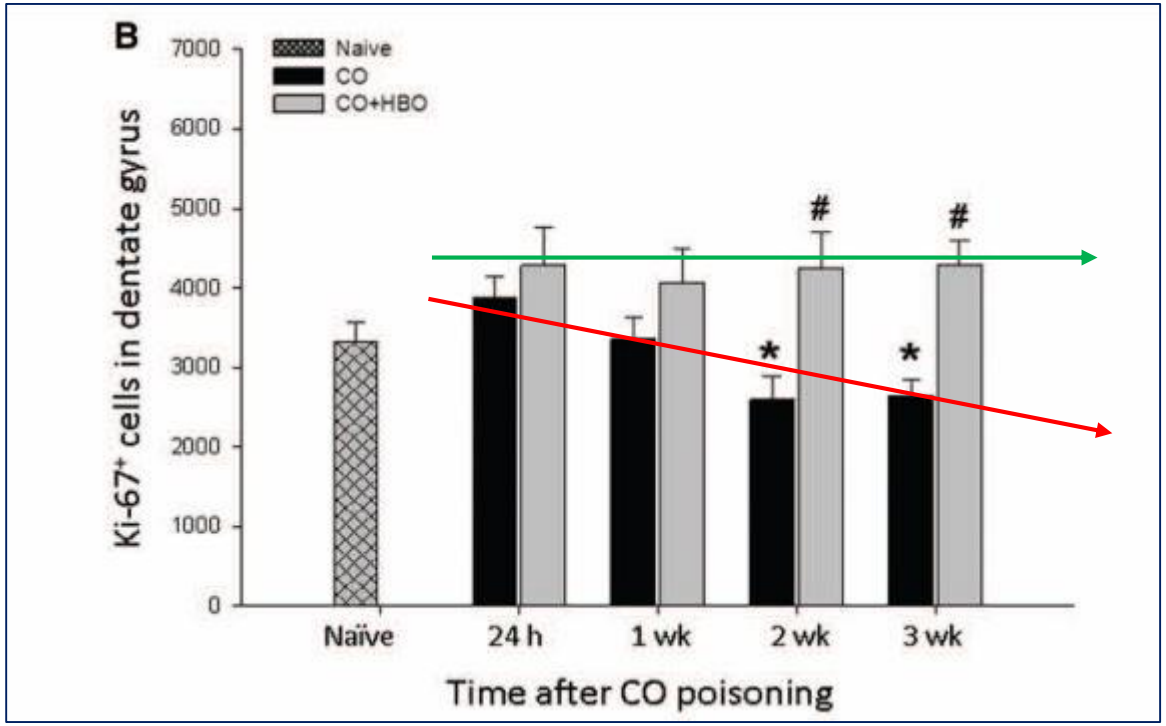
- 최근 연구
  - 고압산소 치료는 hippocampal neurogenesis를 촉진시킨다..

Hyperbaric Oxygen Therapy Alleviates Carbon Monoxide Poisoning–Induced Delayed Memory Impairment by Preserving Brain-Derived Neurotrophic Factor–Dependent Hippocampal Neurogenesis

Wen-Chung Liu, MD[1,2,3]; San-Nan Yang, MD, PhD[4]; Chih-Wei J. Wu, PhD[5]; Lee-Wei Chen, MD, PhD[1,2,3]; Julie Y.H. Chan, PhD[2,5]

Liu WC, et al. Crit care med. 2016;44(1):e25-39.

