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Hepatic dysfunction

Copotoiu SM

Functions of the liver

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- Metabolic
  - Carbohydrate metabolism ≈ 100g of glycogen
  - Protein & lipoprotein metabolism
  - Metabolism of fatty acids (FA)
    - Triacylglycerol
    - Very low densiy 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 [cytocrome P450 (smooth endoplasmic reticulum)]
        - » Reduction, hydrolisys - cytoplasm
    - Phase II – glucuronidation, sulphation, acetylation
      - Cytoplasm
      - The majority are inactive compounds

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    - **Phase II – glucuronidation, sulphation, acetylation**
      - **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

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- **Haematological**
  - Haematopoesis in the fetus
  - Blood reservoir:
    - 450 ml ≈ 30ml/g of tissue
    - ½ mobilized in **HYPOVOLEMIA**

- **Bile production**
  - 1000ml/day concentrated to 1/5
  - Consists of
    - Electolytes
    - Protein
    - Bilirubin
    - Bile salts – emulsification of dietary fats, absorbtion of fat soluble vitamins
    - Bile acids (cholyc & chemodeoxycholic) conjugate with glycine or taurine ➔ bile salts
    - Lipids

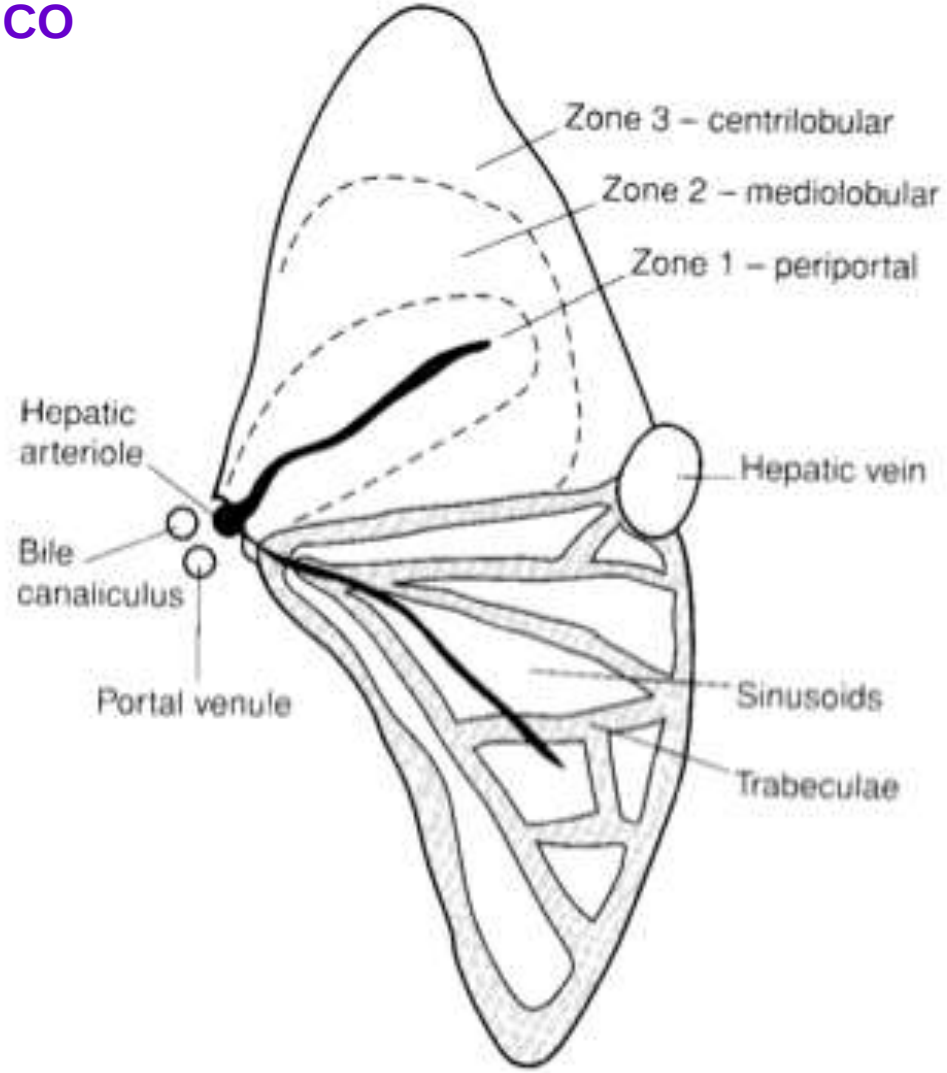
Liver and kidney

- **Urea synthesis**
  - Amino acid (aa) degradation ➔ ammonia **NH_3** toxic >1µg/mL ➔ urea – elimination
  - 100g of protein ➔ ≈ 30g of urea
  - 1 molecule of urea ➔ $2H^+$ ≈ 1000 mmol/day

