Contrôle de la glycémie aux soins intensifs: glycémie optimale en fonction de la pathologie?

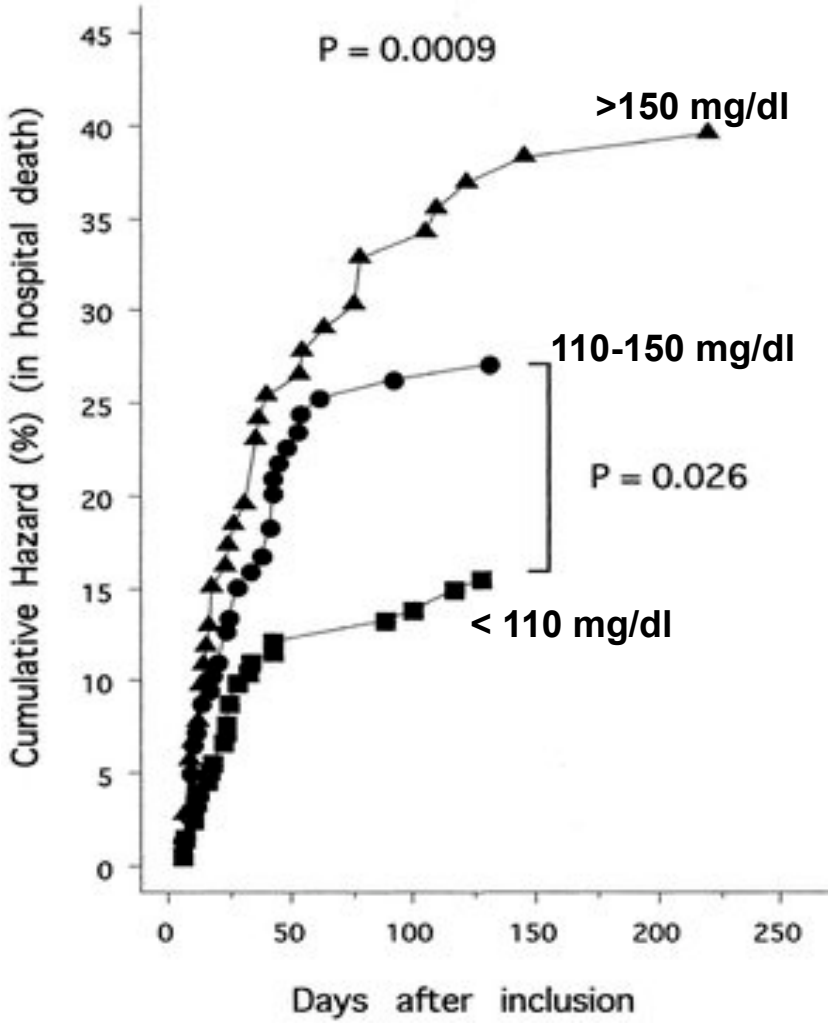
JFN 2010

Luc Tappy (Lausanne, Suisse)


STEREO
MUSIC FROM
MISSION:
IMPOSSIBLE
LALO SCHIFRIN

- « Tight glycemic control » rappel et contexte
- Hyperglycémie et stress
- Valeur « pronostique » de la glycémie
- Sepsis
- Maladie coronarienne
- Accidents vasculaires cérébraux

Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control
G Van der Berghe et al, Leuven, Belgium



1548 surgical ICU patients

Randomized to conventional or TGC

Mortality decreased in TGC group

Effect of glycemia >> insulin doses

Tight Glycemic Control in the ICU

- Leuven 1 (Van den Berghe 2001); 1548 patients; surgical ICU;
  BG target 80-110 vs 180-200 Mortality ↓

Tight Glycemic Control in the ICU

- Leuven 1 (Van den Berghe 2001); 1548 patients; surgical ICU;
  BG target 80-110 vs 180-200 Mortality ↓

- Leuven 2 (Van den Berghe 2006; 1200 patients; medical ICU
  BG target 80-110 vs 180-200. No effect on mortality

Tight Glycemic Control in the ICU

- Leuven 1 (Van den Berghe 2001); 1548 patients; surgical ICU;
  BG target 80-110 vs 180-200 — Mortality ↓

- Leuven 2 (Van den Berghe 200X9; 1200 patients; medical ICU
  BG target 80-110 vs 180-200. — No effect on mortality

- Glucontrol 1101 patients, general ICU
  BG target 80-110 vs 140-180 — No effect on mortality, hypoglycemias

Tight Glycemic Control in the ICU

- Leuven 1 (Van den Berghe 2001); 1548 patients; surgical ICU;
  BG target 80-110 vs 180-200 — Mortality ↓

- Leuven 2 (Van den Berghe 200X9; 1200 patients; medical ICU
  BG target 80-110 vs 180-200. — No effect on mortality

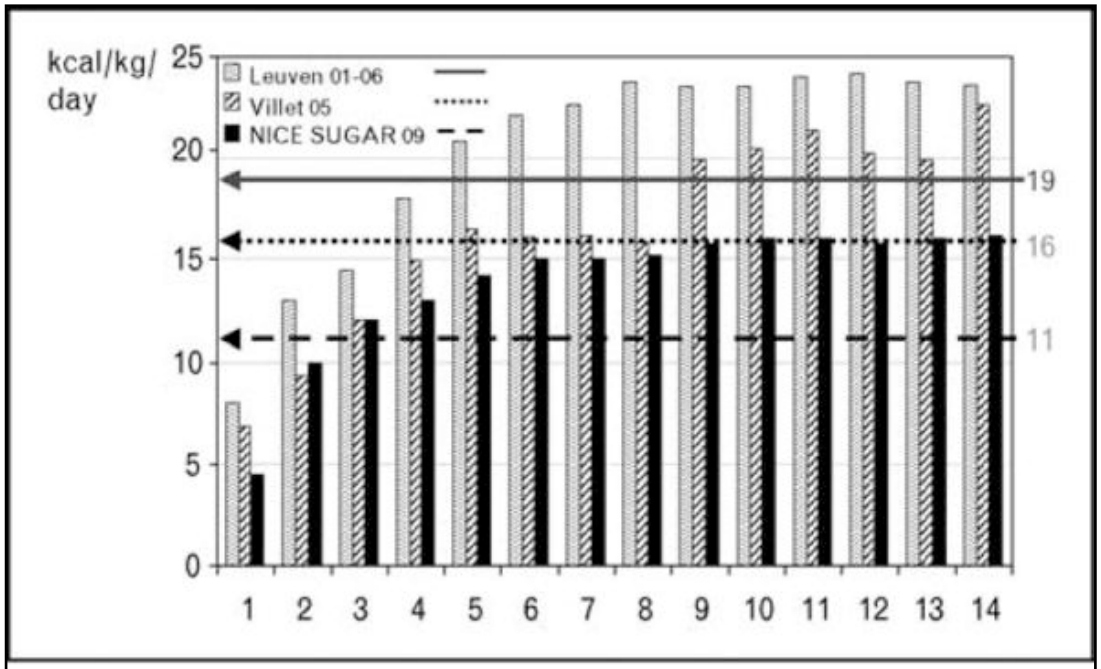
- Glucontrol1101 patients, general ICU
  BG target 80-110 vs 140-180 — No effect on mortality, hypoglycemias