Recent study

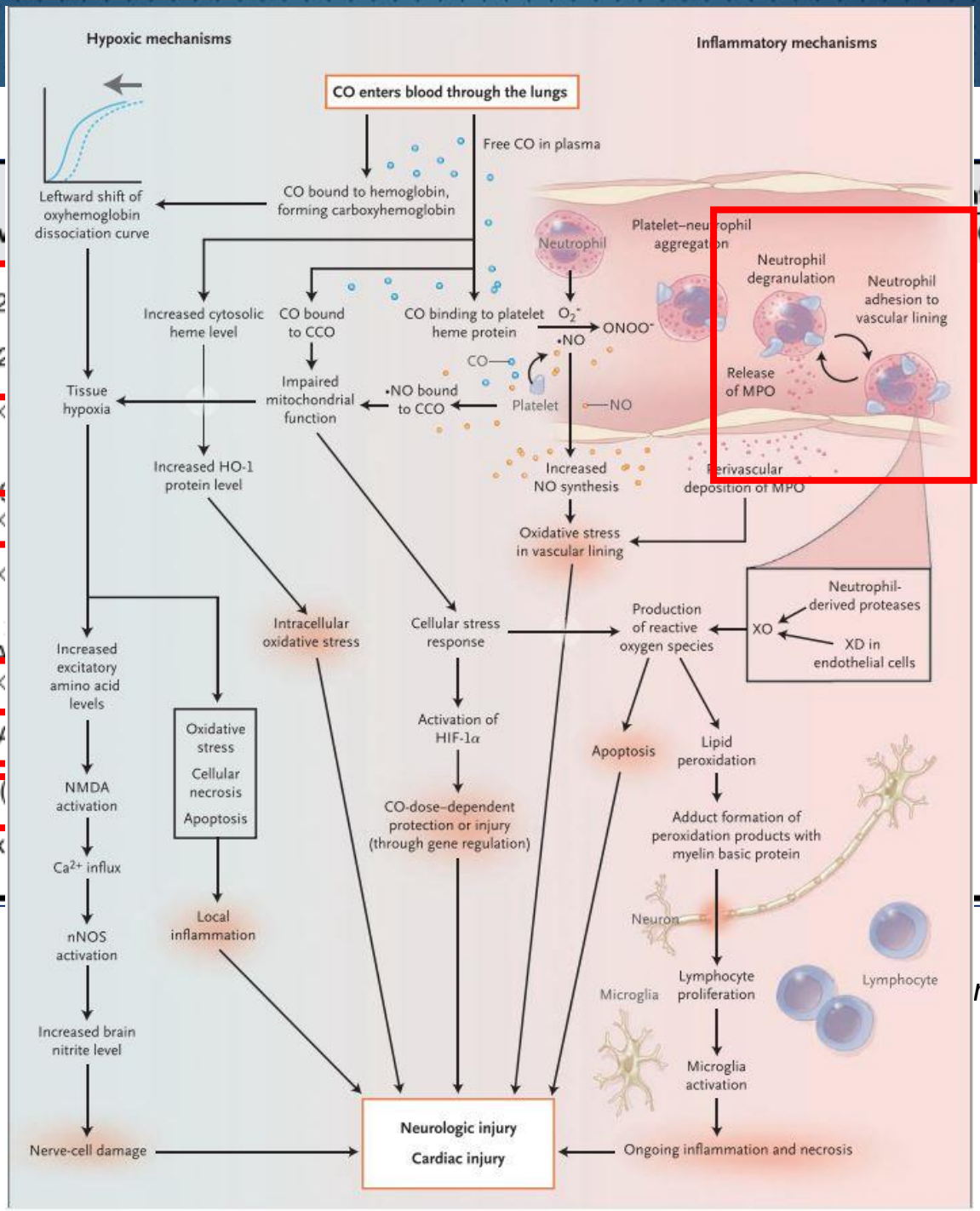


Preservation with HBOT

CO 중독 후
Proliferating cell 소실

6. Evidences for HBO_2 in CO poisoning

Interv	ts Control	Benefit
No LOC: HBO_2 (2	50/158	N
LOC: 2× HBO_2 (2		
HBO_2 (2.8 ATA) ×	7/30	Y
then (2.0 ATA) × (		
HBO_2 (2.5 ATA) ×	73/276	N
HBO_2 (2.8 ATA) ×	20/34	N
HBO_2 1× (3 ATA then 2× (2 ATA	35/76	Y
HBO_2 (2.0 ATA) ×	33/79	N
LOC: HBO_2 (2.0 A NBO	29/86	N
Coma: 2× HBO_2 (NBO	25/101	N
HBO_2 (2.5 ATA) x	6/10	Y



rit Care Med 2017

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Journal of Medicine

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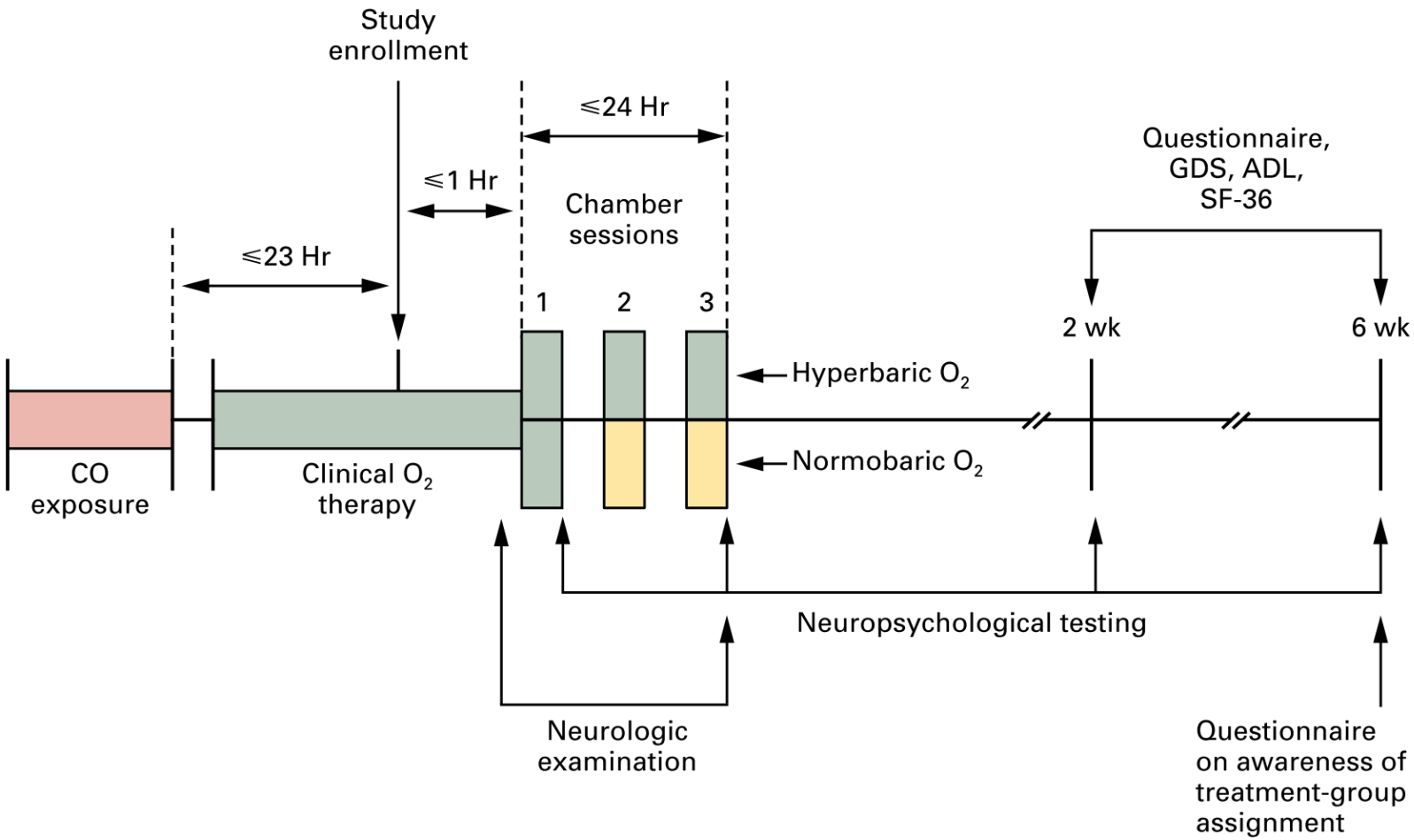
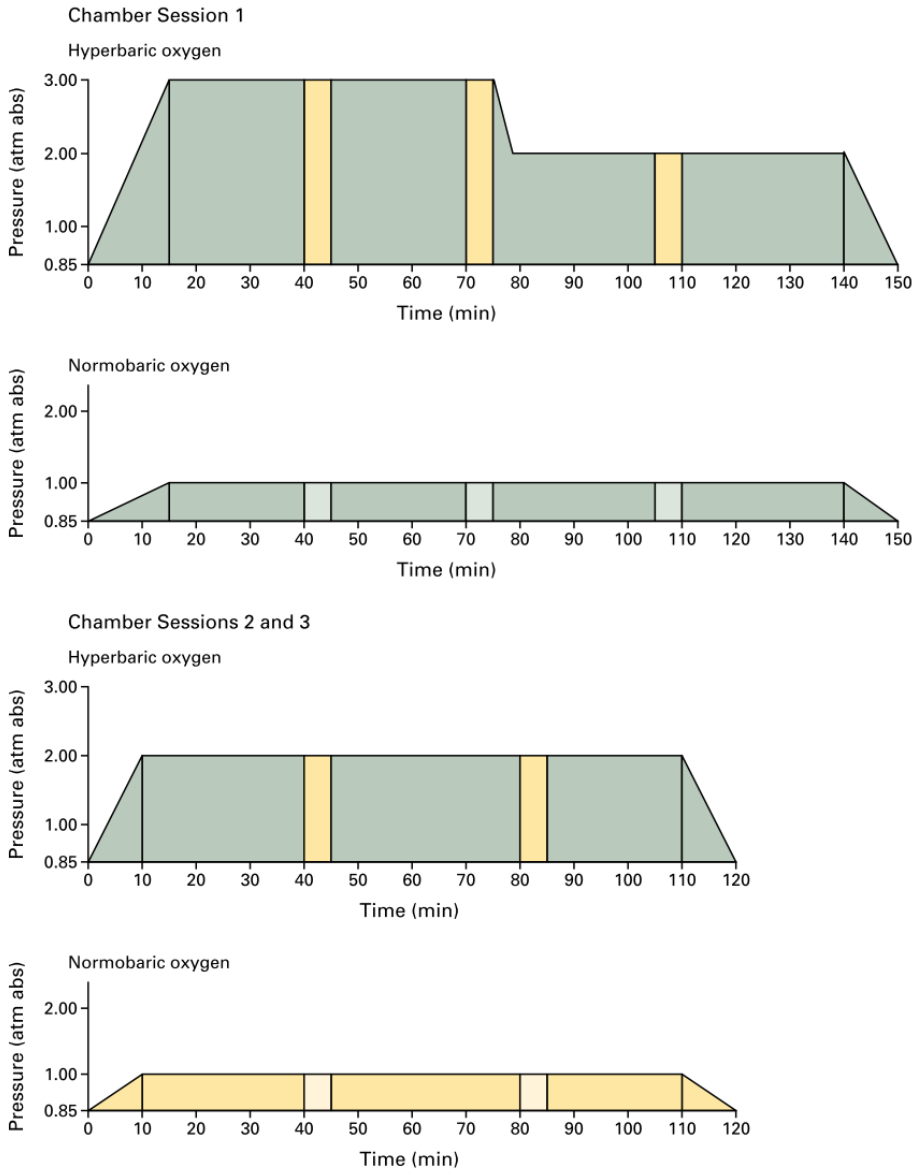
VOLUME 347 OCTOBER 3, 2002 NUMBER 14

