

Hepatic dysfunction



Copotoiu SM



Functions of the liver

- **Metabolic**

- Carbohydrate metabolism \approx 100g of glycogen
- Protein & lipoprotein metabolism
- Metabolism of fatty acids (FA)
 - Triacylglycerol
 - Very low density lipoproteins (VLDL)
 - Partial oxidation of FA to ketone bodies
- Biotransformation of drugs
 - Phase I
 - oxidation, reduction, hydrolysis
 - ↻↑ hydrophilicity of drugs – some products may be pharmacologically active
 - » oxidation [cytochrome P450 (smooth endoplasmic reticulum)]
 - » Reduction, hydrolysis - cytoplasm
 - Phase II – glucuronidation, sulphation, acetylation
 - Cytoplasm
 - The majority are inactive compounds



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 - **Cytoplasm**
 - **The majority are inactive compounds**



Functions of the liver

- **Storage** of vitamins A, D, E and K, iron, copper and glycogen
- **Excretion** of bilirubin & urea formation
- **Immunological** functions
 - Synthesis of immunoglobulin
 - Phagocytic action of Kupffer cells – bacteria, viruses, endotoxins, immune complexes, denaturated albumine, thrombin, fibrin-fibrinogen complexes, tumour cells → lysosomes
- **Filtration** of bacteria & degradation of endotoxins



Functions of the liver

- **Haematological**

- Haematopoiesis in the fetus
- Blood reservoir:
 - 450 ml \approx 30ml/g of tissue
 - $\frac{1}{2}$ mobilized in **HYPOVOLEMIA**

- **Bile production**

- 1000ml/day concentrated to 1/5
- Consists of
 - Electrolytes
 - Protein
 - Bilirubin
 - Bile salts – emulsification of dietary fats, absorption of fat soluble vitamins
 - Bile acids (cholic & chenodeoxycholic) conjugate with glycine or taurine \rightarrow bile salts
 - Lipids



Liver and kidney

- **Urea synthesis**

- Amino acid (aa) degradation → ammonia NH_3 toxic
>1 $\mu\text{g}/\text{mL}$ → urea – elimination
- 100g of protein → \approx 30g of urea
- 1 molecule of urea → $2\text{H}^+ \approx 1000$ mmol/day

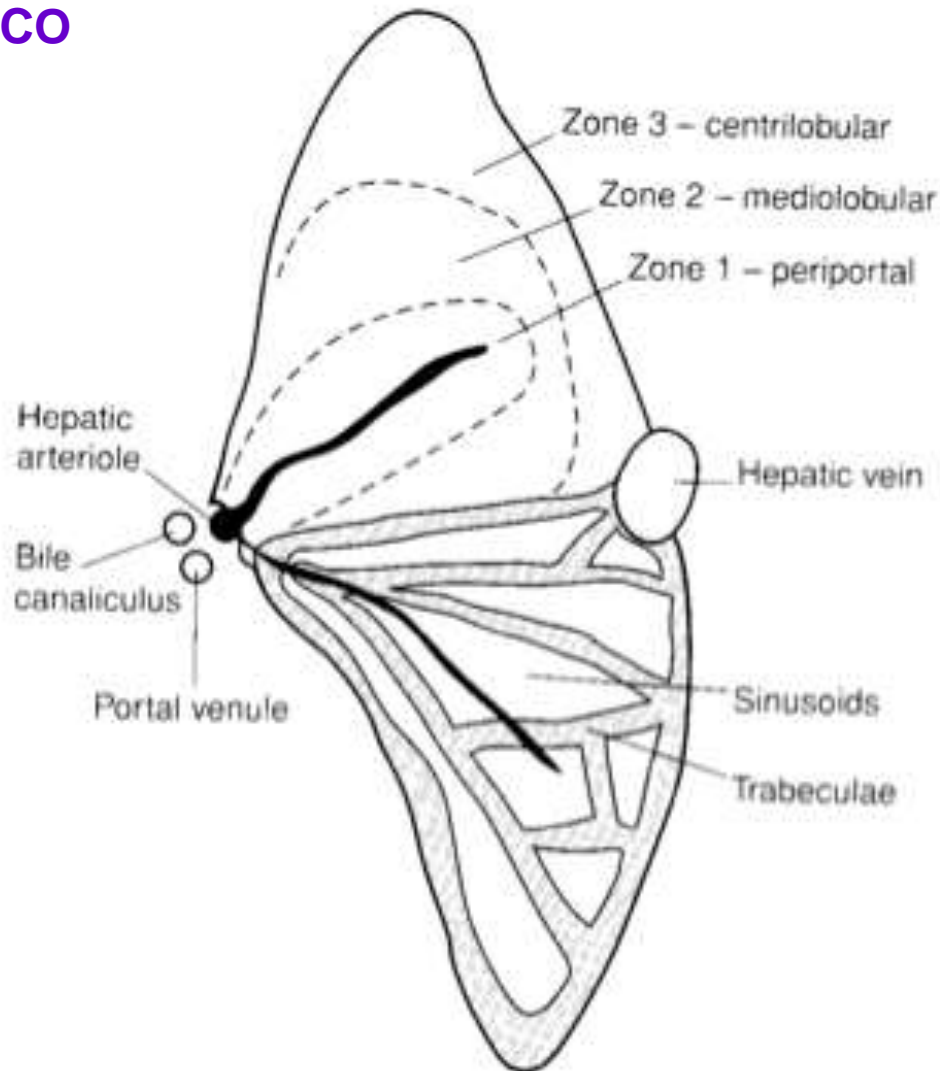
- **Creatinine synthesis**

- Liver: from methionine, glycine and arginine
- Muscle: phosphorylation → phosphocreatine (back-up energy store for ATP production) → creatinine – excreted at a relatively constant rate in urine