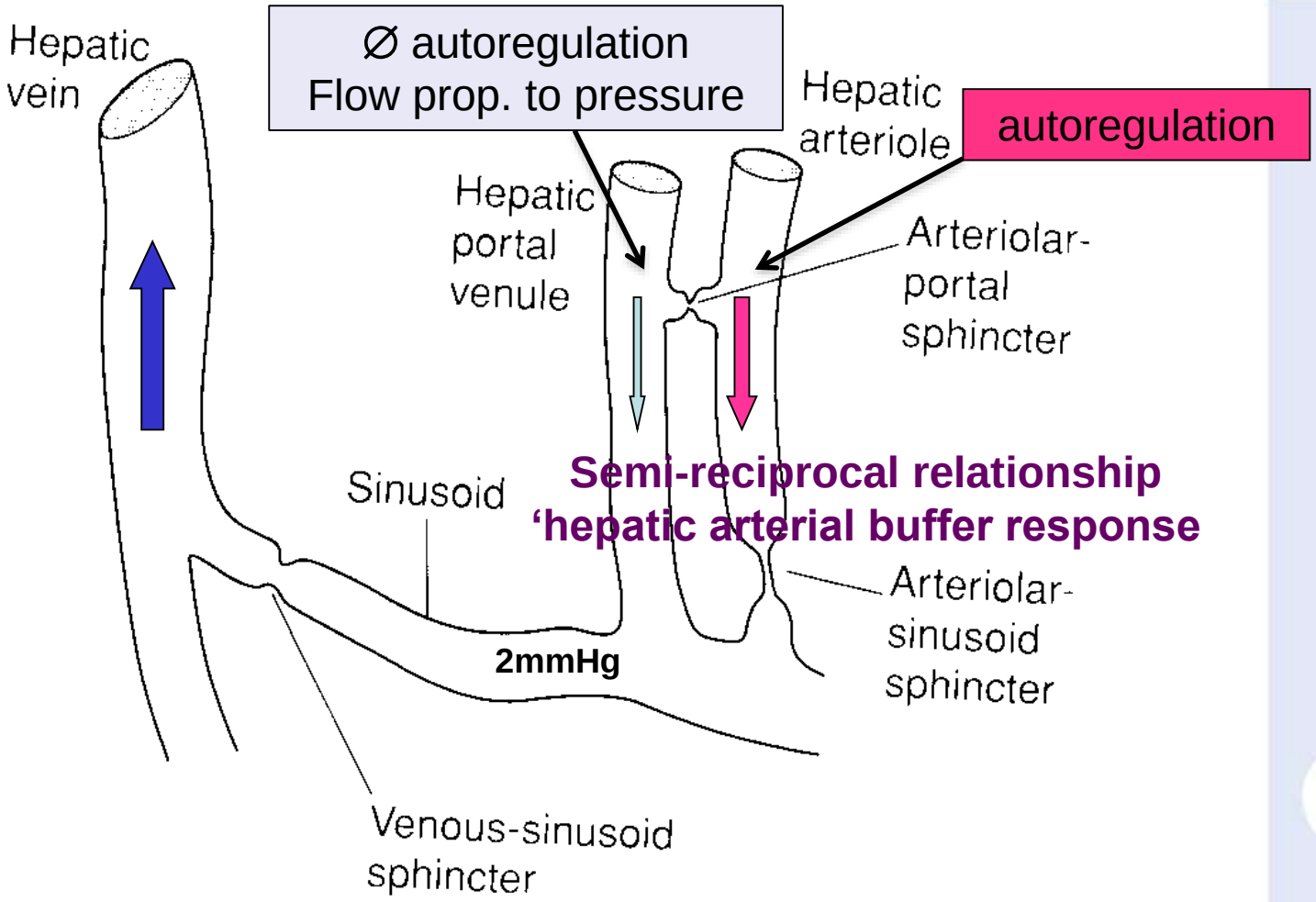
- **Creatinine** synthesis
  - Liver: from methionine, glycine and arginine
  - Muscle: phosphorilation ➔ phosphocreatine (back-up energy store for ATP production) ➔ creatinine – excreted at a relatively constant rate in urine

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**
- **Occurence 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

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- 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

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

Unknown etiology

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Search for IgM, Atg, Ac – viral hepatites

