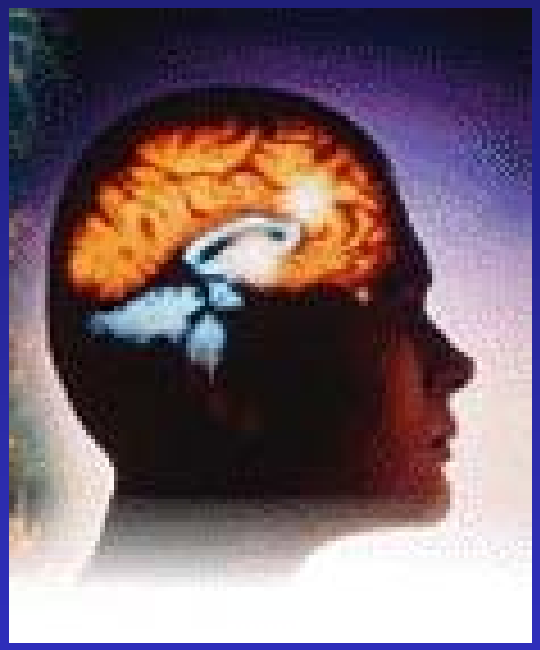
STRATEGIC USE OF OXYGEN TO OPTMIZE NEUROLOGIC OUTCOME AFTER ACUTE BRAIN INJURY



Gary Fiskum, Ph.D.

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R Adams Cowley Shock Trauma Center for Research

When is more than enough too much?

DISCLOSURES

- *NIH NINDS*
- *NIH NICHD*
- *TATRC*
- *Maryland Indusrial Partnerships*

ACKNOWLEDGMENTS

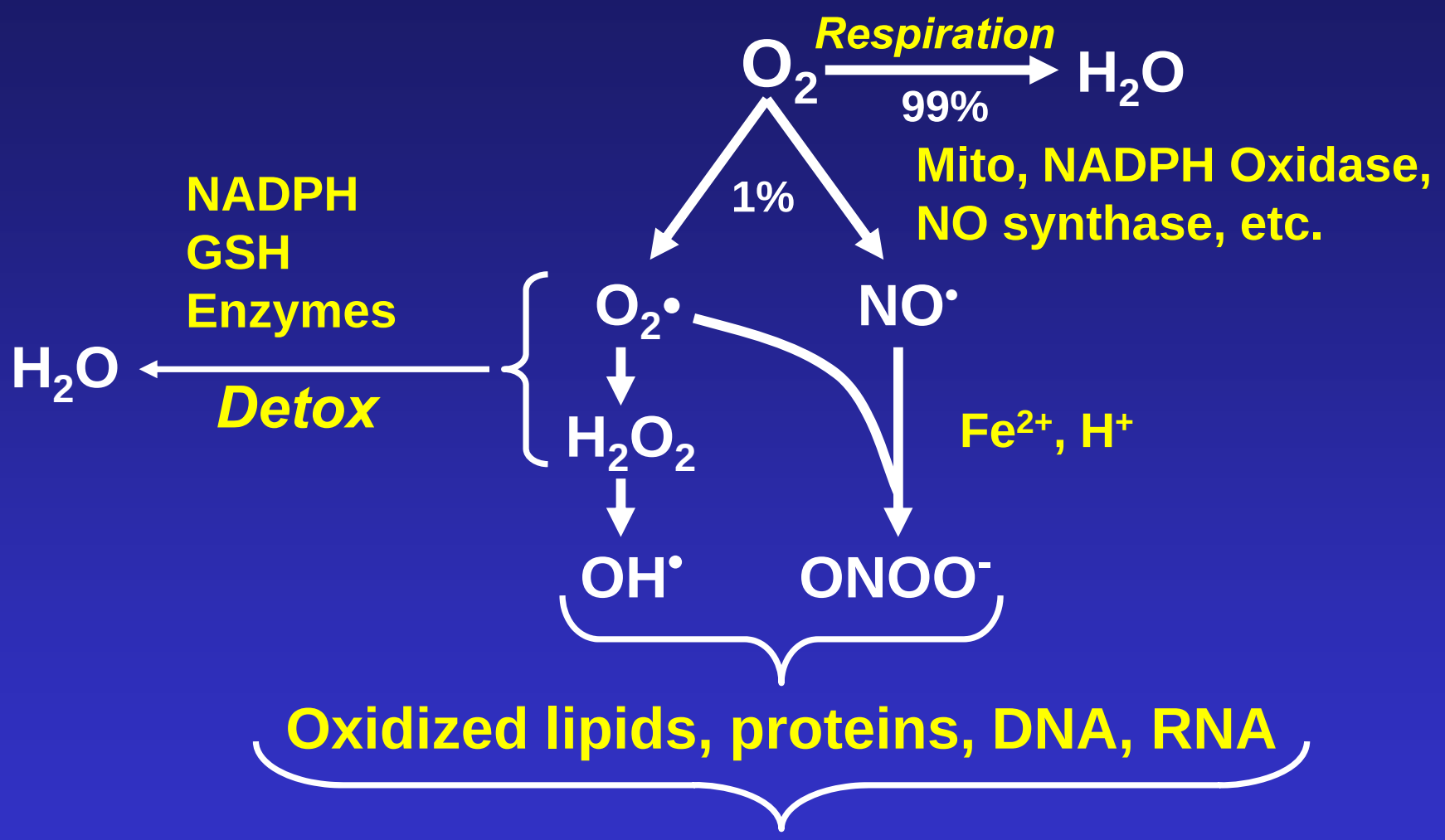
- *Robert E. Rosenthal, M.D., Professor*
- *Mary McKenna, Ph.D., Assoc. Professor*
- *Rao Gullapalli, Ph.D., Assoc. Professor*
- *Tibor Kristian, Ph.D., Asst. Professor*
- *Irina Balan, Ph.D., Postdoc*
- *Erica Martin, M.D., Ph.D. Student*
- *Camelia Danilov, Ph.D. Student*
- *Tiffany Greco, Ph.D. Student*
- *Julie Hazelton, M.S., Res. Specialist*

LESSONS LEARNED FROM STUDIES ON BRAIN INJURY CAUSED BY CARDIAC ARREST

BRAIN INJURY CAUSED BY CARDIAC ARREST

- *Over 250,000 resuscitated from cardiac arrest (CA) per year in US with very high neurologic morbidity and mortality.*
- *Am. Heart Assoc. guidelines indicate use of 100% resuscitative O_2 but no monitoring of PaO_2.*
- *Excessive tissue O_2 not useful for metabolism but can promote formation of reactive O_2 species and oxidative stress.*
- *Clinically, hyperoxia is known to damage lungs and retina.*

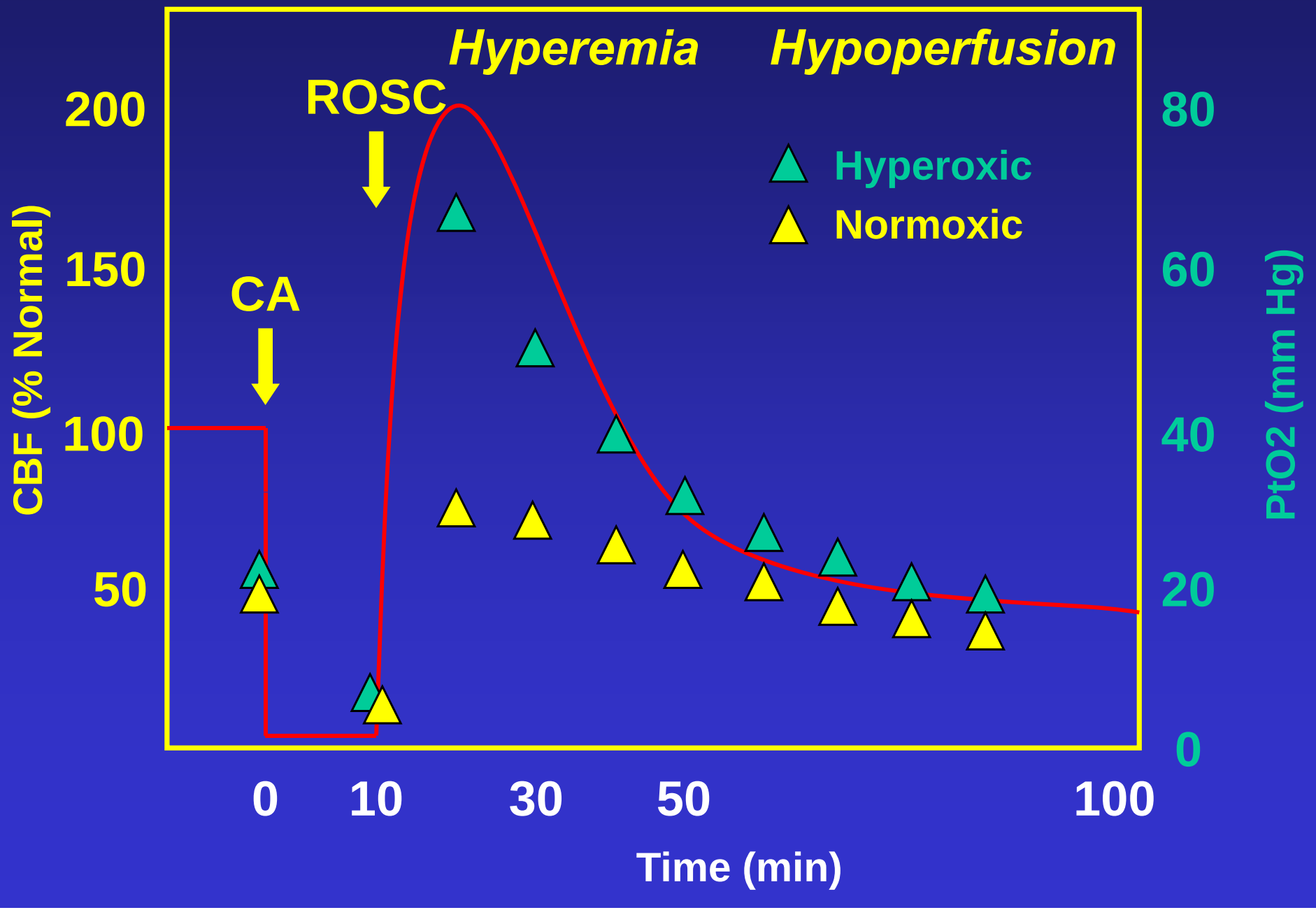
OXIDATIVE STRESS



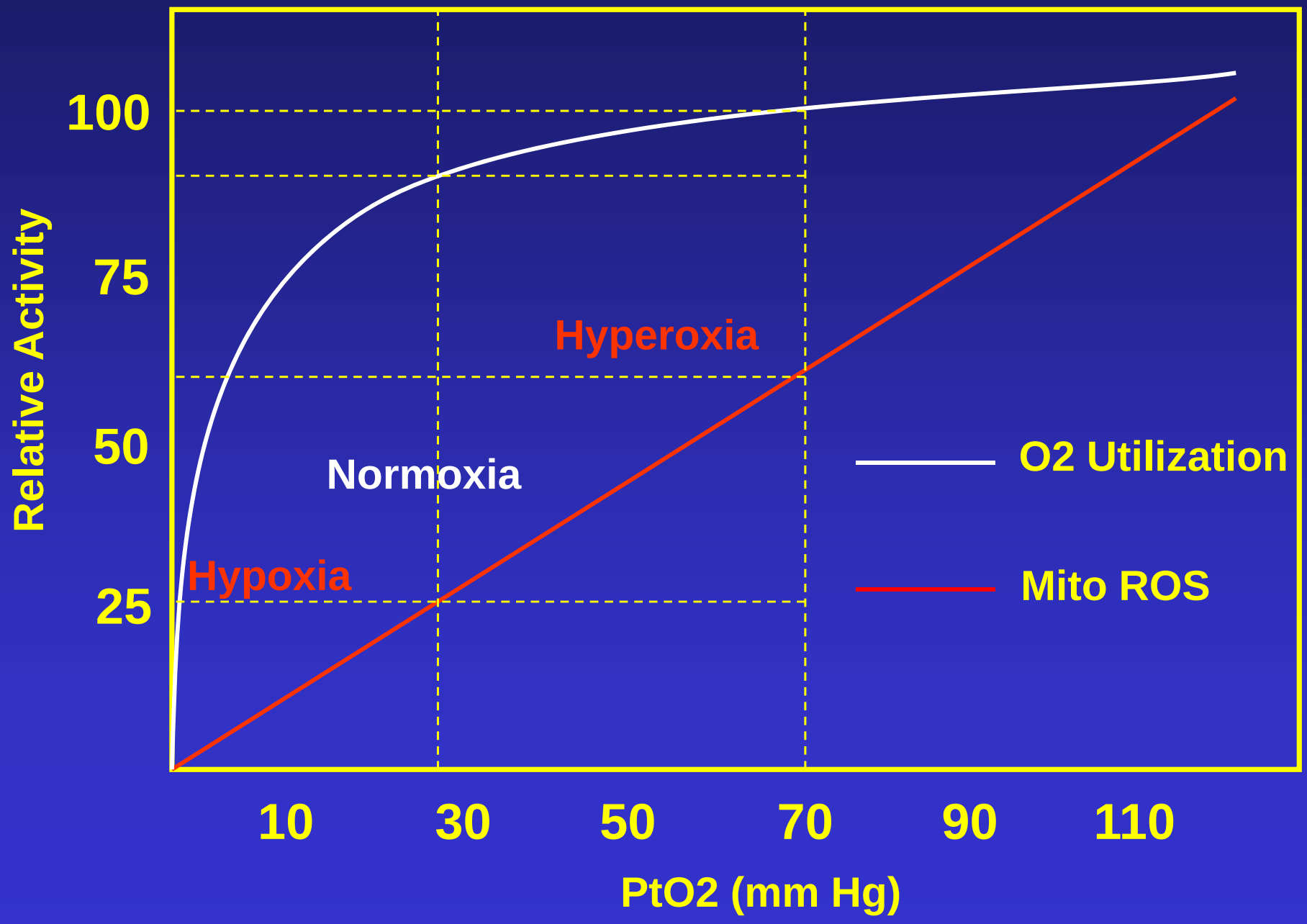
Oxidized lipids, proteins, DNA, RNA

*Ionic dyshomeostasis, enzyme **dysfunction**, metabolic inhibition, apoptotic gene induction, inflammation*

NORMOXIC RESUSCITATION AVOIDS CEREBRAL HYPEROXIA



EFFECTS OF BRAIN PtO2 ON RESPIRATION AND ROS PRODUCTION



Can minimizing the use of high FiO2 during resuscitation after cardiac arrest improve neurologic outcome?

