

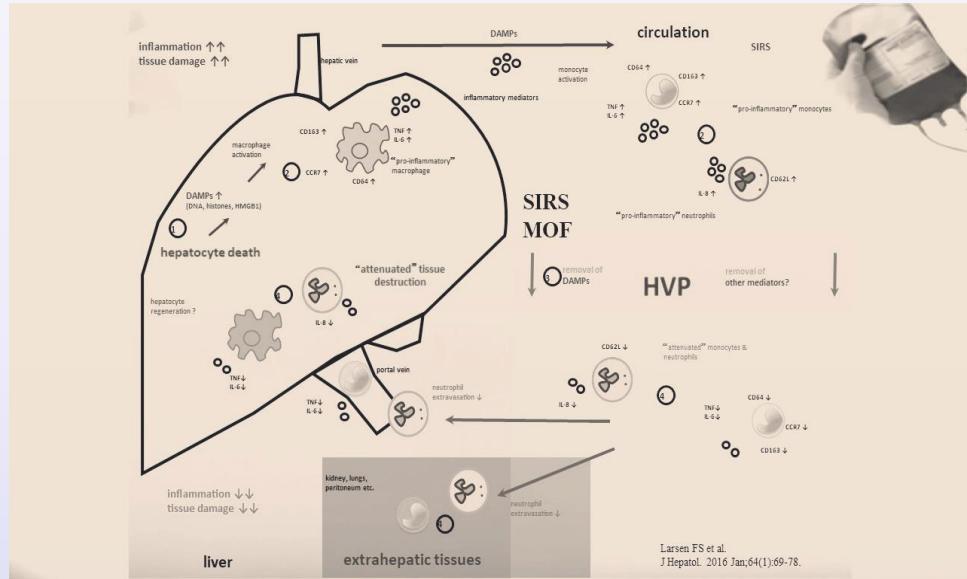
Cerebral blood flow in liver failure

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Liver failure – the problem at hand

- Splanchnic release of
 - Ammonia
 - DAMPS, endotoxins
 - B7 (CD80+86)

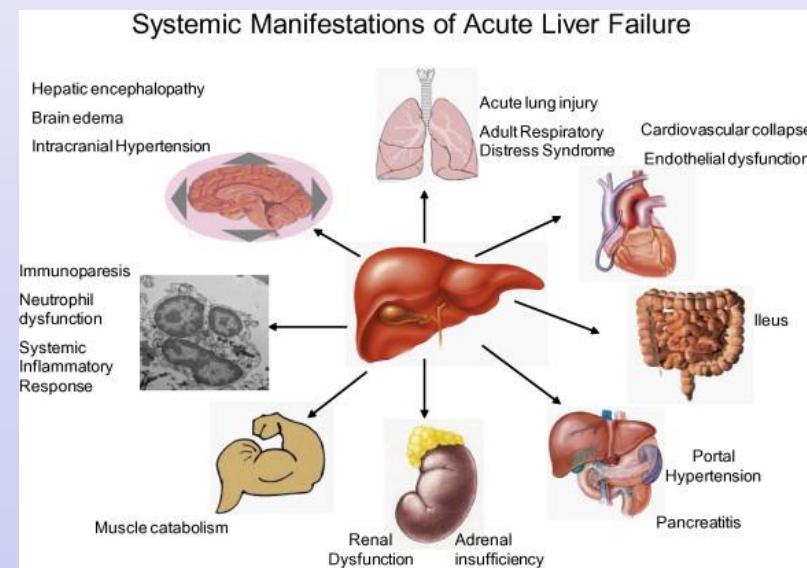
- Cause
 - Hyperammonemia
 - HE and astrocyte swelling
 - Changes in amino acids concentrations
 - DAMPS, cytokines, endotoxin and B7 in the syst. circulation
 - Pro-inflammatory state
 - Low SVR and MAP
 - DAMPS induced activation of monocytes
 - Neutrophil phagocytosis impairment
 - sB7 impairs CD4+ cells
 - Repeated infections – MOF



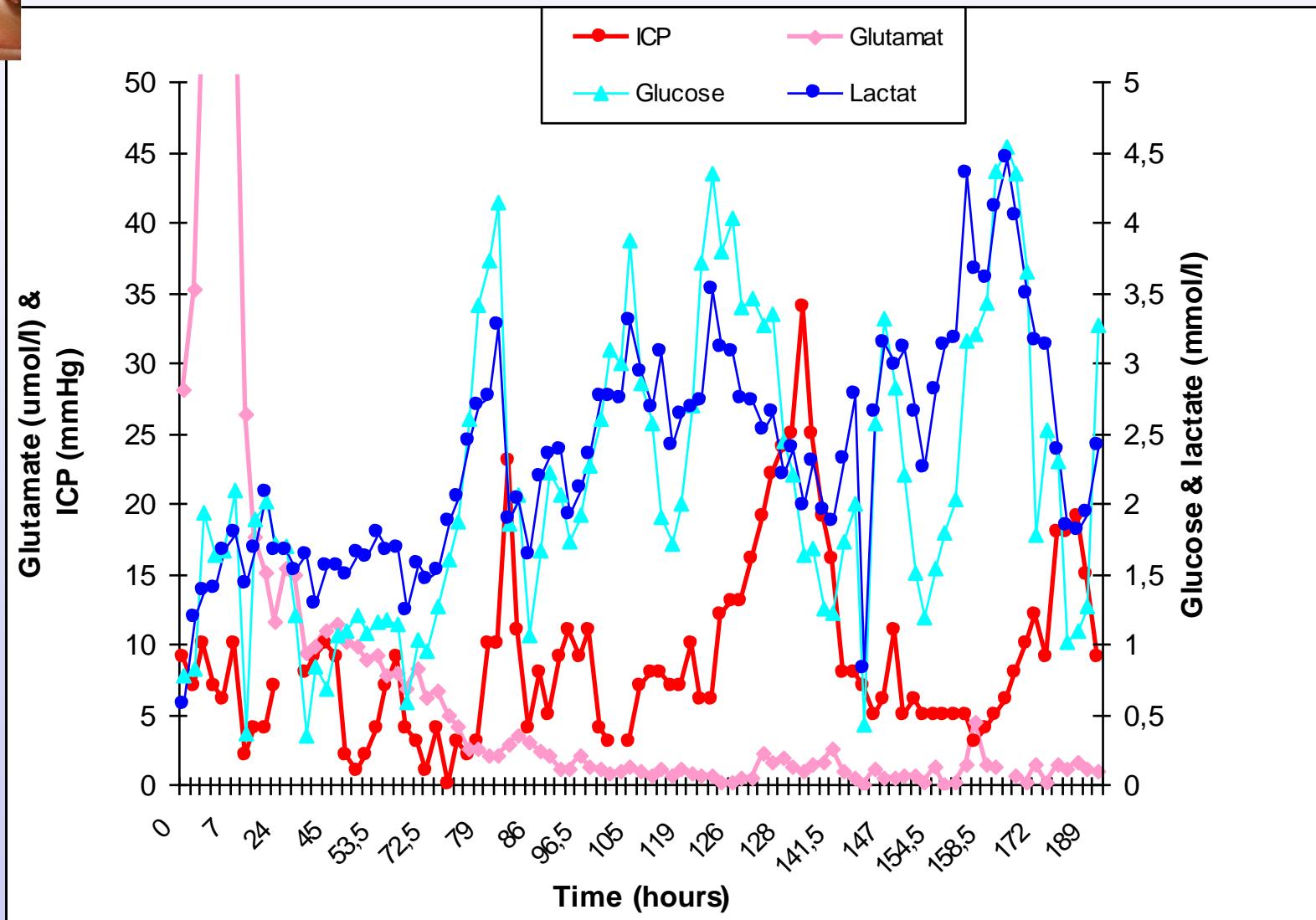
Changes in
Cerebral blood flow?

Liver failure causes complications that influence CBF

- Hepatic encephalopathy
- Cerebral edema and high ICP
- Hyperventilation with low PaCO₂
- hypoglycemia
- Systemic vasodilatation
- Sepsis – DAMPS / (PAMPS)
- Hypoxia / ARDS
- renal failure (ATN, HRS)
- Low sodium and phosphate
- coagulopathy
- thrombocytopenia
- Lactate acidosis



Cerebral microdialysis in patients with liver failure

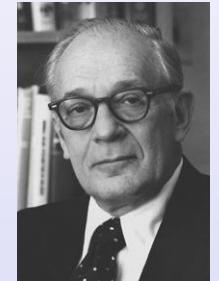
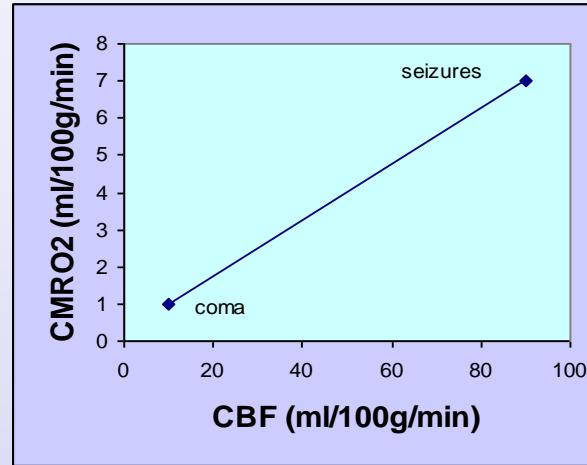


Main regulatory mechanisms of CBF

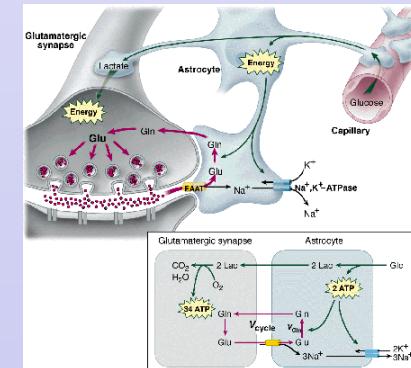
CBF to metabolism coupling



Roy & Sherrington 1893

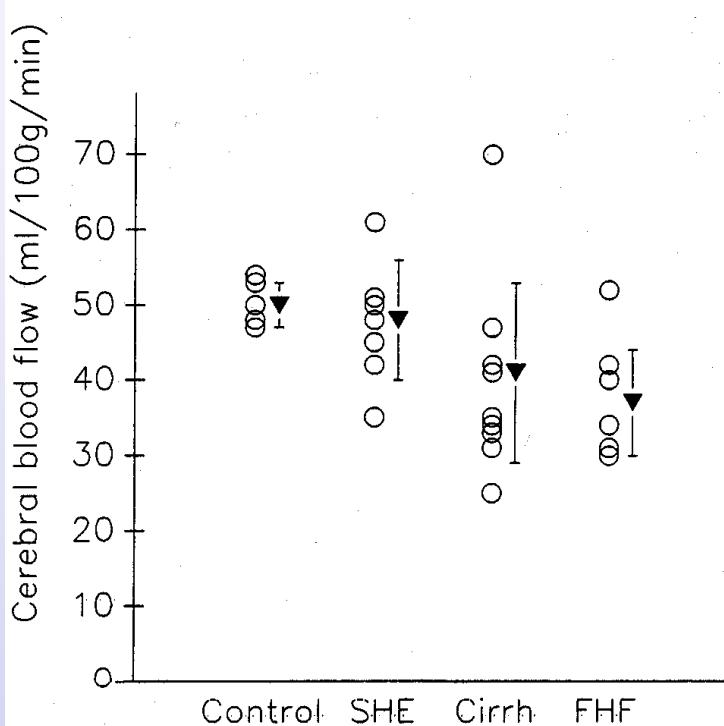


Seymour S. Kety



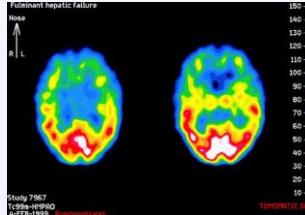
Magistretti

CBF and liver coma



- Global CBF reduced in HE
- Cognitive impairment correlates with rCBF in
 - basal ganglia and limbic cortex
 - cerebellum
 - frontotemporal regions
- Reversible after liver transplantation

- O'Carrol et al. Lancet 1991
- Lockwood et al. J CBF Metab 1991, Hepatology 1993
- Van Thiel et al. J Neuropsychiatry Clin Neurosci 1994
- Larsen et al. Hepatology 1995
- Dam, J Hepatology 1998
- Lockwood et al. Metabol Brain Dis 2001
- Bjerring PN et al. J Clin Exp Hepatol. 2018



CBF in acute liver failure with hepatic encephalopathy

- A wide CBF variation in spite
- CMRO₂ ~ 1.0 ml/100g/min
- Cerebral vasodilation develops during liver failure

(Kindt, J Neurosurgery 1986; Larsen, J Hepatol 1997)

- CBF is higher in patients with edema than in those without

(Larsen. Sem Liv Dis 1999)