HYPERBARIC OXYGEN FOR ACUTE CARBON MONOXIDE POISONING

LINDELL K. WEAVER, M.D., RAMONA O. HOPKINS, PH.D., KAREN J. CHAN, B.S., SUSAN CHURCHILL, N.P., C. GREGORY ELLIOTT, M.D., TERRY P. CLEMMER, M.D., JAMES F. ORME, JR., M.D., FRANK O. THOMAS, M.D., AND ALAN H. MORRIS, M.D.


Study
enrollment
≤24 Hr
≤1 Hr
Chamber
sessions
≤23 Hr
1
2
3
Questionnaire,
GDS, ADL,
SF-36
2 wk
6 wk
Hyperbaric O_2
Normobaric O_2
CO
exposure
Clinical O_2
therapy
Neuropsychological testing
Neurologic
examination
Questionnaire
on awareness of
treatment-group
assignment


Chamber Session 1
Hyperbaric oxygen
Pressure (atm abs)
3.00
2.00
1.00
0.85
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
Time (min)
Normobaric oxygen
Pressure (atm abs)
2.00
1.00
0.85
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
Time (min)
Chamber Sessions 2 and 3
Hyperbaric oxygen
Pressure (atm abs)
3.00
2.00
1.00
0.85
0 10 20 30 40 50 60 70 80 90 100 110 120
Time (min)
Normobaric oxygen
Pressure (atm abs)
2.00
1.00
0.85
0 10 20 30 40 50 60 70 80 90 100 110 120
Time (min)

HBOT 25% VS. 46%

- Not clear which patients should receive hyperbaric-oxygen therapy

- Additional uncertainties
  - The optimal chamber pressure
  - The optimal number of hyperbaric-oxygen sessions
  - The maximal interval after poisoning during which hyperbaric oxygen may still have a favorable effect

- Most clinicians do not administer hyperbaric oxygen if more than 24 hours has elapsed since carbon monoxide poisoning
  - Case reports describe improvement of sequelae with a series of hyperbaric-oxygen sessions beginning days after poisoning, although mechanisms of possible benefit are unknown.

Myers, R. A., et al. Ann Emerg Med 1985

- A single-center, double-blind clinical trial (Clinical Trials. gov number, NCT00465855) is under way to determine the effect of one or three hyperbaric oxygen sessions on rates of cognitive sequelae at 6 weeks among accidentally poisoned patients presenting less than 24 hours after exposure.

Study Description Go to

Brief Summary:

This randomized trial will investigate important clinical outcomes of patients with acute carbon monoxide poisoning randomized to receive either one or three hyperbaric oxygen treatments.

Condition or disease	Intervention/treatment	Phase
Carbon Monoxide Poisoning	Combination Product: Hyperbaric Oxygen (HBO2) - 3 sessions Combination Product: Hyperbaric Oxygen (HBO2) - 1 session	Phase 4

Detailed Description:

All patients presenting with acute carbon monoxide poisoning will receive one hyperbaric oxygen treatment (barring contraindications for hyperbaric oxygen therapy). After this treatment, eligible patients who provide consent will be randomly allocated to receive two sham sessions, or two additional hyperbaric oxygen sessions administered in a double-blind fashion.