OXIMETRY-BASED NORMOXIC RESUSCITATION PROTOCOL

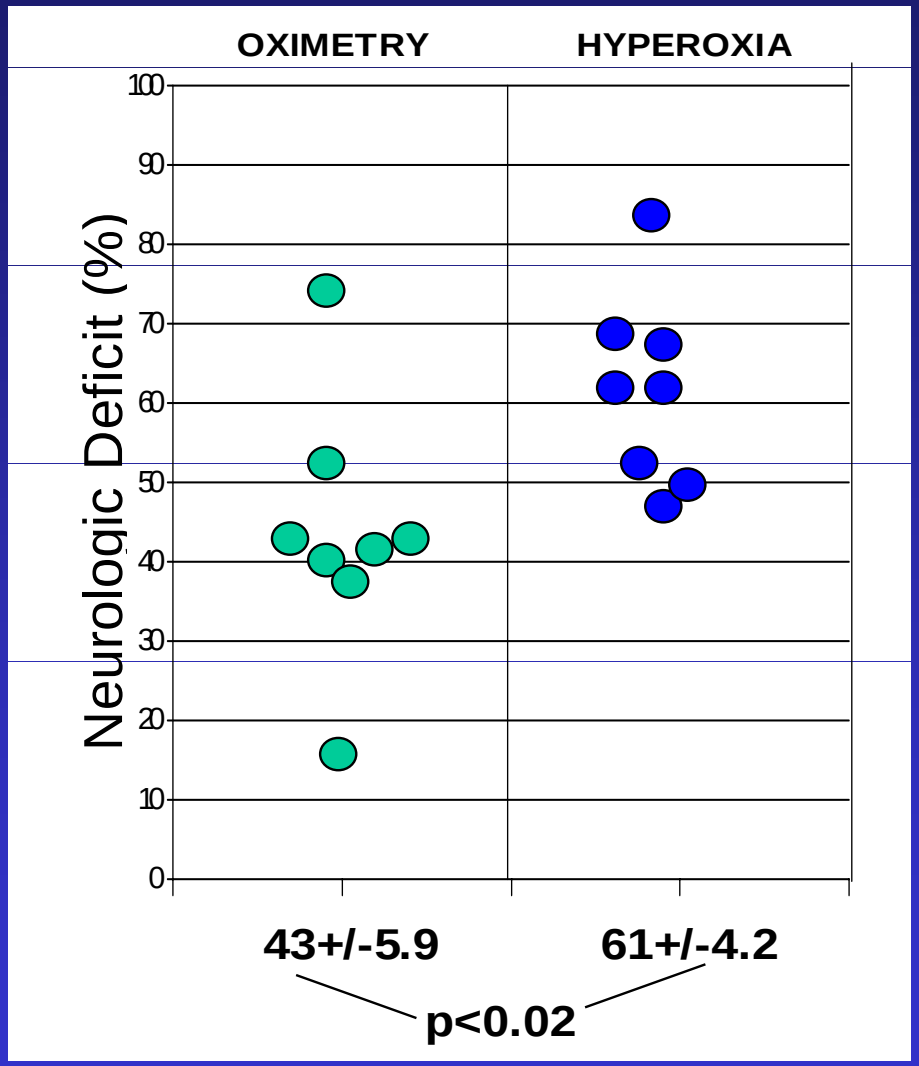
- **100% FiO2 initially**
- **Rapidly adjust FiO2 to maintain SpO2 at 94-98%**
  - **Reduce FiO2 to 50% after ROSC**
  - **Reduce FiO2 by 5% every two minutes until SpO2 at 94-98%**
  - **Increase FiO2 when needed to maintain SpO2 at 94-98%**
- ***Neurochemistry and immunohistochemistry at 2, 6, and 24 hr ROSC, neurologic exam at 23 hr, histopathology at 24 hr.***

