B BRAUN
SHARING EXPERTISE

# ACUTE BLOOD PURIFICATION

## BASIC TRAINING

Dr. Michele Susca

Teheran, 04/2018

# LEARNING OBJECTIVES

## 8 MODULES

1. Understand the causes and phases of Acute Kidney Injury (AKI)
   Rationale of AKI Increase in the ICU field
2. Understand the rationale for each CRRT modality and type of Vascular access
   Rationale for using different type of process & importance of Vascular access
3. Discuss the key parts of Anticoagualtion
   Anticoagulation in CRRT usage
4. Understand the function of Hemofilters
   Importance of Hemofilters
5. Principles of Fluids and Solute management in CRRT
   Rationale for using Substitution and Dialysate Fluids in CRRT
6. Diseases in the intensive care environment
   Complexity of intensive care patient and his complications
7. Principals of PP Therapies
   Understanding basics of plasma separation and plasma treatment
8. TPE and Medical Indications of PP Therapies
   How to treat plasma diseases

# 1. UNDERSTAND THE CAUSES AND PHASES OF ACUTE KIDNEY INJURY (AKI)

## RATIONALE OF AKI INCREASE IN THE ICU FIELD

# Objective of the module

1. Understand anatomy and physiology of the Kidney
2. Understand AKI disease
3. Understand complexity of complications in AKI

# Definition of Acute Kidney Injury (AKI)

Acute, fast and in principal reversible reduction of the kidney function, lasting for days !!

Resulting in:
- retention of uremic substances
- impairment of fluid, electrolyte and acid-base balance

Main symptoms:
- Oligo/Anuria
- SCr increase

**KDIGO** (Kidney Disease: Improving Global Outcomes) 2012:

| **Increase of SCr** | **Decrease of urine volume** |
|---|---|
| >0.3 mg/dl (>26.5 µmol/l) within 2 days or >50% within 7 days | <0.5 ml/kg/h for 6 h |

**Harrisons Innere Medizin,** Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2477
SCr = Serum Creatinine, normal 0.5-1.1 mg/dl (50-120 µmol/l)

# Epidemiology*

6% of acute care hospital admission
30% of intensive care unit admission

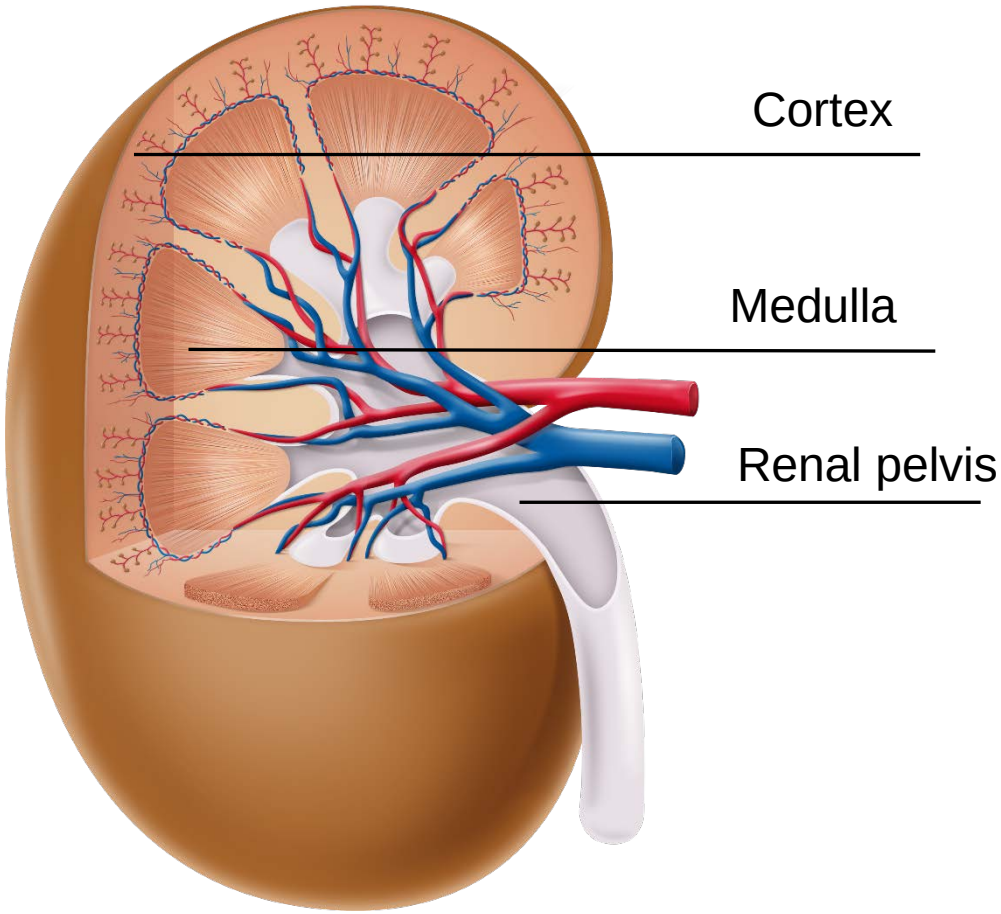
Mortality:
in ICU patient with AKI 50%

Incidence:
500 / 100 000 / Y

***Harrisons Innere Medizin,** Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2477
ICU = Intensive Care Unit

# The Kidney Facts

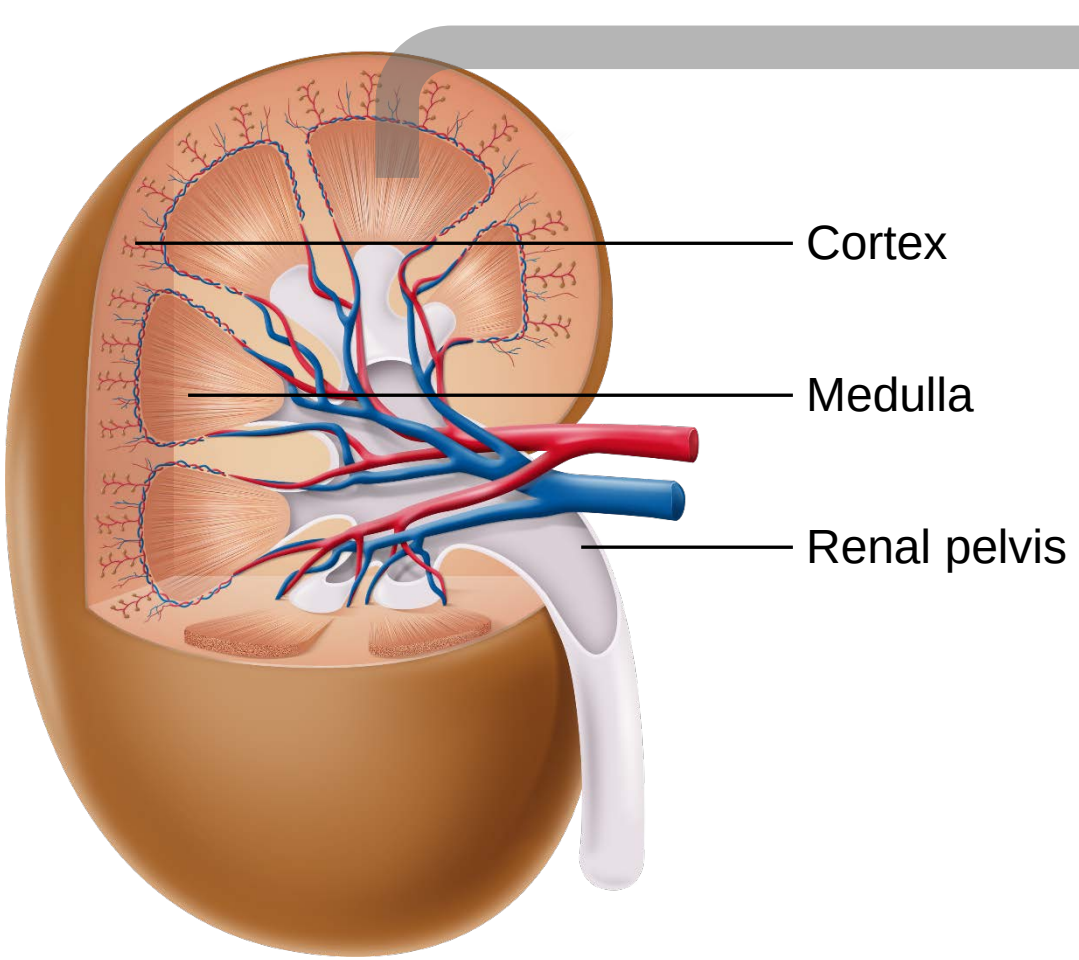
The kidney consists of three parts

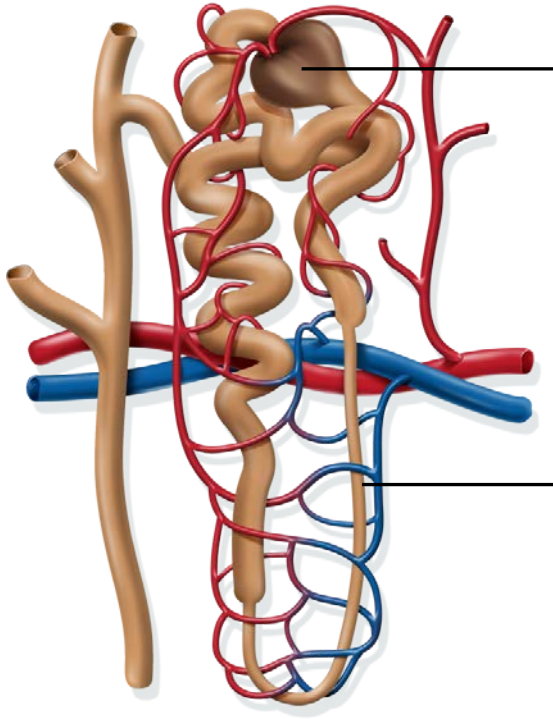



1. The cortex (outer layer)
   - Contains 80% of the nephrons
   - These nephrons filter the blood continuously to maintain balance
2. The medulla (inner layer)
   - Contains 20% of the nephrons
   - These nephrons also filter the blood, but have the added responsibility to concentrate urine
3. The renal pelvis
   - The start of the collecting system, containing the collecting tubules and the ureter
   - Ureters carry urine into the bladder where it is stored until it is eliminated from the body through the urethra

# The Kidney

The kidney consists of three parts




Nephron
1.2 Mio. per kidney*

***Taschenatlas der Physiologie,** 4. überarb. Auflage Broschiert – 1991, von Stefan Silbernagl (Autor), Agamemnon Despopoulos (Autor), 371 Seiten, Verlag: Thieme, Stuttgart (1991), S. 120

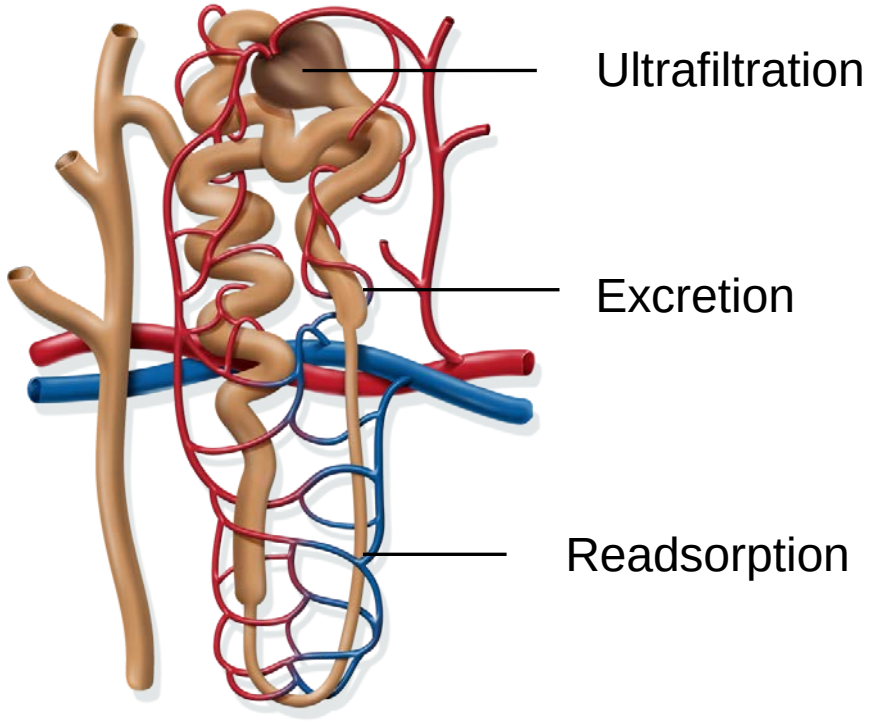
# The Kidney 3 Functions*

**The kidney functions using three principles:**

**1. Excretory Function**
Metabolic Endproducts: Elimination of Urea, Creatinine etc.

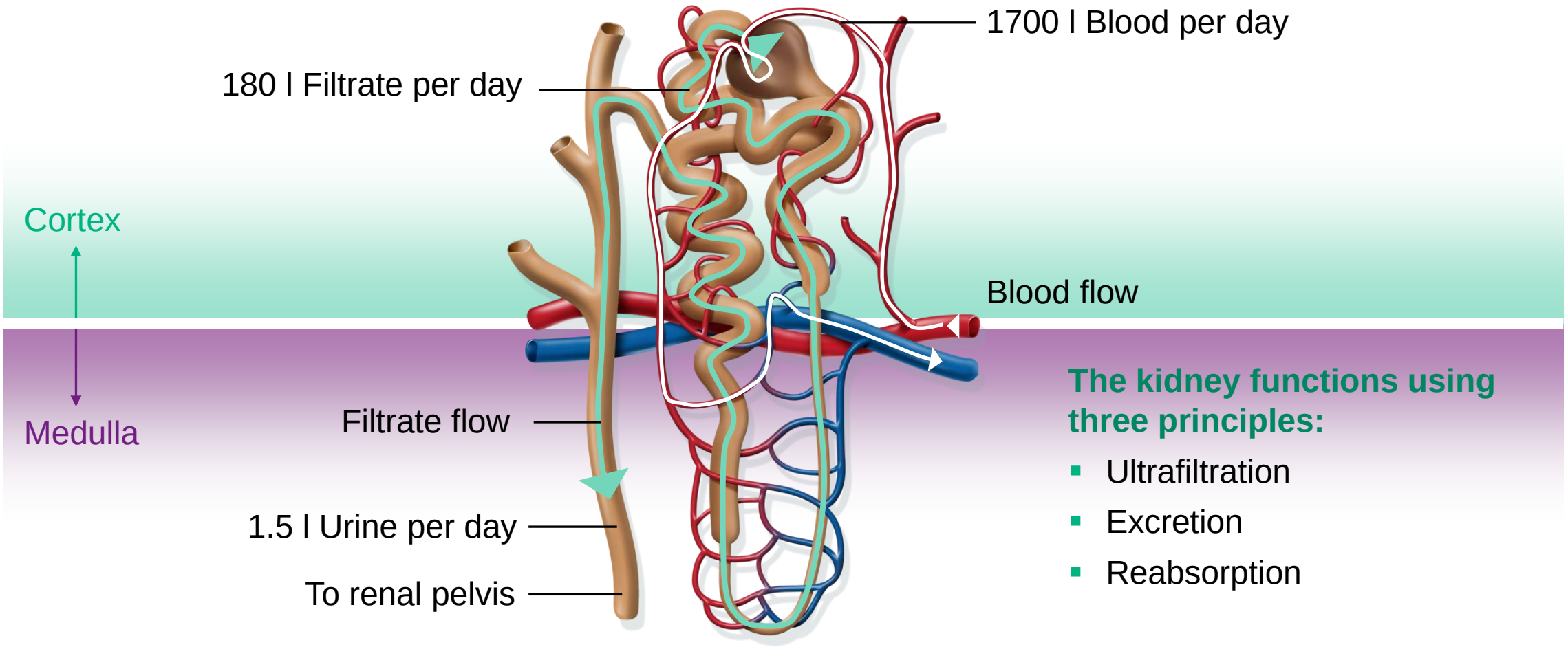
**2. Regulatory Function**
Cardiac Activity: Potassium Balance
Bone Structure: Calcium-Phosphate Balance, Vitamin D-Activation
Blood Pressure: Sodium Balance, Renin Release, Water Balance
Acid-Base Balance: Bicarbonate-Regeneration

**3. Endocrine Function**
Blood Formation: Erythropoietin Synthesis




***Physiologie des Menschen,** von R. F. Schmidt (Herausgeber), G. Thews (Herausgeber), Gebundene Ausgabe: 802 Seiten, Verlag: Springer; Auflage: 22 (28. Februar 1985), S. 669

# Filtration, Excretion and Readsorption*



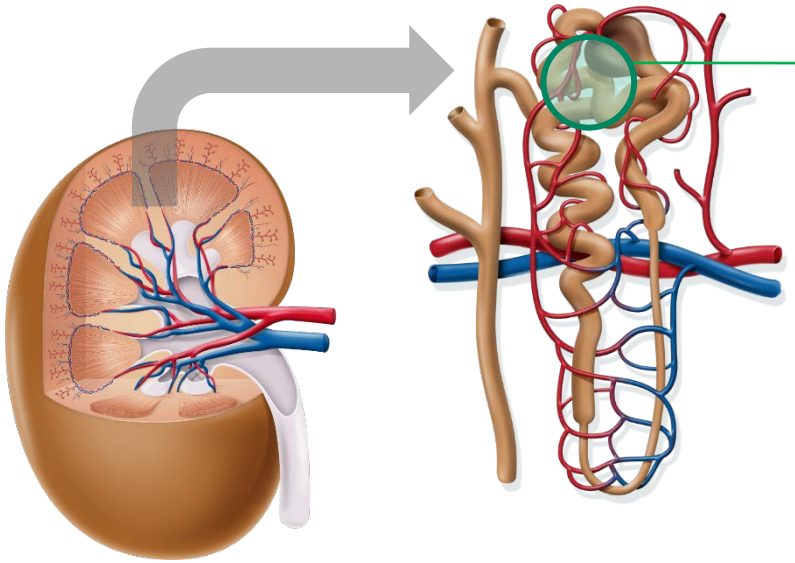

**The kidney functions using three principles:**

- Ultrafiltration
- Excretion
- Reabsorption

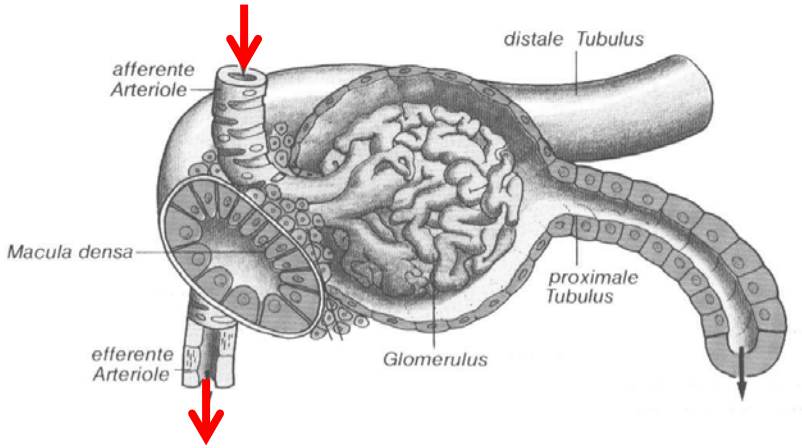
**Cardiac Output 20 – 25%**

* **Taschenatlas der Physiologie,** 4. überarb. Auflage Broschiert – 1991, von Stefan Silbernagl (Autor), Agamemnon Despopoulos (Autor), 371 Seiten, Verlag: Thieme, Stuttgart (1991), S. 122-125

# Autoregulation of Glomerular Filtration



Juxtaglomerular Apparatus

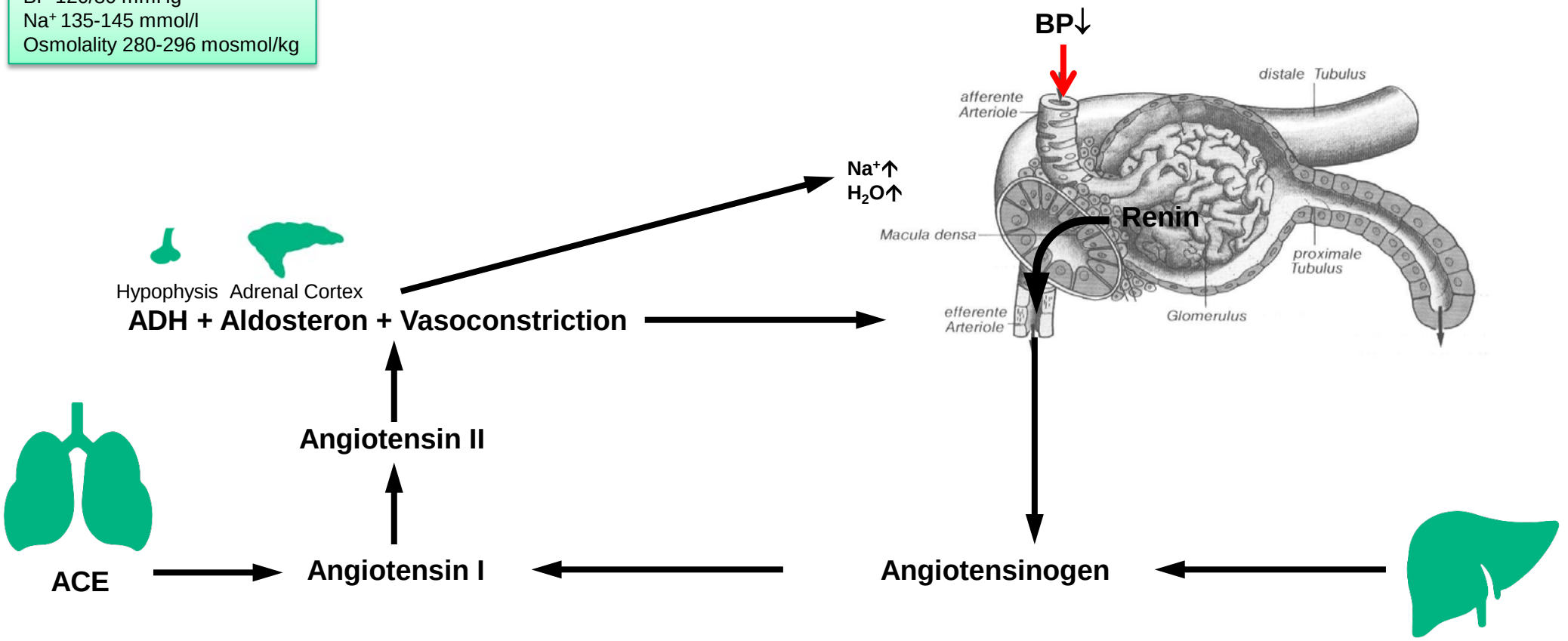



- Renin-Angiotensin-Aldosterone-System (RAAS)
- Sympathetic System
- Tubuloglomerular Feedback (TGF)*

***Harrisons Innere Medizin,** Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2478-2479

# Renin-Angiotensin-Aldosterone System (RAAS)

BP 120/80 mmHg
$Na^+$ 135-145 mmol/l
Osmolality 280-296 mosmol/kg




BP = Blood Pressure
ADH: Antidiuretic Hormone
ACE: Angiotensin-Converting-Enzyme

***Harrisons Innere Medizin,** Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2478-2479

# Risk Factors for AKI*

## Potential AKI provider

Risk Factors

### Chronic

- Arterial hypertension
- Diabetes mellitus
- Cardiac disease
- Kidney disease
- Old age
- Analgeticum misuse

### Severe disease

- Polytrauma
- Sepsis
- Burn
- MOF

### Acute

- Dehydration
- Severe hypotension
- Infection
- Hemolysis
- Rhabdomyolysis
- Acute pancreatitis
- Intravas. coagulation
- Nephrotox. medicine

https://de.wikipedia.org/wiki/Akutes_Nierenversagen

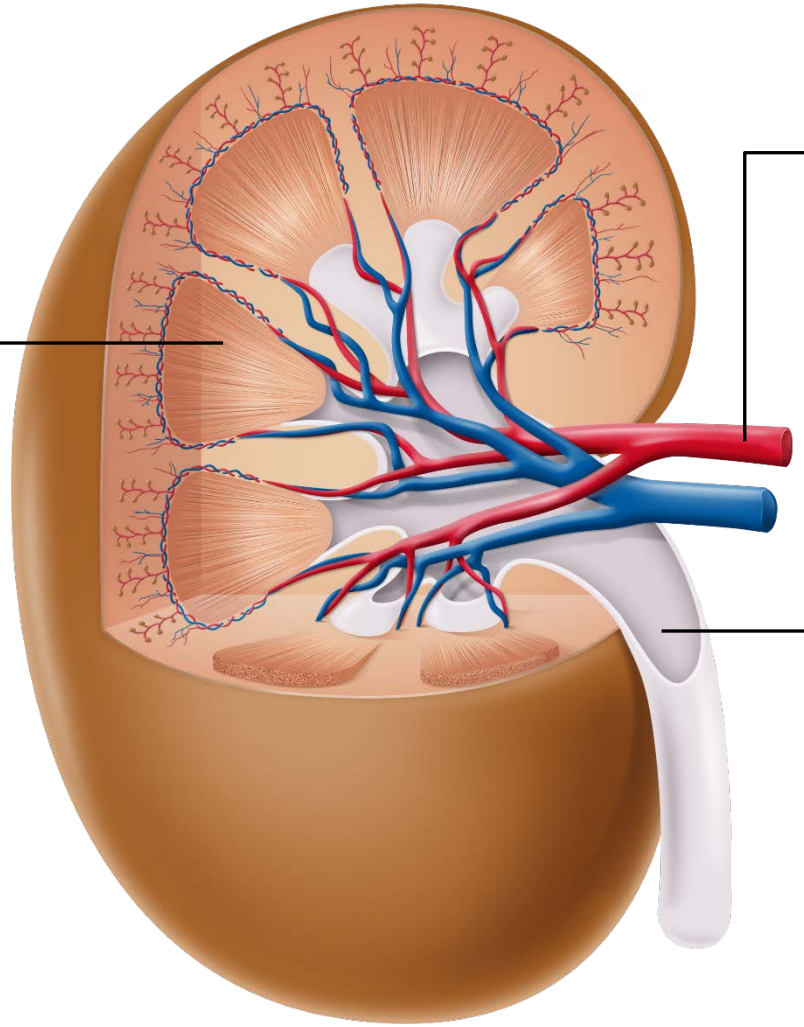
**MOF = Multi Organ Failure**

# Type of Acute Kidney Injury

## Three types of acute kidney injury (AKI) are determinated*:

### Renal (35%)

- Due to functional disturbances
- Direct injury to the kidney itself



### Prerenal (60%)

- Due to circulatory instability
- Decrease of the blood flow in the kidneys

### Postrenal (5%)

- Due to disturbed discharge in the urinary tract
- Bilateral obstruction

* Innere Medizin 2012 Taschenbuch – 1. Oktober 2011, von Gerd Herold (Autor), Taschenbuch: 966 Seiten, Verlag: Herold, Gerd (1. Oktober 2011) , S. 616-617

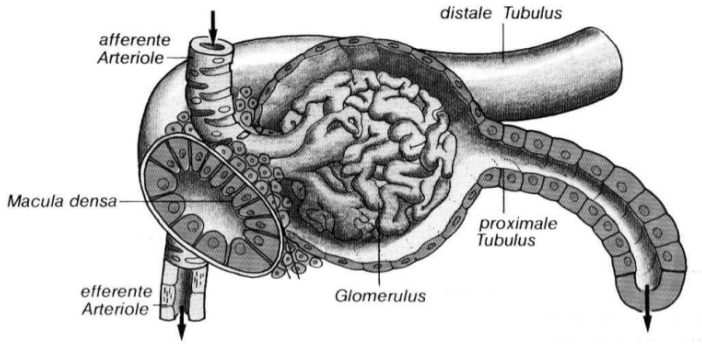
# Prerenal AKI (Prerenal Azotemia)*

too high SCr or BUN due to too low renal plasma flow and too low intraglomerular hydrostatic pressure (without parenchymal change of kidney) !!

## Reasons and risk factors

- blood volume ↓
- cardiac output ↓
- circulating blood volume ↓
  (heart failure, liver failure)
- disturbed autoregulation
  (NSAID's, ACE-I, ARB)

vasodilatory prostaglandins




vasocontractory Angiotensin II

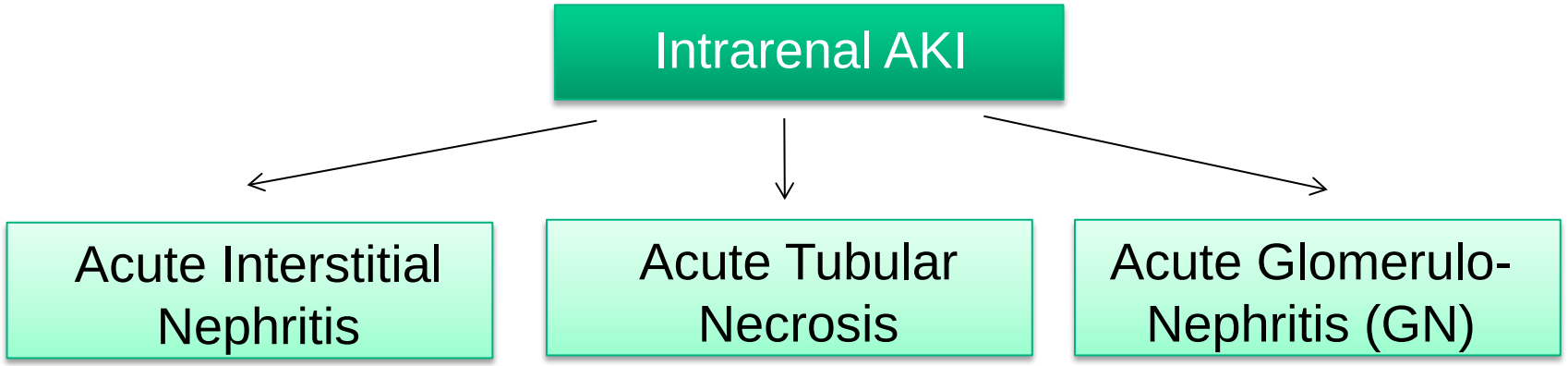
Juxtaglomerular Apparatus and Renal Autoregulation

BUN = Blood Urea Nitrogen
NSAID = Nonsteroidal Anti-Inflammatory Drug
ACE-I = Angiotensin-Converting-Enzyme-Inhibitor
ARB = Angiotensin-Receptor-Blocker

*Innere Medizin 2012 Taschenbuch – 1. Oktober 2011, von Gerd Herold (Autor), Taschenbuch: 966 Seiten, Verlag: Herold, Gerd (1. Oktober 2011), S. 616

*Harrisons Innere Medizin, Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2478-2479

# **Intrarenal AKI** (Intrinsic renal parenchymal disease)*



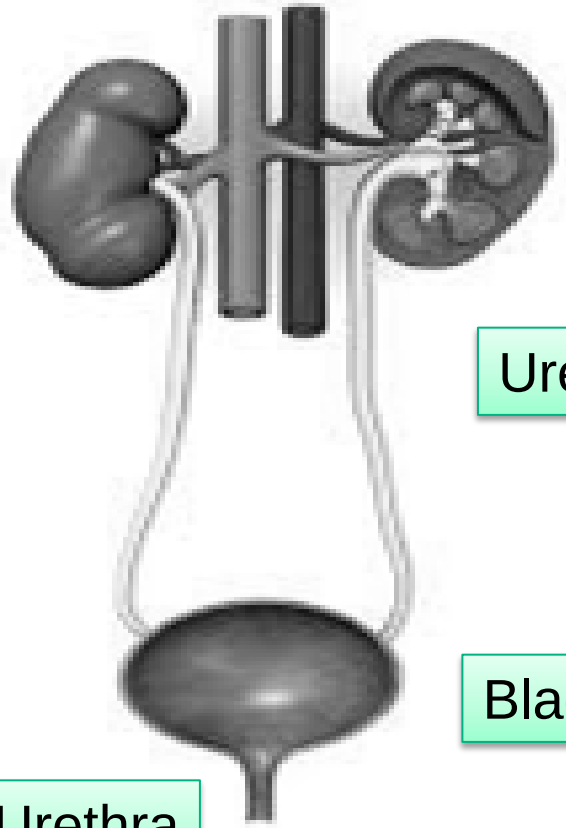
3 main reasons

1. Ischemia
2. Toxic Reaction
3. Sepsis

***Harrisons Innere Medizin,** Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2479-2482

# Postrenal AKI*

## Obstruction of urinary tract



**Ureter**
- Stone
- Cancer
- Scar after OP or inflammation
- Blood clot

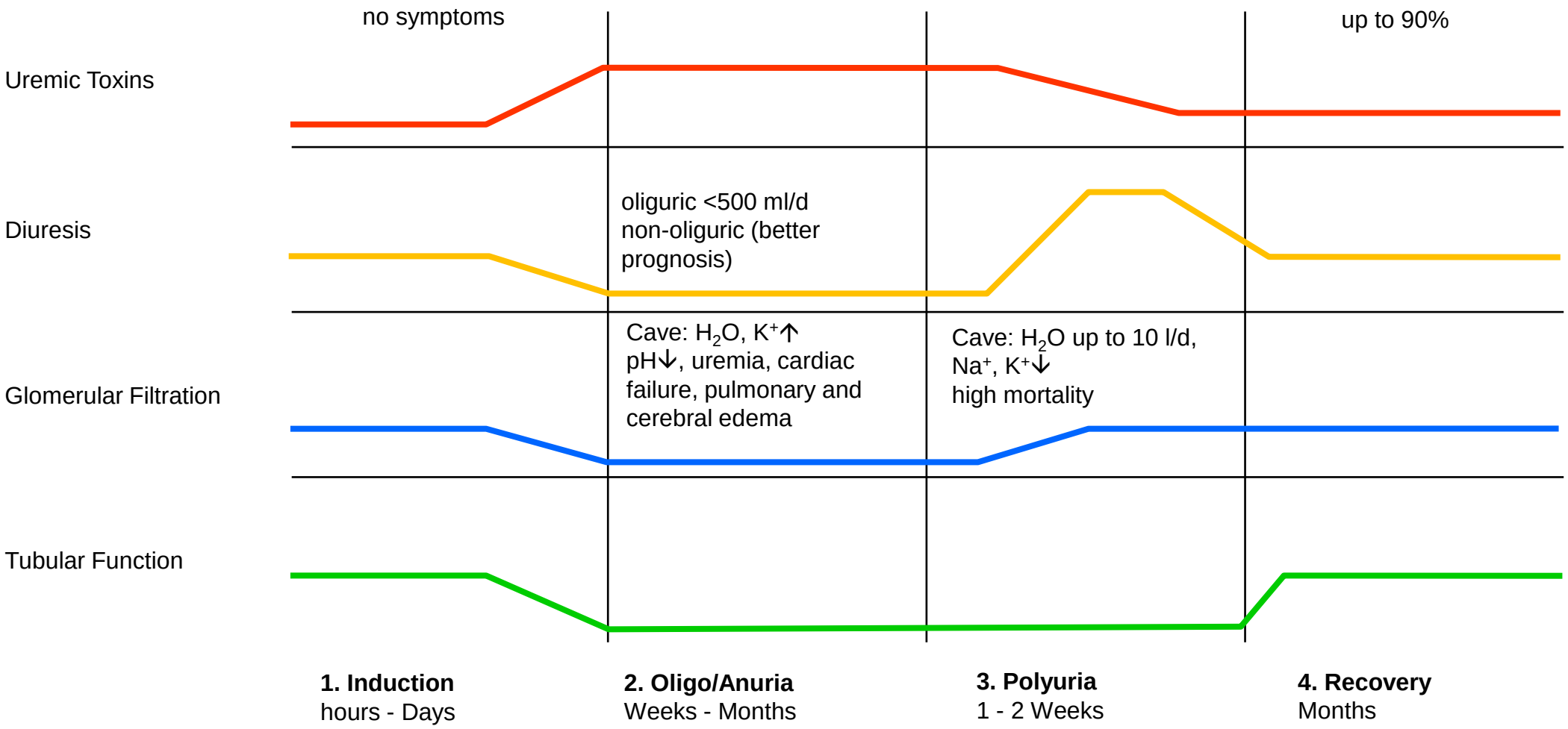
**Bladder**
- Stone
- Cancer
- Catheter
- Blood clot

**Urethra**
- Stone
- Prostate hypertrophy
- Prostate cancer
- Catheter

OP = Operation

***Harrisons Innere Medizin,** Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2482

# Course of AKI*




***Dialysefibel 3. Band 1 & 2, Individualität, Flexibilität und Qualität in der Dialyse**. Gebundene Ausgabe – 2006, von Günther Schönweiß (Autor), Verlag: abakiss Verlag; Auflage: 3, völlig überarbeitete und erweiterte Auflage (2006), S. 164

# Diagnostic Evaluation

Per definition diagnosis of AKI is sure when (KDIGO):*

| **Increase of SCr** | **Decrease of urine volume** |
|---|---|
| >0.3 mg/dl (>26.5 µmol/l) within 2 days or<br>>50% within 7 days | <0.5 ml/kg/h for 6h |

Cave: AKI can be anuric, oliguric or polyuric !!*

**Anamnesis***

Vomit, Diarrhea, Fever, other Diseases, Drugs (Diureticum, NSAID, ACE-I, ARB)

**Examination**

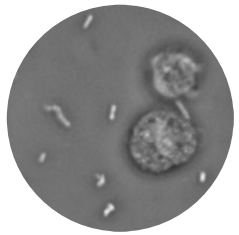
Skin? Smell? Edema? Blood Pressure? Heart Beat? Respiration? Palpation?

