

Brain Dysfunction During Shock



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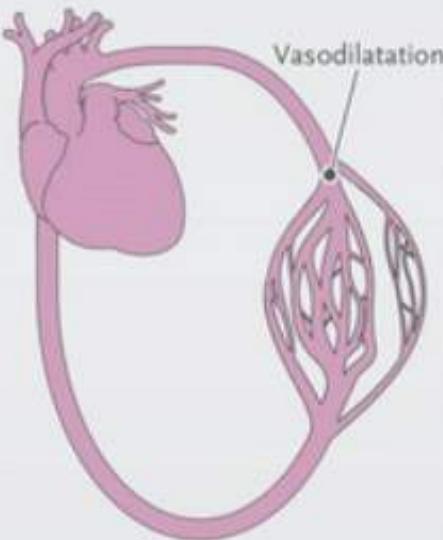
My brain?

It's my second favourite organ

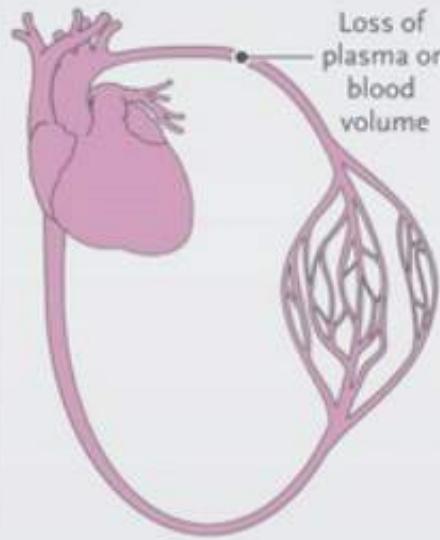


Shock

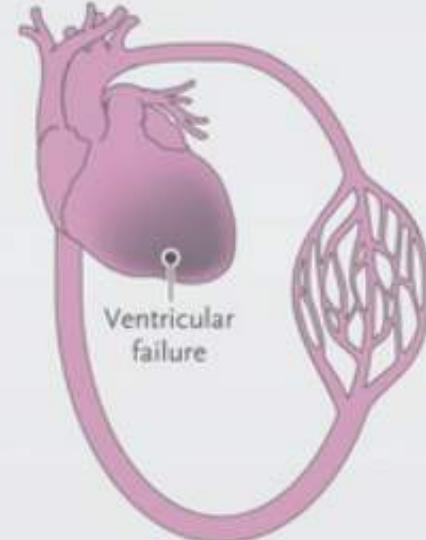
Distributive shock



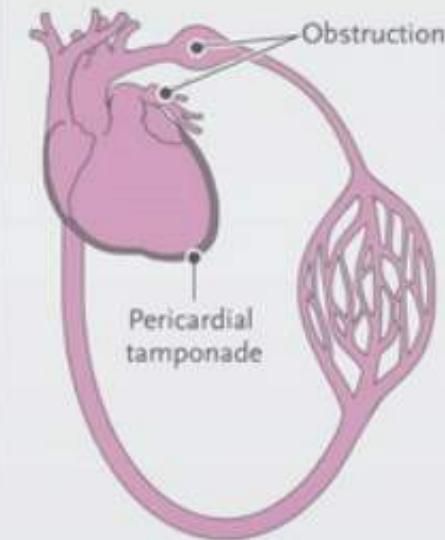
Hypovolemic shock



Cardiogenic shock



Obstructive shock



HIGH
CO

LOW CARDIAC OUTPUT



My brain?

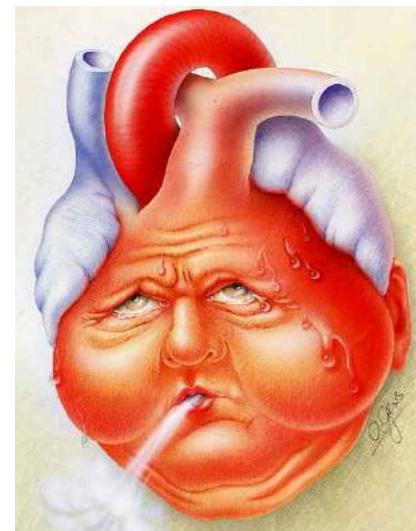
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Low CO



**FLOW
REDISTRIBUTION**



COMPENSATED

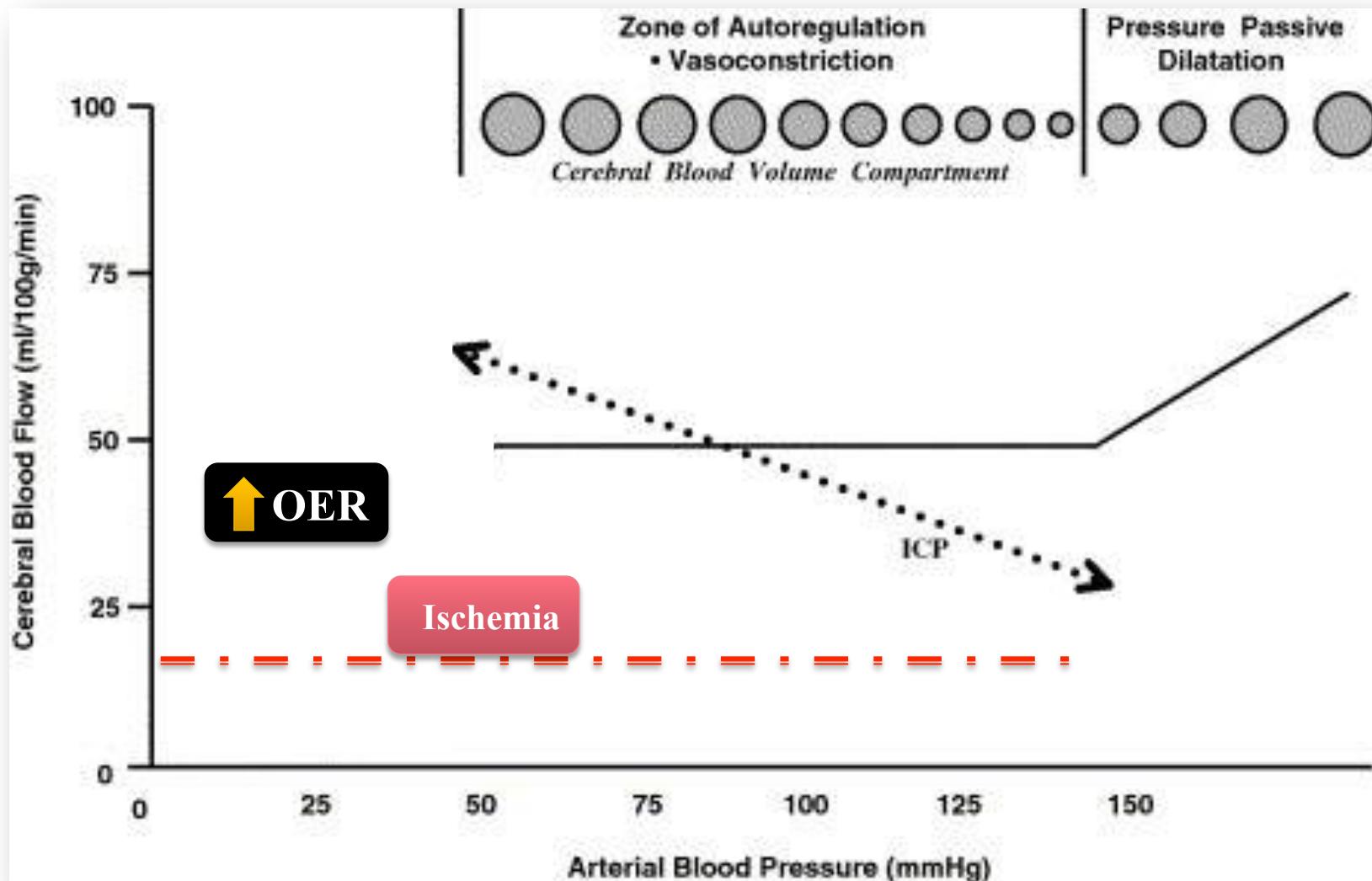


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Pressure Regulation





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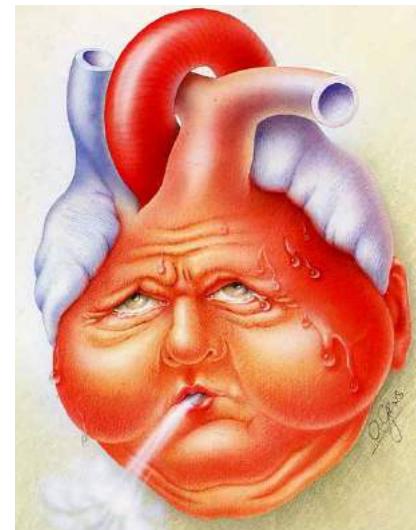
Low CO

REDUCED CBF

**FLOW
REDISTRIBUTION**

DECOMPENSATED

COMPENSATED



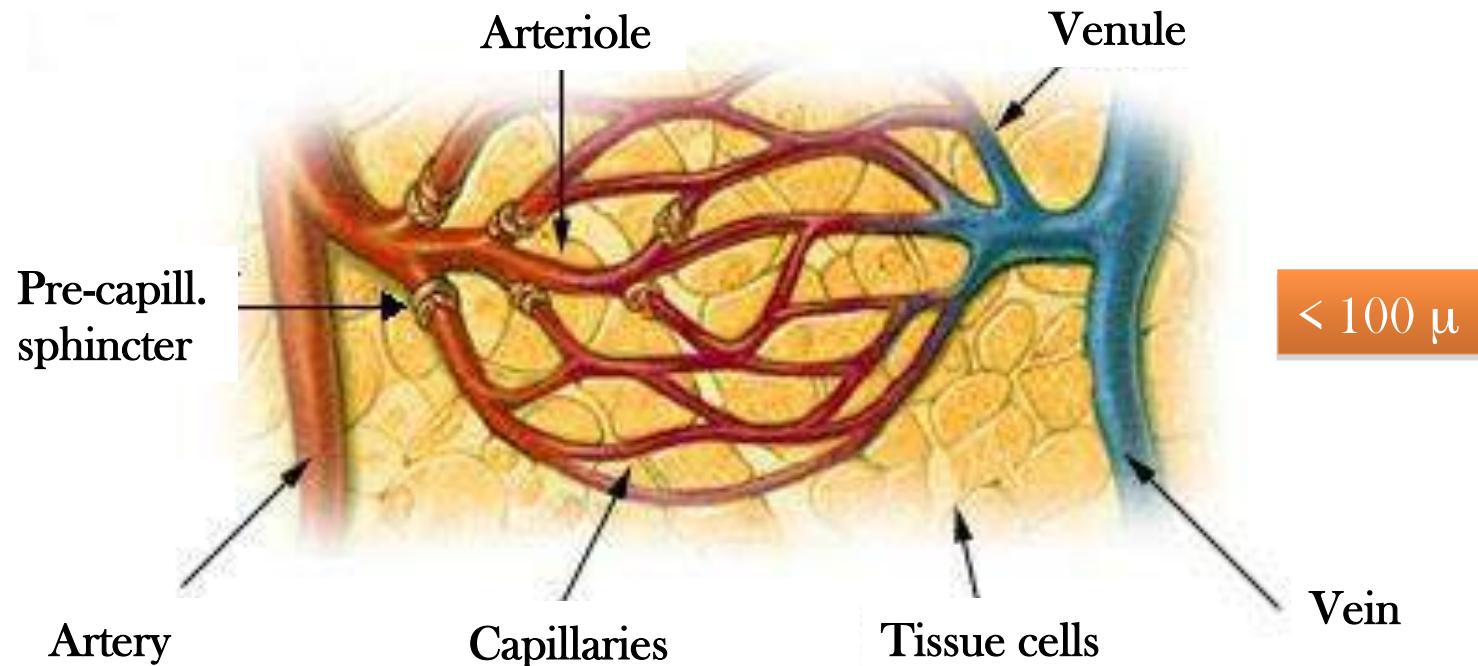


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Low CO and Tissue



1. Blood pressure
2. Blood flow and tissue perfusion
3. Tissue fluid (swelling or edema)
4. Oxygen and nutrients delivery
5. Waste removal
6. Body temperature