- VISEP; 533 patients with sepsis
  BG target 80-110 vs 180-200 — No effect on mortality, hypoglycemias

Tight Glycemic Control in the ICU

- Leuven 1 (Van den Berghe 2001); 1548 patients; surgical ICU;
  BG target 80-110 vs 180-200 — Mortality ↓
- Leuven 2 (Van den Berghe 200X9; 1200 patients; medical ICU
  BG target 80-110 vs 180-200. — No effect on mortality
- Glucontrol1101 patients, general ICU
  BG target 80-110 vs 140-180 — No effect on mortality, hypoglycemias
- VISEP; 533 patients with sepsis
  BG target 80-110 vs 180-200 — No effect on mortality, hypoglycemias
- NICE_SUGAR; 6104 patients; general ICU
  BG target 80-110 vs 140-180 — Mortality ↑ hypoglycemias

Clinical trials on Tight Glycemic Control: nutrition = possible confounding factor…

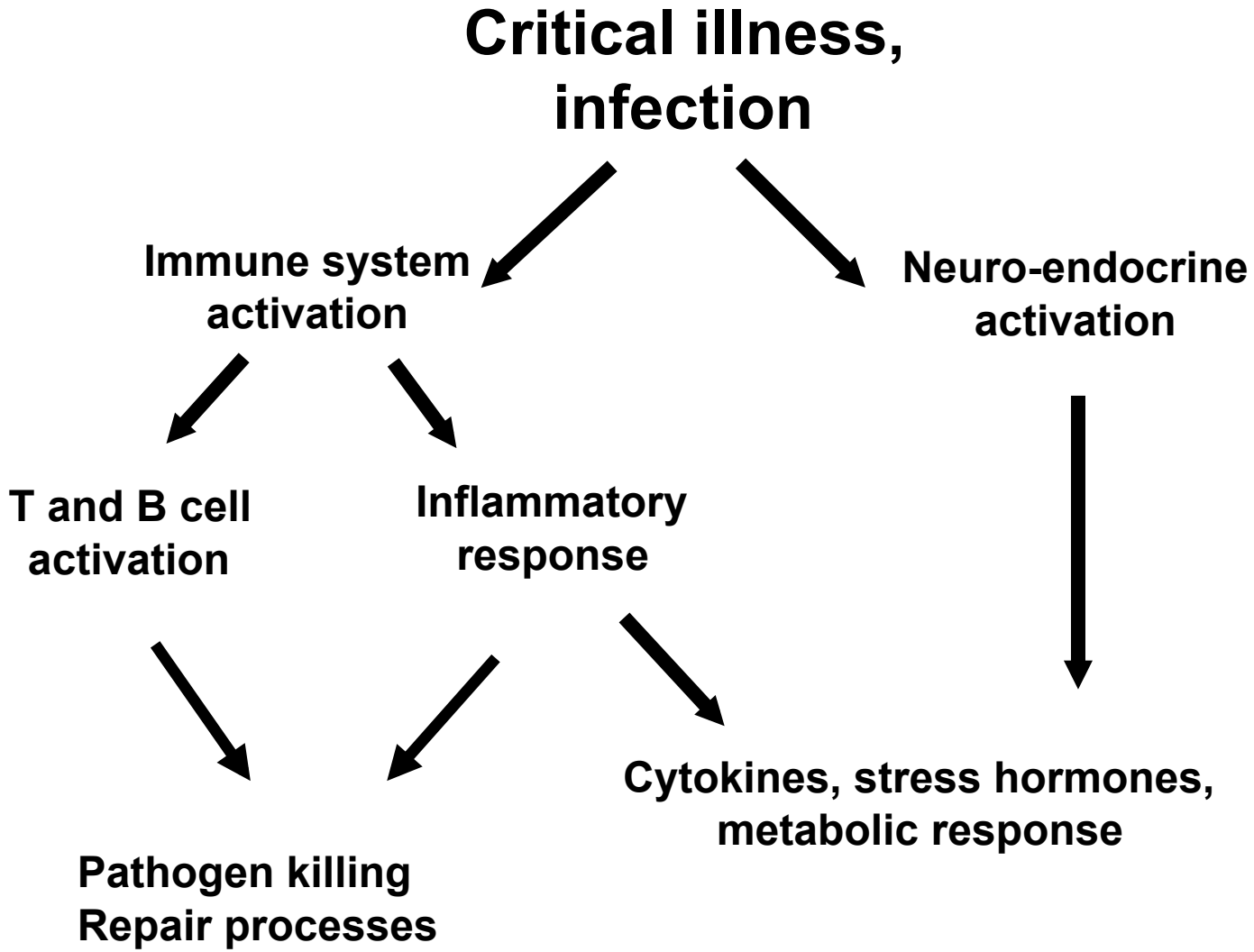


The energy deliveries in the combined two Leuven trials, the study by Villet *et al.* [7], and the NICE-SUGAR trial with mean (global and daily) energy delivery in each study are shown. NICE-SUGAR, Normoglycaemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation.

Figure 1 Mean daily energy deliveries normalized for weight over the first 2 weeks

Berger, Mette; Mechanick, Jeffrey

Current Opinion in Clinical Nutrition & Metabolic Care. 13(2):167-169, March 2010.
DOI : 10.1097/MCO.0b013e328335f2e0


Critical illness, infection
Immune system activation
Neuro-endocrine activation
T and B cell activation
Inflammatory response
Cytokines, stress hormones, metabolic response
Pathogen killing
Repair processes

Hallmarks of metabolic responses to stress and infection

- Energy Metabolism
  - Increased energy expenditure
- Carbohydrate metabolism
  - Increased glucose production
  - Insulin resistance
  - Hyperglycemia
- Lactate metabolism
  - hyperlactatemia
- **Lipid metabolism**
  - Increased lipolysis
  - Increased fat oxidation
- **Protein metabolism**
  - Increased protein turnover
  - Net protein breakdown