Prognostic criteria used for liver transplantation – King's College

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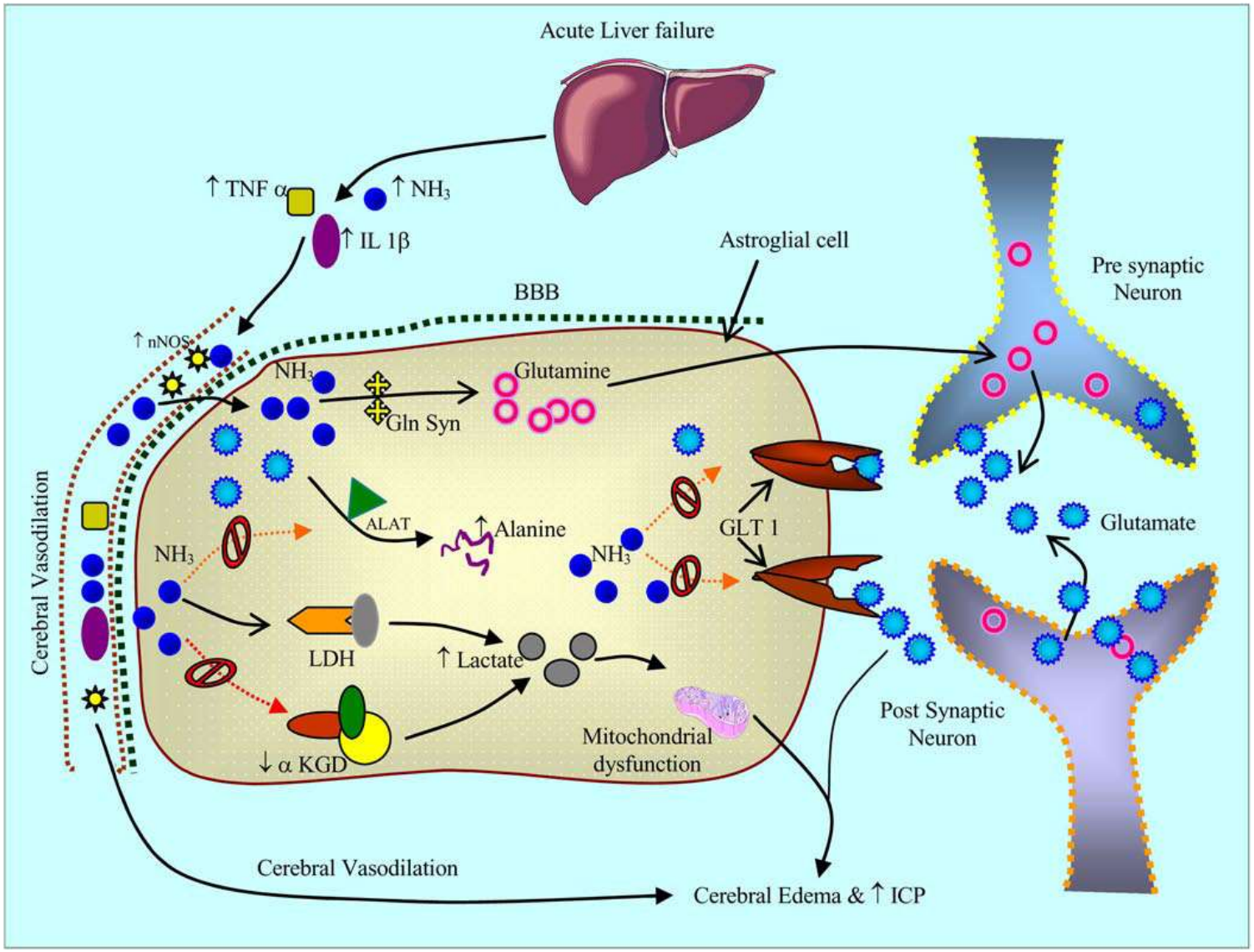
Acetaminophen overdose	Non-acetominophen liver injury
Arterial pH < 7.3 (irrespective of grade of encephalopathy) ***OR***	PT > 100 sec (INR > 6.5) (irrespective of grade of encephalopathy) ***OR any three of the following***
PT > 100 sec (INR > 6.5)	• Age < 10 or > 40 years • Non-A, non-B, halothane 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

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General measures

- Head of bed elevation to 30° angle, pts neck in neutral position
- ETT for grade III or IV HE **GCS≤8**
- Minimaze 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

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Management of intracranial hypertension

- Mannitol boluses: 0.5-1.0 g/kg (if osmolarity <320mOsm/l)
- Hyperventilation: $PaCO_2$ 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
• ***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	• Patients with ***refractary 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

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Major diagnostic criteria - International Ascites Club

- Cirrhosis with ascites
- Creatinine > 1.5 mg/dL
- No improvement od 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

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- 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**
  - ↑ Scr ≥ 0.3 mg/dL inless than 48h ***or***
  - ↑ Scr ≥ 50% from baseline ***or***
  - Baseline GFR < 60 ml/min (MDRD) for > 3 months

Hepatorenal syndrome Management

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Treat the underlying etiology with

- Liver transplantation
- Combined liver-kidney transplantation

3 years survival 60%

Hepatorenal syndrome Management

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- 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**
    - ∅ 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

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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

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- 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 – refractary ascites which require large-volume paracentesis

RRT for transplant candidates

Artificial liver support for research protocols

Hepatorenal syndrome Prevention

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- **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 alchoholic 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)