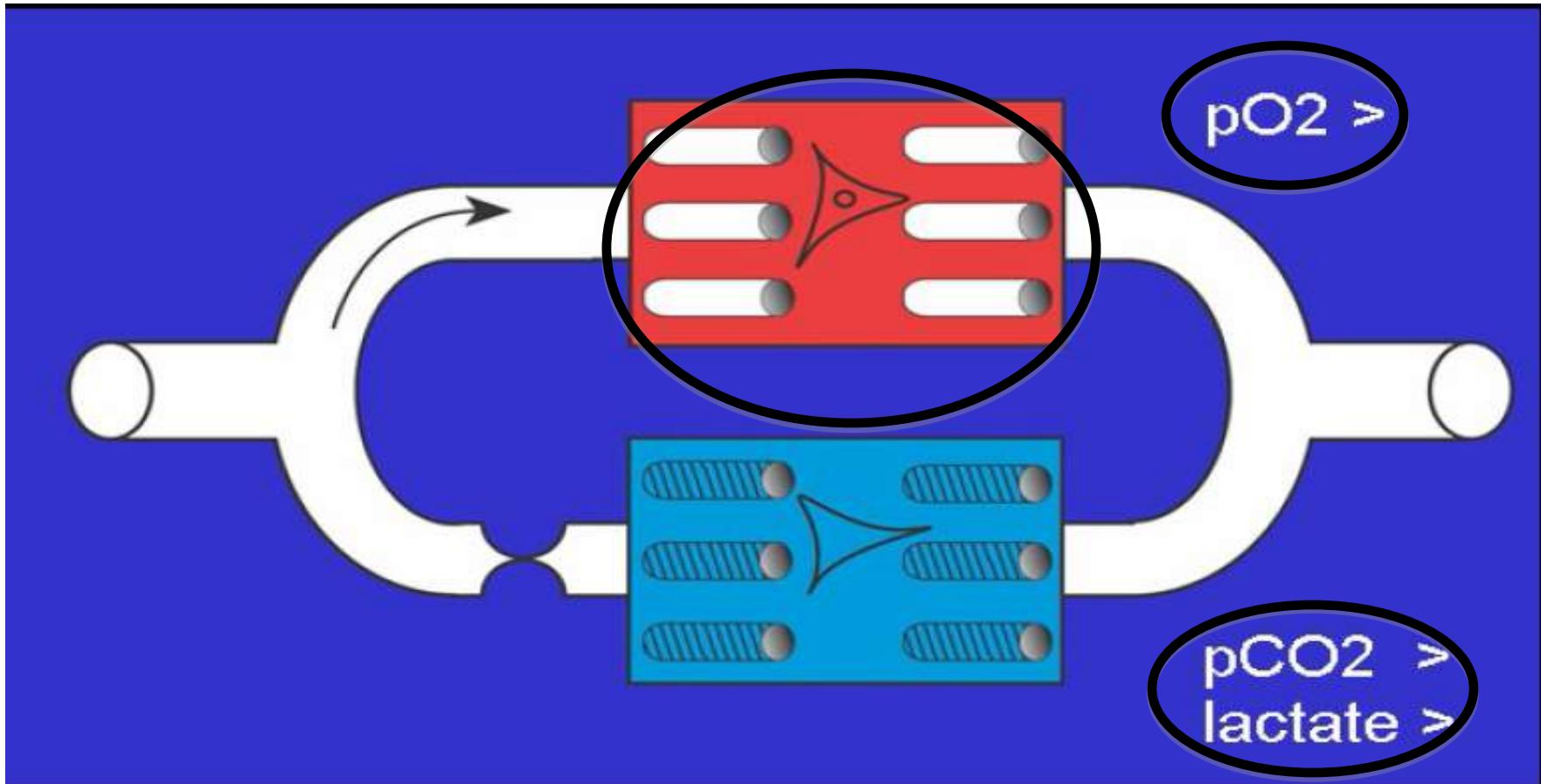


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Low CO and Tissue



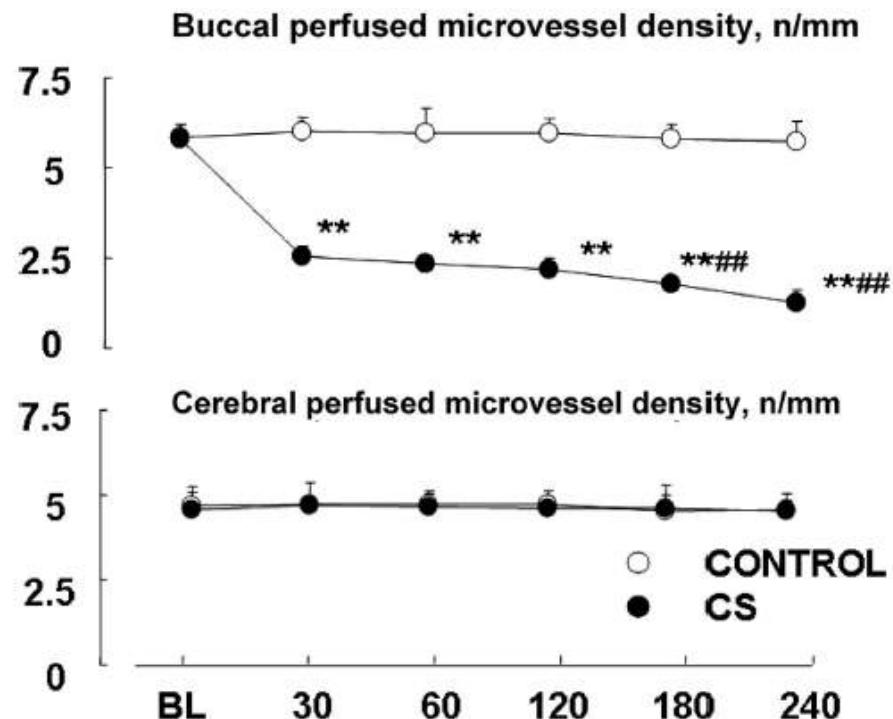
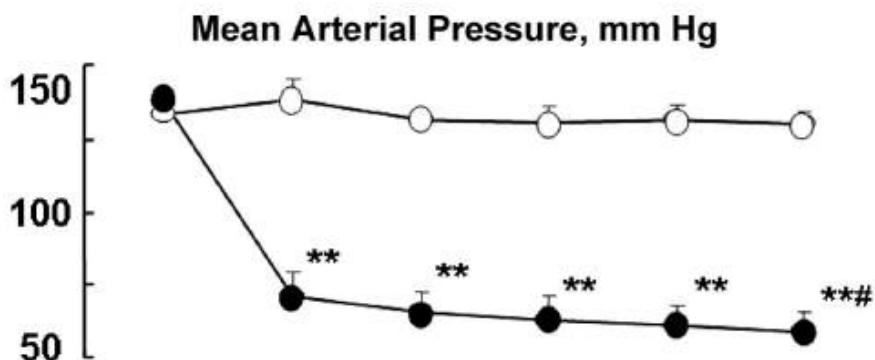


Low CO and Tissue

Preserved cerebral microcirculation during cardiogenic shock*

Zhi Wan, MD; Giuseppe Ristagno, MD; Shijie Sun, MD, FCCM; Yongqin Li, PhD;
Max Harry Weil, MD, PhD, FCCM; Wanchun Tang, MD, FCCM

Crit Care Med 2009;





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Low CO and Coma



STROKE



CEC
ECMO



SEIZURES

ACR



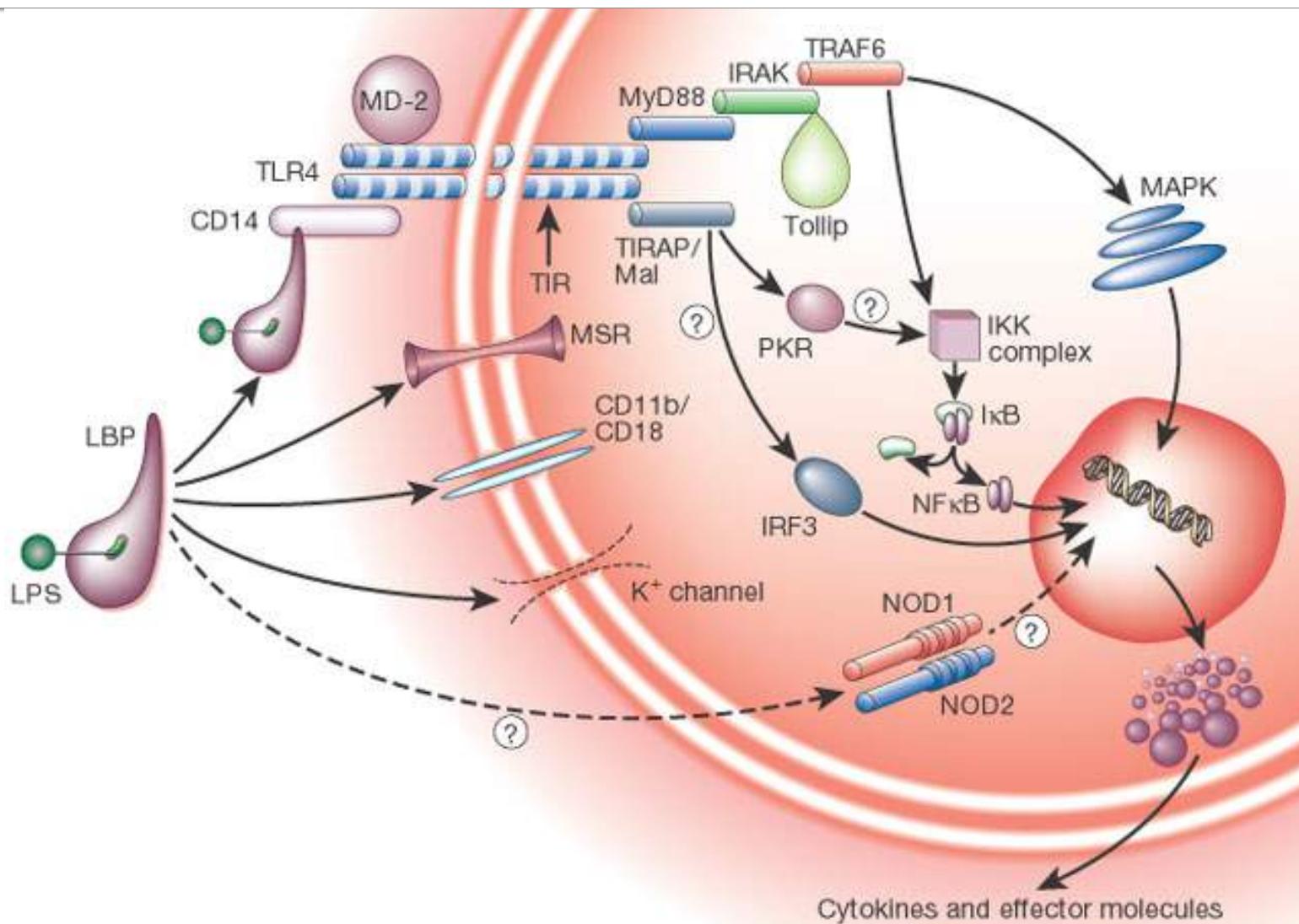


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Brain and Sepsis



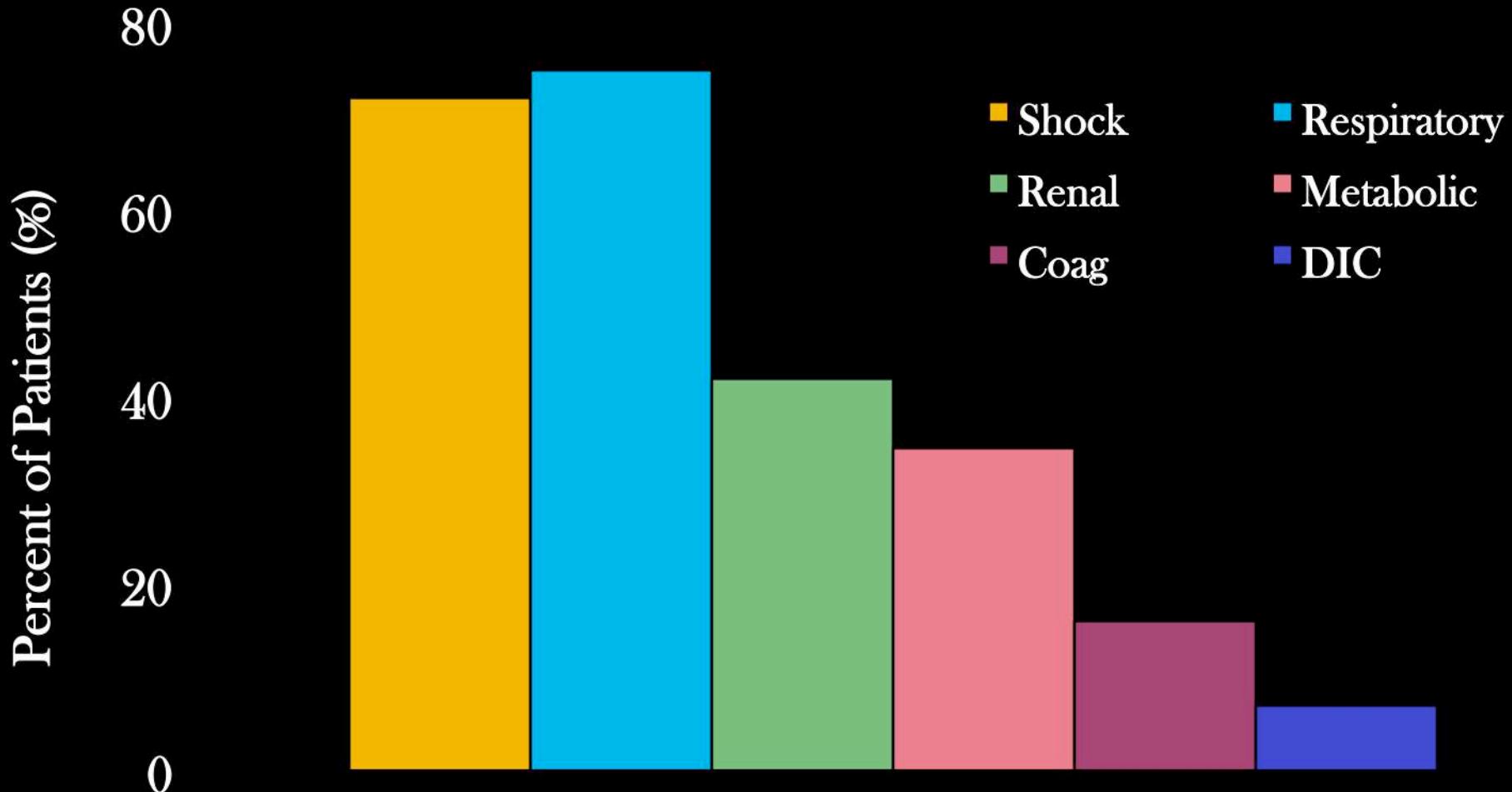


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Brain and Sepsis



Bernard, NEJM 2001



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Brain and Sepsis





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Brain and Sepsis

CLINICS

- Alteration in mental status
- Lethargy
- Personality changes
- Loss of memory
- Loss of ability to speak
- Hallucinations
- Loss of ability to swallow
- Seizures or tremors
- Delirium/Progressive loss of consciousness





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Brain and Sepsis

DEFINITION

- Impairment of consciousness (including coma) often occurs in association with sepsis
- Occur in a range of 8-70% of septic patients
- May as an early sign of sepsis
- The term "septic encephalopathy" :
 - acute confusional episodes or other significant cognitive abnormalities that develop during sepsis
 - as an entity that cannot be explained by hepatic or renal dysfunction, hypotension, or hypoxia



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Brain and Sepsis

BRAIN DYSFUNCTION

DELIRIUM

SEPTIC
ENCEPHALOPATHY



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Brain and Sepsis

Delirium as a Predictor of Mortality in Mechanically Ventilated Patients in the Intensive Care Unit *JAMA 2004*

Table 1. Baseline Characteristics of the Patients*

Characteristic	No. (%)†	
	No Delirium (n = 41)	Delirium (n = 183)
Age, mean (SD), y	54 (17)	55 (17)
Men	18 (44)	95 (52)
Race		
White	32 (78)	145 (79)
Black	9 (22)	38 (21)
Charlson Comorbidity Index, mean (SD)	3.2 (2.8)	3.2 (2.8)
Vision deficits, No./total (%){‡}	23/33 (70)	104/153 (68)
Hearing deficits, No./total (%){‡}	5/32 (16)	29/152 (19)
mBDRS score, mean (SD)	0.14 (0.6)	0.23 (0.8)
Activities of daily living, mean (SD)	0.81 (2.4)	0.91 (2.3)
APACHE II score, mean (SD)	23.2 (9.6)	25.6 (8.1)
SOFA score, mean (SD)	9.5 (2.9)	9.6 (3.4)

81%

E. Wesley Ely, MD, MPH
Ayumi Shintani, PhD, MPH
Brenda Truman, RN, MSN
Theodore Speroff, PhD
Sharon M. Gordon, PsyD
Frank E. Harrell, Jr, PhD
Sharon K. Inouye, MD, MPH
Gordon R. Bernard, MD
Robert S. Dittus, MD, MPH



My brain?