***Innere Medizin 2012** Taschenbuch – 1. Oktober 2011, von Gerd Herold (Autor), Taschenbuch: 966 Seiten, Verlag: Herold, Gerd (1. Oktober 2011), S. 616-619

# Diagnostic Evaluation

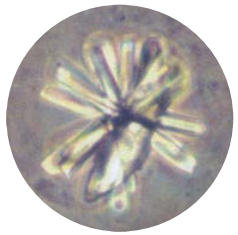
**Laboratory***

| | | |
|---|---|---|
| Urine: Sediment | Inspection, Proteinuria, Glucosuria, Hematuria, Bacteriuria, (Crystals, Cells, Casts), spec. gravity 1.001-1.035 g/l, osmolality 400-1200 mOsm/kg, pH 4.8-7.6 | |
| Diuresis: | Normuria | 500-2000 ml/d |
| | Polyuria | > 2000 ml/d |
| | Oliguria | < 500 ml/d |
| | Anuria | < 100 ml/d |
| Blood: Blood Cells, | Creatinine, Urea, Electrolytes, CK, LDH, Lipase, Gas Check, Hemoglobin, total Protein, Albumin, Immunology, Culture | |

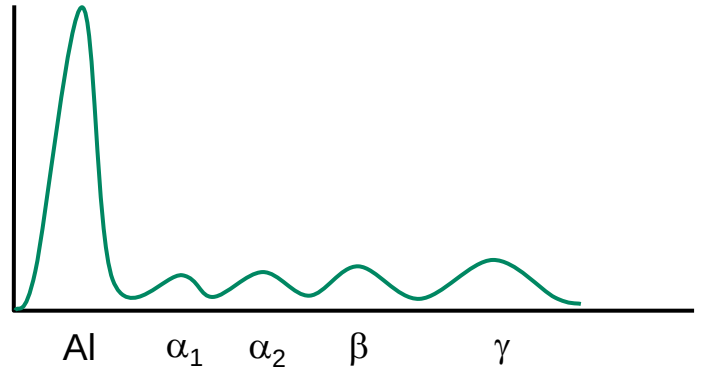


Bacteria
Leucocytes

erythrocyte cast



calcium phosphate crystals

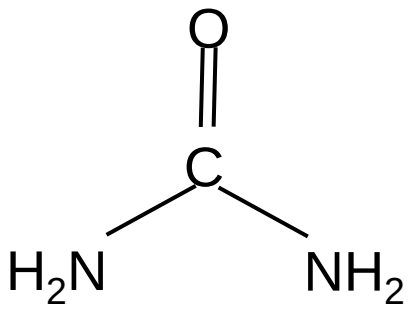


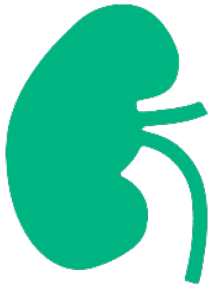

Serum Electrophoresis of proteins

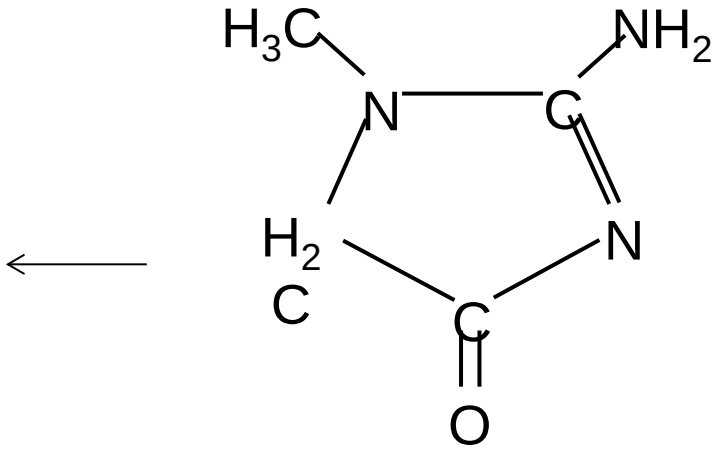
CK = Creatine Kinase
LDH = Lactate Dehydrogenase

***Innere Medizin 2012** Taschenbuch – 1. Oktober 2011, von Gerd Herold (Autor), Taschenbuch: 966 Seiten, Verlag: Herold, Gerd (1. Oktober 2011), S. 587-591

# Metabolic End Products






**Urea 10-50 mg/dl (1.7-8.3 mmol/l)***

End Product of Protein metabolism

**Creatinine 0.5-1.1 mg/dl (50-120 µmol/l)**

End Product of muscle metabolism

When Urea >150 mg/dl (>25 mmol/l) in oligo/anuria
or >300 mg/dl (>50 mmol/l) in polyuria*

When Crea >0.5 mg/dl/d (>50 µmol/l/d)
or Crea-Clearance <5 ml/min

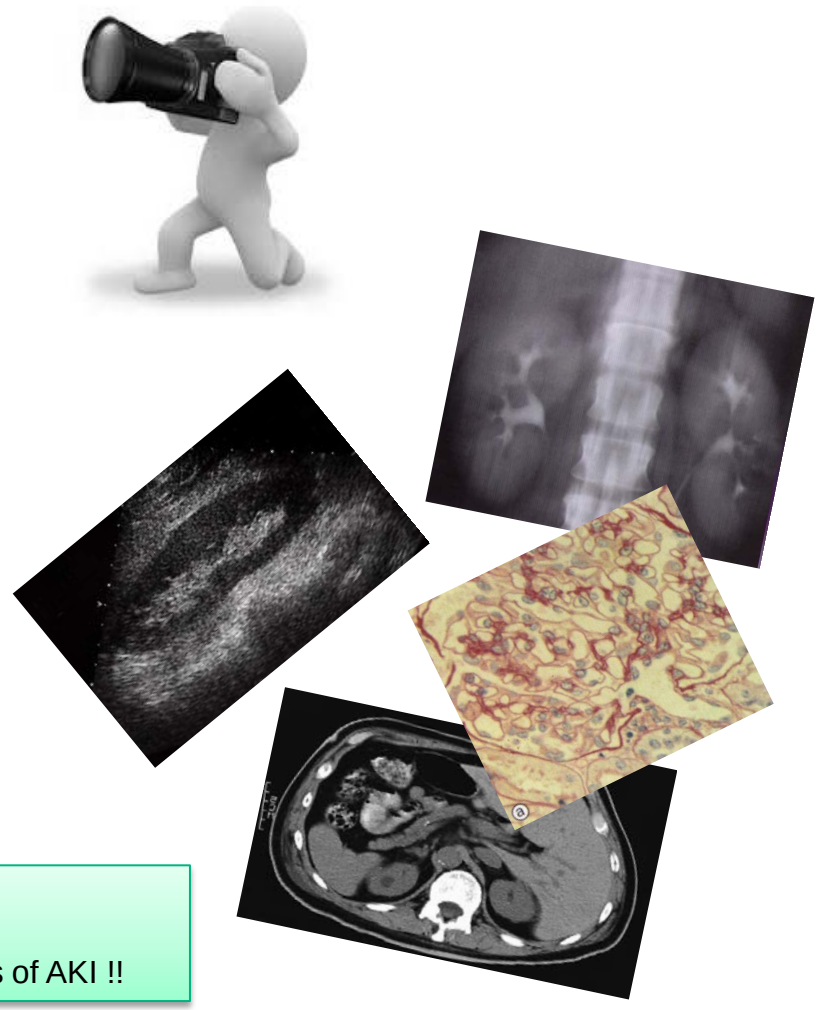
**Dialysis**

* Urea → BUN = Urea x 0.47
BUN 4.7-23.5 mg/dl (1.7-8.5 mmol/l)

***Harrisons Innere Medizin,** Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2491

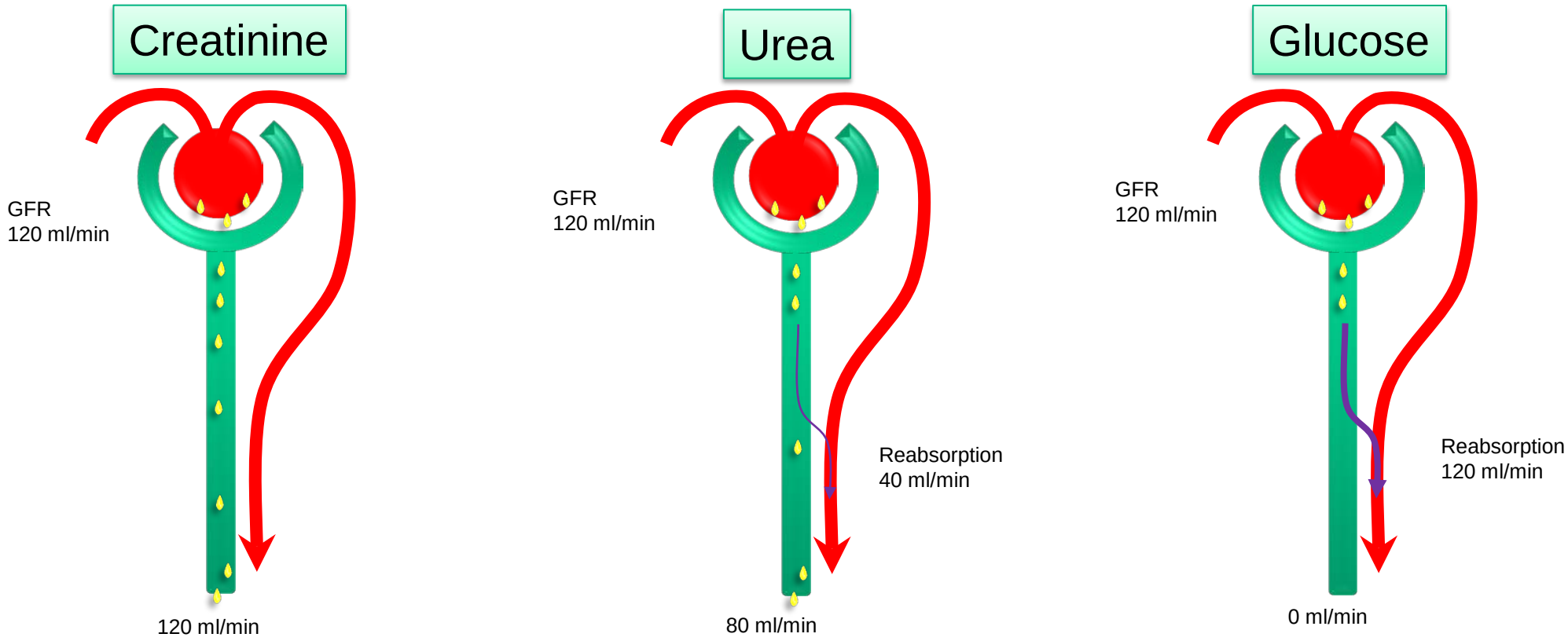
# Diagnosis – Imaging & Biopsy

- Ultrasound, Color Doppler Ultrasound
- Plain Film, intravenous Urography, Pyelography
- Computer Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Angiography
- Radionuclide Evaluation
- Renal Biopsy



Facit:
1. AKI is an exclusion diagnosis !!
2. Often already anamnesis, hydratation, urine inspection and sonography allow the diagnosis of AKI !!

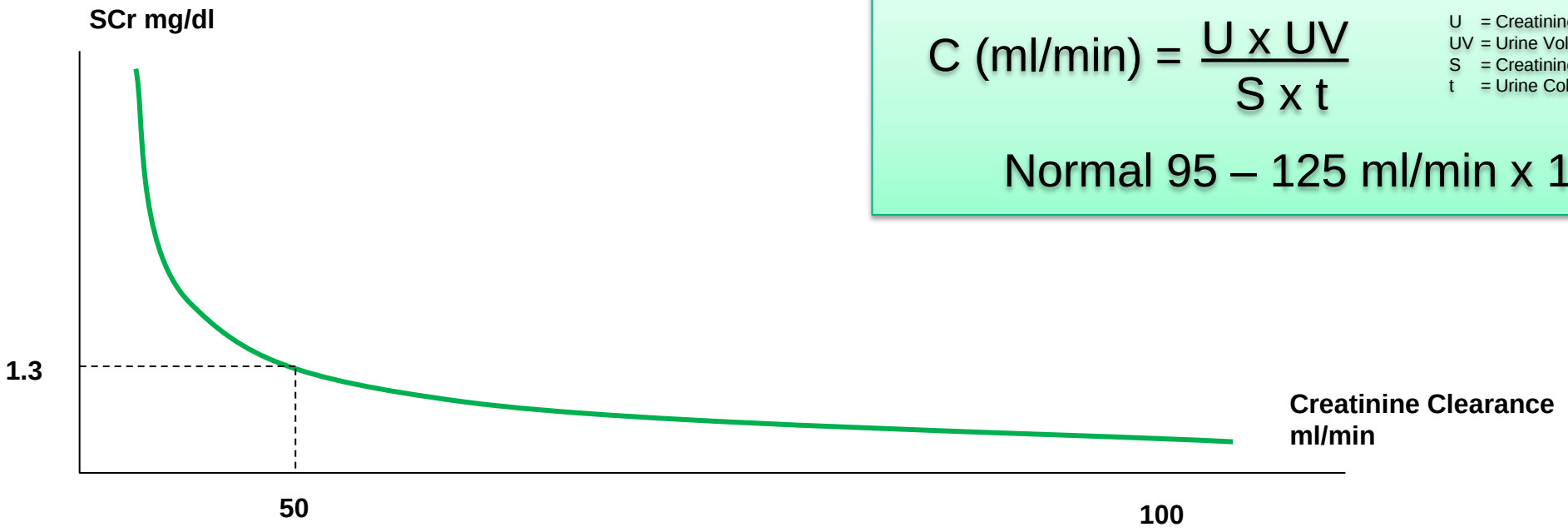
# Clearance of Creatinine, Urea and Glucose



# Glomerular Filtration Rate – GFR

Clearance = Volume of Plasma which has been cleaned from a certain substance within a certain time

## Creatinine Clearance = Glomerular Filtration Rate

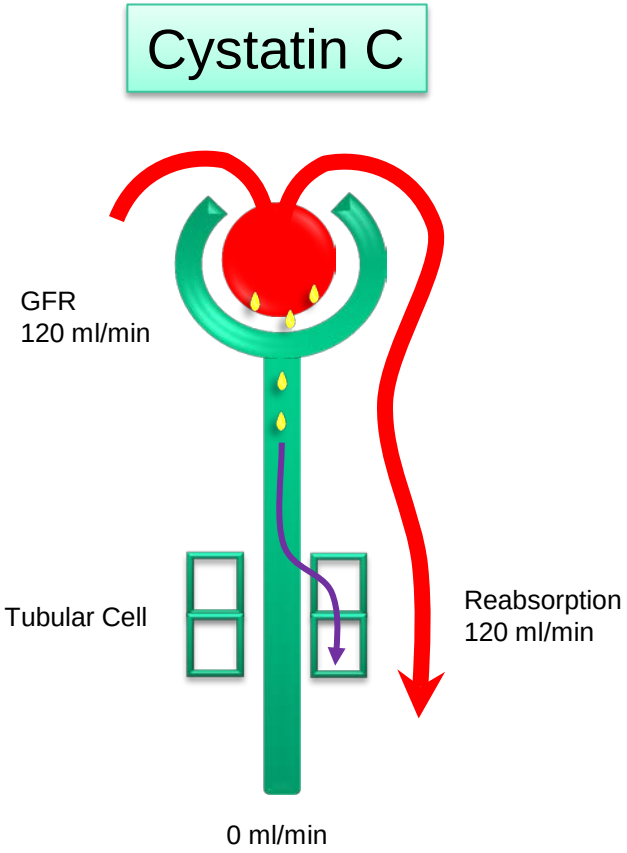



$$C\ (ml/min) = \frac{U \times UV}{S \times t}$$

U = Creatinine iu
UV = Urine Volume within 24h
S = Creatinine i.S.
t = Urine Collection Time in Minute

Normal 95 – 125 ml/min x 1.73 m²

# Clearance of Cystatin C & Biomarker



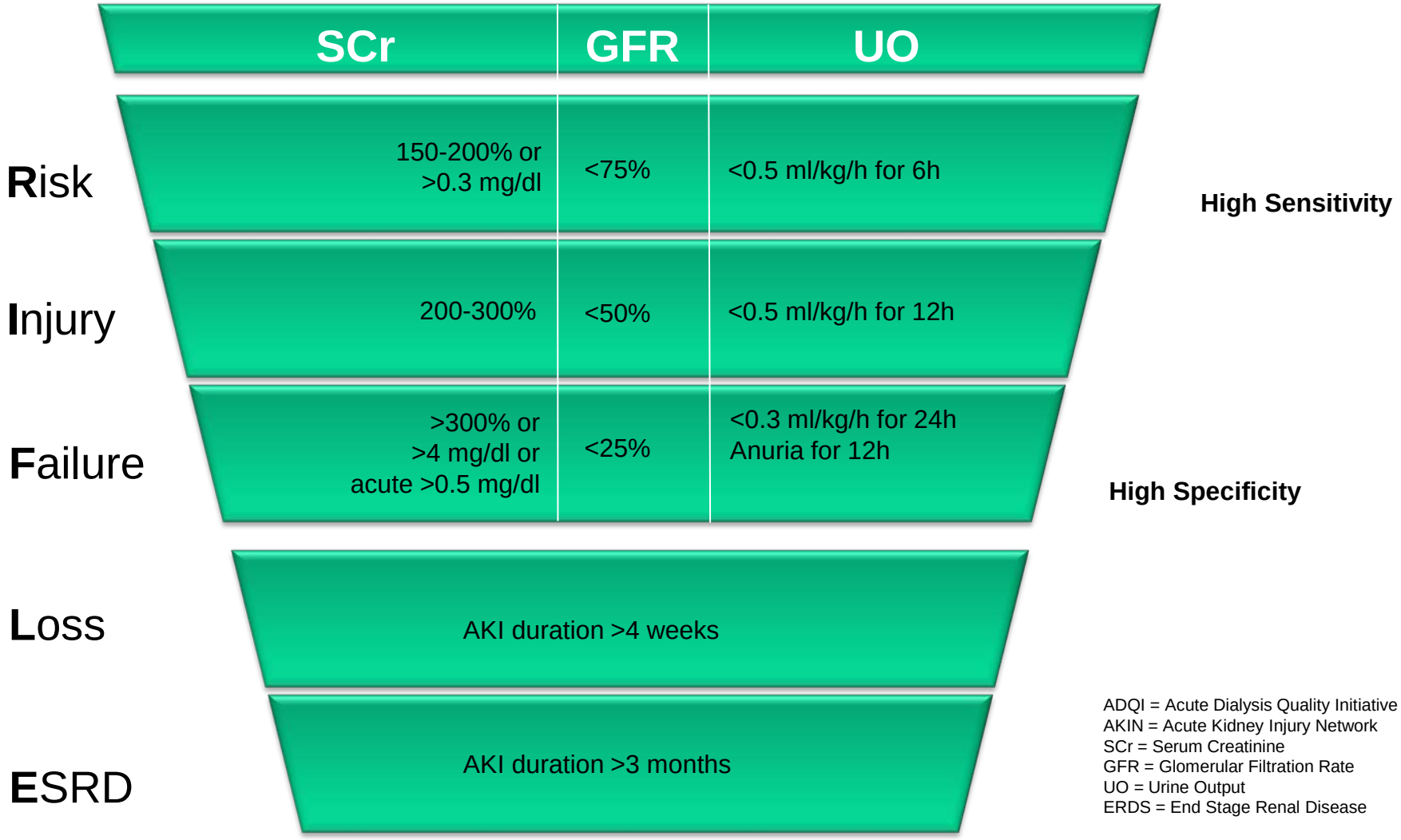

- Cystatin C is a small protein (13.4 kD)
- Product of intracellular protein metabolism
- Concentration in serum is constant
- Elimination through glomerular filtration and readsorption in tubular cell

Normal 0.56-0.96 mg/l

new specific biomarker KIM-1 and NGAL:

- **KIM-1** Kidney-Injury-Molecule-1 shortly after ischemic and toxic injury it appears in urine.
- **NGAL** Neutrophile-Gelatinase-Associated-Lipocalin shortly after ischemic and toxic injury it appears in plasma and urine

# ADQI RIFLE Staging for AKI*




ADQI = Acute Dialysis Quality Initiative
AKIN = Acute Kidney Injury Network
SCr = Serum Creatinine
GFR = Glomerular Filtration Rate
UO = Urine Output
ERDS = End Stage Renal Disease

*José António Lopes and Sofia Jorge, The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review, Clin Kidney J (2013) 6: 8–14Clin Kidney J (2013) 6: 8–14

# Complications of AKI*

Uremia

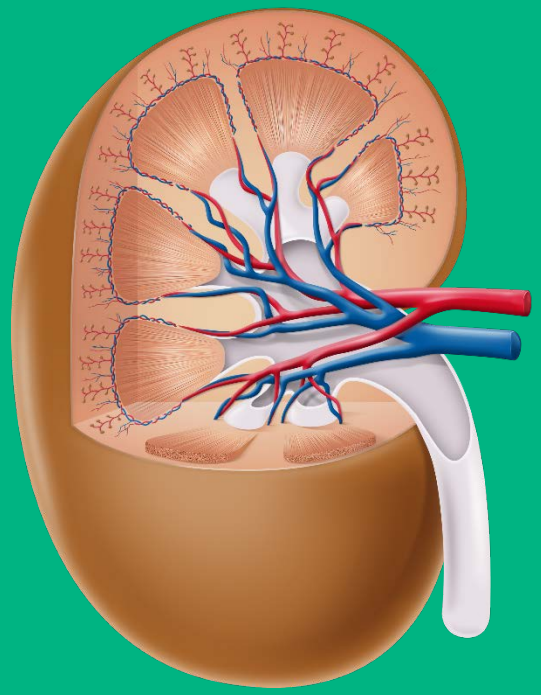
Hyper / Hypovolemia

Hyponatremia

Hyperkalemia

Acidiosis

Cardiac problems



Hyperphosphatemia

Hypocalcemia

Anemia/Bleeding

Infection

Malnutrition

CNS

* Harrisons Innere Medizin, Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2486-2489

# Prophylaxy of AKI

First target is always to keep the hemodynamic of the kidney for sufficient oxygen supply!

## 3 Rules for prophylaxy*

1. Stabilize hemodynamic for optimal blood circulation and oxygen supply in kidney!
2. Correct balance of fluid and electrolytes!
3. Stop potential nephrotoxic medication and adjust dose of necessary medication!

Adequate indication for contrast agents and nephrotoxic drugs!

* **Harrisons Innere Medizin,** Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2489

# Hemodynamic Stabilization

stable hemodynamic for optimal blood circulation and oxygen supply !!

If necessary give Catecholamines for stabilization of cardiocirculation.

Recommended are:

- **Dobutamin**
- **Noradrenalin**[1]

Not recommended → Dopamin due to cardiac side effects and not better prognosis[2] !!

(low-dose Dopamin may cause a transient increase of water and salt excretion but can cause arrhythmia and bowel ischemia!)

1. Ravindra L Mehta et al.:: *Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury.* In: *Critical Care.* Nr. 11, S. R31.
2. Bellomo et al. *Lowdose dopamin in patients with early renal dysfunction: a placebo-controlled randomized trial. Australian and New Zealand Intensive Care Society (ANZICS) clinical trials group.* In: *Lancet* 2000, 356:2139–2143

# Fluid and Electrolyte Balance

Correction of fluid and electrolytes balance !!

## Hypovolemia

If necessary give **volume substitution**.

Cave: risk of fluid overload → pulmonary edema therefore CVP control and weight control every day !!

Give **crystalloids** depending on electrolyte status.

In **severe hypovolemia** → isotonic crystalloids (e.g. 0.9% NaCl) or colloids
In less severe hypovolemia → hypotonic crystalloids (e.g. 0.45% NaCl)

## Hypervolemia

**Diuretics** (loop diuretics such as Furosemide) are in principal nephrotoxic !!

If possible only for fluid balance control or in case of emergency !!

In severe fluid overload → furosemide 250 mg in 1h, then 80 mg in 4h, max. total dose 500 mg → in case no effect → interruption !!

# Medication in AKI

Stop potential nephrotoxic medication and adjust dose of necessary medication !!

Check all known nephrotoxic drugs:

- Antimicrobial Agents: Penicillin, Amoxicillin, Ampicillin, Ciprofloxacim, Cephalosporin, Sulfonamide, Rifampicin, Co-trimoxazole, Gentamicin, Aminoglycoside, Amphotericin B, Vancomycin, Aciclovir
- Iodated Contrast Agents
- NSAID's/Salicylates: Ibuprofen, Naproxen, Indomethacin, Piroxicam
- Antiulcer Agents: Cimetidine, Omeprazole
- Others: ACE-I, ARB, Cyclosporine, NSAR, Phenytoin, Thiacide Diuretics, Furosemide, Allopurinol, Mesalazine

For adjustment of dose for necessary medication check e.g. www.dosing.de !!

# Summary

AKI stands for Acute Kidney Injury and is often one impotant complication in ICU patient

Anatomy and physiology of the kidney

- Nephron, glomerulus, tubular system, glomerualr filtration, excretion, readsorption, excretory, regulatory and endocrine function

Definition, reasons, course, diagnosis and clinic of AKI

- Prerenal, intrarenal and postrenal AKI, glomerular filtration rate (GFR), RIFLE criteria, complications

Prophylaxis and therapy of AKI

- 3 rules of prophylaxis therapy, hemodynamic stabilization, fluid and electrolyte balance, medication

early diagnosis and prophylaxis are important measures !!

# 2. UNDERSTAND THE RATIONALE FOR EACH CRRT MODALITY AND TYPE OF VASCULAR ACCESS

## RATIONALE FOR USING DIFFERENT TYPE OF PROCESS & IMPORTANCE OF VASCULAR ACCESS

CRRT MODALITY

# Objective of the module

1. Understand structure of CRRT on OMNI
2. Understand extracorporeal blood circuit
3. Understand fluid circuit
4. Understand all components of OMNI system (machine and disposables)

# When is the right time to begin?

too early risk of
- bleeding
- hypotension
- infection
- postoperative complications

too late risk of
- life threatening complications

Cave:

there is no rule or guide line for clear indication and initiation !!

Clinicians have to make individual decision taking in consideration not only urea, crea and diuresis but also basic disease, catabolism, other organ failures and complete patient's status !!

# Indication for Renal Replacement Therapy (RRT)

| Indication | Comment |
|---|---|
| Azotemia | BUN >60-80 mg/dl (>21-29 mmol/l), especially when >20 mg/dl/d (>7 mmol/l/d)<br>Urea >150 mg/dl (>25 mmol/l) in oligo/anuria or >300 mg/dl (>50 mmol/l) in polyuria<br>SCr >0.5 mg/dl/d (>50 µmol/l/d) or Crea-Clearance <5 ml/min |
| Uremia | severe uremic symptoms such as pericarditis, bleeding, neuropathy, encephalopathy |
| Acidosis | Severe metabolic acidosis of pH <7.2 |
| Hypervolemia | for better control of fluid balance, pulmonary edema |
| Anuria/Oliguria | anuria for 6h<br>severe oliguria with <200 ml for 12h |
| Hyperkalemia | in severe hyperkalemia (>6.5 mmol/l) |
| Non-Renal | exogenous dialyzable toxins: lithium, methanol, ethylene glycol,<br>CHF, ARDS, MODS, sepsis, pancreatitis<br>Others such as hypothermia, metabolic alkalosis, hyperuricemia |

# Dialysis Therapies

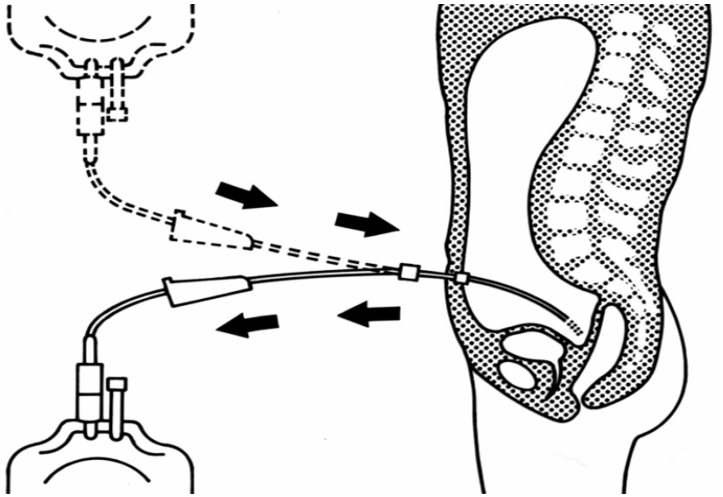
| | |
|---|---|
| **Peritoneal dialysis (PD)** | continuous ambulatory peritoneal dialysis (CAPD)<br>continuous cyclical peritoneal dialysis (CCPD)<br>intermittent peritoneal dialysis (IPD) |
| **Hemodialysis (HD)** | hemodialysis (HD)<br>hemofiltration (HF)<br>hemodiafiltration (HDF) |

# Peritoneal Therapy

In advanced countries seldom used because poor efficiency!
Used more when dialysis technology not available!

