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Blood Brain Barrier in Delirium

U13 Delirium Conference

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Outline

- Blood brain barrier physiology and pathophysiology in acute illness
- Astrocyte damage and delirium
- Endothelial dysfunction and delirium
- Limitations
- Future directions

BBB and Brain Parenchyma

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González-Scarano F et al. *Nat. Rev. Immun.* 2005; 5: 569-81

Blood Brain Barrier Function

- Protects the brain through selective permeability
  - When damaged, allows inappropriate passage of molecules from the plasma into the CNS and from the CNS into the plasma
  - Biomarkers of neurologic injury in the plasma may result from direct damage to the BBB of from direct neuronal damage leading increased diffusion through the BBB

Altered BBB Permeability

- In vitro studies have shown IL-1β and VEGF-A increase BBB permeability
- VEGF increases BBB permeability after ischemia in rats
- Circulating TNF-α increased BBB permeability in mouse model of *E coli* and *Strep pneumo* sepsis
- Permeability changes in multiple rat sepsis models
- Procalcitonin, IL-8, and CRP have been associated with acute brain dysfunction in critically ill patients
  - Via BBB permeability?

Tsao N et al. *J Med Microbiol.* 2001; 50: 812-21
Argaw A et al. *J Immunol.* 2006; 177: 5574-84
Van den Boogaard M et al. *Crit Care.* 2011; 15: R297
Zhang ZG et al. *J Cereb Blood Flow Met.* 2002; 22: 379-92

BBB Permeability with Increasing Age

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Farrall AJ et al. *Neuro of Aging.* 2009; 30: 337-52

Brain's Response

- Production of cytokines, cell infiltration, and tissue damage
- Altered patterns of neuronal activity by modulating synthesis of neurotransmitters and changing expression of neurotransmitter receptors
  - Clinical symptom = delirium?

Mostly based on animal and autopsy data

Sharshar T et al. *Crit Care.* 2005; 9: 37-44

Signalling in Pathological Conditions

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Abbott NJ et al. *Nat. Rev. Neuro.* 2006; 7: 41–53

Astrocyte Injury

- S100B is expressed and secreted by astrocytes after CNS injury/ischemia and cell death
  - Plasma S100B validated as a measure of BBB injury against CSF-serum albumin ratios and MRI
  - Correlate with endothelial cell structural changes in cortical biopsy specimens
  - Plasma levels increases in brain trauma, ischemia, toxic injury, and neurodegenerative diseases
  - Exact function unknown, may be involved in neuronal and glial growth, proliferation, and activation
  - Values may differ depending on the assay used

Cata JP et al. *BJA.* 2011; 107: 844-58
Blyth BJ et al. *J Neurotrauma*. 2009; 26: 1497-1507
Kanner AA et al. *Cancer*. 2003; 97: 2806-13
Kochanek PM et al. *Curr Opin Crit Care.* 2008; 14: 135-41

S100B and Elderly

- Levels correlated with delirium (CAM) in 120 elderly hip fracture patients
  - Highest levels during delirium, but before and after were also higher than non-delirious patients
- Image removed for copyright