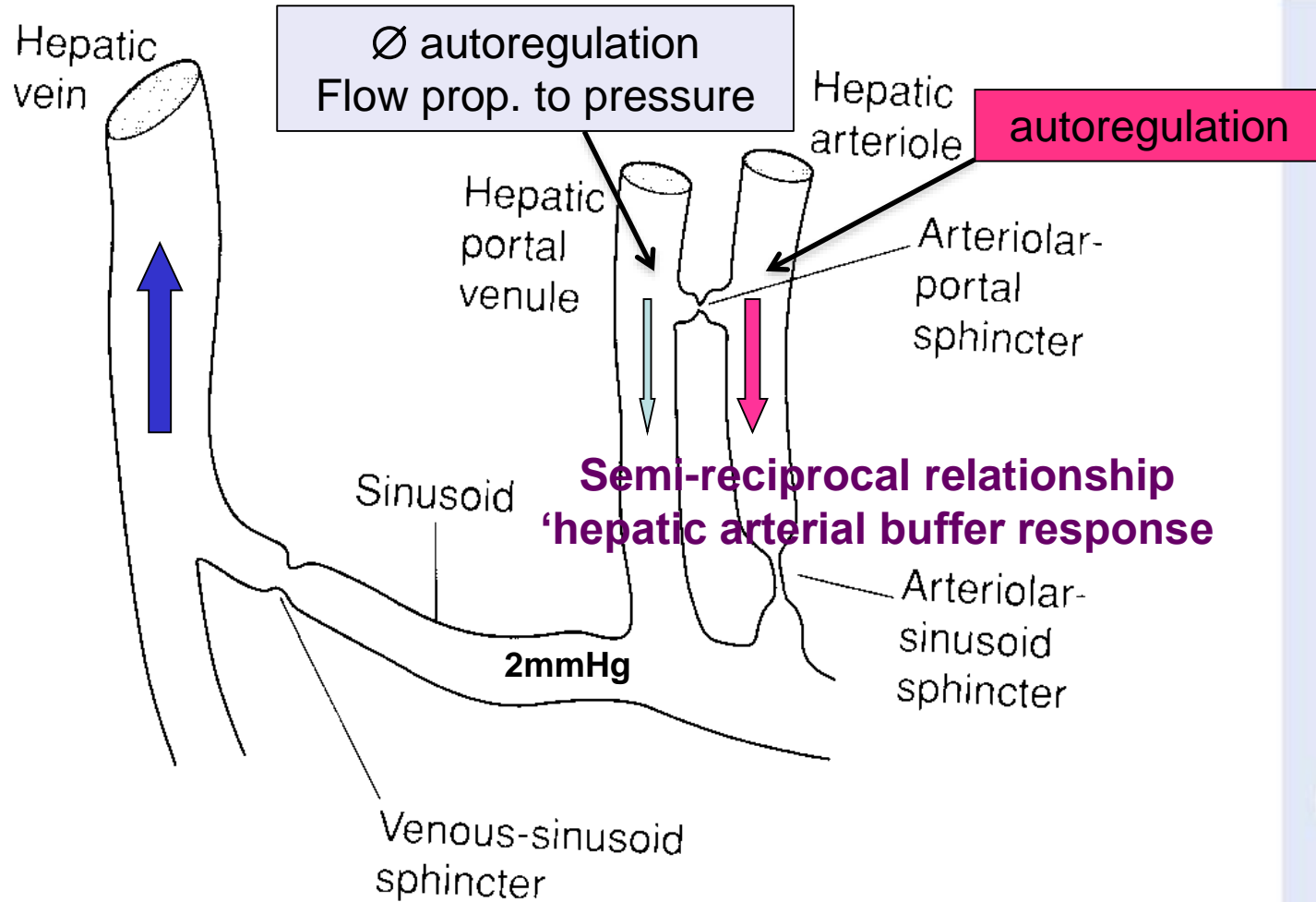


The blood supply of the acinus

25% of CO



The microcirculation system of the liver



Acute liver failure (ALF) - Definition

- Rapid evolving severe hepatic dysfunction
- No previous history of underlying liver disease
- Occurrence of encephalopathy within 8 (UK) / 4 (international) weeks after onset of symptoms
- ⑩ ↑ bilirubin
- Severe coagulopathy

**4th cause of death in USA for 45-54ys old pts
– after cancer, cardiac disease and trauma**



Fulminant hepatic failure (FHF)

Subclassification depending on the interval
between jaundice and HE

- **Hyperacute:** 0-7 days
- **Acute:** 8-28 days
- **Subacute:** 29-72 days
- **Late onset:** 56-182 days



Etiology

- Drug injury
- Viral
- Toxins
- Vascular
- Miscellaneous
 - AFLP (acute fatty liver of pregnancy)
 - HELLP
 - autoimmune



Gordolobo tea pyrrolizidine alkaloids→veno-occlusive disease



Comfrey pyrrolizidine alkaloids → veno-occlusive disease

ass year; block root; black wort



Chinese herbal tea



Jin Bu Huan

Lycopodium serratum, fern **acute hepatitis, steatosis**



Germander toxic: Teucrin A

Hepatitis



Chaparral leaf *Larrea tridentata*: necrosis chronic hepatitis



Natural laxatives, senna, podophyllin → ↑ aminotransferases



Dai-saiko-to & Sho-saiko-to Scutellaria

hepatitis, fibrosis, steatosis



Kava-kava kavalactones Hepatitis



- Piper methysticum



Mistletoe, skullcap, valerian → hepatitis



Herbal remedies

- Most reactions are idiosyncratic
- Treatment: discontinue herbal medication
- Do not rechallenge
- Monitor liver enzymes + liver biopsy if not normalized within several weeks



Clinical features

- Encephalopathy – grade 1-4
- Jaundice
- Hepatomegaly
- Ascites
- Vascular
- Vital signs: ↓BP (hyperdynamic and low vascular peripheral resistance), hyperventilation, metabolic derangements

Mortality: 50-80%



Laboratory findings

- ⑩ ↑↑↑ INR, aPTT
- ⑩ ↑↑↑ bilirubin
- ⑩ ↑↑↑ ALT, AST
- ⑩ ↑, ↑↑ LDH
- Late renal abnormalities
- ⑩ ↑ Cr – direct toxic effects of acetaminophen, liver ischemia