- Cerebral hyperperfusion is reversed by hepatectomy

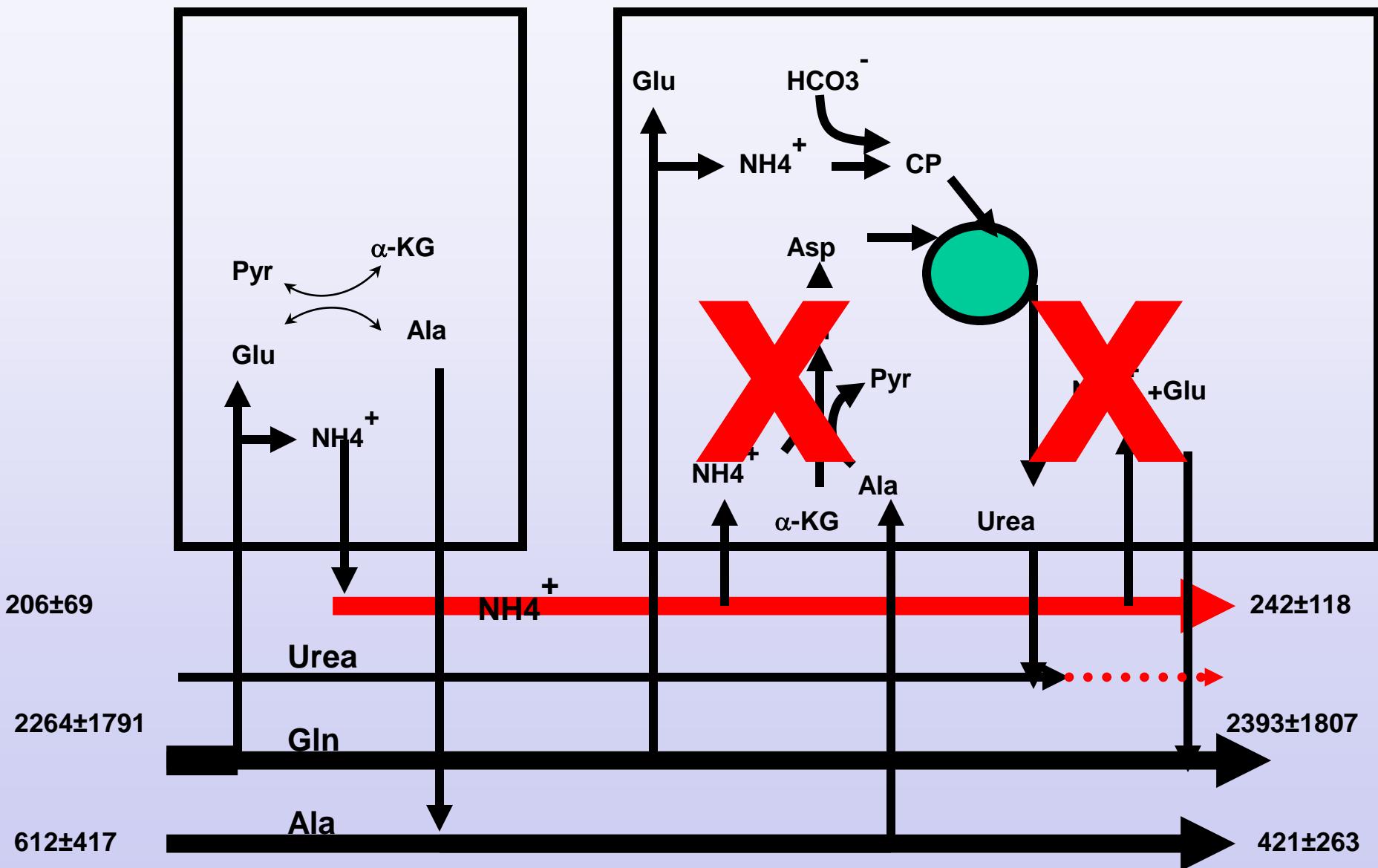
(Ellen Ejlersen & Secher. Transpl Proc 1994)



Severe hyperammonemia

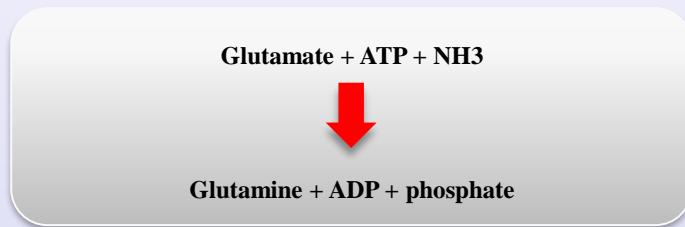
Intestine

Liver

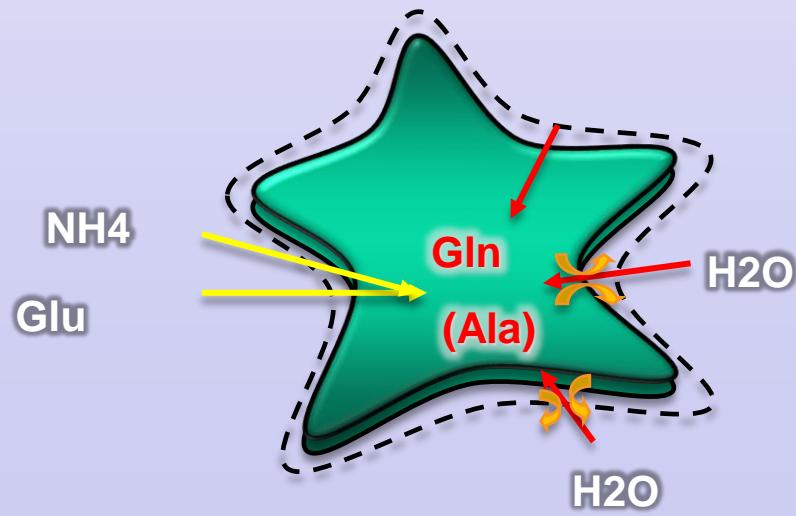


Cerebral mechanisms in HE: astrocyte swelling

Ammonia is metabolised in brain astrocytes by glutamine synthetase:



Intra-cellular glutamine is osmotically active and draws H₂O into astrocytes



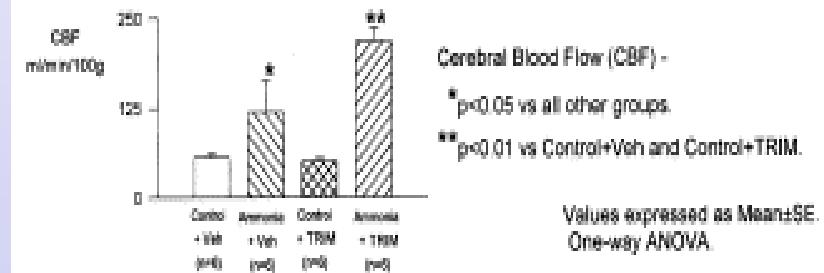
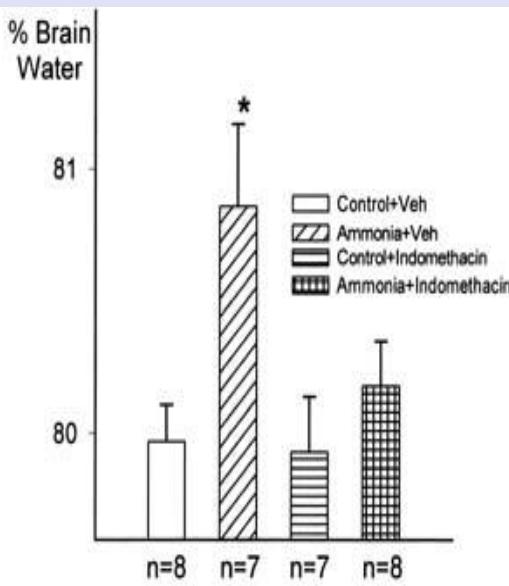
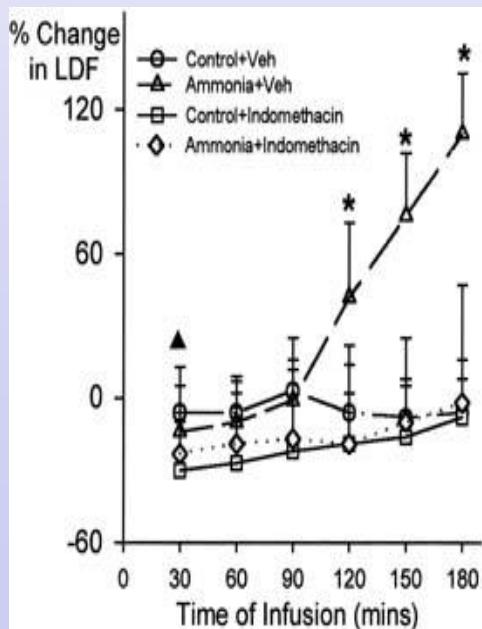
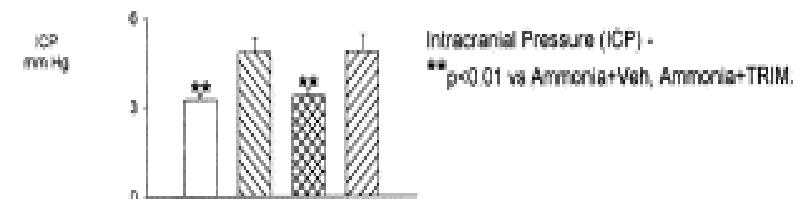
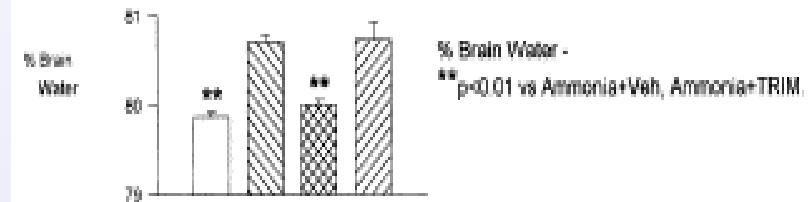
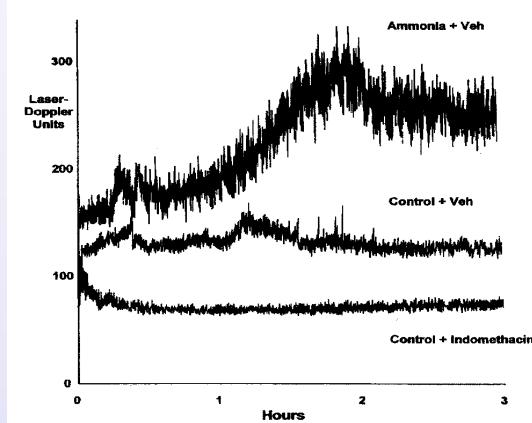
- Although ammonia is important in pathogenesis, levels do not necessarily correlate with severity
- Other factors can precipitate HE ¹ without high ammonia concentrations
 - Hyponatraemia
 - Benzodiazepines (sedatives)
 - Inflammatory cytokines etc
 - Induce astrocyte swelling *in vitro* ²
 - Different neurotoxins may contribute to astrocyte swelling and precipitate HE

¹Haussinger et al, Gut, 2012.

²Haussinger et al, J Hepatol, 2000; 32(6):1035–8.