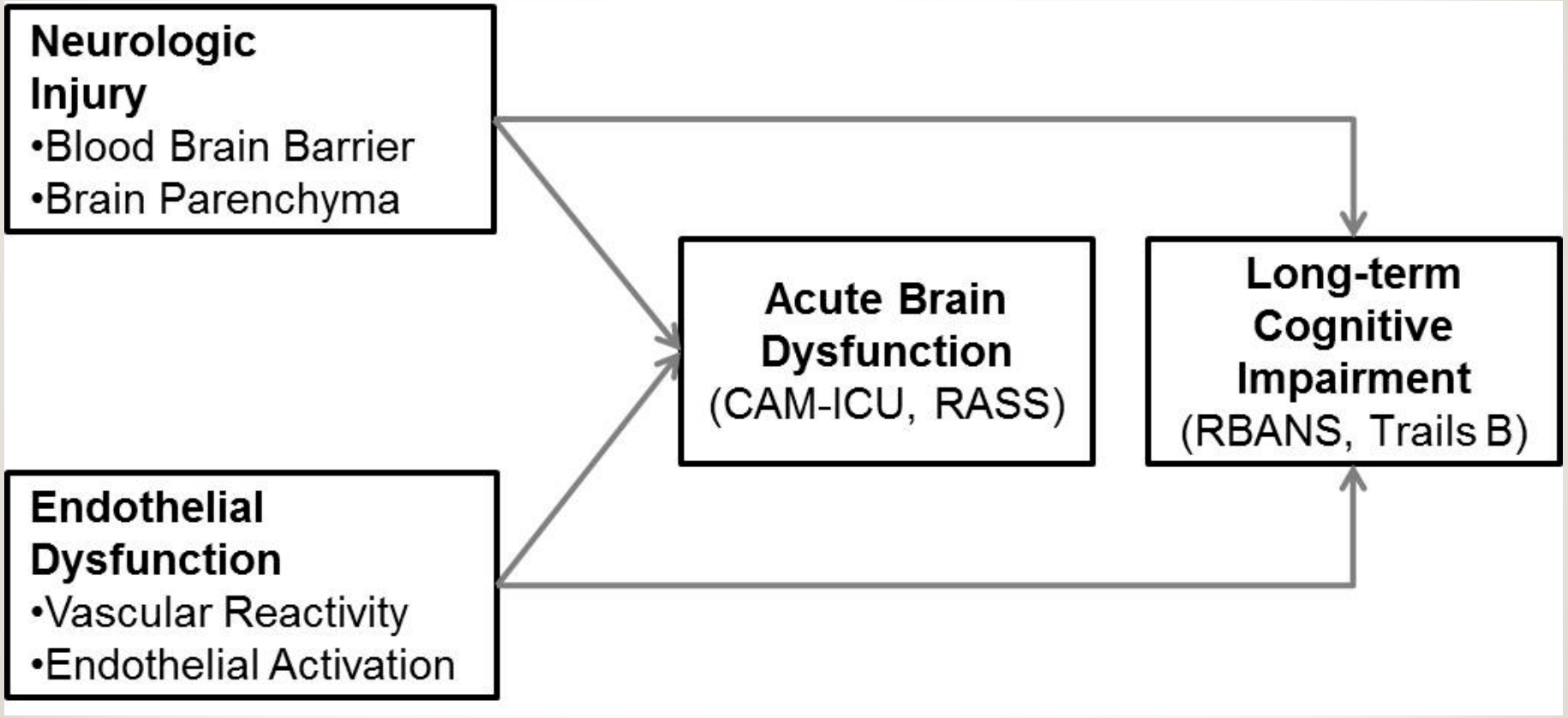
Van Muster BC et al. *BMC Neurology*. 2009; 9: 21

S100B and Septic Encephalopathy

- 170 patients with severe sepsis or septic shock
- S100B and NSE measured daily x 4 days
- Encephalopathy determined by ICU physician
- Elevated levels of S100B were associated with low consciousness (coma, stupor, somnolence) encephalopathy (p=0.004), brain lesions, and mortality (p=0.04)
- NSE failed to predict outcome

Nguyen DN et al. *Crit Care Med.* 2006; 34: 1967-74

Our Studies


Neurologic Injury
•Blood Brain Barrier
•Brain Parenchyma
Endothelial Dysfunction
•Vascular Reactivity
•Endothelial Activation
Acute Brain Dysfunction
(CAM-ICU, RASS)
Long-term Cognitive Impairment
(RBANS, Trails B)

S100B and Delirium

- Prospective cohort of 134 patients in shock or respiratory failure
- Median age 57 years, median APACHE II of 26 with 2 days of severe sepsis
- Median ICU LOS of 5 days
- Measured S100B at enrollment
- Daily RASS and CAM-ICU assessments
- Manuscript with results pending

Endothelial Dysfunction Hypothesis

- Impaired perfusion
- Altered permeability
- Toxin exposure
- Neuronal injury

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Hughes CG et al. *Anesthesiology.* 2013; 118: 631-9