Unknown etiology

Search for IgM, Atg, Ac – viral hepatites



Prognostic criteria used for liver transplantation – King's College

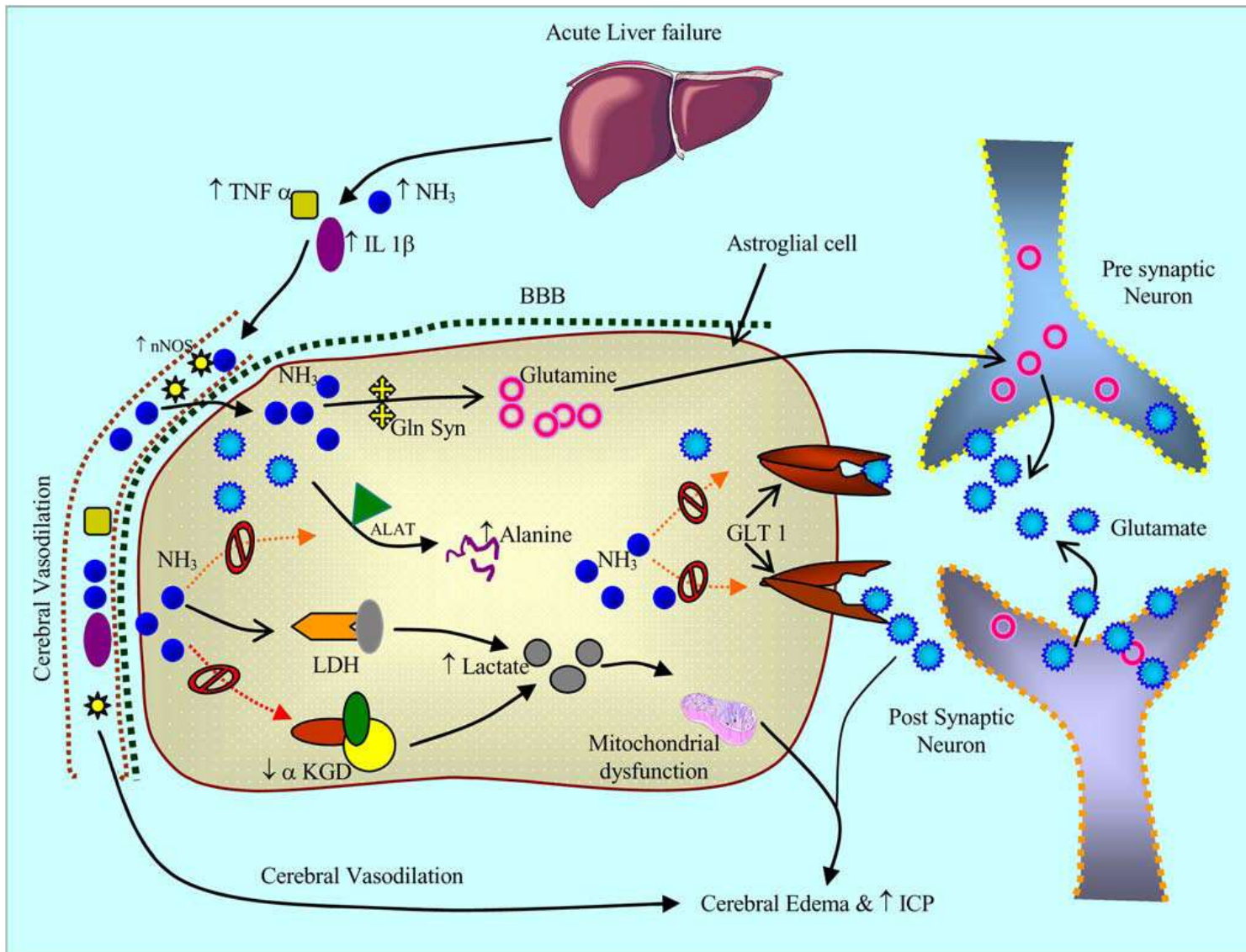
Acetaminophen overdose	Non-acetaminophen liver injury
Arterial pH < 7.3 (irrespective of grade of encephalopathy) OR	PT > 100 sec (INR > 6.5) (irrespective of grade of encephalopathy) OR any three of the following
PT > 100 sec (INR > 6.5)	<ul style="list-style-type: none">• Age < 10 or > 40 years• Non-A, non-B, halothane hepatitis, idiosyncratic drug reactions• Jaundice > 7 days before onset of encephalopathy• Serum bilirubin > 17.4 mg/dL (>300 μmol/L)• PT > 50 sec
Serum creatinine > 3.4 mg/dL (>300 μmol/L)	
Grade III and IV hepatic encephalopathy	

Complications

- **Neurological** – encephalopathy, cerebral edema
- **Cardiovascular** and hemodynamic
- **Respiratory**
- **Coagulation**: excessive thrombosis, DIC
- **Renal**
- **Acid-base derangements**: lactic acidosis, alkalosis
- **Metabolic derangements**: hypoglycemia, hyponatremia, hypokalemia, hypophosphatemia
- **Bacterial & fungal infections**



Cerebral edema in FHF



Interventions for cerebral edema and intracranial hypertension

General measures

- Head of bed elevation to 30° angle, pts neck in neutral position
- ETT for grade III or IV HE **GCS ≤ 8**
- Minimize tactile and tracheal stimulation
- Avoid hypovolemia & hypervolemia
- Avoid hypertension
- Avoid hypercapnia & hypoxemia
- Monitor & maintain **ICP < 15 mmHg**
- Maintain **CPP > 50 mmHg**



Interventions for cerebral edema and intracranial hypertension

Management of intracranial hypertension

- Mannitol boluses: 0.5-1.0 g/kg (if osmolarity <320mOsm/l)
- Hyperventilation: PaCO₂ 28-30 mmHg
- Induced moderate hypothermia: 32-33° C
- Na levels: 145-155 mEq/L
- Induced coma with propofol/pentobarbital
- CVVH for oliguria and hyperosmolarity (>310 mOsm/L)



Hepatorenal syndrome

Renal vasoconstriction in the setting of systemic and splanchnic arterial vasodilation in patients with advanced cirrhosis

- 18% within 1 year of diagnosis of advanced cirrhosis
- 40% at 5 years

HRS type 1	HRS type 2
<ul style="list-style-type: none">• Rapid deterioration in kidney function• Scr increasing by more than 100% from baseline to greater than 2.5 mg/dL within a 2 week period• Untreated – median survival 2 weeks	<ul style="list-style-type: none">• Patients with refractory ascites• Steady but moderate degree of functional renal failure (< 1.5 mg/dL) or• Deterioration in kidney failure that does not fulfill the criteria for HRS type 1• Untreated – median survival 4-6 months