1 hr POST-RESUSCITATIVE pO2

Normoxic = 83.8 ± 3.7 mm Hg

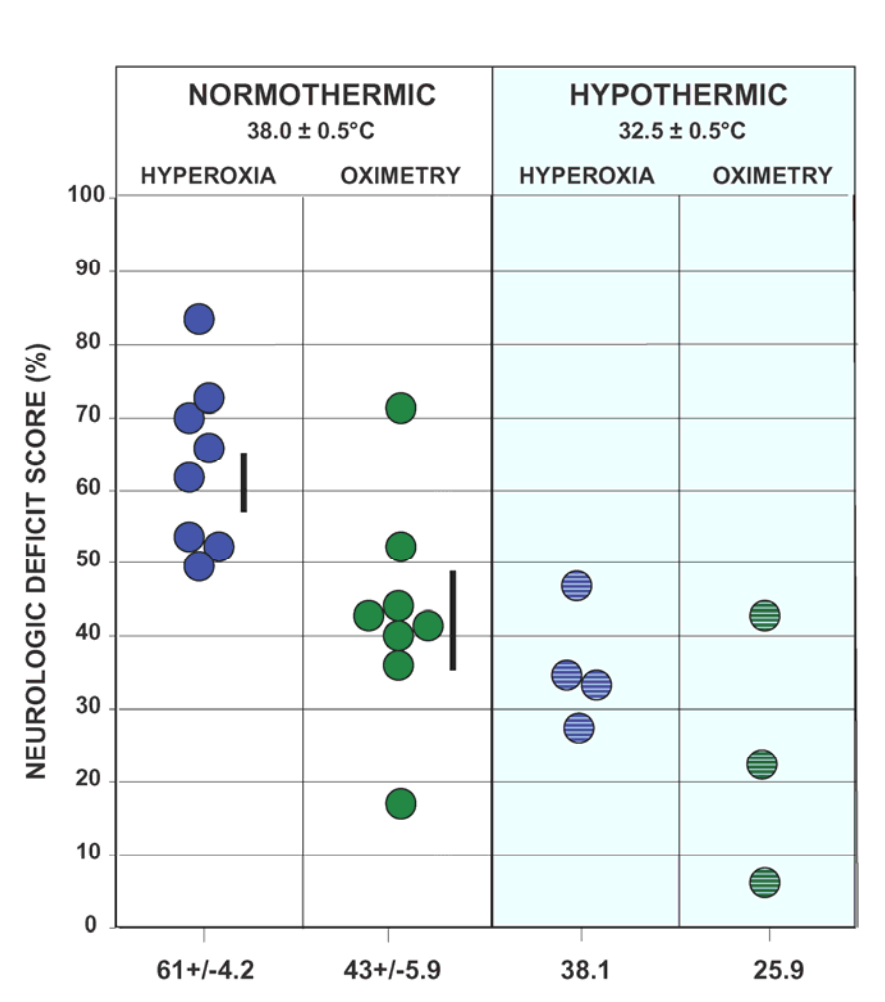
Hyperoxic = 454 ± 34.2 mm Hg

OXIMETRY-GUIDED RESUSCITATION REDUCES NEUROLOGIC IMPAIRMENT

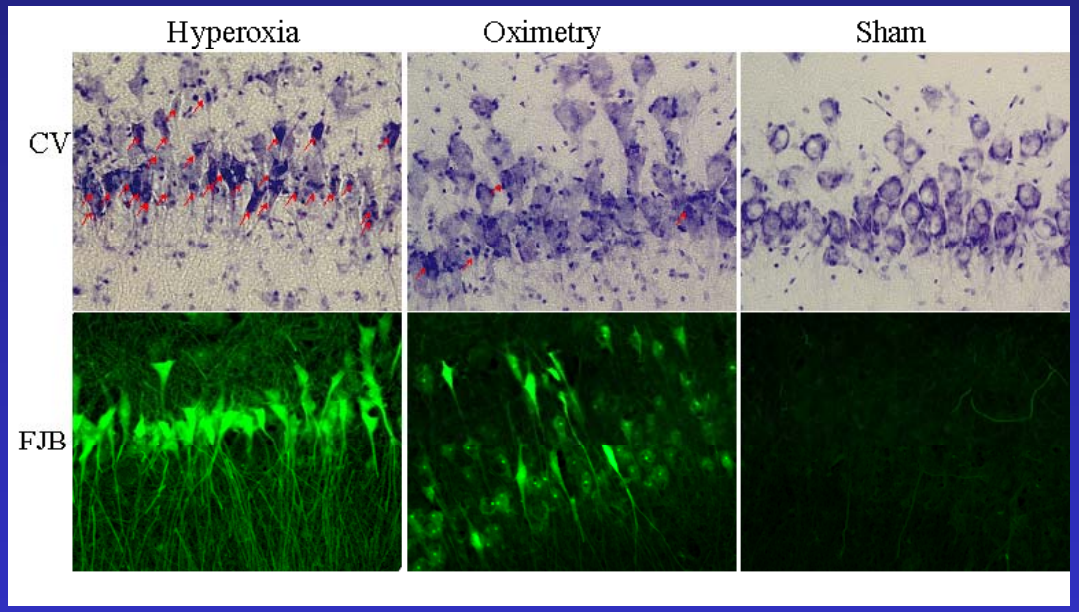


Balan et al., Stroke, 2006

NORMOXIC RESUSCITATION AFTER CANINE CARDIAC ARREST IMPROVES NEUROLOGIC OUTCOME WHEN FOLLOWED BY HYPOTHERMIA

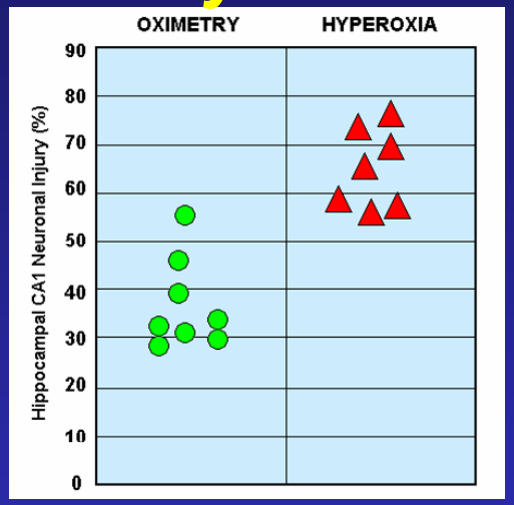


OXIMETRY-GUIDED RESUSCITATION REDUCES NEURONAL CELL DEATH



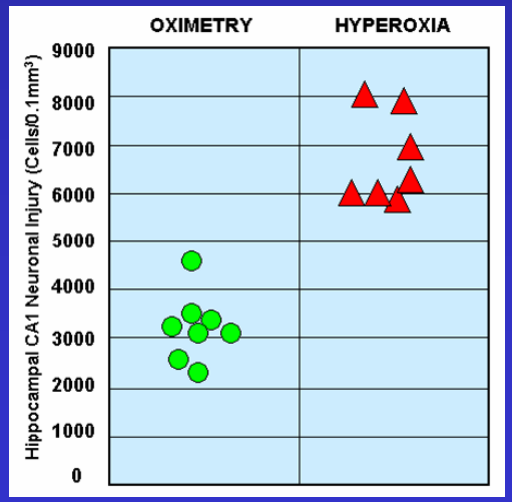
Balan et al., Stroke, 2006

Cresyl Violet



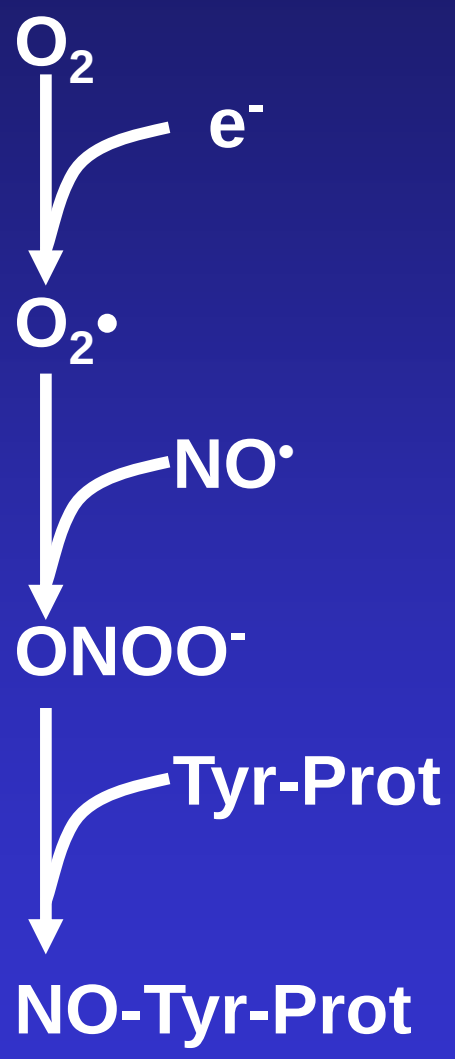
P < 0.001

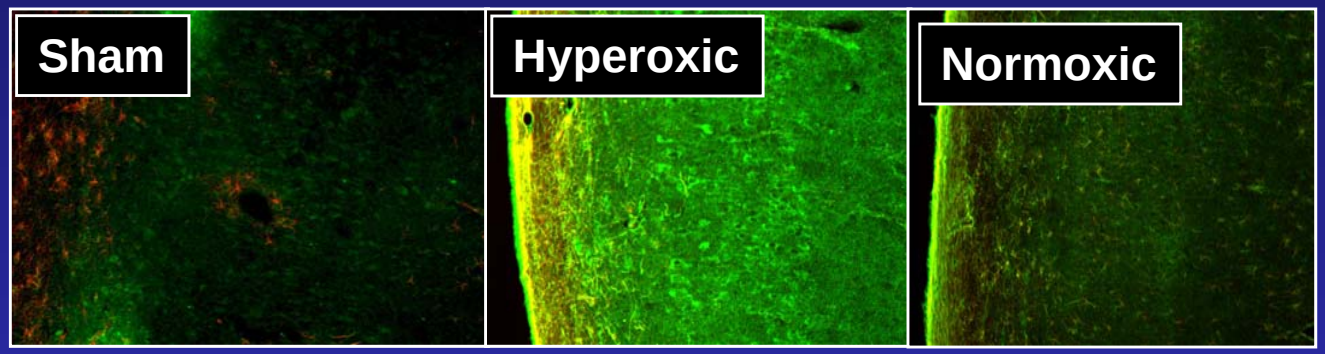
Fluoro-Jade B

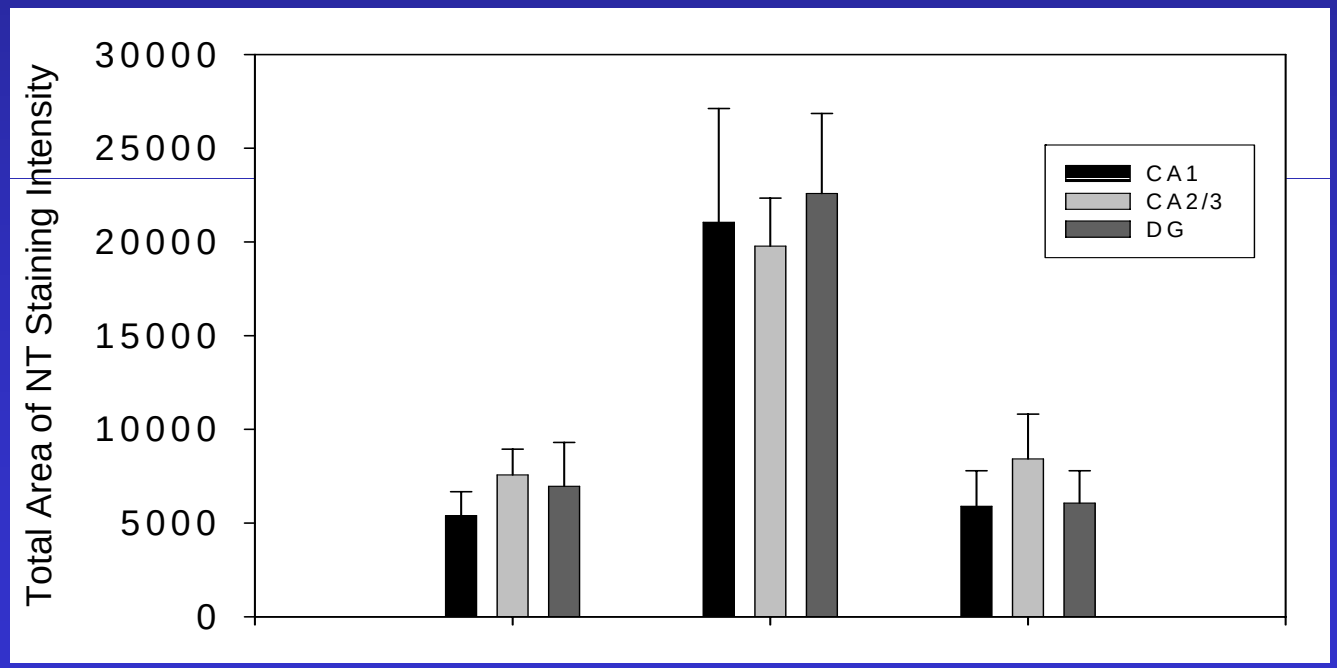


P < 0.001

NORMOXIC RESUSCITATION REDUCES HIPPOCAMPAL PROTEIN NITRATION



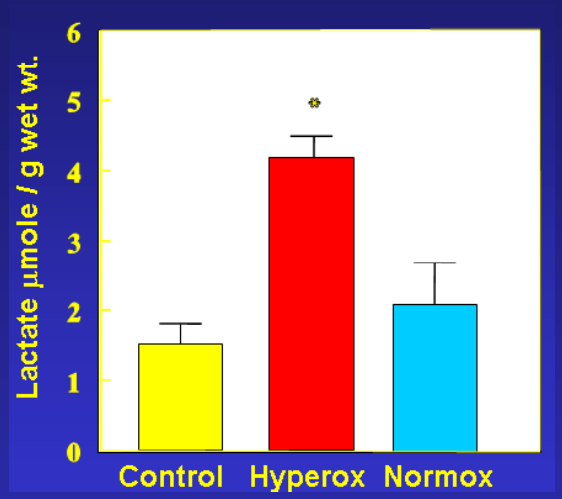


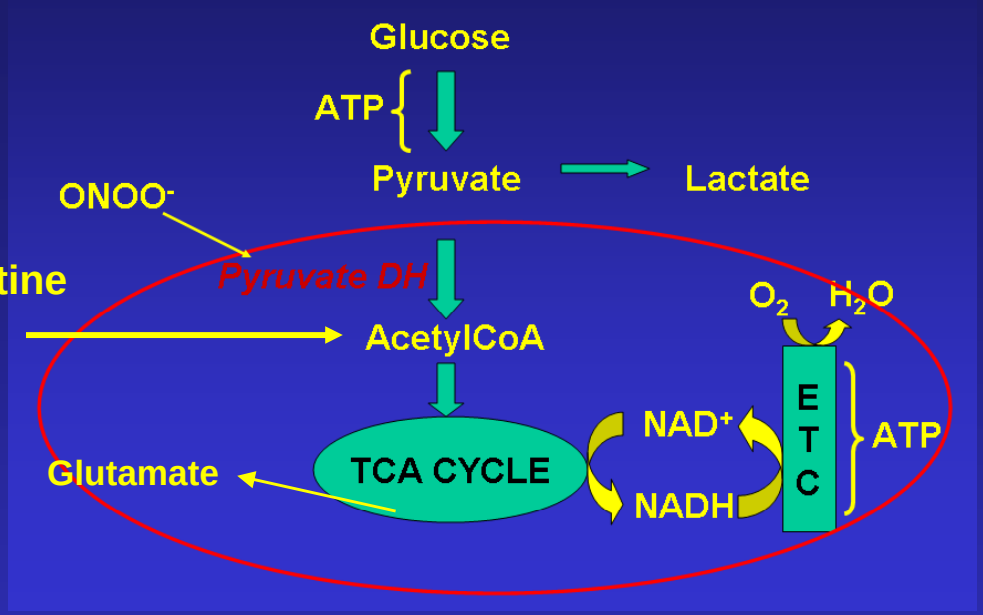


Vereczki et al., J Cereb Blood Flow Metab 2006

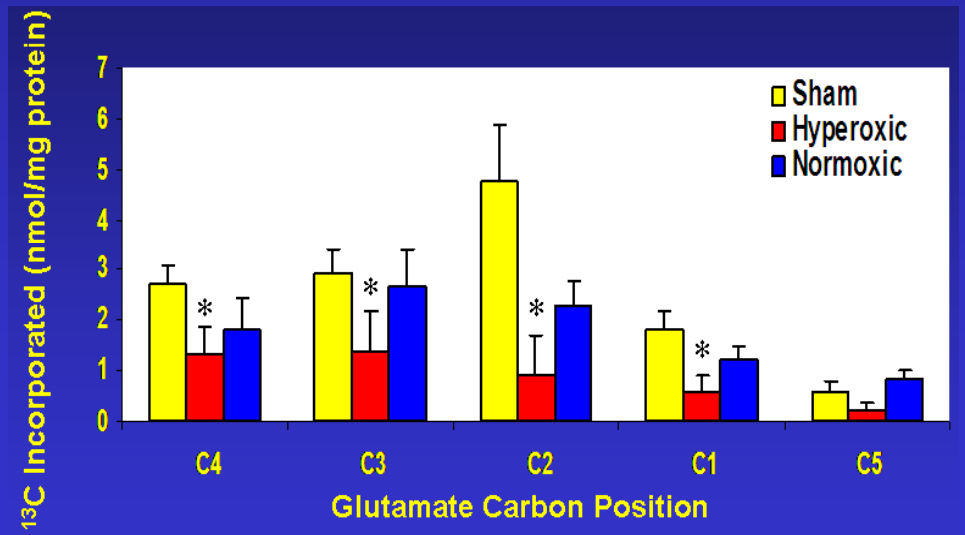
NORMOXIC RESUSCITATION IMPROVES CEREBRAL ENERGY METABOLISM

Normoxia Lowers Lactate



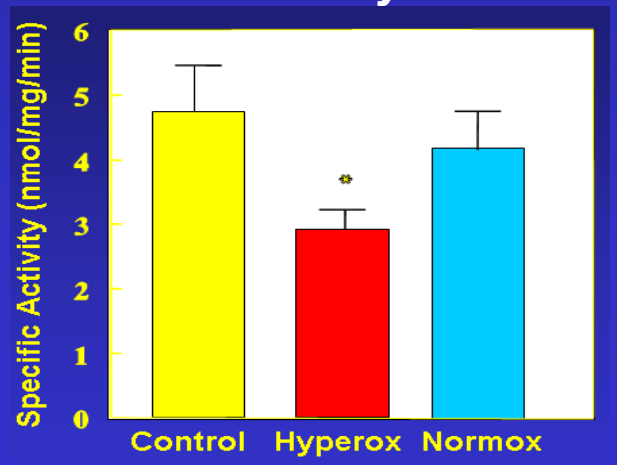


Normoxia Improves Aerobic Metabolism



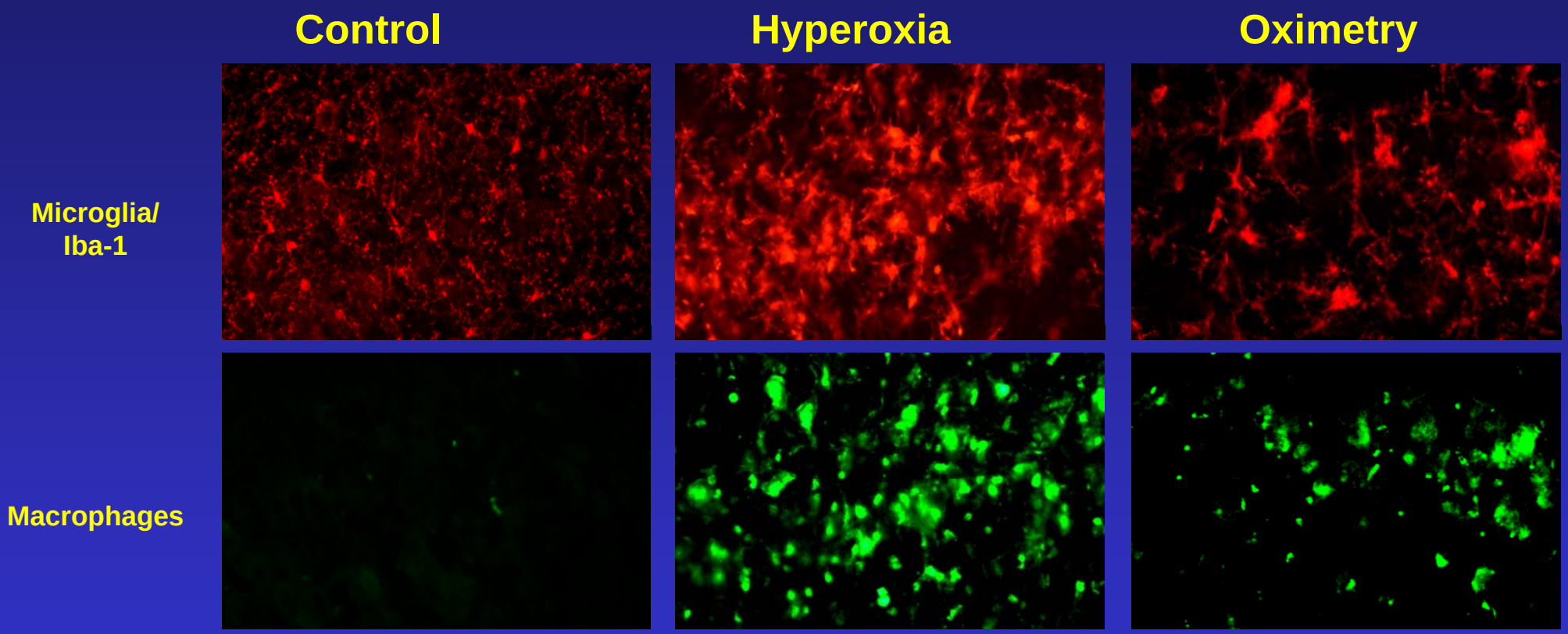
Richards et al., Stroke 2007

Normoxia Protects Pyruvate DH Activity

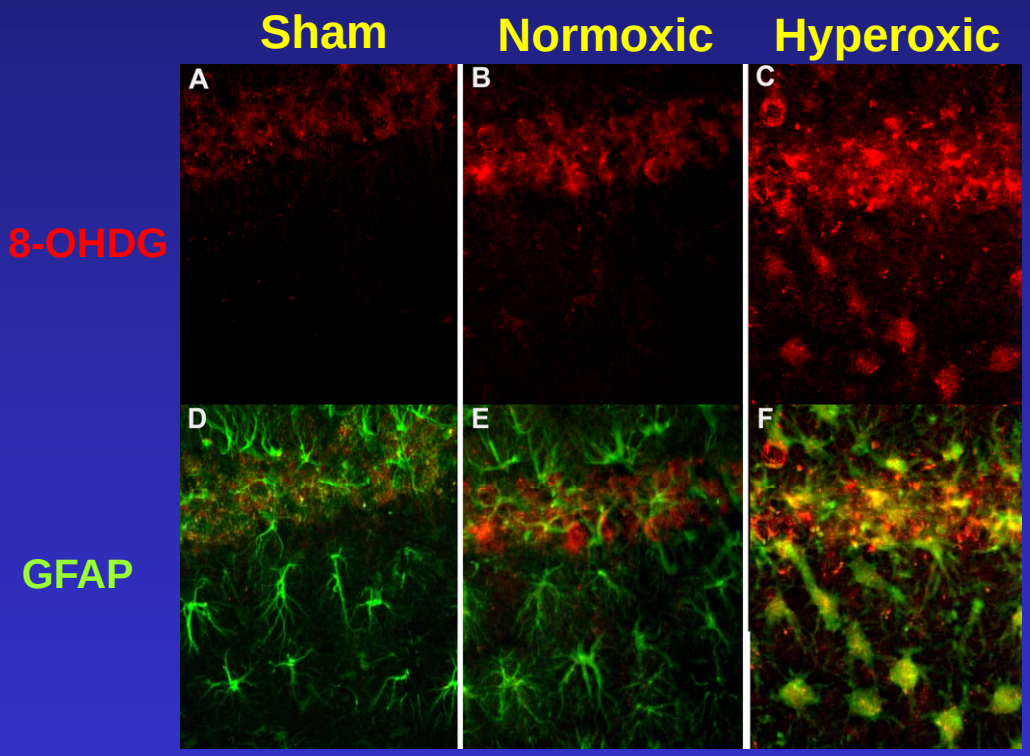


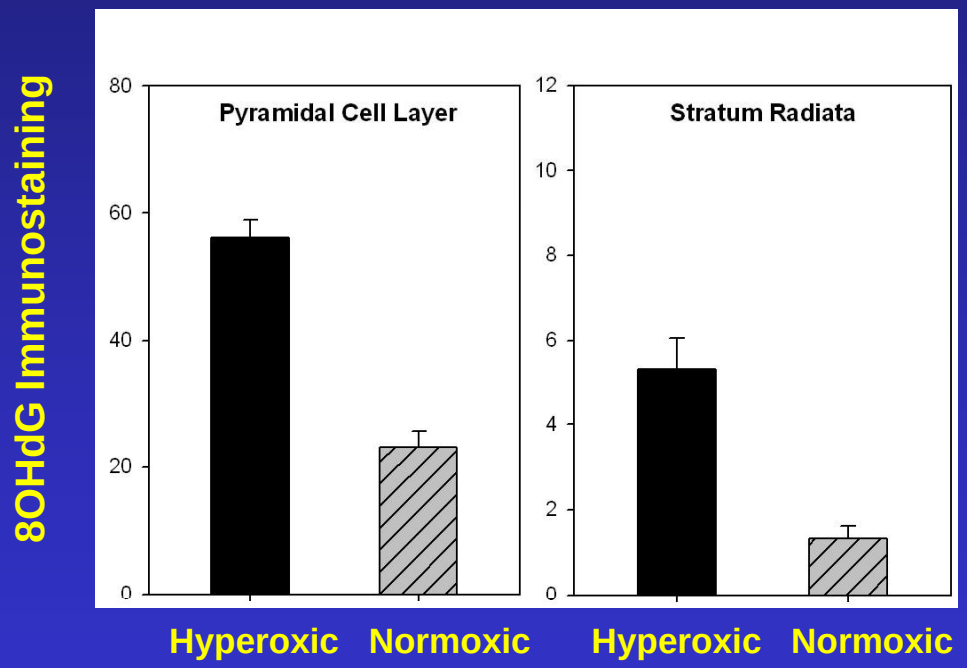
Richards et al., Free Rad Biol Med 2006

NORMOXIC RESUSCITATION REDUCES BRAIN INFLAMMATION 24 HR AFTER CARDIAC ARREST



NORMOXIC RESUSCITATION REDUCES SECONDARY OXIDATIVE STRESS DNA/RNA OXIDATION @ 24 hr





Qualitatively similar results have been observed with a long-term (30 day) rat model of global cerbral ischemia/reperfusion.

ILCOR Consensus Statement

Post–Cardiac Arrest Syndrome

Epidemiology, Pathophysiology, Treatment, and Prognostication

A Consensus Statement From the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council

Endorsed by the American College of Emergency Physicians, Society for Academic Emergency Medicine, Society of Critical Care Medicine, and Neurocritical Care Society