Endothelium Pathophysiology

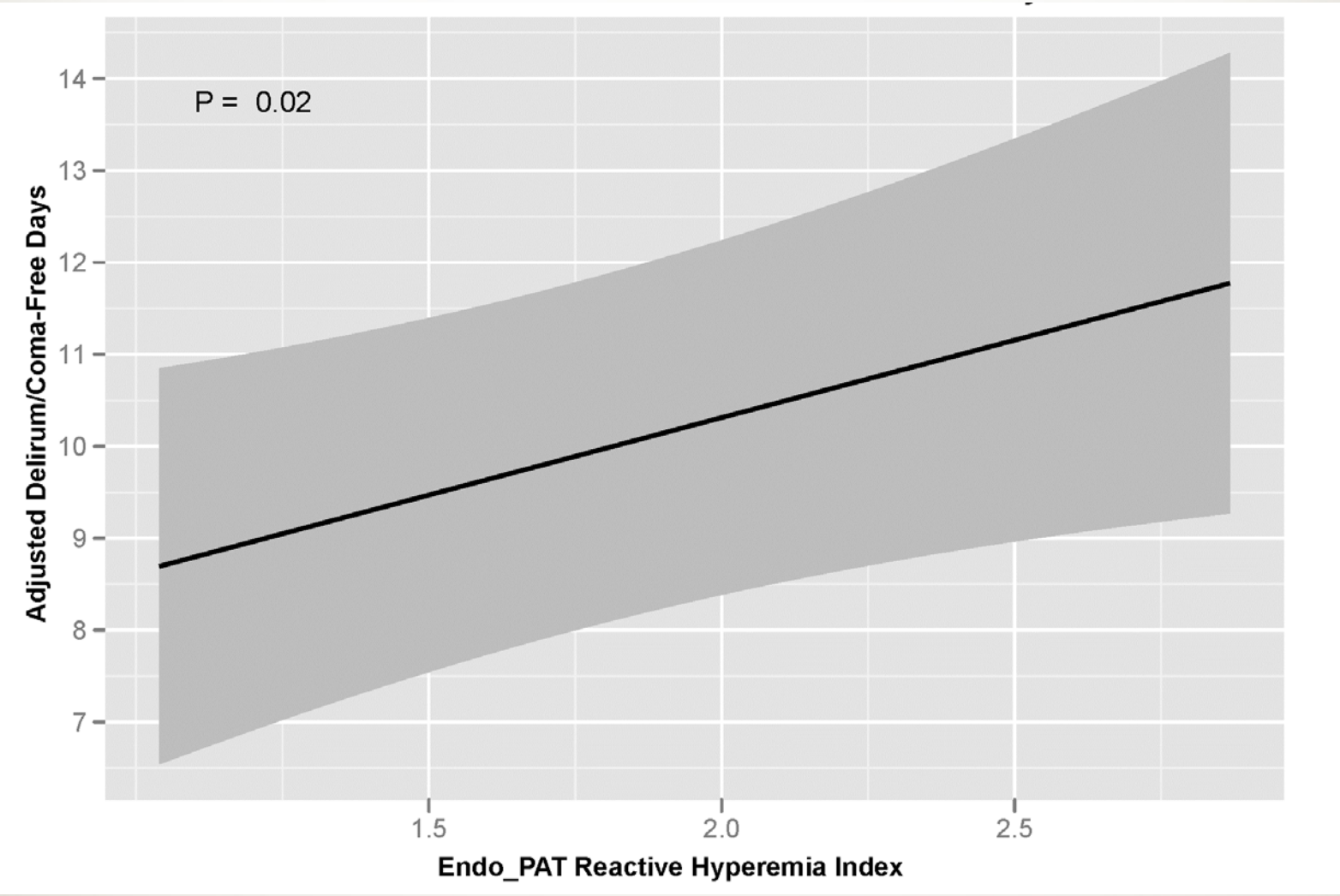
- Upregulation of inducible nitric oxide synthase and superoxide production in brains of septic mice
- Hypoxia leads to activation of protein kinase C and BBB endothelial cell permeability changes via tight junction protein phosphorylation
- E-selectin associated with BBB leukocyte adhesion and BBB dysfunction in septic mice
- Structural and functional alterations of BBB endothelial cells associated with microvascular permeability and impaired microcirculation

Yokoo H et al. *PLOS One*. 2012; 7: e51539
Fleegal MA et al. *Am J Physiol Heart Circ Physiol*. 2005; 289: H2012-19
Vachharajani V et al. *Obesity.* 2011; 20: 498-504
Gavins F et al. *Microcirculation*. 2007; 14: 681-7
Vajtr D et al. *Physiol Res*. 2009; 58: 263-8