Possible indications:

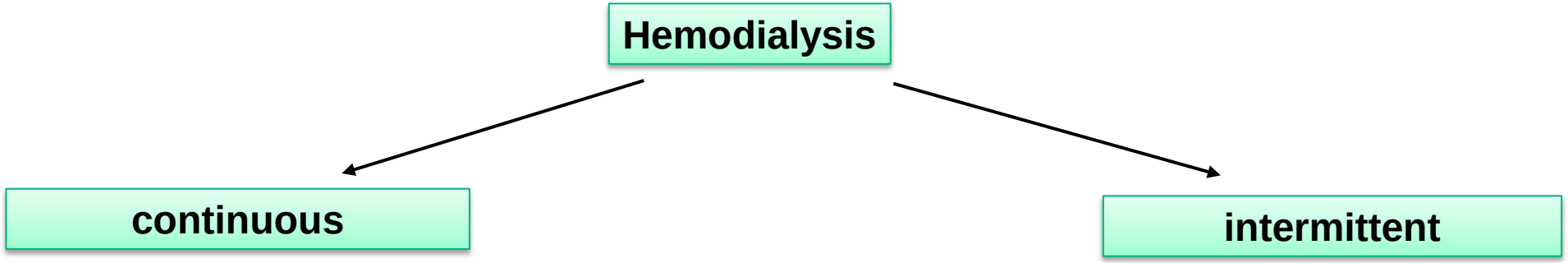
- Hypotension
- Bleeding
- Small patient
- no blood access



Cave:
in hypercatabolic patient not sufficient enough !!*

***Harrisons Innere Medizin,** Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2491

# Hemodialysis (HD)




- Slow Continuous Ultrafiltration SCUF
- Continuous Veno-Venous Hemofiltration CVVH
- Continuous Veno-Venous Hemodialysis CVVHD
- Continuous Veno-Venous Hemodiafiltration CVVHDF

- SLED
- Hemodialysis HD
- Hemofiltration HF
- Hemodiafiltration HDF

SLED = Sustained Low Efficiency Dialysis

# Blood Purification Procedures in ICU

B BRAUN
SHARING EXPERTISE

## intermittent

intermittent peritoneal dialysis (IPD)

hemoperfusion (HP)

hemoconcentration

ther. plasmapheresis (PEX, PAP)

hemodialysis (HD)

hemofiltration (HF)

hemodiafiltration (HDF)

## continuous

continuous ambulatory peritoneal dialysis (CAPD)

continuous cyclical peritoneal dialysis (CCPD)

slow continuous ultrafiltration (SCUF)

continuous arterio-venous hemofiltration (CAVH)

continuous arterio-venous hemodialysis (CAVHD)

continuous arterio-venous hemodiafiltration (CAVHDF)

continuous veno-venous hemofiltration (CVVH)

continuous veno-venous hemodialysis (CVVHD)

continuous veno-venous hemodiafiltration (CVVHDF)

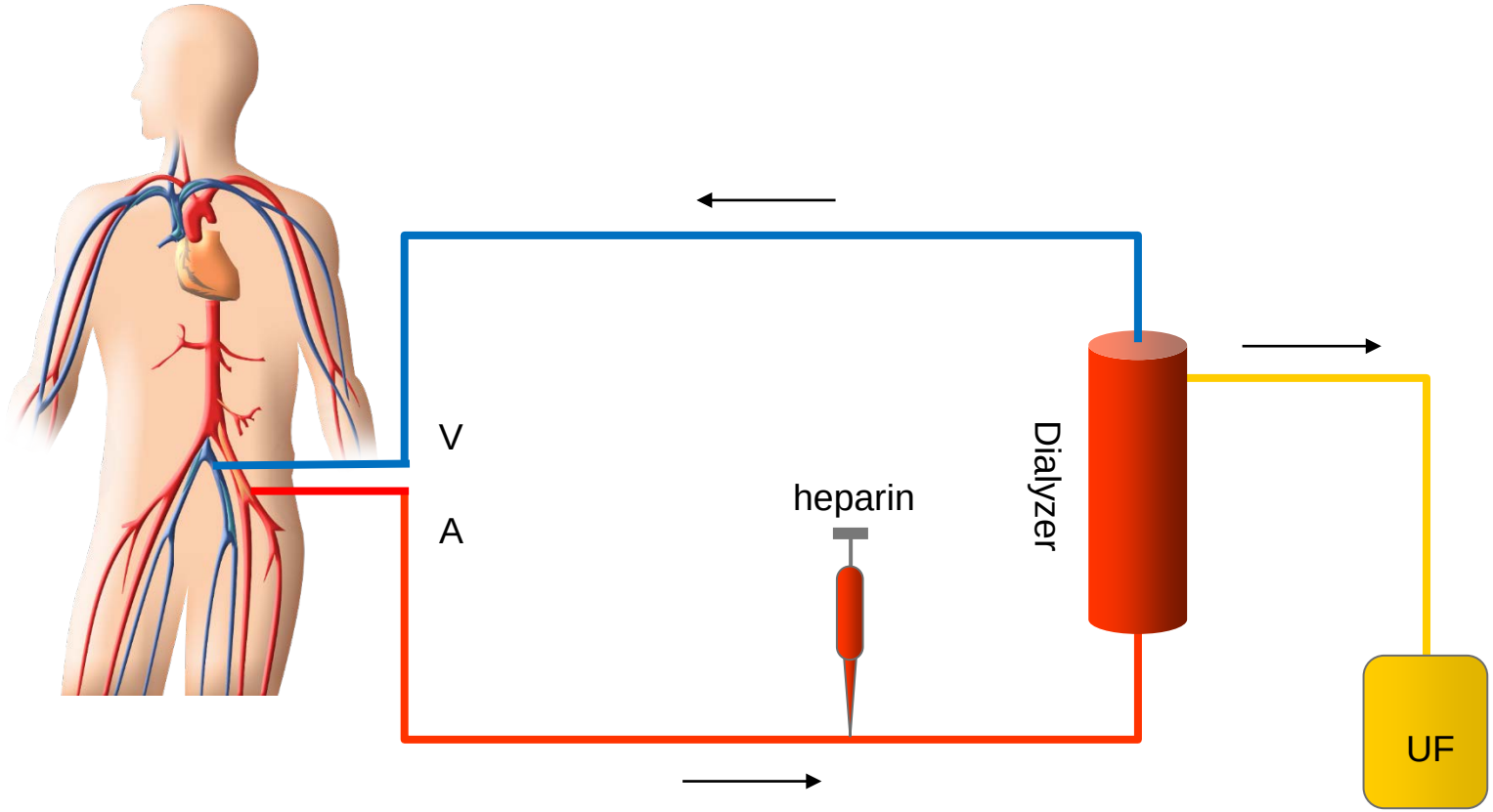
CRRT

PEX = Plasma Exchange
PAP = Plasma Adsorption/Perfusion

# History

| 1977 (CAVH) | 1981 (CVVH) | 1985 (CAVHD) | 1987 (CVVHD) | Today |
|---|---|---|---|---|
| Kramer et al. Report for the first time on continuous arterio-verous hemofiltration (CVAH) | Bischoff develops a pump-driven procedure as continuous veno-venous hemofiltration (CVVH) | Geronemus further develops continuous arterio-venous hemodialysis (CAVHD) | Uldall introduces continuous veno-venous hemodialysis (CVVHD) | |

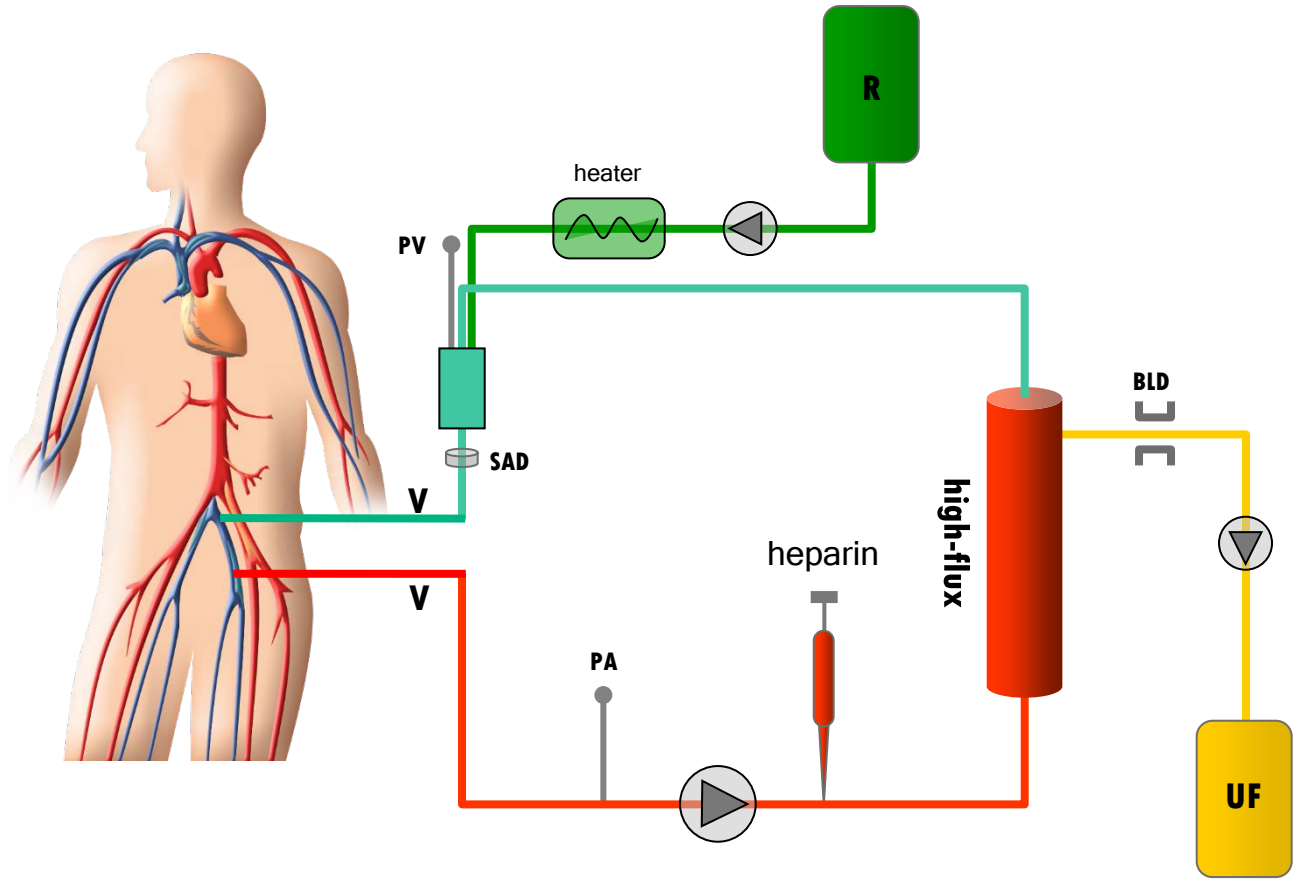
# CAVH Continuous arterio-venous hemofiltration




| Advantage |
| --- |
| • technically not complicated |

| Disadvantages |
| --- |
| • filtration depends on blood flow (low efficiency) |
| • arterial access (bleeding, clot formation) |

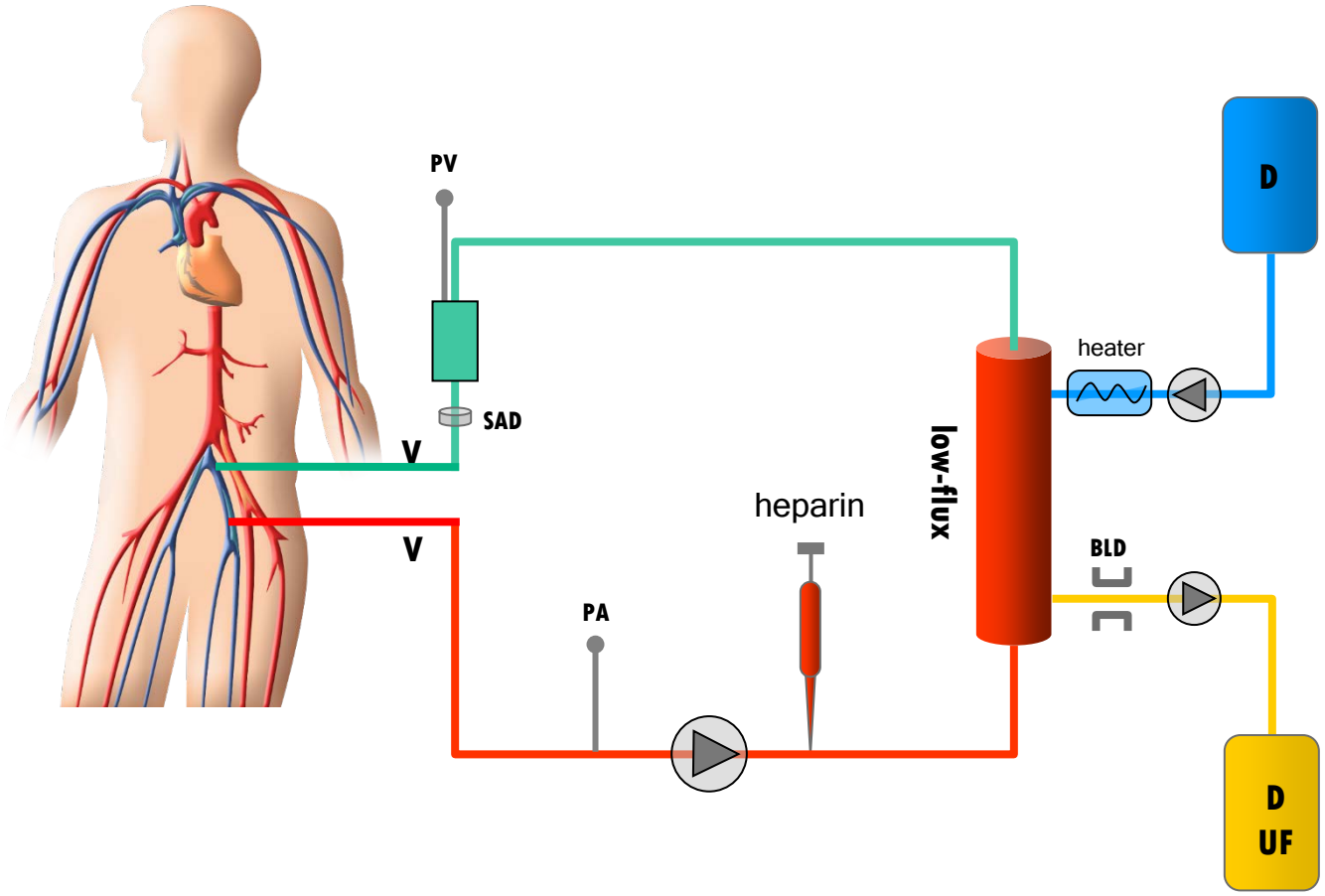
# CVVH Continuous veno-venous hemofiltration




| Advantage |
| --- |
| • no arterial access |
| • blood flow sufficient |
| • good elimination of large molecules |
| • good filtration |

| Disadvantages |
| --- |
| • complex machinery |
| • expensive |
| • fluid balance complicated |

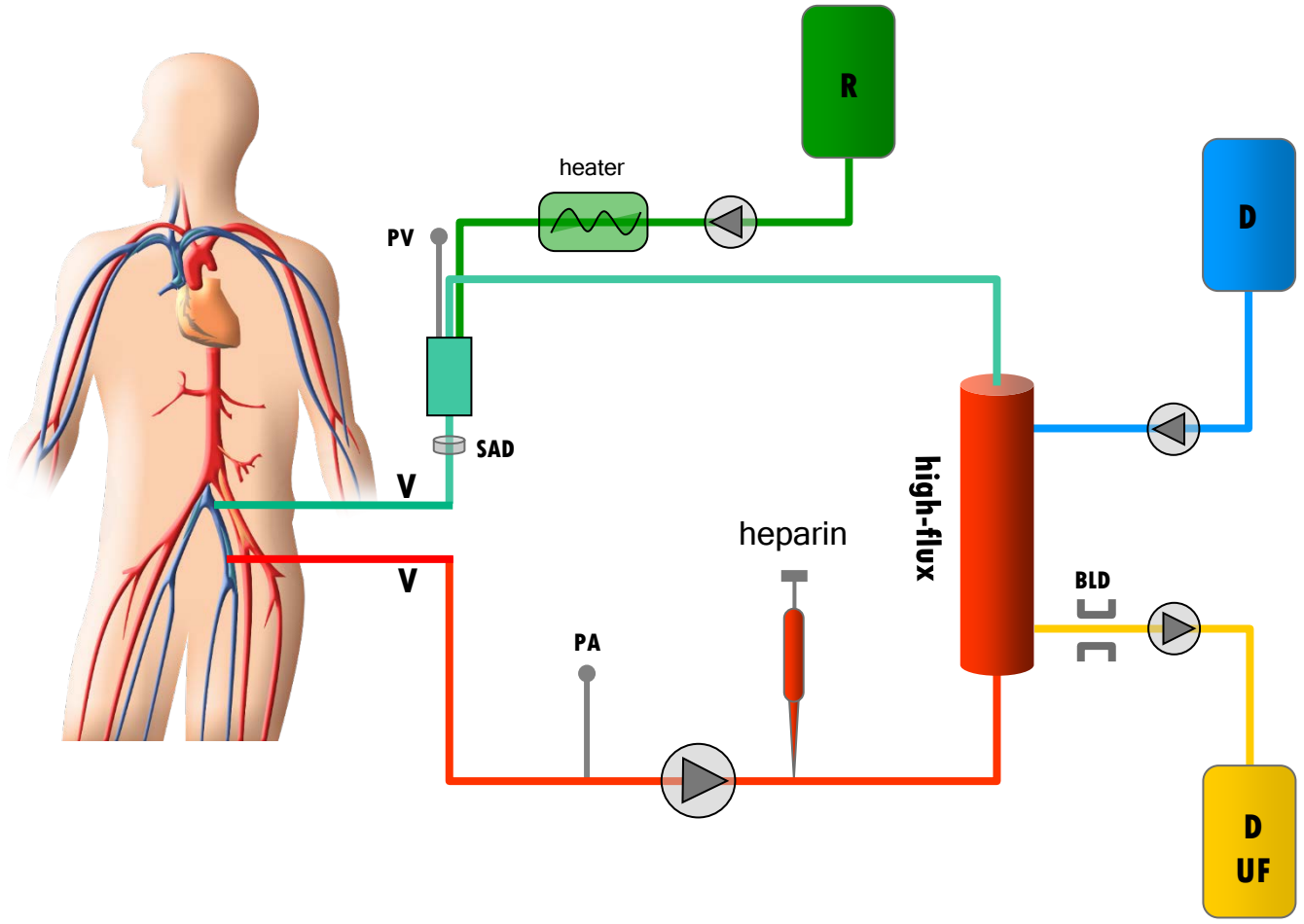
# CVVHD Continuous veno-venous hemodialysis




| Advantage |
| --- |
| • no arterial access |
| • blood flow sufficient |
| • good elimination of small molecules |
| • good filtration |

| Disadvantages |
| --- |
| • complex machinery |
| • expensive |
| • fluid balance complicated |

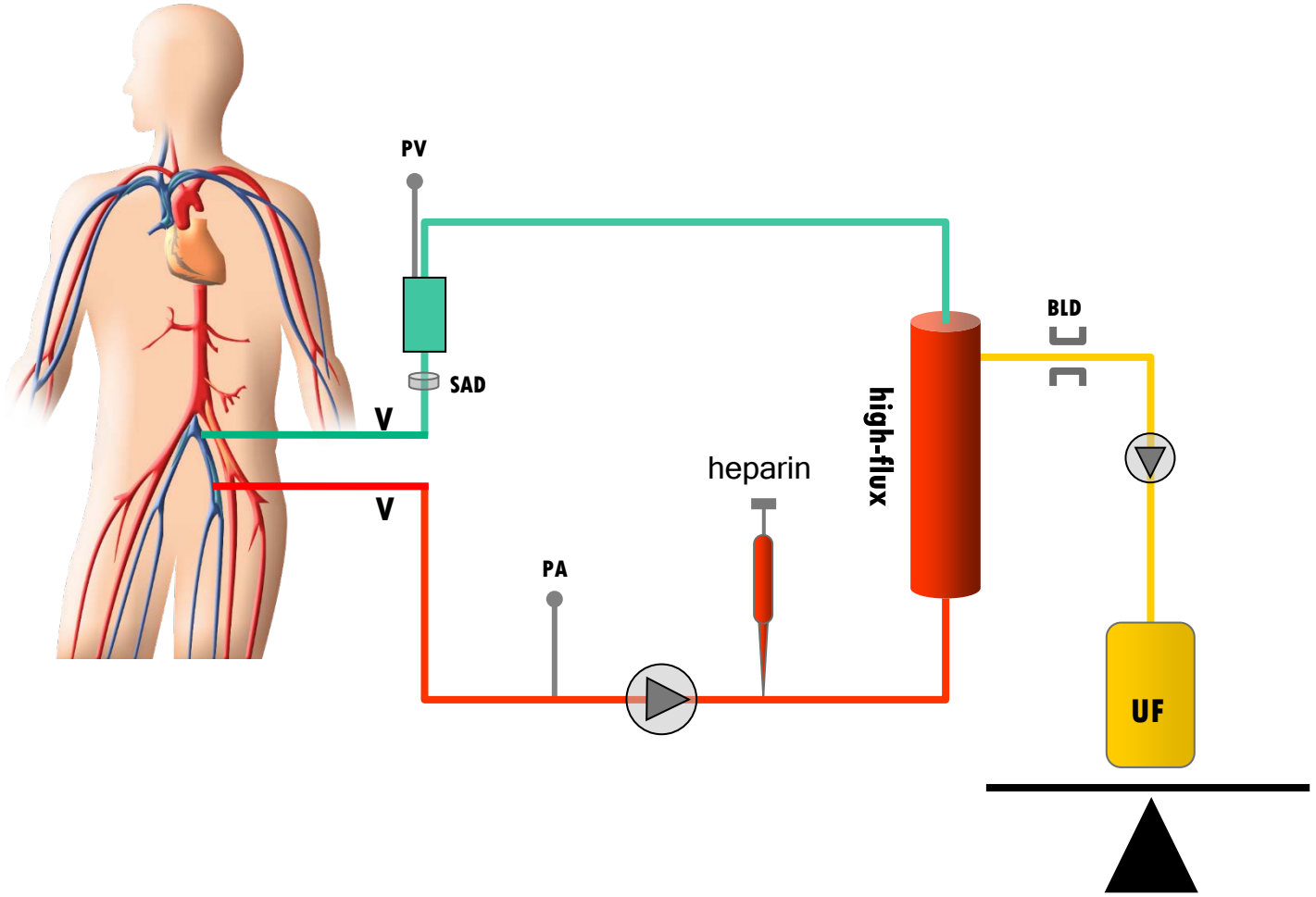
# CVVHDF Continuous veno-venous hemodiafiltration




| Advantage |
| --- |
| • no arterial access |
| • blood flow sufficient |
| • good elimination of small and large molecules |
| • good filtration |

| Disadvantages |
| --- |
| • complex machinery |
| • expensive |
| • fluid balance complicated |

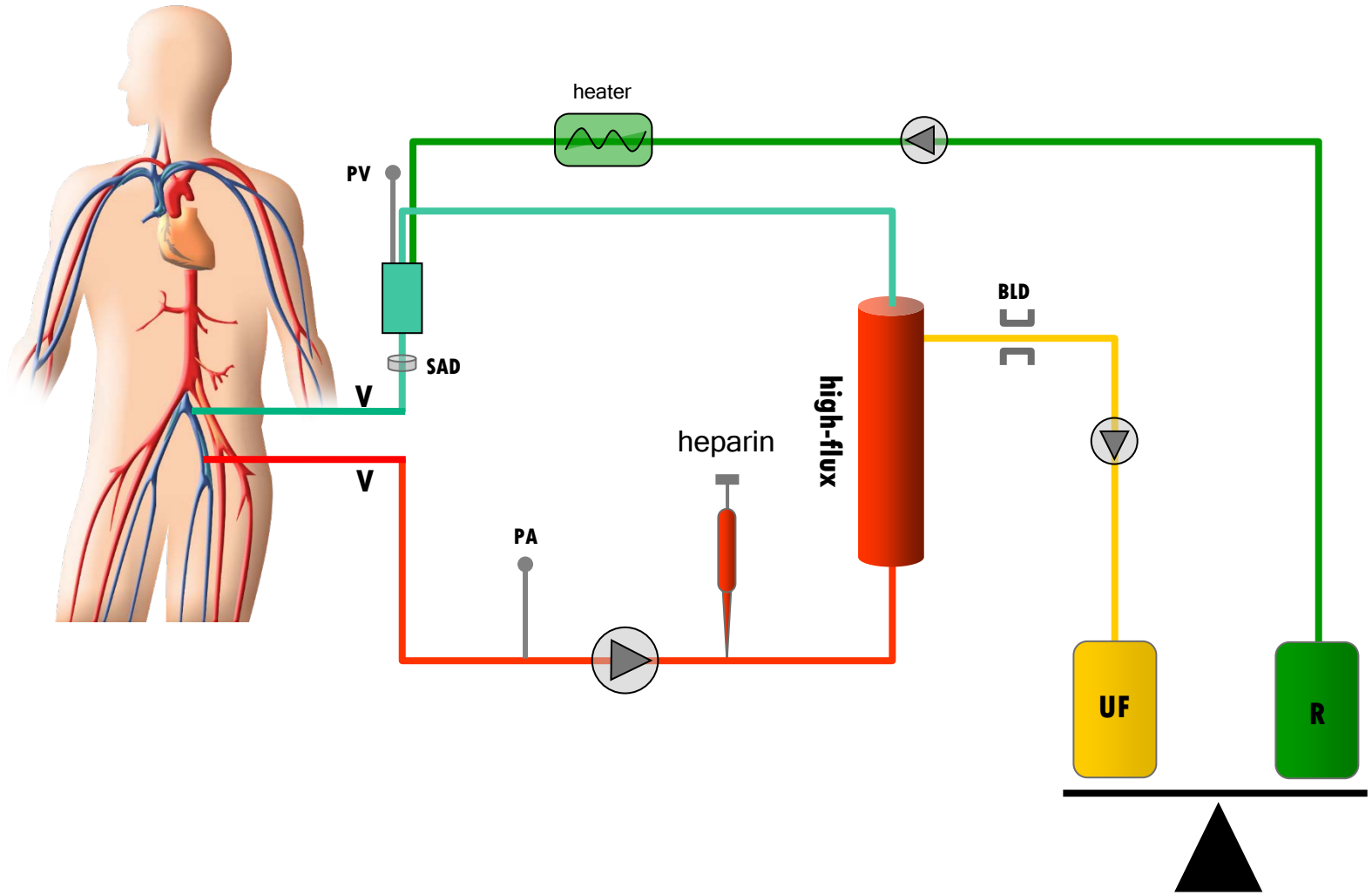
# SCUF Slow continuous ultrafiltration




| Advantage |
| --- |
| • no arterial access |
| • blood flow sufficient |
| • good filtration |

| Disadvantages |
| --- |
| • complex machinery |
| • expensive |
| • fluid balance complicated |

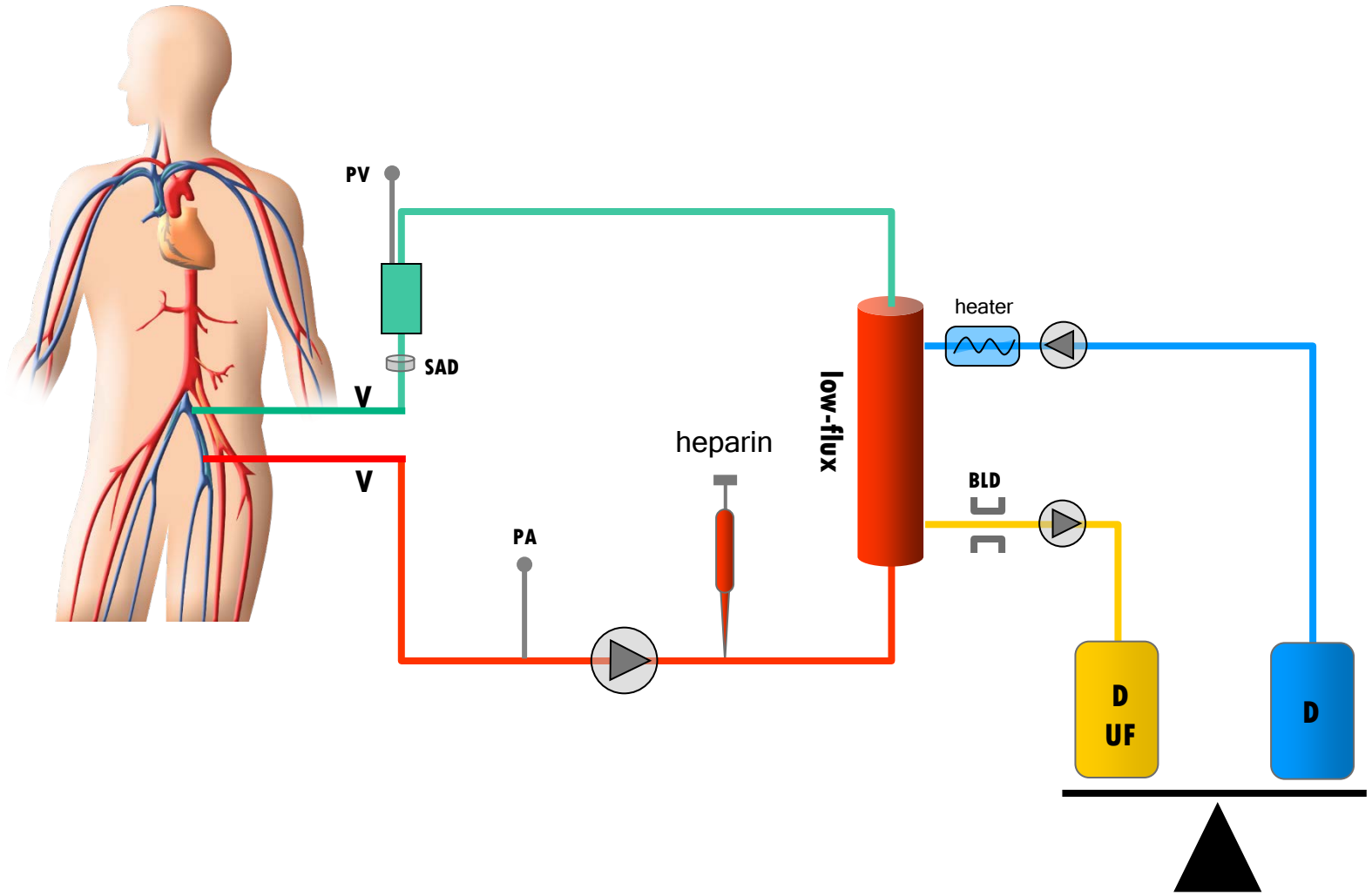
# CVVH Continuous veno-venous hemofiltration




| Advantage |
| --- |
| • no arterial access |
| • blood flow sufficient |
| • good elimination of large molecules |
| • exact filtration |

| Disadvantages |
| --- |
| • complex machinery |
| • expensive |

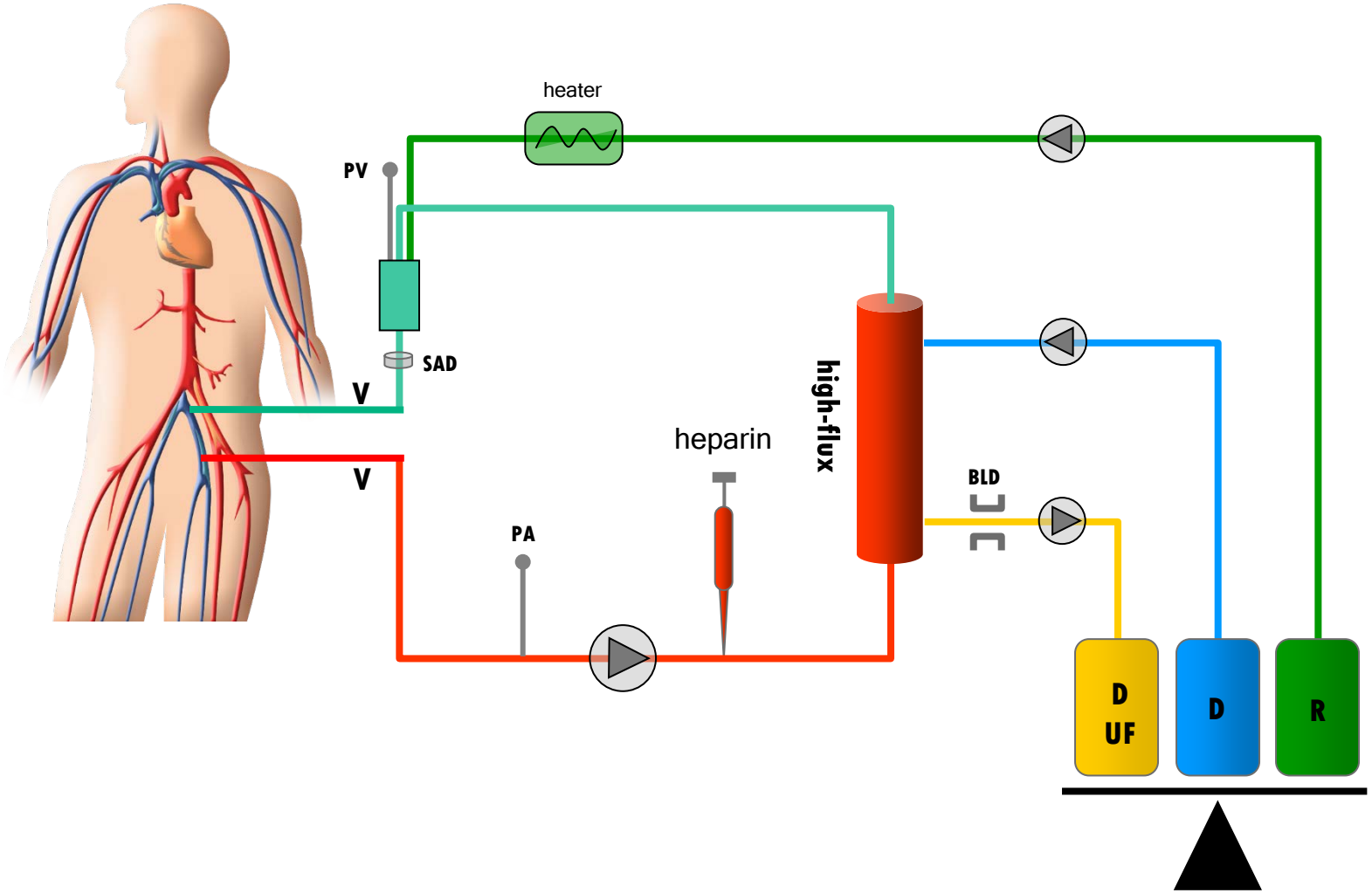
# CVVHD Continuous veno-venous hemodialysis