Prevalence of hyperglycemia in sepsis

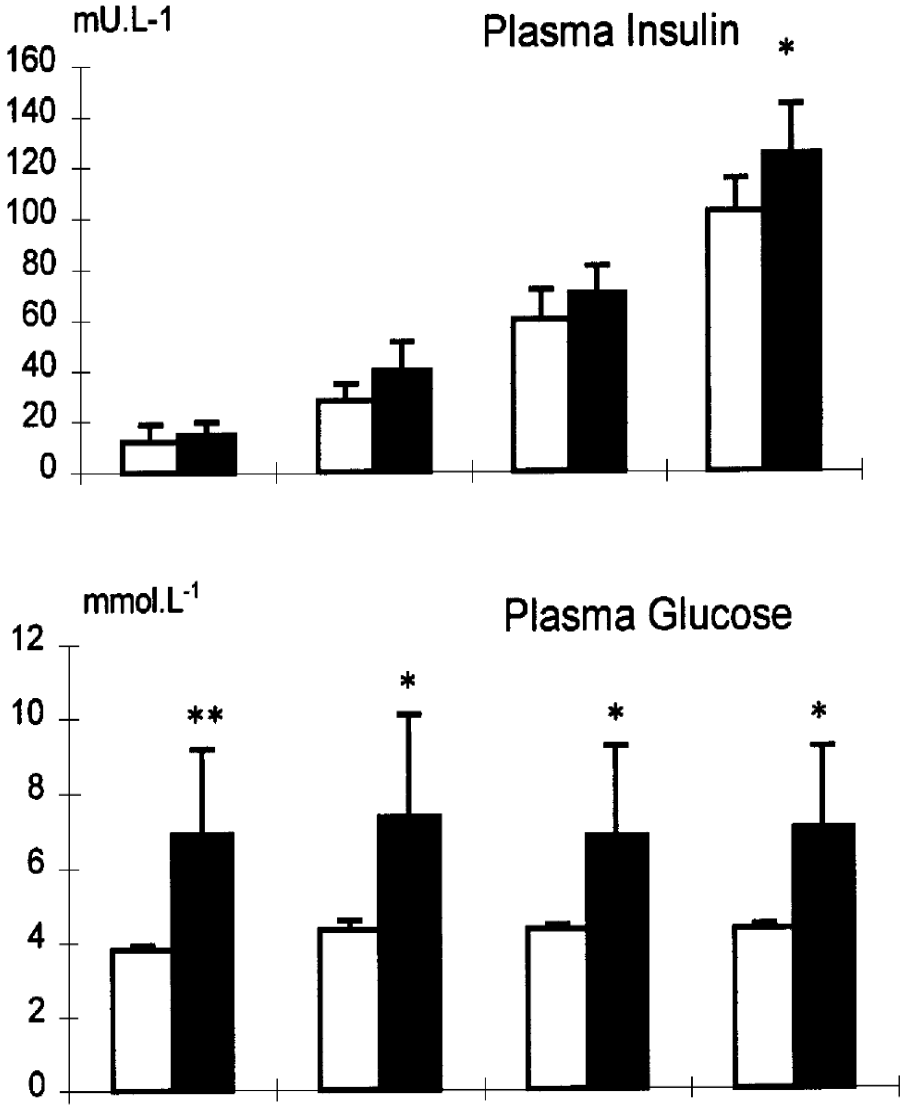
Frankenfield JPEN 1994, 18(5):398-403

	Traum Trauma + sepsis	a
Patients	26	30
Body weight	7288*	
Glucose (mmol/L)	9.010.7*	

→ 75% of septic critically ill trauma patients with glucose > 6.1 mmol/L

Insulin sensitivity and metabolic changes in sepsis

Chambrier C, Clinical Science 2000; 99: 321



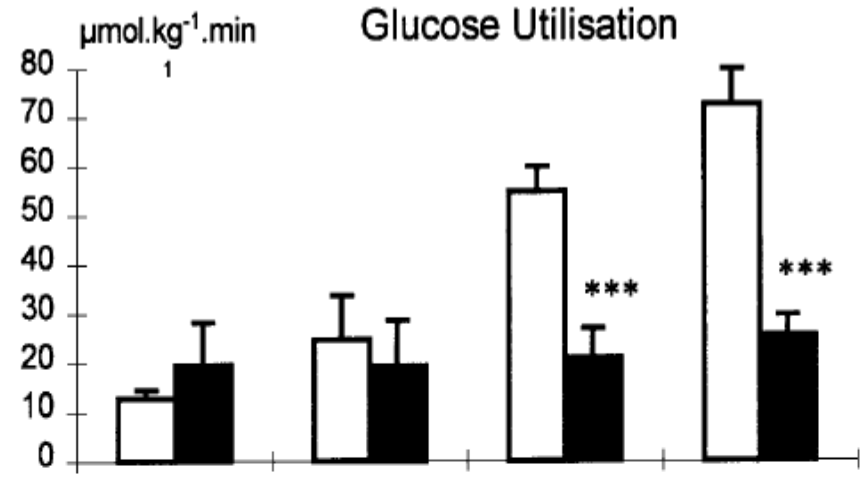
Severe sepsis (n=5),
Healthy subj. (n=5)

Isoglycemic clamp:
Increasing insulin doses
(0.5, 1.0, 2 mU/kg/min)