On the basis of preclinical evidence alone, unnecessary arterial hyperoxia should be avoided, especially during the initial post–cardiac arrest period. This can be achieved by adjusting the F_{IO_2} to produce an arterial oxygen saturation of 94% to 96%. However, controlled reoxygenation has yet to be studied in randomized prospective clinical trials.

Neumar RW, et al., Circulation Epub Oct 23 (2008)

Resuscitation Epub Oct 27

HYPEROXIA AND TBI

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J Neurosurg. 106:687-94.

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Effect of hyperoxia on cerebral metabolic rate for oxygen measured using positron emission tomography in patients with acute severe head injury.
J Neurosurg. 106:526-9.

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Normobaric hyperoxia--induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: a prospective historical cohort-matched study.
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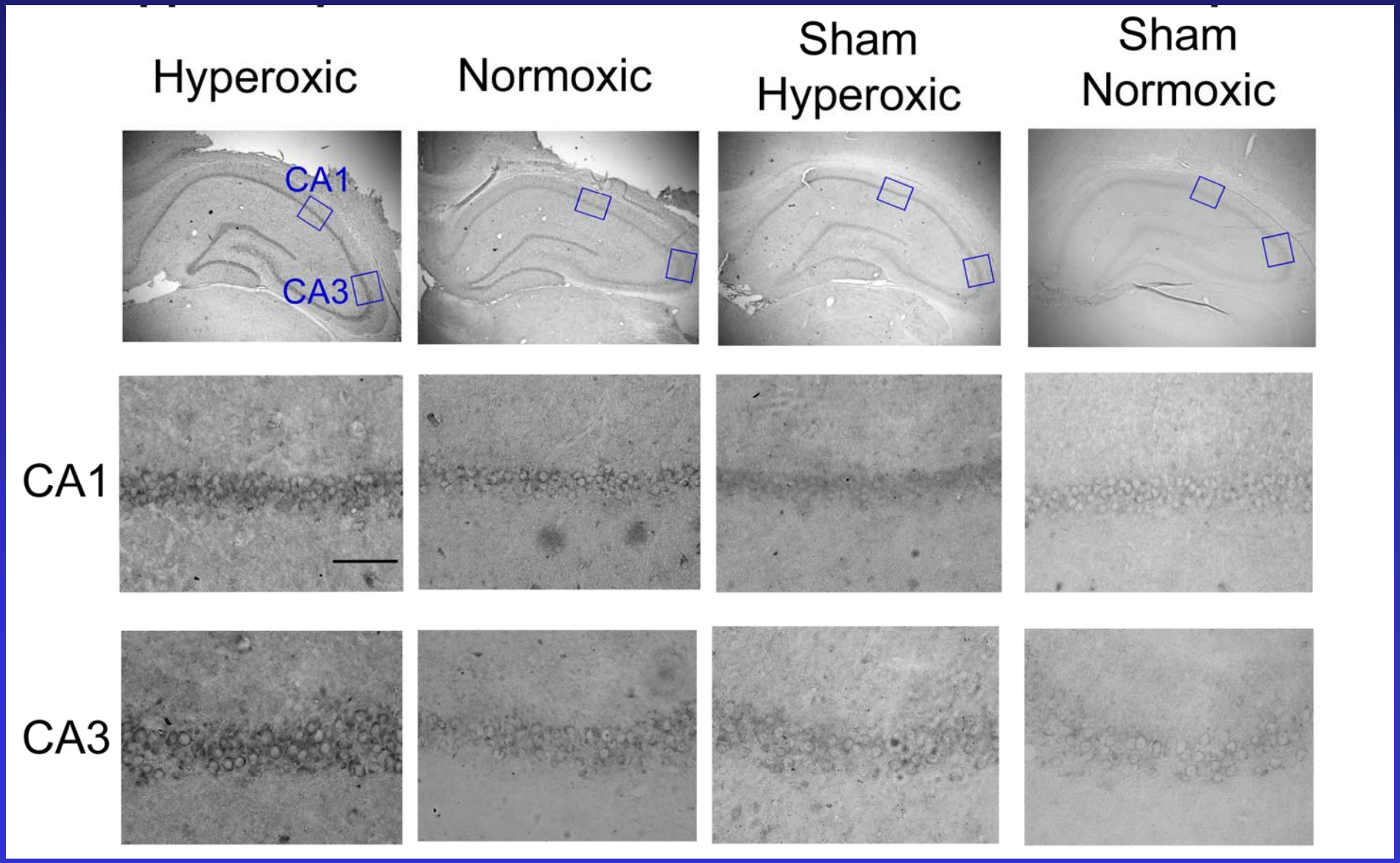
Palzur E, et al., 2004.
Hyperbaric oxygen therapy for reduction of secondary brain damage in head injury: an animal model of brain contusion.
J Neurotrauma. 21:41-8.

Ahn ES,et al., 2008
Normoxic ventilatory resuscitation following controlled cortical impact reduces peroxynitrite-mediated protein nitration in the hippocampus.
J Neurosurg. 108:124-31.

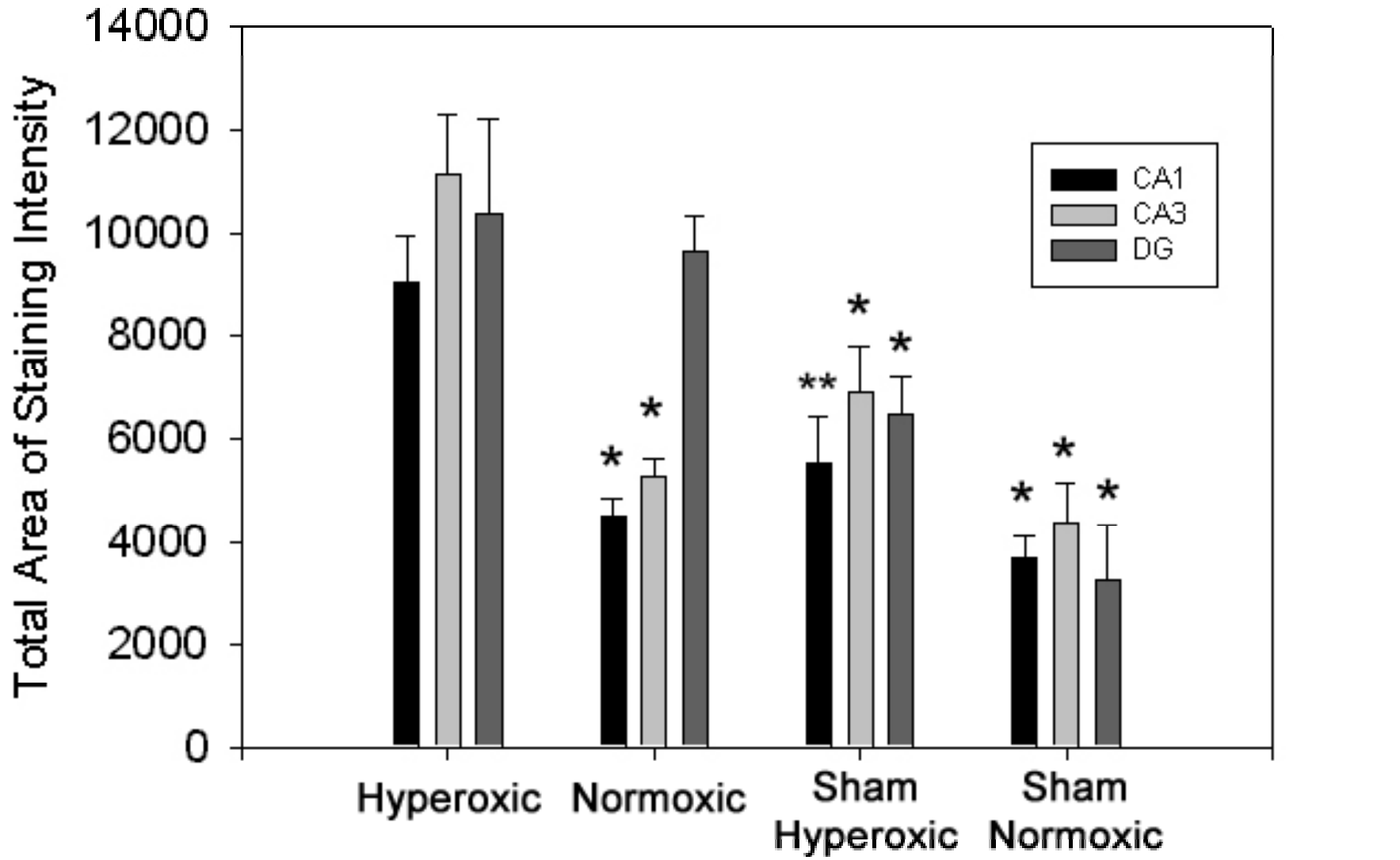
EFFECTS OF HYPEROXIA ON OXIDATIVE STRESS AND CELL DEATH AFTER TBI

- *Isoflurane-induced anesthesia and intubation*
- *Left parietal craniotomy and Controlled Cortical Impact (CCI). Craniotomy alone in sham-operated animals*
- *One hour ventilatory resuscitation with 100% FIO_2 (pO_2= 397) vs. 21% FIO_2 (pO_2 = 105)*
- *Perfusion at 24 hours and mmunohistochemistry with anti-nitrotyrosine antibody*
- *Cortical infarct volume and hippocampal cell death measured at 7 days*