Hepatorenal syndrome

Major diagnostic criteria - International Ascites Club

- Cirrhosis with ascites
- Creatinine > 1.5 mg/dL
- No improvement of serum creatinine after at least 2 days of diuretic withdrawal and volume expansion with albumine (1g/kg of body weight per day, max of 100g/day)
- Absence of shock
- No current or recent treatment with nephrotic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria (> 500 mg/day), microhematuria (> 50 RBC/high power field) and/or abnormal renal ultrasonography



Hepatorenal syndrome

Evaluation of renal function

- Serum creatinine measurements should be used to evaluate renal function until more reliable methods of measuring become generally available
- **GFR** derived equations should be used cautiously since they tend to overestimate GFR
- Classify **AKI** according to RIFLE criteria
- Acute on **CKD**
 - ↳ \uparrow Scr ≥ 0.3 mg/dL in less than 48h **or**
 - ↳ \uparrow Scr $\geq 50\%$ from baseline **or**
 - Baseline GFR < 60 ml/min (MDRD) for > 3 months



Hepatorenal syndrome Management

Treat the underlying etiology with

- Liver transplantation
- Combined liver-kidney transplantation

3 years survival 60%



Hepatorenal syndrome

Management

- Hemodynamic monitoring for fluid management
 - Prevent relative renal hypoperfusion
 - Maintain an effective circulating volume
 - Renal perfusion pressure
- HRS type 1 – allow survival to transplantation
 - **evaluation after 4 days**
 - Ø in nonresponders (no decrease Scr < 1.5 mg/dL)
 - Albumine
 - 1g/kg for 2 days (max 100mg/day)
 - 20-40g/day + vasoconstrictor



Hepatorenal syndrome

Management

HRS type 1

- Vasoconstrictor
 - CI
 - Ischemic heart disease
 - Peripheral vascular disease
 - Cerebrovascular disease

Drug	Dose	Goal	Duration
Terlipressin	0.5-2.0 mg IV every 4-6 h with stepwise dose increment every few days up to 12 mg/day	Scr decrease to < 1.5 mg/dL in two measurements	Min 3-5 d Max 14 d
Vasopressin	0.01-0.8 U/min	MAP ↑ 10 mmHg from baseline or MAP > 70 mmHg	
Noradrenaline	0.5-3 mg/h	MAP ↑ 10 mmHg	
Midodrine + Octreotide	7.5-12.5 mg PO TID 100-200 µg sc TID or Bolus 25 µg + 25 µg/h	MAP ↑ 15 mmHg	outpatient

Hepatorenal syndrome Management

•HRS type 1

- TIPS (Transjugular Intrahepatic Portosystemic Shunt)
 - CI
 - Severe liver failure
 - » Bilirubin > 5 mg/dL
 - » INR > 2
 - » Child-Pugh score > 11
 - » HE
 - Severe cardiopulmonary disease

•HRS type 2

- Vasoconstrictor
 - Midodrine + octreotide
- TIPS – refractory ascites which require large-volume paracentesis

RRT for transplant candidates
Artificial liver support for research protocols



Hepatorenal syndrome

Prevention

- **SBP !!!!!**
 - Albumin (1.5 g/kg IV at infection diagnosis and 1 g/kg 48 h later) + cefataxim
 - Oral prophylaxy with norfloxacin
 - Pentoxifylline 400 mg TID to pts with severe acute alcoholic hepatitis



Hepatopulmonary syndrome

**Abnormal oxygen exchange
+
intrapulmonary vascular dilatation
in pts with liver disease**

Clinical features

- Dyspnea
- Platypnea – relieved when lying down
- Orthodeoxia – hypoxia worse in the standing position (corrected with supplemental oxygen)



Hepatopulmonary syndrome

- **Pathophysiology**
Functional excess of pulmonary vasodilators **NO**
- **Prevalence**
Depends on diagnosis
- **Prognosis**
- **Diagnosis ??????**
- **Therapy**
Liver transplantation – the only effective therapy