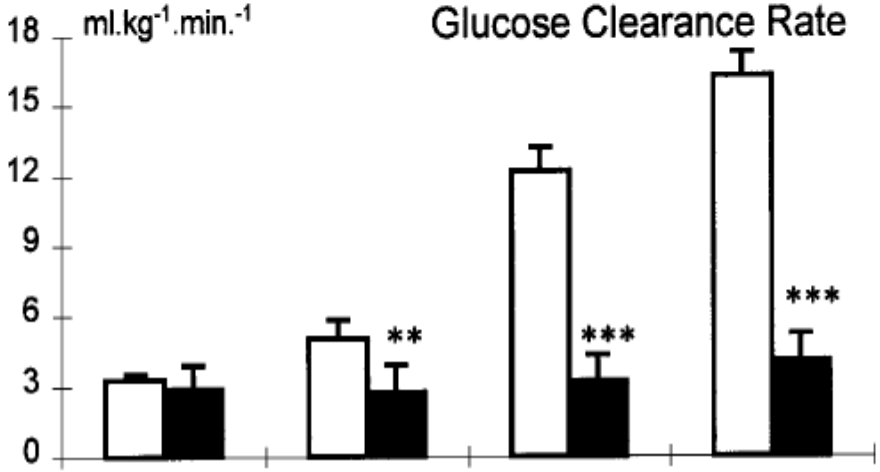
Plasma insulin and glucose

Insulin sensitivity and metabolic changes in sepsis

Chambrier C, Clinical Science 2000; 99: 321

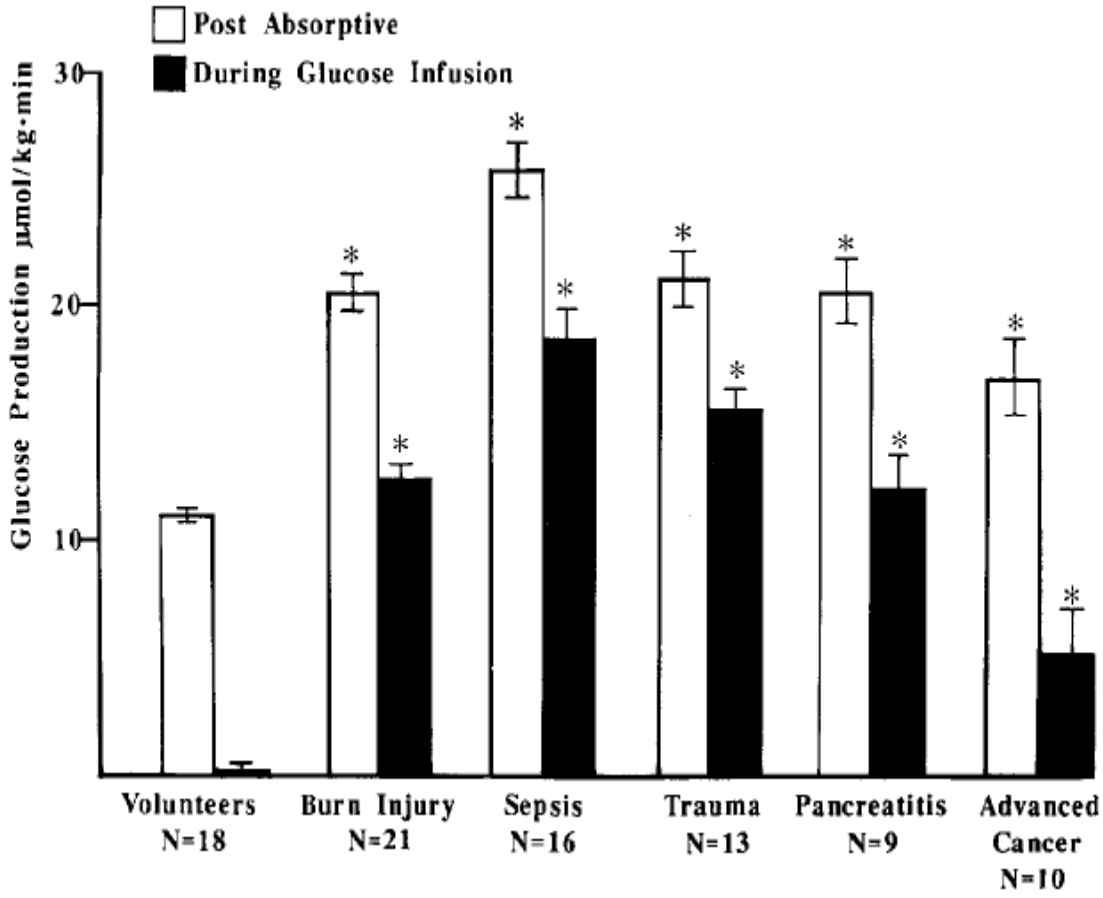


Glucose utilisation

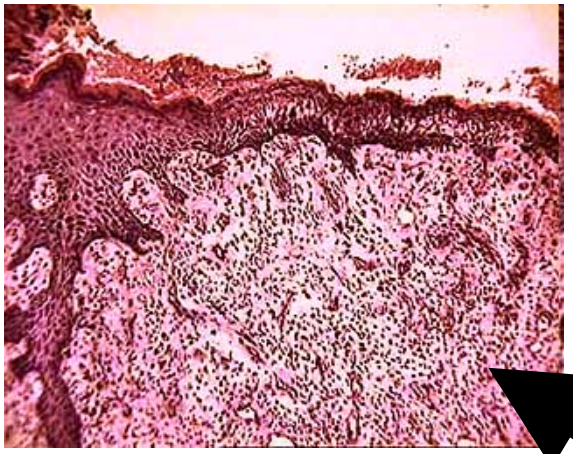


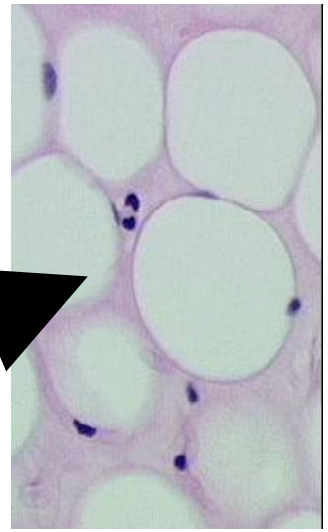
Glucose clearance

Rate of basal glucose production and endogenous production during glucose infusion in critical illnesses