HIPPOCAMPAL NITROTYROSINE IMMUNOSTAINING AT 24 HR POST CCI

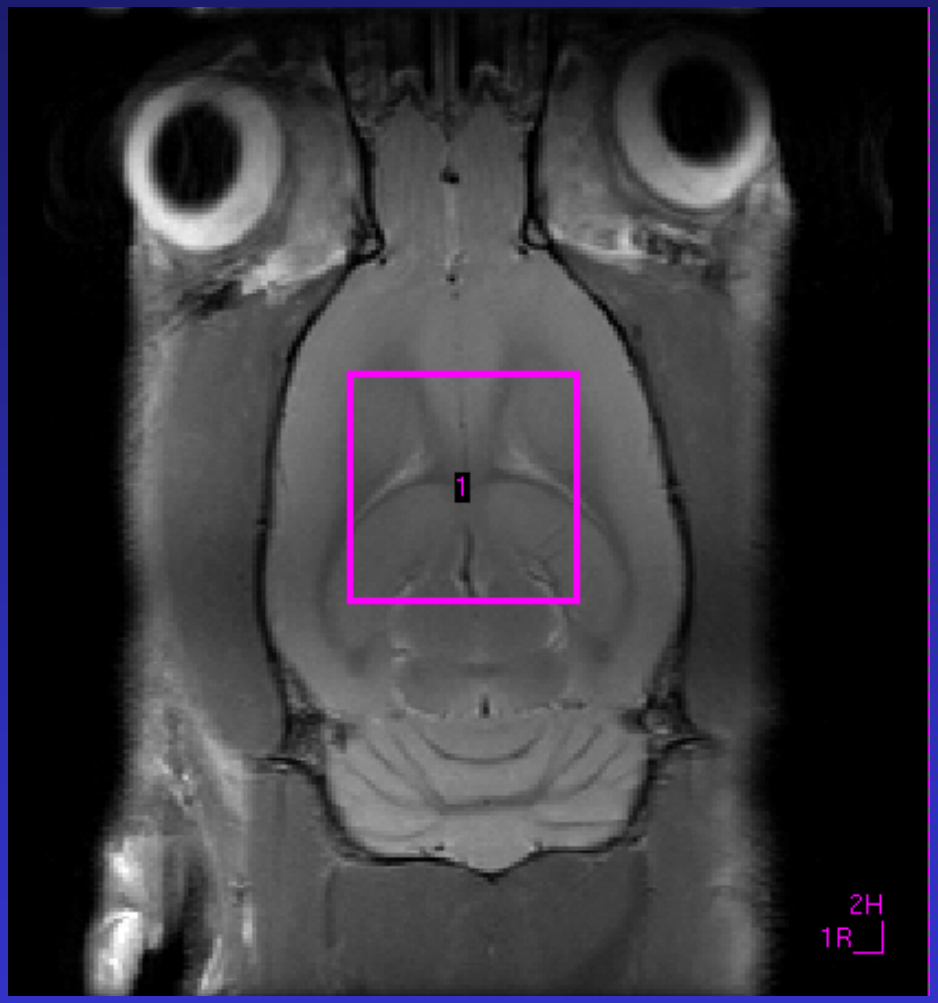


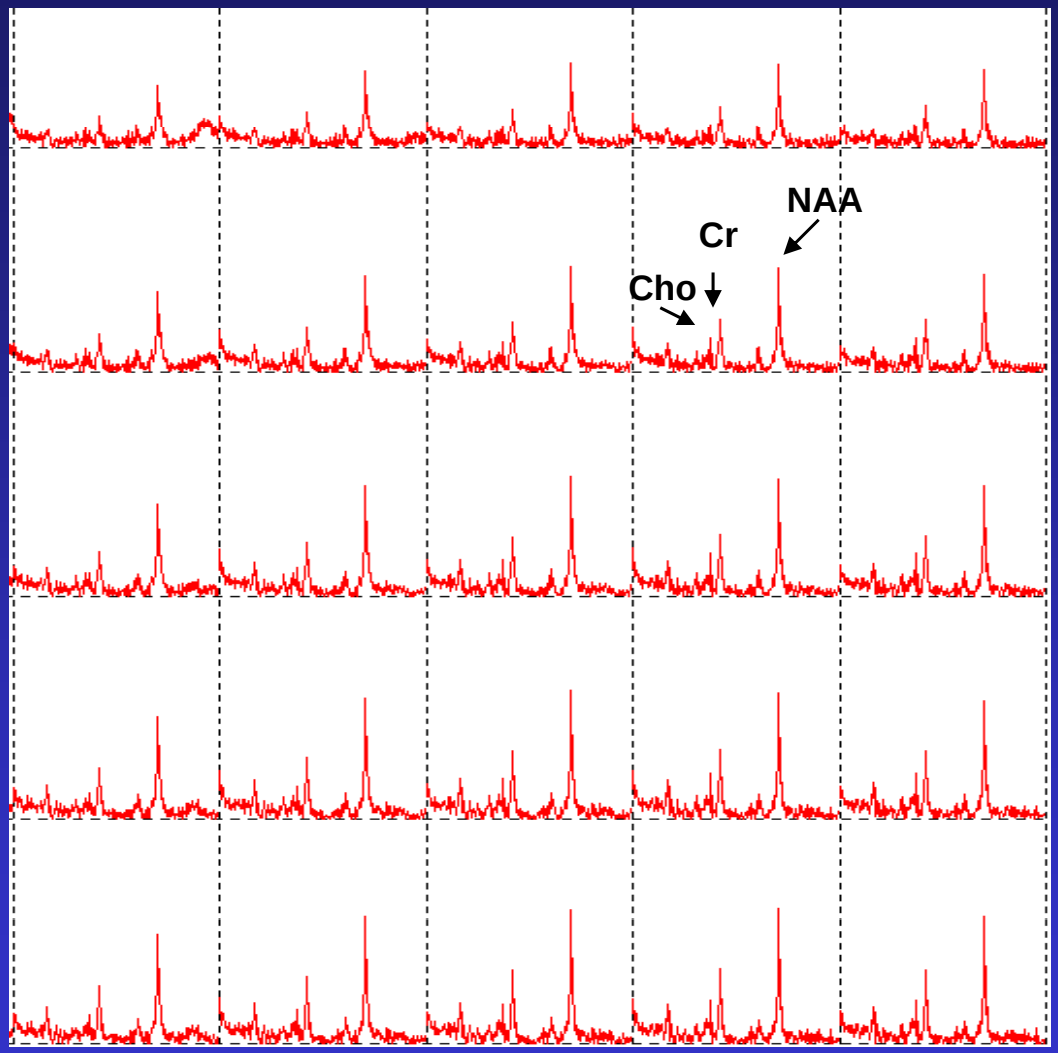
IPSILATERAL HIPPOCAMPAL NITROTYROSINE IMMUNOSTAINING AT 24 HR POST CCI



* $p < 0.05$ for equivalent region in hyperoxic injured group
** $p = 0.05$ for equivalent region in hyperoxic injured group

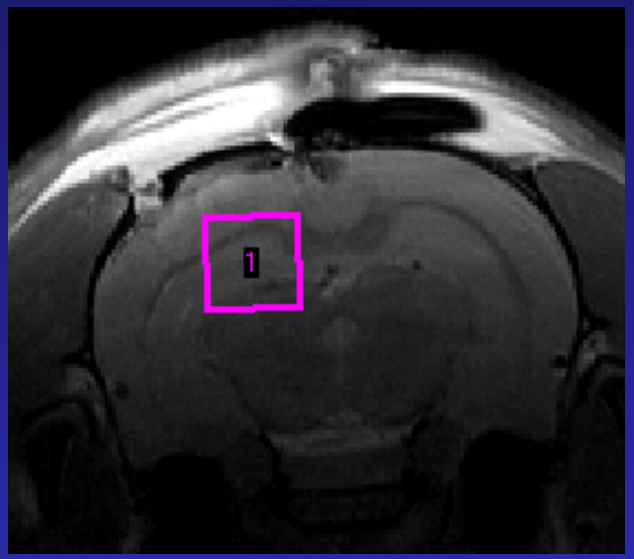
MULTI-VOXEL MR SPECTROSCOPY TO DEFINE LOCATION-SPECIFIC METABOLIC ALTERATIONS

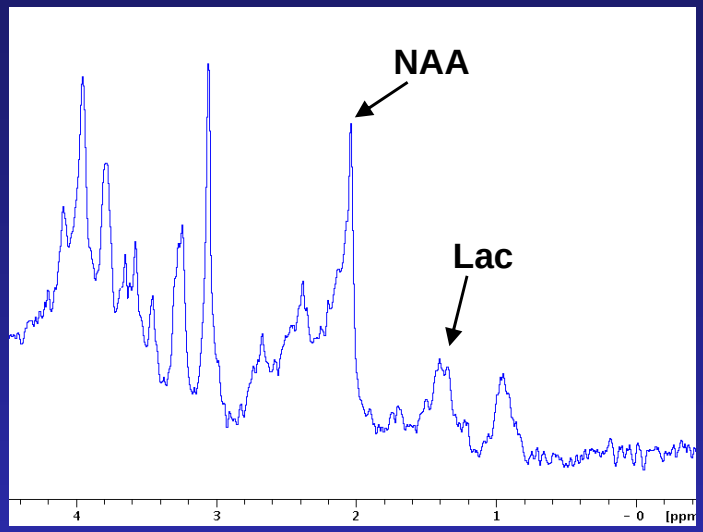


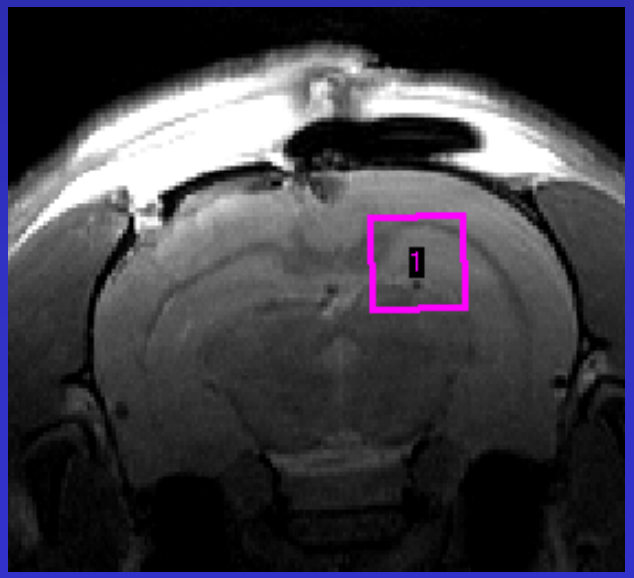


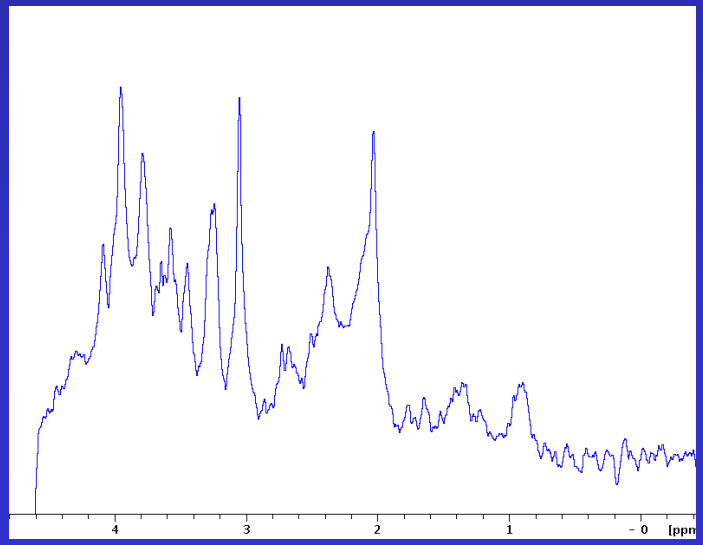
Each spectra is from a voxel of size 1 mm^3

DOES HYPEROXIA IMPROVE OR WORSEN CEREBRAL ENERGY METABOLISM AFTER TBI?







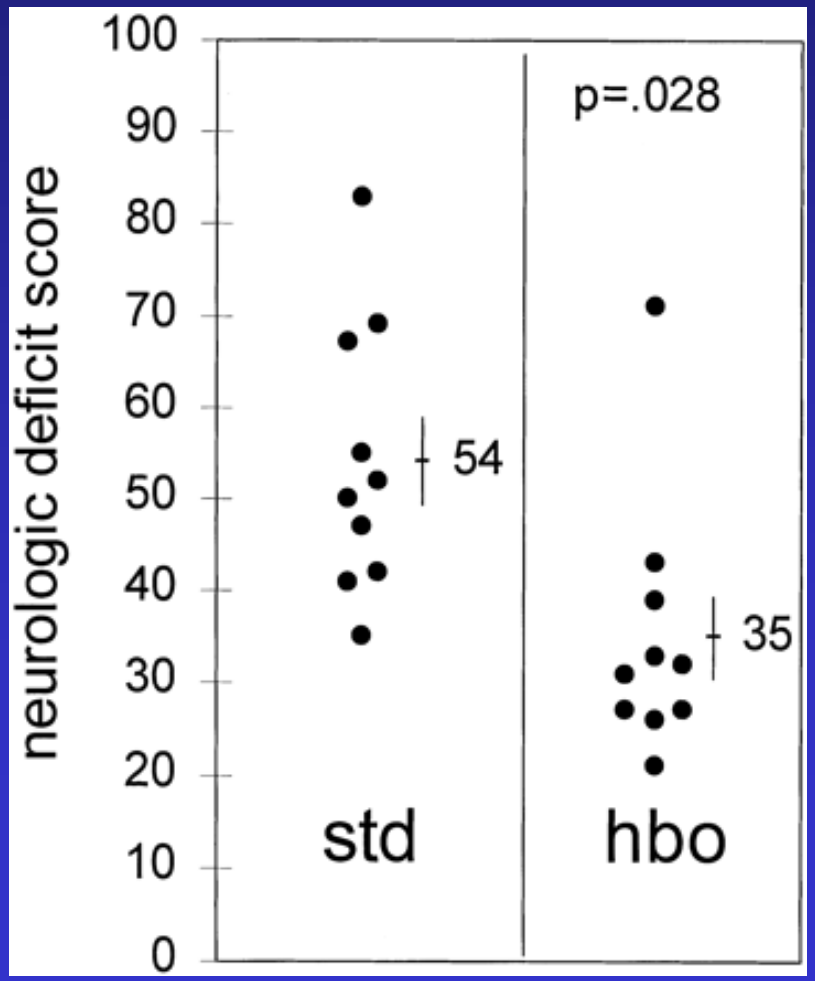


Timing of hyperoxia after TBI may be critical and is still warranted with evidence of secondary ischemia (hypoxia) but not high ICP alone.