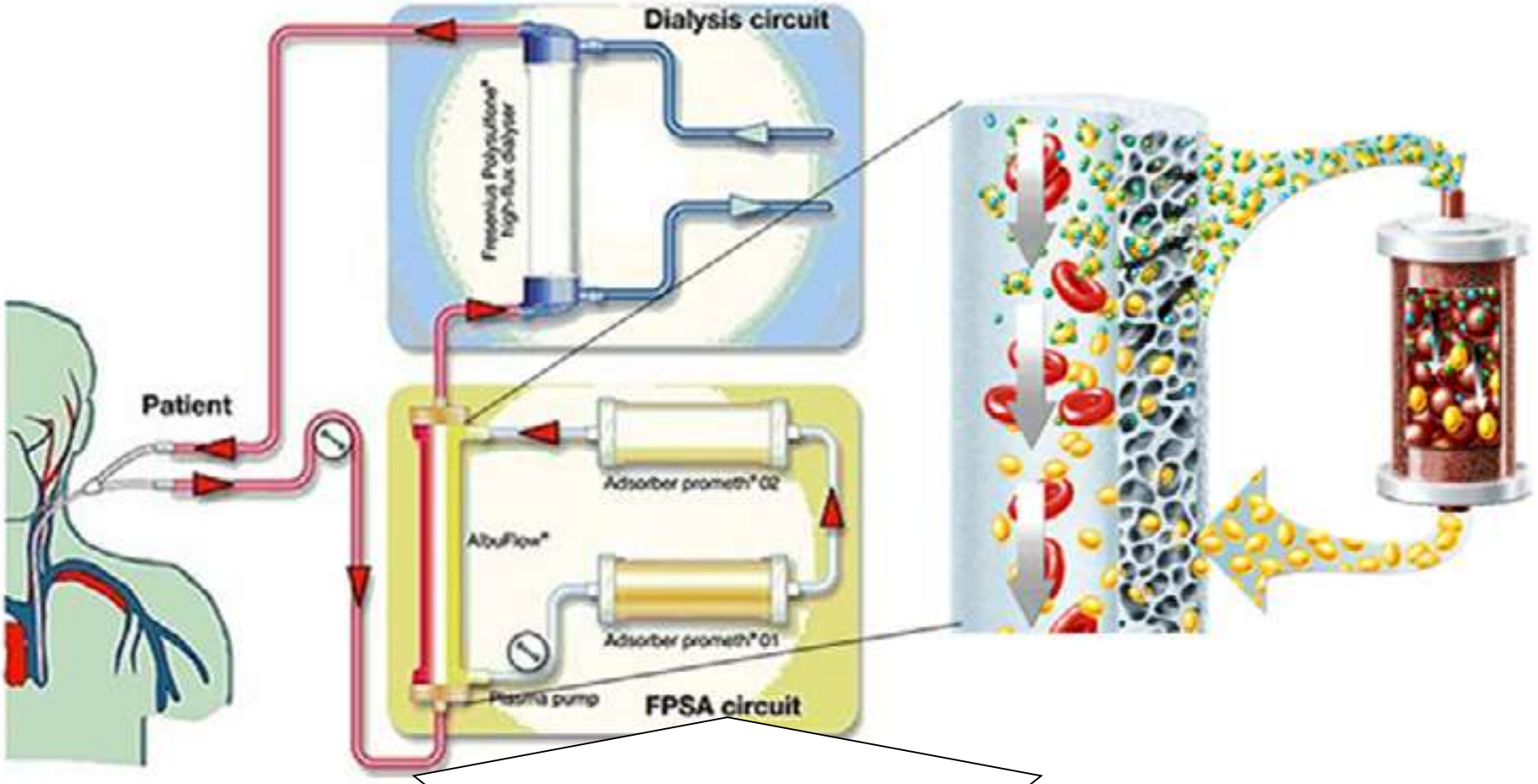
Hepatopulmonary syndrome

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

Device management

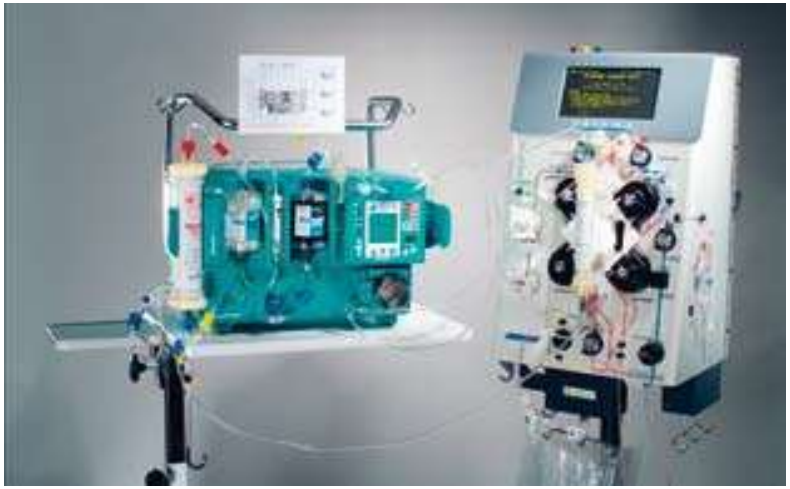
- **Prometheus**
- **Mars (Molecular Adsorbents Recirculation System)**