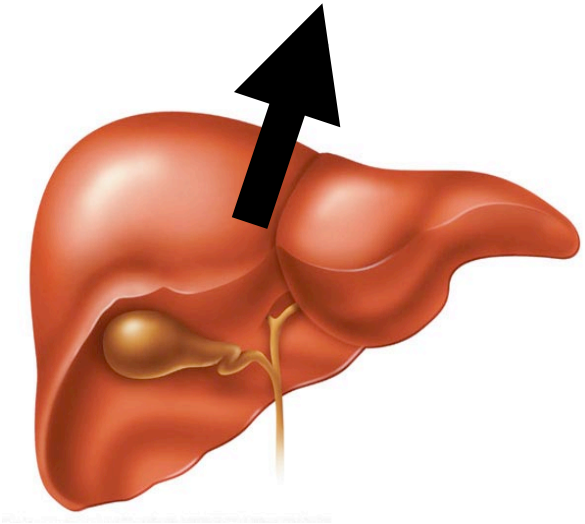


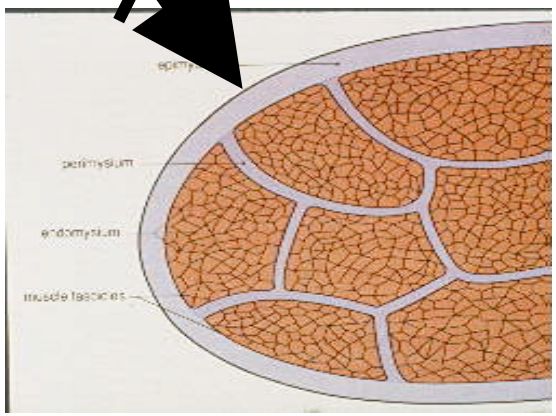
Wolfe RR, Eur J Clin Nutr 1999



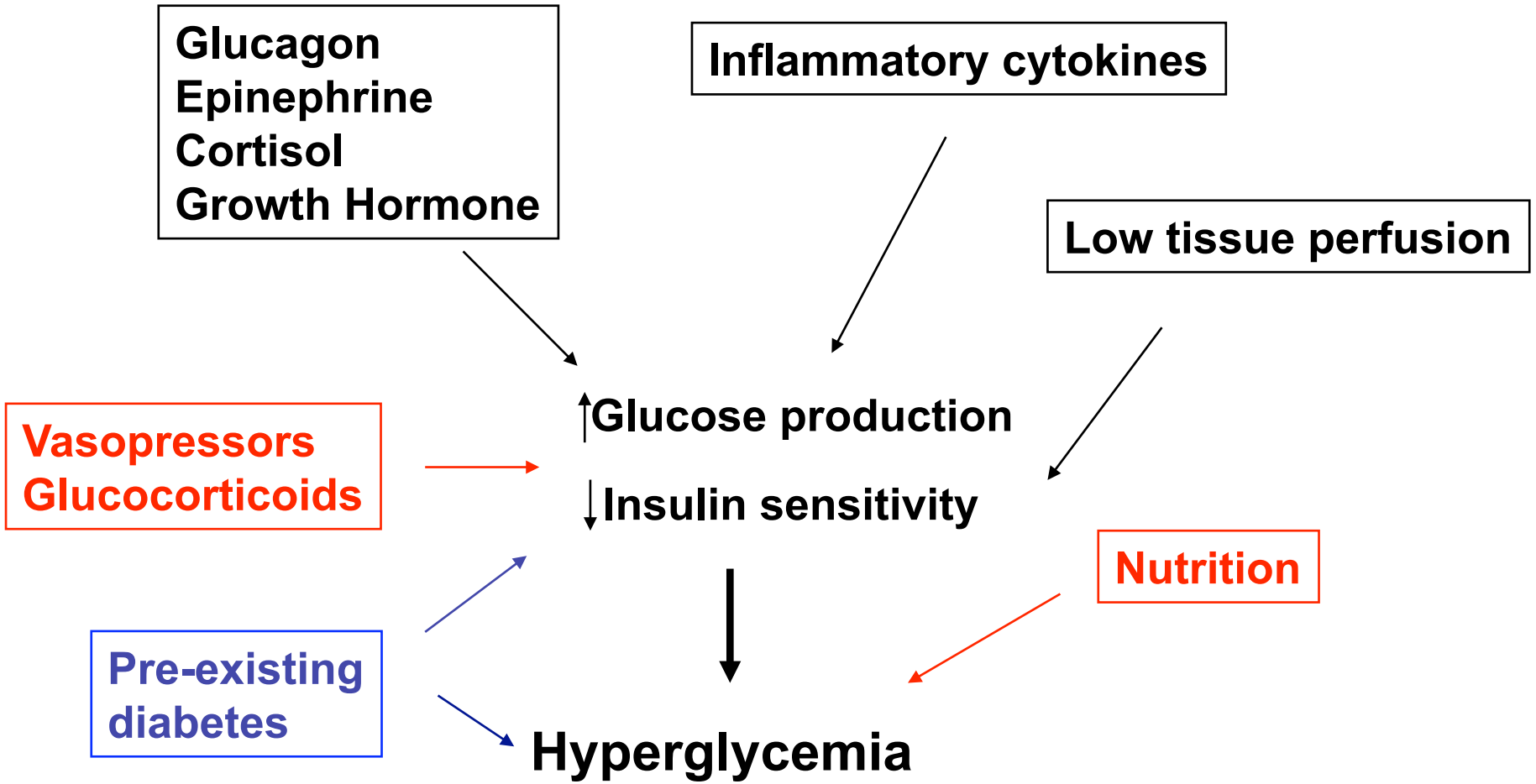


↑Blood Glucose

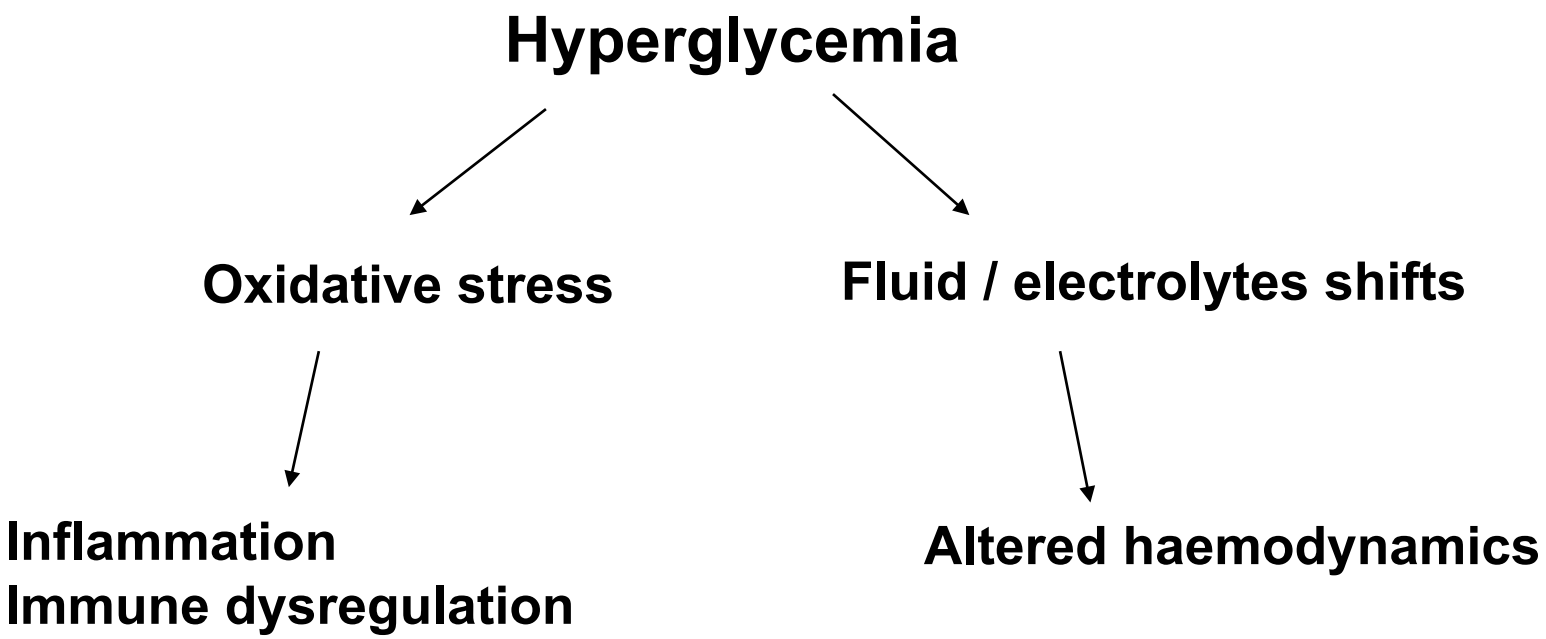




Stress hyperglycemia



Deleterious effects of hyperglycemia



Differences according to specific conditions?