Outcome measures will be administered at 6 weeks and 6 months.

Study Design Go to

Study Type:	Interventional (Clinical Trial)
Actual Enrollment:	75 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	Randomized Trial of One Versus Three Hyperbaric Oxygen Treatments for Acute CO Poisoning
Actual Study Start Date:	June 3, 2007
Actual Primary Completion Date:	September 10, 2016
Actual Study Completion Date:	January 28, 2017

Resource links provided by the National Library of Medicine NIH NLM

MedlinePlus related topics: Carbon Monoxide Poisoning Oxygen Therapy Poisoning

U.S. FDA Resources

1 VS 3 double blinded sham controlled RCT

A randomized trial of one v. three hyperbaric oxygen sessions for acute carbon monoxide poisoning

Weaver LK 1,2, Churchill S 1, Deru K 1, Handrahan D 3

1 Division of Hyperbaric Medicine Intermountain Medical Center, Murray, Utah, and Intermountain LDS Hospital, Salt Lake City, Utah

2 University of Utah School of Medicine, Salt Lake City, Utah

3 Statistical Data Center, Intermountain Medical Center, Murray, Utah

Presenting Author: Lindell K. Weaver, MD

lindell.weaver@imail.org

Weaver LK, et al. UHM ASM 2018 SESSION D: CLINICAL HBO2 THERAPY

결과

Sham 50% VS. HBOT 52%

Effect of Hyperbaric Oxygen Therapy Initiation Time in Acute Carbon Monoxide Poisoning

Yoonsuk Lee, MD[1,2]
Yong Sung Cha, MD[1,2]
Sung Hwa Kim, BS[3]
Hyun Kim , MD, PhD[1,2]

OBJECTIVES: Hyperbaric oxygen therapy (HBO_2) is recommended for symptomatic patients within 24-hour postcarbon monoxide poisoning. Previous studies have reported significantly better outcomes with treatment administered within 6 hours after carbon monoxide poisoning. Thus, we aimed to compare the neurocognitive outcomes according to HBO_2 delay intervals.

DESIGN: Retrospective analysis of data from our prospectively collected carbon monoxide poisoning registry.

SETTING: A single academic medical center in Wonju, Republic of Korea.

PATIENTS: We analyzed the data of 706 patients older than 16 years treated with HBO_2 with propensity score matching. Based on carbon monoxide exposure-to-HBO_2 delay intervals, we classified patients into the early (control, less than or equal to 6 hr) and late (case, 6–24 hr) groups. The late group was further divided into Case-1 (6–12 hr) and Case-2 (12–24 hr) groups. We also compared mild (nonintubated) and severe (intubated) groups.

INTERVENTIONS: HBO_2.

MEASUREMENTS AND MAIN RESULTS: After propensity score matching, Global Deterioration Scale scores at 6 months postcarbon monoxide exposure showed significantly fewer poor outcome patients in the early than in the late group ($p = 0.027$). The early group had significantly fewer patients with poor outcomes than the Case-2 group ($p = 0.035$) at 1 month and than the Case-1 ($p = 0.033$) and Case-2 ($p = 0.004$) groups at 6 months. There were significantly more patients with poor prognoses at 6 months as treatment interval increased ($p = 0.008$). In the mild cohort, the early group had significantly fewer patients with poor 6-month outcomes than the late group ($p = 0.033$).

CONCLUSIONS: Patients who received HBO_2 within 6 hours of carbon monoxide exposure had a better 6-month neurocognitive prognosis than those treated within 6–24 hours. An increase in the interval to treatment led to an increase in poor outcomes.

KEY WORDS: carbon monoxide poisoning; cognitive dysfunction; hyperbaric oxygen therapy; prognosis; propensity score; time-to-treatment

In the United States, 50,000 patients with carbon monoxide (CO) poisoning are admitted to hospital emergency departments (EDs) (1), and CO poisoning causes 1,500 deaths annually (2, 3). CO poisoning can have severe neurologic sequelae. Hyperbaric oxygen therapy (HBO_2) within 24 hours of CO poisoning is a reasonable recommendation for patients with symptomatic CO poisoning (2). Most physicians do not treat with HBO_2 later than 24 hours after CO poisoning (4).

Weaver et al (5) conducted a double-blind, randomized controlled trial (RCT) satisfying all Consolidated Standards for the Reporting of Trials guidelines, which showed that HBO_2 significantly reduced the cognitive sequelae rate compared with normobaric oxygen therapy (NBO_2), at 6-week and 12-month

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TABLE 1.
Baseline Characteristics of the Propensity Score–Matched a

Variables	Unmatched			
	Early Group ($n = 407$)	Late Group ($n = 299$)	p	Early Gr ($n = 28$
Age (y)	49.0 (37.0–62.0)	50.0 (38.0–5		
Sex (male)	249 (61.2)	186 (62.2		
Intentionality	157 (38.6)	102 (34.1		
Source of CO				
Nonfire	378 (92.9)	279 (93.3		
Fire	29 (7.1)	20 (6.7)		
Duration of CO exposure (hr)	4.0 (1.0–8.0)	4.5 (2.0–		
Comorbidities				
Diabetes mellitus	45 (11.1)	32 (10.7		
Hypertension	81 (19.9)	57 (19.1		
Dyslipidemia	20 (4.9)	12 (4.0)		
Chronic kidney disease	2 (0.5)	1 (0.3)		
Heart disease	21 (5.2)	10 (3.3)		
Advanced liver disease	1 (0.3)	3 (1.0)		
Cancer	9 (2.2)	17 (5.7)		
Loss of consciousness	253 (62.2)	161 (53.9		
Initial patient status				
Shock	8 (2.0)	7 (2.3)		
Intubation	75 (18.4)	60 (20.1		
Glasgow Coma Scale	15.0 (13.0–15.0)	15.0 (13.0–1		
HBO_2-related information				
Time from rescue to first HBO_2 (hr)	3.8 (2.5–4.8)	9.1 (7.5–12		
Number within 24 hr after ED arrival	1.0 (1.0–1.0)	1.0 (1.0–1		
Total number	1.0 (1.0–2.0)	1.0 (1.0–		
Laboratory tests				
Initial carboxyhemoglobin	23.0 (11.1–32.3)	18.5 (7.3–		
Peak troponin I within 24 hr after ED arrival	0.02 (0.02–0.27)	0.02 (0.02–0		
Lactate	2.3 (1.5–3.7)	1.9 (1.3–		
Bicarbonate	20.9 (18.4–23.1)	21.4 (19.3–2		
Outcomes				
GDS				
At 1 mo	1.0 (1.0–2.0)	1.0 (1.0–		
At 6 mo	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.378	1.0 (1.0–
Poor GDS				
At 1 mo	34 (8.4)	35 (11.7)	0.138	19 (6.7)
At 6 mo	26 (6.4)	33 (11.0)	0.027	14 (4.9)