| Advantage |
| --- |
| • no arterial access |
| • blood flow sufficient |
| • good elimination of small molecules |
| • exact filtration |

| Disadvantages |
| --- |
| • complex machinery |
| • expensive |

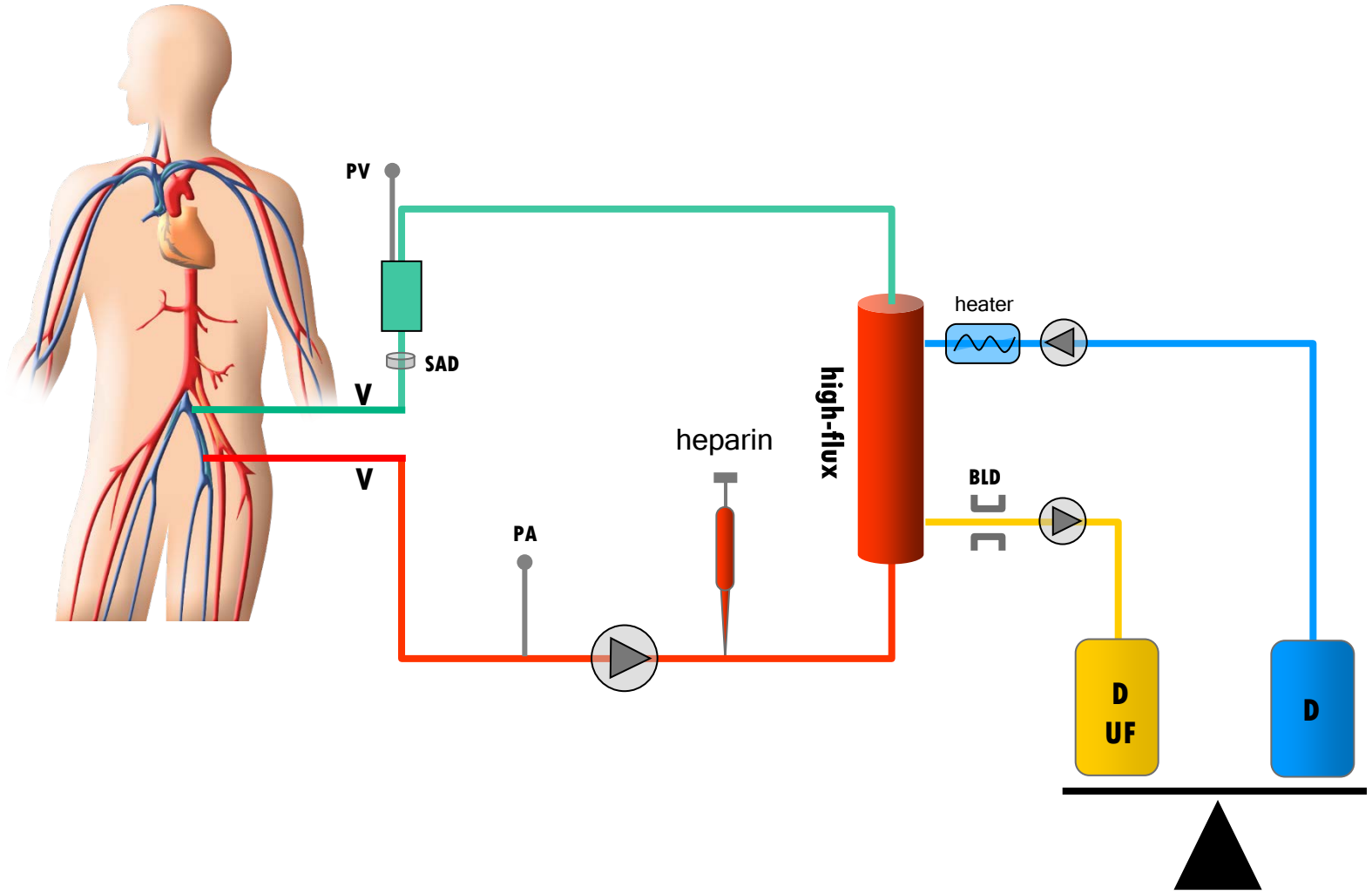
# CVVHDF Continuous veno-venous hemodiafiltration




| Advantage |
| --- |
| • no arterial access |
| • blood flow sufficient |
| • good elimination of small and large molecules |
| • exact filtration |

| Disadvantages |
| --- |
| • complex machinery |
| • expensive |

# CVVHFD Continuous veno-venous high flux dialysis




| Advantage |
| --- |
| • no arterial access |
| • blood flow sufficient |
| • good elimination of small and large molecules |
| • exact filtration |

| Disadvantages |
| --- |
| • complex machinery |
| • expensive |

# IHD – Intermittent Hemodialysis

Common HD, same like in chronic HD

- it requires reverse osmosis
- can be done daily
- low anticoagulation and less filter clotting problems

Therapy time 3-6 h
Blood flow rate $Q_B$ 250-350 ml/min
Dialysate flow rate $Q_D$ 300-800 ml/min

can be adapted

# SLEDD – Sustained Low-Efficiency Daily Dialysis

Therapy time 8-12 h
Blood flow rate flow $Q_B$ 100-200 ml/min
Dialysate flow rate $Q_D$ 100-300 ml/min
Ultrafiltration flow arte $Q_{UF}$ <350 ml/h

## Compromise between CVVHD and IHD

Combination of advantages between CVVHD and IHD

- it requires reverse osmosis
- slow but physiological efficiency
- daily dialysis for  less accumulation effect
- more hemodynamic stability
- better phosphate clearance
- low anticoagulation and less filter clotting problems

# Hemodialysis Techniques

| | SCUF | CVVH | CVVHD | CVVHDF | SLEDD | HD | HF | HDF |
|---|---|---|---|---|---|---|---|---|
| **Membrane permeability** | high-flux | high-flux | high-flux | high-flux | low/high-flux | low/high-flux | high-flux | high-flux |
| **Blood flow (ml/min)** | 100-250 | 100-250 | 100-250 | 100-250 | 100-200 | 250-350 | 250-350 | 250-350 |
| **Dialysate flow (ml/min)** | ---- | ---- | 15-45 (ml/h/kg) | 15-45 (ml/h/kg) | 100-300 | 300-800 | 300-800 | 300-800 |
| **Substitution flow (ml/min)** | ---- | 15-45 (ml/h/kg) | ---- | 15-45 (ml/h/kg) | ---- | ---- | 50-200 | 50-200 |
| **Duration (h)** | variable | >24 | >24 | >24 | 8-12 | 3-6 | 3-6 | 3-6 |

# Mortality

**50-70%**

**Patient spectrum** has been changed:

- less uncomplicated or radiopaque material induced AKI
- more post-operative or post-traumatic AKI with sepsis and MOF

Inter . . . mittent

↕

**C o n t i n u o u s**

Dose

Beginning

Access

Buffer

Mediator

Anticoagulation

Membrane

Hemodynamic

Loss of Energy

..... What about adequate therapy?

# Dialysis Treatment

## Intermittent

| Advantages |
| --- |
| low heparinisation |
| easy patient mobilization |
| high clearance of small molecules |

| Disadvantages |
| --- |
| disequilibrium syndrome |
| hemodynamic instability |
| accumulation of fluid and toxins |

## Continuous

| Disadvantages |
| --- |
| continuous heparinisation |
| difficult patient mobilization |
| low clearance of small molecules |

| Advantages |
| --- |
| continuous and slow elimination |
| hemodynamic stability |
| continuous removal of fluid and toxins |

# Complications

| Intermittent |
| --- |
| 1. Hypotension |
| 2. Arrhythmia |
| 3. Hemolysis |
| 4. Muscle Cramps |
| 5. Air Embolism |
| 6. Disequilibrium Syndrome |
| 7. Fluid Lung |
| 8. Hyperkalemia |
| 9. Hypertension |

| Continuous |
| --- |
| 1. Fluid Balance Error |
| 2. Filter Clotting |
| 3. Low Temperature |
| 4. Access Problems |
| 5. Coagulation Problems |
| 6. Hypotension |
| 7. Infection/Sepsis |
| 8. Air Embolism |
| 9. Disconnection |

# Summary

## CRRT is a very valuable and validated option for critical ill patients with AKI

Provide support for renal and non-renal indications

- SCUF, CVVH, CVVHD and CVVHDF

Recent studies suggest that CRRT is superior to IHD with respect to recovery of renal function

- Especially for patient with hemodynamic instability

CRRT main goals are removal of waste products, restoration of acid/base balance, and correction of fluid and electrolyte abnormalities,

- While maintaining hemodynamic stability

**Replace, at the best, the lost function of the native kidney**

B|BRAUN
SHARING EXPERTISE

# 2. UNDERSTAND THE RATIONALE FOR EACH CRRT MODALITY AND TYPE OF VASCULAR ACCESS

## RATIONALE FOR USING DIFFERENT TYPE OF PROCESS & IMPORTANCE OF VASCULAR ACCESS

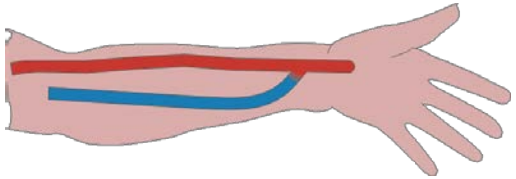
# Objective of the module

1. Understand type of vascular access in CRRT
2. Understand the importance of blood flow rate

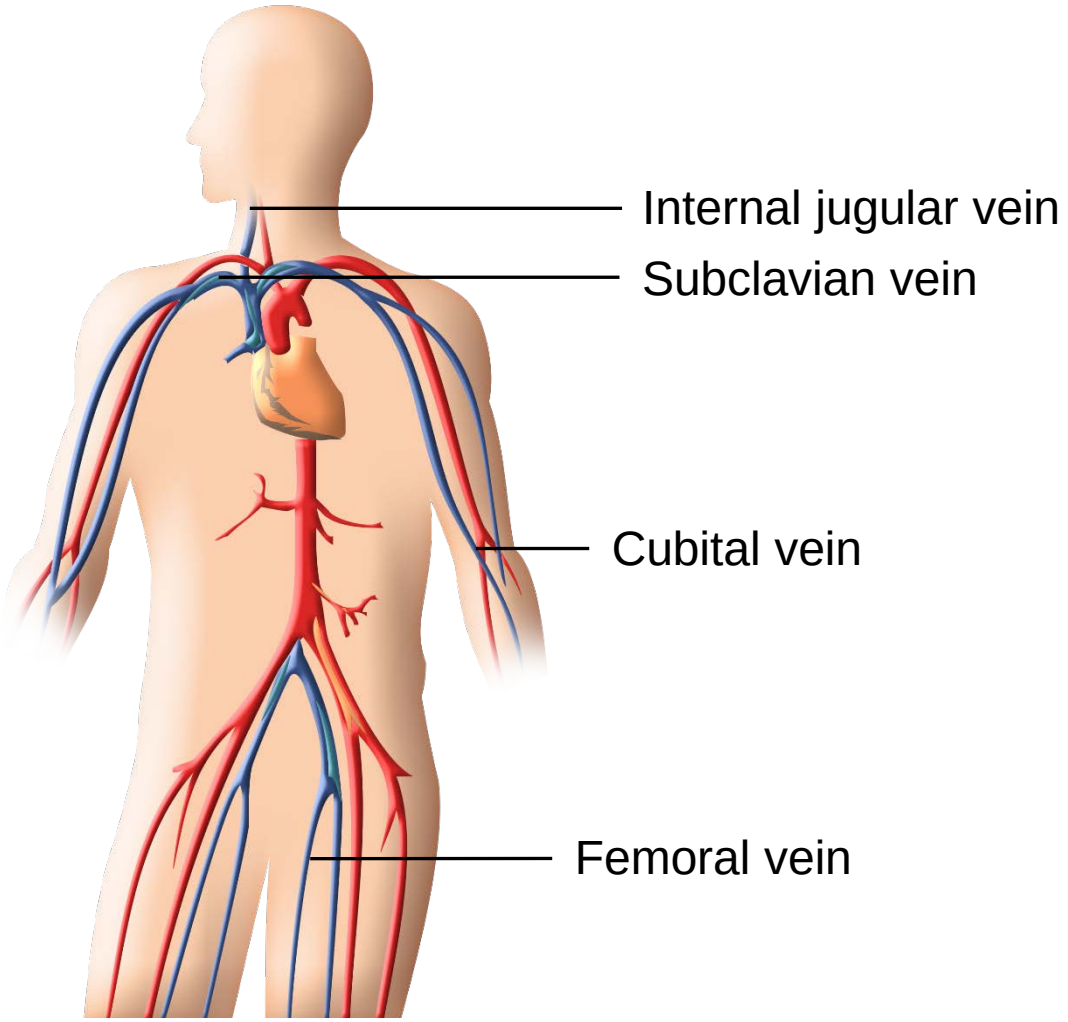
# Vascular access

## Vessel access

- Peripheral vein
- Arterio-venous fistula
- Central-venous access



Cimino Fistula



# Catheter Type

## Jugular

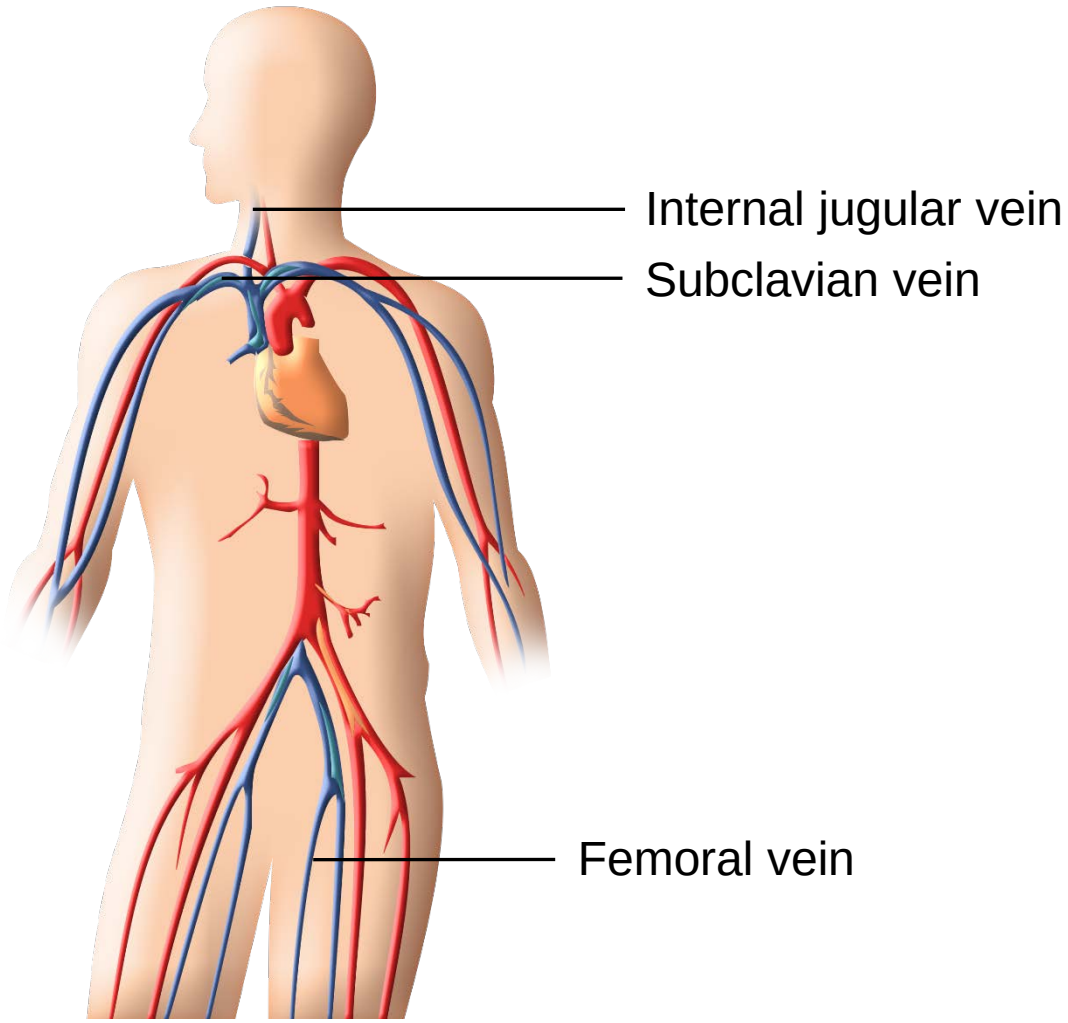
- Most used
- Low complication rate
- Checking by ECG or x-ray

## Subclavian

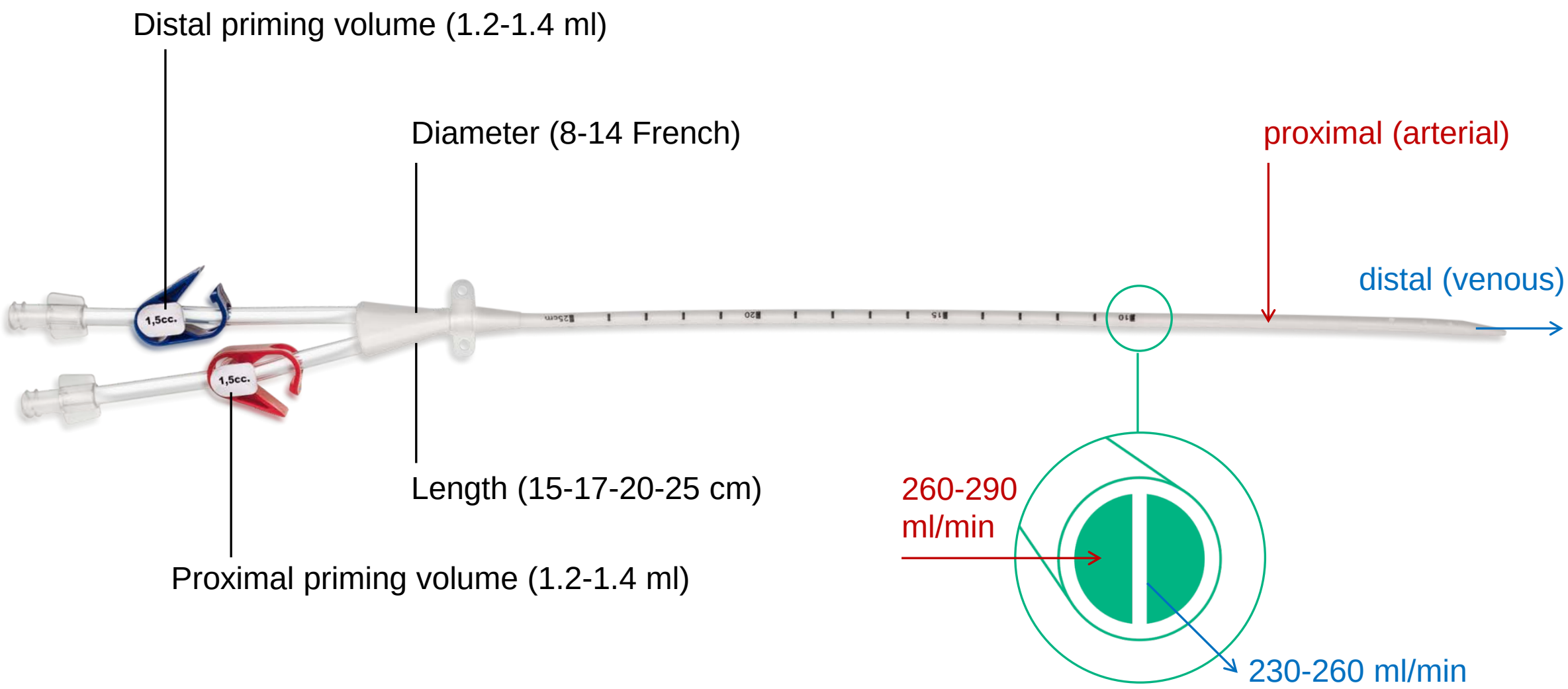
- Less used
- Higher complication rate
- Checking by x-ray

## Femoral

- Seldom used
- Some complication rate
- Time and cost intensive



# Temporary double lumen catheter



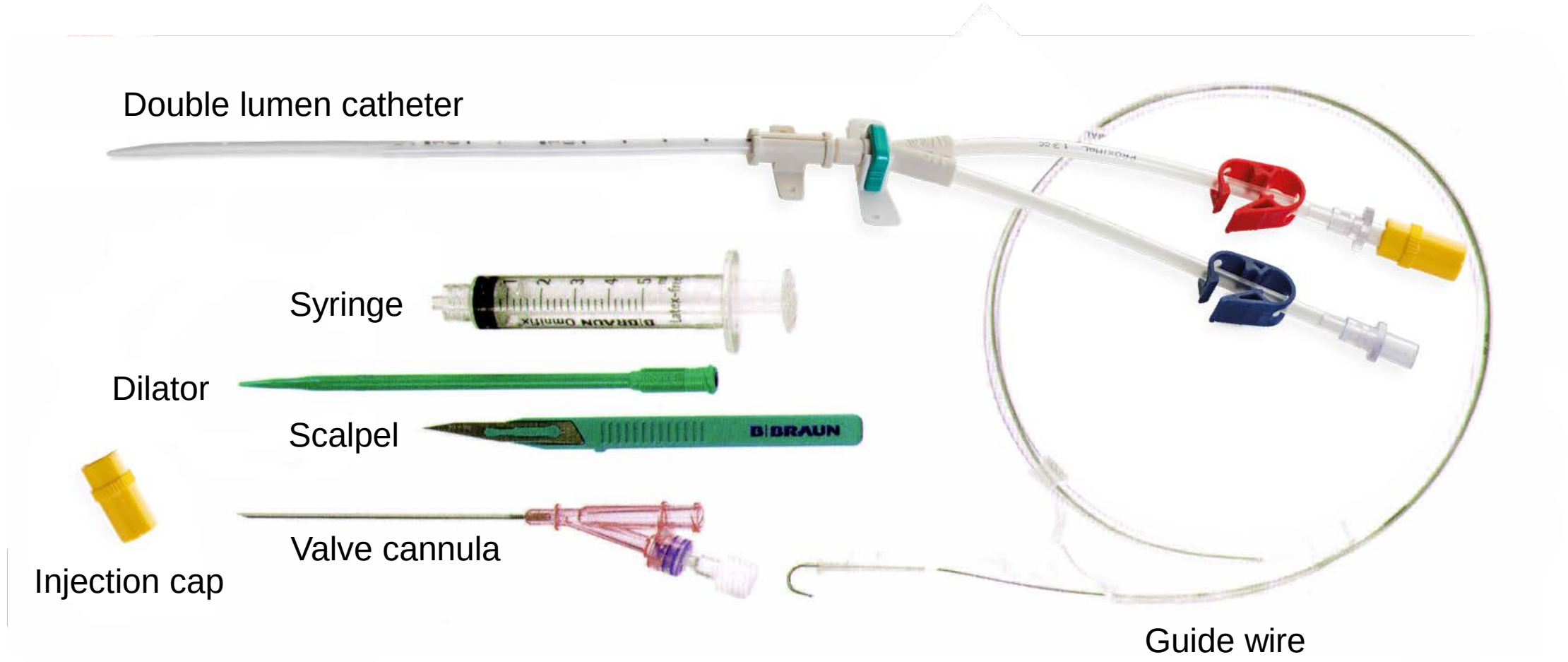
# The catheter set

Length and placement site of catheter

- For jugular placement, it’s usually 12.5 cm on the right side and 15 cm on the left side
- For subclavian placement, it’s usually 15 cm on the right side and 20 cm on the left side
- The femoral vein should have an extra long catheter (24 -28 cm)
- Right side is anatomically easier to cannulate for jugular & subclavian
- As a rule, the left side needs the longer catheter (Left-Long)

# Catheter set

## Hemocat Signo



# Hygiene and Care of CVC

- take care of aseptic handling during patient‘s connection and disconnection
- permanent observation for signs of skin inflammation at catheter site
- after every therapy rinse with NaCl and fill with anticoagulant to prevent any clotting and infections (catheter-lock)
- change regularly catheter bandage in septic way

# Summary

## Double lumen CVC is first choice of vascular access in critical ill patients with AKI

Different positions of CVC

- Jugular, subclavian and femoral

Different sizes of CVC

- Length (15-17-20-25 cm)
- Diameter (8-14 French)
- Priming volume of each lumen (1.2-1.4 ml)

Different measures to prevent clotting and infections

- Catheter Lock, regular change of bandage, regular inspection

**Take care of aseptic handling !!**

# 3. DISCUSS THE KEY PARTS ANTICOAGULATION

## IMPORTANCE OF ANTICOAGULATION IN CRRT USAGE

# Objective of the module

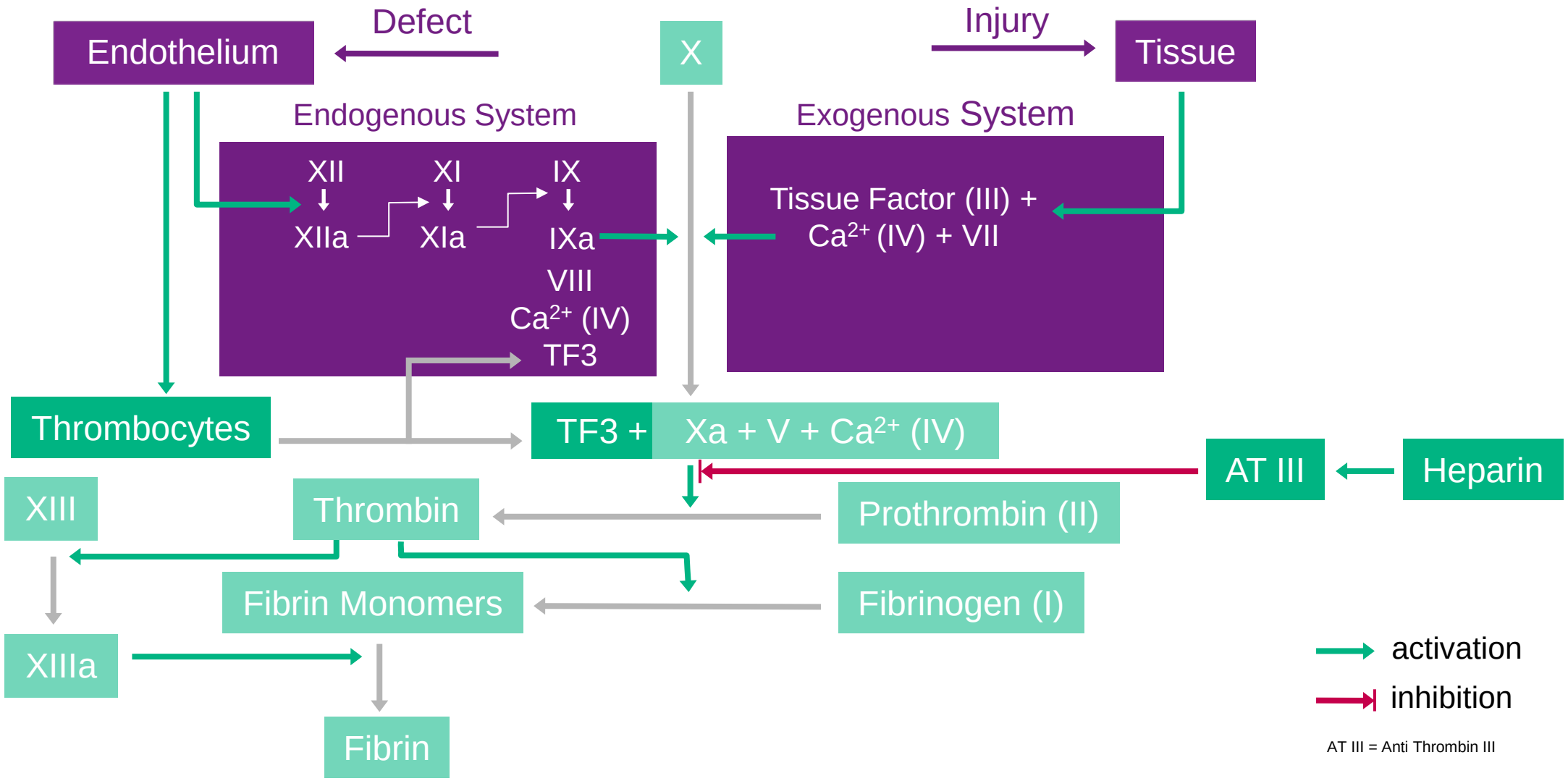
1. Understand importance of anticoagulation in ICU patient
2. Understand usage of heparin
3. Understand alternative anticoagulation

# Anticoagulation in CRRT

| | Comments |
|---|---|
| **Heparin** | Standard method, control by aPTT/ACT, risk of thrombocytopenia, antidote Protamine |
| **Minimal Heparin** | Low dosing in case of bleeding risk, control by aPTT/ACT, risk of thrombocytopenia, antidote Protamine |
| **Intermittent Heparin** | Hourly application, control by aPTT/ACT, risk of thrombocytopenia, antidote Protamine |
| **Regional Heparin** | Heparin prefilter, Protamin postfilter, reduced bleeding risk, Protamin side effects |
| **Heparin-free** | In case of bleeding risk, 20000 IU Heparin in 2 l rinsing solution and 30‘ recirculation, treatment without Heparin |
| **LMWH** | In case of bleeding risk, control by Anti F Xa |
| **Danaparoid** | Heparin-like, in case of bleeding risk, control by Anti F Xa |
| **Hirudin** | In case of Heparin Contraindication, low experience, half-life time up to 2 days |
| **Citrate** | Tris-Na-Citrate prefilter, $CaCl_2$ postfilter, hypocalcemia, alkalosis, requires diffusive system (CVVHD) |
| **Prostacyclin** | Often used with Heparin, thrombocytes aggregation inhibitor, hypotension |
| **Nafamostate Mesilate** | In case of bleeding risk, low experience, serine protease inhibitor (thrombin block) |
| **Predilution** | In case anticoagulation not allowed, low clearance for middle molecules |
| **Intermittent Rinsing** | In case anticoagulation not allowed, 100-200 ml NaCl every ½ h |

aPTT = activated Partial Thromboplastin Time
ACT = Activated Clotting Time
IU = International Unit

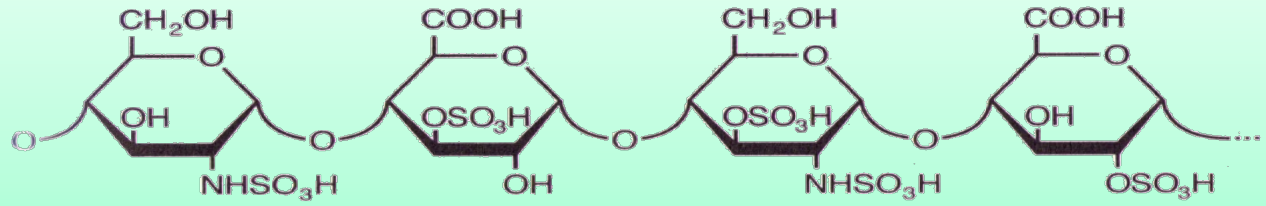
# Heparin Anticoagulation



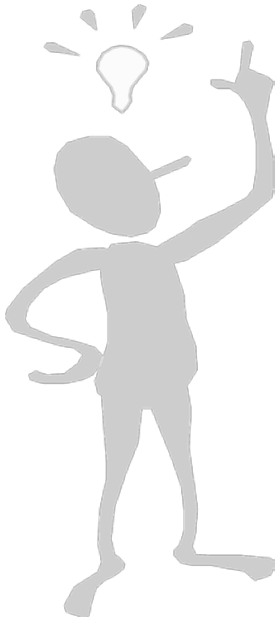
# Heparinisation in CRRT

| Bleeding Risk | Initial IU/kg | Continuous IU/kg/h | aPTT sec. | ACT sec. |
|---|---|---|---|---|
| **No Risk** | 50 | 10-20 | 60 | <250 |
| **Small Risk** | 15-25 | 5-10 | 45 | 160-180 |
| **High Risk** | 10 | 2.5-5 | 30 | 120 |

# Heparin

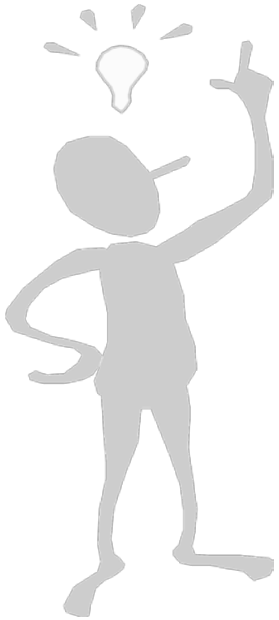



Heparin (sulfated glycosaminglycan)



- Molecular Weight 3000-30000 Da (Ø 15000 Da)
- Effects through Antithrombin III (AT III) !!!
- Half Live ca. 1h
- Antidote: Protamine, Effect 1:1