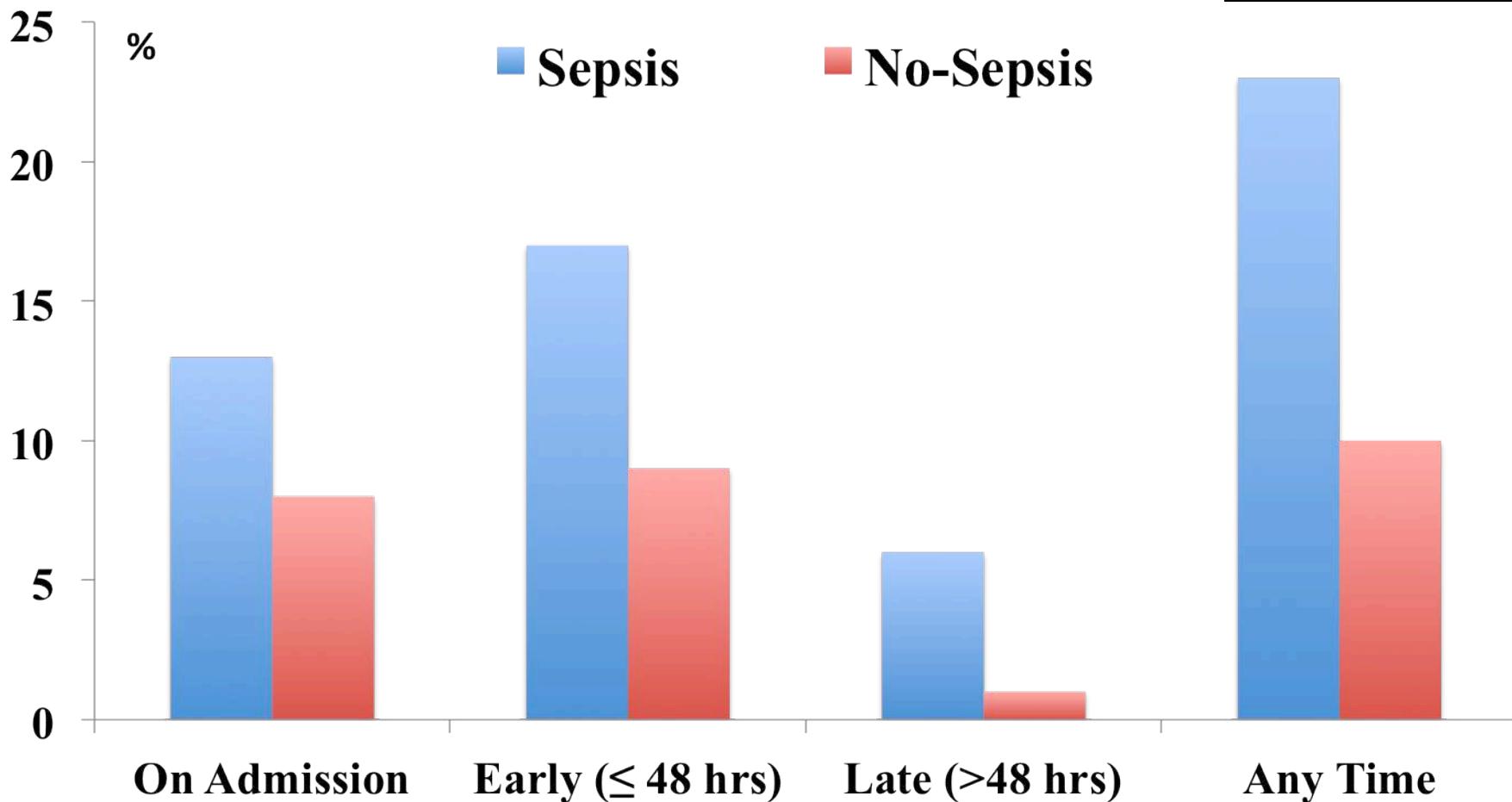
It's my second favourite organ

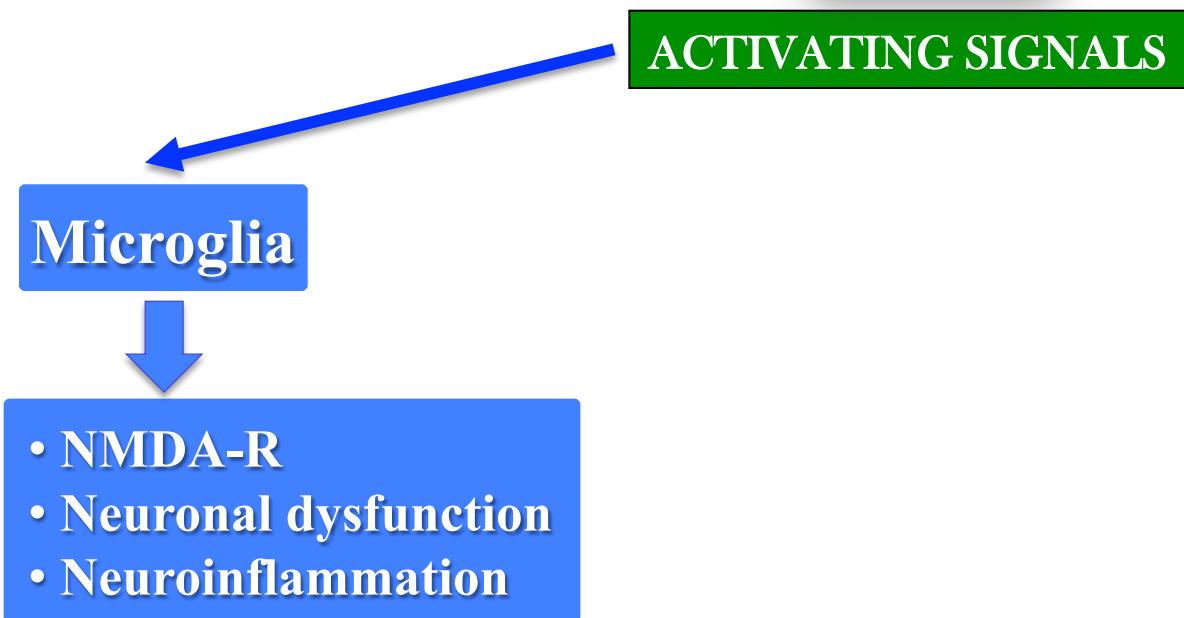
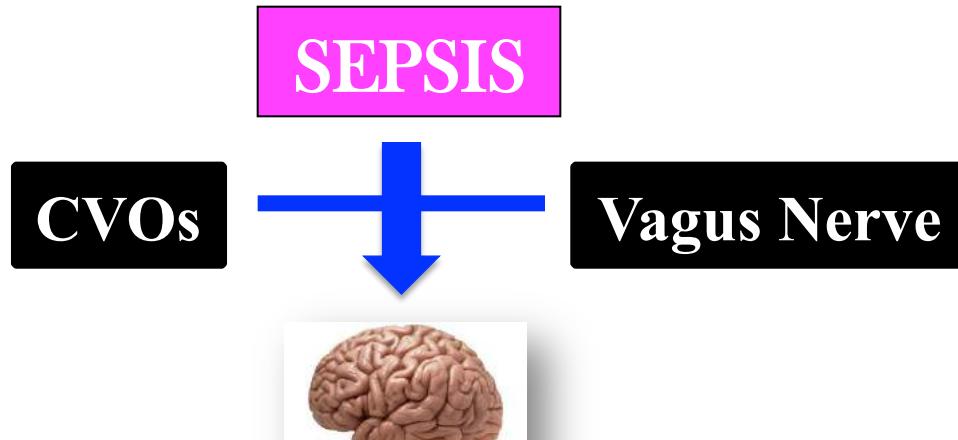


Brain and Sepsis

CNS Failure at different time-points

SOAP Study







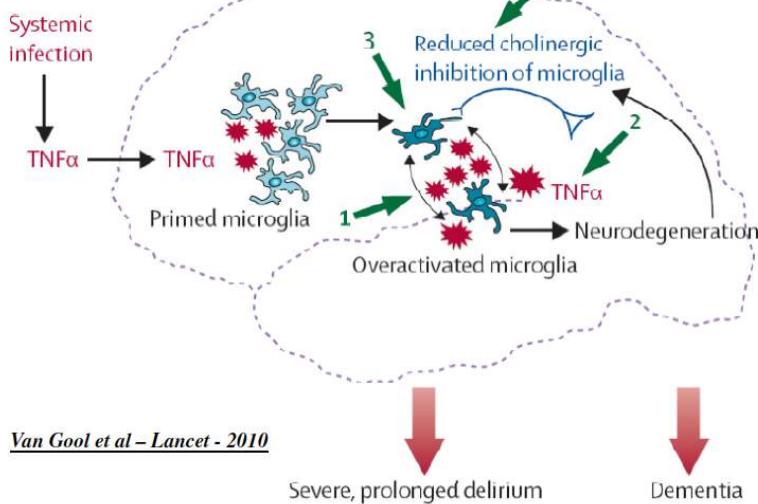
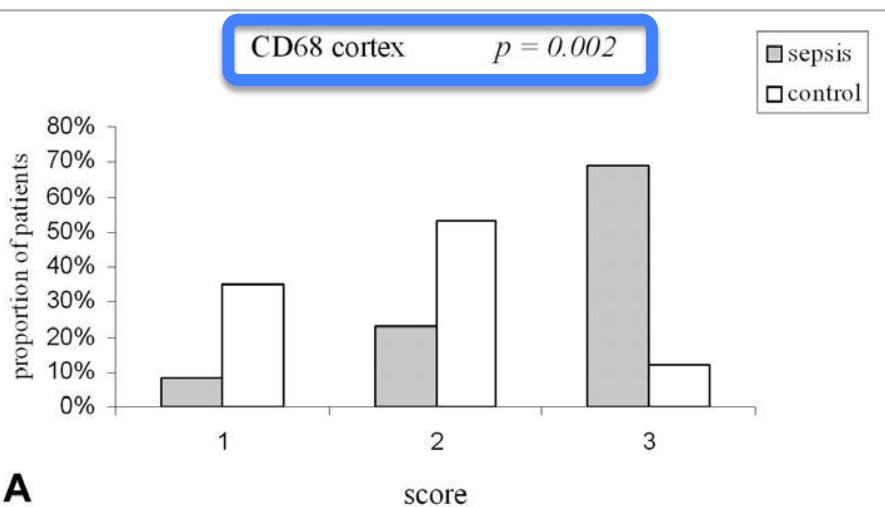
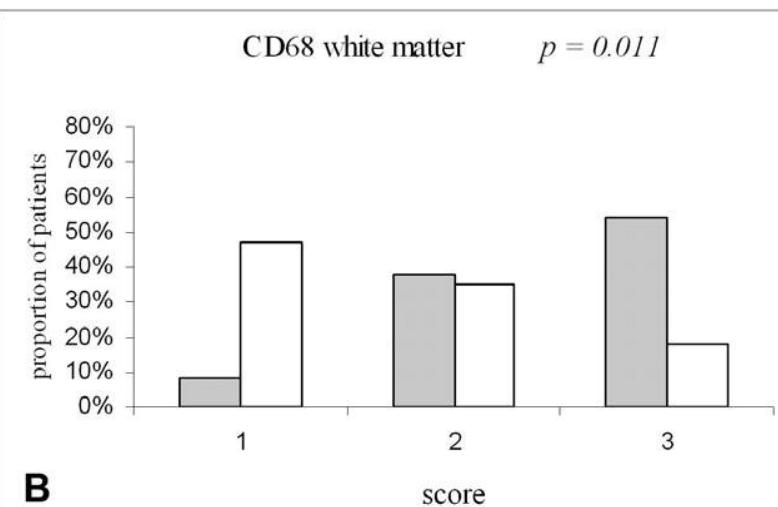
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Microglial Activation

MICROGLIAL ACTIVATION

**A****B**

Microglia activation in sepsis: a case-control study

Afina W Lemstra^{*1}, Jacqueline CM Groen in't Woud¹,
Jeroen JM Hoozemans², Elise S van Haastert², Annemiek JM Rozemuller²,
Piet Eikelenboom¹ and Willem A van Gool¹

Journal of Neuroinflammation 2007, 4:4

Post-mortem study
Sepsis, n=13
Controls, n=17



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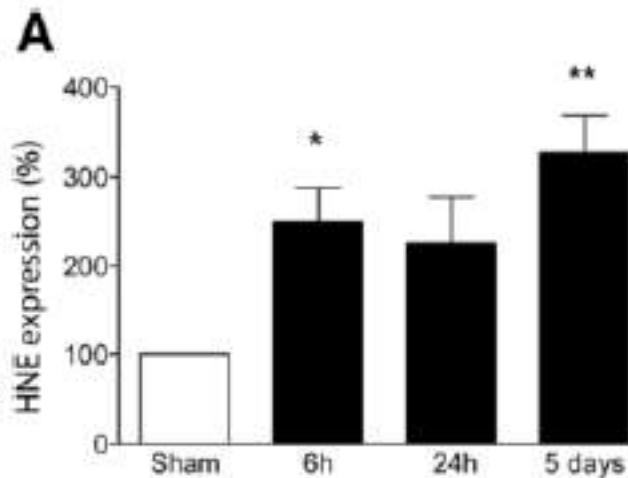
Astrocytes Activation

The role of Nox2-derived ROS in the development of cognitive impairment after sepsis

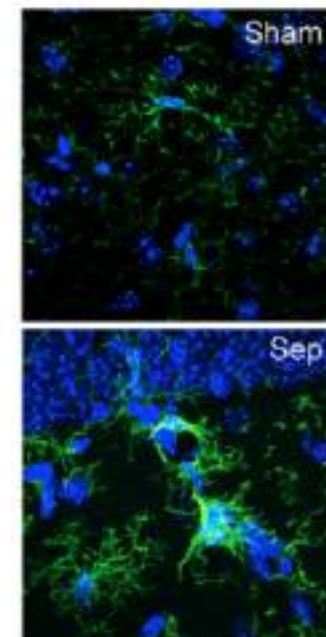
CLP Rats

Marina S Hernandes^{1,6*}, Joana C D'Avila^{3†}, Silvia C Trevelin⁴, Patricia A Reis³, Erika R Kinjo¹, Lucia R Lopes², Hugo C Castro-Faria-Neto³, Fernando Q Cunha⁴, Luiz RG Britto¹ and Fernando A Bozza^{5,7*}

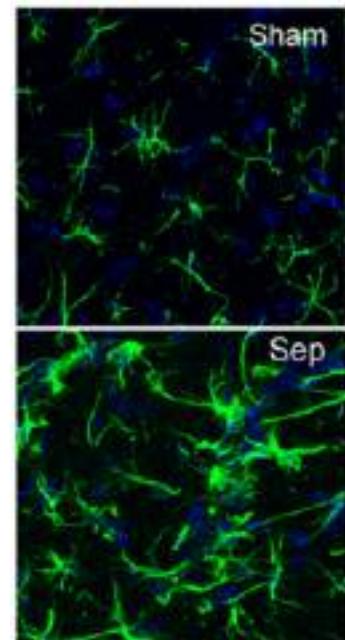
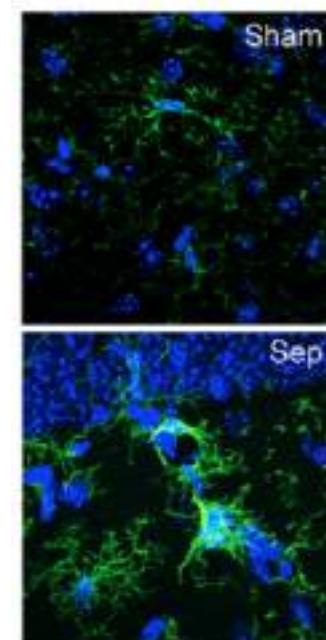
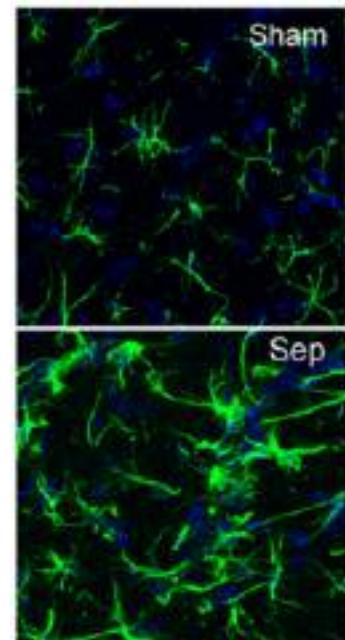
Journal of Neuroinflammation 2014, **11**:36



Microglia



Astrocytes





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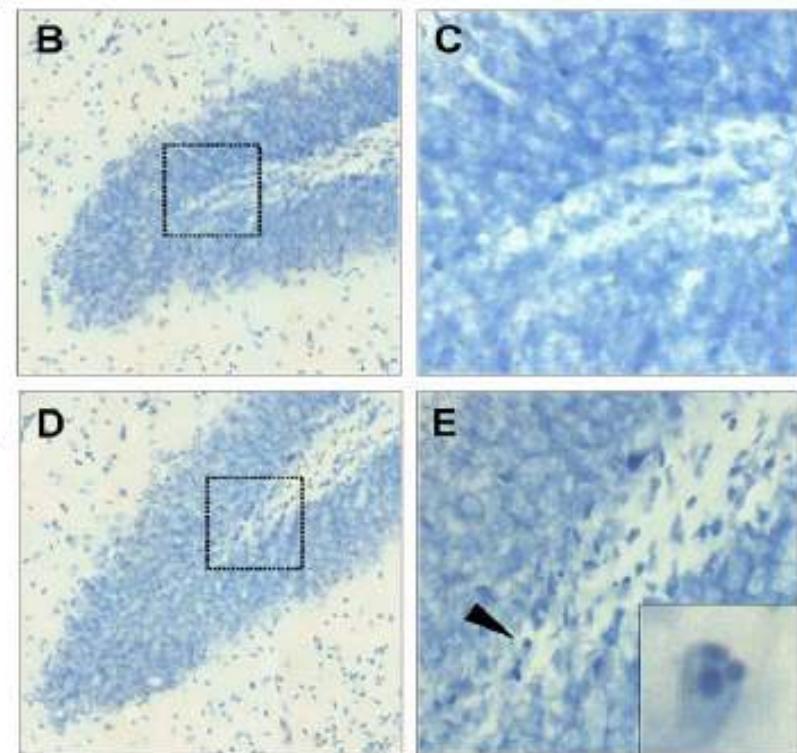
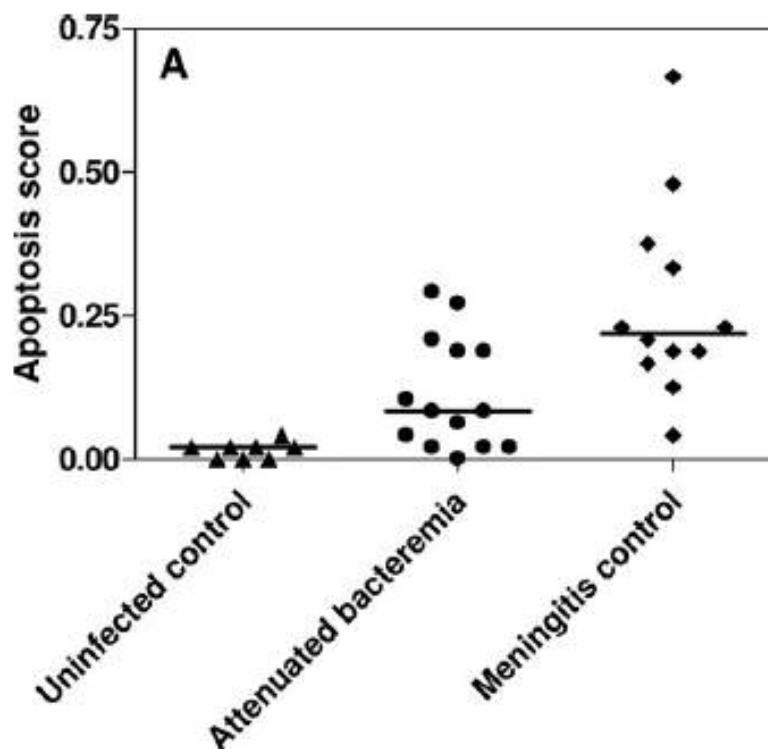


