Cerebral Oximetry and Traumatic Brain Injury

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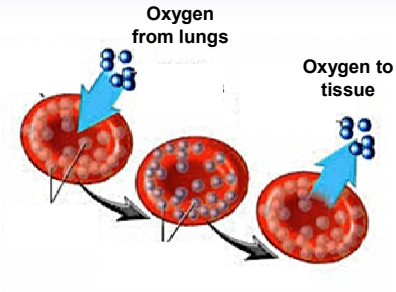
Objectives

- Review historical data on PbtO2 monitoring
- Discuss integration of PbtO2 neuromonitoring into management of critically ill neurological patients
- Present current PbtO2 studies

Goal of Resuscitation



- Provide adequate oxygen delivery
- Avoid hypoperfusion
- Prevent / minimize end organ injury

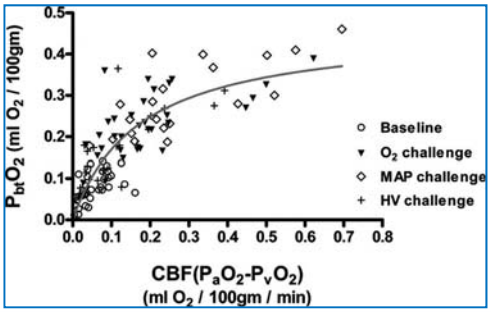
PbtO2 Monitors

- FDA-approval:
  - Integra Licox® in 2000; Raumedic Neurovent PTO in 2007
- Measures $PbtO_2$ in mm3 region around catheter tip
- No Class I data that it improves outcome
- Variable use in NICUs

What Does $PbtO_2$ Represent?

- Prospective observation study; n = 14 sTBI
  - $PbtO_2$ & CBF monitoring with FiO_2, MAP, CO_2 challenges
  - Measured: $PaO2_2$, CaO_2, PVO_2, CVO_2, $AVDO_2$, locCMRO$_2$
- **Best association: CBF x (PaO_2-PvO_2)**
  - Represents diffusion of dissolved plasma O_2 across the BBB & reflect brain accumulation of O_2