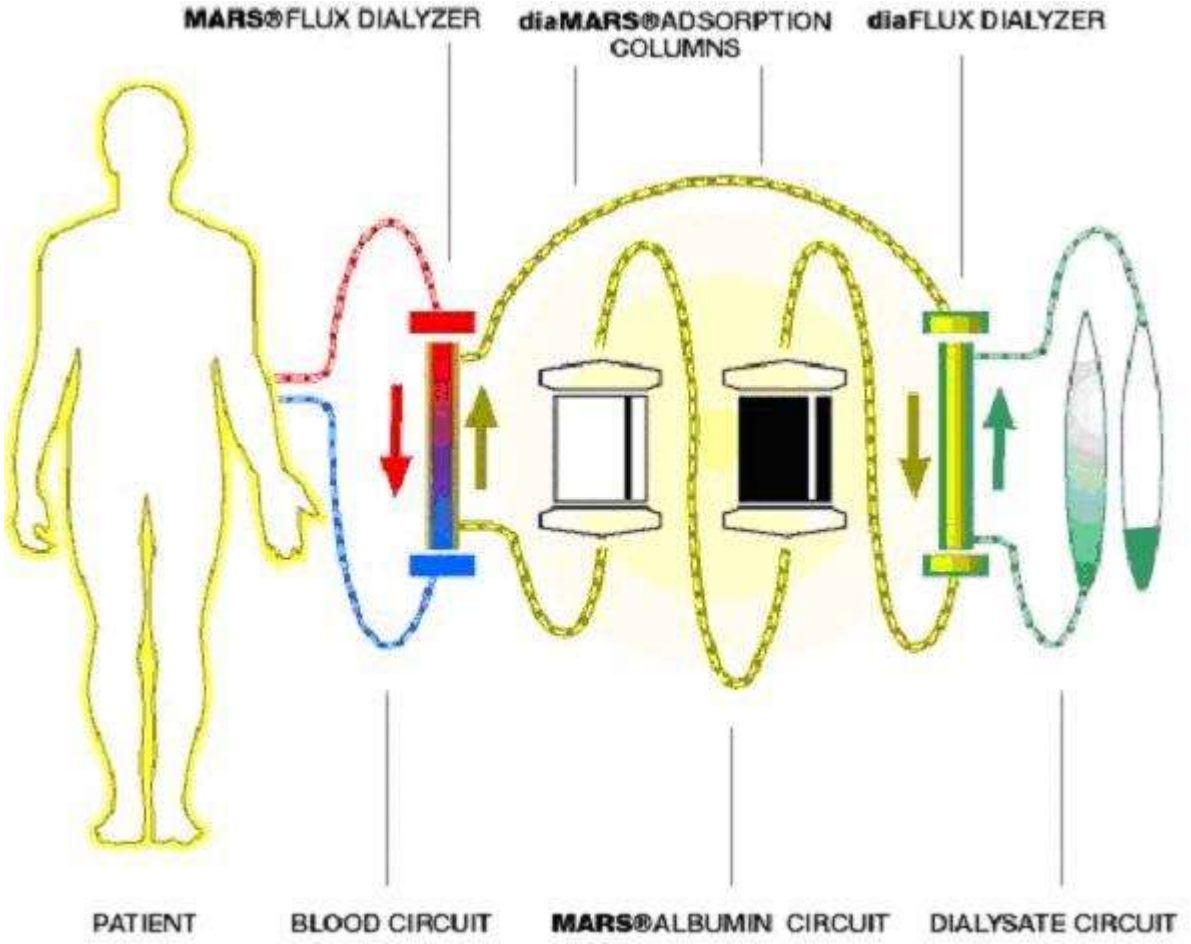
Prometheus



Fractionated Plasma Separation & Adsobtion

MARS





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Monitoring liver function

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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?

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Open Access

Research

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

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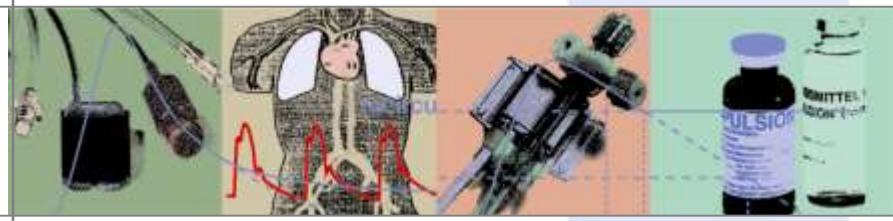
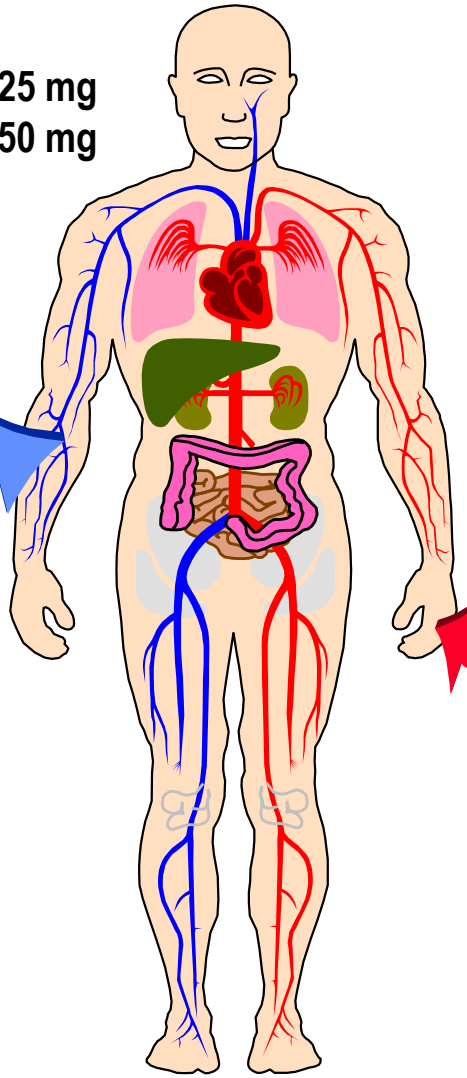
PULSION LiMON