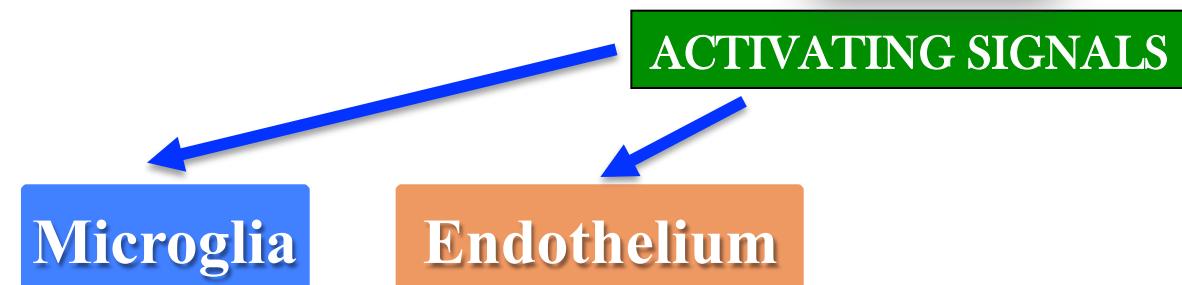
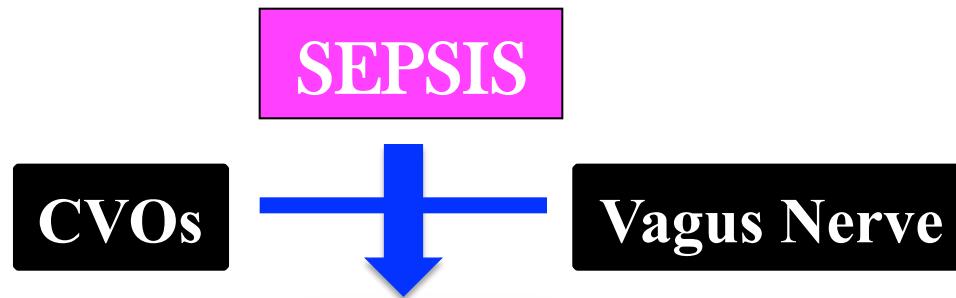
Neuronal Apoptosis

Bacteremia causes hippocampal apoptosis in experimental pneumococcal meningitis

Christian Østergaard^{1,2*}, Stephen L Leib³, Ian Rowland^{4,5}, Christian T Brandt^{2,6}

BMC Infectious Diseases 2010, 10:1





- NMDA-R
- Neuronal dysfunction
- Neuroinflammation



- BBB alterations
- Edema (AQP4)
- Astrocytes activation (TLRs)



My brain?

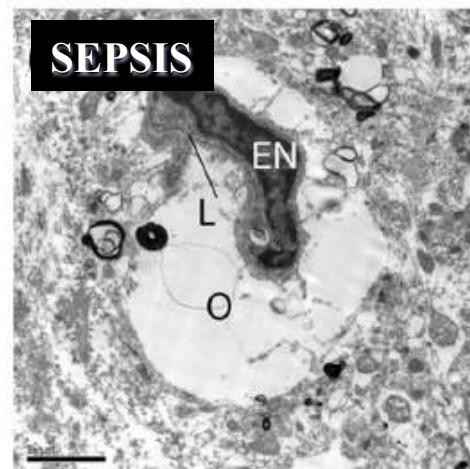
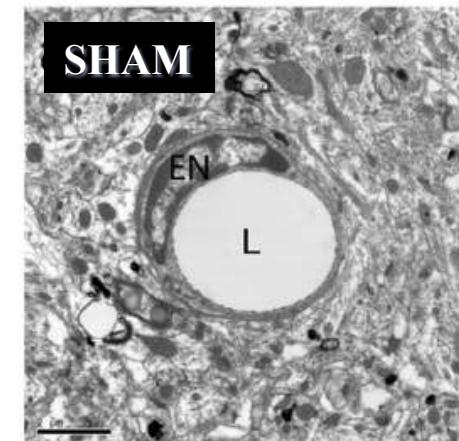
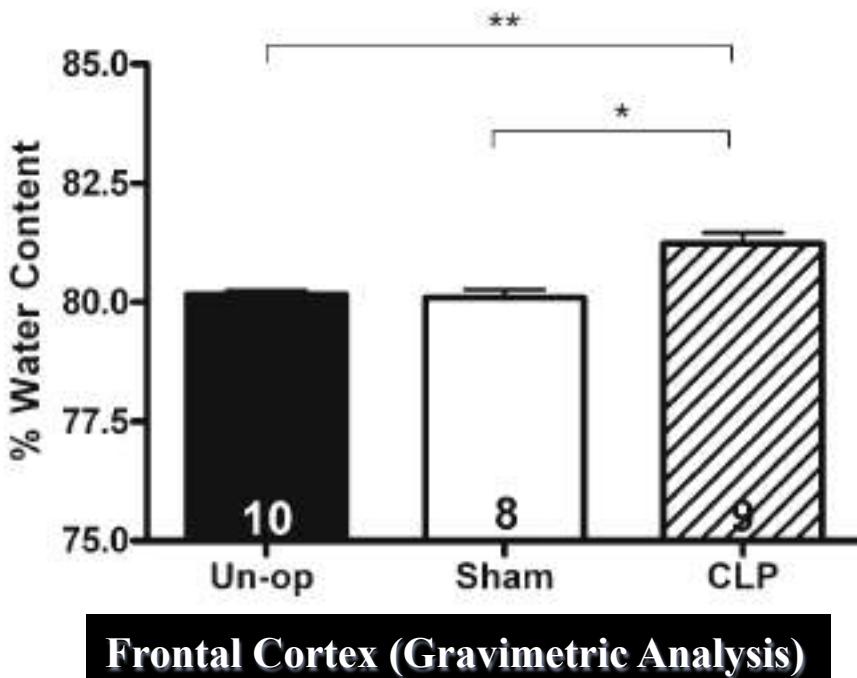
It's my second favourite organ



Endothelial Activation

Caecal ligation and puncture induced sepsis in the rat results in increased brain water content and perimicrovessel oedema

Heather F. Brooks • Raymond F. Moss •
Nathan A. Davies • Rajiv Jalan • D. Ceri Davies



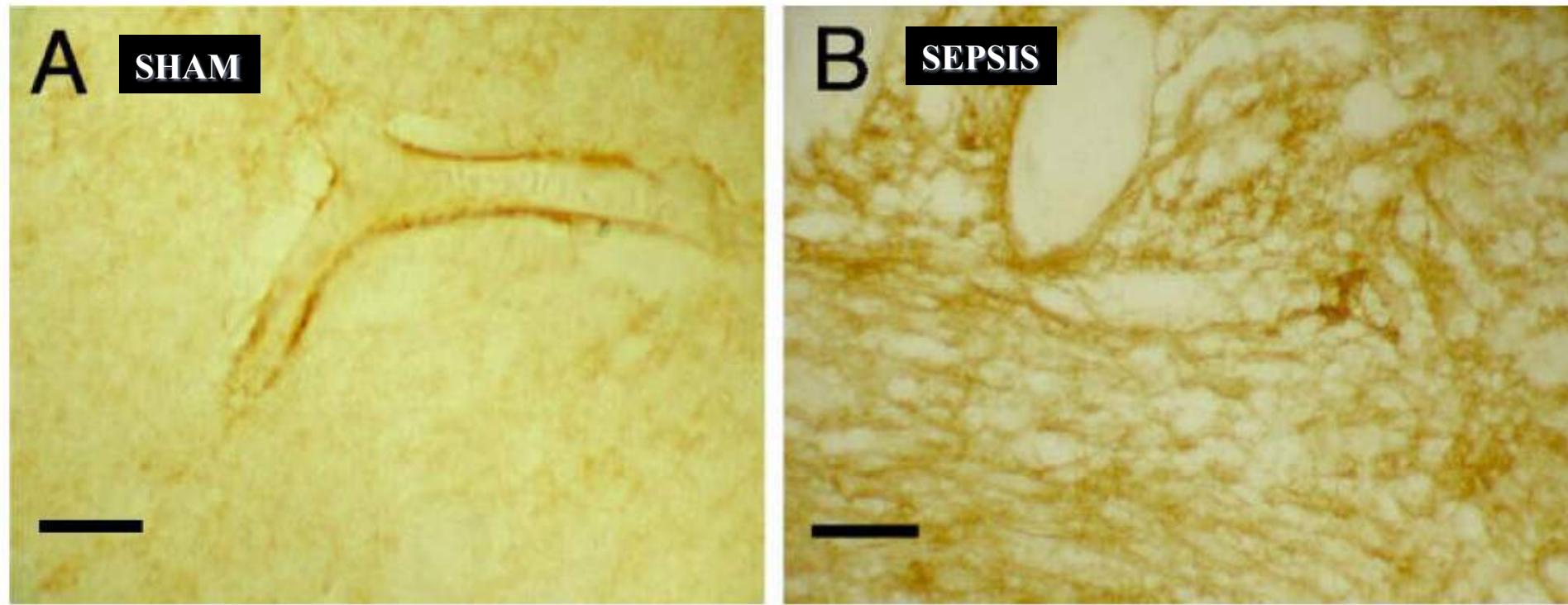


AQ4

Blood-brain barrier breakdown in septic encephalopathy and brain tumours*

D. C. Davies

J. Anat. (2002) **200**, pp639–646





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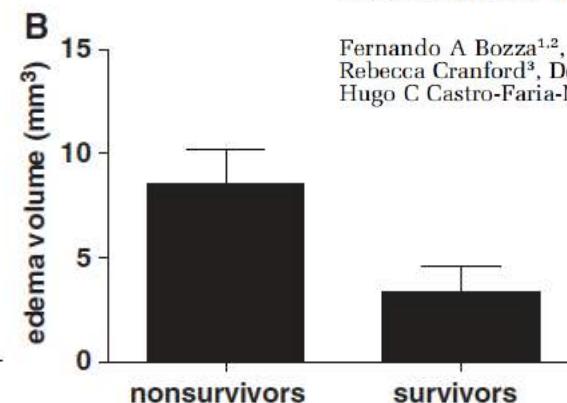
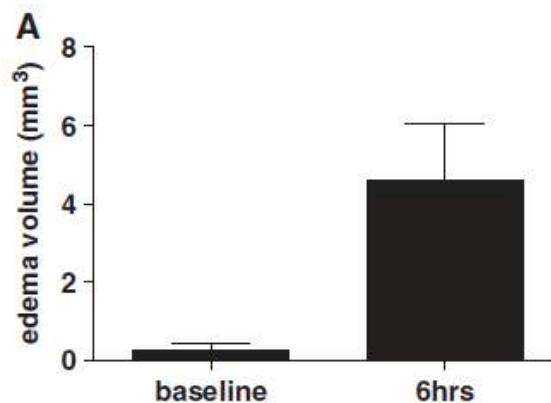


Brain Edema

Journal of Cerebral Blood Flow & Metabolism (2010) 30, 440–448

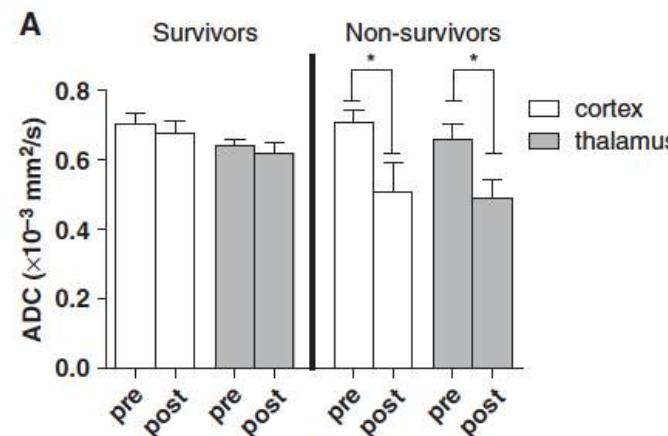
Sepsis-associated encephalopathy: a magnetic resonance imaging and spectroscopy study

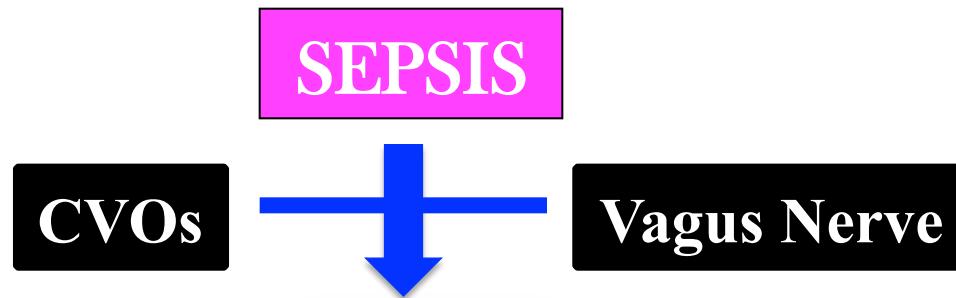
Fernando A Bozza^{1,2}, Philippe Garteiser³, Marcus F Oliveira^{2,4}, Sabrina Doblas³, Rebecca Cranford³, Debra Saunders³, Inna Jones³, Rheal A Towner³ and Hugo C Castro-Faria-Neto⁵



Mice, CLP Sepsis

ADC = cytotoxic edema





ACTIVATING SIGNALS

Microglia

Endothelium

Neurotransmission

- NMDA-R
- Neuronal dysfunction
- Neuroinflammation

- Ach
- NH₄, Tyr, Trypt
- 5-HT
- β-adrenergic

- BBB alterations
- Edema (AQP4)
- Astrocytes activation (TLRs)



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Neurotransmission

Cerebral net exchange of large neutral amino acids after lipopolysaccharide infusion in healthy humans

Critical Care 2010, **14**:R16

Ronan MG Berg^{1*}, Sarah Taudorf¹, Damian M Bailey², Carsten Lundby³, Fin Stolze Larsen⁴,
Bente Klarlund Pedersen^{1,3}, Kirsten Møller^{1,5}

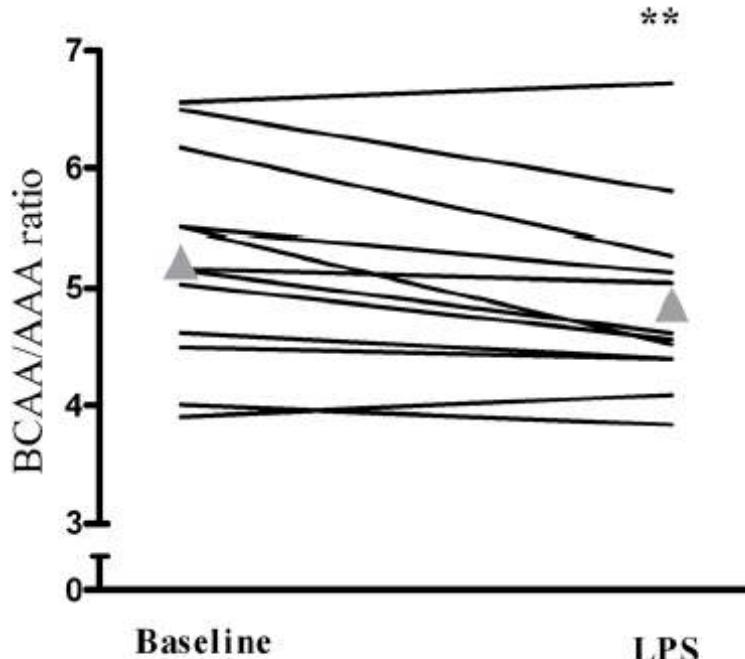


Figure 1 Branched-chain to aromatic amino acid (BCAA/AAA) ratio after lipopolysaccharide (LPS) infusion in healthy humans.