Rosenthal G, et al. CCM 2008; 36:1917-24



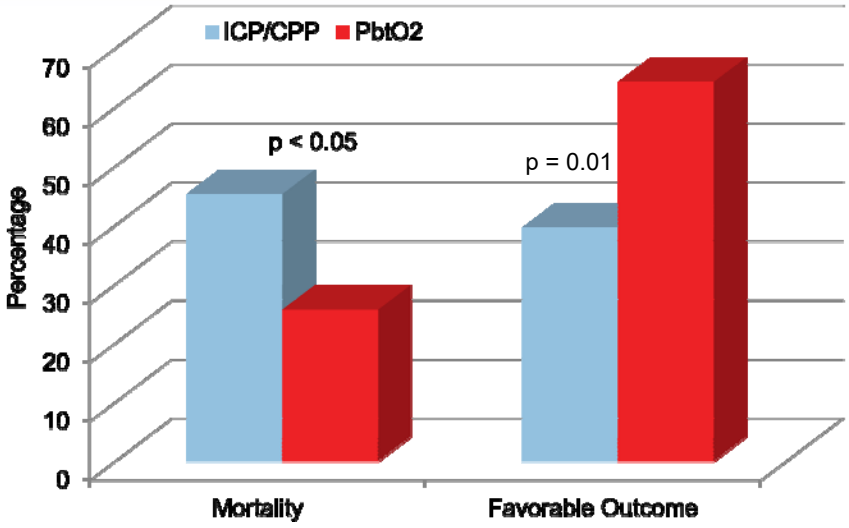
Rationale for $PbtO_2$ monitoring

- Episodes of low $PbtO_2$ are common after TBI
  1. *van den Brink WA, et al. Neurosurgery 2000; 46:868-878.*
  2. *Longhi L, et al. Intensive Care Med 2007; 33:2136-2142.*
  3. *Chang JJ, et al. Crit Care Med 2009;37:283-290.*
- Low $PbtO_2$ is associated with worse outcomes (no $PbtO_2$ interventions)
  1. *Bardt TF, et al. Acta Neurochir 1998; Suppl. 71:153-156*
  2. *Valadka A, et al. Crit Care Med 1998;26:1576-81; Puccio; #1 & 3*
- Interventions can rectify low $PbtO_2$
  - Hyperoxia *(Tolias, CM, et al. J Neurosurgery 2004; 101:435-444; Nortje J, et al. Crit Care Med 2008; 36:273-280)*
  - CPP augmentation *(Johnston AJ, et al. Int. Care Med. 2004; 30:791-797 & Crit Care Med 2005; 33:189-195)*
  - RBC transfusions *(Zygun DA, et al. Crit Care Med 2009;37:1074-1078)*

Rationale for $PbtO_2$ monitoring

- Impact on mortality
  - **No randomized clinical trials available**
- Stiefel M, et al. *(J Neurosurg 2005 103:805–811)*
  - Prospective data, cohort comparison; sTBI , n = 53
  - Mortality ICP/CPP vs $PbtO_2$ = **44% vs 25%** ($p<0.05$)
- Narotam PK, et al. *(J Neurosurg 2009; 111:672–682)*
  - Prospective data, historical cohort; sTBI, n = 139
  - Mortality ICP vs $PbtO_2$ = **41.5% vs 25.9%**
- Martini RP, et al. *(J Neurosurg 2009; 111:644–649)*
  - Cohort study, n = 629 (506 ICP, 123 ICP/$PbtO_2$), sTBI
  - Mortality rates similar

Is $PbtO^2$ Important?



Spiotta et al. J Neurosurg 113:571–580, 2010

Rationale for $PbtO_2$ monitoring

- Does $PbtO_2$ based therapy improve outcome?
- Systemic literature review NCC 2012
  - **No randomized clinical trials available**
  - Four studies with 491 patients from 1993 – 2010
    - Used historical or concurrent (physician choice) controls
  - Outcome based on GOS, not just mortality
- Results
  - $PbtO_2$ based therapy: favorable outcome in **191 (61%)** vs. unfavorable in 121(39%).
  - ICP/CPP based therapy: favorable outcome in 75 (42%) vs. unfavorable in 104 (58%)

Nangunoori R, et al. Neurocrit Care 2012;17:131-8.

Neurologic Critical Care

BOOST-II

Okonkwo DO, et al. Crit Care Med 2017;45(11):1907-1914.

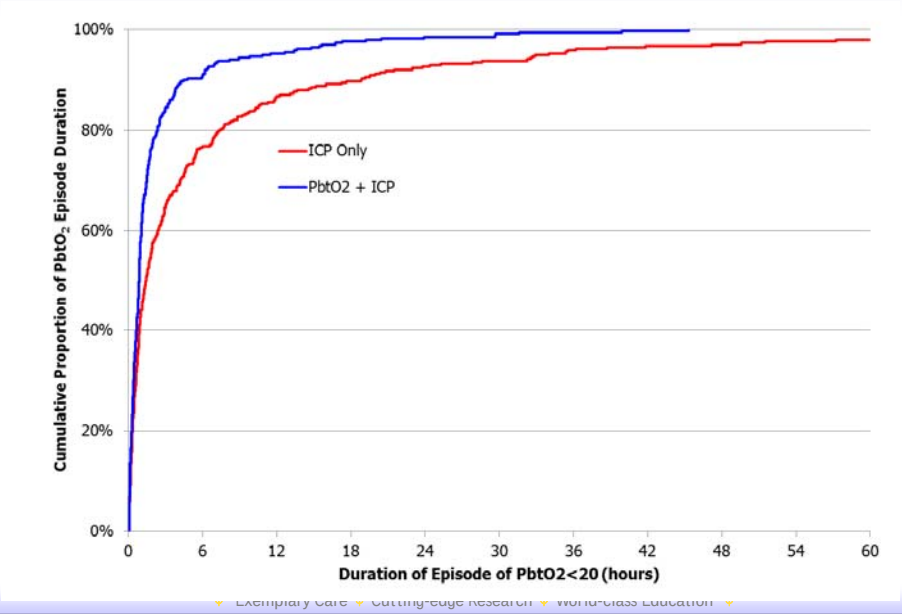
Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial*