Non-invasive

liver function monitoring

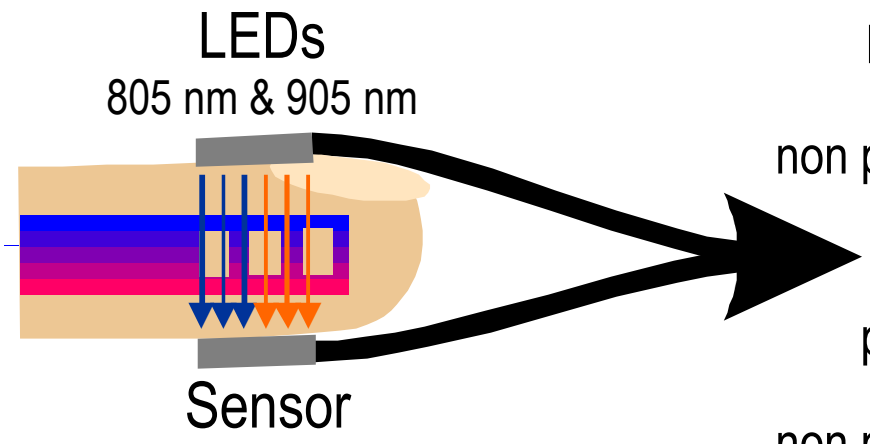
PICG0025 ICG-PULSION 25 mg
PICG0050 ICG-PULSION 50 mg