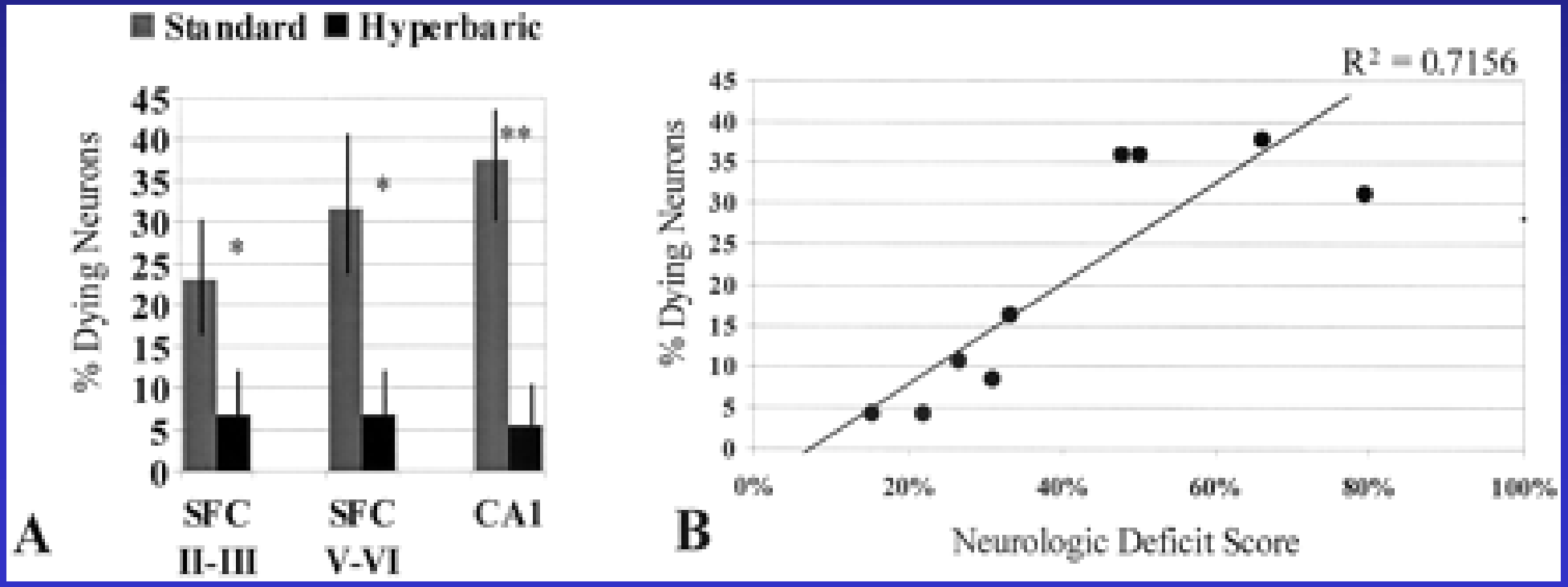
Is there any therapeutic role for hyperoxia after cardiac arrest?

DELAYED HBO AFTER CA/ROSC IMPROVES NEUROLOGIC OUTCOME

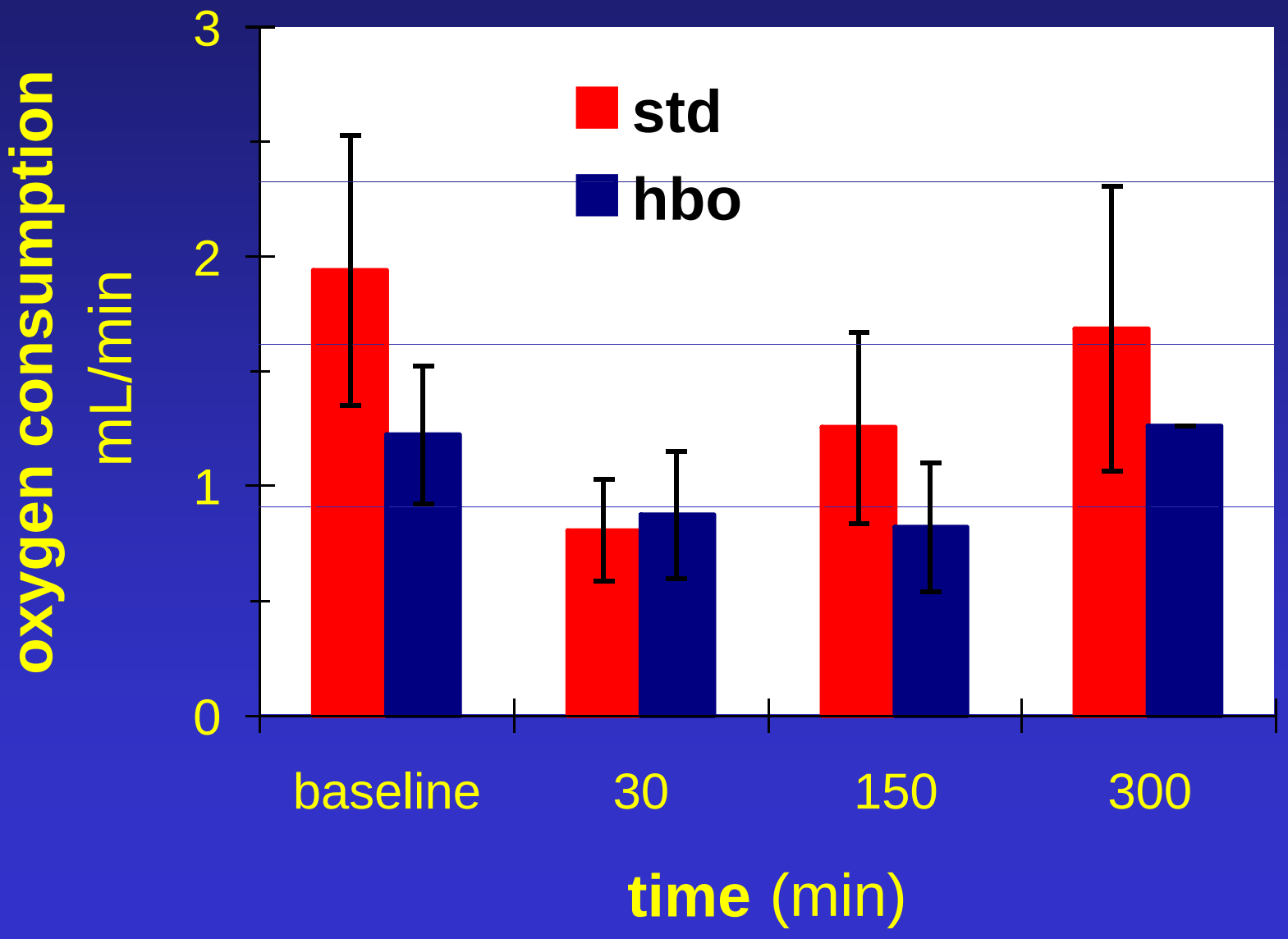
- 10 min CA
- Resuscitated with 100/70/30% O_2
- HBO at 2.7 atm at 1 - 3 hr later



DELAYED HBO AFTER CA/ROSC PROTECTS AGAINST CORTICAL AND HIPPOCAMPAL NEURONAL DEATH



HBO DOES NOT CHANGE CEREBRAL O_2 CONSUMPTION

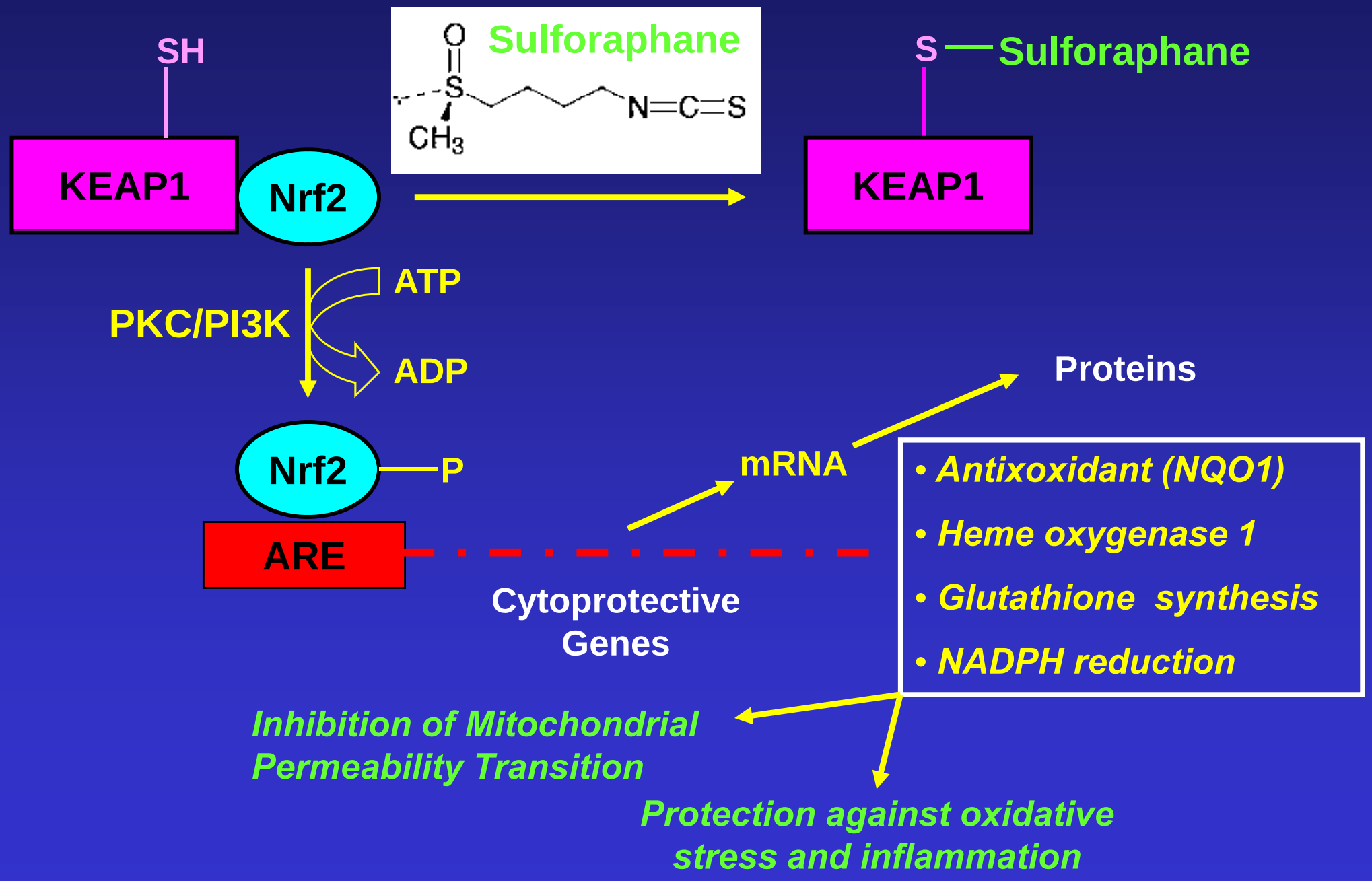


GENOMIC MECHANISMS OF NEUROPROTECTION BY DELAYED HYPEROXIA

- *Inhibition of neutrophil infiltration (ICAM)*
- *Inhibition of HIF-1α*
- *Inhibition of MMP-9*
- *Inhibition of cyclooxygenase-2*
- *Inhibition of myeloperoxidase activity*
- *Up-regulation of Bcl-2*
- *Up-regulation of superoxide dismutase*
- *Stimulation of neural stem cell proliferation and migration*

Are there pharmacologic approaches to genomic pre- and post-conditioning against neurologic impairment caused by acute brain injury?

Nrf2-MEDIATED GENOMIC POST-CONDITIONING AGAINST ISCHEMIC BRAIN INJURY



Neuroscience Letters 460 (2009) 103–107

Contents lists available at ScienceDirect

Neuroscience Letters

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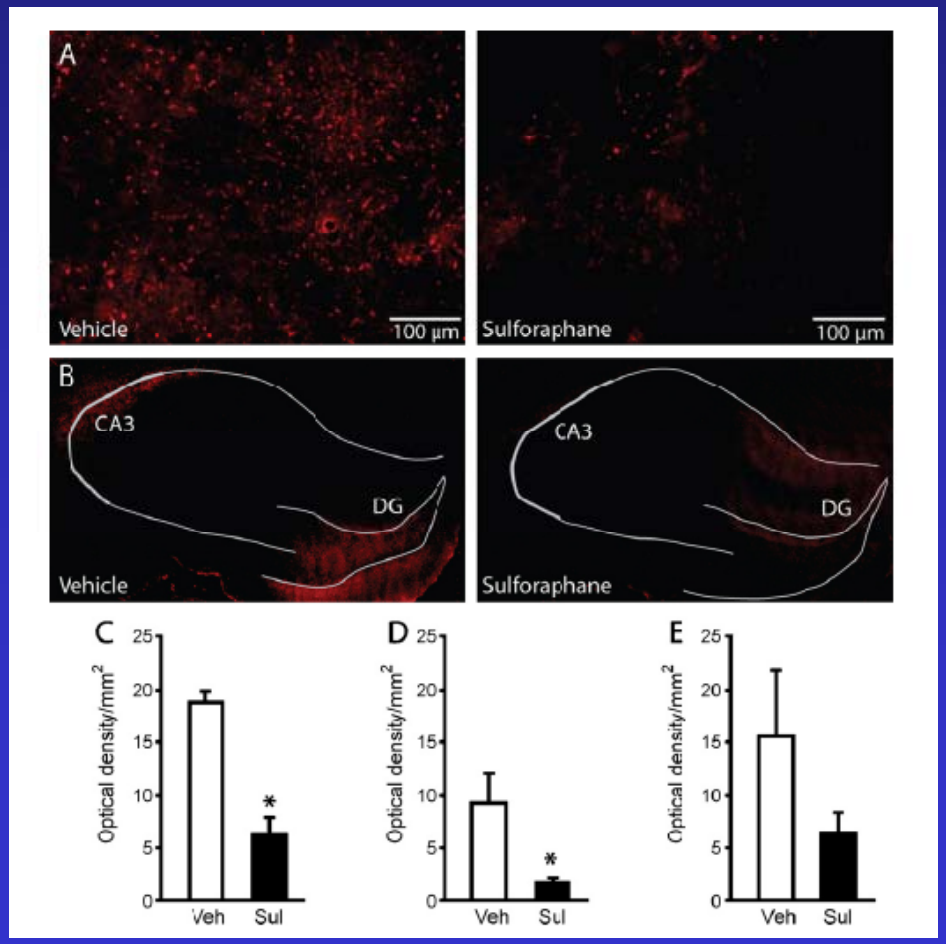
Sulforaphane improves cognitive function administered following traumatic brain injury