Endothelial Dysfunction Study

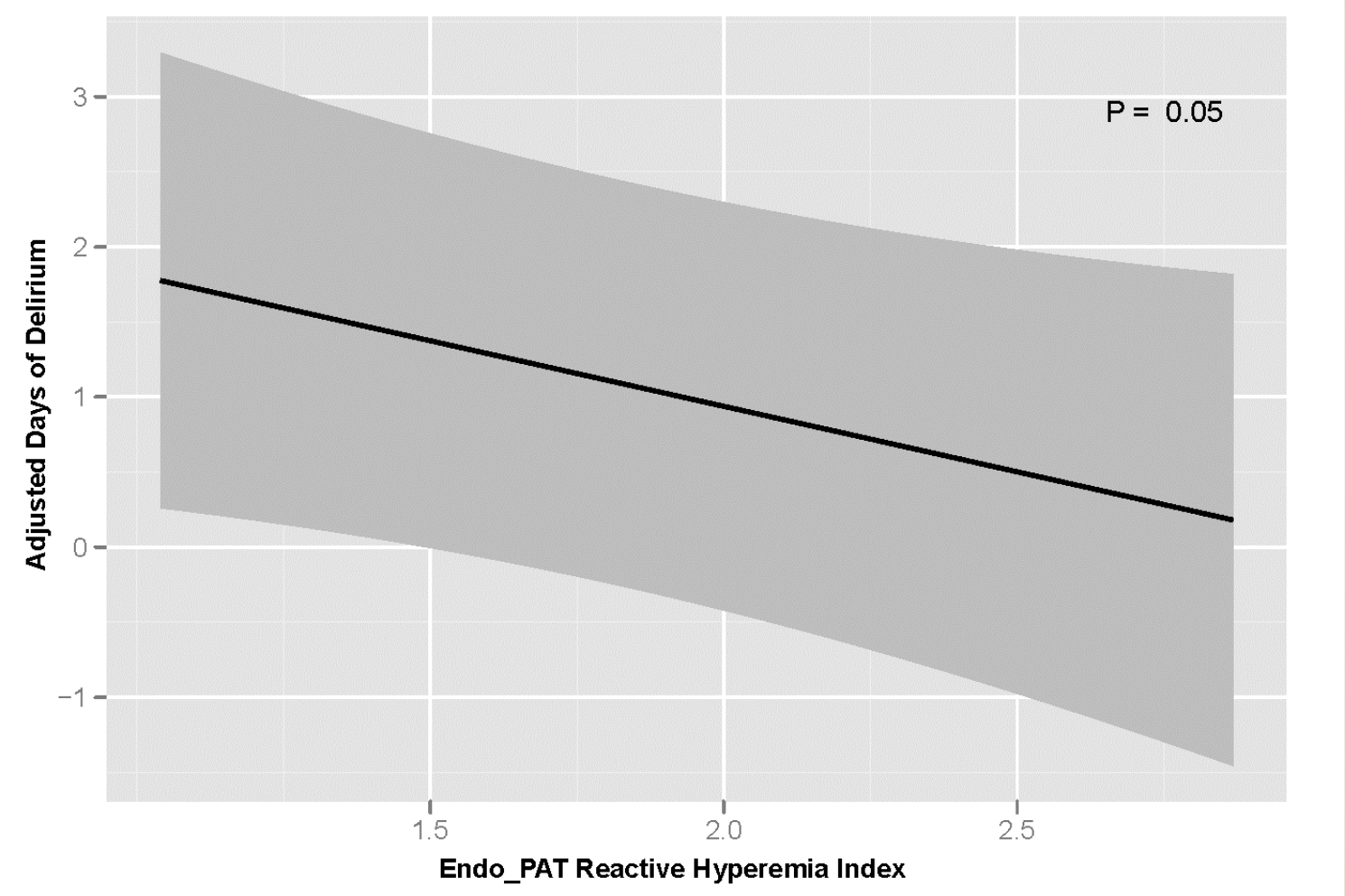
- Prospective cohort of 134 patients in shock or respiratory failure
- Median age 57 years, median APACHE II of 26 with 2 days of severe sepsis and 5-day ICU stay
- Measured endothelial vascular reactivity with peripheral artery tonometry at enrollment
- Daily RASS and CAM-ICU assessments