Hyperammonemia increases CBF

252 CHUNG, GOTTSSTEIN, AND BLEI



Chung et al. Hepatology 2001

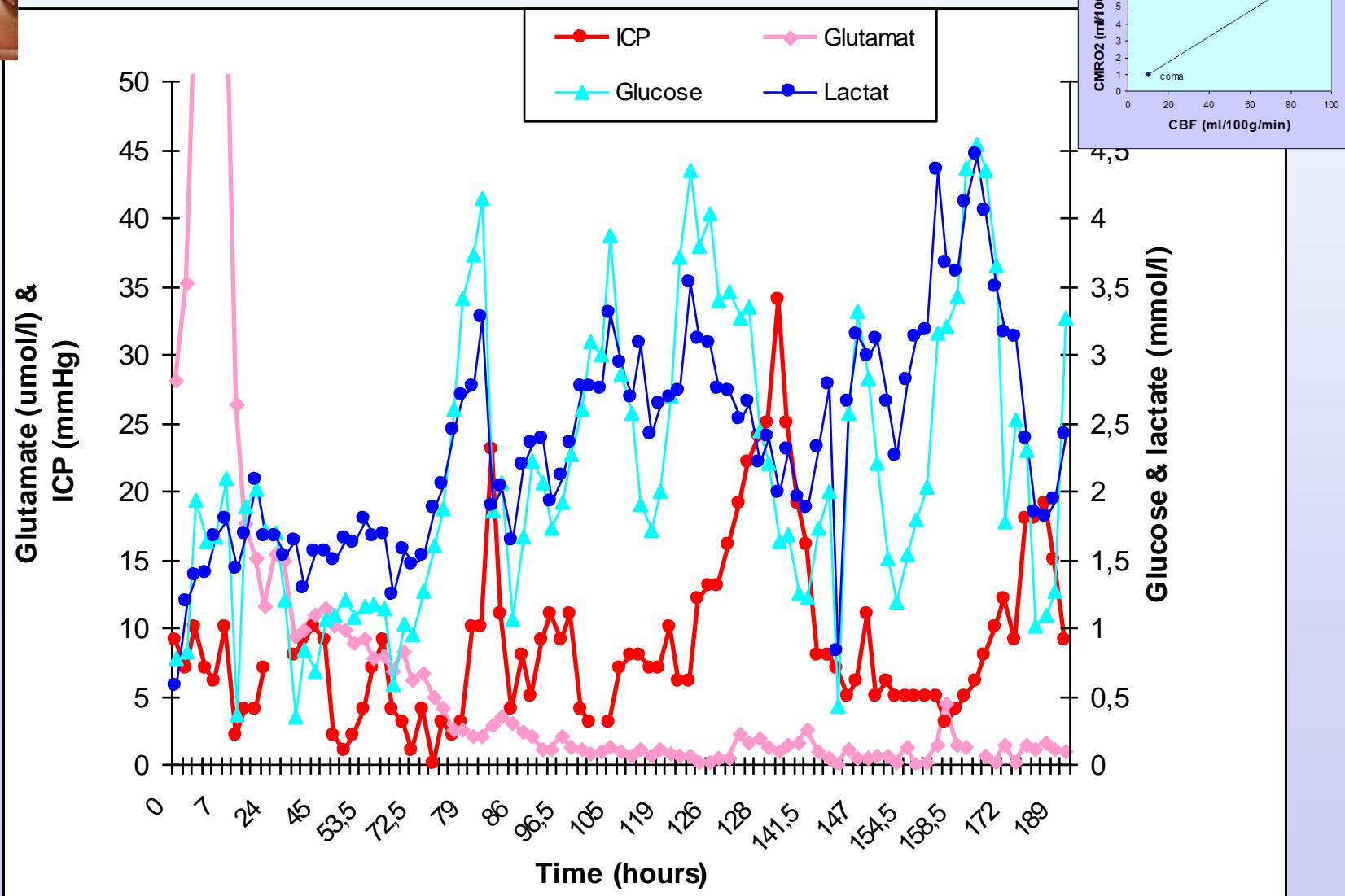
Larsen et al. J Hepatol 2001

**How does hyperammonemia
increase CBF?**

Cerebral microdialysis in patients with liver failure

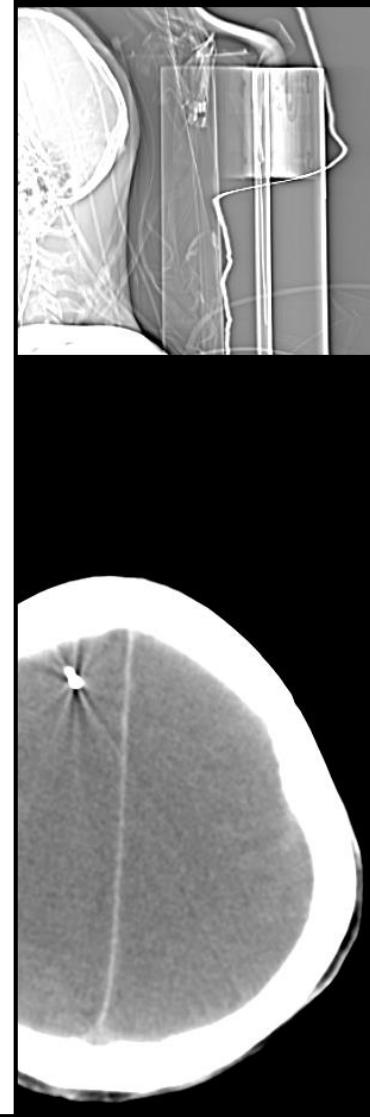
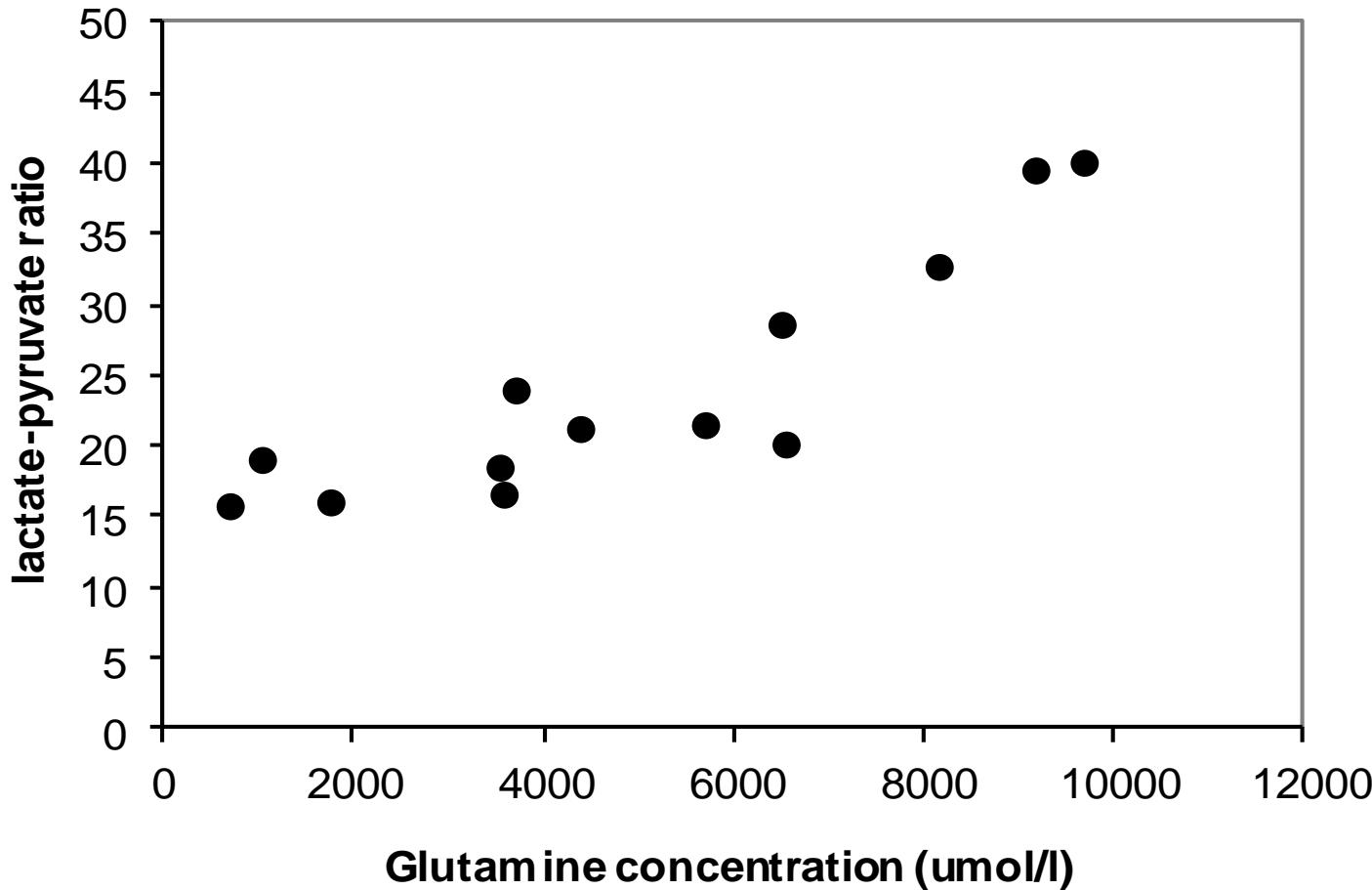


Focus on lactate



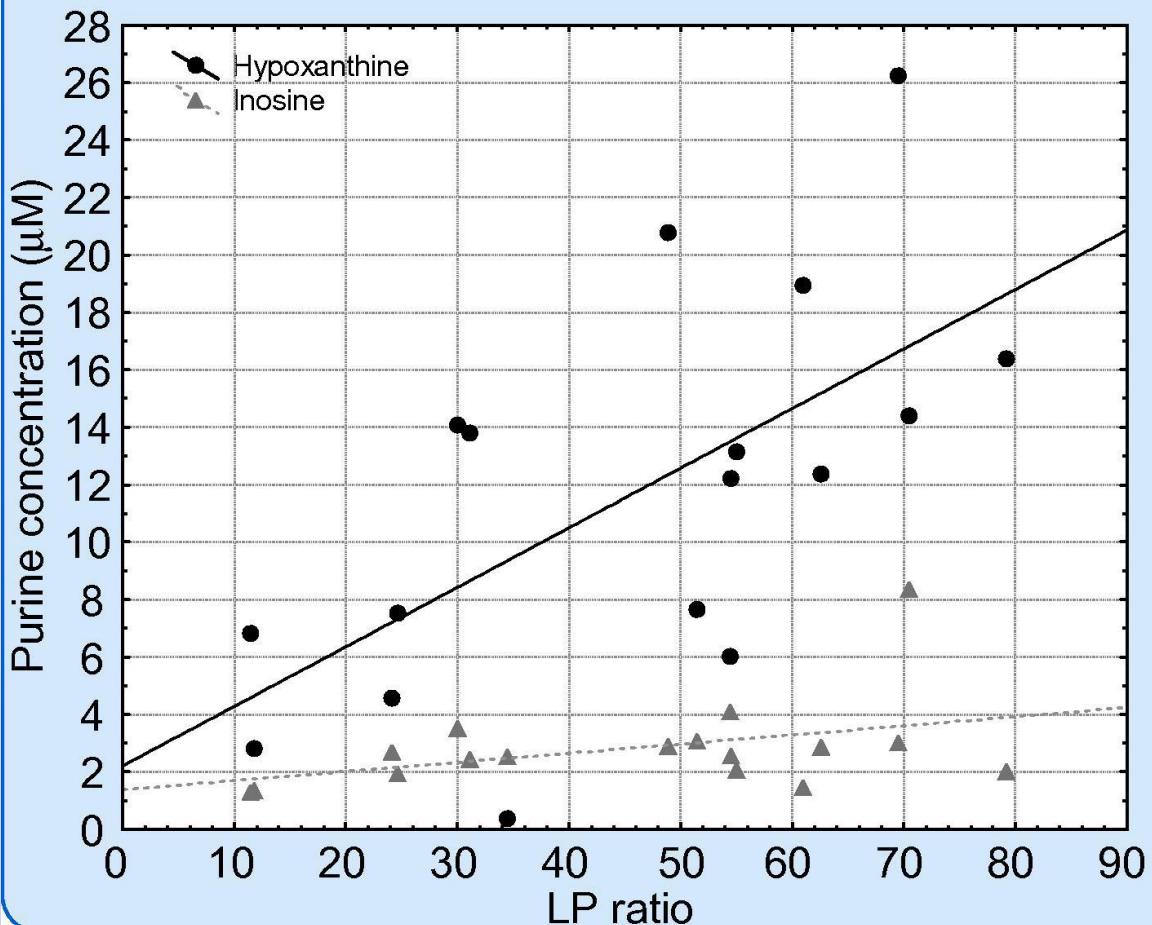
Glutamine causes mitochondrial failure in the brain in liver failure?