# Heparinisation



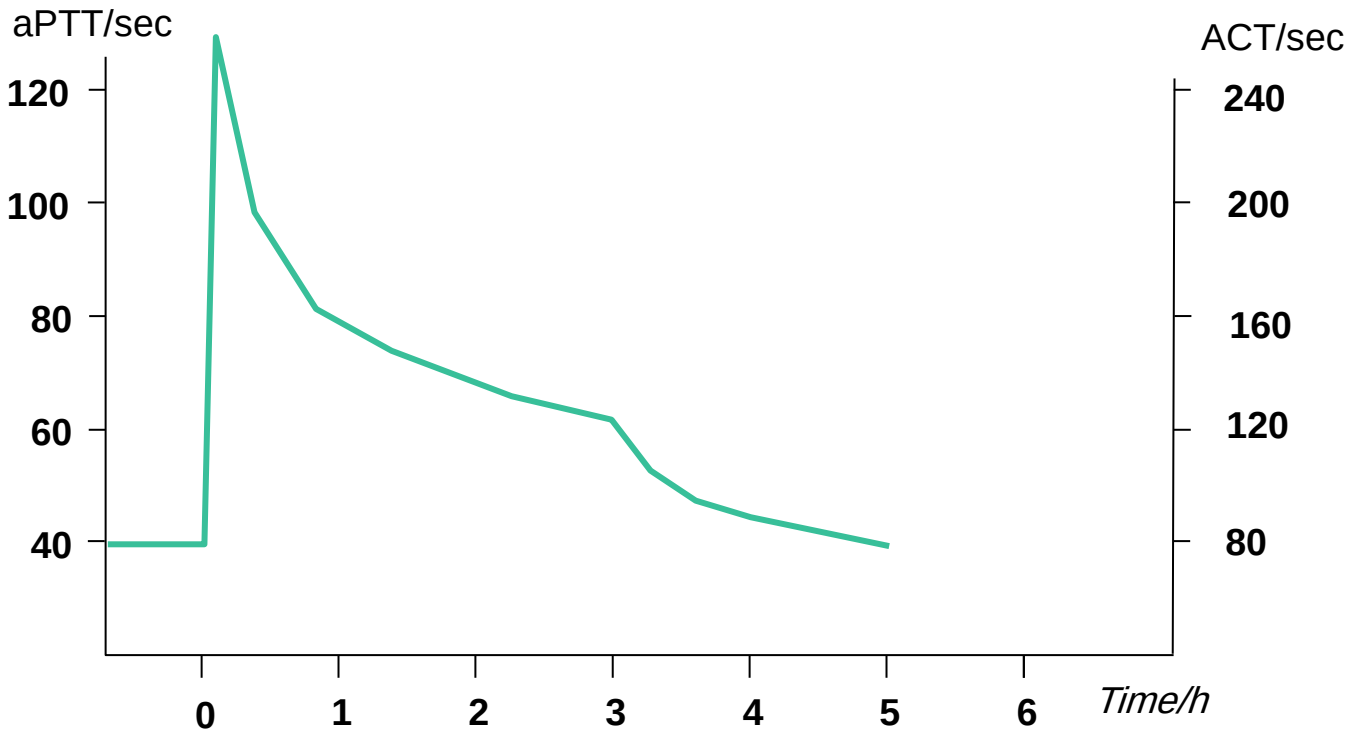
- Standard Heparin 5000 IU/ml
- Heparin Solution:
  2 ml Standard Heparin + 18 ml NaCl → 500 IU/ml
- Dose at first Dialysis:
  3000-5000 IU as Initial Bolus
  15-20 IU/kgBW/h continuously
- Max. Heparin Dose in each Dialysis 10000 IU

## Control by aPTT or ACT:

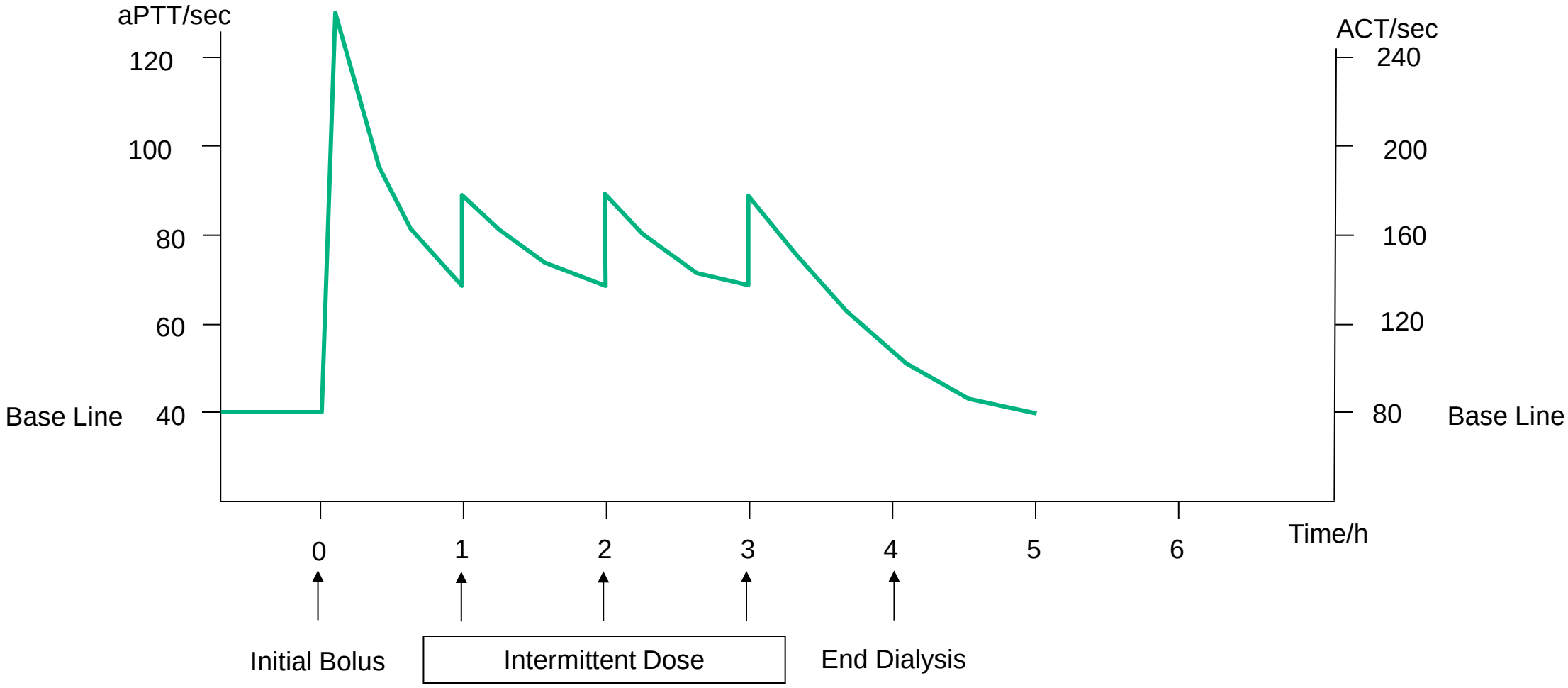
aPTT = activated Partial Thromboplastin Time, Baseline 30-40”, Therapy value ca. double
ACT = Activated Clotting Time, Baseline ca. 80” (by AC-Tester), Therapy value <150”

# Heparinisation Methods

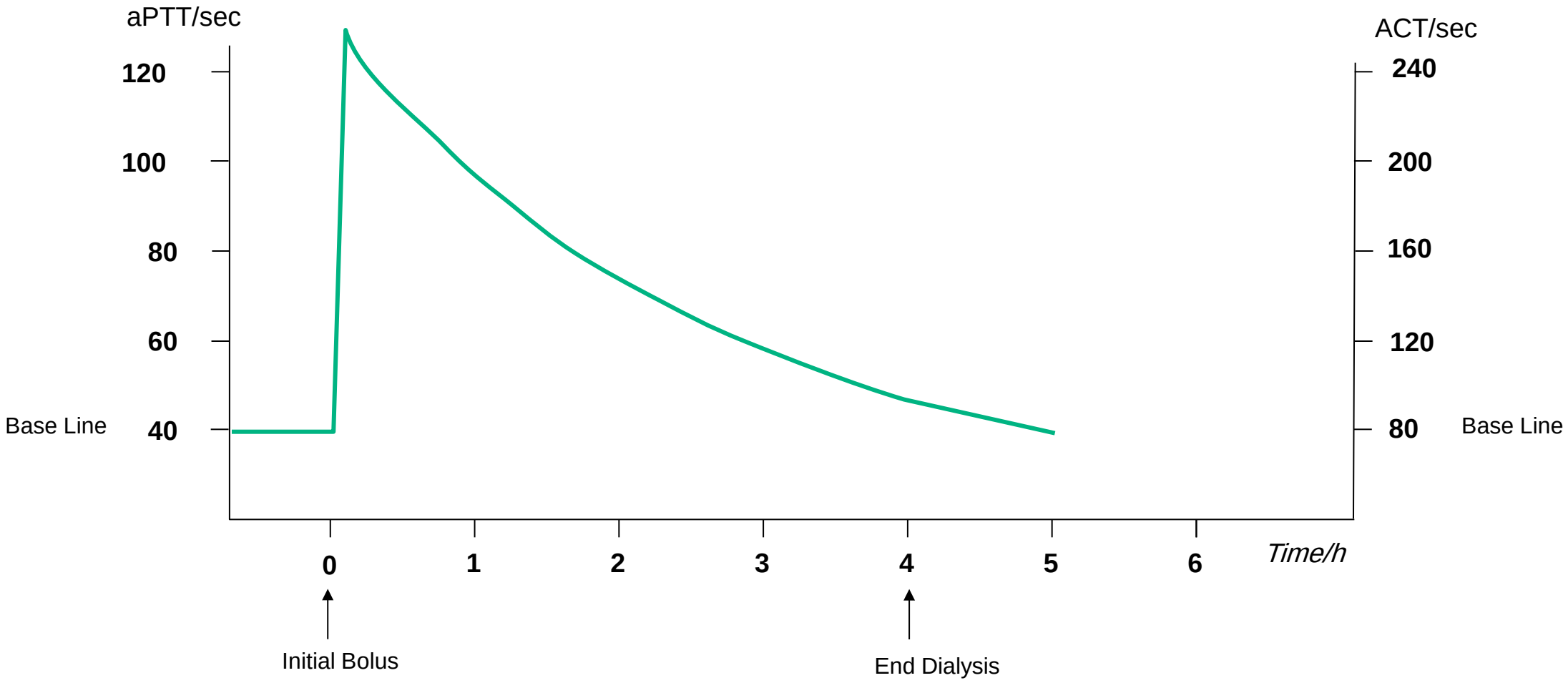
- Continuous Heparinisation
- Intermittent Heparinisation
- “Single-Shot” Heparinisation
- Regional Heparinisation
- Minimal Heparinisation
- Heparin free Dialysis



# Intermittent Heparinisation



# “Single-Shot” Heparinisation



# Heparin – Side Effects

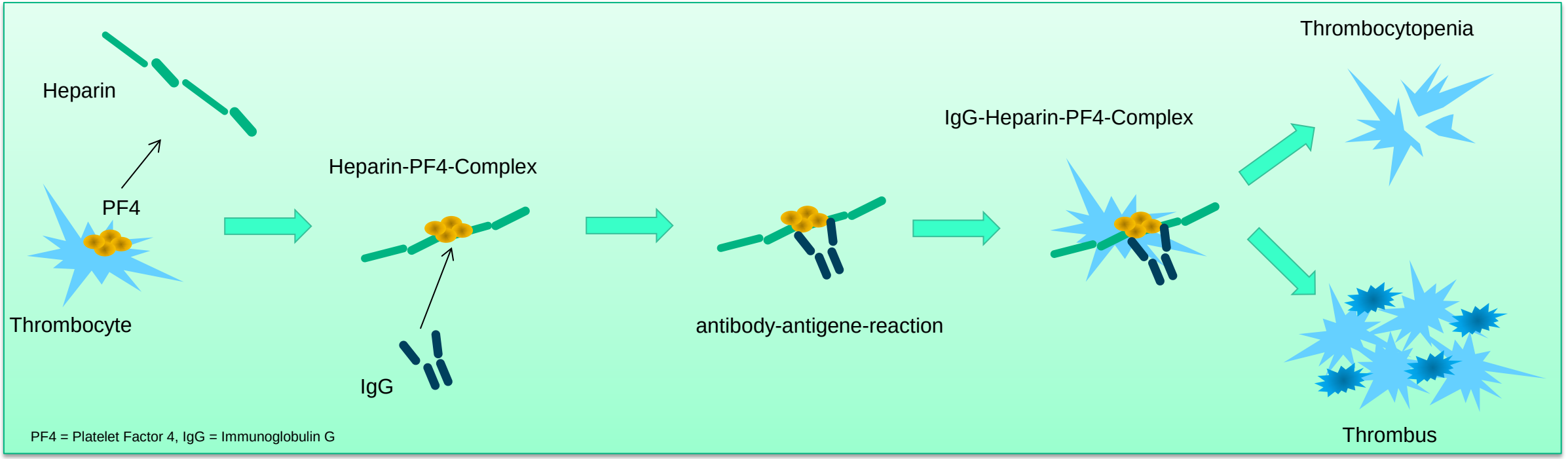
- Loss of hair
- Hyperlipidemia
- Osteoporosis
- Allergy
- Pruritus
- Thrombocytopenia
- HIT I, HIT II

HIT = Heparin Induced Thrombocytopenia

# HIT – Heparin Induced Thrombocytopenia

2 types:

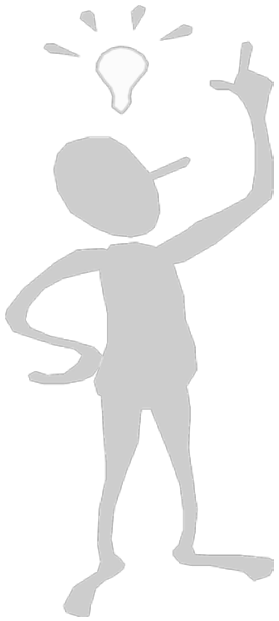
- HIT 1 after 5 days in ca. 5%, Thrombocytopenia >100,000/µl, asymptomatic
- **HIT 2** after 5-10 days in ca. 3%, Thrombocytopenia <100,000/µl, “white clot syndrome”, immune reaction, in sensitized patient after few hours, heparin contraindicated !!*




*Innere Medizin 2012 Taschenbuch – 1. Oktober 2011 von Gerd Herold (Autor) , Taschenbuch: 966 Seiten, Verlag: Herold, Gerd (1. Oktober 2011), S. 808

# Low Molecular Weight Heparin

- Fragmin
- Fraxiparin
- Clexane



In case of low molecular weight heparin often intermittent method is used !
For therapy control are aPTT or ACT not usable, but Anti-Factor Xa Activity !
Indication especially in high bleeding risk patients !

# Summary

## Anticoagulation is in extracorporeal therapies necessary but sometimes not indicated in critical ill patients with AKI

Heparin as systemic anticoagulation

- Molecular structure, half-life time, application, dose, side effects

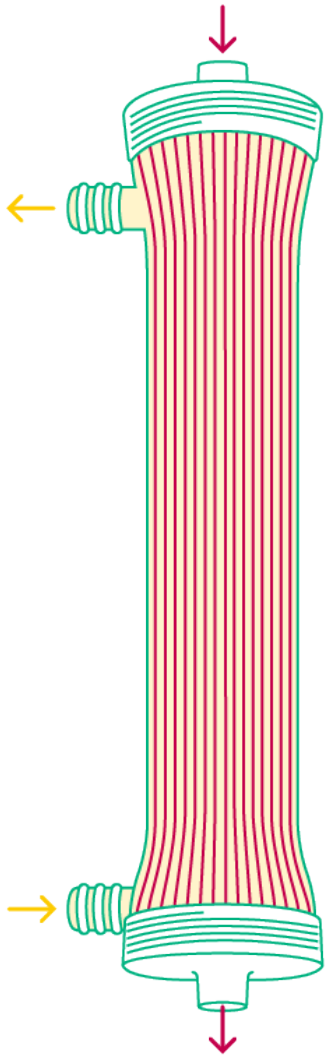
# 4. UNDERSTAND THE FUNCTION OF HEMOFILTERS

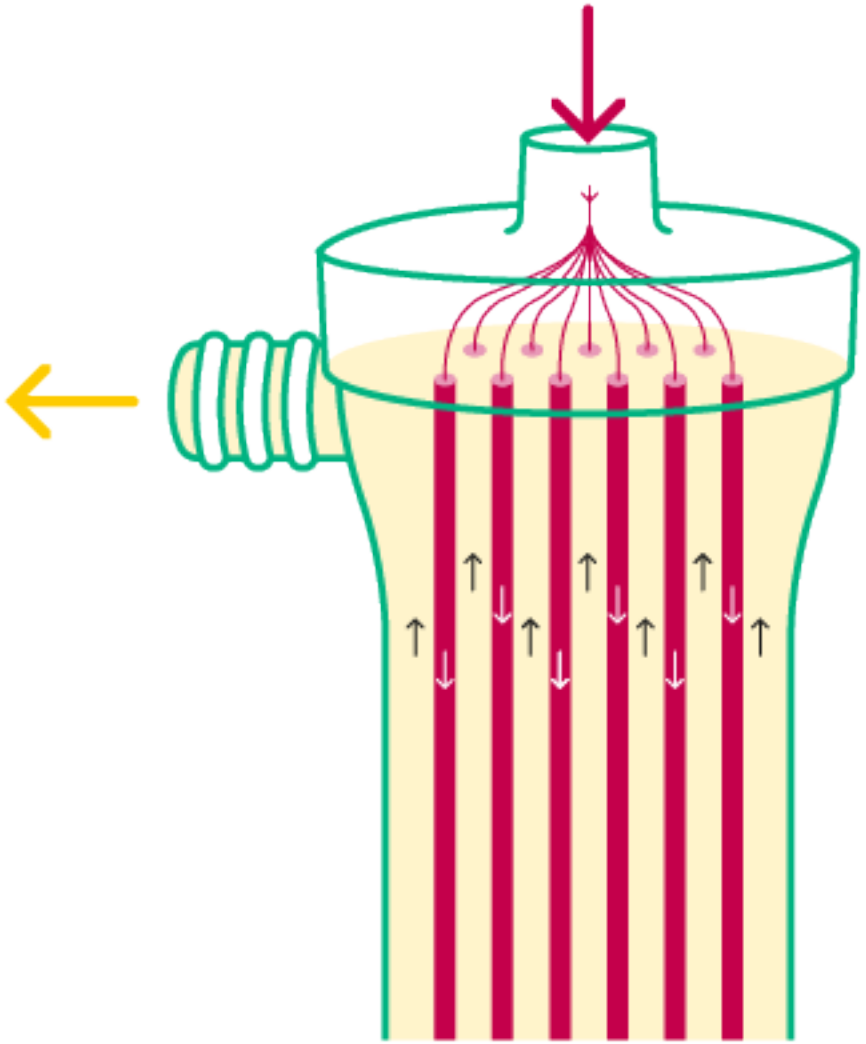
## IMPORTANCE OF HEMOFILTERS AND RATIONALE FOR USING SUBSTITUTION

# Objective of the module

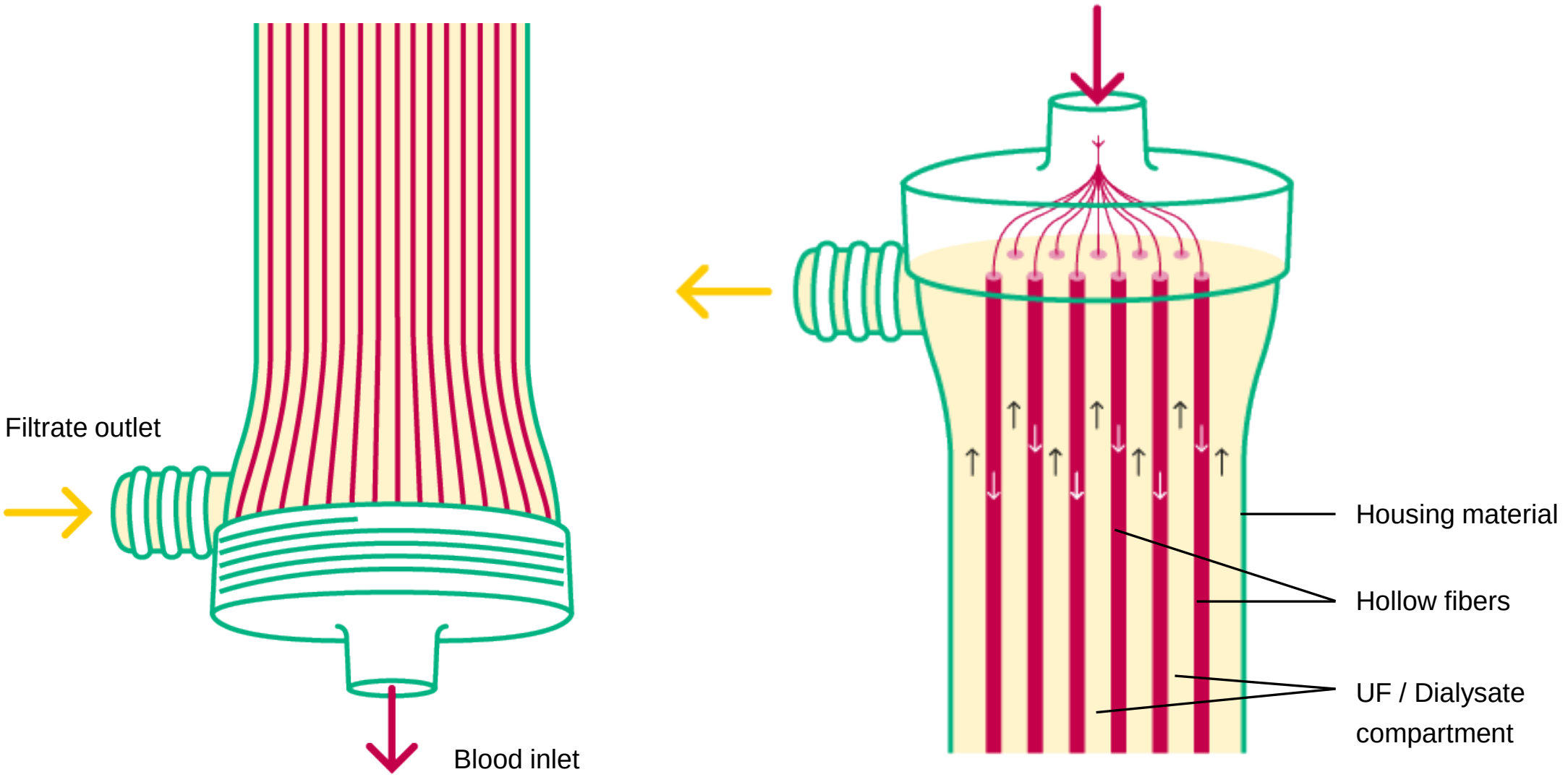
1. Understand importance of hemofilter in CRRT
2. Understand structure of hemofilter
3. Understand different types of membranes
4. Understand types of clearances and ultrafiltration

# Hemofilter structure

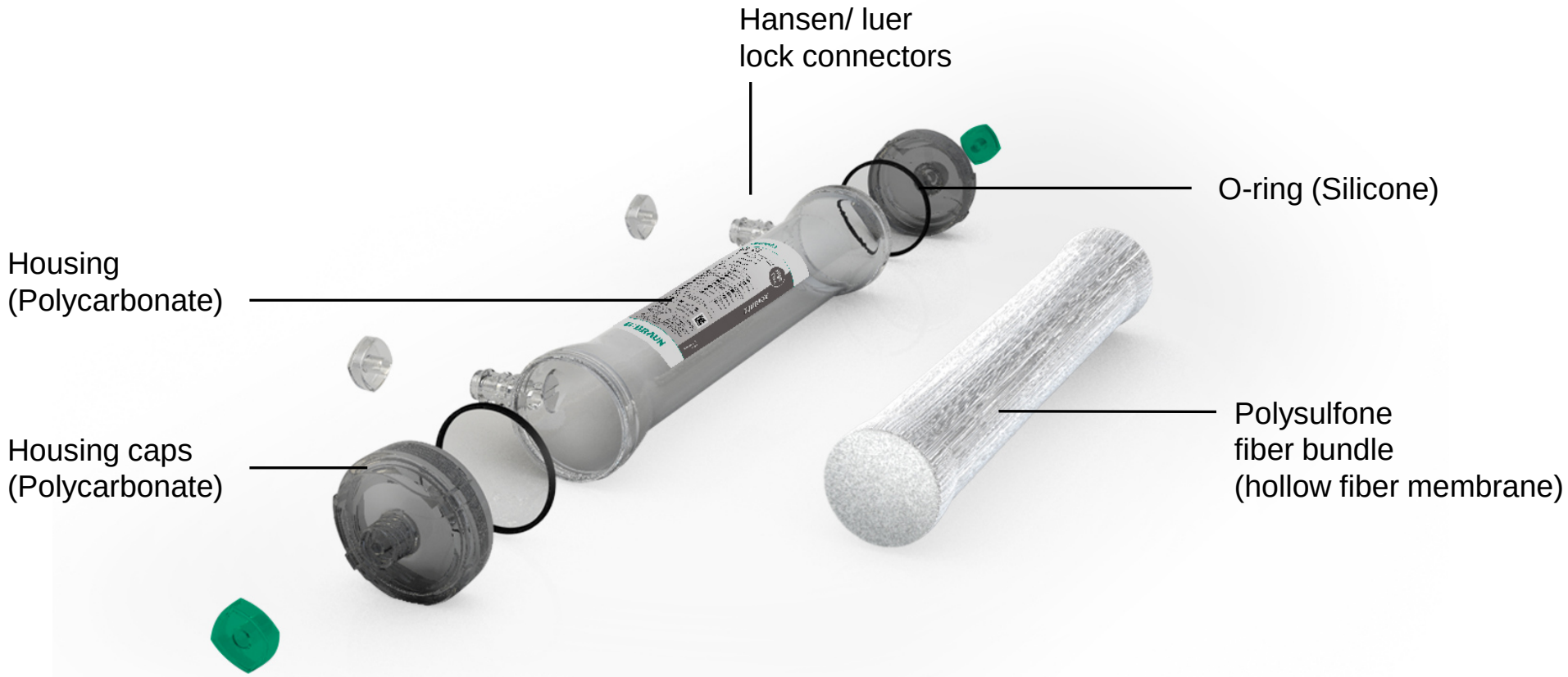




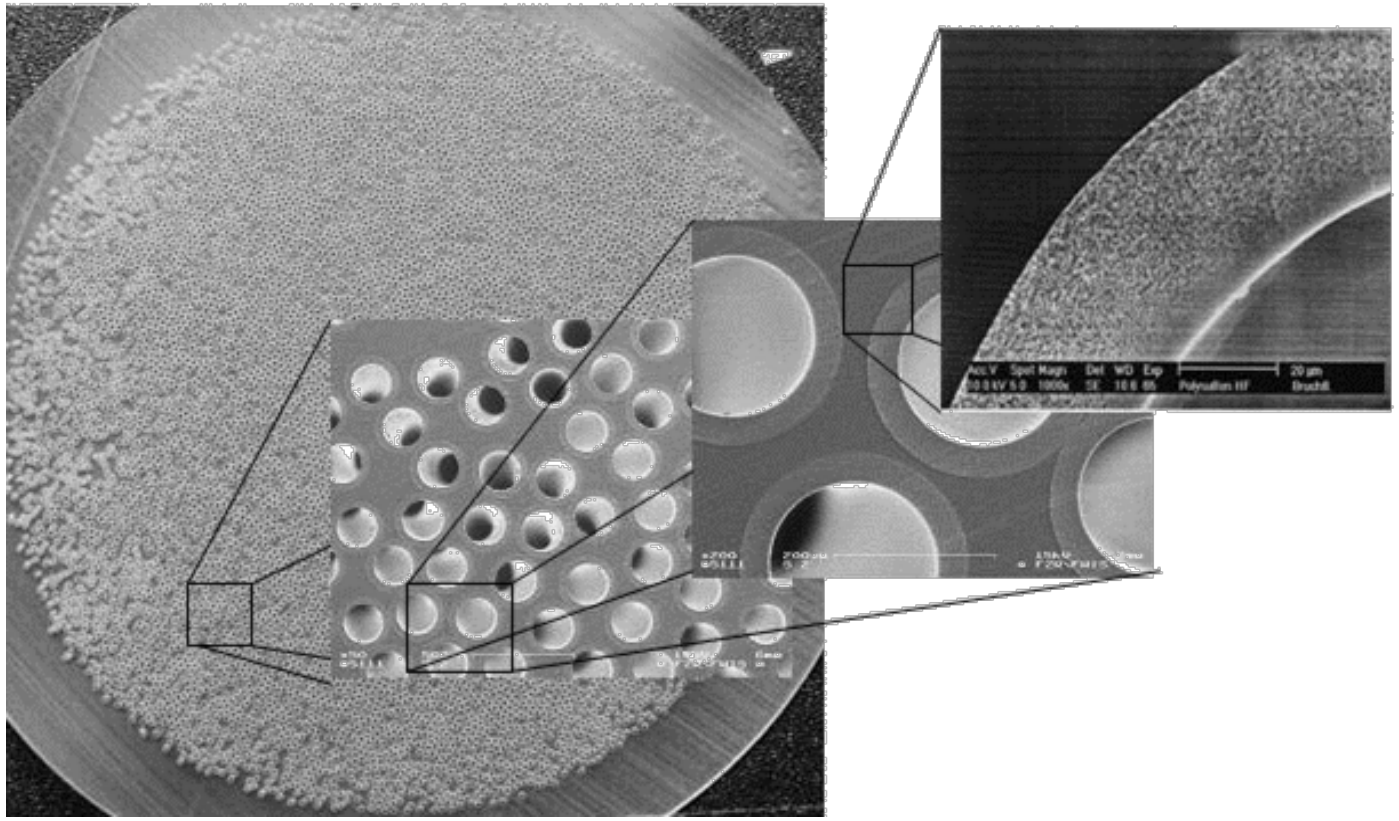
# Hemofilter structure



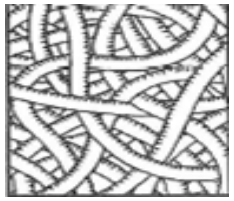
# Components of the Hemofilter



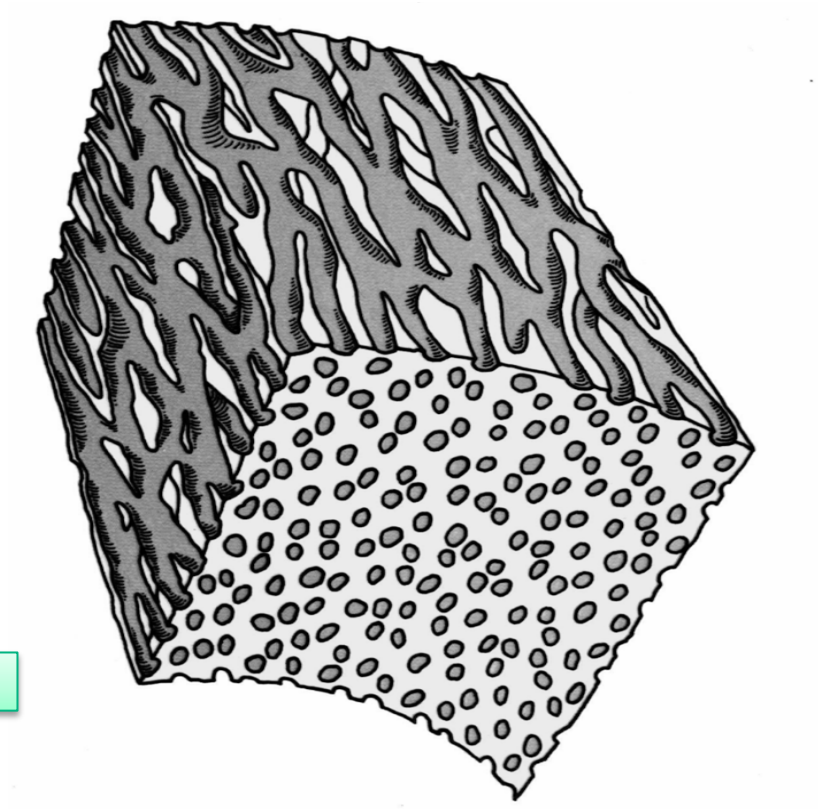
# Potting of Dialyser



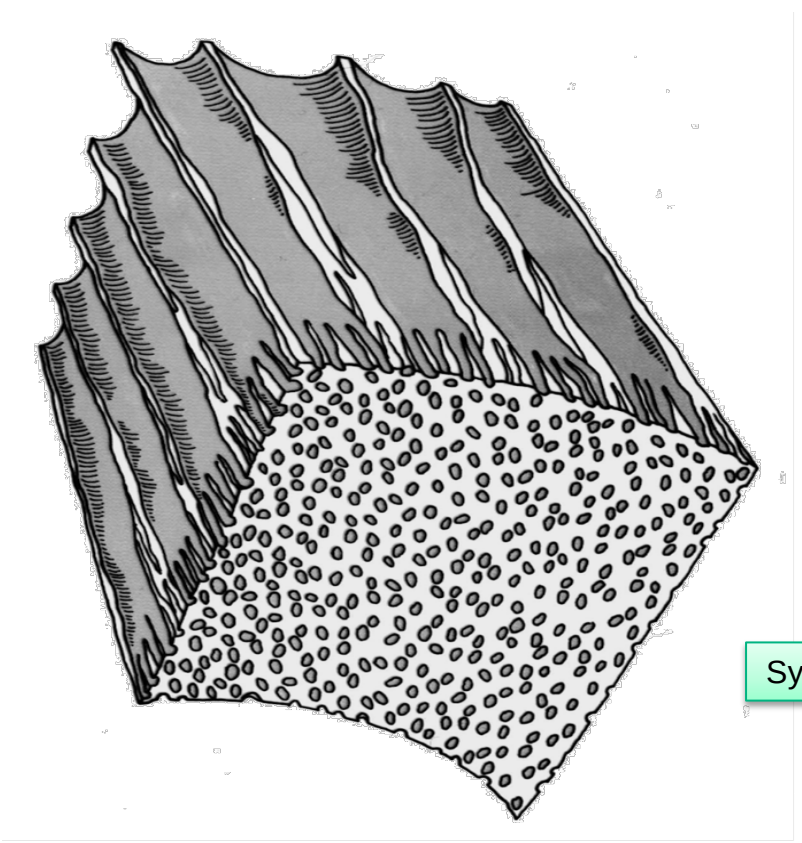
# Membrane Structure

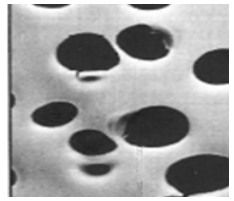


Cellulosic Membrane



Symmetric Membrane





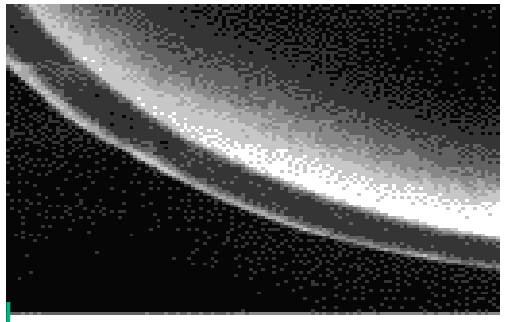
Synthetic Membrane

Asymmetric Membrane

# Membrane Structure

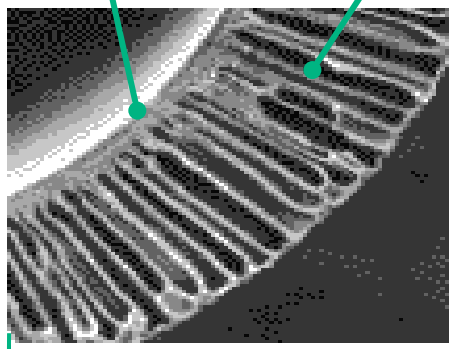
## Symmetric vs. Asymmetric Structure

The symmetric structure is no barrier for endotoxins.