Pramod K. Dash*, Jing Zhao, Sara A. Orsi, Min Zhang, Anthony N. Moore

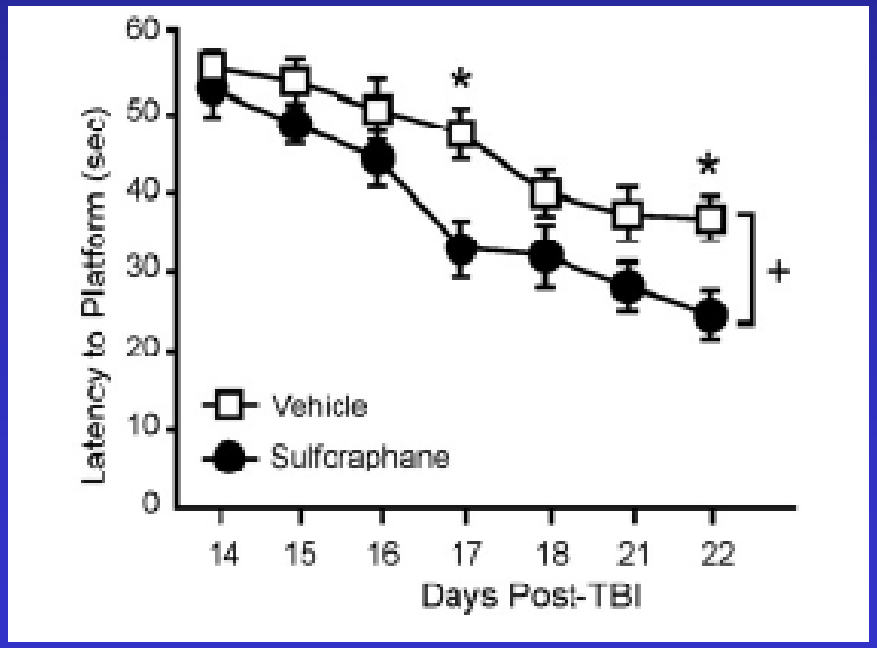
Department of Neurobiology and Anatomy, The University of Texas Medical School, Houston, Texas 77225, United States

SULFORAPHANE POST-TREATMENT REDUCES OXIDATIVE DAMAGE AND IMPROVES NEUROLOGIC OUTCOME AFTER RAT CONTROLED CORTICAL IMPACT

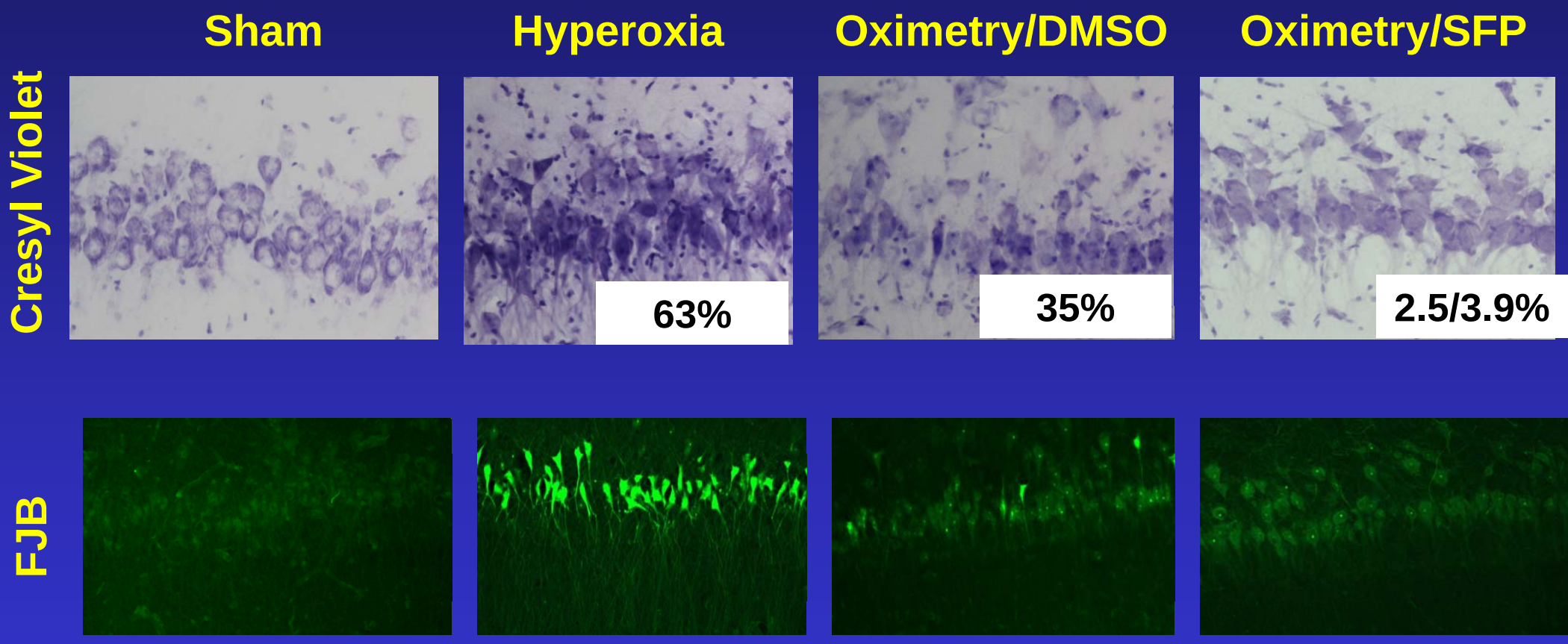
Hydroxynonenal Immunoreactivity



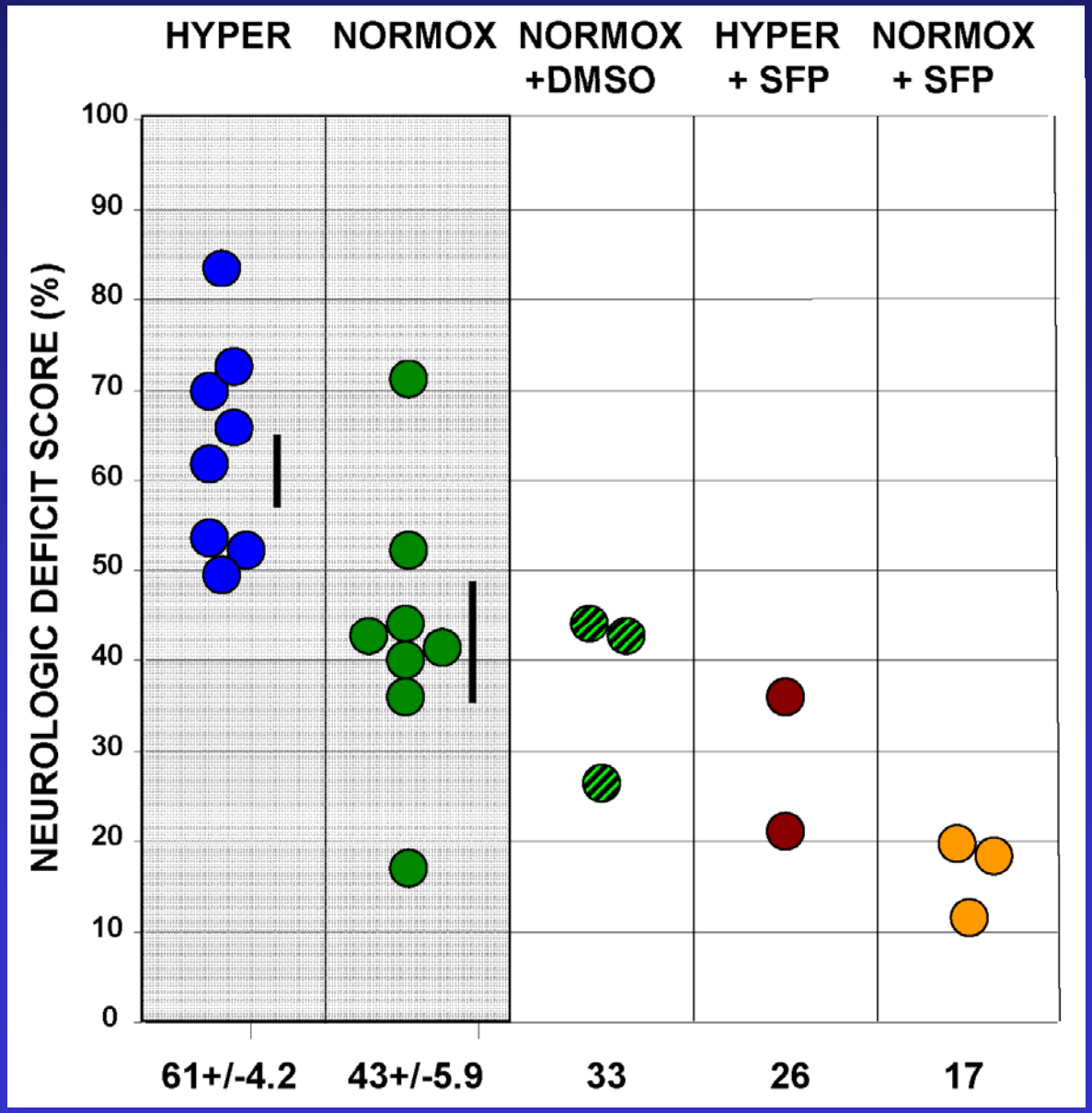
Morris Water Maze Test of Spatial Learning and Memory



Sulforaphane iv @ 2.5 mg/kg at 1 hr post CA protects against hippocampal neuronal death at 24 hr