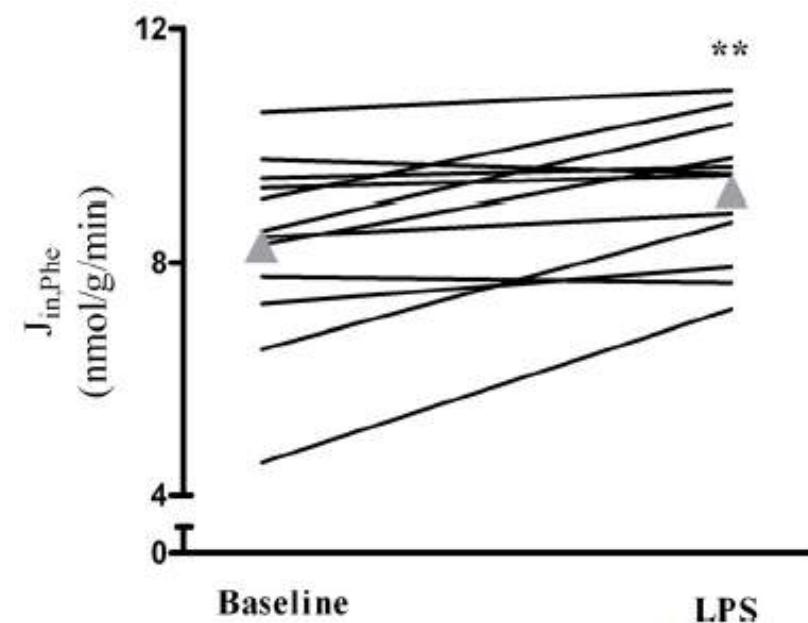
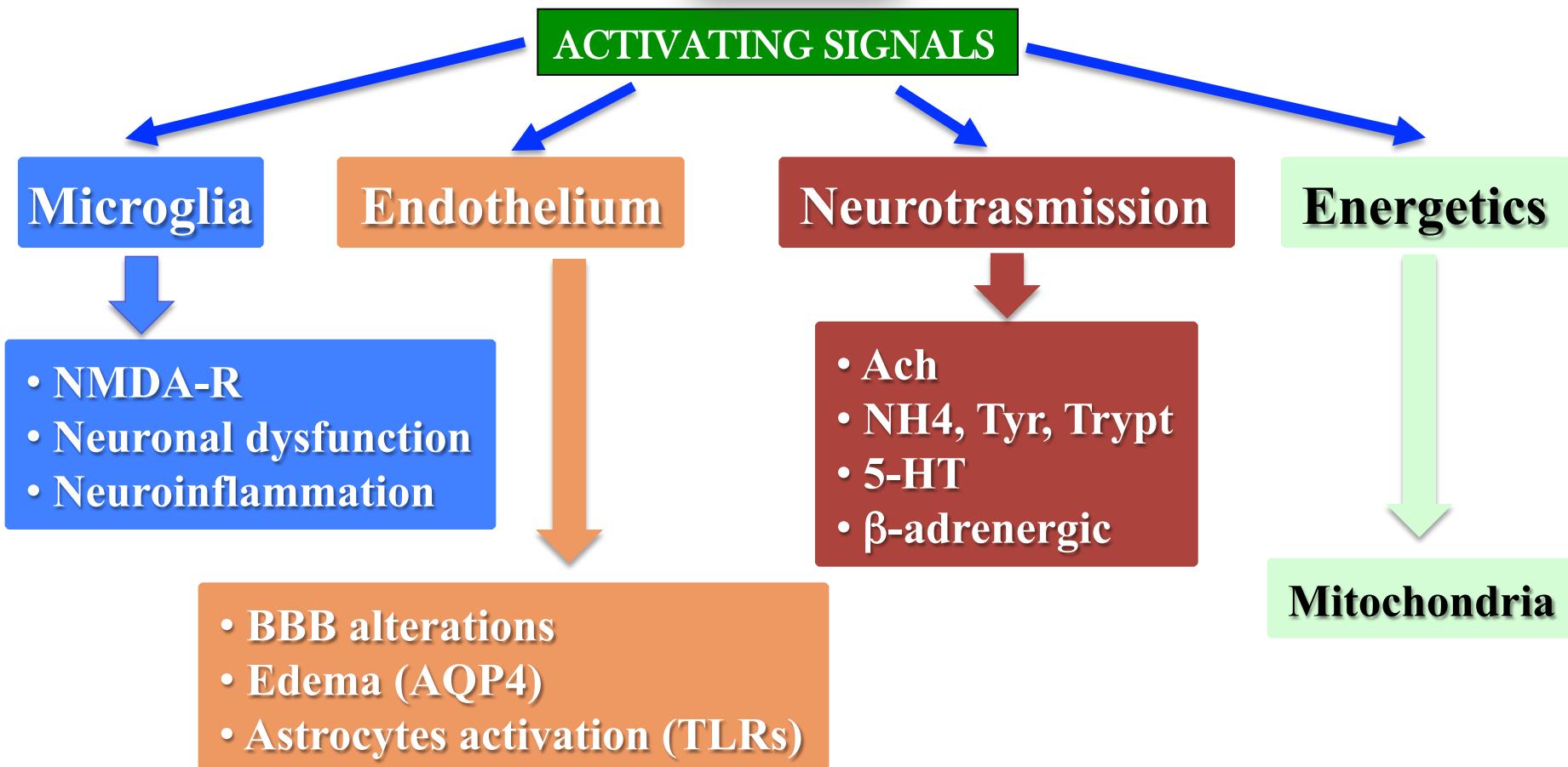
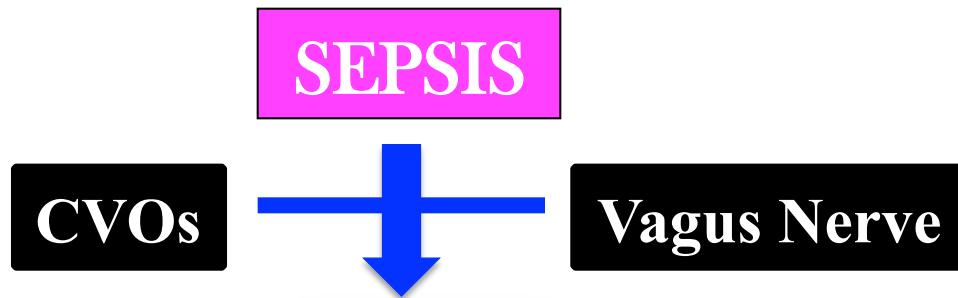


Figure 2 Unidirectional cerebral influx of phenylalanine ($J_{in,Phe}$) after lipopolysaccharide (LPS) infusion in healthy humans.





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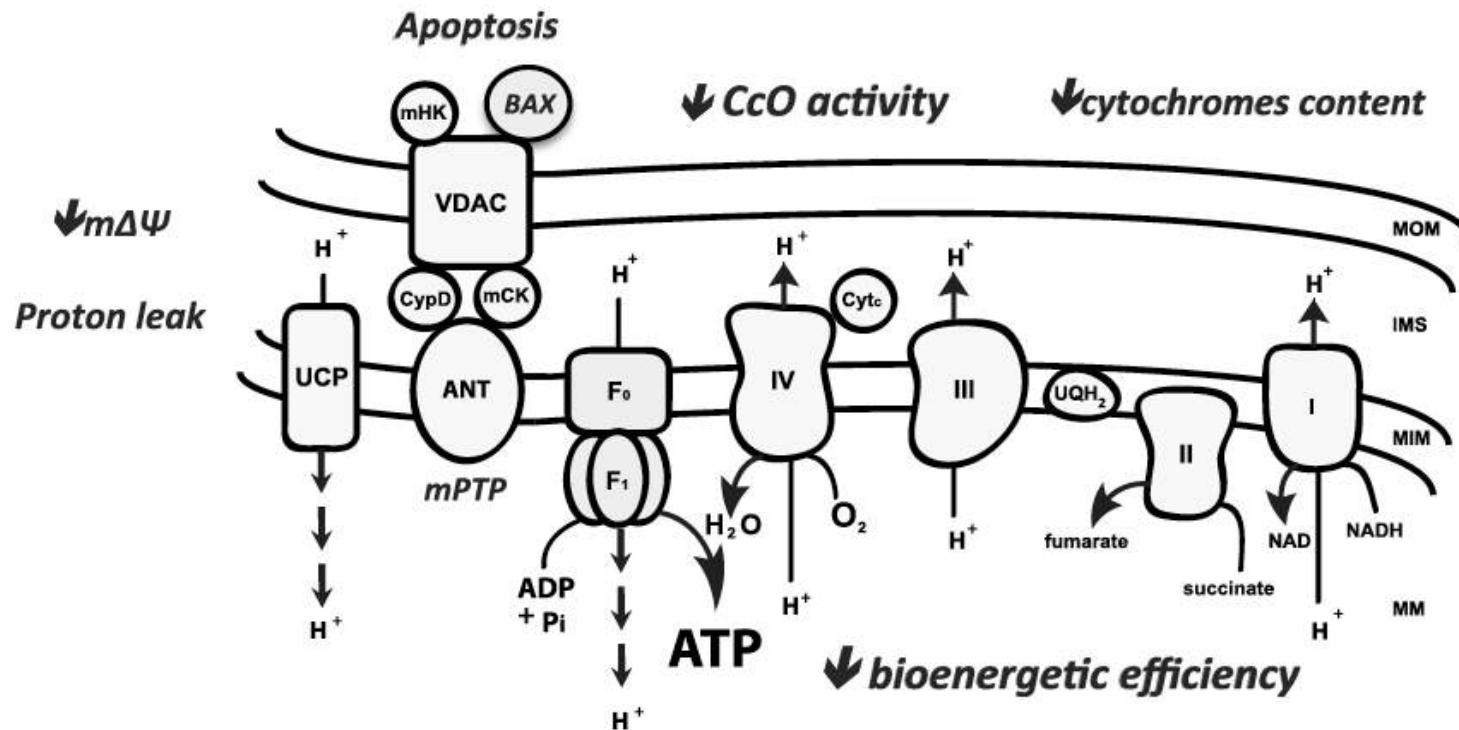
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Bioenergetics

BIOENERGETICS, MITOCHONDRIAL DYSFUNCTION, AND OXIDATIVE STRESS IN THE PATHOPHYSIOLOGY OF SEPTIC ENCEPHALOPATHY

Fernando A. Bozza,^{*†} Joana C. D'Avila,^{*‡} Cristiane Ritter,^{§||} Romain Sonneville,[¶]
Tarek Sharshar,[¶] and Felipe Dal-Pizzol^{§||}





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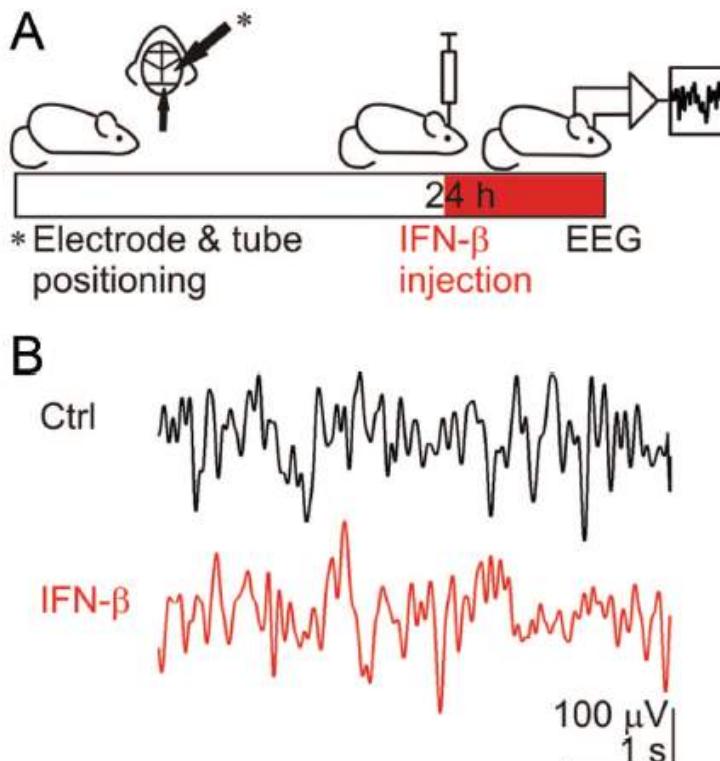
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Cerebral Metabolism

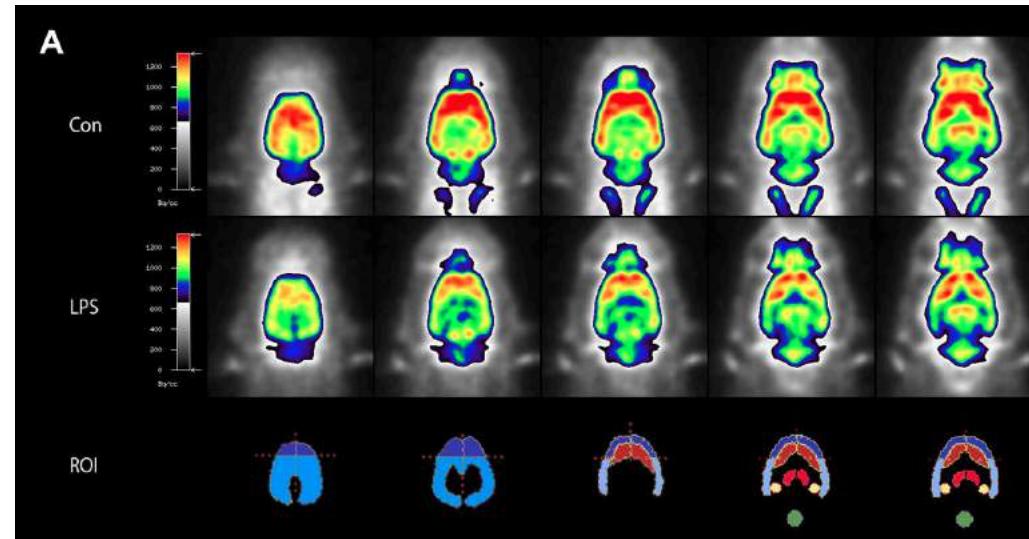
Elevation in Type I Interferons Inhibits HCN1 and Slows Cortical Neuronal Oscillations

Konstantin Stadler¹, Claudia Bierwirth⁴, Luminita Stoenica¹, Arne Battefeld¹, Olivia Reetz¹, Eilhard Mix⁴, Sebastian Schuchmann^{2,5}, Tanja Velmans¹, Karen Rosenberger³, Anja U. Bräuer¹, Seija Lehnardt^{1,3}, Robert Nitsch⁶, Matthias Budt⁷, Thorsten Wolff⁷, Maarten H.P. Kole⁸ and Ulf Strauss^{1,4}

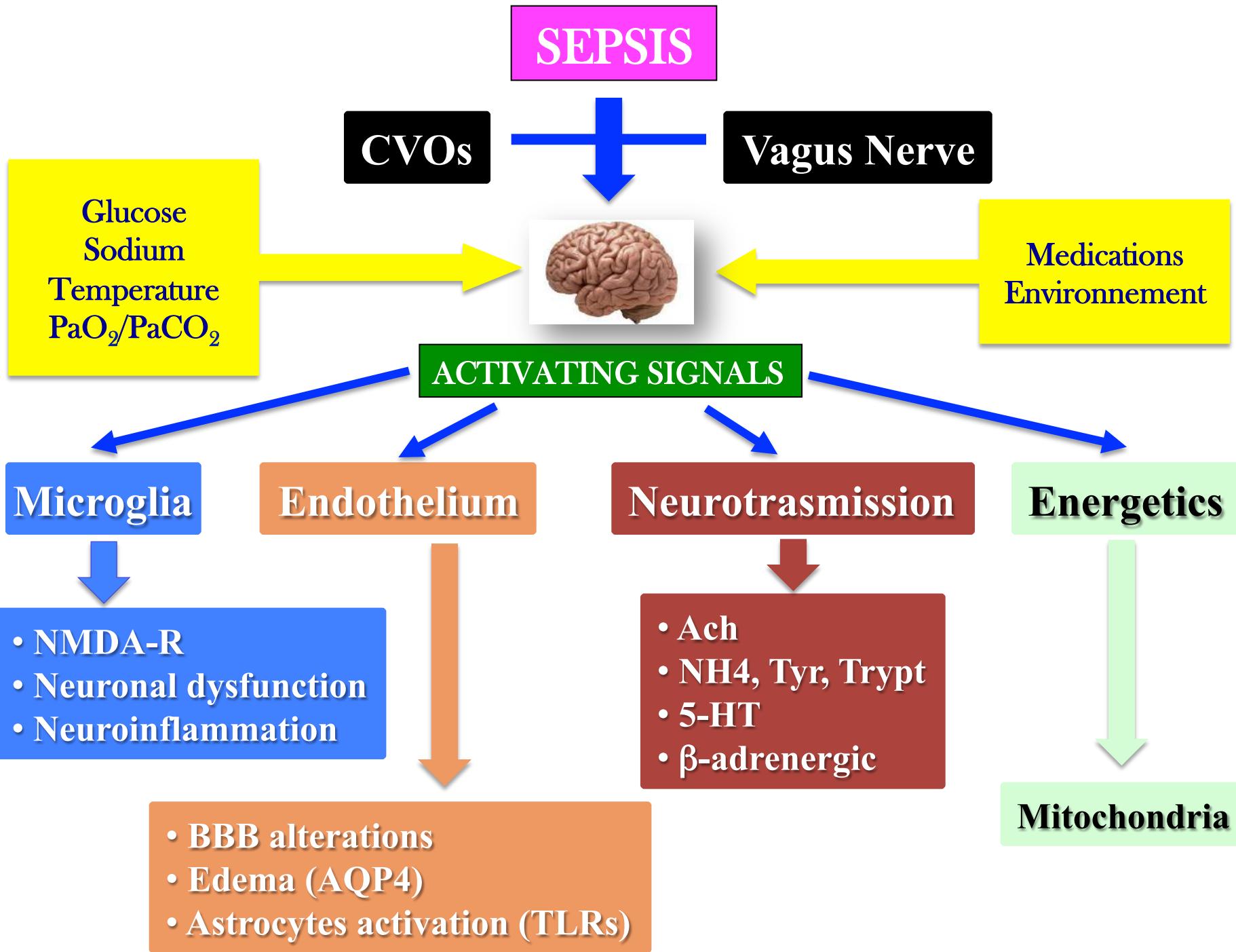


Sepsis causes neuroinflammation and concomitant decrease of cerebral metabolism

Alexander Semmler¹, Sven Hermann², Florian Mormann³, Marc Weerpals¹, Stephan A Paxian¹, Thorsten Okulla¹, Michael Schäfers², Markus P Kummer¹, Thomas Klockgether¹ and Michael T Heneka^{*1}



Journal of Neuroinflammation 2008, 5:38





My brain?