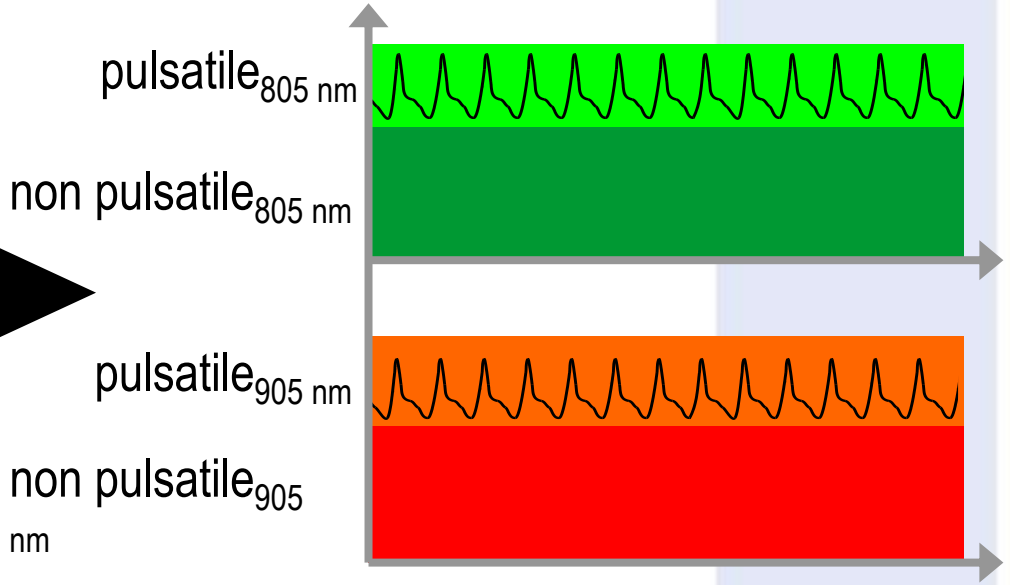


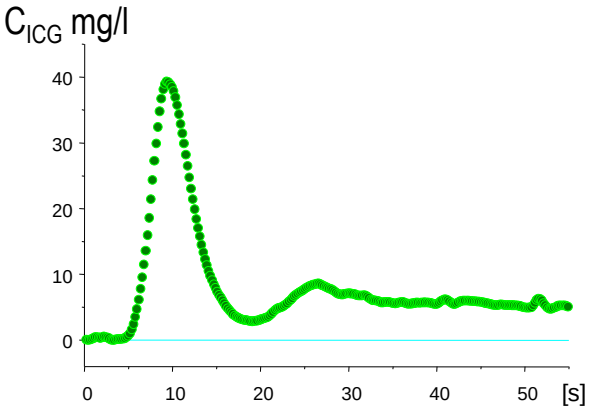
PC5000 LiMON

PC50150 LiMON reusable sensor for adults and infants

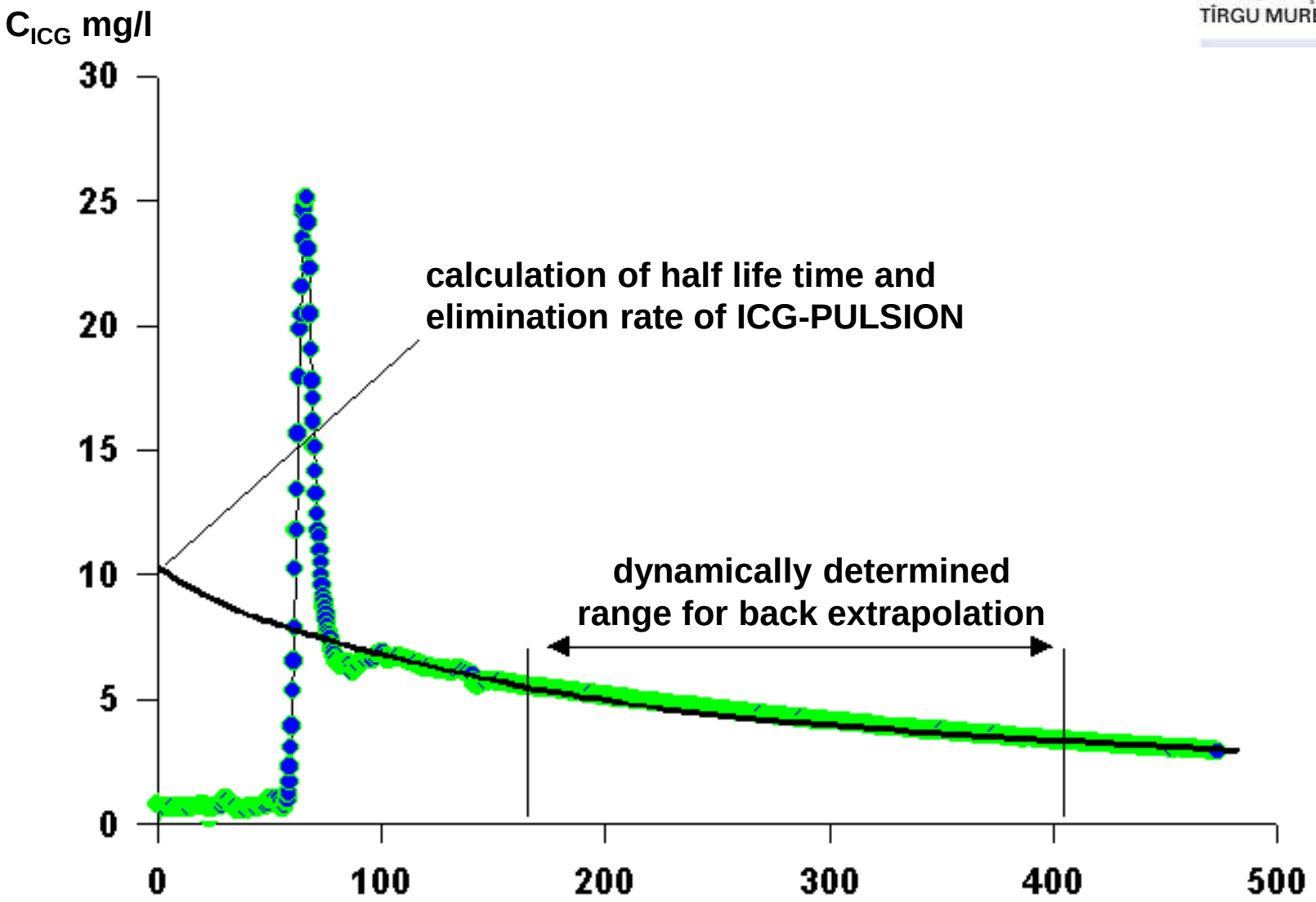
PV50100 LiMON disposable sensor for adults and infants
PV50200 LiMON disposable sensor for neonates







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


C_{ICG} mg/l
30
25
20
15
10
5
0
0
100
200
300
400
500
calculation of half life time and
elimination rate of ICG-PULSION
dynamically determined
range for back extrapolation

Global liver from elimination of ICG - PULSION

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Plasma Disappearance Rate of ICG (%/min)	**PDR**
• ICG Retention Rate after 15 min	**R15 (%)**
• ICG Clearance (ml/min)	**CB**
• Circulating Blood Volume	**BV (ml)**
Pulse oximetry	
• Oxygen Saturation	**SpO2 (%)**
• Heart Rate	**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