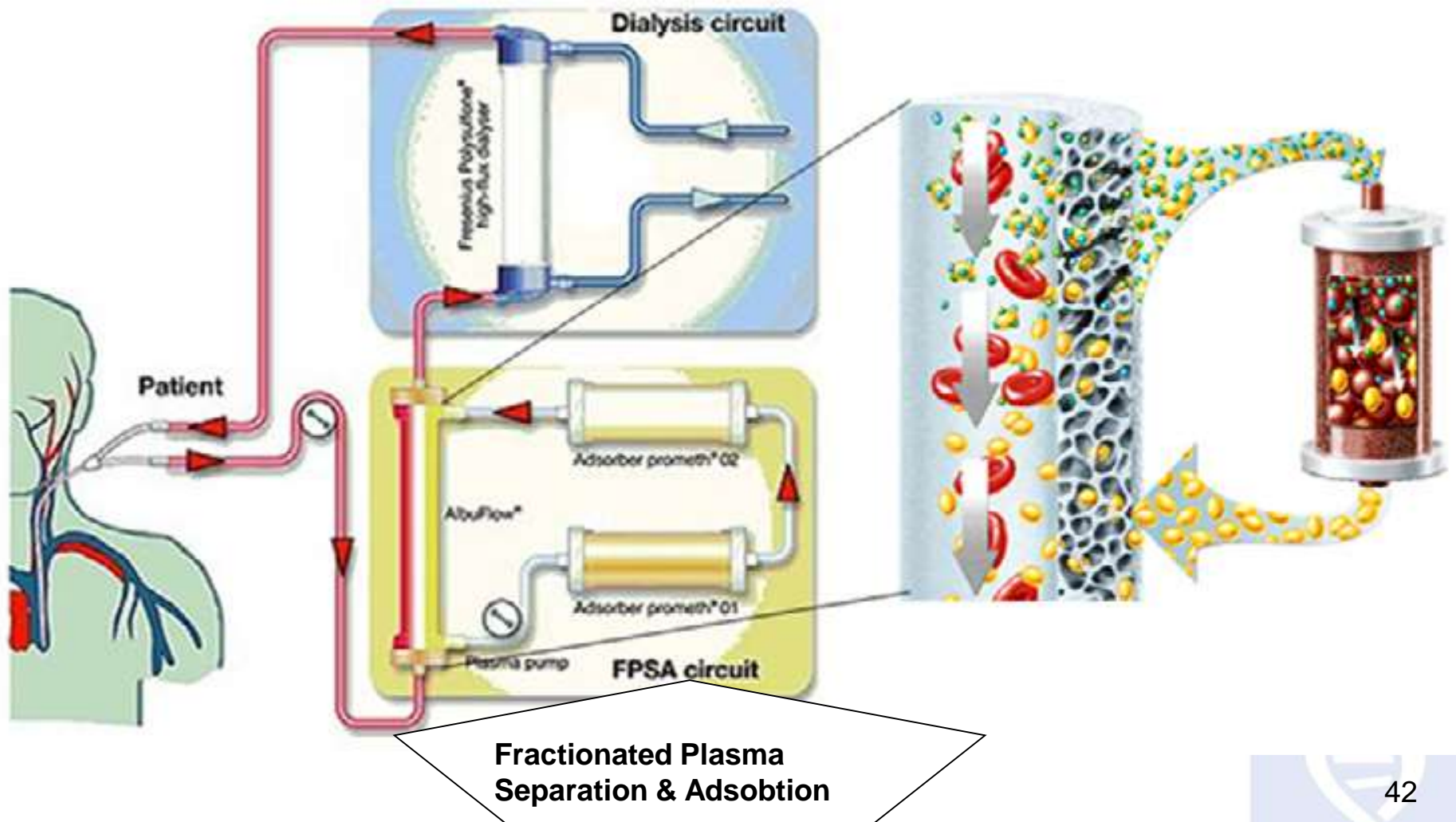


Device management

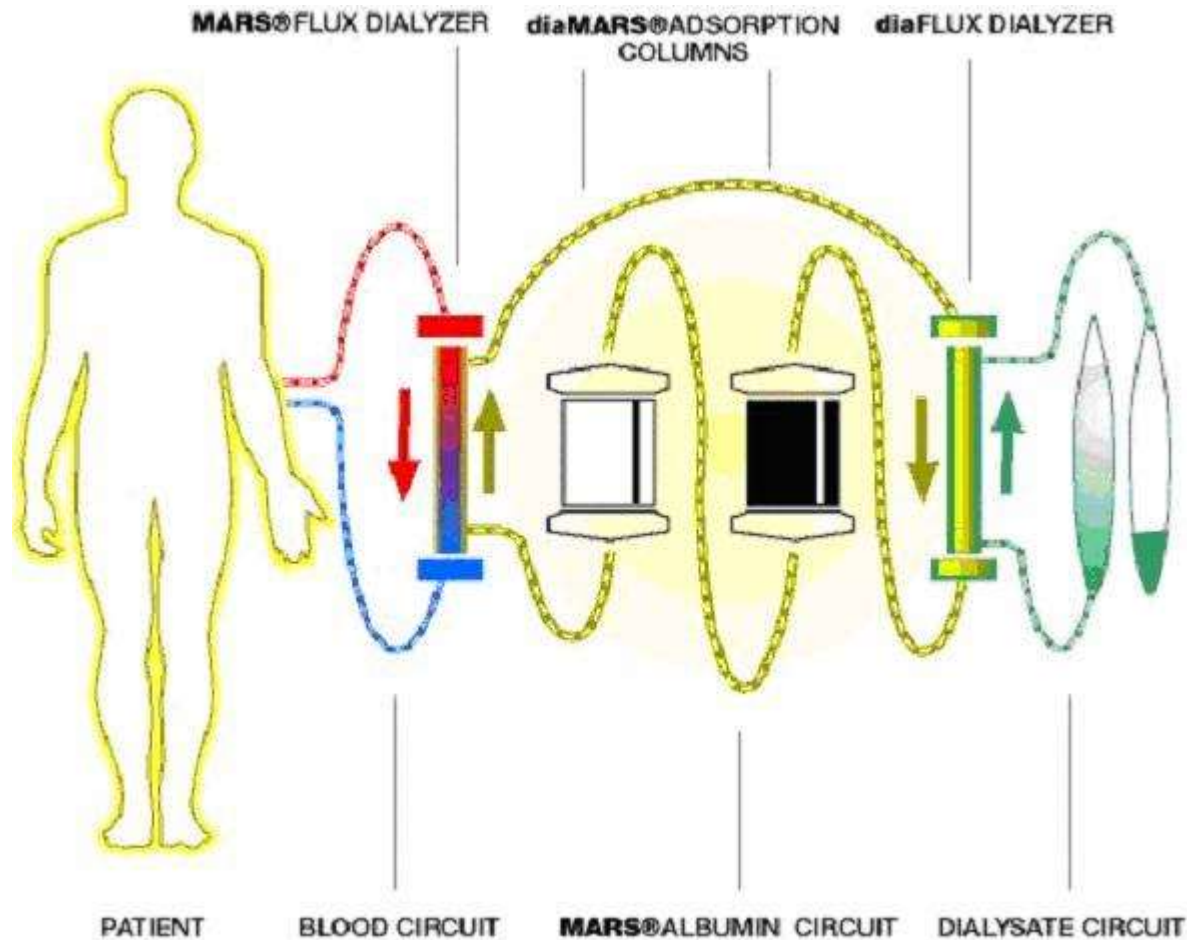
- **Prometheus**
- **Mars (Molecular Adsorbents Recirculation System)**



Prometheus



MARS



Monitoring liver function

Motivation

- **Change in management**
- **Risc stratification**
- **Prognostic value**



Synthesis

- Albumin
 - ↻ ↓ sensibility
 - T1/2 20 days
 - Influenced by
 - Nutritional status
 - Renal function
- PT
 - ↻ ↓ synthesis
 - ↻ ↓ vit K absorbtion (bile obstruction, cholestasis)



Liver failure and ICU

Austrian study – 40000 pts

- At admission 10-25%
- Developed in ICU 15%

Krenn Claus G. Bedside assessment of hepatic function and functional reserve – the time has come for all!



Liver – still in transition?