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Hyperglycemia

Hyperglycaemia and apoptosis of microglial cells in human septic shock

Andrea Polito¹, Jean-Philippe Brouland², Raphael Porcher³, Romain Sonneville^{1,6}, Shidas Siami¹, Robert D Stevens⁴, Céline Guidoux¹, Virginie Maxime¹, Geoffroy Lorin de la Grandmaison⁵, Fabrice C Chrétien⁶, Françoise Gray², Djillali Annane¹ and Tarek Sharshar^{1*}

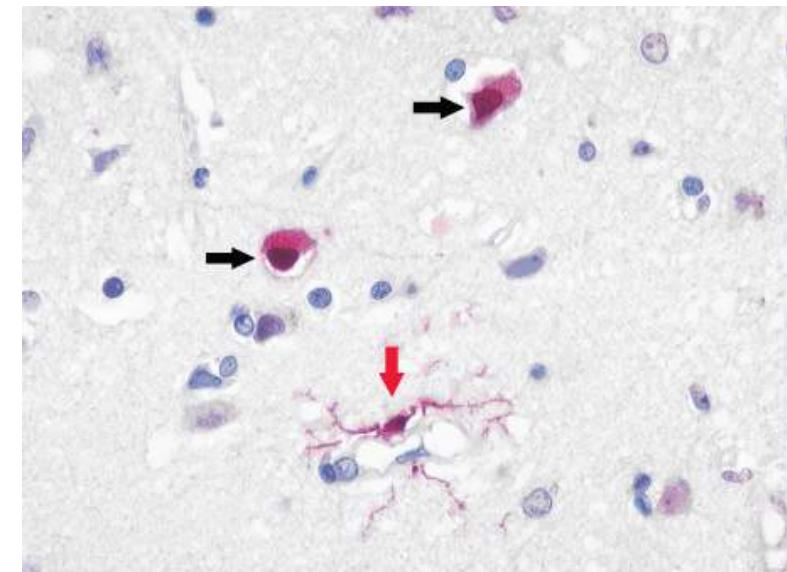
Critical Care 2011, 15:R131

Table 2 Association of the area under the BG curve above 2 g/l with clinical characteristics and neuropathological findings

	Spearman ρ (95%CI)	P
SAPS-II at admission	0.34 (-0.17 to 0.71)	0.18
Knauss	-0.21 (-0.63 to 0.30)	0.43
McCabe	0.05 (-0.44 to 0.52)	0.85
Neuropathological findings		
Neuronal ischaemia	0.05 (-0.43 to 0.53)	0.82
Gliosis	0.15 (-0.36 to 0.59)	0.57
GFAP expression	0.11 (-0.39 to 0.56)	0.67
HLA-DR expression	0.06 (-0.43 to 0.53)	0.81
CD68 expression	0.44 (-0.05 to 0.76)	0.08
Beta-APP expression	0.61 (0.06 to 0.88)	0.03
Neuronal apoptosis	0.53 (0.07 to 0.81)	0.028
Microglial apoptosis	0.70 (0.33 to 0.88)	0.002
Glial TNF α expression	-0.04 (-0.51 to 0.45)	0.86
Endothelial iNOS expression	0.04 (-0.45 to 0.51)	0.87

Each neuropathological finding was score from 0 to 3 (see methods). beta-APP, beta-amyloid precursor protein; CD68, Cluster of Differentiation; GFAP, glial fibrillary acidic protein; HLA-DR, Major Histocompatibility Complex Class II cell surface receptor; iNOS, inducible Nitric Oxide Synthase; TNF α , tumor necrosis factor alpha.

Post-mortem analysis 17 pts in septic shock



Neuronal and microglial apoptosis in the amygdala



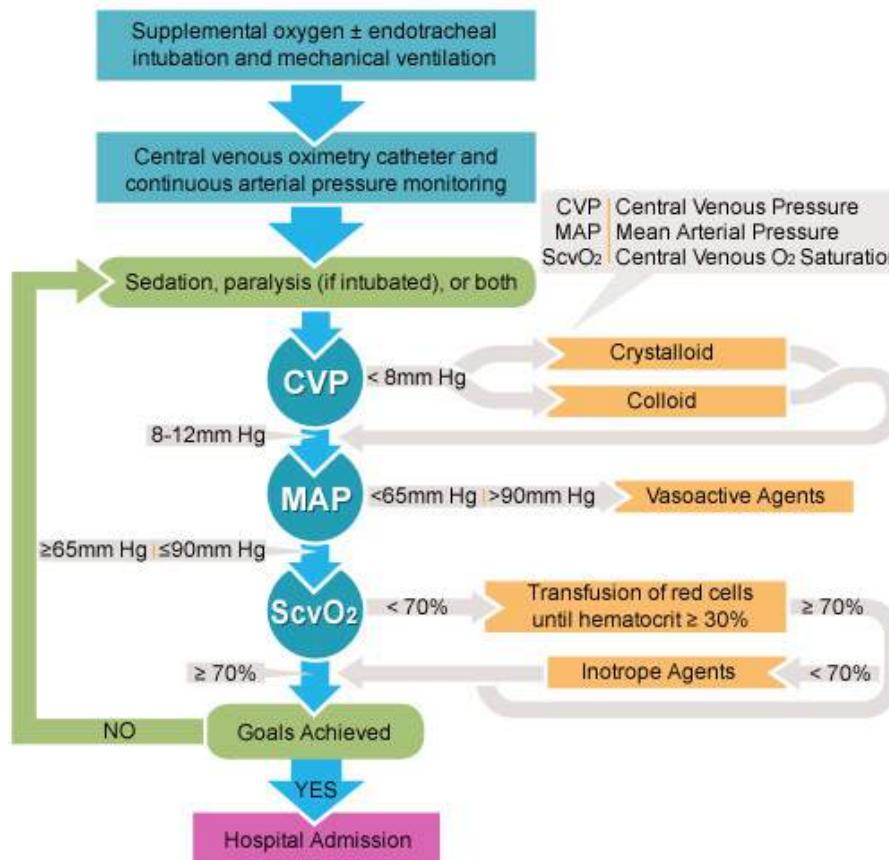
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Brain Perfusion

Perfusion Pressure



Microcirculation

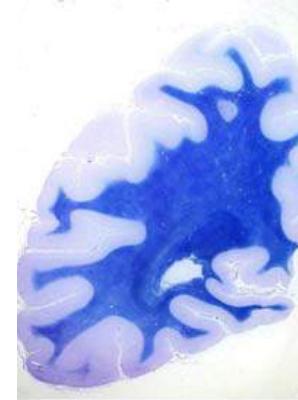
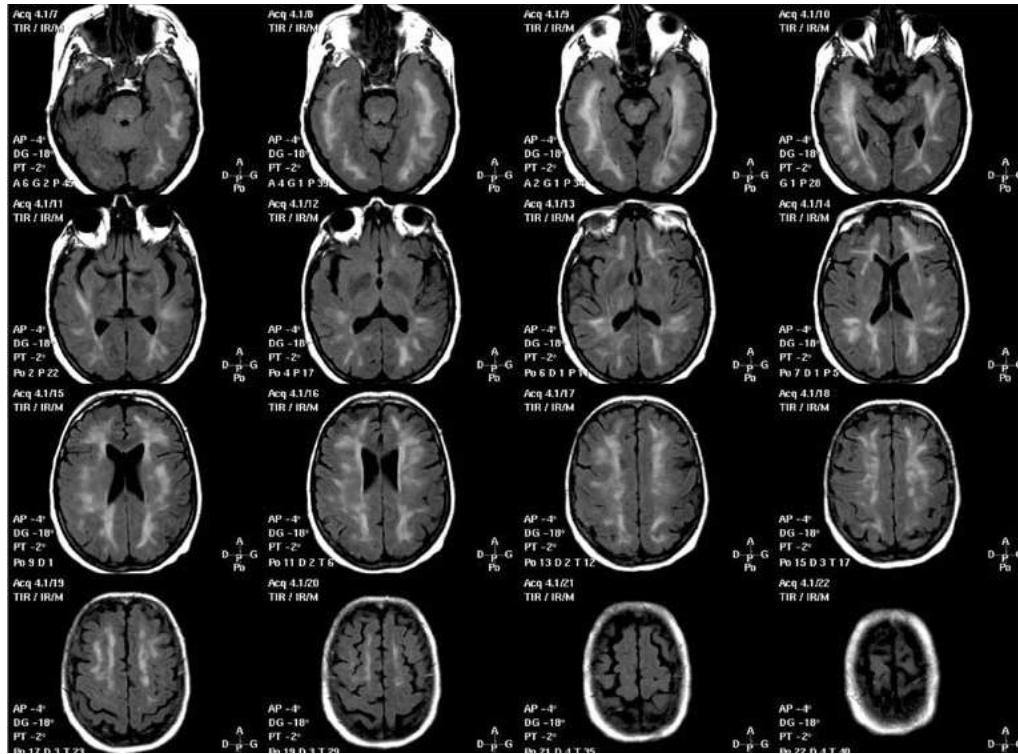




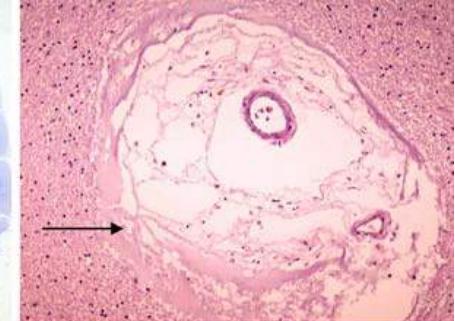
My brain?

(See page numbers following right)

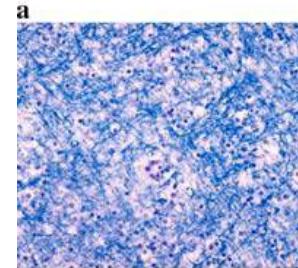
Brain Perfusion



2



1



Wijdicks, Arch Neurol 1996
Pfister, Acta Neurochir 2008
Sharshar, Brain Pathol 2004
Sharshar, Intensive Care Med 2004



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Brain Perfusion

Cerebral Circulation and Metabolism in Patients With Septic Encephalopathy

TSUYOSHI MAEKAWA, MD, YUKIMASA FUJII, MD, DAIKAI SADAMITSU, MD, KIMIO YOKOTA, MD, YOSHIIYUKI SOEJIMA, MD, TOSHIZOH ISHIKAWA, MD, YOSHITOYO MIYAUCHI, MD, HIROSHI TAKESHITA, MD

Case	CPP (mm Hg)	jvP (mm Hg)	CBF (mL/ 100 g/min)	CVR (mm Hg/mL/ 100 g/min)	CaO ₂ (vol %)	CdO ₂ (mL/ 100g/min)	CMRO ₂ (mL/ 100g/min)	Pjvo ₂ (mm Hg)	Body Temp. (°C)	CO (L/min)
1	69	12	37	1.9	14.3	5.3	1.3	44	28.9	37.3
2	72	10	24	3.1	12.9	3.0	1.4	52	17.2	36.3
3	89	5	23	3.9	14.5	3.4	1.6	40	14.1	37.1
4	64	7	17	3.8	13.2	2.2	0.5	50	34.4	36.8
5	112	10	30	3.7	14.7	4.4	1.5	41	20.1	37.0
6	68	19	37	1.9	12.0	4.4	1.2	40	30.6	36.4
Sepsis	79	11	28	3.0	13.6	3.8	1.2	45	24.2	36.8
	± 7	± 2*	± 3*	± 0.4*	± 0.4*	± 0.5*	± 0.2*	± 2	± 3.3*	± 0.2
Control†	90	6	46	2.0	20.6	9.4	3.1	40	15.1	36.5
	± 3	± 1	± 2	± 0.1	± 0.6	± 0.4	± 0.2	± 1	± 0.8	± 0.3

Sedation - Hypocapnia ??

Am J Emerg Med 1991

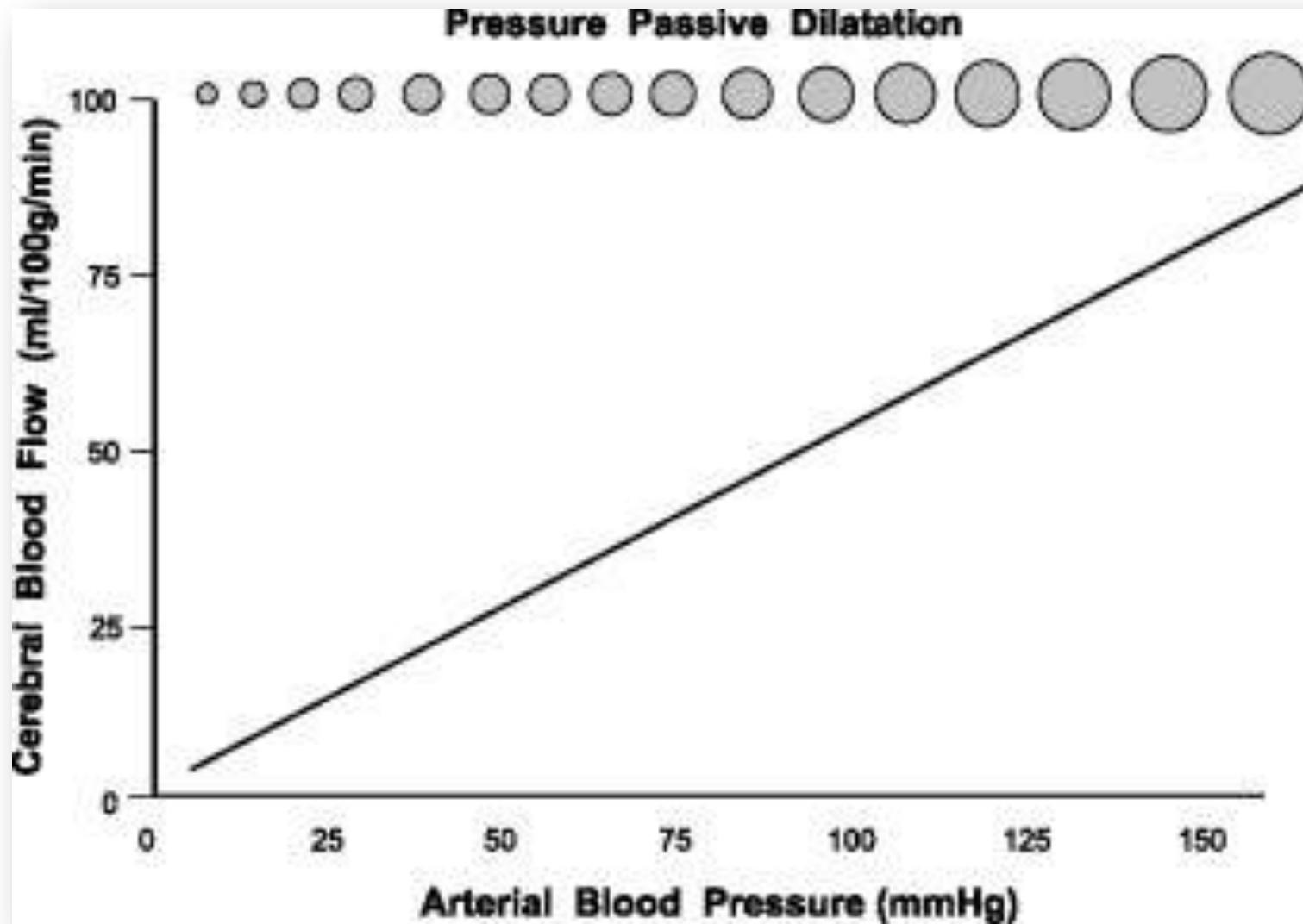


My brain?