Bjerrings et al. Neurocritical Care 2008



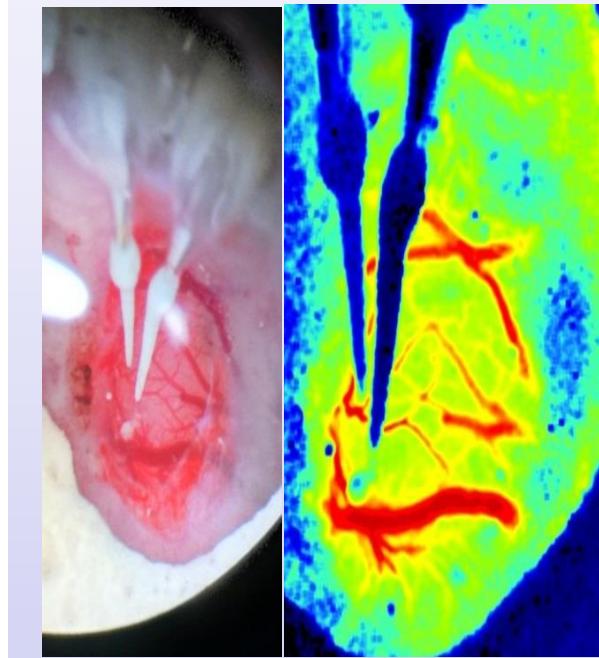
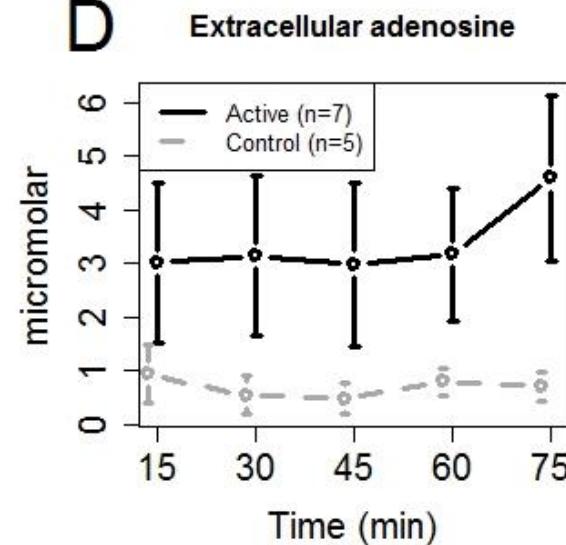
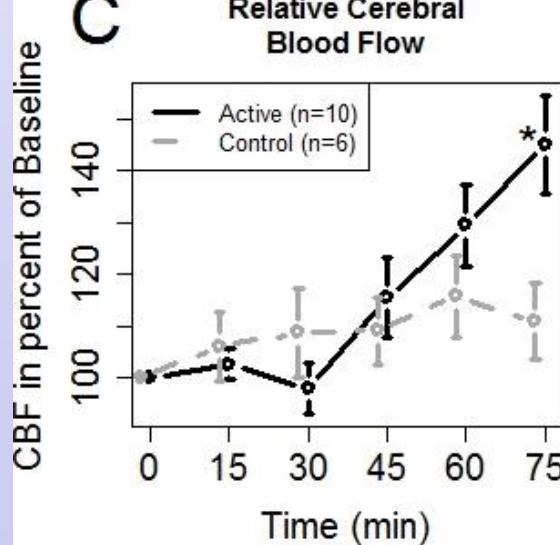
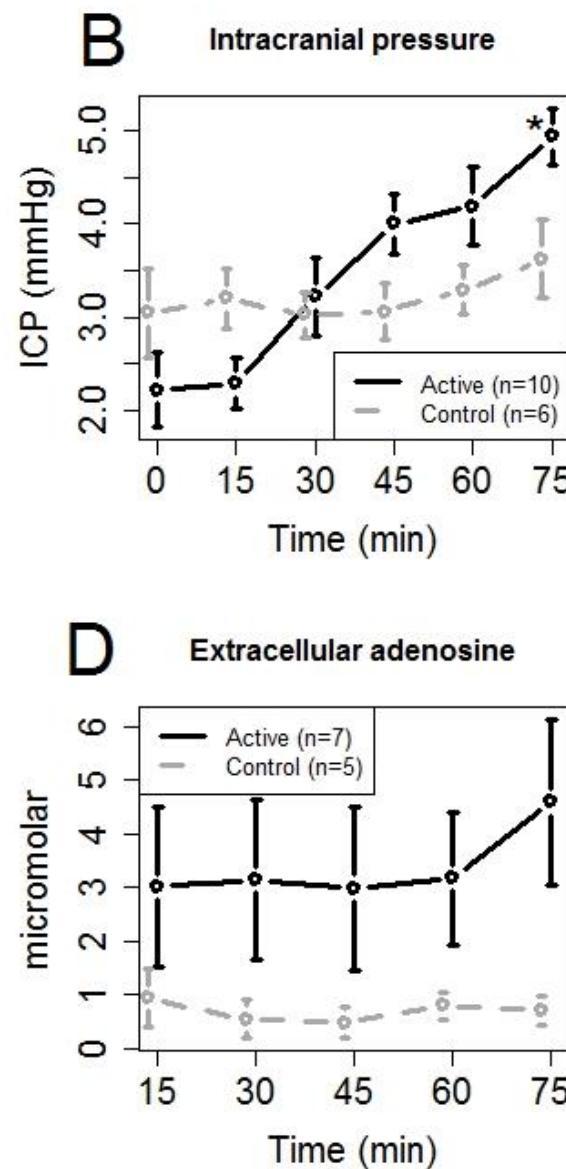
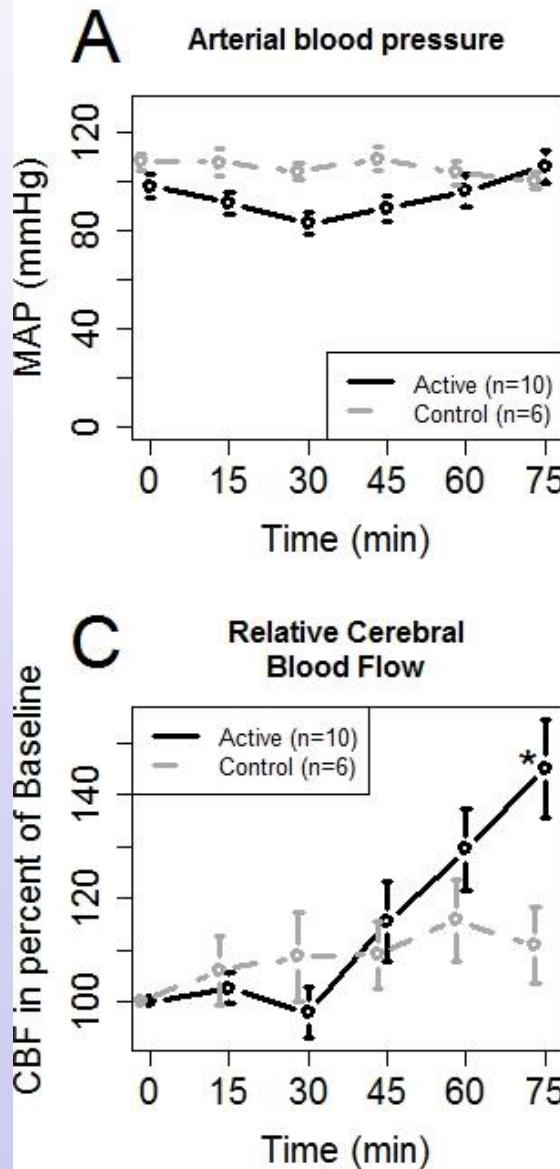
The higher LP ratio the higher hypoxanthine in the brain during liver failure: A microdialysis study

LP ratio:Hypoxanthine: $r = 0.6358; p = 0.0061; r^2 = 0.4042$
LP ratio:Inosine: $r = 0.4109; p = 0.1014; r^2 = 0.1688$



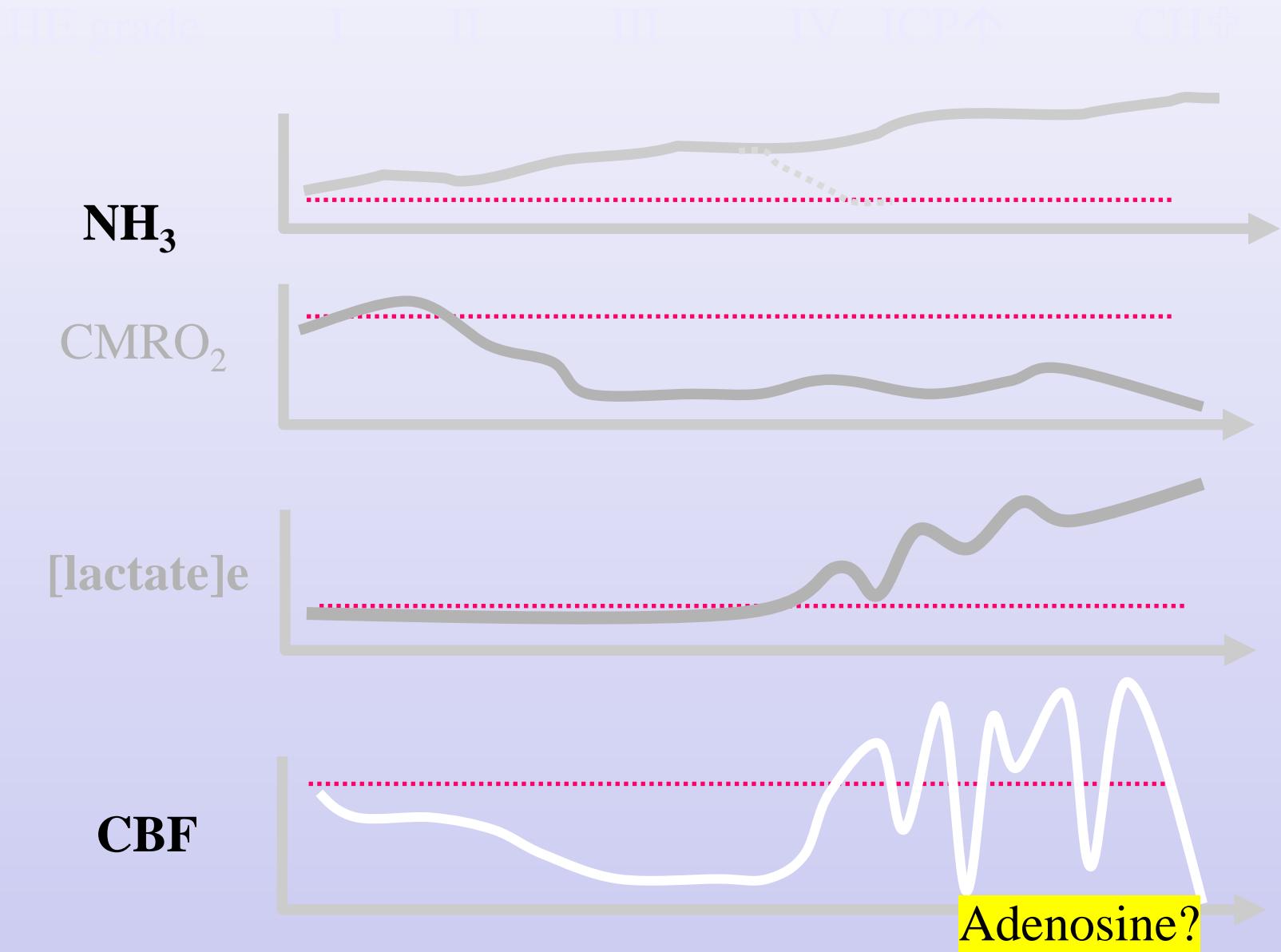


Adenosine and CBF in liver failure: Biosensor study



Bjerring P, Larsen FS.
Neurochem Res. 2014

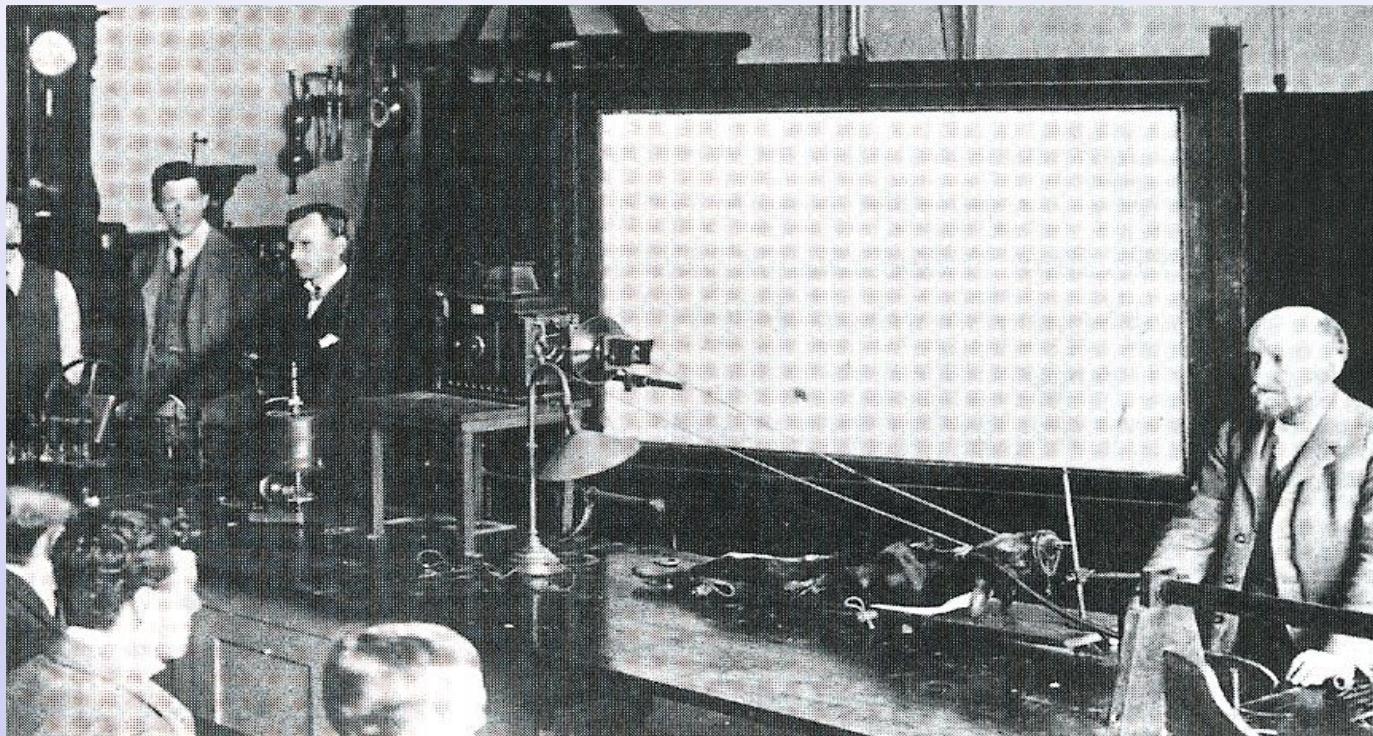
CBF in severe liver failure - interpretation