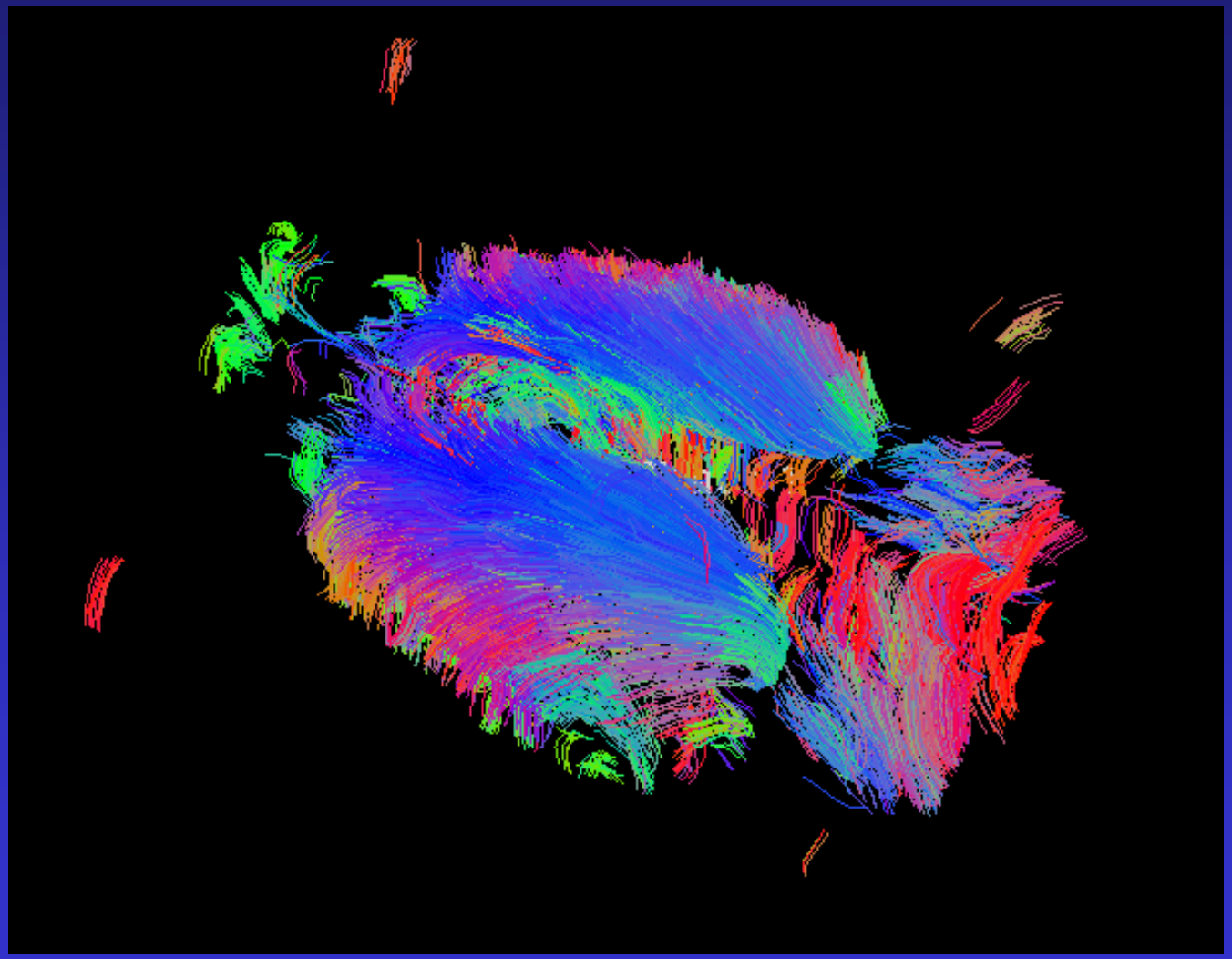
SULFORAPHANE IMPROVES NEUROLOGIC OUTCOME AFTER CARDIAC ARREST



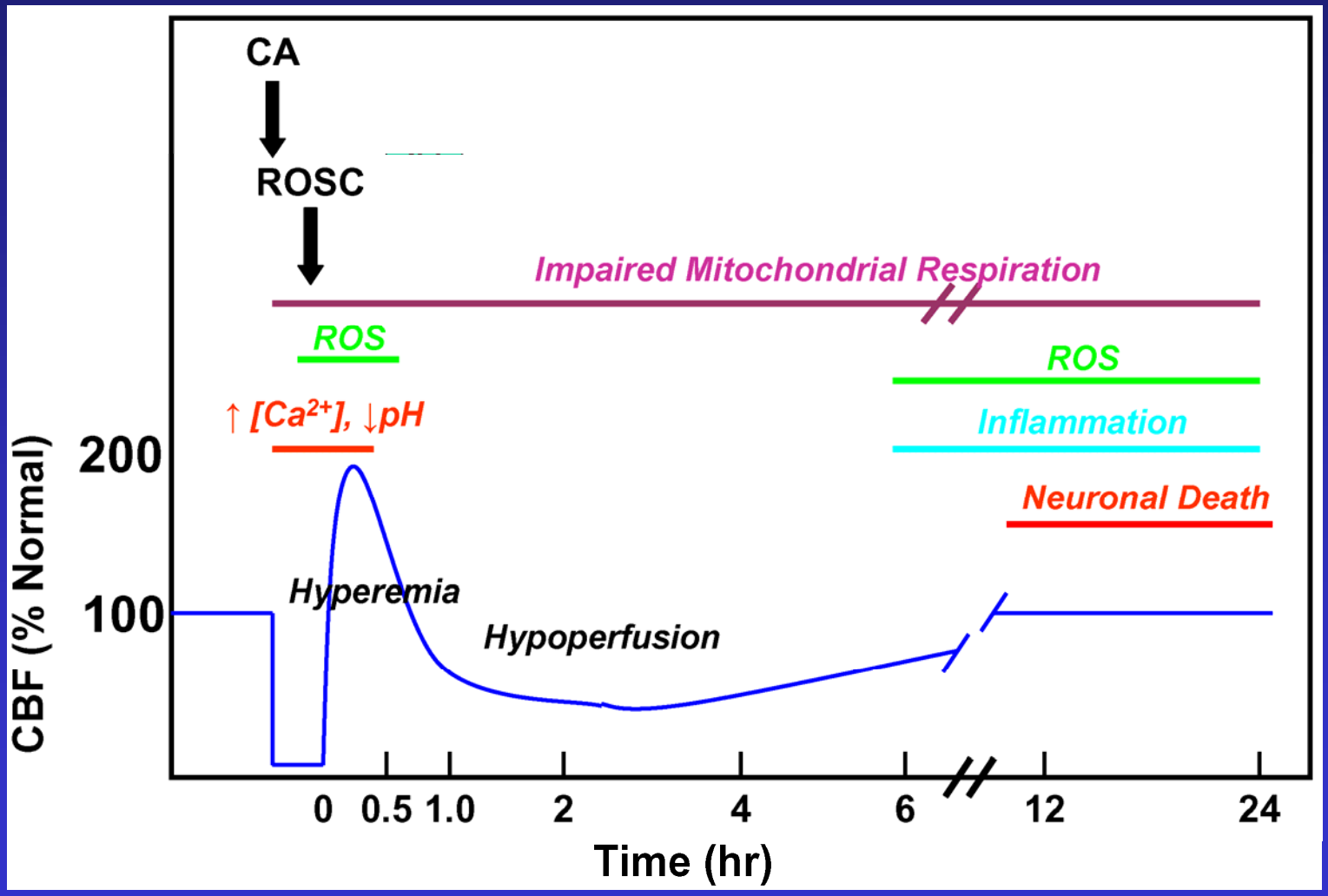
FUTURE DIRECTIONS

- *Hyperoxic vs. normoxic resuscitation after TBI polytrauma (including blast)*
  - *WRAIR and Pitt*
- *Sulforaphane pre- and post-conditioning against injury caused by TBI polytrauma*
- *Advanced MRI to detect structural and metabolic changes with diffuse axonal injury models (including blast)*

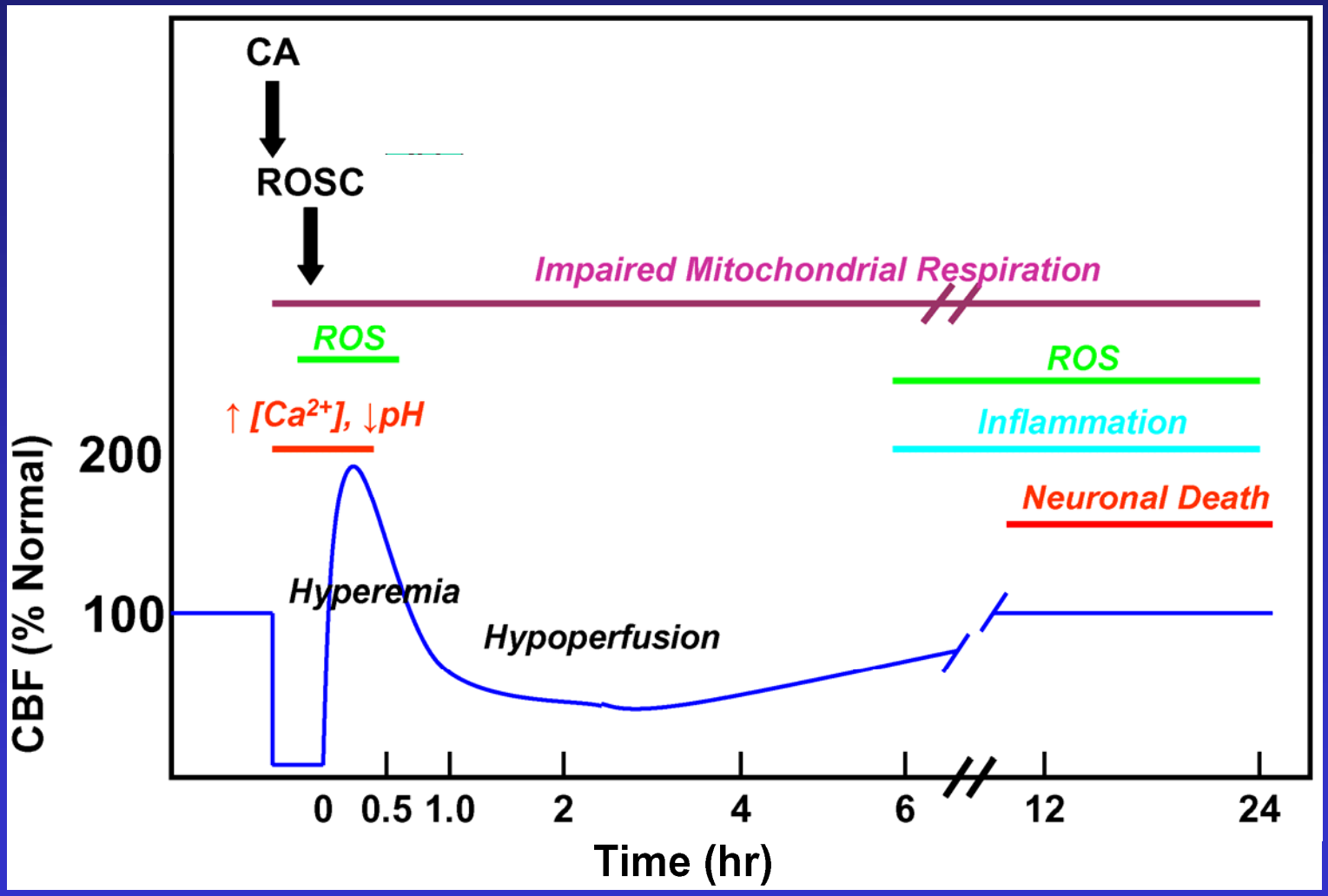
Thanks you for your interest.



PRIMARY AND SECONDARY OXIDATIVE STRESS AFTER CARDIAC ARREST



PRIMARY AND SECONDARY OXIDATIVE STRESS AFTER CARDIAC ARREST



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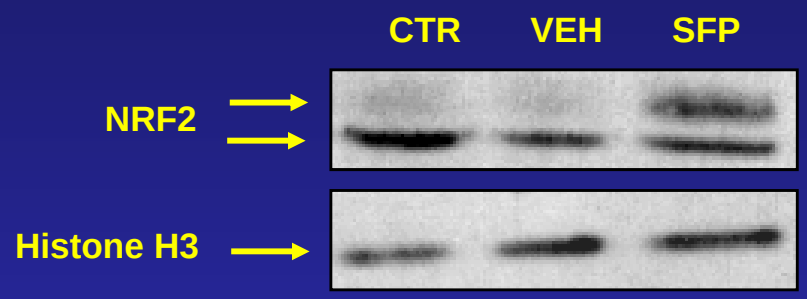
Hyperbaric oxygen reduces blood-brain barrier damage and edema after transient focal cerebral ischemia.
Stroke. 36:1679-83.

Singhal AB, et al., 2005.
A pilot study of normobaric oxygen therapy in acute ischemic stroke.
Stroke. 36:797-802.

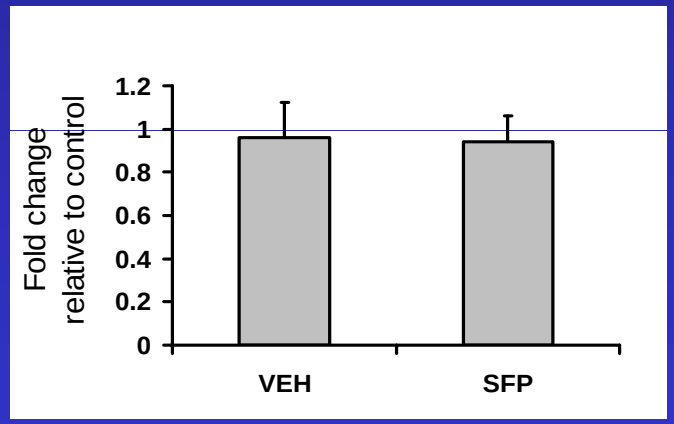
OXYGEN IS A DRUG

- *Use to avoid hypoxemia or to counteract tissue hypoxia*
- *Dose is patient-dependent*
  - *better indicators of PtO2, energy metabolism, and oxidative stress are needed*
- *Avoid oxidative stress through tight control or antioxidant co-administration*

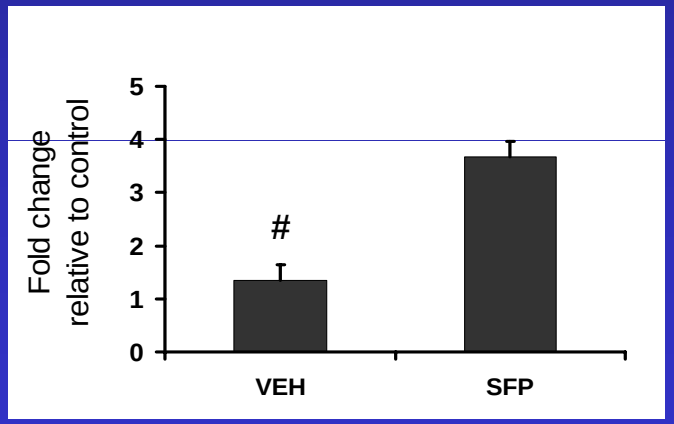
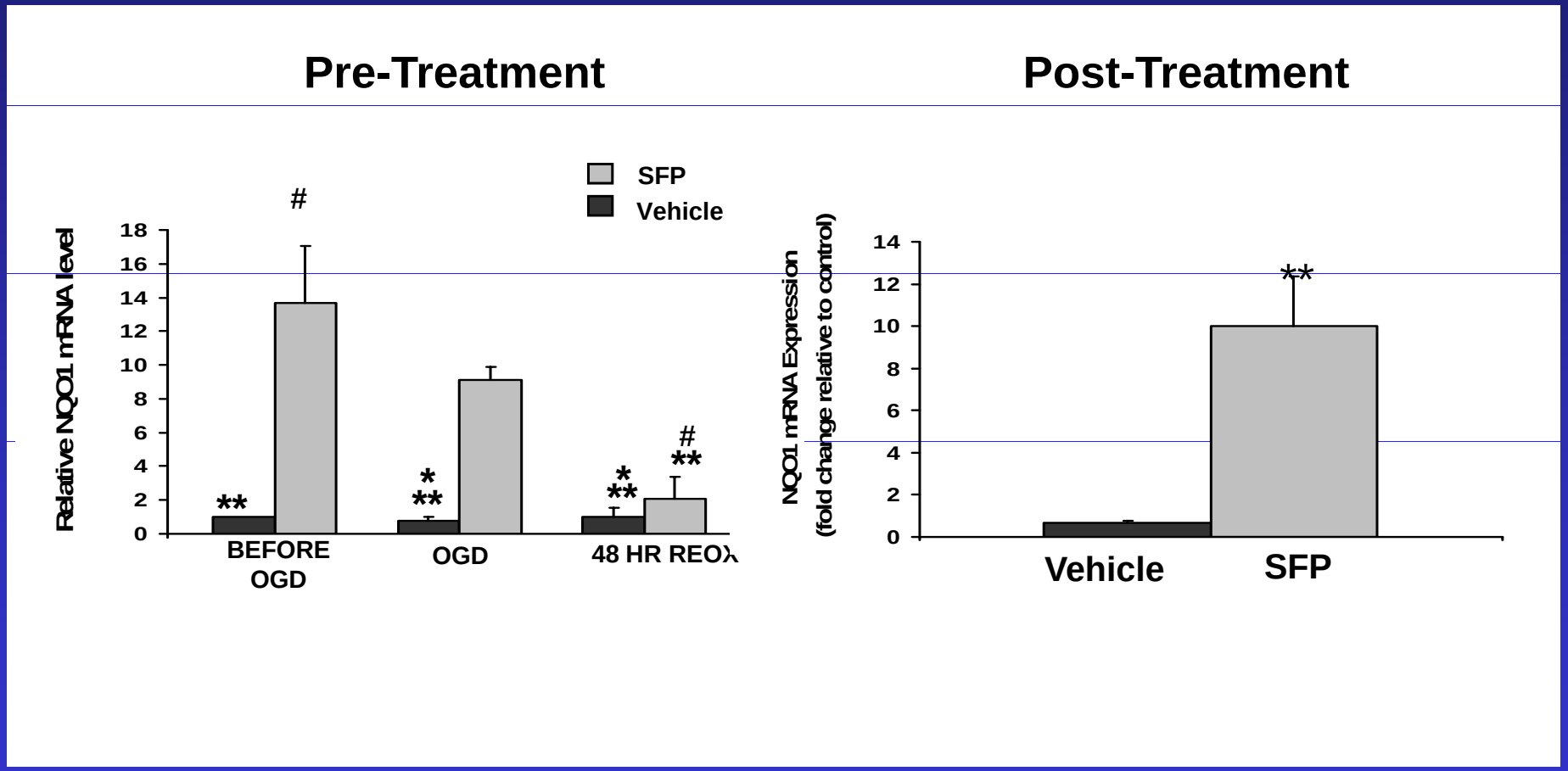
SULFORAPHANE PRE-TREATMENT INCREASES NUCLEAR Nrf2 LOCALIZATION



Lower Band



Upper Band



SULFORAPHANE PRE- AND POST-TREATMENT INCREASES NAD(P)H: QUINONE OXIDOREDUCTASE 1(NQO1) GENE EXPRESSION