- Sepsis
- Acute coronary heart disease
- Stroke

Energy metabolism in critically ill cardiac and septic patients

Martinez A, Clin Physiol Funct Imaging 2003; 23: 286

- **5 patients with severe sepsis**
  - **- 3/5 with inotropes (NE and/or dobutamine)**
  - **- Cardiac index 3.8 +/- (SD) 0.9 L/m-2/min**
  - **-CRP 221.4 +/- (SD) 57.6 mg/L**
- **6 patients with cardiogenic shock after cardiac surgery**
  - **-6/6 with inotropes**
  - **-Cardiac index 2.2 +/- (SD) 0.3**
  - **-CRP 100.7 +/- (SD) 64.5**

Clin Physiol Funct Imaging (2003) 23, pp286–292

Assessment of adipose tissue metabolism by means of subcutaneous microdialysis in patients with sepsis or circulatory failure

Alexandre Martinez[1], Rene Chiolero[1], Marc Bollman[1], Jean-Pierre Revelly[1], Mette Berger[1], Christine Cayeux[1] and Luc Tappy[2]

[1]Surgical Intensive Care Unit, University Hospital, Lausanne, and [2]Institute of Physiology, School of Medicine, University of Lausanne, Lausanne, Switzerland

	Glucose (mmol l^{-1})	Insulin (pmol l^{-1})	Free fatty acids (mmol l^{-1})
Healthy subjects	5·2 (4·5–5·7)	46·8 (40·8–57·0)	0·49 (0·33–0·80)
Sepsis/septic shock	8·9 (5·7–12·4)*	83·4 (67·2–179·4)*	0·34 (0·20–0·58)
Circulatory failure	10·0 (8·9–11·4)*	285·0 (168·6–594·0)*,**	0·34 (0·16–0·44)

*$P<0·05$ or less versus healthy subjects.

**$P<0·05$ or less versus sepsis/septic shock.

Adipose tissue metabolism with microdialysis in patients with severe sepsis or circulatory failure

Table 4 Energy expenditure and substrates oxidation rates.

	Energy expenditure (kcal day^{-1})	Net glucose oxidation (μmol kg^{-1} min^{-1})	Lipid oxidation (mg kg^{-1} min^{-1})	Glucose turnover (μmol kg^{-1} min^{-1})	Non-oxidative glucose disposal (μmol kg^{-1} min^{-1})
Healthy subjects	1640 (1478–2259)	6·1 (1·7–8·7)	0·89 (0·64–1·15)	10·2 (9·8–11·4)	4·4 (2·0–5·8)
Sepsis/septic shock	1710 (1250–1731)	1·75 (0·0–7·0)*	1·26 (0·30–1·26)	20·7 (10·4–29·1)*	18·0 (5·0–31·9)*
Circulatory failure	1390 (1000–1500)	4·3 (1·6–15·7)	0·60 (0·00–1·09)	20·7 (12·1–32·4)*	14·2 (7·2–18·0)*

*P<0·05 or less versus healthy subjects.

	Plasma glycerol (μmol l^{-1})	Adipose interstitial glycerol (μmol l^{-1})	Δ Adipose-systemic glycerol gradient (μmol l^{-1})
Healthy subjects	50 (27–73)	229 (100–483)	211 (73–429)
Sepsis/septic shock	66 (46–115)	402 (115–627)*	356 (136–534)*
Circulatory failure	174 (142–226)*	280 (192–1105)	131 (10–872)

*P<0·05 or less versus healthy subjects.

In patients with sepsis and with cardiogenic shock:

- Hyperglycemia
- Insulin resistance
- Increased glucose turnover/ endogenous glucose production
- Normal or low glucose oxidation

In patients with sepsis *vs* cardiogenic shock:

- Higher EE
- Increased lipolysis
- Higher lipid oxidation

In patients with sepsis and with cardiogenic shock:

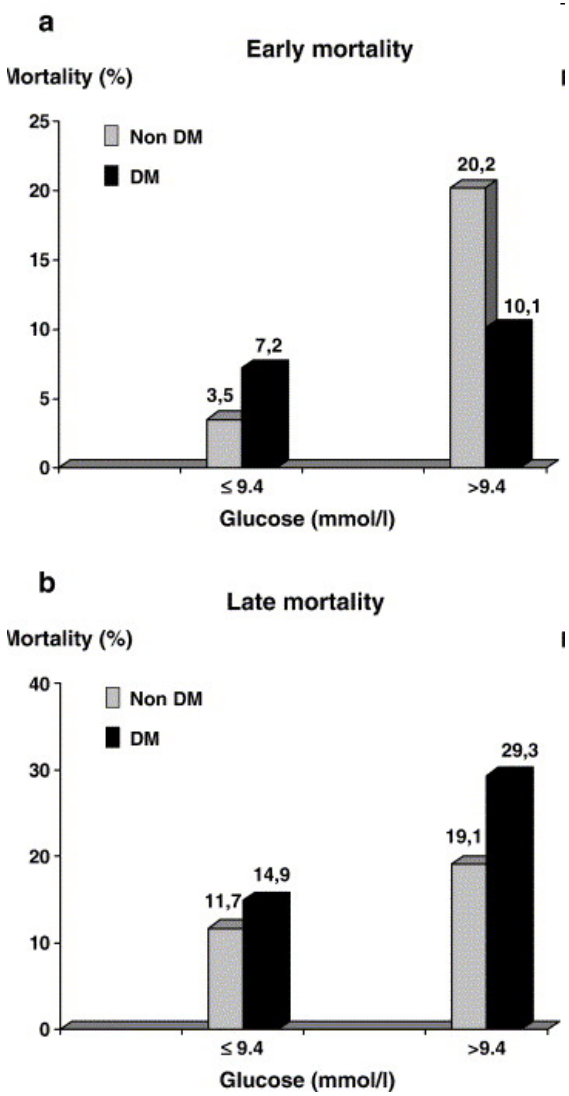
- Hyperglycemia
- Insulin resistance
- Increased glucose turnover/ endogenous glucose production
- Normal or low glucose oxidation

In patients with sepsis *vs* cardiogenic shock:

- Higher EE
- Increased lipolysis
- Higher lipid oxidation

- Effects of TGC in cardiogenic shock related to improved hemodynamics?