Main regulatory mechanisms of CBF II

Vasoreactivity

EH Starling



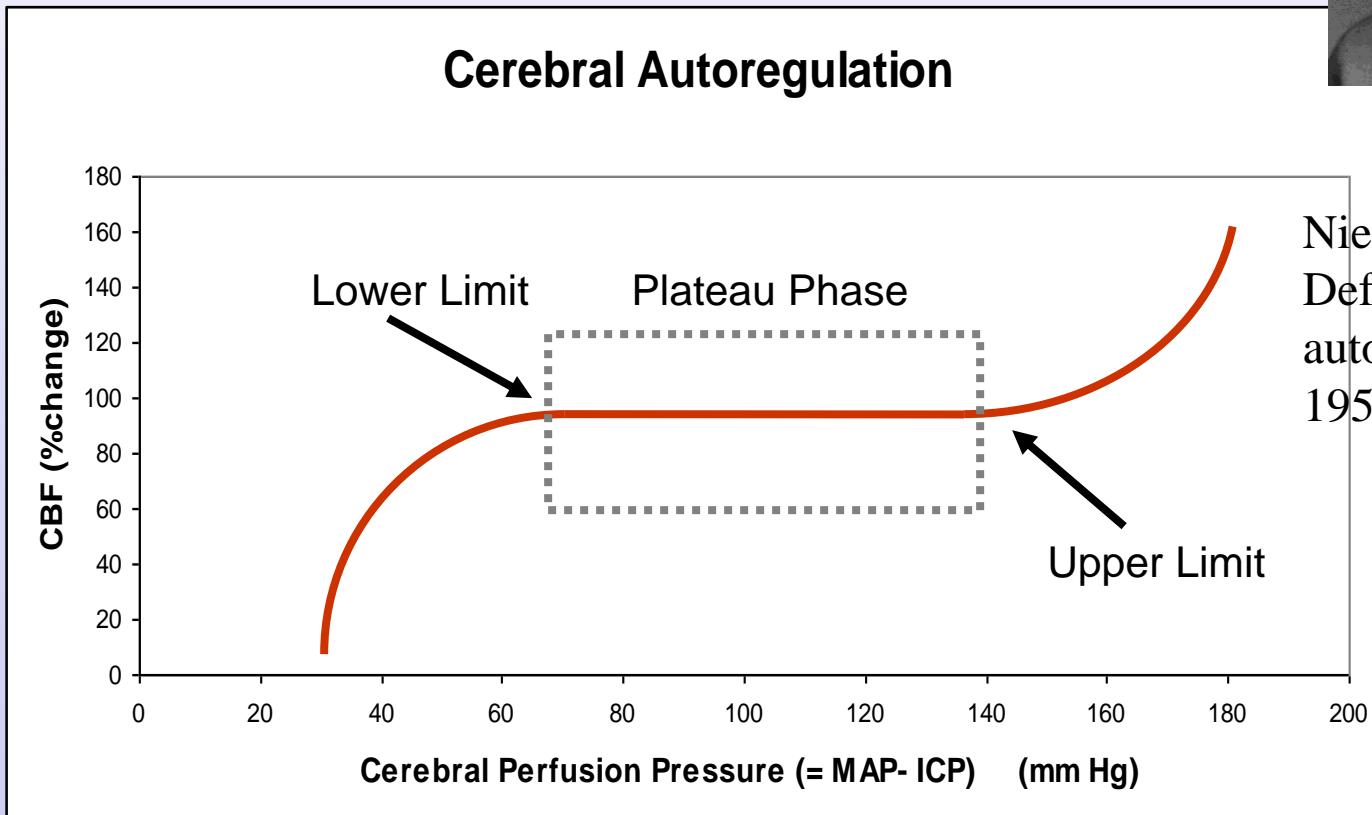
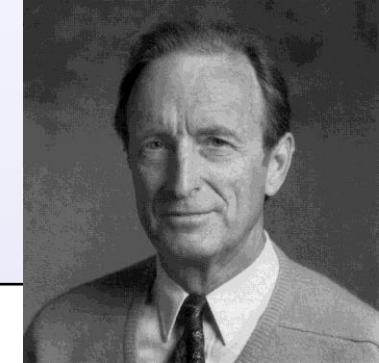
WM Bayliss

1903, London

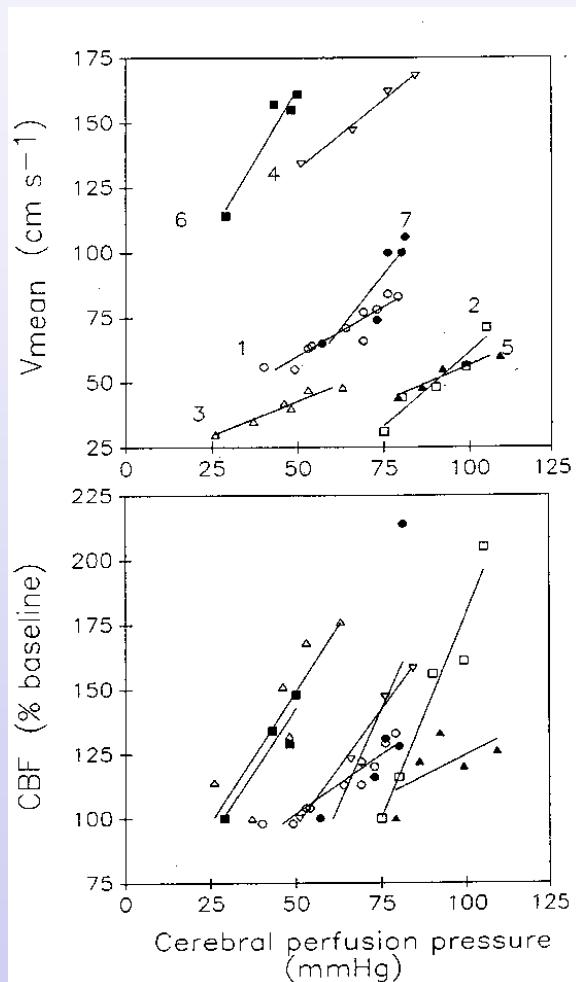


Main regulatory mechanisms of CBF - II

Mogens Fog. Cerebral circulation.
Arch Neurol Psychiatry 1937; 37:351–364



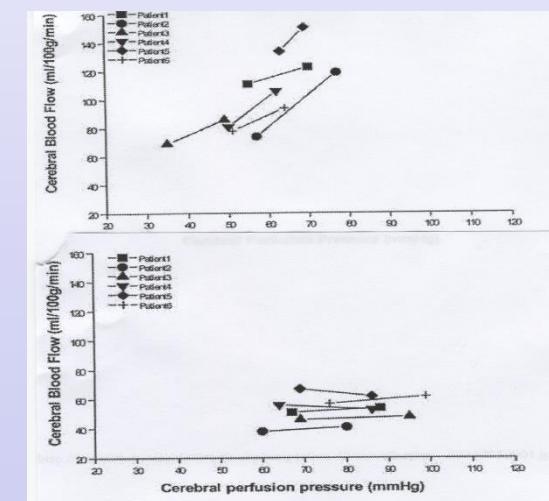
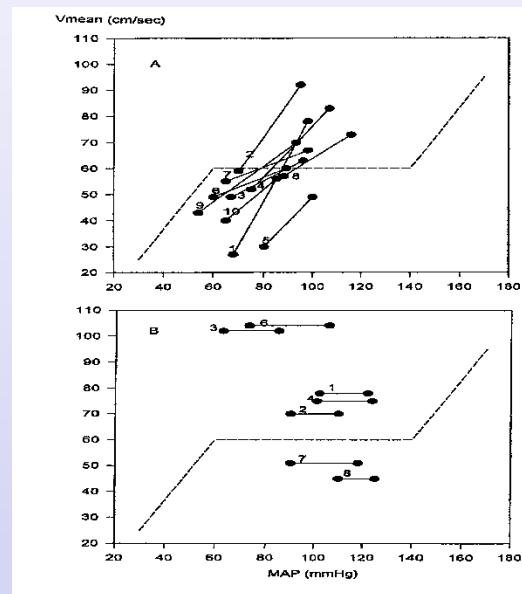
CBF autoregulation is impaired in liver failure



Strauss & Larsen. Hepatol 1997
and J Hepatol 1998

Larsen FS & Secher N. J Hepatol
1995, Crit Care Med 1997

Tofteng & Larsen. J CBF & M 2004



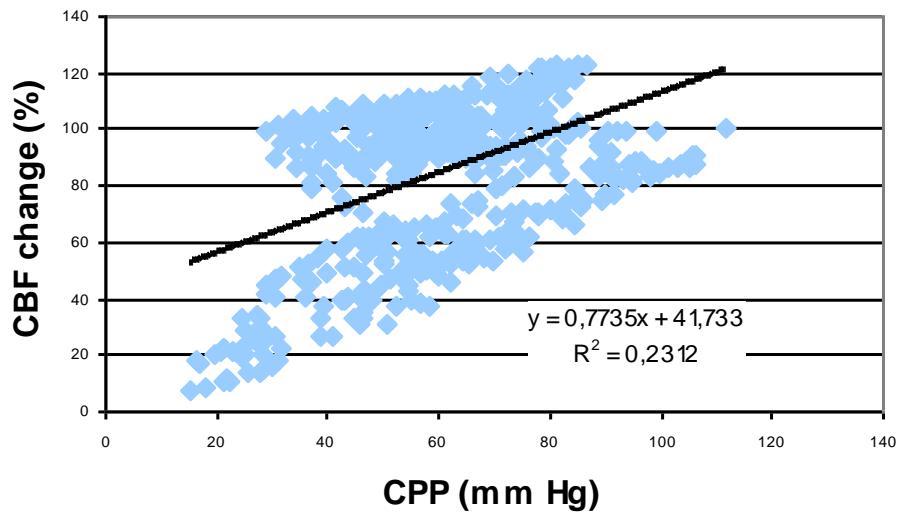
Jalan et al. Hepatology 2001

What impairs CBF autoregulation in liver failure ?

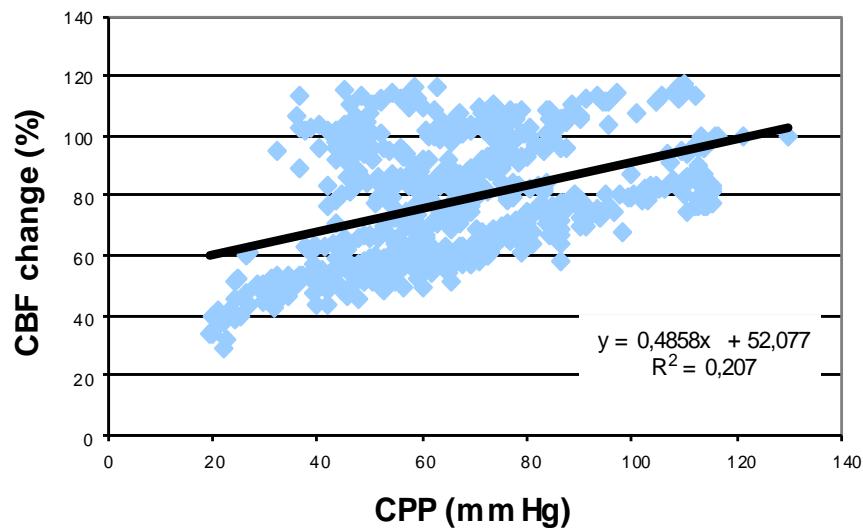
Which molecule is the mediator ?!