Open Access

Research

Liver dysfunction after lung recruitment manoeuvres during pressure-controlled ventilation in experimental acute respiratory distress

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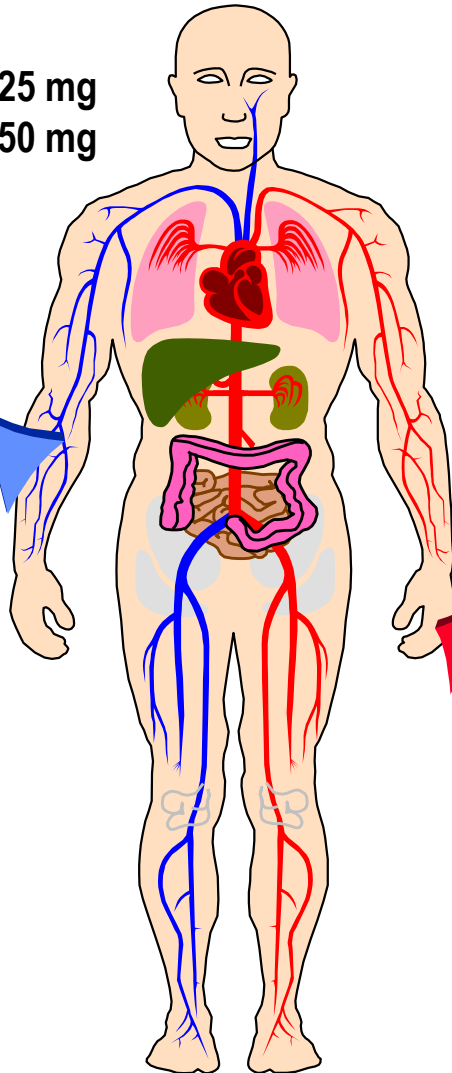


PULSION LIMON

***Non-invasive
liver function monitoring***

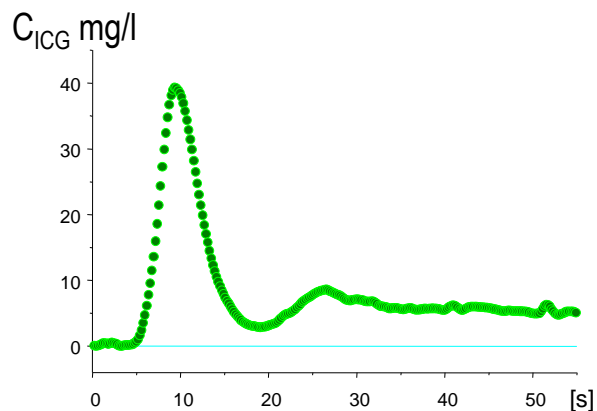
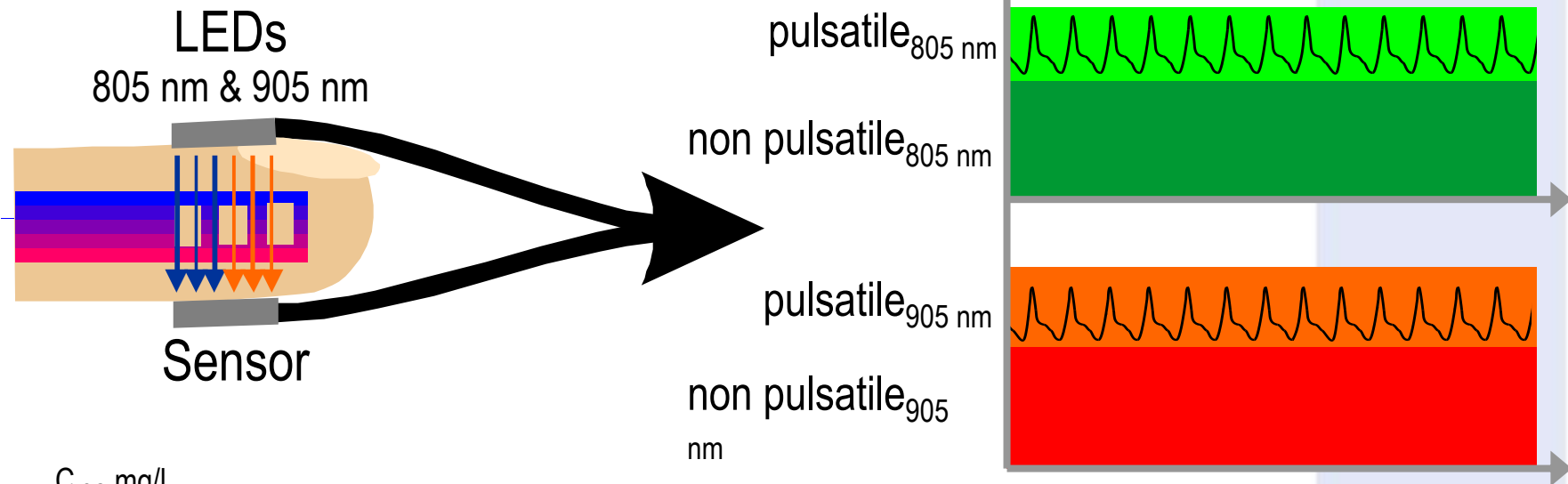