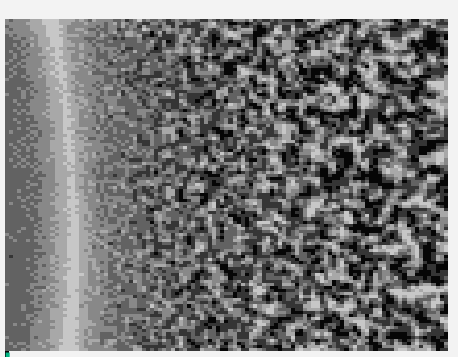


cellulosic membrane (Haemophane)

separating layer supporting layer



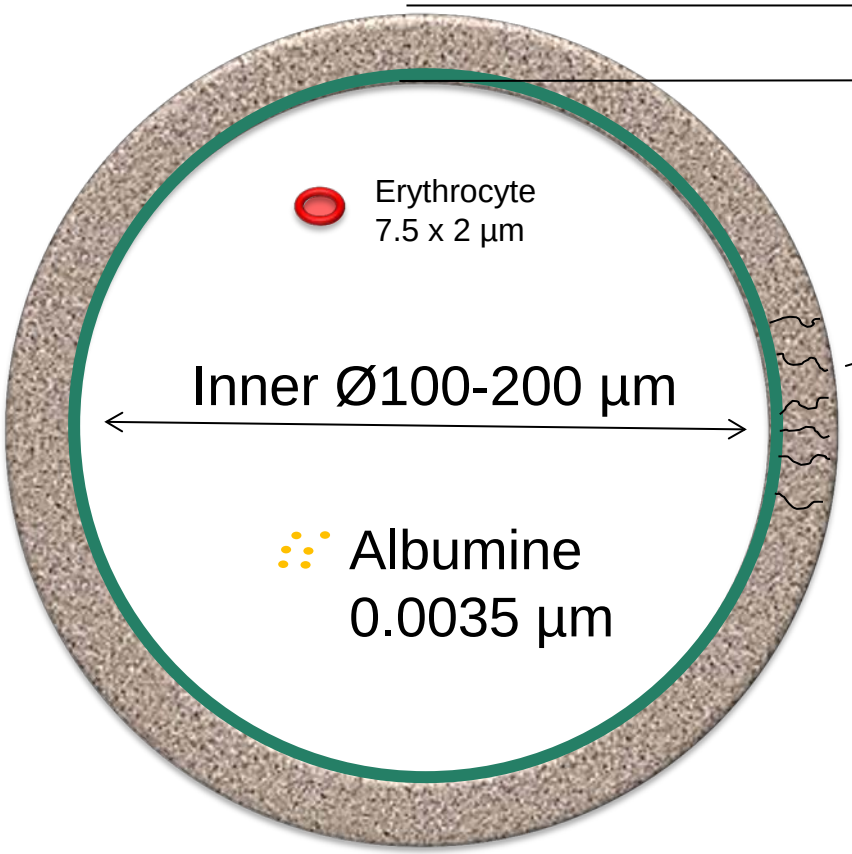
synthetic membrane “finger”-structure (polyamide)



synthetic membrane (polysulfone)

# Dimensions of hollow fibre

Surface area 1.0-2.0 m²
Fibers 5000-20000
priming volume 60-120 ml




Wall
5-40 µm

Pores
0.001-0.003 µm

# Sieving Coefficient & Cut-off

## Sieving Coefficient:

Ratio between concentration of a substance in filtrate to the concentration in blood

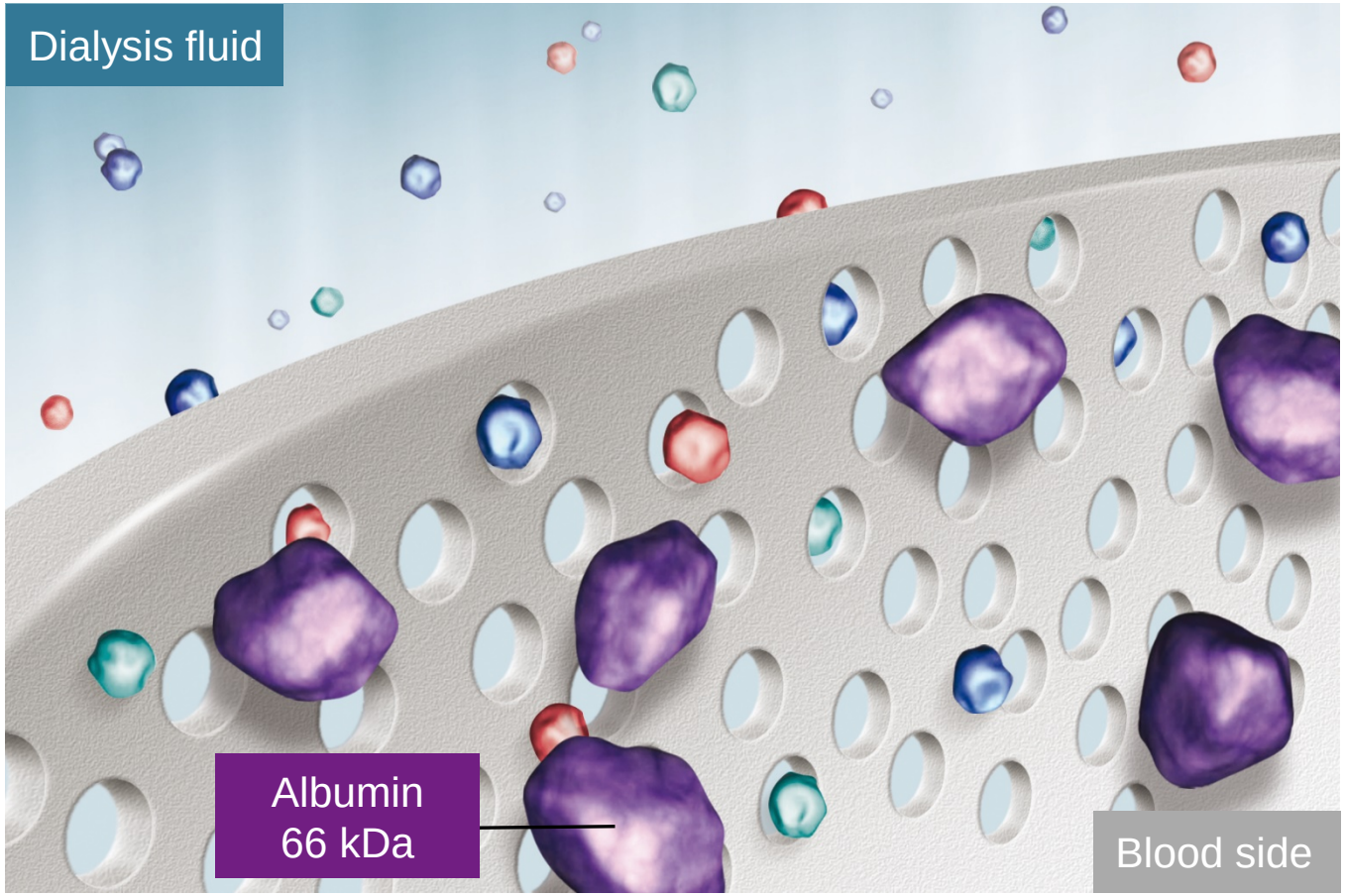
## Cut-off:

max. molecular size, which can pass through a membrane.

- In low-flux filters up to 10 kDa
- In high-flux filters up to 40-60 kDa

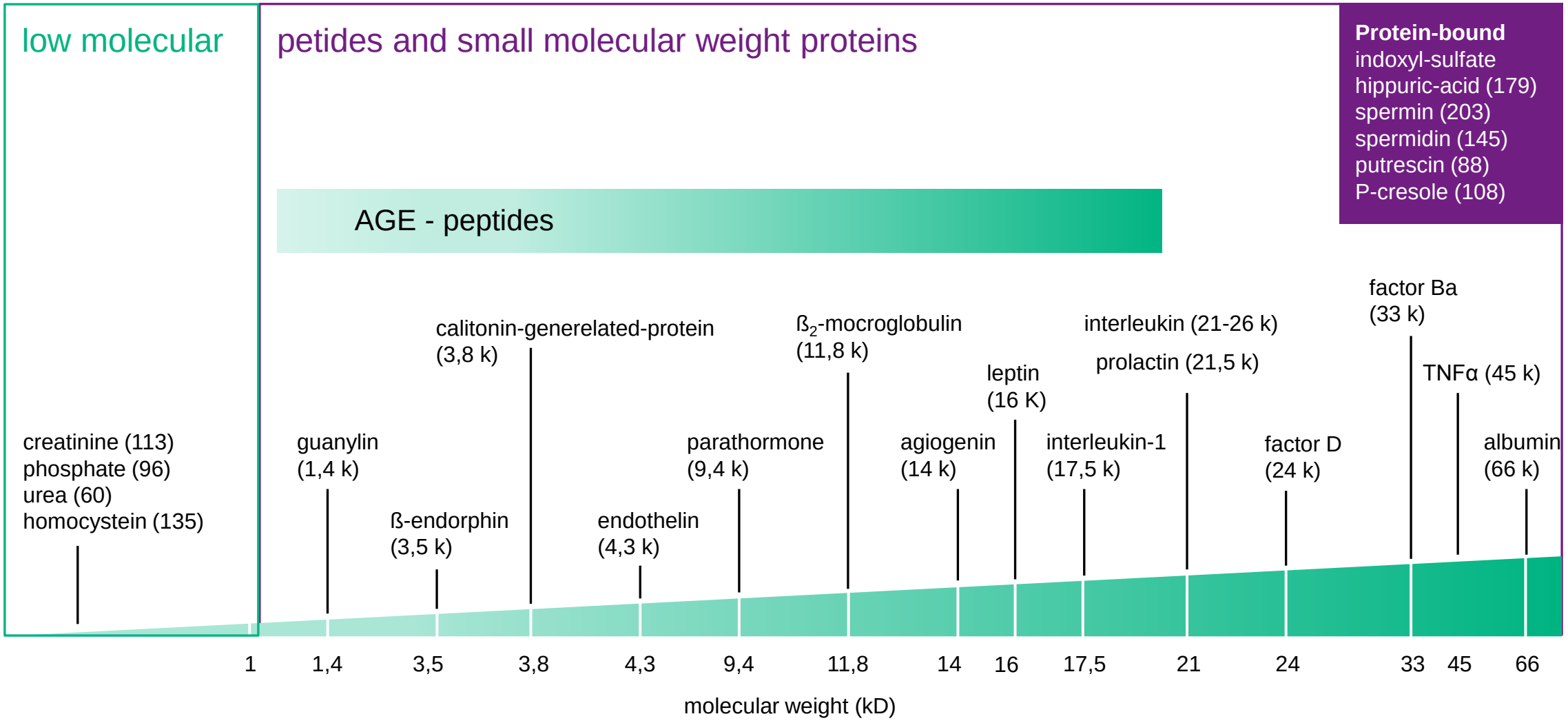
- Uric Acid 170 Da
- Creatinine 110 Da
- Urea 60 Da
- Albumin

## Semi-permeable Membrane

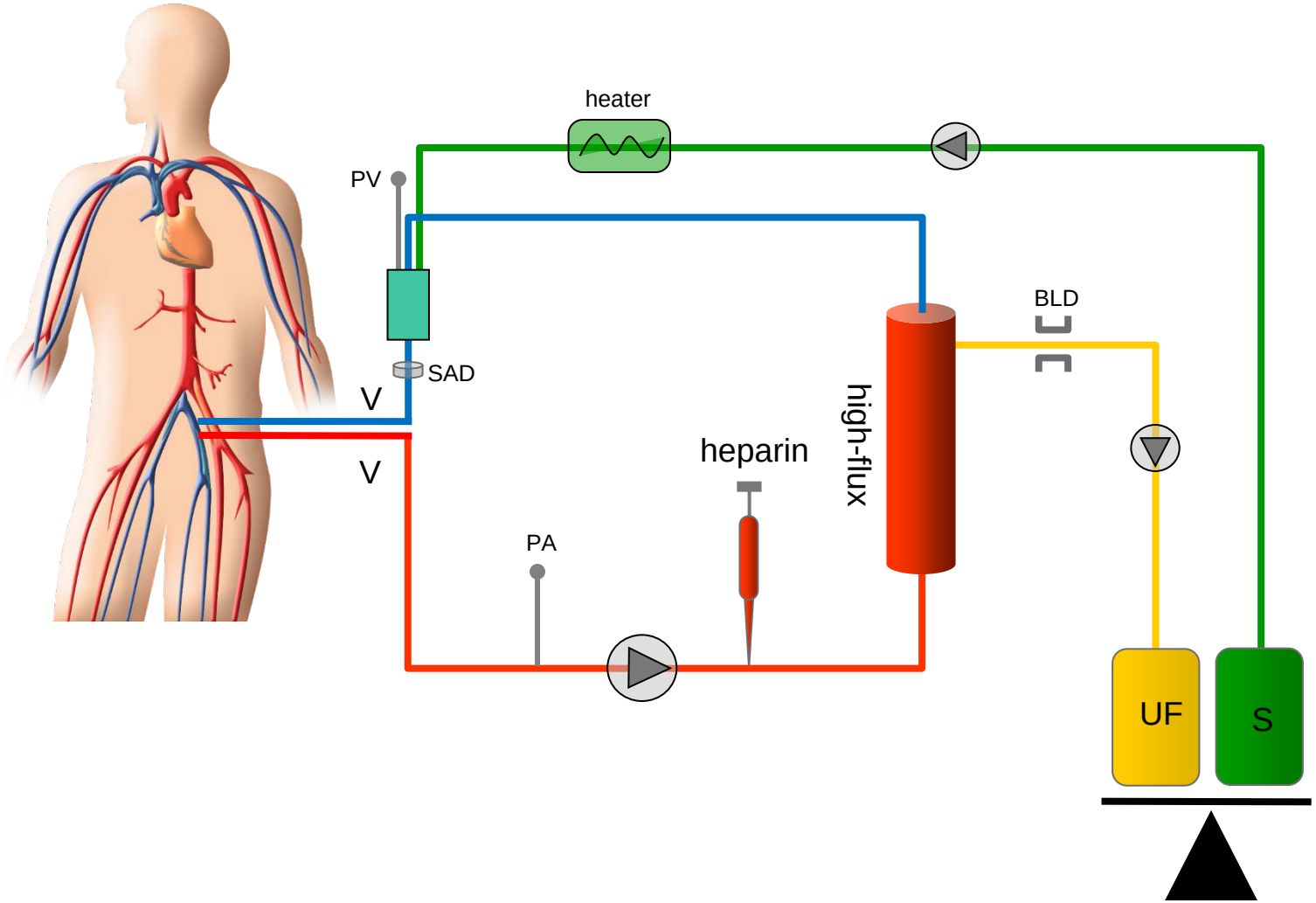


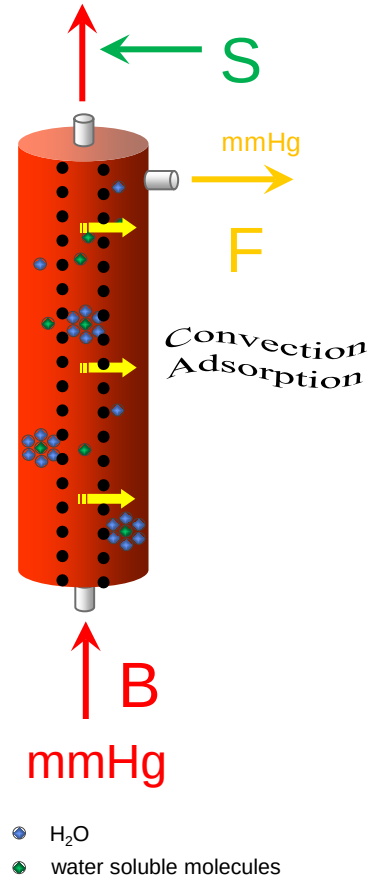
# Membrane Cut-off

## Uraemic Toxins

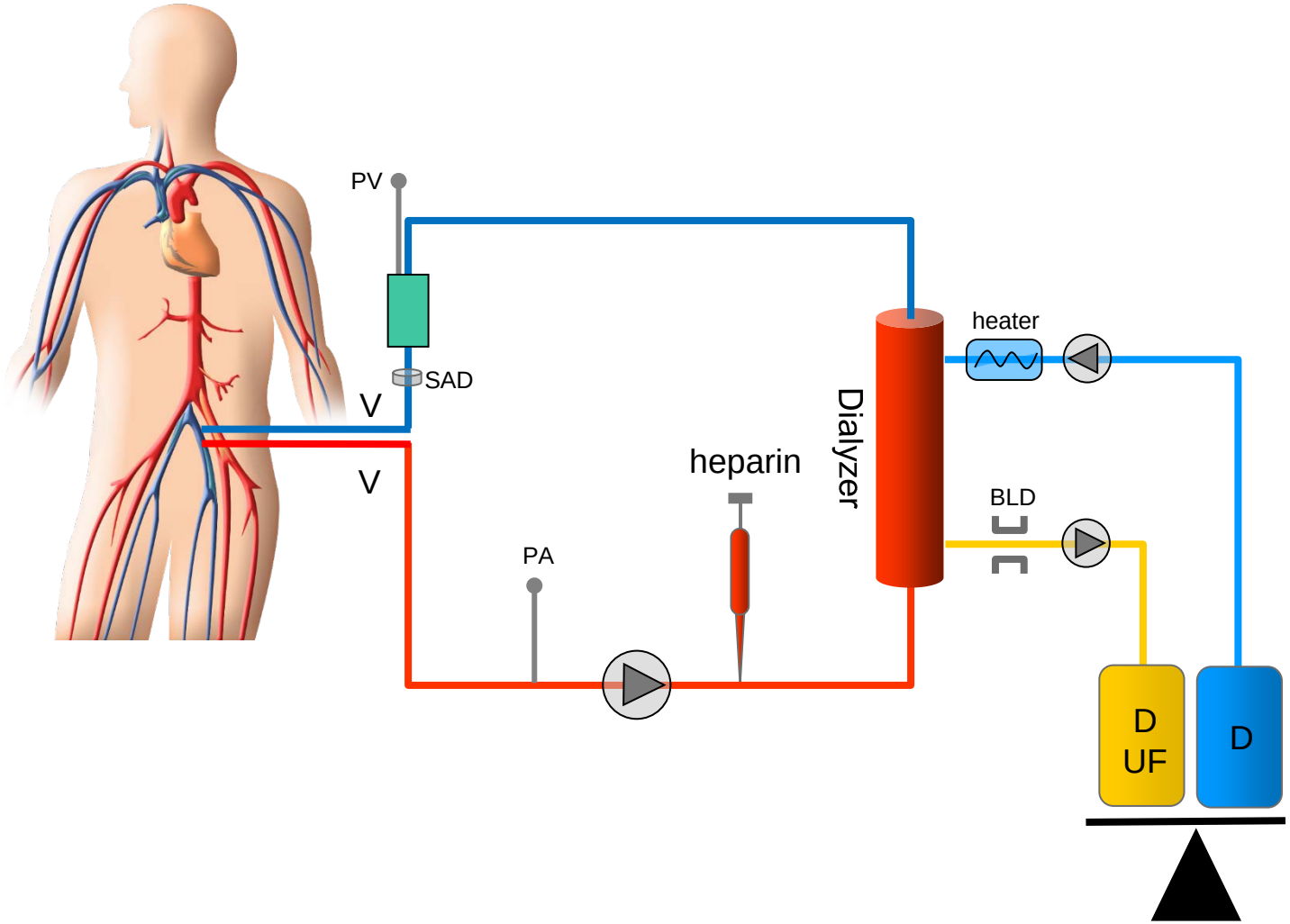


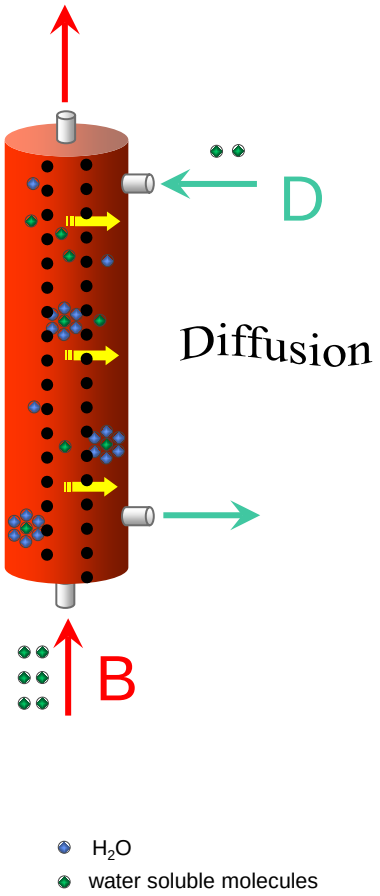
# CVVH Continuous veno-venous hemofiltration



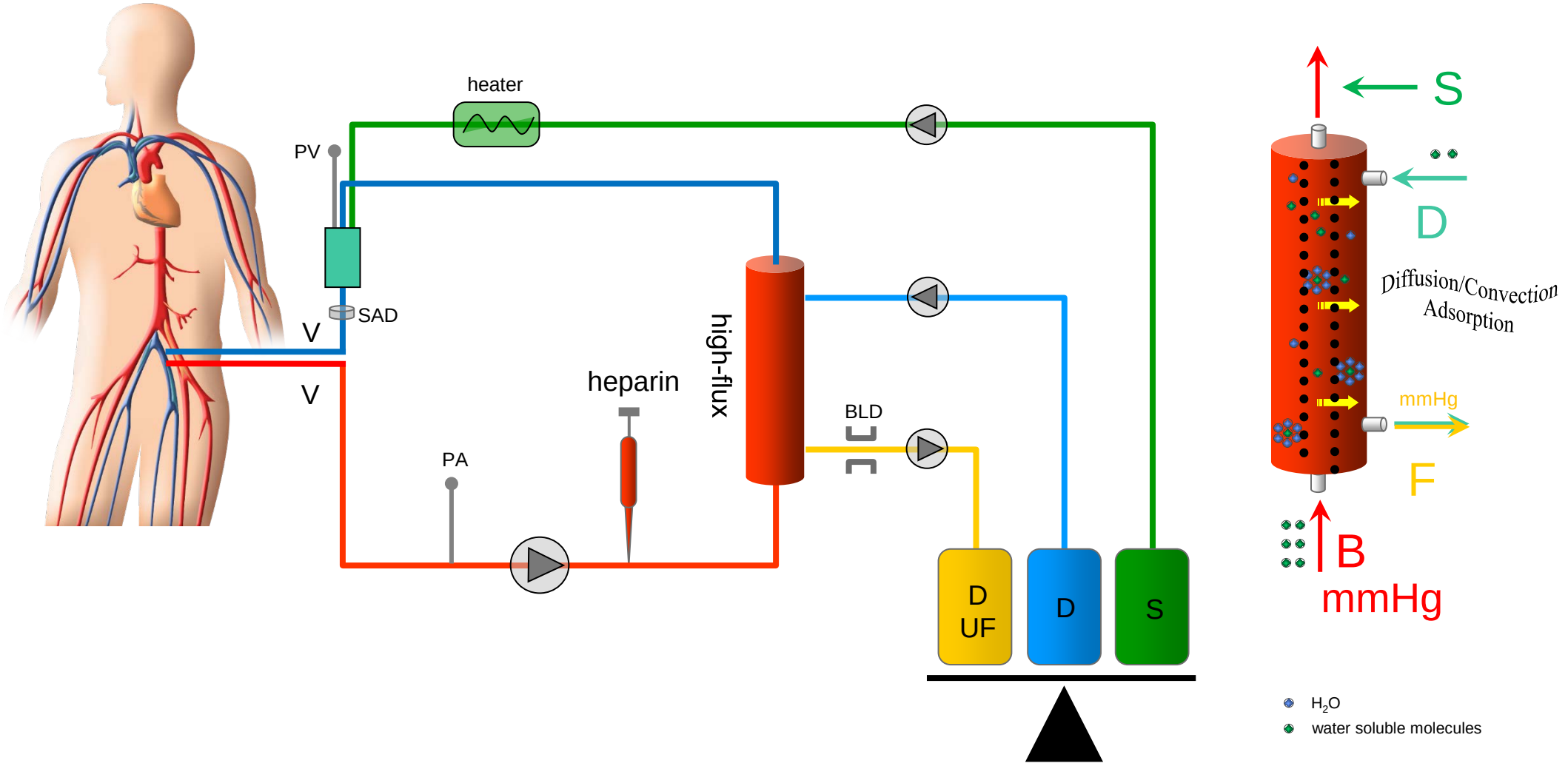



# CVVHD Continuous veno-venous hemodialysis

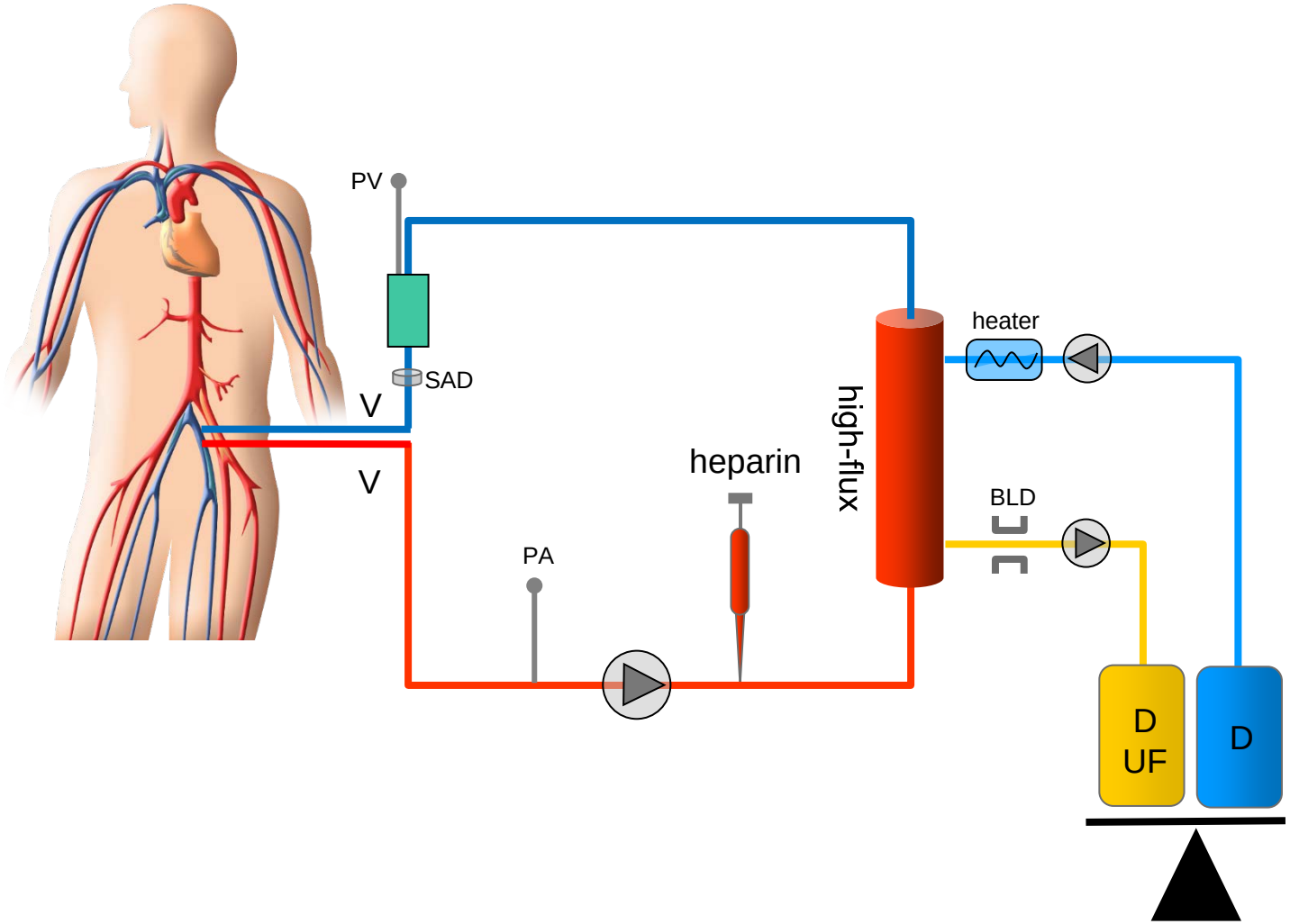


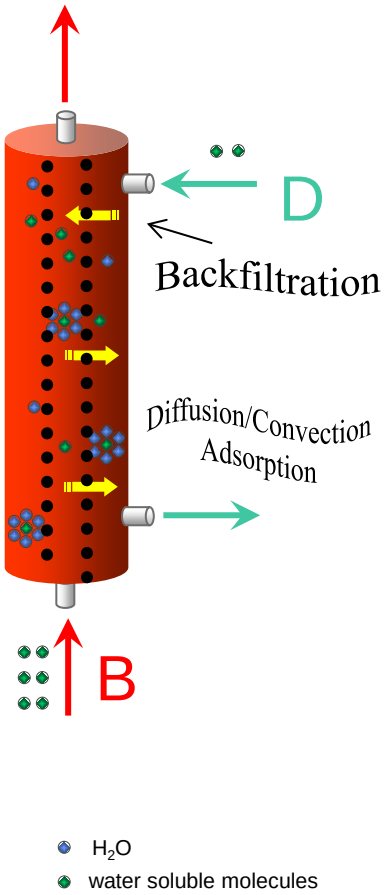



# CVVHDF Continuous veno-venous hemodiafiltration

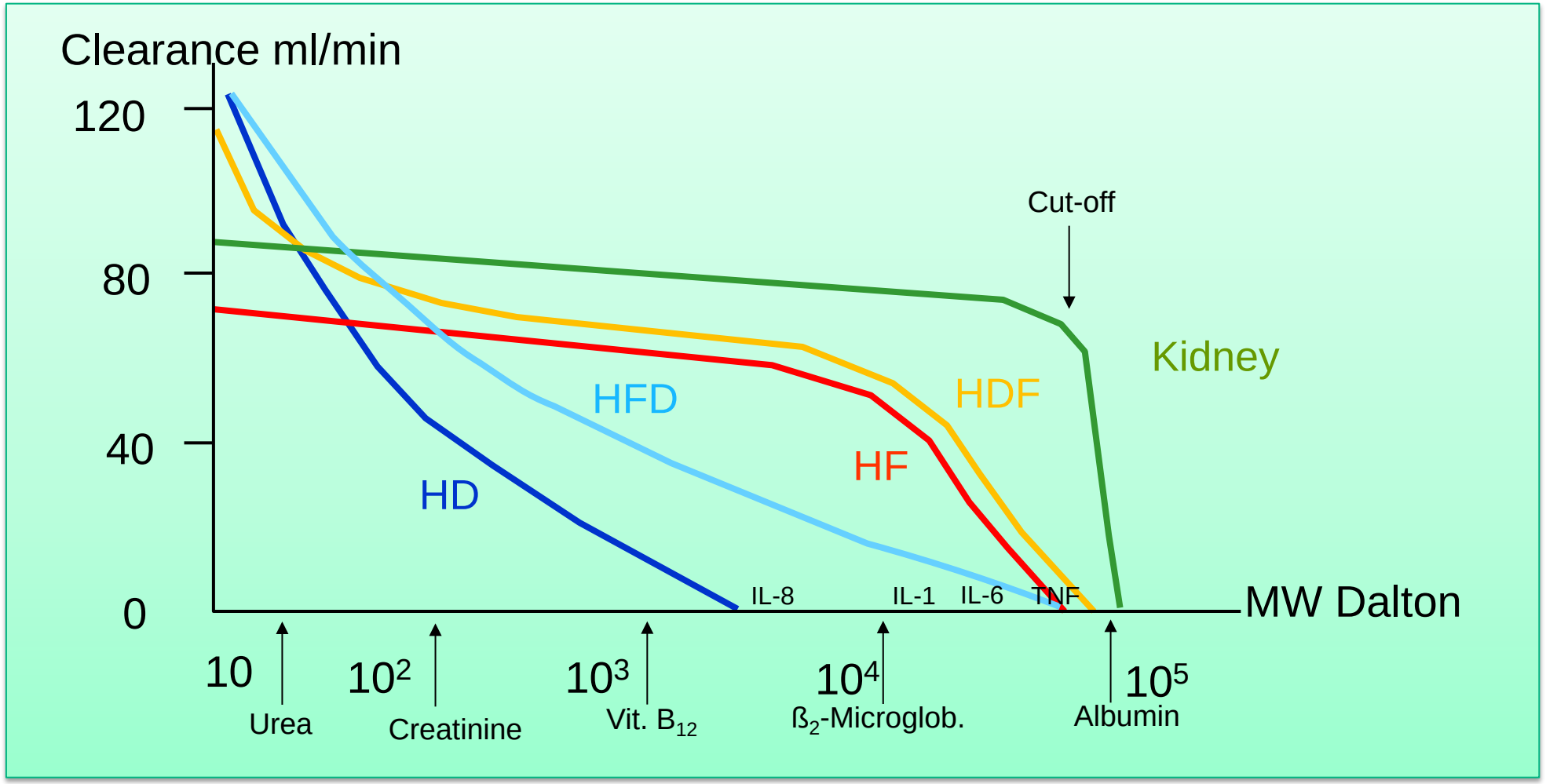


# CVVHFD Continuous veno-venous hemodialysis



# Clearance in HD, HF and HDF



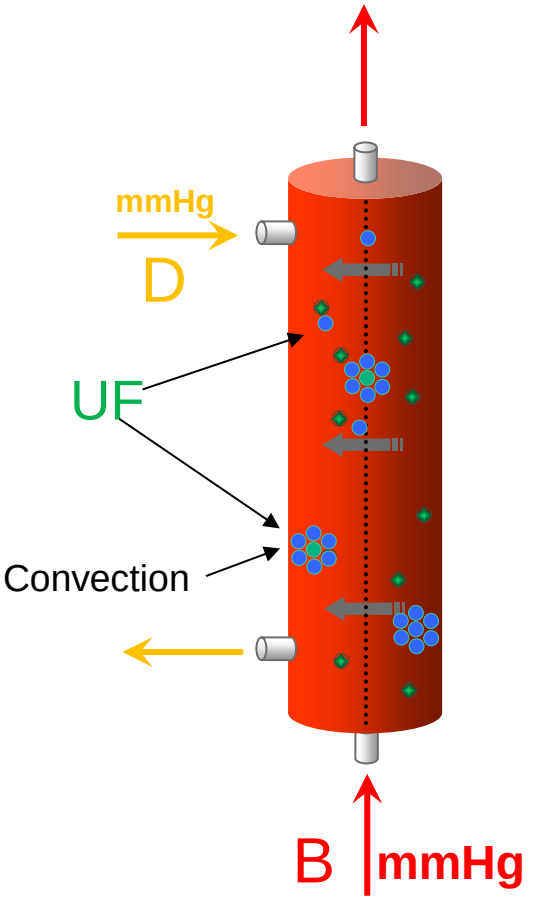

IL = Interleukin
TNF = Tumor Necrosis Factor
MW = Molecular Weight

# Ultrafiltration

Transport of water through a semi permeable membrane, which is caused by difference of pressure around the membrane