David O. Okonkwo, MD, PhD[1]; Lori A. Shutter, MD[1]; Carol Moore, MA[2]; Nancy R. Temkin, PhD[3]; Ava M. Puccio, RN, PhD[1]; Christopher J. Madden, MD[4]; Norberto Andaluz, MD[5]; Randall M. Chesnut, MD[3]; M. Ross Bullock, MD, PhD[6]; Gerald A. Grant, MD, FACS[7]; John McGregor, MD[8]; Michael Weaver, PhD[9]; Jack Jallo, MD, PhD[10]; Peter D. LeRoux, MD, FACS[11]; Dick Moberg, MSE[12]; Jason Barber, MS[3]; Christos Lazaridis, MD[13]; Ramon R. Diaz-Arrastia, MD, PhD[14]

Multicenter USA (10 sites)
N = 119

- Primary Objective:
  - A treatment protocol based on $PbtO_2$ monitoring results in less time below 20 mm Hg in patients with severe TBI
- Secondary Objectives:
  - Safety, Feasibility, Non-futility

Primary Outcome: Duration of PbtO2 < 20mm Hg



Secondary Outcome: Non-futility

Glasgow Outcome Score-Extended distribution between ICP only and PbtO2 + ICP groups.

Okonkwo DO, et al. Crit Care Med 2017;45(11):1907-1914.

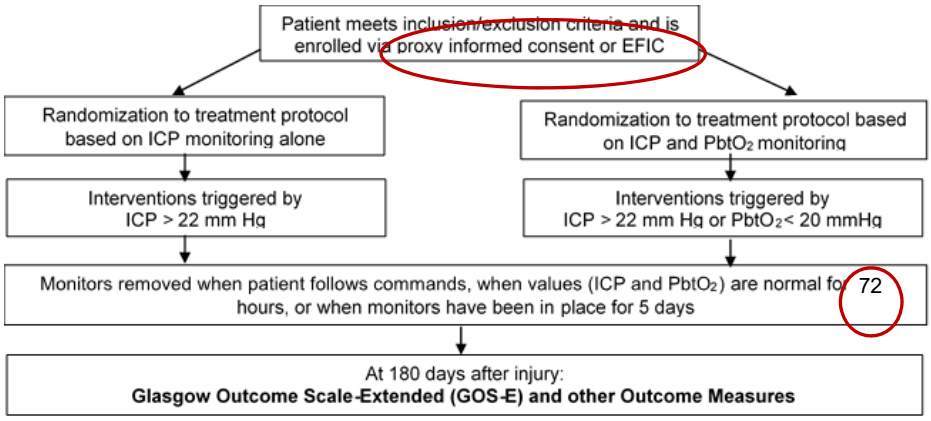
BRAIN OXYGEN AND OUTCOME IN SEVERE TRAUMATIC BRAIN INJURY: PHASE 3

BOOST-3 Design

- Two-arm, single-blind, randomized, controlled, phase III, multi-center trial addressing **a pathophysiology seen in TBI**
  - Approved by NINDS Council 9/2017, funded Aug 2018
  - Planned 47 sites
  - Central IRB & EFIC (delayed consent)
  - Target enrollment 1094
    - Sufficient to detect a 10% absolute improvement in good outcome
    - Outcome: Blinded GOS-E with Sliding Dichotomy
      - **6 month prognosis determined on admission based on the IMPACT Core Model**
  - Management based on BTF/ACS TQIP Guidelines