Loss of liver mass and liver function

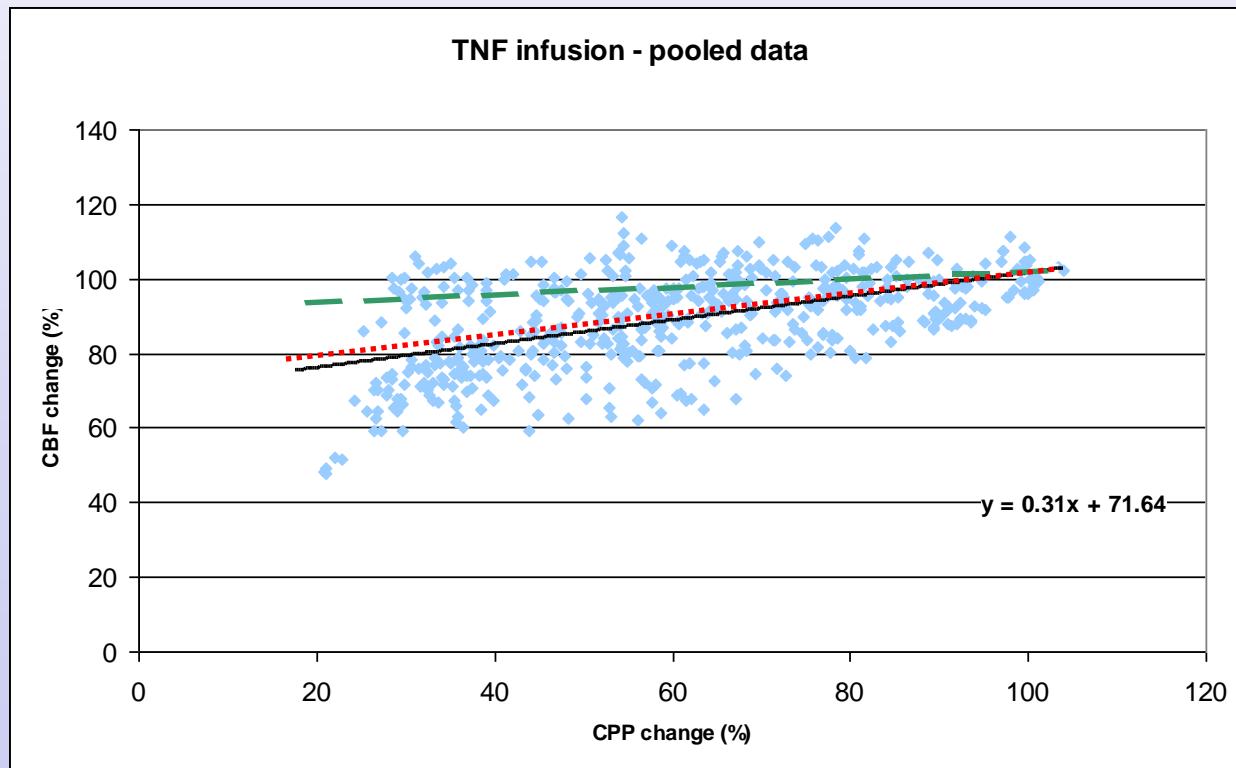
PHx 90% - pooled data, plateau



Paracetamol intoxication - pooled data, plateau

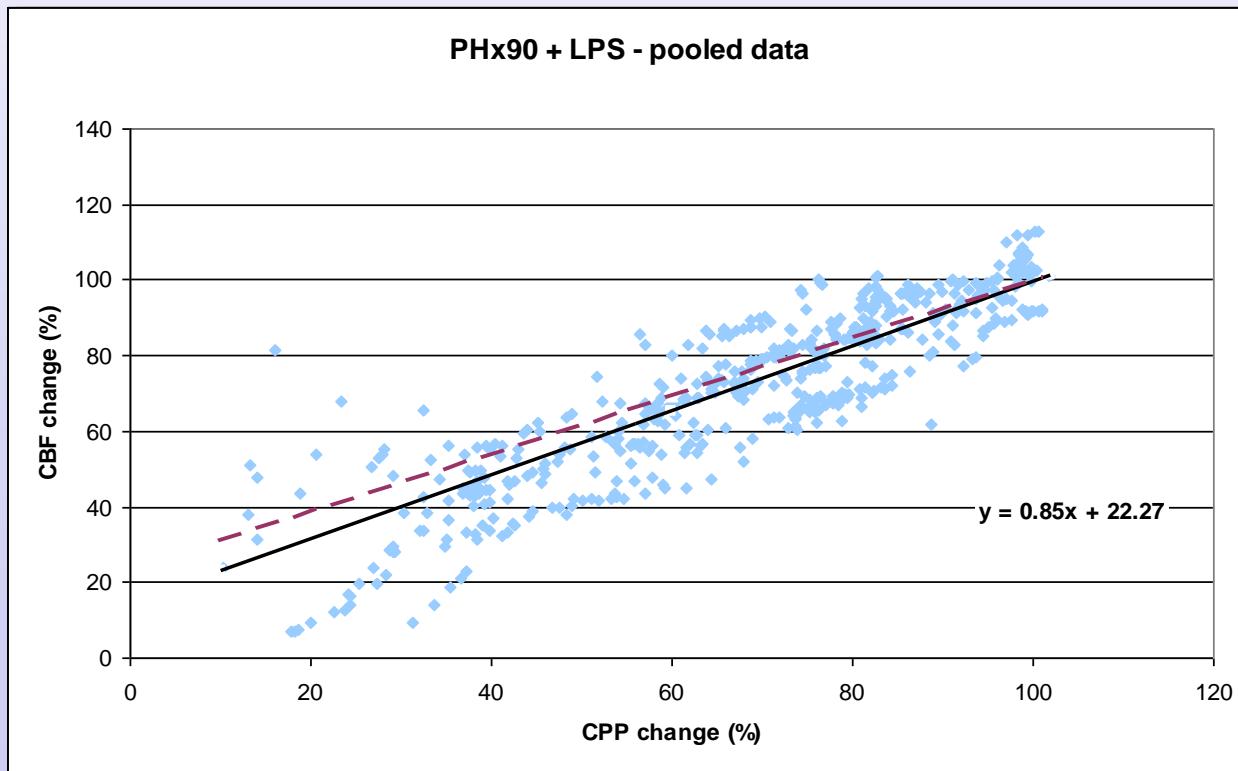


Systemic inflammation and CBF autoregulation: Effect of LPS and TNF α



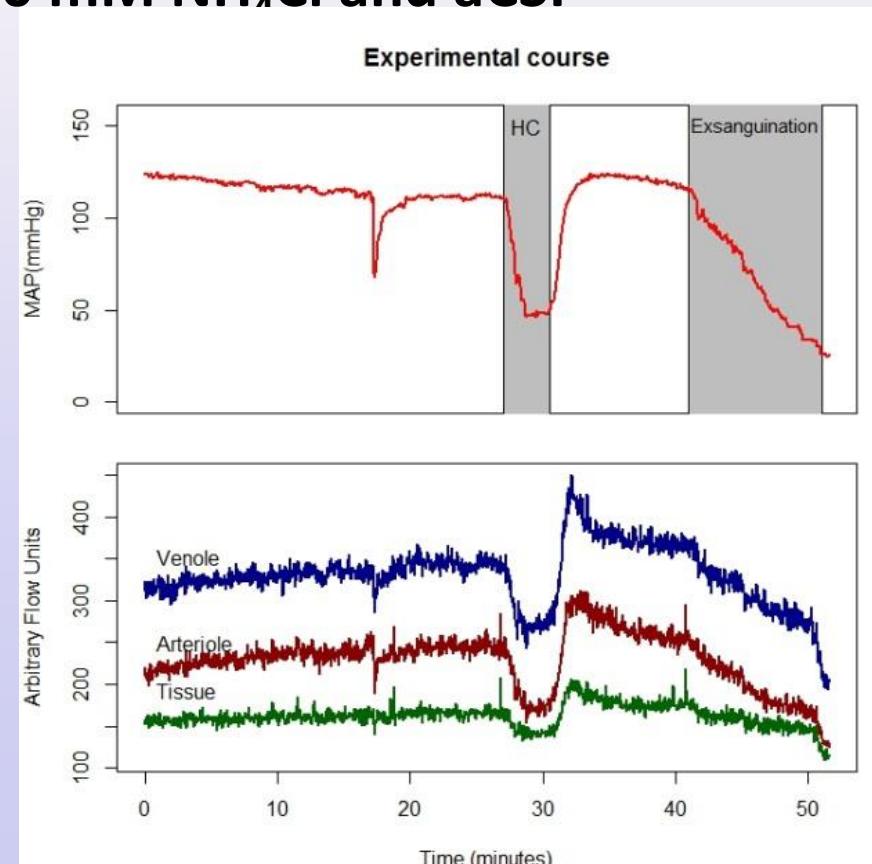
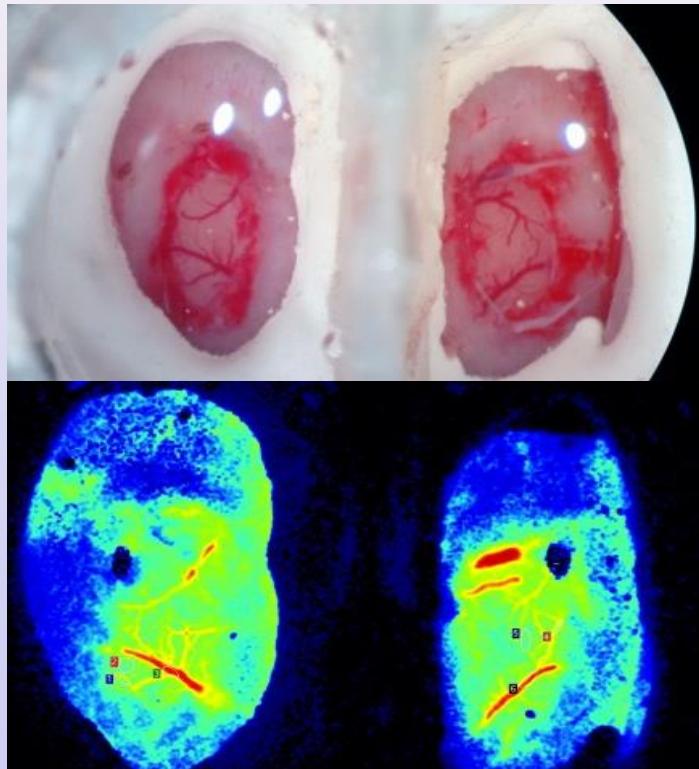
Additional effect of systemic inflammation on CBF autoregulation

— · — · — · = Corresponding group without LPS

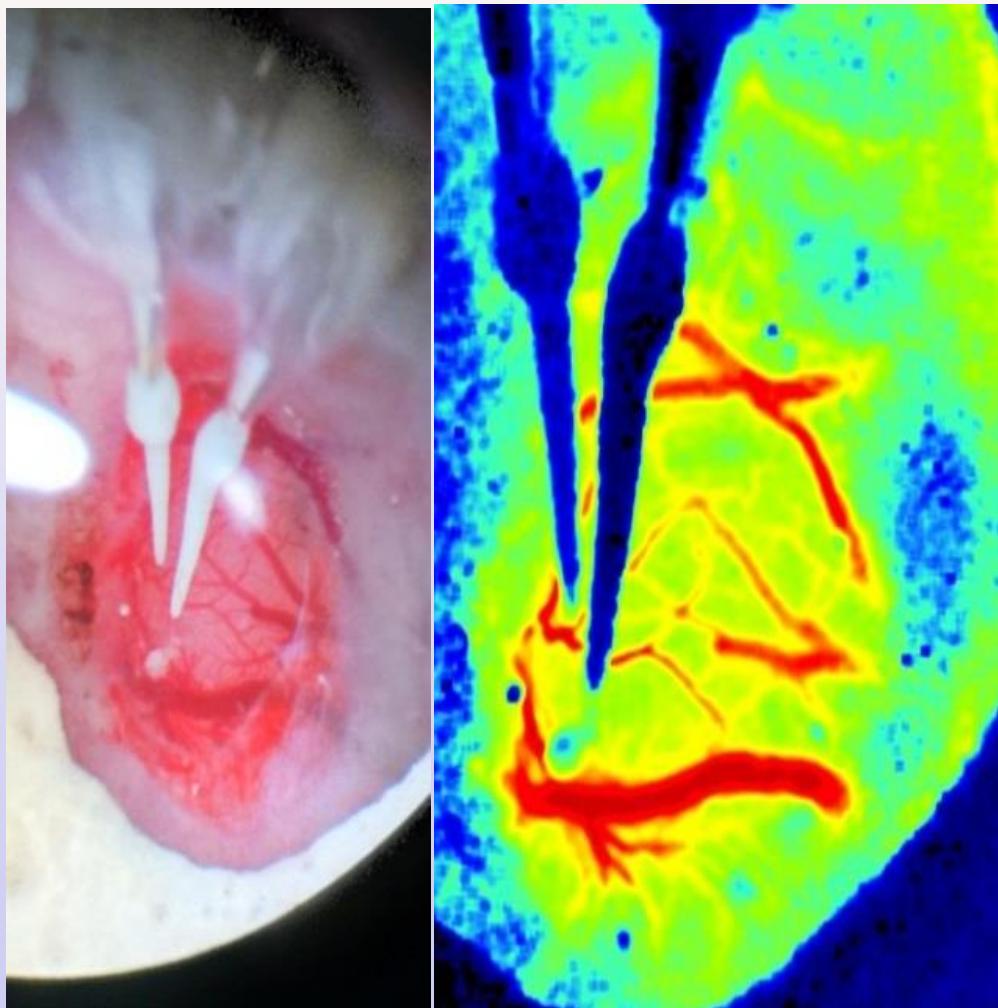


New method needed to detect adenosine *in vivo* - not microdialysis

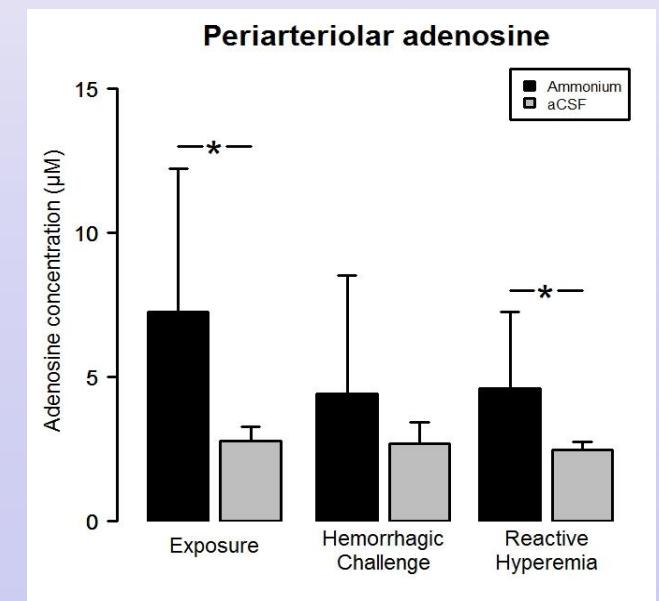
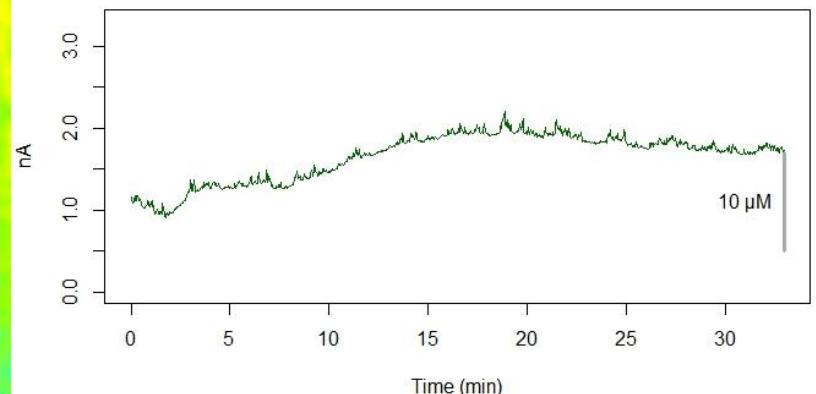
- Bilateral cranial windows on anaesthetized rats
- Brain surface perfusion was evaluated with **speckle contrast imaging**.
- 30 min topical **exposure to 10 mM NH₄Cl and aCSF**