Admission glycemia and outcome after acute coronary syndrome
P. Petursson et al, Göteborg, Sweden
Int. J. Cardiol. 116:315-320, 2007

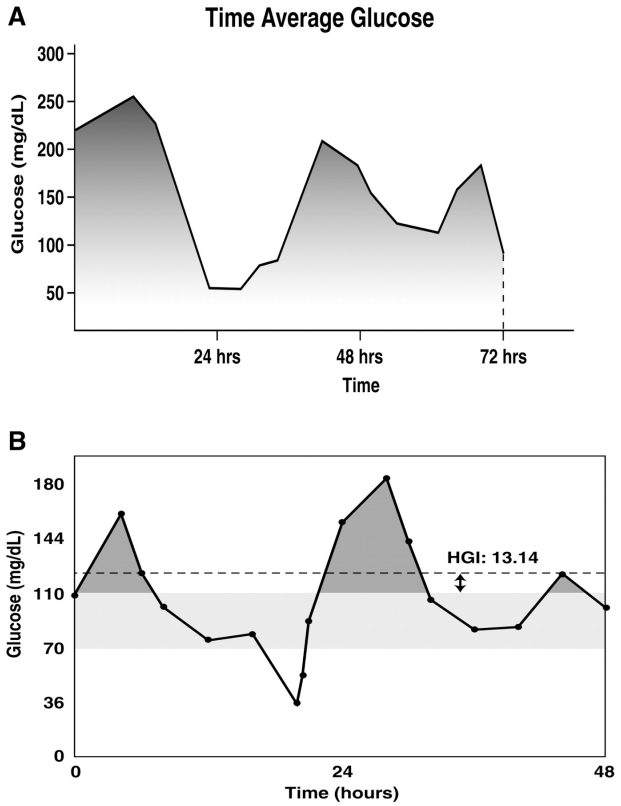


1957 patients with acute coronary syndrome

Admission hyperglycemia = strong risk factor for mortality

Impact of glycemia on mortality non-diabetic > diabetic patients

Glucometrics in Patients with Acute Myocardial Infarction
Kosiborod, M. et al., Kansas City, USA
Circulation 2008;117:1018-1027



16 871 patients with AMI

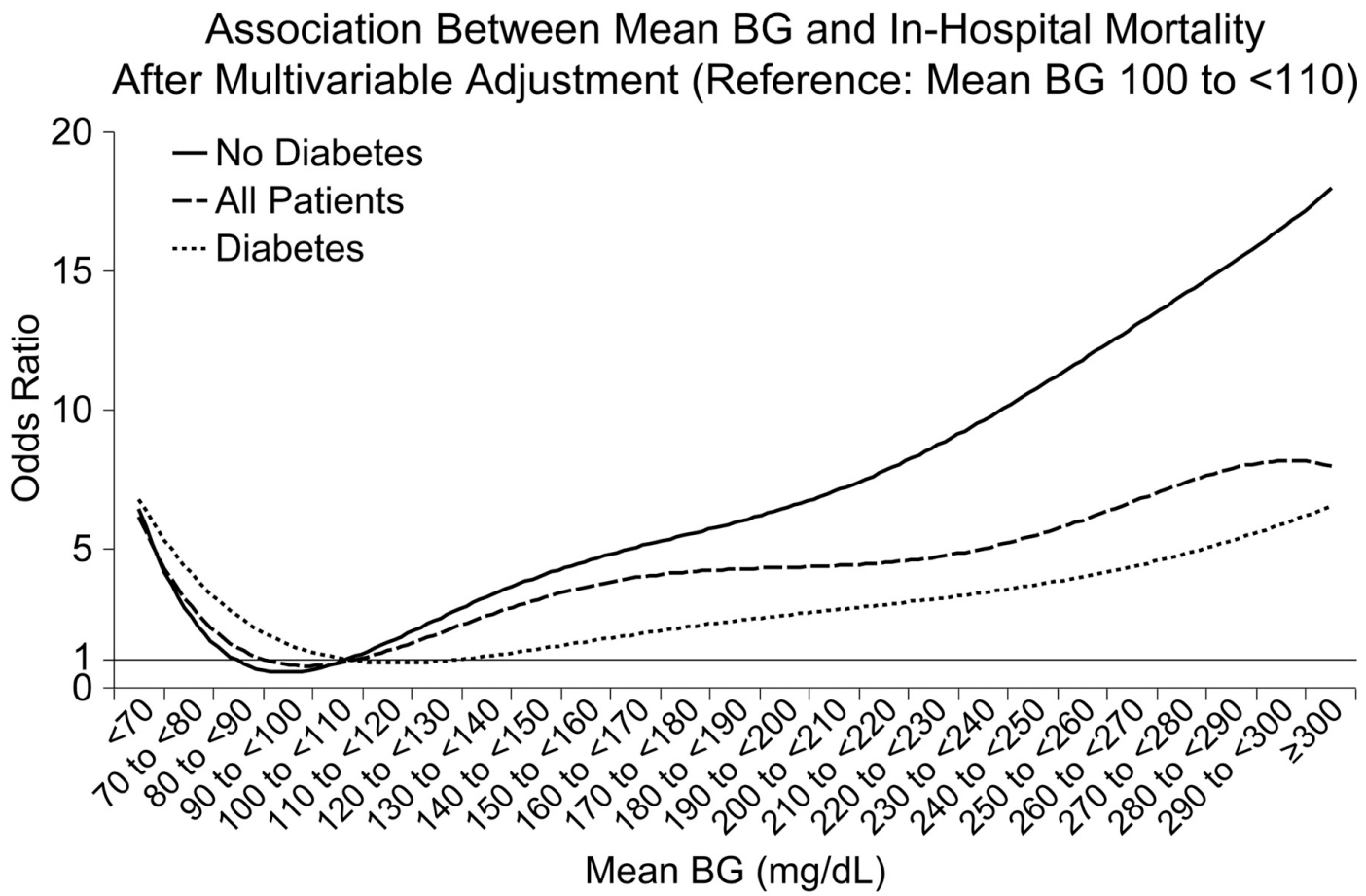
Admission hyperglycemia and glycemia during hospitalisation predicts mortality

Hospital glycemia is a better predictor

Hypoglycemia associated with adverse prognosis

Circulation

American Heart Association
Learn and Live

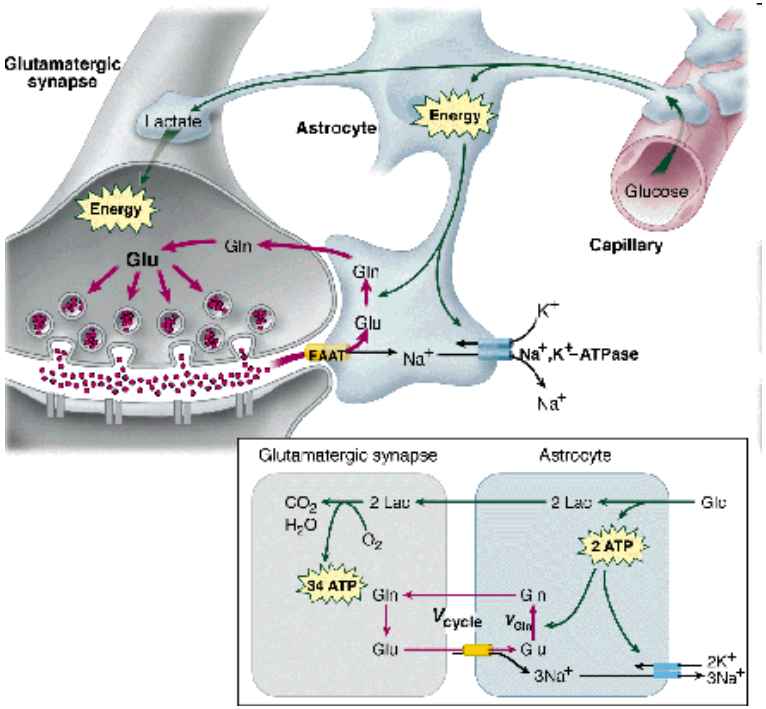


Kosiborod, M. et al. Circulation 2008;117:1018-1027

Circulation

Blood glucose control and the brain

- Glucose = obligatory substrate for the brain
- Brain glucose supply depends on glycemia (no substantial glycogen stores)
- Glucose diffusion from plasma to neurons and astrocytes (concentration-dependent)
- Brain energy deprivation and dysfunction occurs whith hypoglycemia