Exemplary Care Cutting-edge Research World-class Education

Study Schematic



BOOST-3

Integrating Physiology Based on $PbtO_2$ 'Challenges' into Daily Care

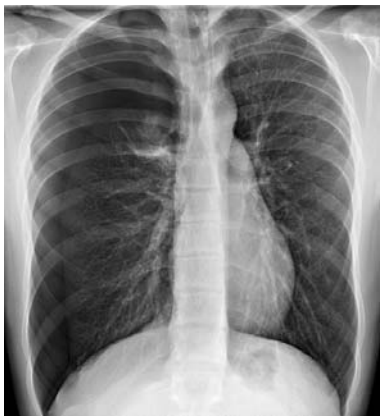
- Clinical interventions can be performed at beside to assess both reliability of $PbtO_2$ data and cerebral physiology
- These interventions are called 'challenges'
- The goal is to assess the $PbtO_2$ response to these challenges to help guide clinical management
  - Challenges focus on adjustments of FiO_2, MAP and CO_2

FiO_2, MAP, and CO_2 Challenges

- FiO_2 challenge: assesses probe reliability & provides information on both cerebral and systemic physiology.
  - Guides ventilator settings, provides insight on lung physiology
- MAP challenge: helps assess cerebral autoregulation.
  - Guides both MAP and CPP goals
- CO_2 challenge: can assess cerebral CO_2 vasoreactivity to guide ventilator adjustments, may provide input regarding potential hyperemia.
  - Can use either hyperventilation or hypoventilation based on the clinical situation

Case Presentation

- Severe TBI patient, probes placed and FiO_2 challenge done 1 hour later:
  - At start: $PbtO_2$ = 19, ICP = 18, and SaO_2 = 94%
  - At end: $PbtO_2$ = 30, ICP = 17, and SaO_2 = 97%
  - At end: $PbtO_2$ = 19, ICP = 20, and SaO_2 = 94%
    - ABG: PaO_2 = 75



Case Presentation: Challenges

- Severe TBI patient, day 3 FiO2 challenge done
  - At start: $PbtO_2$ = 22, ICP = 18, and SaO_2 = 94%
  - At end: $PbtO_2$ = 30, ICP = 17, and SaO_2 = 98%
- MAP Challenge
  - At start: $PbtO_2$ = 22, ICP = 15, MAP = 75, CPP = 60
  - At end: $PbtO_2$ = 29, ICP = 16, MAP = 85, CPP = 69
  - At end: $PbtO_2$ = 24, ICP = 25, MAP = 85, CPP = 60
  - At end: $PbtO_2$ = 29, ICP = 20, MAP = 85, CPP = 65

Case Presentation: Challenges

- CO2 Challenge – Hyperventilation
  - At start: $PbtO_2$ = 23, ICP = 19, $ETCO_2$ = 38
  - At end: $PbtO_2$ = 22, ICP = 14, $ETCO_2$ = 32
  - At end: $PbtO_2$ = 17, ICP = 14, $ETCO_2$ = 32
  - At end: $PbtO_2$ = 28, ICP = 18, $ETCO_2$ = 32
- CO2 Challenge - Hypoventilation
  - At start: $PbtO_2$ = 23, ICP = 19, $ETCO_2$ = 35
  - At end: $PbtO_2$ = 28, ICP = 19, $ETCO_2$ = 42
  - At end: $PbtO_2$ = 24, ICP = 24, $ETCO_2$ = 42
  - At end: $PbtO_2$ = 18, ICP = 28, $ETCO_2$ = 42

Types of events		ICP < 22 mm Hg	ICP ≥ 22 mm Hg
$PbtO_2 \geq 20$		**Type A** No interventions directed at $PbtO_2$ or ICP needed	**Type B** Interventions directed at lowering ICP
$PbtO_2 < 20$		**Type C** Interventions directed at increasing $PbtO_2$	**Type D** Interventions directed at lowering ICP and increasing $PbtO_2$

BOOST-3

Managing ICP & PbtO2

- Tiered algorithm based approach
  - Tiers are hierarchical, with increased aggressiveness of interventions
- Physiology guided management
  - Interventions used within any tier should be based on and aimed at addressing the presumed underlying pathophysiology contributing to that individual episode
- For any treatment chosen, a rapid response to that treatment is expected.
  - If no response – reassess physiology