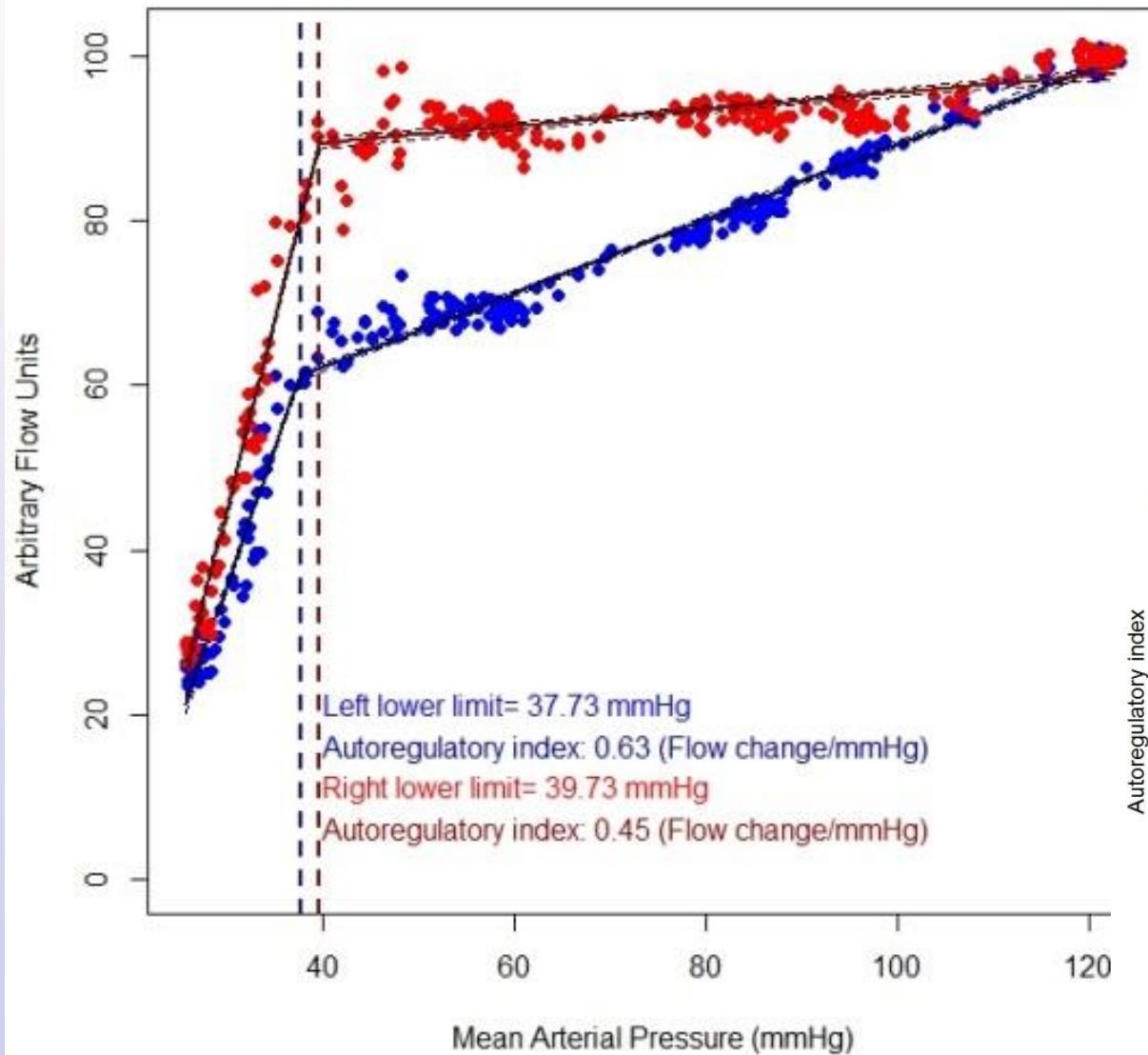
Biosensors to measure adenosine in real-time in rats exposed to NH₃



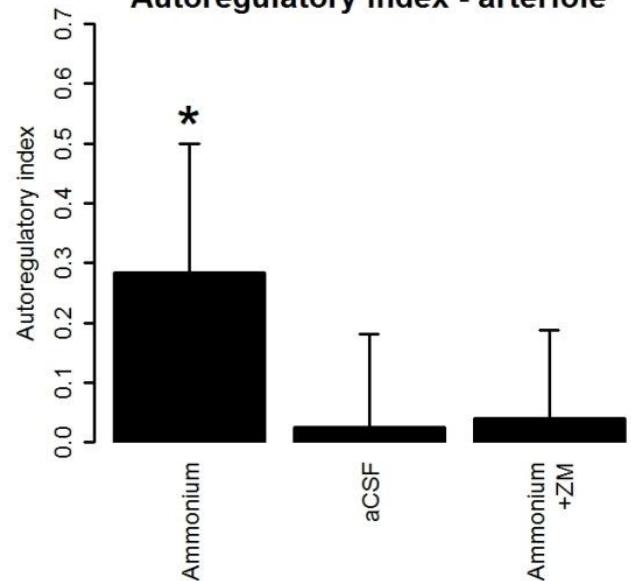
Perivascular adenosine signal



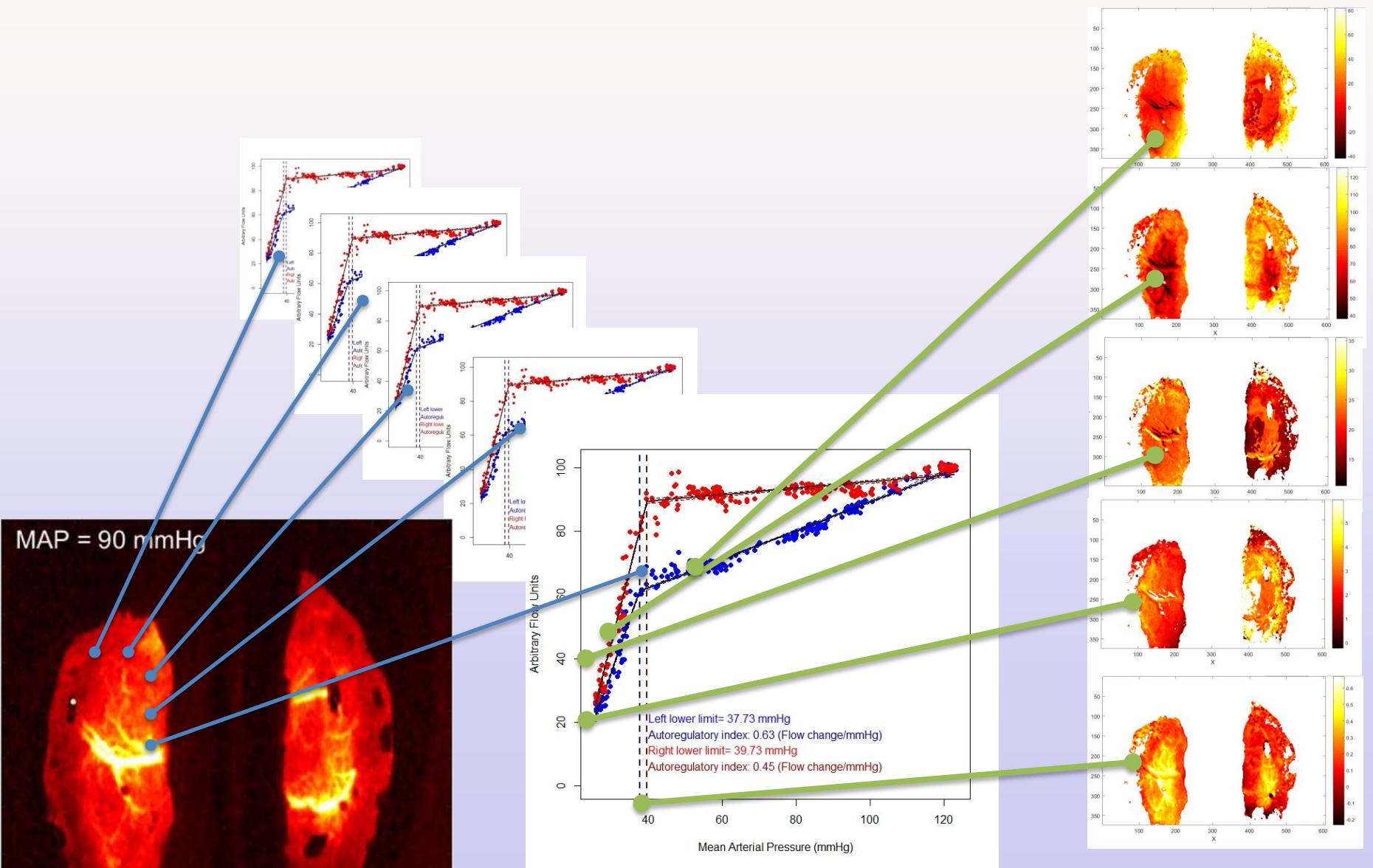
CBF autoregulation is impaired by high NH₃



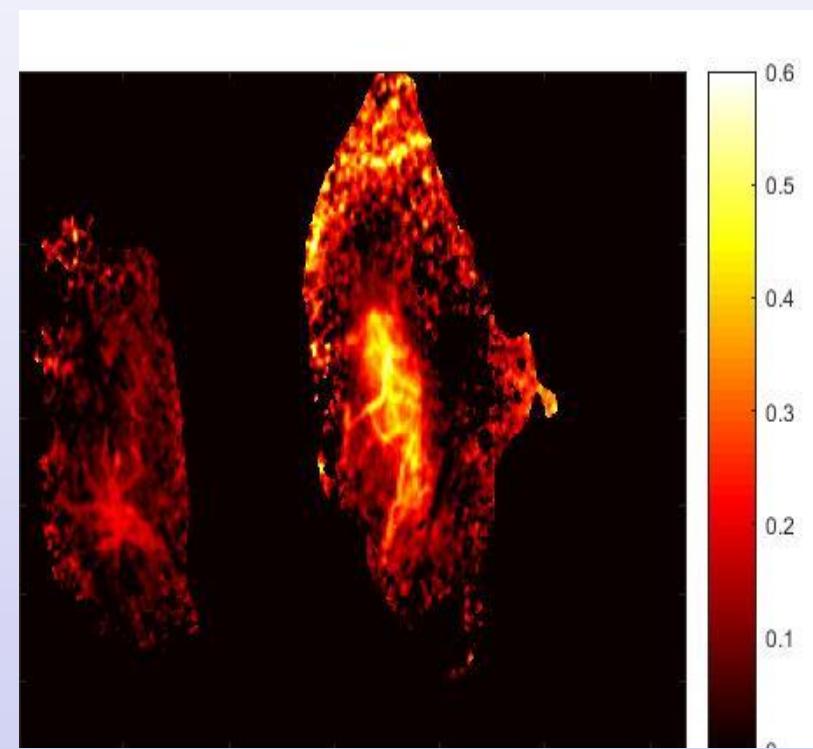
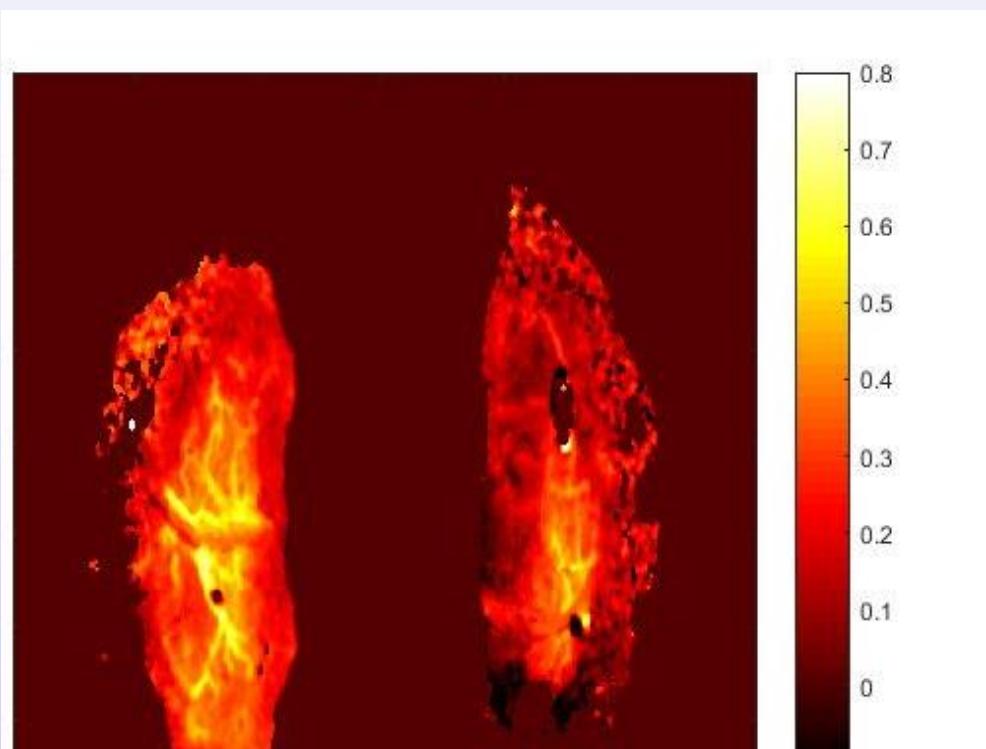
Autoregulatory index - arteriole