It's my second favourite organ



Pressure Regulation





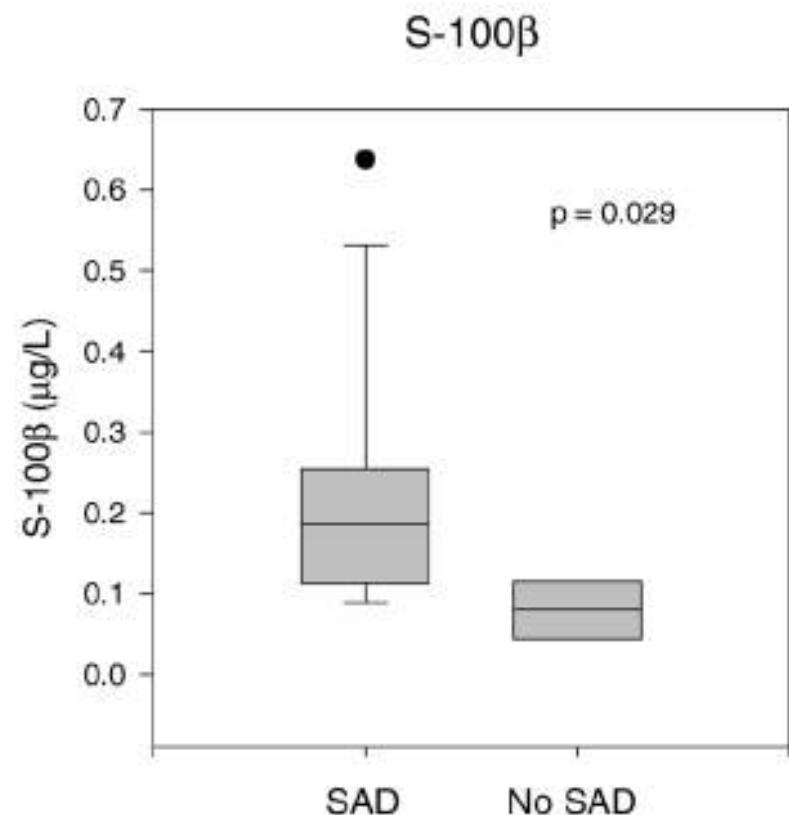
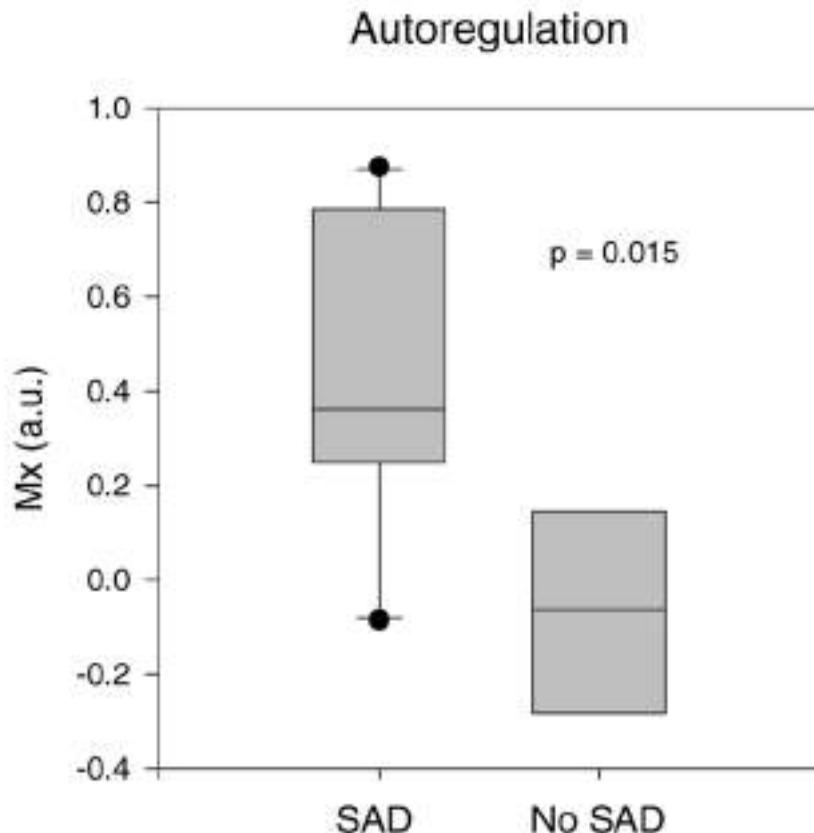
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It's my second favourite organ



CBF Autoregulation

Cerebral Autoregulation





My brain?

It's my second favourite organ



Microcirculation

COMMENTARY

Open Access

Septic-associated encephalopathy - everything starts at a microlevel

Tarek Sharshar^{1*}, Andrea Polito¹, Anthony Checinski¹, Robert D Stevens²

See related research by Taccone *et al.*, <http://ccforum.com/content/14/4/R140>



CRITICAL CARE

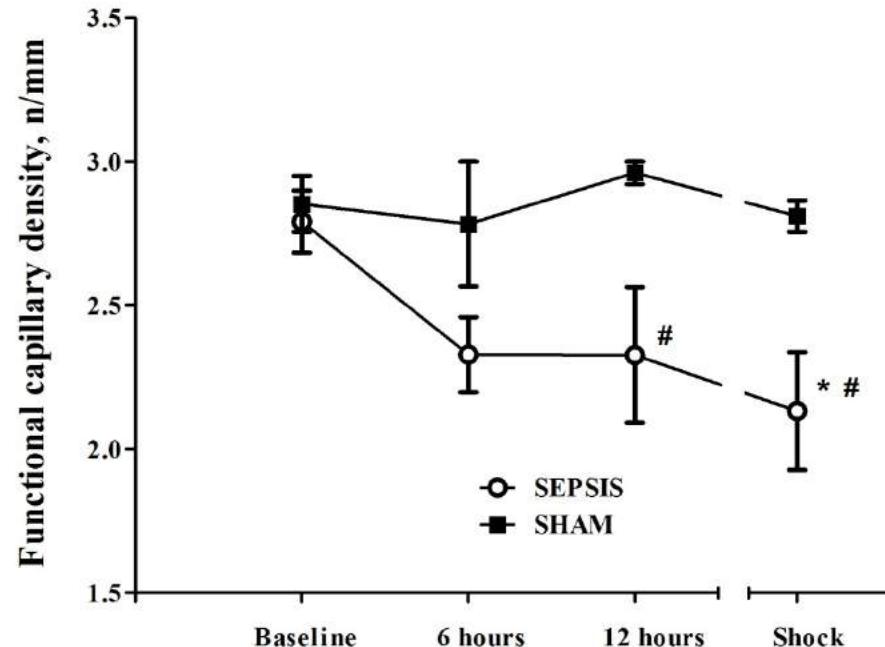


My brain?

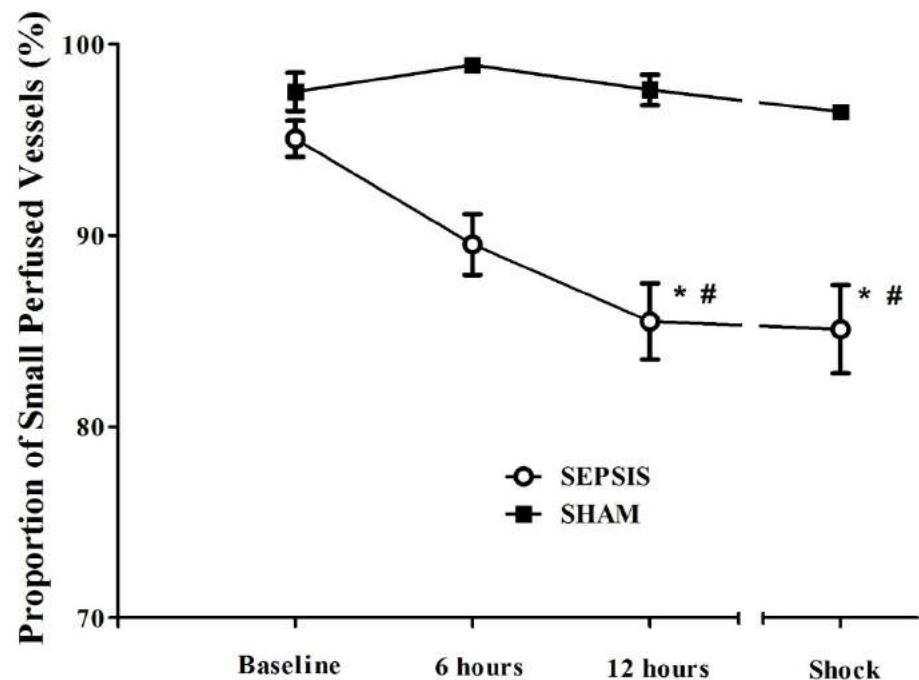
It's my second favourite organ



Microcirculation



- Early development of heterogeneity
- Independent from systemic hemodynamics





My brain?

It's my second favourite organ

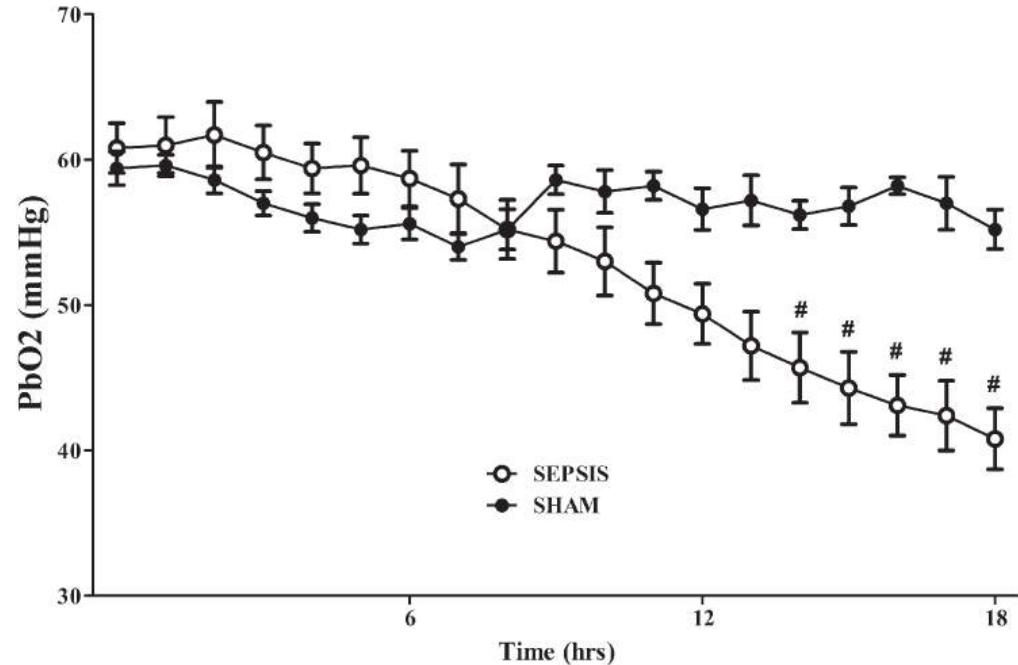
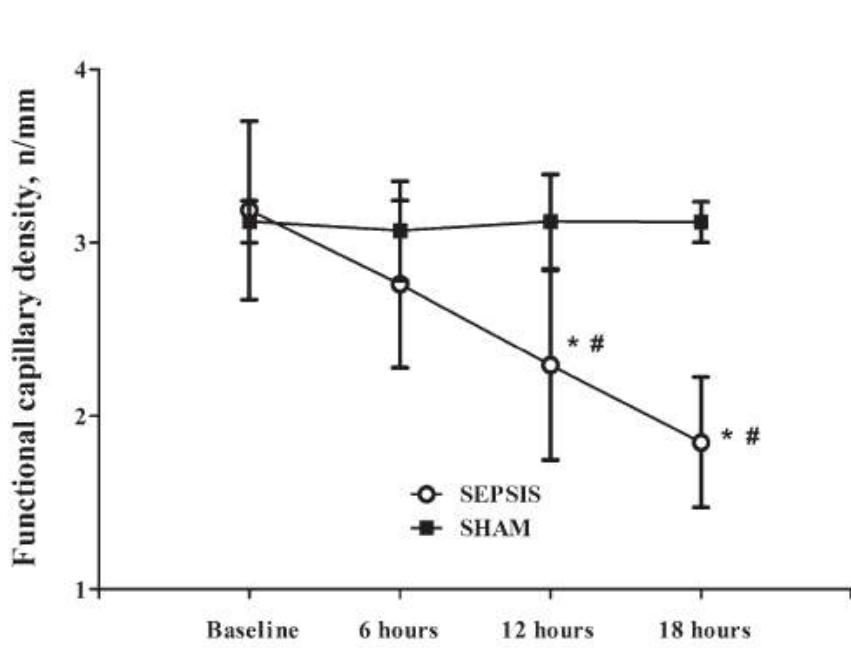


Microcirculation

Sepsis Is Associated With Altered Cerebral Microcirculation and Tissue Hypoxia in Experimental Peritonitis*

Crit Care Med 2014; 42:e114–e122

Fabio Silvio Taccone, MD¹; Fuhong Su, MD, PhD¹; Cathy De Deyne, MD, PhD²; Ali Abdellhai, MD¹; Charalampos Pierrakos, MD¹; Xinrong He, MD¹; Katia Donadello, MD¹; Olivier Dewitte, MD, PhD³; Jean-Louis Vincent, MD, PhD, FCCM¹; Daniel De Backer, MD, PhD¹





My brain?

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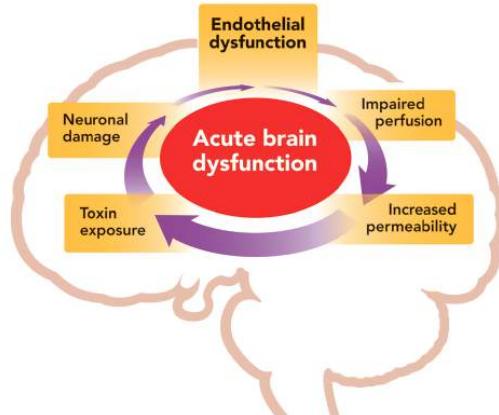


Microcirculation

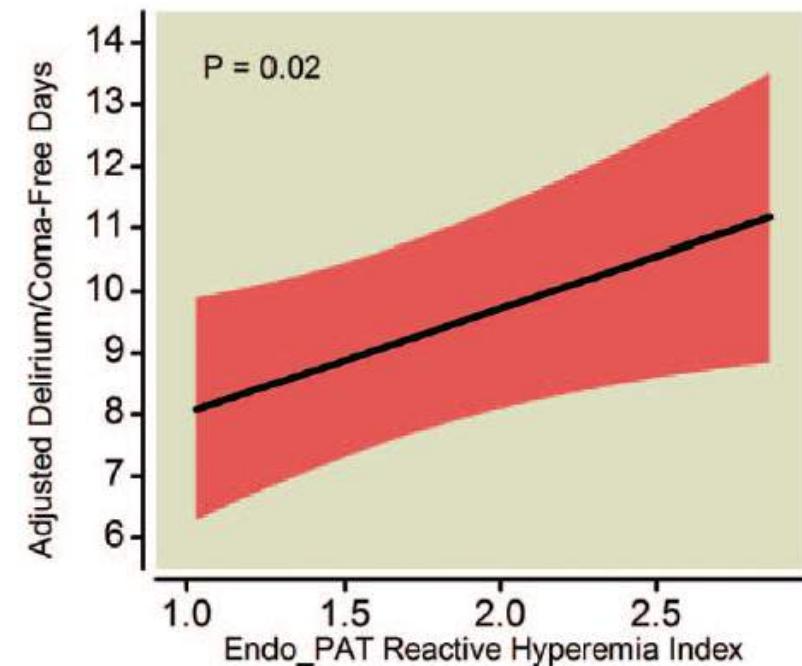
Association between Endothelial Dysfunction and Acute Brain Dysfunction during Critical Illness

Anesthesiology 2013; 118:631-9

Christopher G. Hughes, M.D., * Alessandro Morandi, M.D., † Timothy D. Girard, M.D., ‡
Bernhard Riedel, M.D., Ph.D., § Jennifer L. Thompson, M.P.H., || Ayumi K. Shintani, Ph.D., #
Brenda T. Pun, M.S.N., ** E. Wesley Ely, M.D., †† Pratik P. Pandharipande, M.D. ‡‡



N=134





My brain?