Vasc Reactivity vs. DCFDs



Hughes CG et al. *Anesthesiology.* 2013; 118: 631-9

Vasc Reactivity vs. Delirium Duration



Hughes CG et al. *Anesthesiology.* 2013; 118: 631-9

Endothelial Activation

- Measured endothelial activation with PAI-1, E-selectin, Ang-2 at enrollment of previously described cohort
- Manuscript with results pending

Mediation

- Adjustment for BBB injury in systemic endothelial dysfunction models to assess if BBB injury mediates association between endothelial vascular reactivity and activation with acute brain dysfunction
- Manuscript with results pending

Endothelial Modulation and Brain Dysfunction

- Physical therapy (PT) has been shown to improve endothelial function in outpatients and reduce delirium duration in ICU patients
- Hypotheses:
  - Improvement in endothelial function over time is associated with less brain dysfunction in ICU patients
  - Early PT is associated with improvement in endothelial function in ICU patients

ACT Endo Function Study

- Prospective cohort study of 72 patients nested within a RCT of early PT versus usual care in adult medical and surgical ICU patients with shock or respiratory failure
- Endothelial vascular reactivity was assessed at enrollment and at 7 days or hospital discharge via peripheral artery tonometry
- Daily RASS and CAM-ICU assessments
- Manuscript with results pending

Limitations

- Functional assessment of the BBB is limited by anatomical characteristics and current technology
  - MRI: complicated scanning protocols, including dynamic contrast enhanced MRI, long scanning sessions, difficult algorithms
- CSF to serum albumin quotient to determine BBB permeability is invasive and impractical
  - Elevated in elderly at baseline
  - Necessitates use of plasma biomarkers
- Transcranial doppler and near-infrared spectroscopy
  - Large vessels and superficial structures
  - Microdialysis assessment invasive

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Necessitates use of surrogate markers

Future Assessment

- "Post-pre" and "linear dynamic" methods with MRI
  - Semi-quantitative permeability assessment
  - Localization of dysfunctional BBB
  - Partial dynamic imaging protocol with easier to apply algorithms
- Surrogate markers
  - Is there a better indicator of BBB function?
  - Does systemic endothelial dysfunction = cerebral endothelial dysfunction?

Chassidim Y et al. *Fluids & Barriers CNS.* 2013; 10: 9

Therapeutic Options for BBB

- Improved BBB disruption in animal models of sepsis, neoplasm, and seizure

Heme oxygenase-1	Steroids
Magnesium	Calcium channel blockers
Immunoglobulins	Free radical scavenging
Anti-epileptics	ARBs

Esen F et al. *Crit Care*. 2005; 9: R18-23
Esen F et al. *Crit Care Med*. 2012; 40: 1214-20
Gurses C et al. *Brain Res.* 2009; 1281: 71-83
Gurses C et al. *Brain Res.* 2013; 1494: 91-100

Cucullo L et al. *Brain Res*. 2004; 997: 147-51
Turkel NA et al. *Int J Neurosci.* 2004; 114: 517-28
Brown RC et al. *Am J Cell Physiol.* 2004; 286: C1045-52
Yokoo H et al. *PLOS One*. 2012; 7: e51539
Fleegal-DeMotta MA et al. *J Cereb Blood Flow Metab*. 2009; 29: 640-7

Therapeutic Options for BBB

- Early Mobility
  - Serial measurements of S100B, endothelial vascular reactivity, endothelial activation in larger mobility cohorts with delirium monitoring
- Statin Pharmacotherapy
  - Known modifiers of the endothelium and reduce inflammation
  - May be protective of delirium
  - Measure S100B, endothelial vascular reactivity, and endothelial activation in upcoming RCTs of statin vs. placebo

Key Points

- Both BBB injury and endothelial dysfunction are independently associated with acute brain dysfunction during critical illness
- BBB injury does not appear to mediate the effects of endothelial dysfunction on acute brain dysfunction
  - Perfusion, autoregulation, and permeability separate with regards to delirium?
- Many potential routes of future investigation, including therapeutic trials, high-risk populations, long-term outcomes

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Questions?