PICG0025 ICG-PULSION 25 mg
PICG0050 ICG-PULSION 50 mg

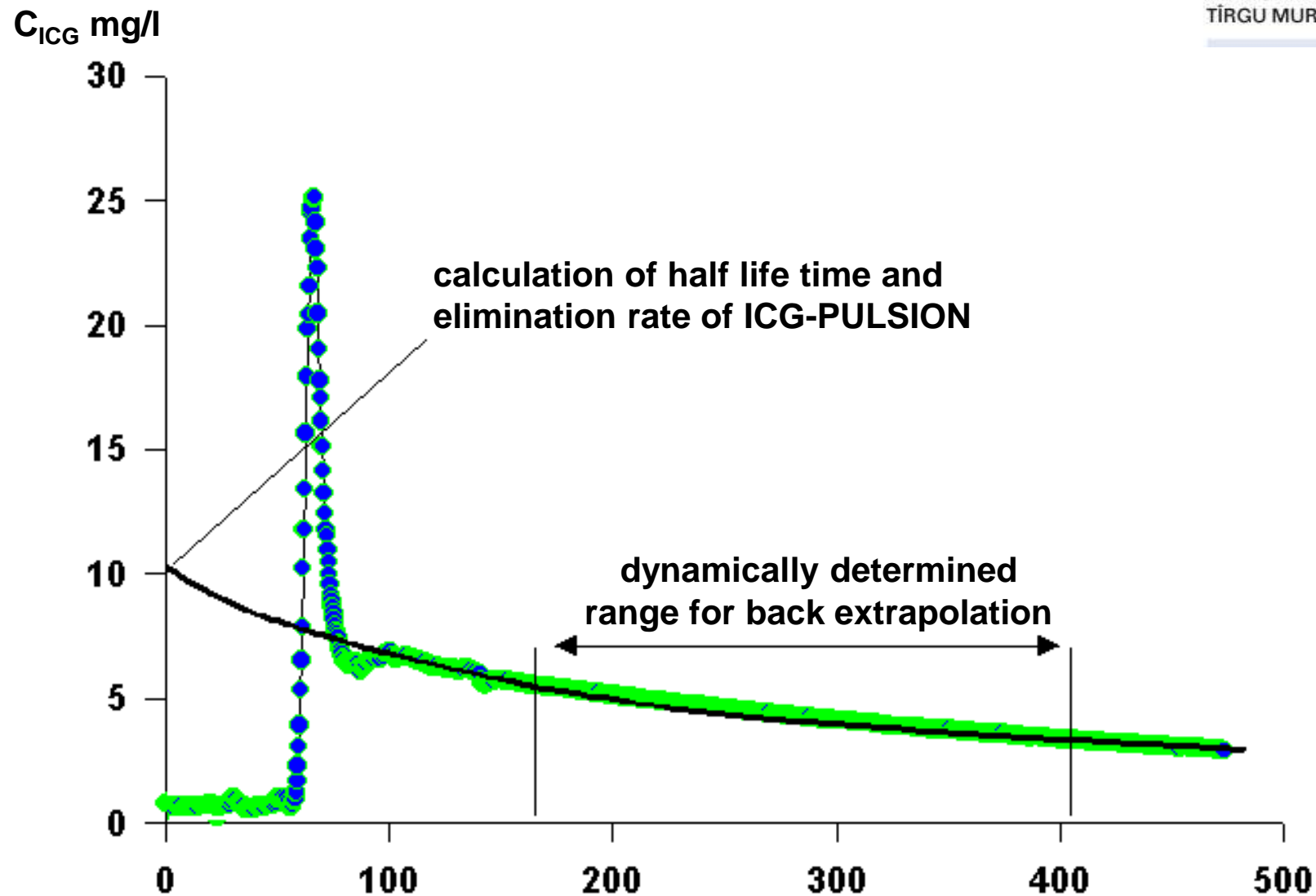


PC5000 LiMON

- PC50150 LiMON reusable sensor for adults and infants**
- PV50100 LiMON disposable sensor for adults and infants**
- PV50200 LiMON disposable sensor for neonates**



$$C_{ICG} = \frac{\frac{\text{pulsatile}_{905 \text{ nm}}}{\text{non pulsatile}_{905 \text{ nm}}}}{\frac{\text{pulsatile}_{805 \text{ nm}}}{\text{non pulsatile}_{805 \text{ nm}}}}$$



Global liver from elimination of ICG - PULSION

**Plasma Disappearance Rate of ICG
(%/min)**

- **ICG Retention Rate after 15 min**
- **ICG Clearance
(ml/min)**

- **Circulating Blood Volume**

Pulse oximetry

- **Oxygen Saturation**
- **Heart Rate**

PDR

R15 (%)

CB

BV (ml)

SpO2 (%)

HR (bpm)



Basics

- The Plasma Disappearance Rate of ICG-PULSION (PDR) is influenced by **liver function and liver perfusion.**
- Changes of ICG-PDR within a short period of time are reflecting liver respectively splanchnic perfusion, as the function of liver cells does not change rapidly.
- LiMON provides an easy, fast and non-invasive monitoring of liver and splanchnic perfusion.



Variables

<u>Parameter</u>	<u>Calculation</u>	<u>Normal Range</u>
PDR (%/min)	$\ln 2 / t_{1/2} \bullet 100$	18 – 25
R15 (%)	$C_{\text{ICG}15\text{m}} / C_{\text{ICG } t=0} \bullet 100$	0 – 10
CBI (ml/min/m²)	$BV \bullet PDR / BSA$	500 – 750
BVI (ml/m²)	$[ICG]_{\text{inj}} / C_{\text{ICG } t=0} / BSA$	2600 - 3200