ED — emergency department, GDS — Global Deterioration Scale, HBO_2 — hyperbaric oxyge
Data are expressed as frequency (percentage), mean ± SD, and median (interquartile range)

TABLE 2.
Baseline Characteristics of the Propensity Score–Matched Cohort According to the Hyperbaric Oxygen Therapy Initiation Time Interval

Variables	Early Group ($n = 213$)	Case-1 Group ($n = 213$)	p	Early Group ($n = 76$)	Case-2 Group ($n = 76$)	p
			41	49.3 ± 17.6	49.7 ± 15.7	0.865
			00	45 (59.2)	45 (59.2)	1.000
			53	29 (38.2)	29 (38.2)	1.000
			32	65 (85.5)	68 (89.5)	0.467
				11 (14.5)	8 (10.5)	
			72	4.9 ± 4.5	5.3 ± 4.5	0.669
			66	9 (11.8)	8 (10.5)	0.808
			04	15 (19.7)	13 (17.1)	0.655
			85	4 (5.3)	3 (4.0)	0.706
			00	2 (2.6)	1 (1.3)	0.564
			63	4 (5.3)	3 (4.0)	0.655
			00	0 (0.0)	0 (0.0)	1.000
			17	3 (4.0)	4 (5.3)	0.706
			05	49 (64.5)	47 (61.8)	0.739
			27	1 (1.3)	1 (1.3)	1.000
			89	20 (26.3)	23 (30.3)	0.549
			47	15.0 (12.0–15.0)	15.0 (12.5–15.0)	0.883
			01	3.6 ± 1.4	16.6 ± 3.4	<0.001
			46	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.000
			81	1.0 (1.0–2.0)	1.0 (1.0–3.0)	0.587
			62	20.8 ± 13.8	22.4 ± 15.5	0.520
			65	0.02 (0.01–0.41)	0.06 (0.02–0.69)	0.154
			38	2.3 (1.5–3.8)	2.7 (1.8–3.7)	0.955
			58	21.6 (18.6–23.5)	21.5 (19.2–23.2)	0.871
Outcomes						
Poor Global Deterioration Scale						
At 1 mo	14 (6.6)	23 (10.8)	0.117	2 (2.6)	9 (11.8)	0.035
At 6 mo	9 (4.2)	19 (8.9)	0.033	1 (1.3)	11 (14.5)	0.004

HBO_2 — hyperbaric oxygen therapy.
Data are expressed as frequency (percentage), mean ± SD, and median (interquartile range).

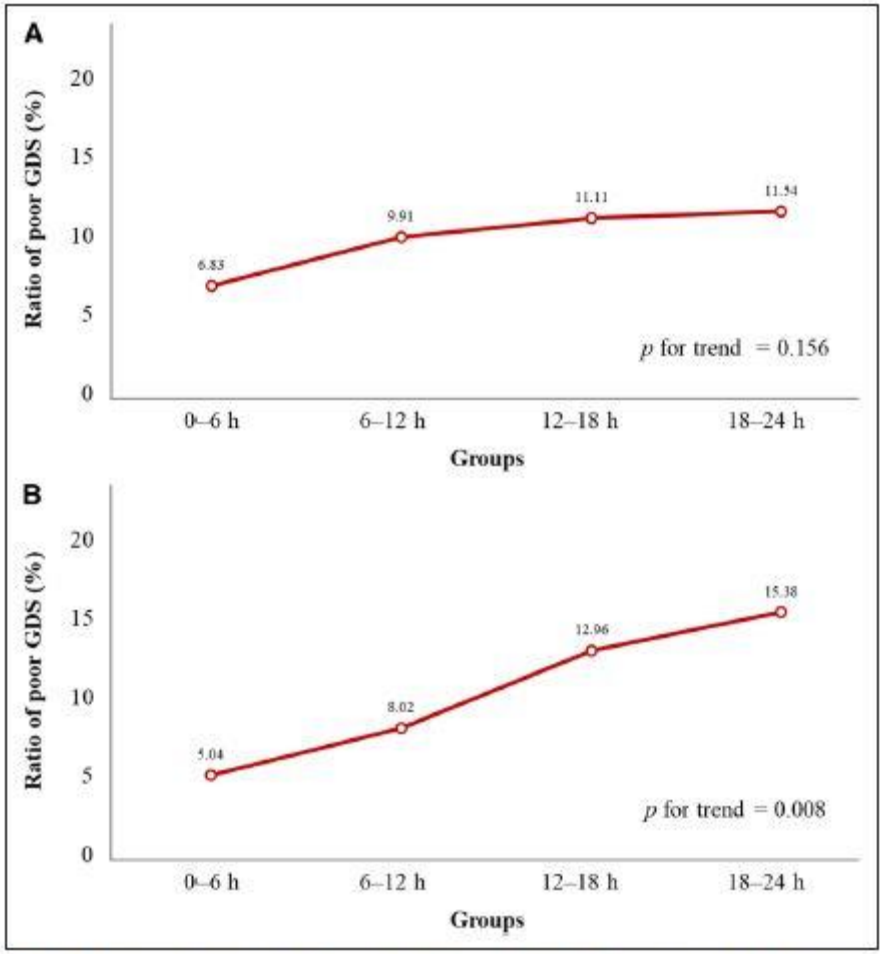


Figure 3. *P* for trend analysis at (**A**) 1 and (**B**) 6 mo according to changes in Global Deterioration Scale (GDS) scores with changes in the start time of hyperbaric oxygen therapy.