Isolated ICP increase	Isolated $PbtO_2$ drop	ICP increase + $PbtO_2$ drop
TIER 1 • Adjust head of the bed to lower ICP • Ensure Temperature < 38°C. • Titrate pharmacologic analgesia or sedation • Optimize CPP to a max of 70 mm Hg with fluid bolus or pressors • CSF drainage (if EVD available) • Low dose Mannitol (0.25 – 0.5 g/kg), to be administered as bolus infusion. • Low dose Hypertonic saline (1.5 – 3%). Titrate to ICP control and avoid serum Na+ above 160. • Initiate or titrate anti-seizure medications (AEDs) • Adjust ventilator for a target PaCO2 of 35 - 40 mm Hg and target pH of 7.35 - 7.45	**TIER 1** • Adjust head of the bed to improve Pbt)2 • Ensure Temperature < 38°C. • Optimize CPP to a max of 70 mm Hg with fluid bolus or pressors. • Optimize hemodynamics by: 1) Treating hypovolemia; 2) Avoid hypervolemia • Adjust PaO2 by: 1) increasing FiO2 up to 60%; 2) adjusting PEEP; 3) Pulmonary toileting (suctioning) • Adjust ventilator for a target PaCO2 of 38-42 mm Hg and target pH of 7.35 - 7.45 • Initiate or titrate anti-seizure medications (AEDs)	**TIER 1** • Adjust head of the bed to lower ICP • Ensure Temperature < 38°C. • Pharmacologic analgesia and sedation • CSF drainage (if EVD available). • Increase CPP to a maximum >70 mm Hg with fluid bolus. • Low dose Mannitol, (0.25 – 0.5 mg/kg) or Hypertonic saline (1.5 – 3%) • Optimize hemodynamics by: 1) Treating hypovolemia; 2) Avoid hypervolemia; • Increase PaO2 by: 1) increasing FiO2 up to 60%; 2) adjusting PEEP; 3) Pulmonary toileting (suctioning) • Adjust ventilator for a target PaCO2 of 38-42 mm Hg and target pH of 7.35 - 7.45 • Initiate or titrate anti-seizure medications (AEDs).
TIER 2 • Adjust ventilatory rate for target PaCO2 of 33 – 38 mm Hg and target pH of 7.30-7.45 • High dose Mannitol 1-1.5 g/kg or higher frequency of standard dose mannitol • High dose Hypertonic saline bolus (i.e., 7.5%, 30 ml of 23.4%). • Increase CPP above 70 mmHg with fluids or pressors. • Treat surgically remediable lesions according to guidelines • Adjust temperature to 35 – 36°C, using active cooling measures. • Neuromuscular blockade with short acting agents, use a bolus dose to determine effect	**TIER 2** • Adjust ventilatory rate to increase PaCO2 to 40 – 45 mm Hg and target pH of 7.35-7.45 • Increase PaO2 by: 1) increasing FiO2 up to 100%; 2) adjusting PEEP; 3) bronchoscopy • Increase CPP above 70 mmHg with fluids or vasopressors. • Neuromuscular blockade with short acting agents, use a bolus dose to determine effect • Transfuse pRBCs. • Decrease ICP to < 15 mm Hg. • CSF drainage. • Increased sedation	**TIER 2.** • High dose Mannitol 1-1.5 g/kg, or frequent boluses standard dose Mannitol • High dose Hypertonic saline bolus (i.e., 30 ml of 23.4%) • Increase CPP above 70 mm Hg with vasopressors. • Increase PaO2 by: 1) increasing FiO2 to 100%; 2) adjusting PEEP; 3) bronchoscopy • Transfuse pRBCs • Treat surgically remediable lesions according to guidelines • Adjust temperature to 35 - 36°C, using active cooling measures. • Neuromuscular paralysis blockade with short acting agents, use a bolus dose to determine effect
TIER 3 (Tier 3 therapies are optional). • Pentobarbital coma, according to local protocol. • Decompressive craniectomy. • Adjust temperature to 32-35°C, using active cooling measures. • Adjust ventilatory rate for target PaCO2 of 30 – 35 mm Hg and target pH of less than 7.50 • Other salvage therapy per local protocol and practice patterns	**TIER 3 (Tier 3 therapies are optional).** • Adjust ventilatory rate to increase PaCO2 to > 45 mm Hg if ICP is < 22 mm Hg and maintain a target ph of 7.30 – 7.45 • Increase cardiac output with inotropes (milrinone, dobutamine) • Assess for vasospasm, if present augment CPP • Consider hyperventilation for reverse Robin-Hood syndrome • Other salvage therapy per local protocol and practice patterns • Consider other causes: PE, CSDs, CST	**TIER 3. (Tier 3 therapies are optional).** • Pentobarbital coma: • Decompressive craniectomy. • Induced hypothermia. hypothermia to 32-35° C. • Increase cardiac output with inotropes (milrinone, dobutamine) • Assess for vasospasm, if present augment CPP • Consider hyperventilation for reverse Robin-Hood syndrome • Other salvage therapy per local protocol and practice patterns • Consider other causes: PE, CSDs, CST