Magistretti et al,
Science, 1999, 283: 496-497

Admission blood glucose and short term survival in hemorrhagic stroke

Fogelholm et al, J Neurol Neurosurg Psychiatry 2005; 76 349-353

416 patients with acute intracranial hemorrhage

	Admission Blood Glucose (mmol/L)	
	Nondiabetics	**Diabetics**
Dead < 1 day	10.6 (0.7)	13.9 (4.0)
Dead 1-28 days	8.6 (0.4)	12.5 (1.3)
Alive > 28 days	6.8 (0.2)	9.3 (0.9)

Impact of TGC on cerebral glucose metabolism

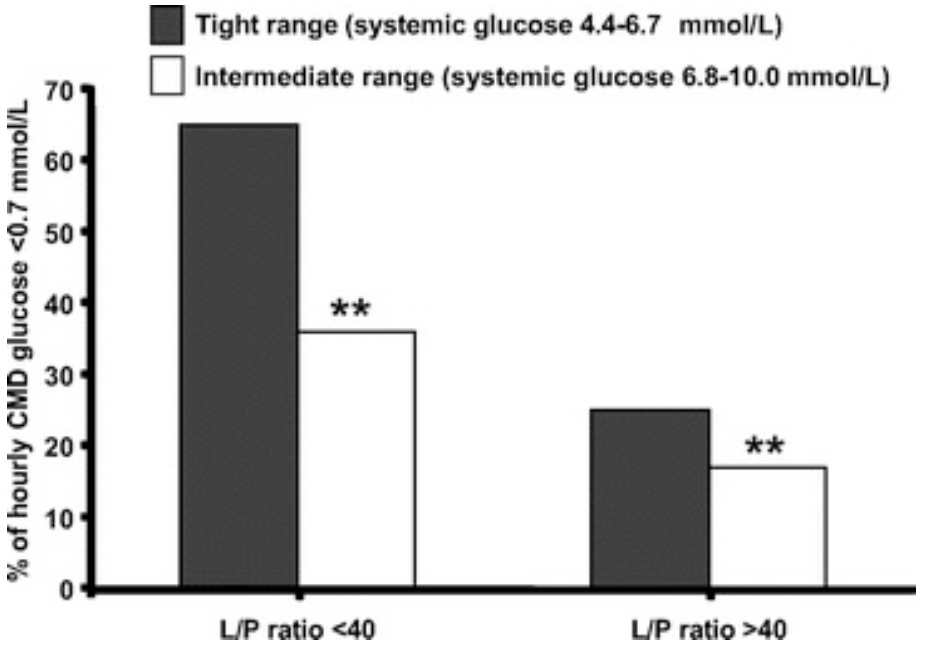
Oddo et al, Crit Care Med 2008;36:3233

20 patients with head trauma

TGC (target 80-120 mg/dl)

Brain glucose, lactate, and pyruvate monitored with microdialysis

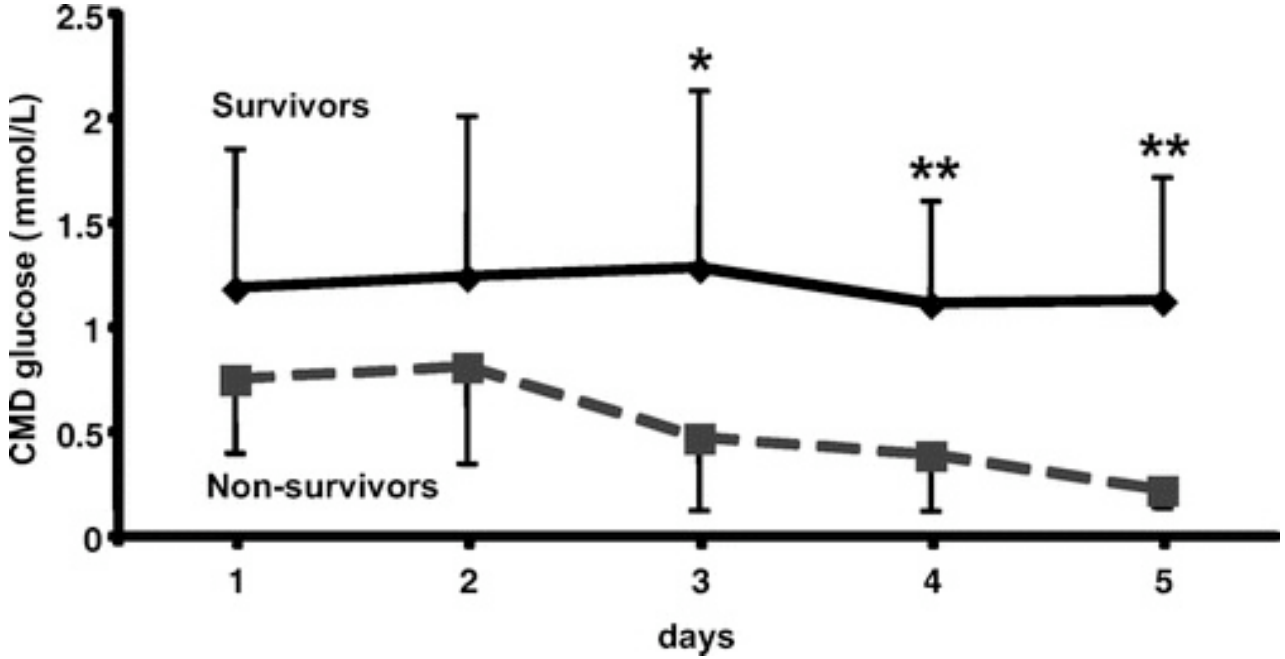
Brain energy crisis defined as:
« Brain glucose < 0.7 mmol/L
+ brain L:P ratio > 40 »



Blood glucose and insulin dose = predictors of brain energy crisis

Impact of TGC on cerebral glucose metabolism

Oddo et al, Crit Care Med 2008;36:3233



Brain energy crisis associated with increased mortality

Conclusions

- Contrôle glycémique bénéfique
- Cible: 80-150 mg/dl
- Hypoglycémies délétères
- Cave hypoglycémies c/o patients en neuro-réanimation et avec syndrome coronarien aigu (cible 100/110-150 mg/dl?)