Depends on: Difference of Pressure

**mmHg** – mmHg **=** Transmembrane Pressure (TMP)



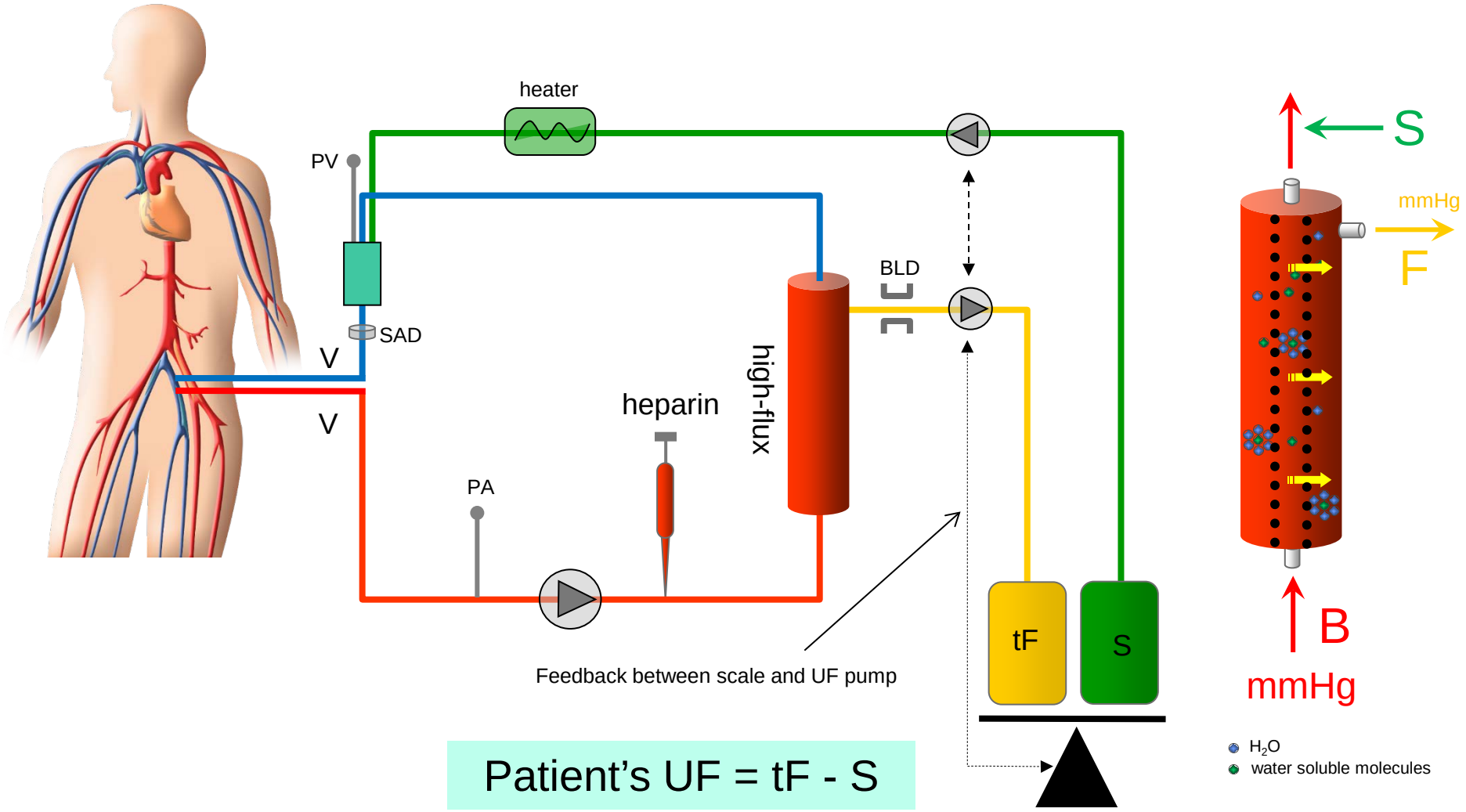

Convection: Transport of Material or Energy by carrier substance

Ultrafiltration Coefficient = $K_{UF}$ ml/h/mmHg

$K_{UF}$ < 10 Low-flux

$K_{UF}$ > 10 High-flux

# CVVH Continuous veno-venous hemofiltration



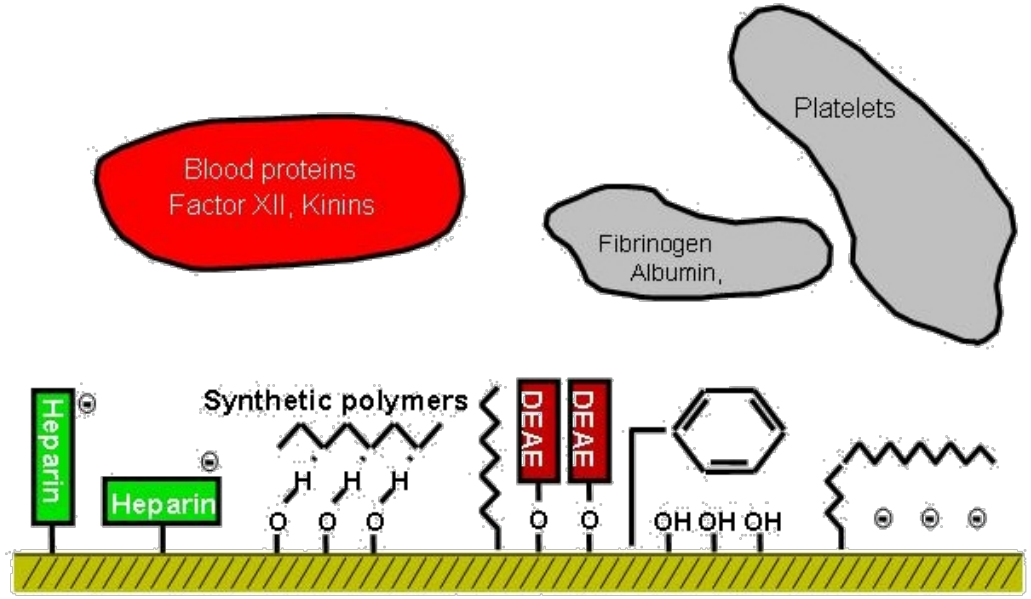

Patient's UF = tF - S

tF = total Filtration

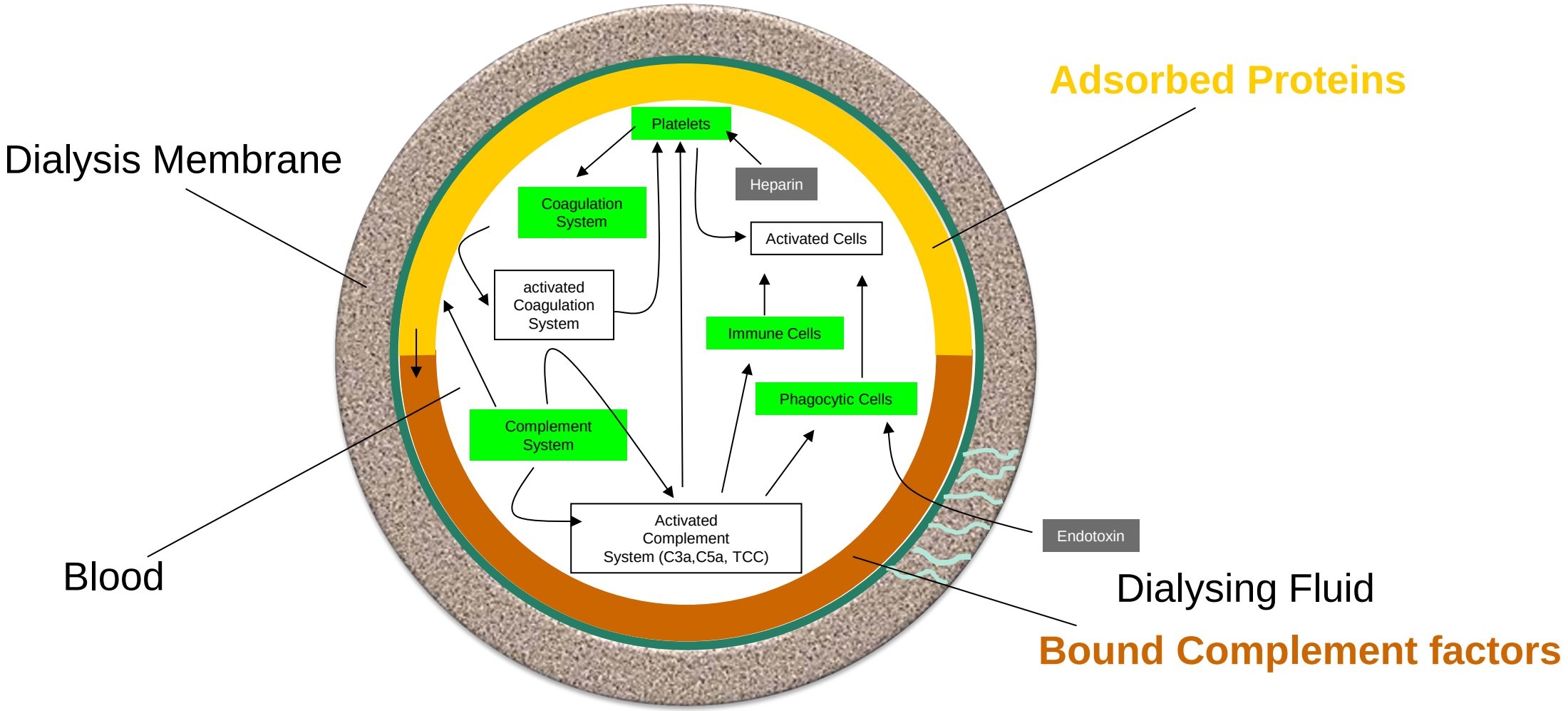
# Biocompatibility of Membranes

**How membranes influence biological responses**

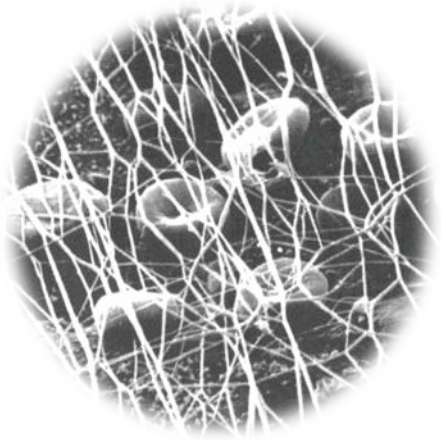
- Hydrophilic membranes (cellulose): activate complement system
- Hydrophobic membranes and positively charged membranes: cause platelet adhesion
- Negatively charged surfaces: promote coagulation and clotting



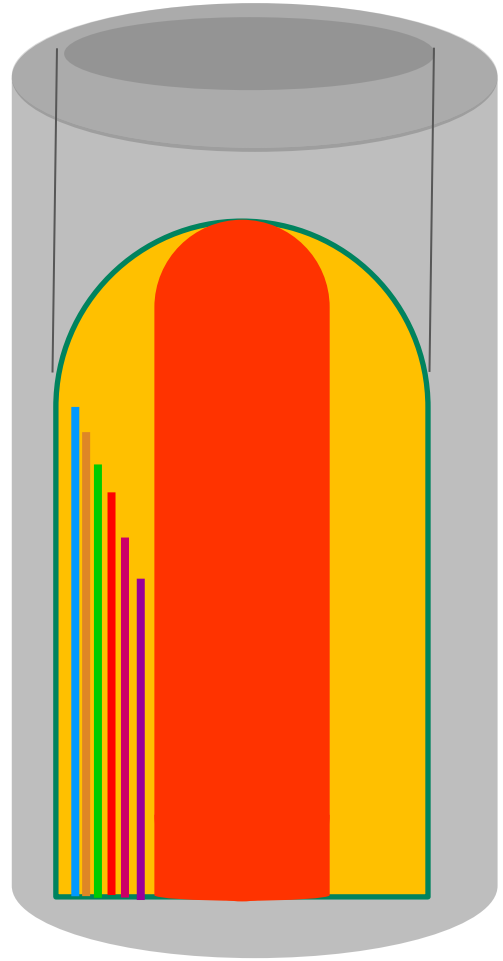
# Blood-Membrane Interaction



# Secondary Membrane



| | |
|---|---|
| Fluid Membrane | Immidiate |
| Protein adsorption | Seconds |
| Thrombocyte & Cell Adhesion | First Minute |
| Thrombocyte + Cell Aggregation | |
| Blood Coagulation + Fibrin Formation | |
| Thrombus (Thrombos, Leukos, Erys, Fibrin) | Minutes |



# Summary

Hemofilter is most important component of extracorporeal dialysis therapies.

Filter membrane

- Cellulotic and synthetic membranes,

Clearance

- Difusive and convective clearance

Ultrafiltration

- Low-flux and high-flux filter Kuf, Cut off

Biocompatibility

- Secondary membrane, Glogging

Beside the performance also the biocompatibility of a filter is important !!

B BRAUN
SHARING EXPERTISE

# 5. UNDERSTAND THE PRINCIPLES OF FLUIDS AND SOLUTE MANAGEMENT IN CRRT

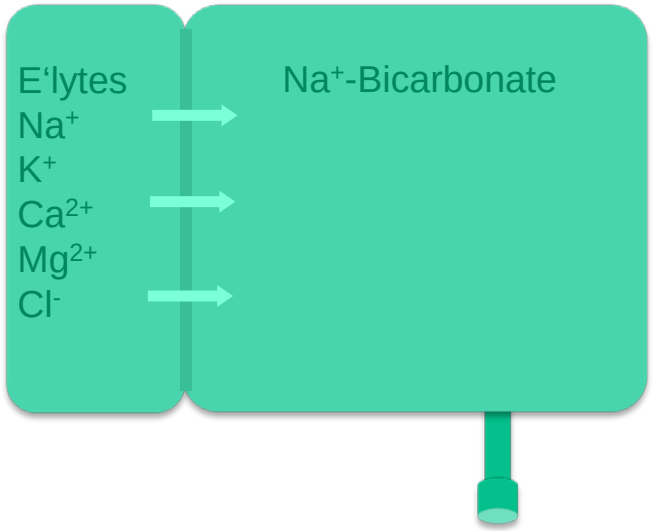
## RATIONALE FOR USING SUBSTITUTION AND DIALYSATE FLUIDS IN CRRT

# Objective of the module

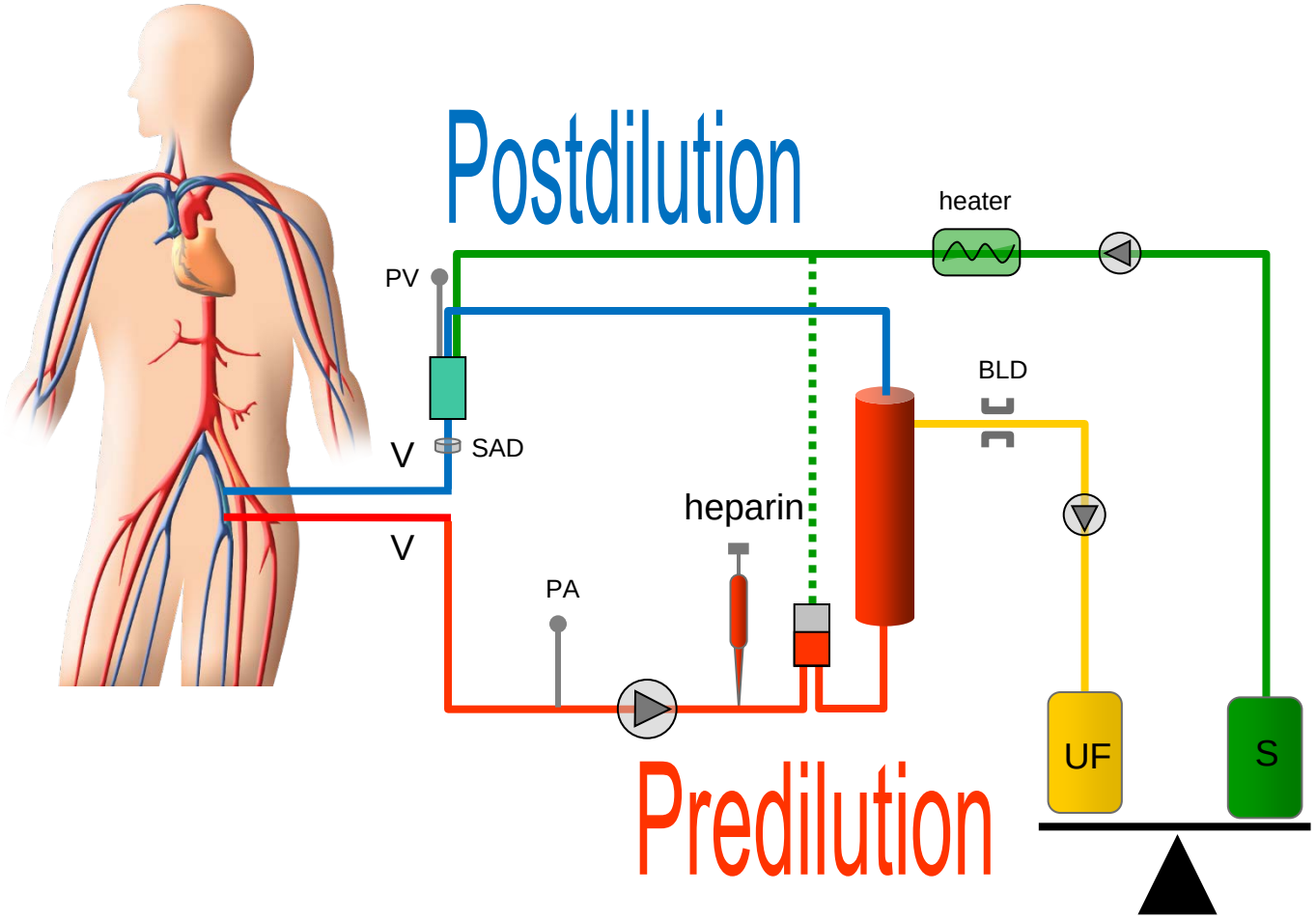
1. Understand the management of the fluids
2. Understand how to balance all fluids including patient

# Substitution Solution

| | Lactate | Bicarbonate |
|---|---|---|
| $Na^+$ mmol/l | 135-150 | 140 |
| $K^+$ mmol/l | 0-4 | 0-4 |
| $Ca^{2+}$ mmol/l | 1.5-2.0 | 1.5 |
| $Mg^{2+}$ mmol/l | 0.50-0.75 | 0.5 |
| $Cl^-$ mmol/l | 100-113 | 109-113 |
| Lac. mmol/l | 35-45 | --- |
| Bic. mmol/l | --- | 35 |
| Glucose g/l | 0-2.0 | 1.0 |
| Osmol. momol/l | 285-312 | 290-300 |



# Predilution? Postdilution?



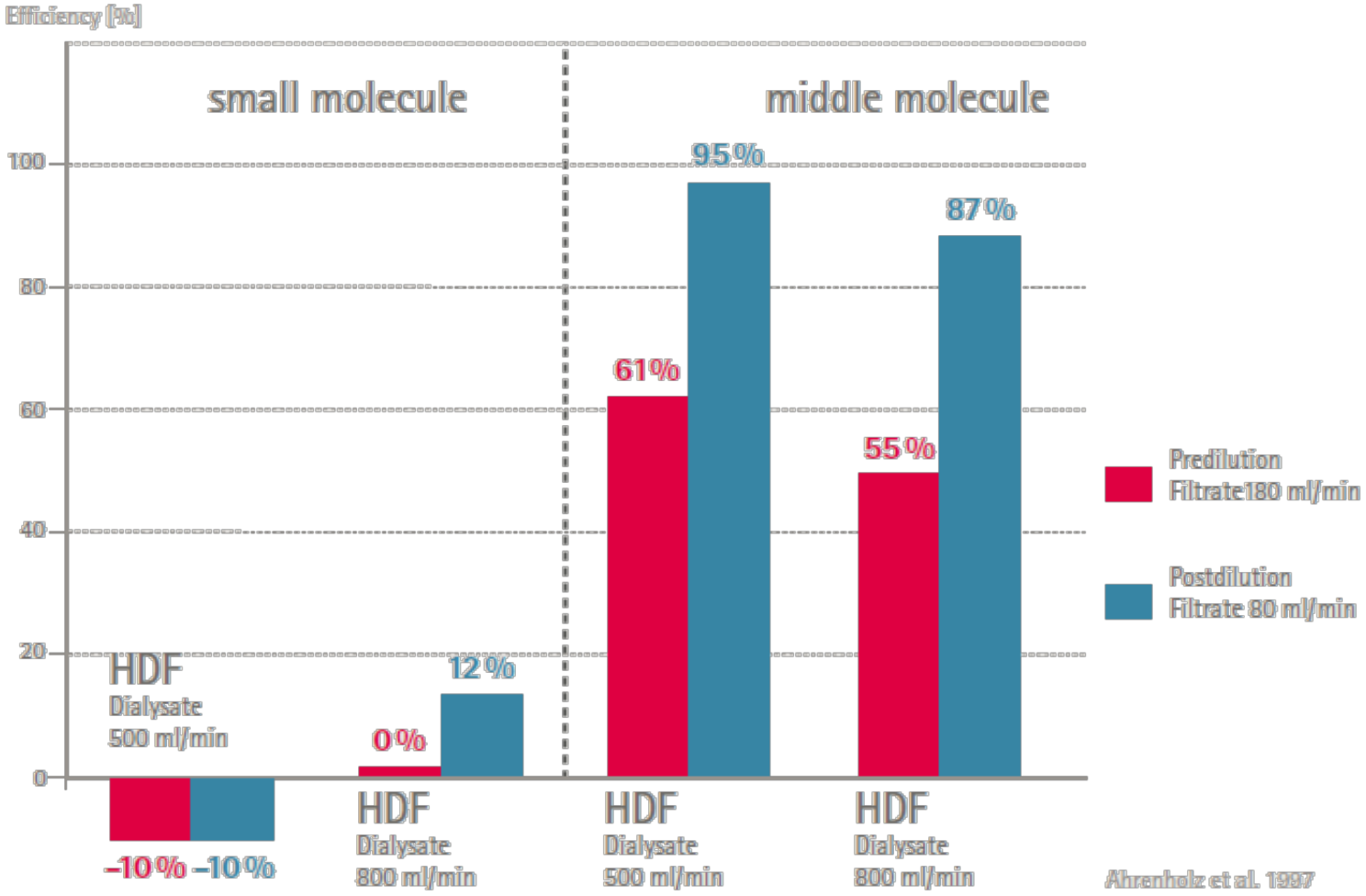

| Postdilution |
| --- |
| • Clearance ↑ |
| • Sub. Volume ↓ |

| Predilution |
| --- |
| • Clearance ↓ |
| • Sub. Volume ↑ |
| • Filter Clotting ↓ |
| • Expensive |

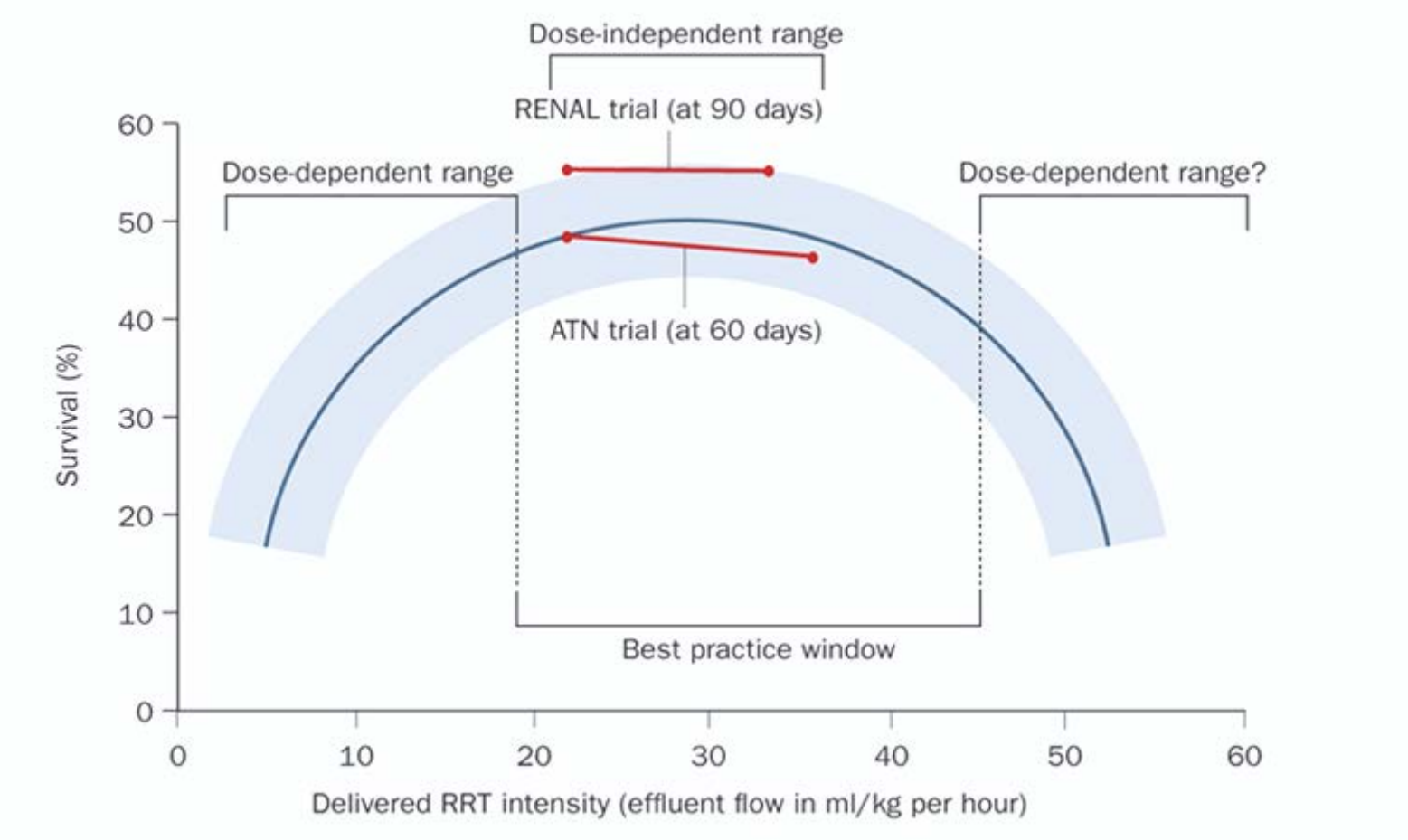
# Dilution Mode

| | Postdilution | Predilution | Mixed Dilution |
|---|---|---|---|
| **Pros** | ▪ High clearance for all molecules (small, middle and high)<br>▪ Less substitution volume | ▪ Hemodilution<br>▪ Better clearance of protein bound solutes | ▪ Avoids disadvanges of post- and predilution<br>▪ Good for non-optimal blood flow and unfavorable hemorheology |
| **Cons** | ▪ Hemoconcentration<br>▪ Reduced membrane permeability | ▪ Reduced clearance of small moleculs<br>▪ More substitution volume | ▪ 2 infusion pumps and 2 substitution lines<br>▪ Specific software |

# Clearance HD ↔ HDF



# Dosing of Substitution




Relationship between delivered RRT intensity and survival in critically ill patients with acute kidney injury (AKI)*

*Dialysis: Results of RENAL – what is the optimal CRRT target dose? John A. Kellum & Claudio Ronco, Nature Reviews Nephrology 6, 191-192 (April 2010)

# Total patient fluid balance

## Doctor’s total daily patient fluid balance

IN

infusion therapy parenteral nutrition enteral nutrition transfusion

IN

substitution

Setting in machine

eB = external balance

**IN - OUT**

mB = machine balance?

**IN - OUT**

tB = total patient fluid balance = eB + mB

OUT

urine, stool, vomit, diarrhea, exudation, stomach tube, wound secret, bleeding (perspiration)

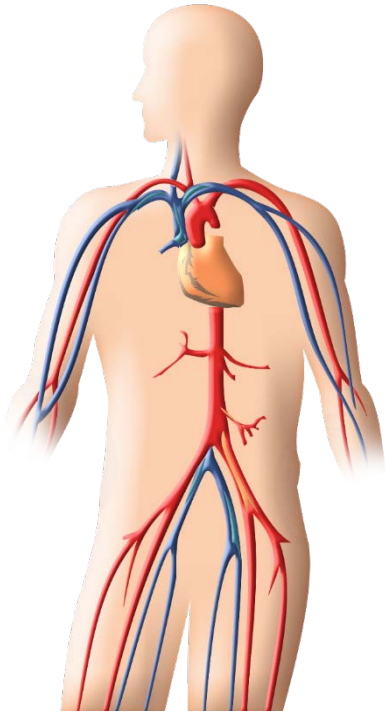
OUT

total UF

# Total patient fluid balance: e.g. hourly balance

Doctor’s total daily patient fluid balance = **+600 ml/24h**
which is hourly 600/24 = **+25 ml/h**

# Patient’s Daily Total Fluid Balance



Patient’s daily total fluid balance in Doctor’s prescription !!
It is usually “estimated” every day !!
It is usually positive due to “perspiratio insensibilis” !!
For instance +600 ml/d !!
It means the hourly balance is +25 ml/h !!

Check all the fluids every hour, because situation can change every hour !!

Also weight patient every day !!