CBF mapping of autoregulation in various brain areas (per pixel)



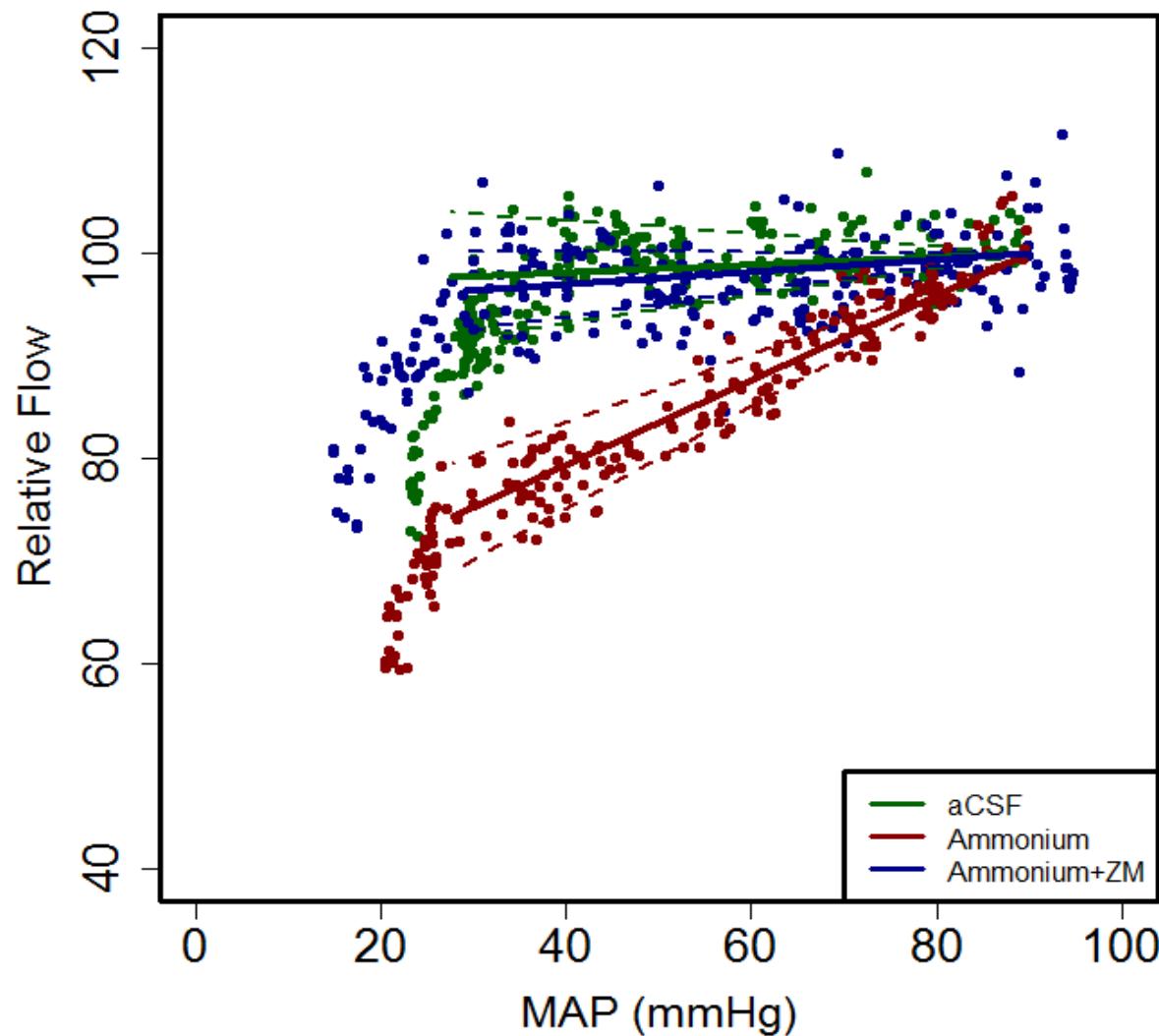
Inhibition of adenosine receptor A2a by ZM 241385 prevents a high CBF during experimental hyperammonia



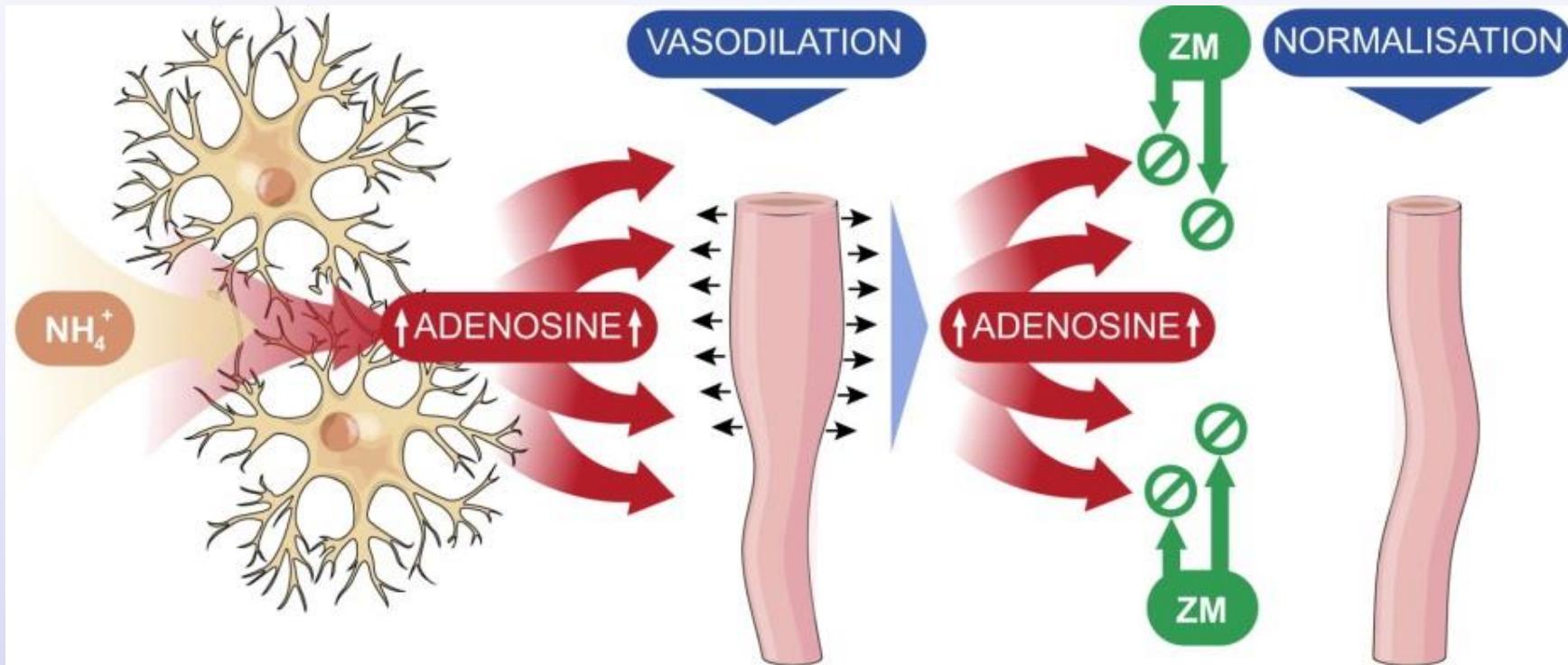
Bjerring P & Larsen FS.
J Hepatol 2018; 68 j 1137–1143

Impaired CBF autoregulation in experimental liver failure is mediated through adenosin receptors

A



Cerebral microcirculation in hyperammonemia



- Cerebral microcirculation is disturbed by topical NH_3 exposure.
- NH_3 exposure leads to increased perivascular adenosine tone.
- Adenosine receptor antagonism can restore the regulation of microcirculation during arterial hypotension.

Conclusion - 1

- CBF fluctuates in liver failure
- CBF autoregulation is impaired
- Cerebral vasodilation evolves due to
 - hyperammonemia
 - Sterile sepsis (DAMPS) / systemic inflammation

Conclusion - 2

The mediator of cerebral vasodilation and loss of autoregulation is **Adenosine**

Antagonism of **Adenosine** receptor A2a restores CBF and CBF autoregulation

Thanks to

- Prof. Niels Secher
- Dr. Peter Bjerring
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- Dr. John Hauerberg
- Dr. Flemming Tofteng
- Prof. Andres Blei
- Prof. Kirsten Møller
- Dr. Hans-Jørgen Frederiksen
- Dr. Peter Nissen Bjerring

Hyperammonemia also causes brain edema and death

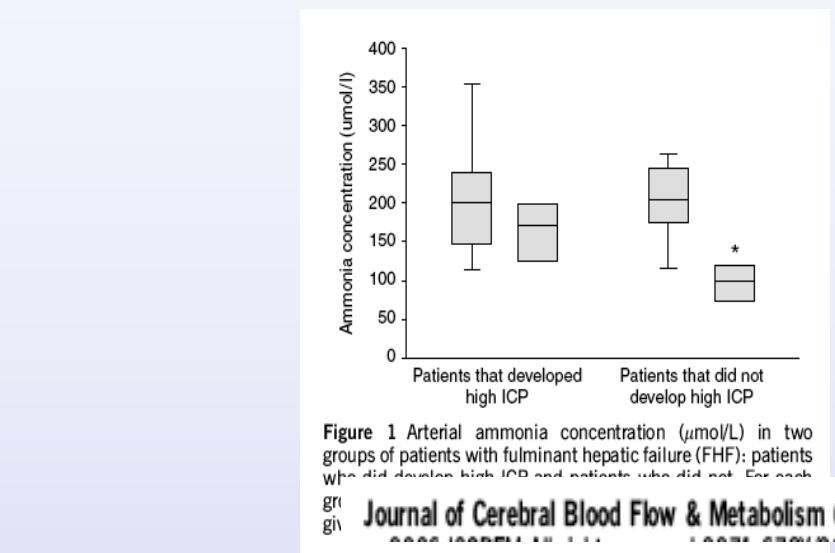
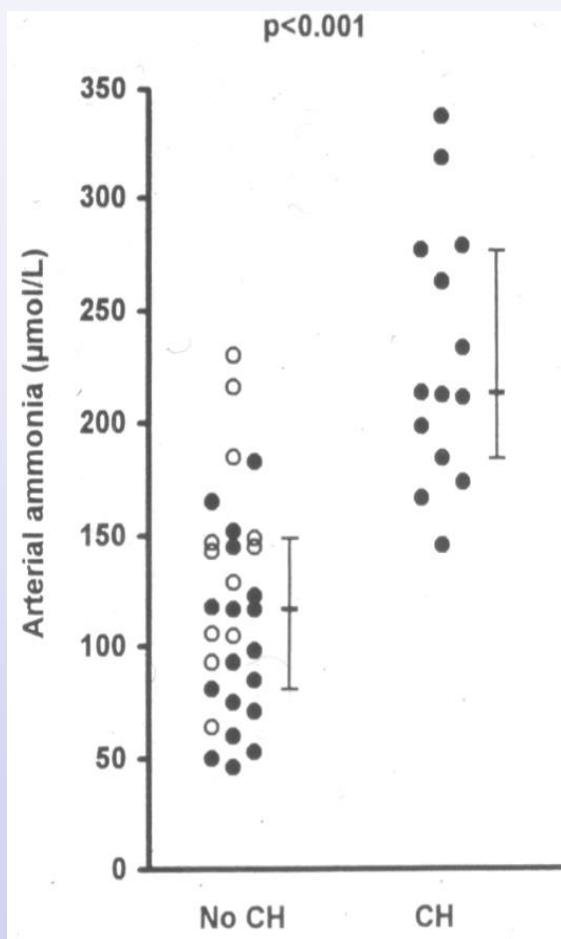
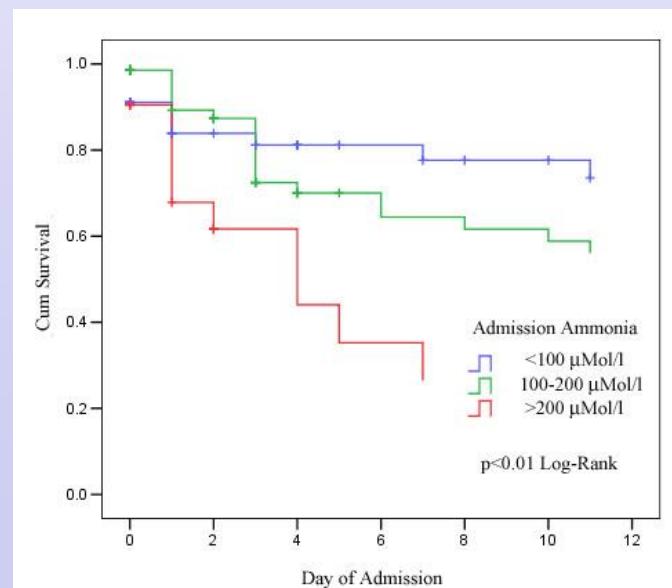


Figure 1 Arterial ammonia concentration ($\mu\text{mol/L}$) in two groups of patients with fulminant hepatic failure (FHF): patients who did develop high ICP and patients who did not. For each group

Journal of Cerebral Blood Flow & Metabolism (2006) 26, 21–27



Clemmesen JO, Larsen fs & Ott P.
Hepatology 1999;29:648-653

Bernal W Hepatology 2007