Current evidences + Expert opinions

Concise Clinical Review

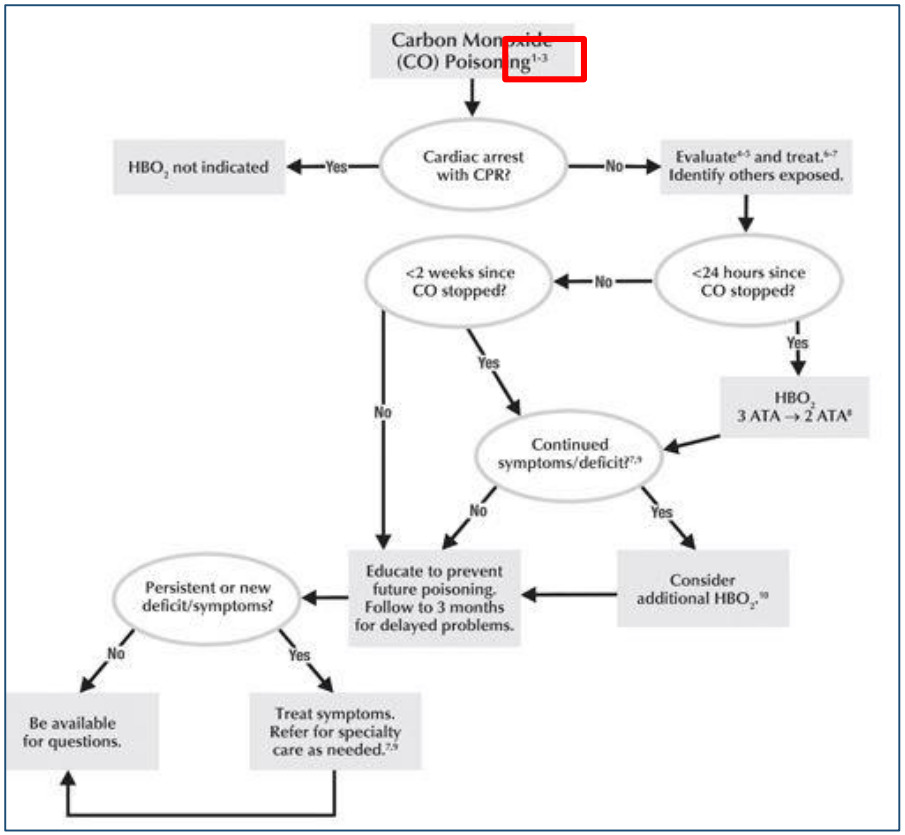
Practice Recommendations in the Diagnosis, Management, and Prevention of Carbon Monoxide Poisoning

Neil B. Hampson[1], Claude A. Piantadosi[2], Stephen R. Thom[3], and Lindell K. Weaver[4]

[1]Virginia Mason Medical Center, Seattle, Washington; [2]Duke University Medical Center, Durham, North Carolina; [3]University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; and [4]Intermountain Medical Center, Salt Lake City, Utah

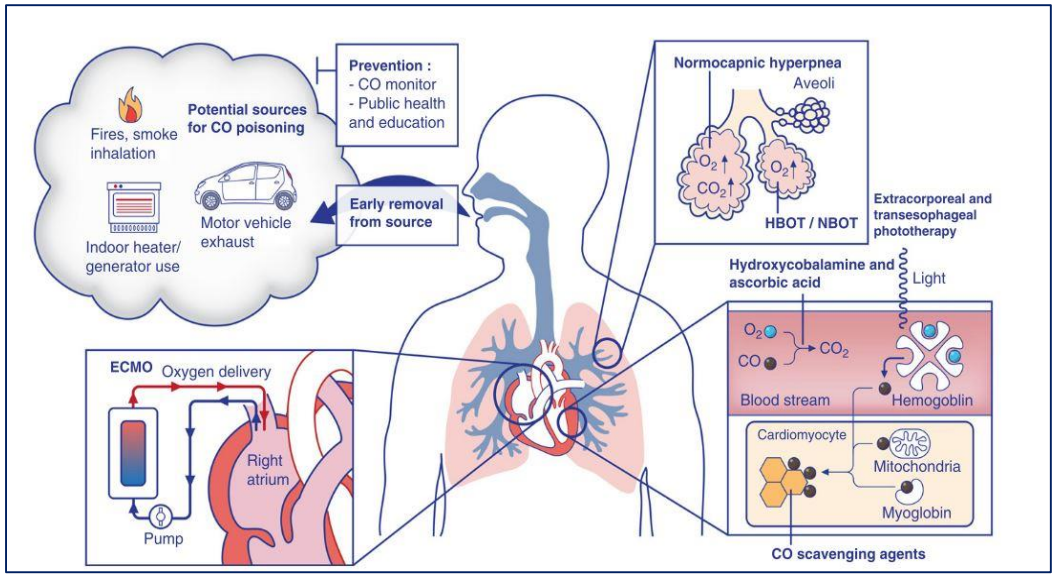
Hampson NB, et al. Am J Respir Crit Care Med. 2012.

UHMS indications (14th edition)



1. CO poisoning = CO exposure + Symptoms
2. May be acute or chronic
3. CO-Hb and SpCO may be elevated or normal due to time from and oxygen administration.