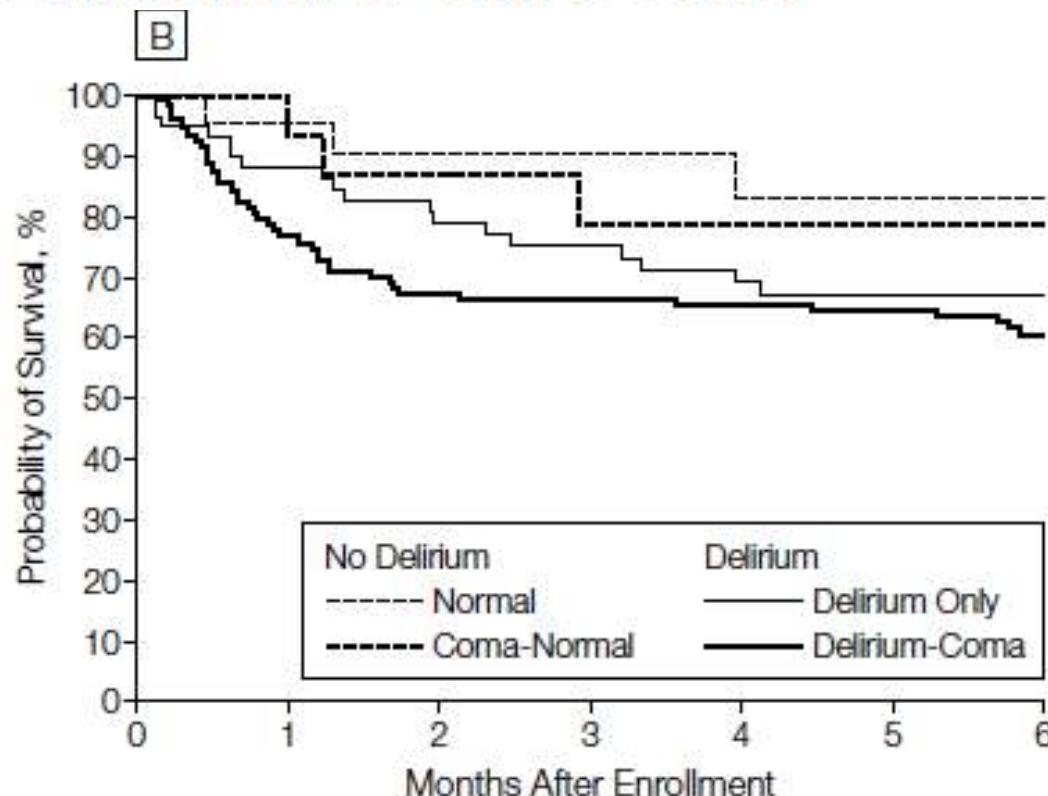
It's my second favorite organ

Outcome



Delirium as a Predictor of Mortality in Mechanically Ventilated Patients in the Intensive Care Unit

JAMA 2004



- E. Wesley Ely, MD, MPH
Ayumi Shintani, PhD, MPH
Brenda Truman, RN, MSN
Theodore Speroff, PhD
Sharon M. Gordon, PsyD
Frank E. Harrell, Jr, PhD
Sharon K. Inouye, MD, MPH
Gordon R. Bernard, MD
Robert S. Dittus, MD, MPH



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Outcome

The Spectrum of Septic Encephalopathy

Definitions, Etiologies, and Mortalities

Leonid A. Eidelman, MD; Debby Putterman, MD; Chaim Putterman, MD; Charles L. Sprung, MD

(JAMA. 1996;275:470-473)

Table 2.—Septic Encephalopathy and Mortality

Altered mental status, No. (%)

No	6/23 (26)	P=.6
Yes	9/27 (33)	

Clinical grade of encephalopathy, No. (%)

0	7/26 (27)	P=.5
1-2	5/18 (28)	
3-4	3/6 (50)	

Glasgow Coma Score, No. (%)

15	3/19 (16)	P<.05
13-14	3/15 (20)	
9-12	4/8 (50)	
3-8	5/8 (63)	



Sharshar et al.
Intensive Care Med 2007

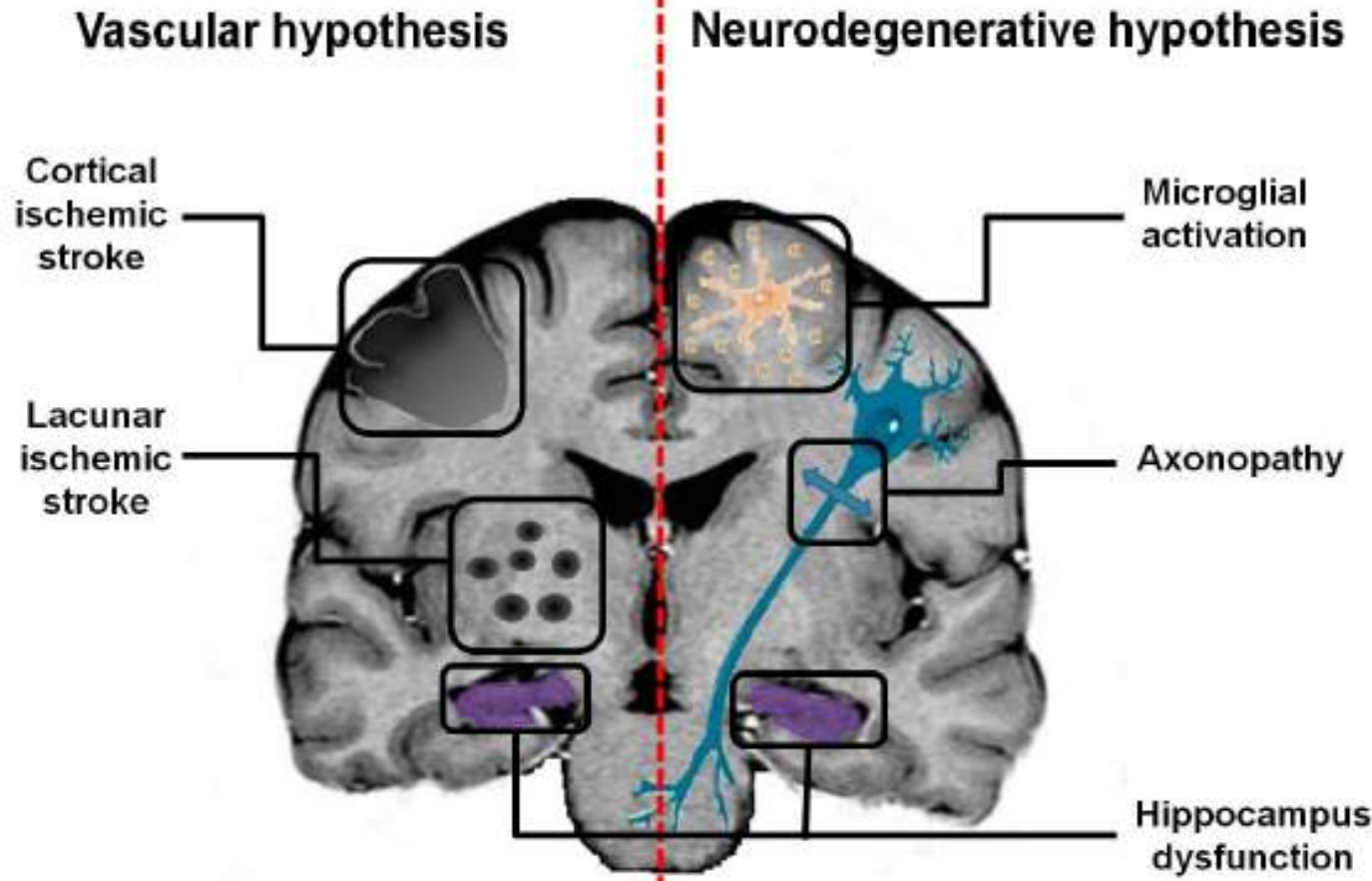


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Outcome





My brain?

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Outcome

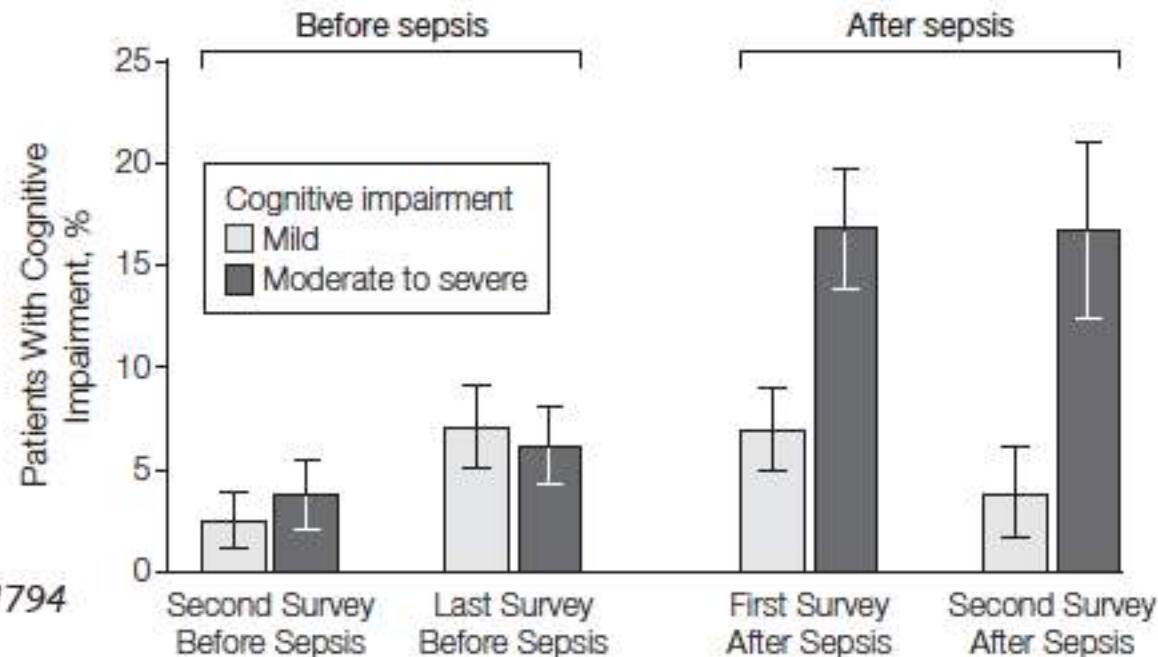
Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis

Theodore J. Iwashyna, MD, PhD

E. Wesley Ely, MD, MPH

Dylan M. Smith, PhD

Kenneth M. Langa, MD, PhD



JAMA. 2010;304(16):1787-1794

Time to sepsis admission,
median (IQR), y

-3.1
(-3.7 to -2.7)

-1.1
(-1.7 to -0.7)

0.9
(0.4 to 1.4)

2.8
(2.3 to 3.4)

No. of patients

484

623

623

288



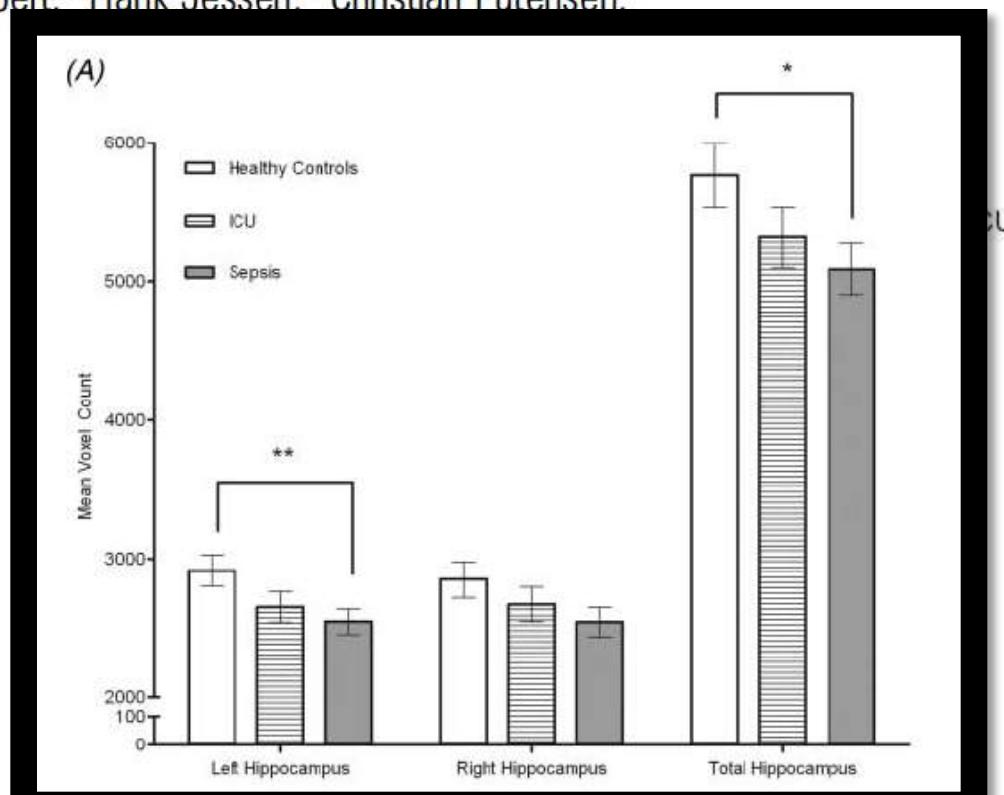
Outcome

Persistent cognitive impairment, hippocampal atrophy and EEG changes in sepsis survivors

JNNP 2013

Alexander Semmler,^{1,6} Catherine Nichols Widmann,¹ Thorsten Okulla,¹ Horst Urbach,² Markus Kaiser,^{3,7} Guido Widman,⁴ Florian Mormann,^{4,8} Julia Weide,¹ Klaus Fliessbach,⁴ Andreas Hoeft,³ Frank Jessen,⁵ Christian Putensen,³ Michael T Heneka¹

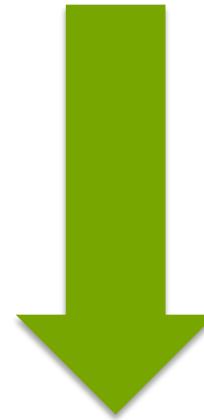
C_{comp}
Digit Span
2-Back Test
Alertness
Go Nogo
Interference
Verbal Memory
Figural Memory





Therapy

Currently, there is no specific treatment !!!



AVOID
SECONDARY INJURIES



My brain?

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Therapy

Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an *a priori*-designed analysis of the MENDS randomized controlled trial

Table 2: Outcomes of patients with and without sepsis*

Outcome variable	Patients with sepsis			Patients without sepsis		
	DEX (n = 31)	LZ (n = 32)	Adjusted P value**	DEX (n = 20)	LZ (n = 19)	Adjusted P value**
Duration of brain organ dysfunction						
Delirium/coma-free days**	6.1 (4.3)	2.9 (3.2)	0.005	6 (4.7)	5.5 (3.6)	0.97
Delirium-free days†	8.1 (3.1)	6.7 (2.9)	0.06	8.1 (3.5)	7.9 (2.8)	0.80
Coma-free days§	9.4 (2.9)	5.9 (4.2)	<0.001	8.9 (4)	8.8 (2.6)	1



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Conclusions

- In Low CO = few data (more complications!!!)
- Encephalopathy is a frequent complication of sepsis
- Complex pathophysiology
- Poor outcome (especially if brain ischemia?)
- No Specific Therapy



THANKS



*Join Us at our International Course
Brain Critical Care and Emergencies (BRACE)
with demonstrations*

Erasme Hospital, Brussels, June 22-23, 2015

www.intensive.org