PbtO2 Management

Tier 1	Tier 2	Tier 3 (optional)
• Adjust head of the bed to improve Pbt02 • Ensure Temperature < 38°C. • Optimize CPP to a max of 70 mm Hg with fluid bolus or pressors. • Optimize hemodynamics by: 1) Treating hypovolemia; 2) Avoid hypervolemia • Adjust PaO2 by: 1) increasing FiO2 up to 60%; 2) adjusting PEEP; 3) Pulmonary toileting (suctioning) • Adjust ventilator for a target PaCO2 of 38-42 mm Hg and target pH of 7.35 - 7.45 • Initiate or titrate anti-seizure medications (AEDs)	• Adjust ventilatory rate to increase PaCO2 to 40 – 45 mm Hg and target pH of 7.35-7.45 • Increase PaO2 by: 1) increasing FiO2 up to 100%; 2) adjusting PEEP; 3) bronchoscopy • Increase CPP above 70 mmHg with fluids or vasopressors. • Neuromuscular blockade with short acting agents, use a bolus dose to determine effect • Transfuse pRBCs. • Decrease ICP to < 15 mm Hg. • CSF drainage. • Increased sedation	• Adjust ventilatory rate to increase PaCO2 to > 45 mm Hg if ICP is < 22 mm Hg and maintain a target ph of 7.30 – 7.45 • Increase cardiac output with inotropes (milrinone, dobutamine) • Assess for vasospasm, if present augment CPP • Consider hyperventilation for reverse Robin-Hood syndrome • Other salvage therapy per local protocol and practice patterns • Consider other causes: PE, CSDs, CST

PbtO2 vs ICP Management Trials

- Impact of Early Optimization of Brain Oxygenation on Neurological Outcome After Severe Traumatic Brain Injury (OXY-TC)
  - France; 22 sites; 300 patients
- Brain Oxygen and Outcome in Severe Traumatic Brain Injury: Phase 3
  - US & Canada; 47 sites; 1094 patients

BOOST-3

- Brain Oxygen Neuromonitoring in Australia and New Zealand Assessment (BONANZA)
  - ANZ & Europe; 15 – 18 sites; 860 patients

International, > 80 sites, goal enrollment = 2254 patients

Summary

- Brain tissue oxygen monitoring provides additional information regarding a patient's unique physiology
- Brain hypoxia is common after TBI
  - Interventions exist that can treat brain hypoxia
  - A Phase II study of PbtO2 guided management in severe TBI demonstrated feasibility and safety
- Three multi-center studies comparing management guided by PbtO2 versus ICP alone are in progress
  - International locations, > 80 sites, goal enrollment of 2254 patients

Questions?

www.ccm.pitt.edu