다른 치료법들…



Agent (Ref. No.)	Species	Effect
Inflammation		
Allopurinol (110)	Rats	Reduced neuronal death, reduced expression of proinflammatory markers, and improved performance in Morris water maze
Corticosteroids plus amifostine (111)	Rats	Reduced lipid peroxides
Methylprednisolone plus memantine (112)	Humans	Case report: reversed delayed neurocognitive deficits that appeared at Week 3 by Week 12
Ketamine (113)	Rats	Reduced cerebral edema, blood lactate levels, and improved survival
Oxidative stress		
Hydrogen sulfide (114)	Rats	Improved cognitive function, reduced apoptosis and inflammatory response, decreased oxidative damage in brains
Fructose-1,6-diphosphate (115)	Mice	Reduced impairment of memory function, improved mortality
Magnesium sulfate (116)	Rats	Protective versus oxidative damage in cerebrum
Cardiac dysfunction		
Levosimendan (117)	Humans	Case report: improved ejection fraction in stunned myocardium
Atenolol (118)	Rats	Pretreatment associated with increased contraction band necrosis
Nimodipine (115)	Mice	Decreased impairment of memory function and improved mortality rate
Verapamil (113)	Rats	No improvement in survival, blood pressure, blood lactate, or cerebral edema

저체온치료

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

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

Kim SJ, et al. Crit care med. 2020.

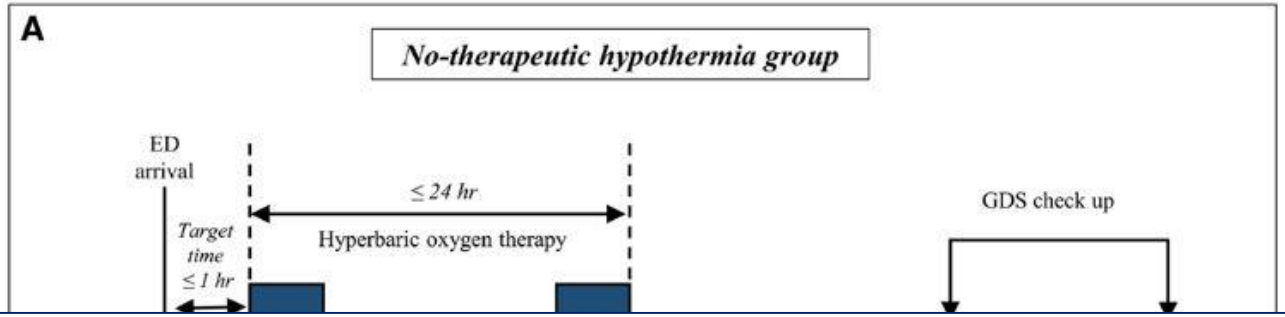


TABLE 2. Outcome Data for the No-Therapeutic Hypothermia and Therapeutic Hypothermia Groups

Variables	No-TH ($n = 16$)	TH ($n = 21$)	p
GDS			
1 mo	7.0 (3.0–7.0)	5.0 (1.0–7.0)	0.078
Favorable outcome (GDS, 1–3)	1 (6.3)	7 (33.3)	0.104
Poor outcome (GDS, 4–7)	15 (93.8)	14 (66.7)	
6 mo	7.0 (2.0–7.0)	3.0 (1.0–7.0)	0.015
Favorable outcome (GDS, 1–3)	2 (12.5)	11 (55.0)	0.008
Poor outcome (GDS, 4–7)	14 (87.5)	9 (45.0)	
Improvement in GDS score at 6 mo than at 1 mo	3 (18.8)	13 (65.0)	0.006
Carbon monoxide–related mortality	4 (25.0)	4 (19.0)	0.705

GDS = Global Deterioration Scale, TH = therapeutic hypothermia.

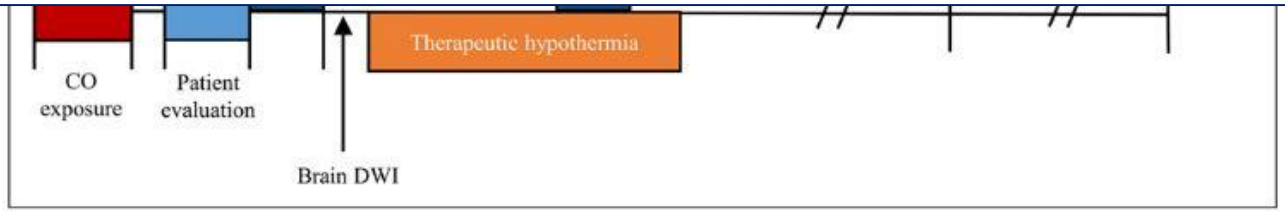


Figure 1. Schematic treatment flow between no-therapeutic hypothermia (TH) (**A**) and TH (**B**) groups. CO = carbon monoxide, DWI = diffusion-weighted image, ED = emergency department, GDS = Global Deterioration Scale.

7. 객관적 예후 마커들

PLASMA LACTATE

Benaissa, et al. Intensive Care Med. 29: 1372, 2003

NATRIURITIC PEPTIDES

Pach, et al. Przeglad. Lekarski 62: 465, 2005

Davutoglu, et al. Inhalation Toxicol. 18: 155, 2006

PLASMA S-100β/NEURON SPECIFIC ENOLASE

Brvar, et al. Resuscitation 61: 357, ’04

Rasmussen, et al. Acta Anaesth. Scand. 48:469,’04

Cakir, et al. Am. J. Emerg. Med. 28: 61, 2010

Akelma, et al. Am. J. Emerg. Med. 31: 524, 2013

HEART-TYPE FATTY ACID BINDING PROTEIN

Erenler, et al. Am. J. Emerg. Med. 31: 1165, 2013

PLASMA COPEPTIN (Pro-vasopressin fragment)

Pang, et al. Peptides in press, 2014

NEUTROPHIL β_2 INTEGRINS

Thom et al. Am. J. Resp. Crit. Care Med. 174: 1239, ‘06

PLASMA INFLAMMATORY MARKERS (99 !)