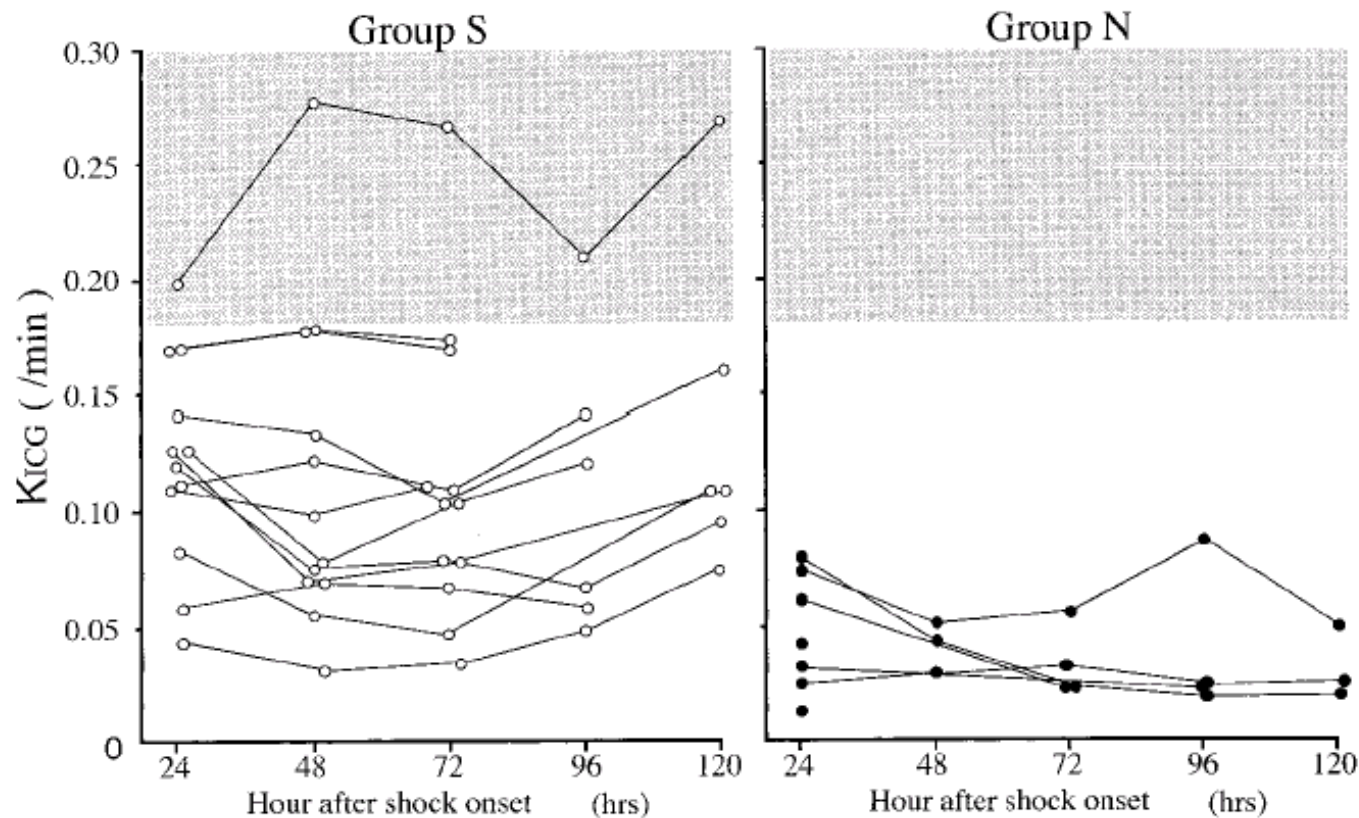


Indications

- **All critically patients, especially those with sepsis, acute liver or multi-organ failure, and after multiple trauma**
- **Patients with chronically reduced hepatic function (hepatitis, liver cirrhosis)**
- **Evaluation of liver function in organ donors and recipients**
- **Monitoring of liver function during liver or abdominal surgery (resection, porto-caval shunt)**
- **Diagnosis and monitoring of congenital liver failure in children and neonates**



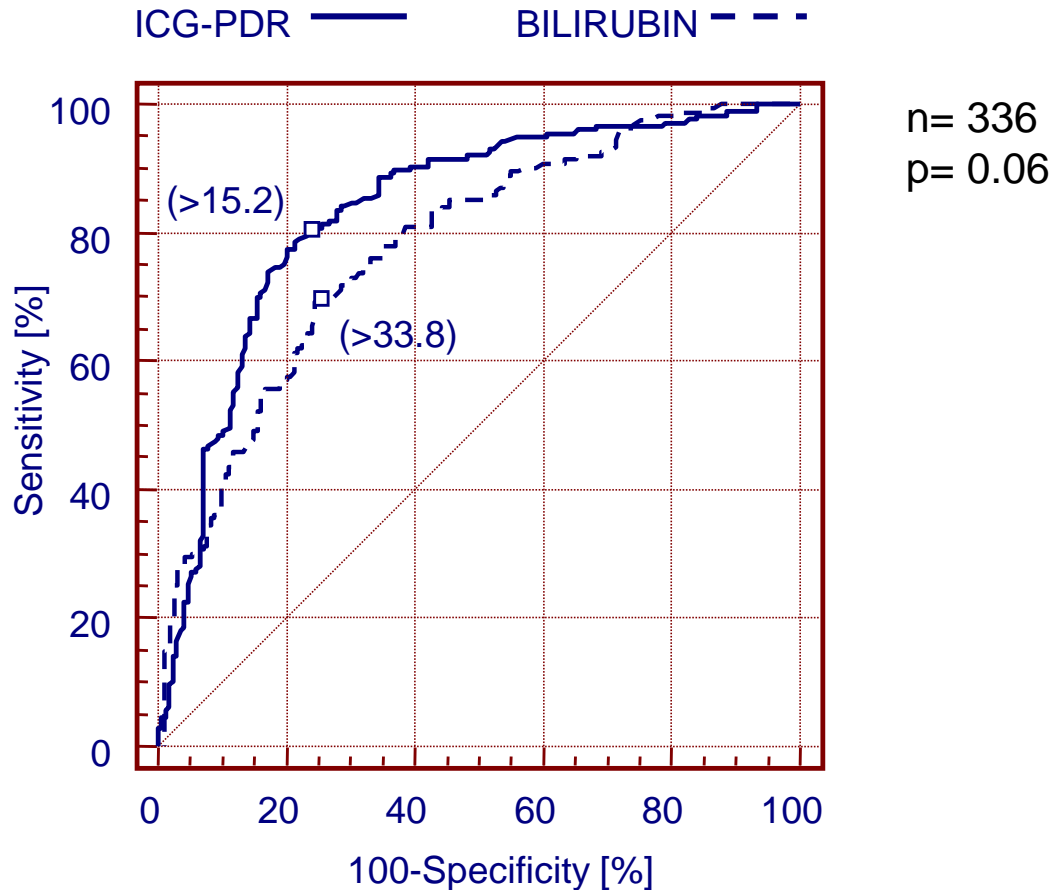
Prognosis of survival in septic ICU patients



Conclusion: Increase of reduced ICG elimination during the first 120 hours of septic shock predicts survival, whereas no change or even further decrease of ICG elimination predicts non-survival

Value as liver function test in intensive care

Higher sensitivity and specificity than bilirubin



Hepatic failure key points

- Distinguished from severe acute hepatitis by the presence of HE. Without liver transplantation, the mortality rate is 50% to 80%.
- Intentional/accidental acetaminophen overdose - the dominant cause of FHF in Western countries.
- Hepatotoxic effects are potentiated by concurrent alcohol ingestion, glycogen depletion and/or anticonvulsant medications.



Hepatic failure key points

- The King's College Criteria remain the most widely used prognostic scoring system for FHF; failure to fulfill the criteria does not reliably predict survival.
- Transjugular liver biopsy – determines prognosis based on the amount of hepatic necrosis (70% necrosis is discriminant of 90% mortality).
- The onset of grade III or IV HE is an indication for endotracheal intubation and the performance of diagnostic and therapeutic modalities for ICP.



Hepatic failure key points

- Intracranial hypertension is the major cause for early mortality.
- Prophylactic administration of FFP does not improve survival and may aggravate volume overload and cerebral edema
- CVVH – preferred method for artificial renal replacement
- Liver transplantation is the only proven liver replacement therapy to reduce mortality.