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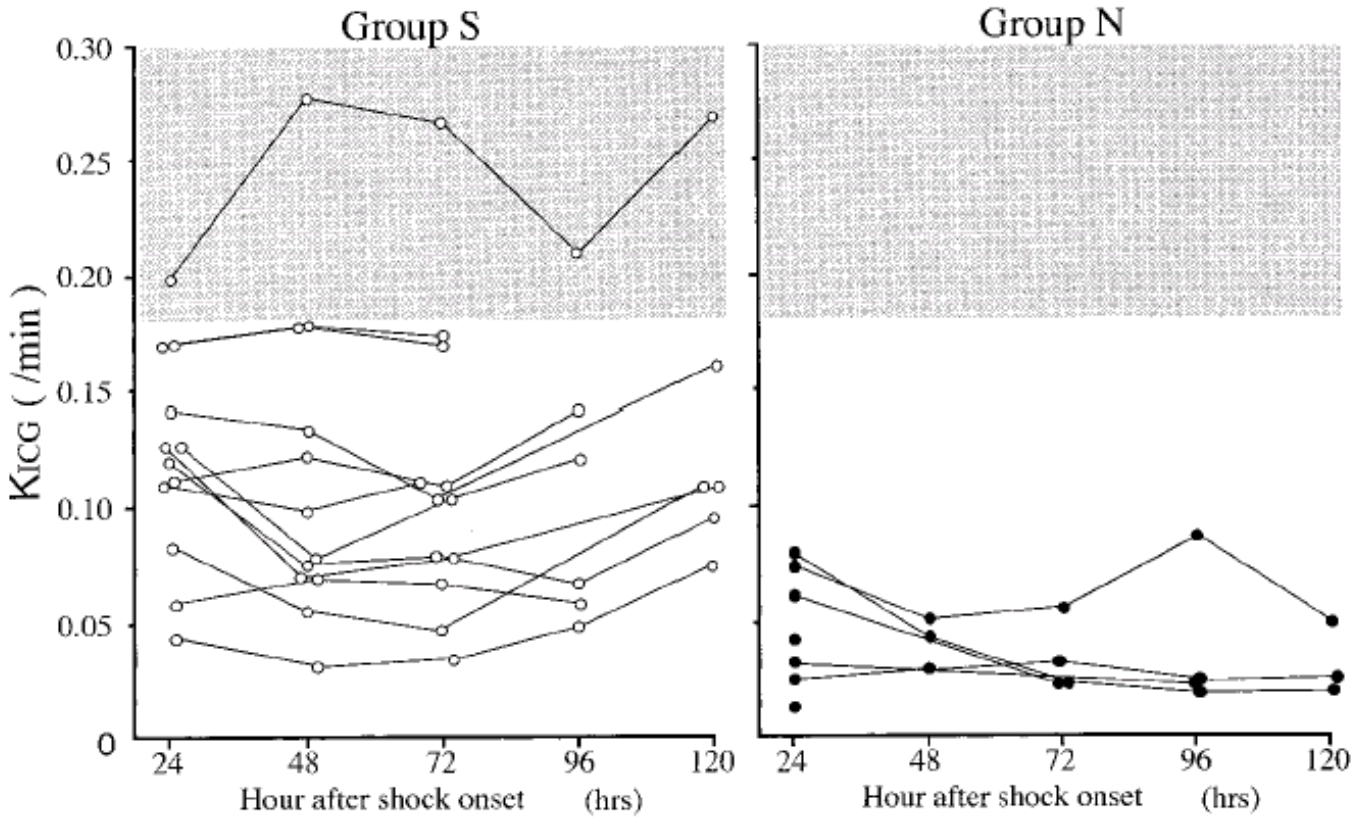
Parameter	Calculation	Normal Range
PDR (%/min)	$\ln 2/t_{1/2} \bullet 100$	18 – 25
R15 (%)	$C_{ICG15m} / C_{ICG\ t=0} \bullet 100$	0 – 10
CBI (ml/min/m^2)	BV • PDR / BSA	500 – 750
BVI (ml/m^2)	$[ICG]_{inj} / C_{ICG\ t=0}$ / BSA	2600 - 3200

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

Kimura S et al: Crit Care Med 2001

Value as liver function test in intensive care

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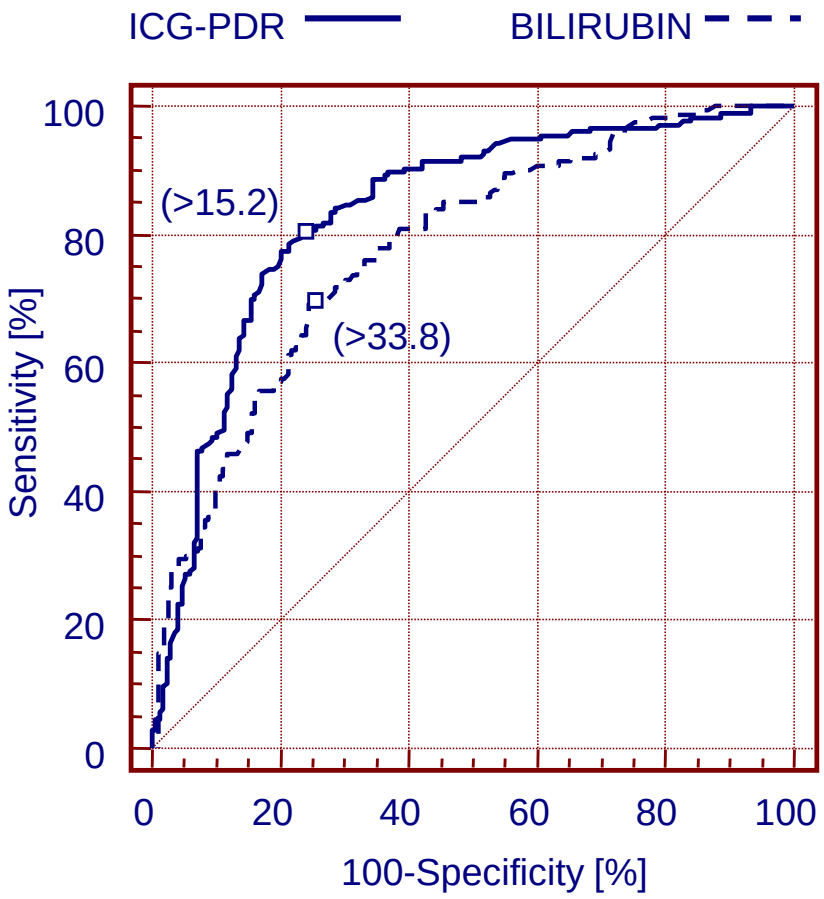
Higher sensitivity and specificity than bilirubin



n= 336
p= 0.06

Sakka SG, Meier-Hellmann A: Yearbook of Intensive Care and Emergency Medicine, 2001

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 dominat cause of FHF in Western countries.

- Hepatotoxic effects are potentiated by concurrent alcohol ingestion, glycogen depletion and/or anticonvuldsant 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.