Thom, et al. Clin. Toxicol. 48: 47-56, 2010

Myelin Basic Protein

J Neurol (2012) 259:1698–1705
DOI 10.1007/s00415-011-6402-5

ORIGINAL COMMUNICATION

Fractional anisotropy in the centrum semiovale as a quantitative indicator of cerebral white matter damage in the subacute phase in patients with carbon monoxide poisoning: correlation with the concentration of myelin basic protein in cerebrospinal fluid

Takaaki Beppu · Shunrou Fujiwara · Hideaki Nishimoto · Atsuhiko Koeda · Shinsuke Narumi · Kiyoshi Mori · Kuniaki Ogasawara · Makoto Sasaki

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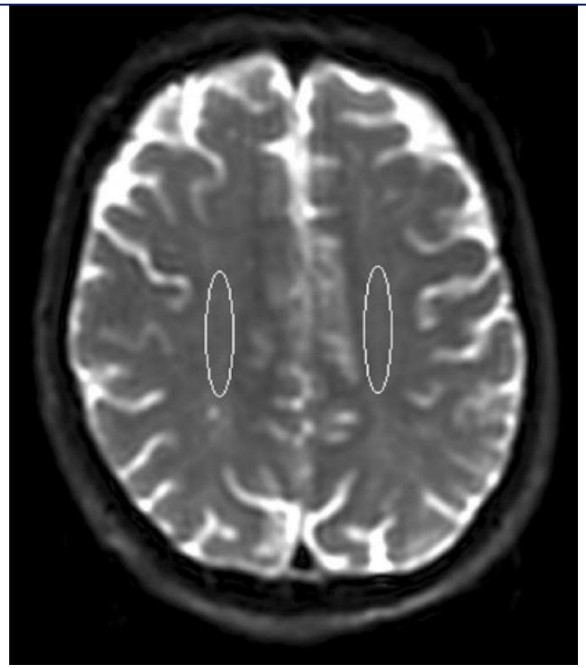
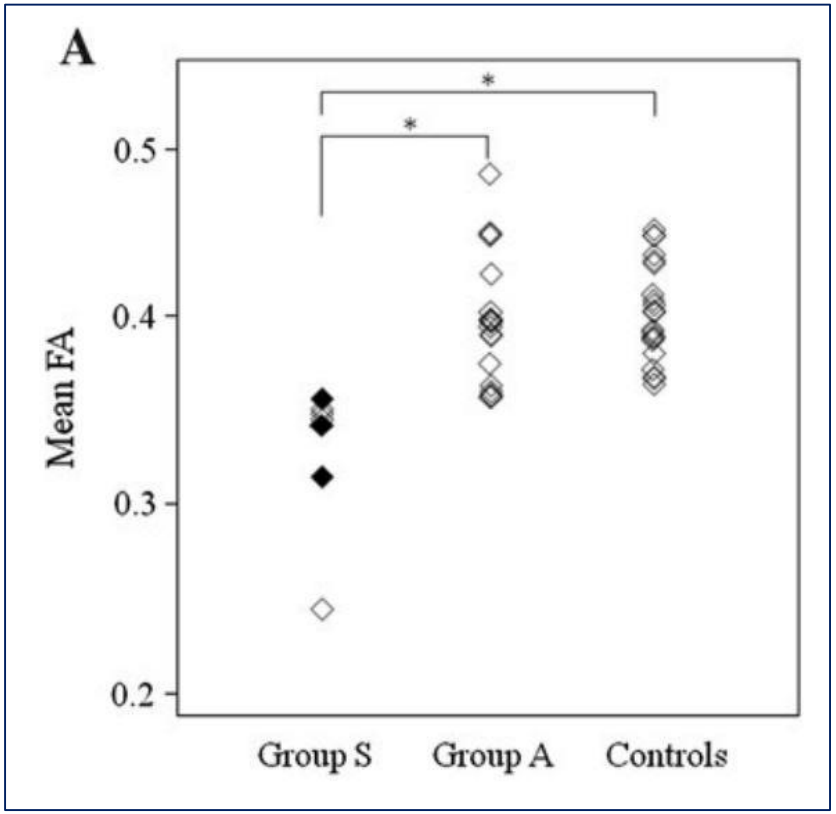


Fig. 1 Measurements of FA and ADC value at the centrum semiovale in a patient (case 7 in group S). Regions of interest (ROIs) were placed bilaterally on the centrum semiovale in non-diffusion-weighted image



급성기 brain MRI

Research

JAMA Neurology | Original Investigation

Acute Brain Lesions on Magnetic Resonance Imaging and Delayed Neurological Sequelae in Carbon Monoxide Poisoning

Sang-Beom Jeon, MD, PhD; Chang Hwan Sohn, MD, PhD; Dong-Woo Seo, MD, PhD; Bum Jin Oh, MD, PhD; Kyoung Soo Lim, MD, PhD; Dong-Wha Kang, MD, PhD; Won Young Kim, MD, PhD

Jeon SB, et al. JAMA neurology. 2018;75(4):436-43.

Dr. Weaver의 의견

Dr. Thom의 의견

asic and Clinical Researc
: 2018년 10월 16일 화
후 1시
오후 6시
장소 : 연세대
: 연세대학교 원주의과대
급의학교실
주관 : 연세대

Take home messages

I. Basic pathophysiology: CO-Hb 형성에 의한 hypoxia 이외에도 여러 기전이 존재.

II. 진단
   I. 증상: 비특이적. 흔한 증상은 두통, 어지러움, 오심/구토, 의식변화, 피로, 흉통, 호흡곤란, 의식소실…
   II. CO-Hb 역할: 임상적 진단을 confirm한다. 하지만 증상 또는 예후와 상관성이 떨어진다.

III. 치료
   I. NBOT: 100% 산소를 nonrebreather facemask 또는 intubation tube로 CO-Hb 3%미만까지 준다. 그리고 환자가 증상이 없을 때까지…(보통 6시간 이내)
   II. HBOT selection
      I. 현재까지 완벽한 Ix은 없다.
      II. LOC, ischemic cardiac change, neurologic deficits, 중증의 metabolic acidosis, 또는 CO-Hb>25%
      III. 위에 포함되지 않더라도 의사의 결정에 따라… (증상이 있다면 하자.)
   III. HBOT의 목표: neurocognitive sequelae의 예방
   IV. Optimal HBOT protocol
      I. 아직 모르지만 Weaver protocol이…(현실적으로 어렵다.)
      II. 그래서 Thom의 RCT protocol을 많이 사용한다.

IV. Follow-up
   I. Cognitive sequelae의 screening을 위하여 4-6주는 실시
   II. Intentional poisoning: 정신과

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Thank you
for Your Attention

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