# SUMMARY

## For CRRT sterile electrolyte solution containing bicarbonate are necessary

Same solutions can be used as dialyzing fluid in CVVHD or as substitution solutions in CVVH

- Pre and post dilution

Renal dose

- Down time, renal dose in CVVH and CVVHD

Patient balance

- Reduction of fluid overload while maintaining hemodynamic stability

**Daily patient balance is very important to keep hemodynamic stability !!**

B BRAUN
SHARING EXPERTISE

# 6. DISEASES IN THE INTENSIVE CARE ENVIRONMENT

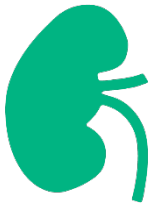
# Objective of the module

1. Understand what kind of primary diseases can lead to acute kidney injury
2. Understand the prognosis of acute kidney injury
3. Know the most common diseases for acute blood purification therapies

# Multi Organ Support (MOS)

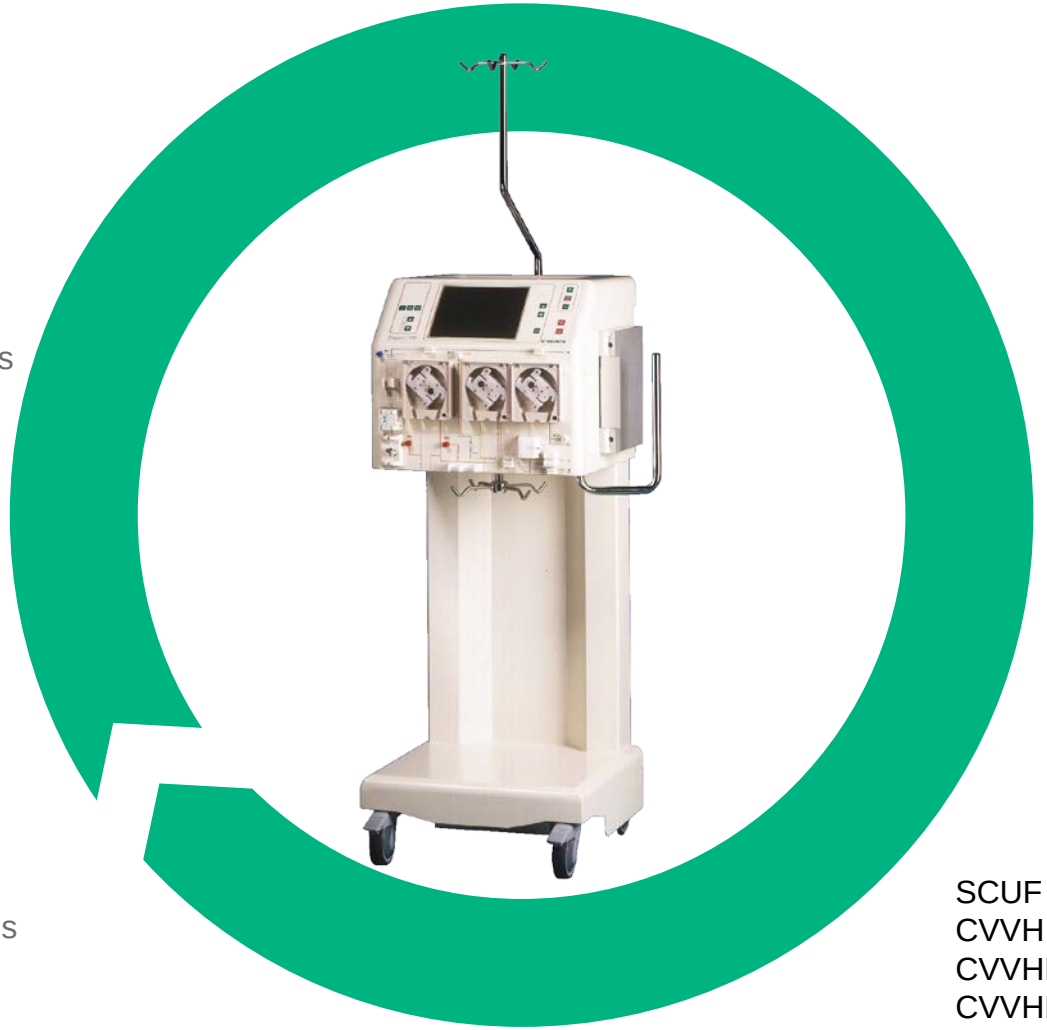
Fluid overload
Pulmonary Edema
Cerebral edema
Transplantation

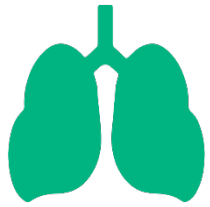
SCUF
CVVH
Plasmapheresis



Azotemia
Acidosis
Uremia
Hypervolemia
Anuria/Oliguria
Hyperkalemia
Transplantation

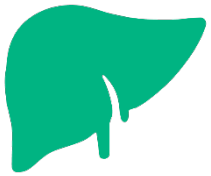
SCUF
CVVH
CVVHD
CVVHDF
Plasmapheresis





Fluid overload
Pulmonary Edema
Transplantation

SCUF
CVVH
Plasmapheresis
ECMO

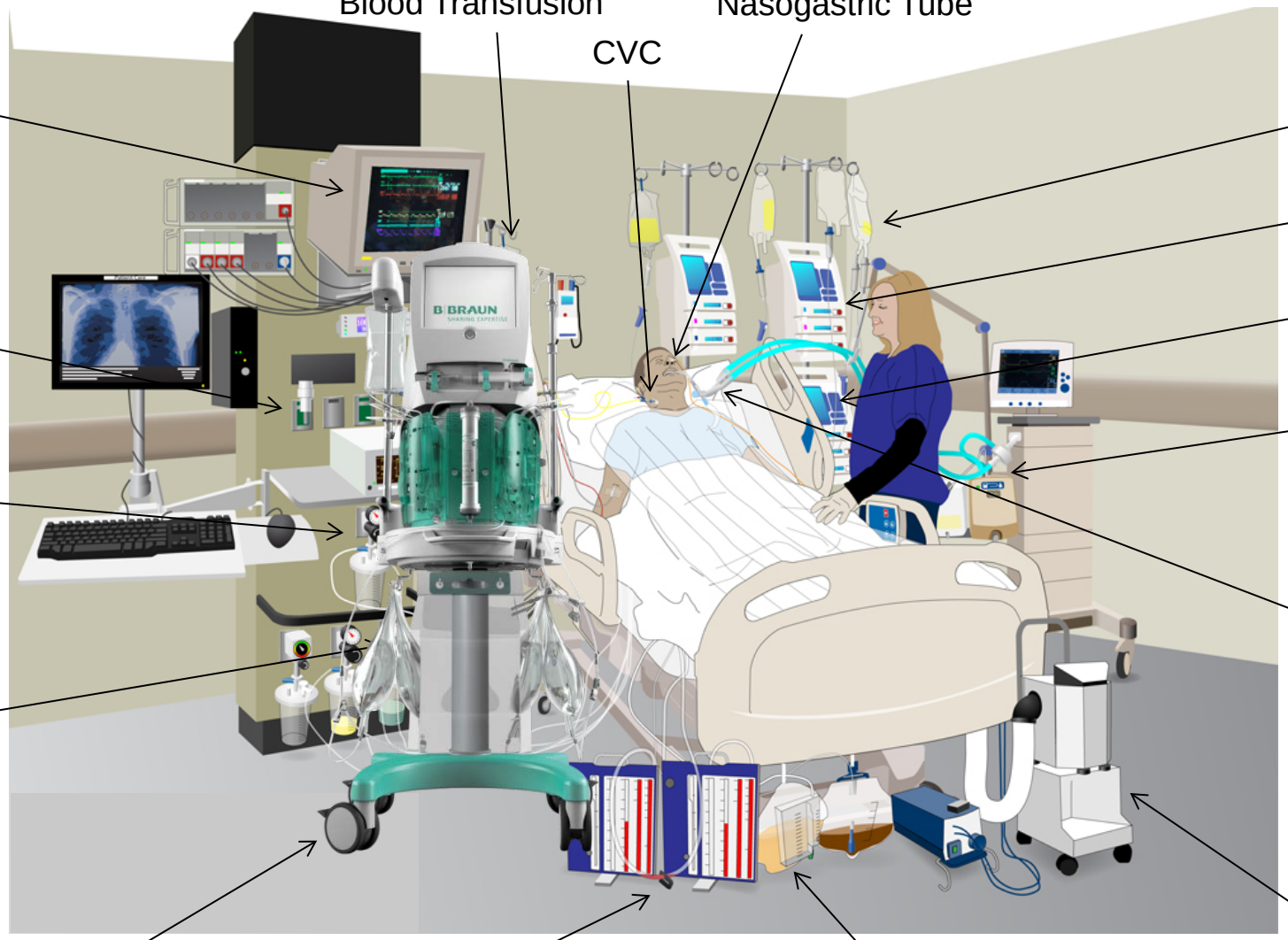


SIRS/Sepsis
Transplantation

Plasmapheresis
ECMO

SCUF = Slow Continuous Ultrafiltration
CVVH = Continuous Veno-Venous Hemofiltration
CVVHD = Continuous Veno-Venous Hemodialysis
CVVHDF = Continuous Veno-Venous Hemodiafiltration

# ICU patient environment



# Intensive Care Patient*

B|BRAUN SHARING EXPERTISE

## Toxic / Allergic
Shock, AKI
Bleeding, DIC

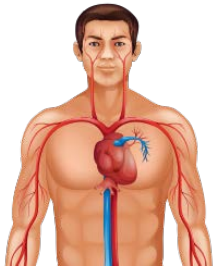
## Severe Burn
Shock
Sepsis
MODS
Catabolism

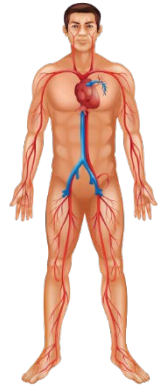
## Post OP
Bleeding
Sepsis
AKI
Catabolism

## CNS
Sedation
Stroke
Delirium
Coma

## Shock
Cardiogenic
Septic
Anaphylactic
Hypovolemic
MODS

## MODS
Acute Pancreatitis
ARDS, ALI
ALF
AKI
CHF
GI Infection, Bleeding
Thrombocytopenia,
Immuno Deficiency, DIC





## Polytrauma
Broken Spine, Pelvis, Thorax
Cranio-Cerebral-Injury (CCI)
Muscle crush
Hemolysis, Rhabdomyolysis
Hyperpotassiemia
Arterial Bleeding
Hypovolemia, Shock
AKI, ALI

## Severe Sepsis
MODS, Catabolism

* Harrisons Innere Medizin, Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl.
* Innere Medizin 2012 Taschenbuch – 1. Oktober 2011, von Gerd Herold (Autor), Taschenbuch: 966 Seiten, Verlag: Herold, Gerd (1. Oktober 2011)

# Scoring Systems*

Scoring systems are needed to find an **objective severity status** of different diseases and patients linked with **elevated mortality**!!

Most common scoring systems are:

**APACHE II**

**A**cute **P**hysiology **A**nd **C**hronic **H**ealth **E**valuation

acute score used more in USA.
Points from: Acute physiology score (vital, oxygenation and laboratory parameter) + Glasgow coma score (GCS) + age + anamnesis

**SAPS II**

**S**implified **A**cute **P**hysiology **S**core

like APACHE II as acute score used more in Europe

**SOFA**

**S**equential **O**rgan **F**ailure **A**ssessment

progressive score much used in Europe
Degree of organ-dysfunction:
Lung, Glasgow coma score, Heart, Coagulation, Liver, Kidney**

**GCS** =

- neurological scale indicating the conscious state of a patient
- done during the first aid
- used also as part of ICU scoring systems
- considering 1. Eye, 2. Verbal and 3. Motor response
- giving points between 3 (deep coma) and 15 (full consciousness)

* Harrisons Innere Medizin, Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2371-2373
** DocCheck Flexicon

# SOFA - Example

[Sequential Organ Failure Assessment (SOFA) Calculator - ClinCalc.com]

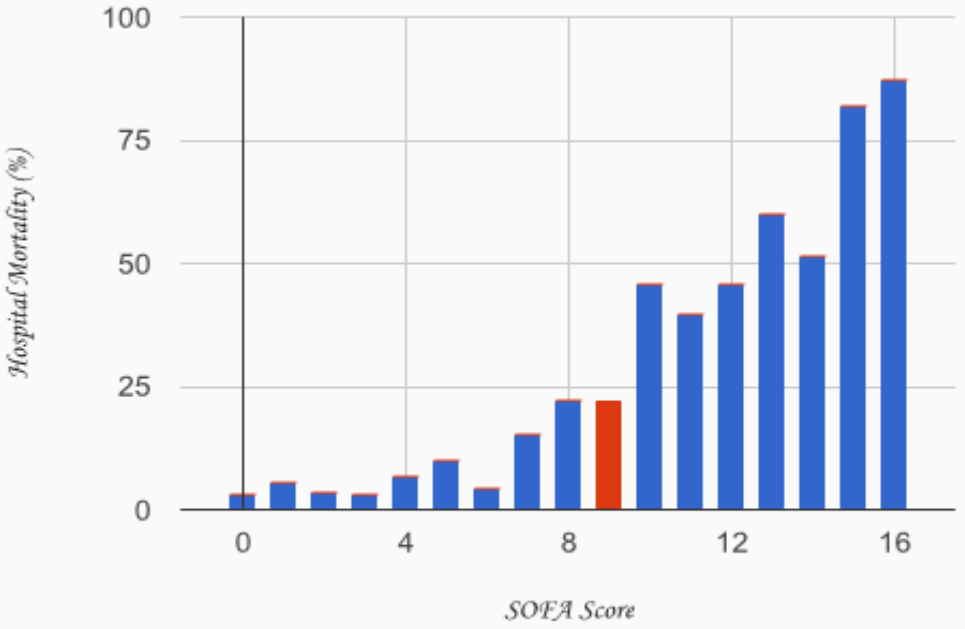
Total score:

9 pts

Estimated mortality:

15 - 20%

| Variable | Points | % Points |
|---|---|---|
| 1. Glasgow coma score < 6 | 4 | 44.4% |
| 2. $PaO_2$:$FiO_2$ ratio ≤ 200 with resp support | 3 | 33.3% |
| 3. MAP < 70 mmHg (without pressors) | 1 | 11.1% |
| 4. Creatinine 1.2 - 1.9 mg/dL | 1 | 11.1% |
| *5. Bilirubin < 1.2 mg/dL* | *0* | *0%* |
| *6. Platelets > 150 ($x10^3/mm^3$)* | *0* | *0%* |
| **Total** | **9** | **100%** |




*Above: Hospital mortality rate associated with maximum SOFA score. The mortality rate was nearly 90% in patients with a SOFA score of more than 15.* [1]

[1] Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med.* 1998;26(11):1793-800. PMID 9824069.

# Multi Organ Dysfunction Syndrome (MODS)*

## Acute Pancreatittis

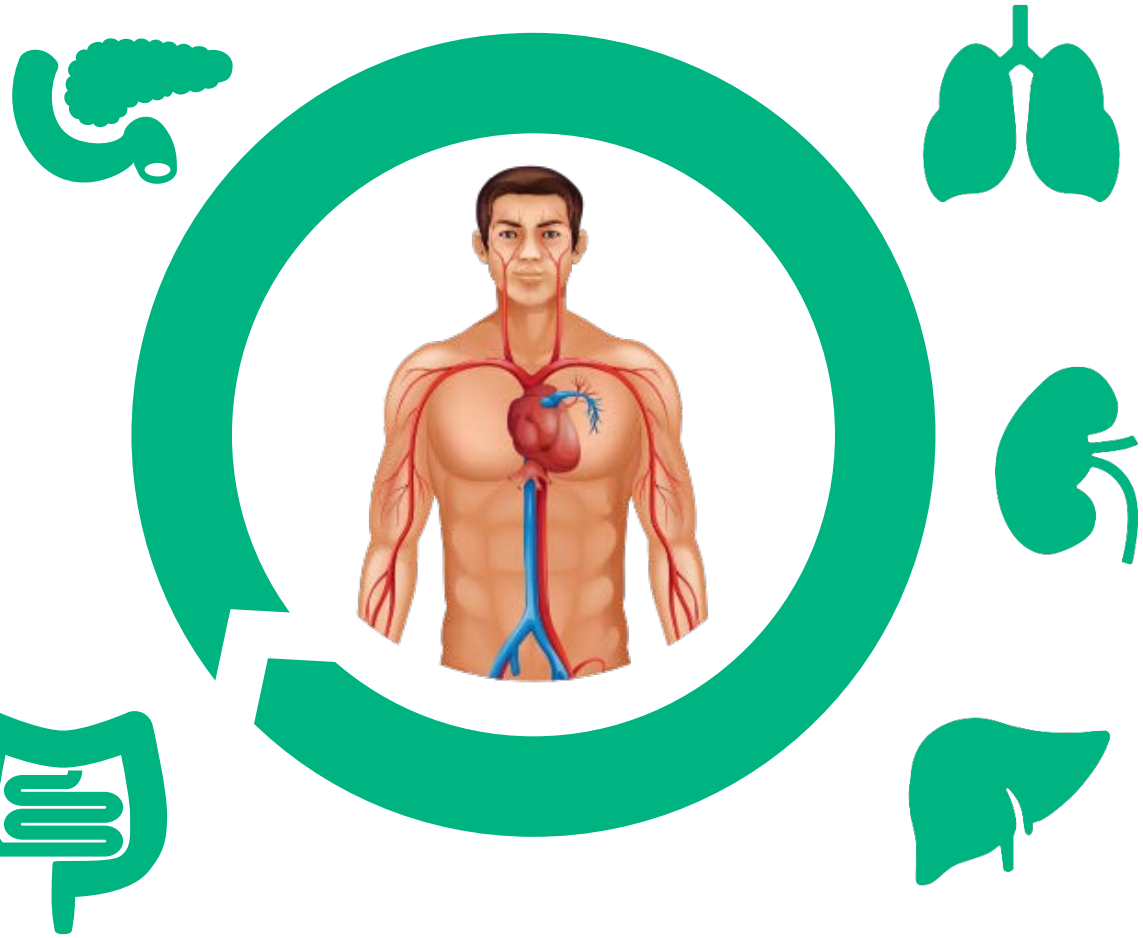
Shock, ARDS, AKI, Sepsis, DIC, GI-Bleeding

## CHF

Fluid overload
Pulmonary edema
Cerebral edema

## GI Impairment

Infection, Bleeding, Ulcer, Thrombocytopenia, Immuno deficiency, DIC



## ALI, ARDS

Respiratory Acidosis/Alkalosis, Hypercapnia, Hypoxemia

## AKI

Azotemia, Acidosis Uremia, Hypervolemia, Anuria/Oliguria, Hyperkalemia,

## ALF

Cerebral Edema, GI-Bleeding, Hypoglicemia, HRS, AKI, Infections, Sepsis, DIC

* Harrisons Innere Medizin, Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2039, 2377-2378, 2384
* Innere Medizin 2012 Taschenbuch – 1. Oktober 2011, von Gerd Herold (Autor), Taschenbuch: 966 Seiten, Verlag: Herold, Gerd (1. Oktober 2011), S. 201, 317, 333-335, 548-550, 616-620

# Congestive Heart Failure (CHF)*

CHF is the inability of the heart to pump enough blood volume needed for the organism!

This is linked with:

- Weakness
- Dyspnea
- Leg edemas
- venous thrombus
- cardiac thrombus
- cardiogenic shock
- pulmonary edema

| NYHA Stages (New York Heart Association) | |
|---|---|
| I | no complains, normal body activity |
| II | complains in high body activity |
| III | complains in low body activity |
| IV | complains at rest |

Congestive Heart Failure
by Arcot J Chandrasekhar, M.D.

Also “overload situation” can cause CHF (high-output-failure)

Therapy of acute heart failure:
- Sedation, $O_2$, nitroglycerin, diureticum, positive inotrope and vasoactive substance
- hemofiltration, assist devices, mechanical ventilation

* Innere Medizin 2012 Taschenbuch – 1. Oktober 2011, von Gerd Herold (Autor), Taschenbuch: 966 Seiten, Verlag: Herold, Gerd (1. Oktober 2011), S. 201-209

# Acute Respiratory Distress Syndrome (ARDS)*

Acute respiratory failure due to direct or indirect lung injury leading to $O_2$-intake disturbance:

1. ALI = Acute Lung Injury ($PaO_2/FiO_2$ <300 mmHg)
2. ARDS = Acute Respiratory Distress Syndrome ($PaO_2/FiO_2$ <200 mmHg)

| Stages | |
|---|---|
| I | Hypoxemia & Hyperventilation (res. alkalosis) |
| II | Dyspnoea, Infiltrates in X-ray |
| III | Hypoxemia + Hypercapnia (res. acidosis) |

Typical picture ARDS
by Notfallradiology Medical Imaging

| Therapy |
|---|
| Chest elevated position (45°) |
| PEEP = Positive End-Expiratory Pressure<br>CPAP = Continuous Positive Airway Pressure |
| ECLA = Extra Corporeal Lung Assist<br>• ECMO Extra Corporeal Membrane Oxygenator<br>• $ECCO_2R$ Extra Corporeal $CO_2$ Removal |
| Corticosteroids, antibiotics, nitric oxide (NO) |
| Lung transplantation |

Mortality in ARDS with sepsis and MOF >80% !!

$PaO_2$ = arterial $O_2$ partial pressure, normal 70-100 mmHg
$FiO_2$ = fractional inspired $O_2$, normal 0.21 (21%)
$PaO_2/FiO_2$ = oxygenation index (Horowitz-Index), normal >450 mmHg

* Innere Medizin 2012 Taschenbuch – 1. Oktober 2011, von Gerd Herold (Autor), Taschenbuch: 966 Seiten, Verlag: Herold, Gerd (1. Oktober 2011), S. 333-335

# SIRS – Sepsis*

SIRS (Systemic Inflammatory Response Syndrome) is a systemic infectious or non-infectious inflammation of the whole organism!!

Sepsis when SIRS is caused by infection!!

| SIRS | + Infection | + Organ Dysfunction |
|---|---|---|
| 1. Temperature >38° or <36°<br>2. Tachycardia >90/min<br>3. Tachypnoa >20/min<br>4. Hyperventilation $pCO_2$ <33 mmHg<br>5. Leucocytosis >12,000/µl or Leucopoenia <4,000/µl<br>at least 2 criteria | Microbiological or clinical diagnosis of infection | • Acute encephalopathy<br>• Thrombocytopenia <100,000/mm³<br>• Hypoxia $PaO_2$ <75mmHg or $PaO_2/FiO_2$ <250 mmHg<br>• AKI diuresis <0.5 ml/kg/h and/or creatinine >200%<br>• Metabolic acidosis<br>• Hypotension systolic BP <90 mmHg or MAP <65 mmHg |
| **Sepsis** | | |
| **Severe Sepsis** | | at least 1 dysfunction |
| **Septic shock** | | Hypotension only |

ICU

MAP = Middle Arterial Pressure

Mortality:
- sepsis 40%
- septic shock 60%

* Innere Medizin 2012 Taschenbuch – 1. Oktober 2011, von Gerd Herold (Autor), Taschenbuch: 966 Seiten, Verlag: Herold, Gerd (1. Oktober 2011), S. 316-321

# Prognosis

Several studies show early begin improves prognosis !!

Mortality of ICU patient with AKI is 50%
up to 90% of survivals recover renal function
10% get a end stage kidney disease*

prerenal and postrenal AKI better prognosis !! (exception hepotorenal and cardiorenal syndrome)

***Harrisons Innere Medizin,** Manfred Dietel, Norbert Suttorp, Martin Zeitz (Herausgeber) 2012 | 18., veränd. Aufl., S. 2477+2492

# SUMMARY

## Acute kidney injury is a complex condition and mortality rates have remained high at approximately 50%

AKI is an increasing disease due to:

- older patient population
- increased number of heavy surgeries, particular older patients
- higher number of comorbidities

Acute kidney injury may lead to chronic kidney disease regardless of the cause of the acute injury

Septic patient are prone to get AKI

MODS failure of mostly more than 2 organs where the body can not sustain homeostasis !!

B BRAUN
SHARING EXPERTISE

# 7. PRINCIPALS OF PP THERAPIES

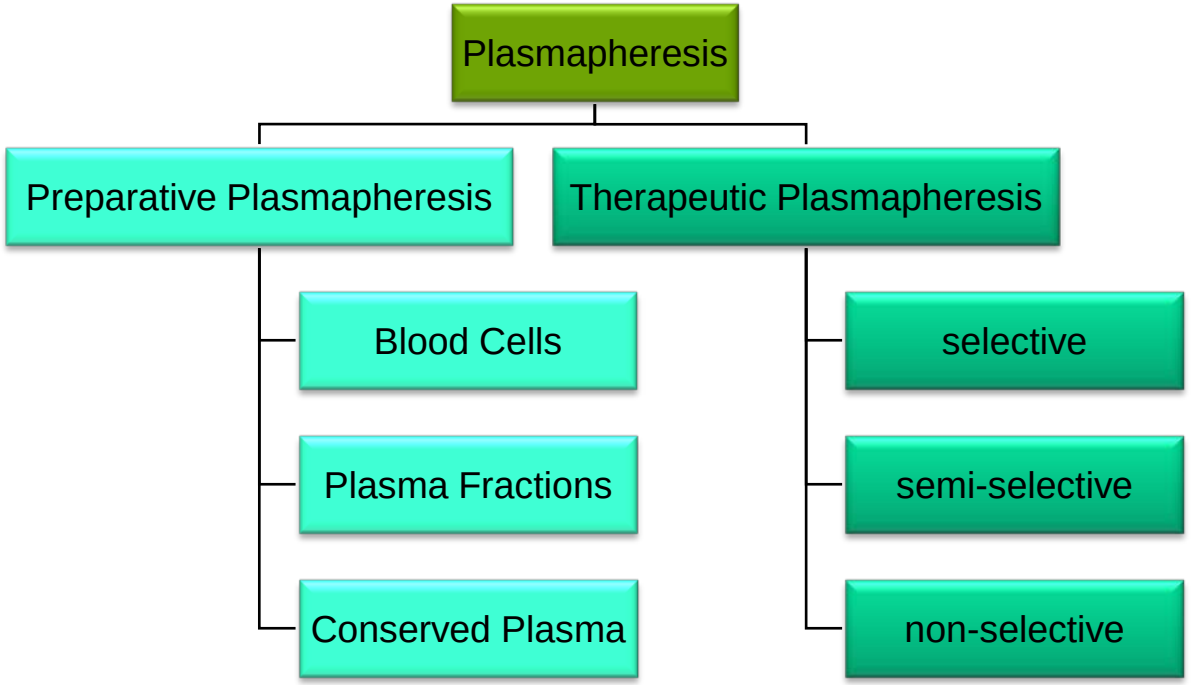
## UNDERSTANDING BASICS OF PLASMA SEPARATION AND PLASMA TREATMENT

# Definition

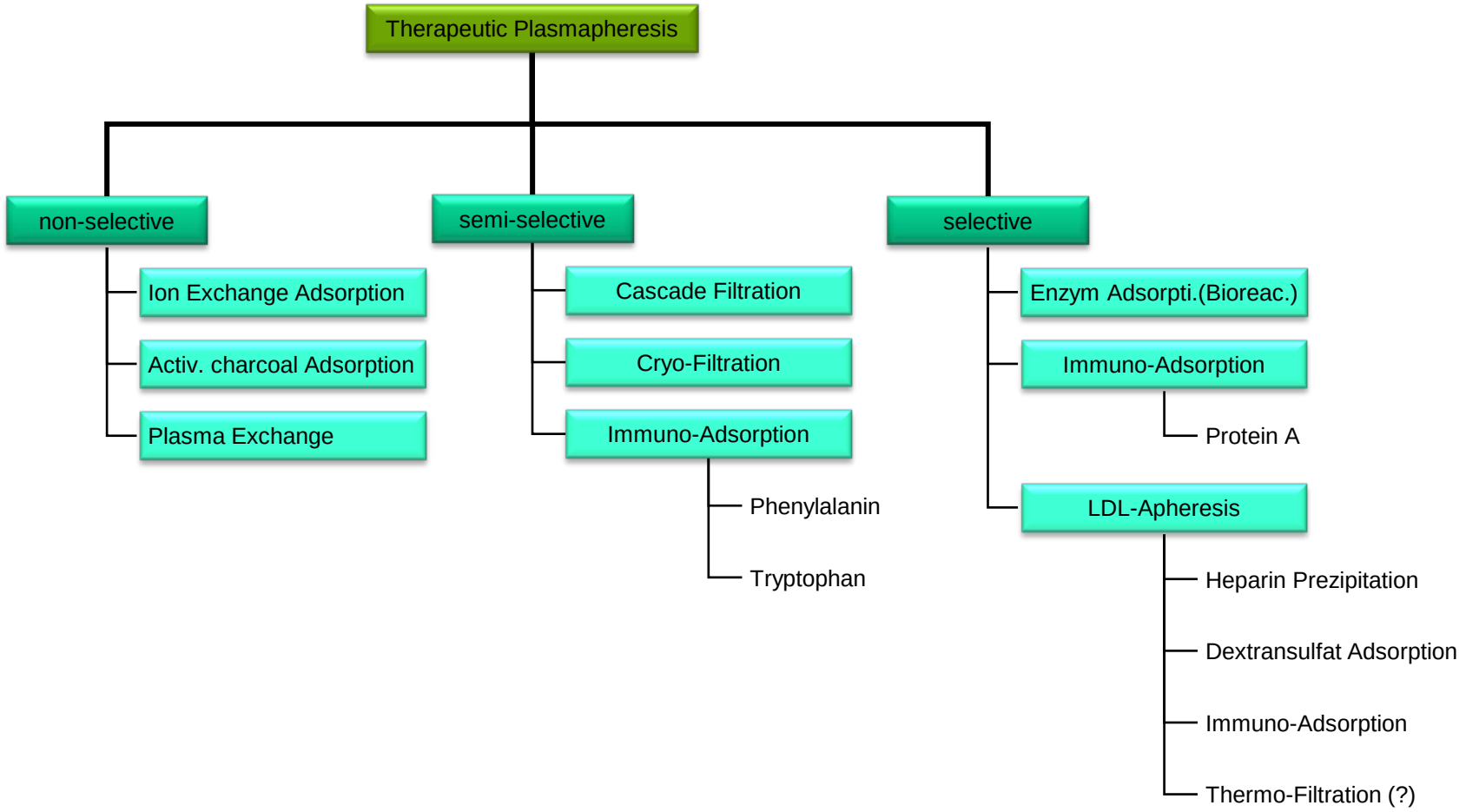
**Plasma** ⟹ **pheresis**

From Greek „Apheresis“
„separation“ of plasma through membrane filter or centrifuge

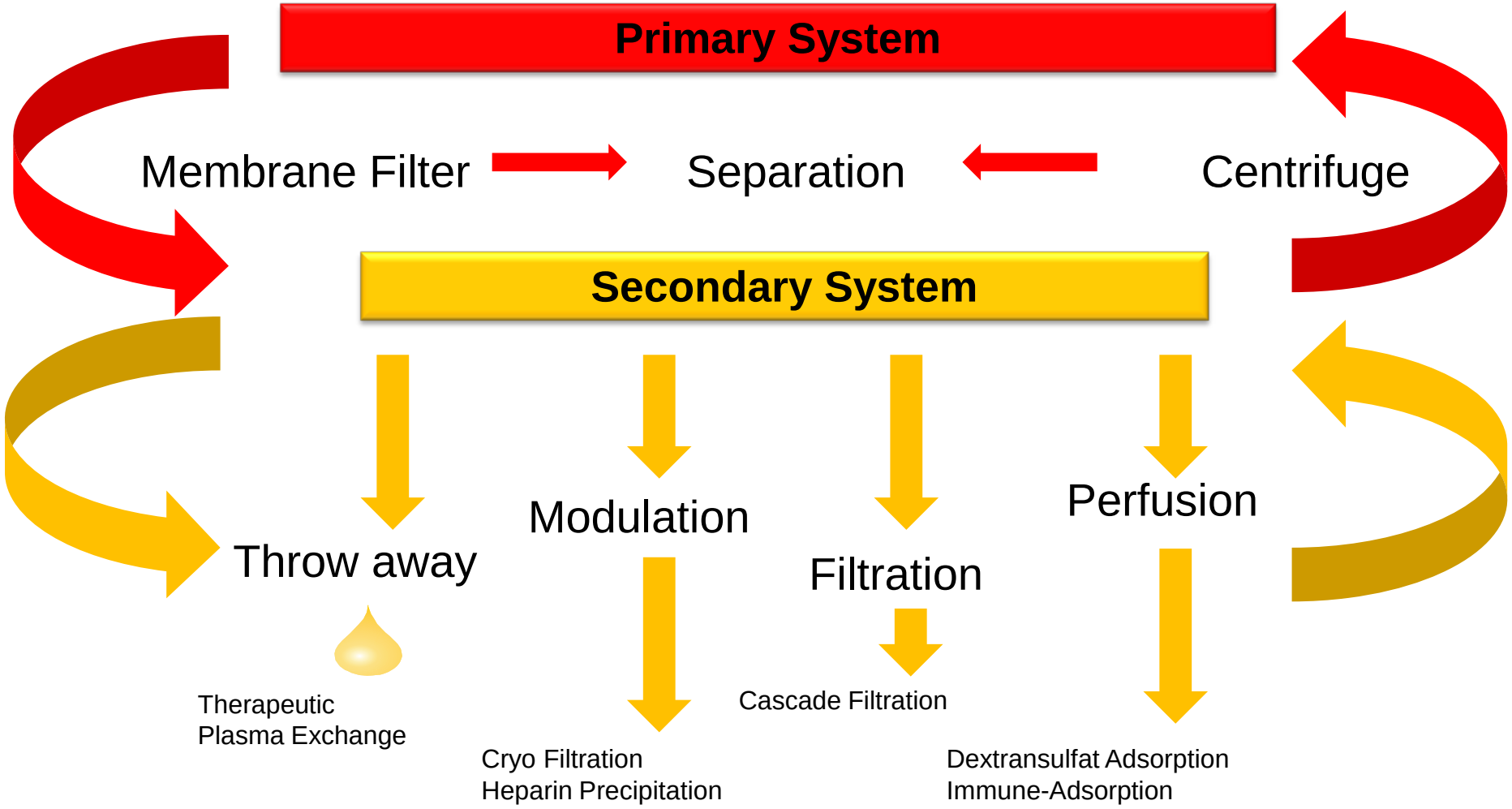
# Overview Plasmapheresis



# Overview Therapeutic Plasmapheresis



# Principals of Plasmapheresis



| | **Membrane Plasma Separation** | **Centrifuge Plasma Separation** |
|---|---|---|
| Application | Therapeutic Plasma Pheresis | Preparative Plasma Pheresis |
| Anticoagulation | Cont. Heparinisation | Citrate with Heparin Initialbolus |
| Side Effects | Filter Clotting, mech. Hemolysis | Thrombocytopenia, mech. Hemolysis |

# Membrane Filter Separation

TMP <100 mmHg

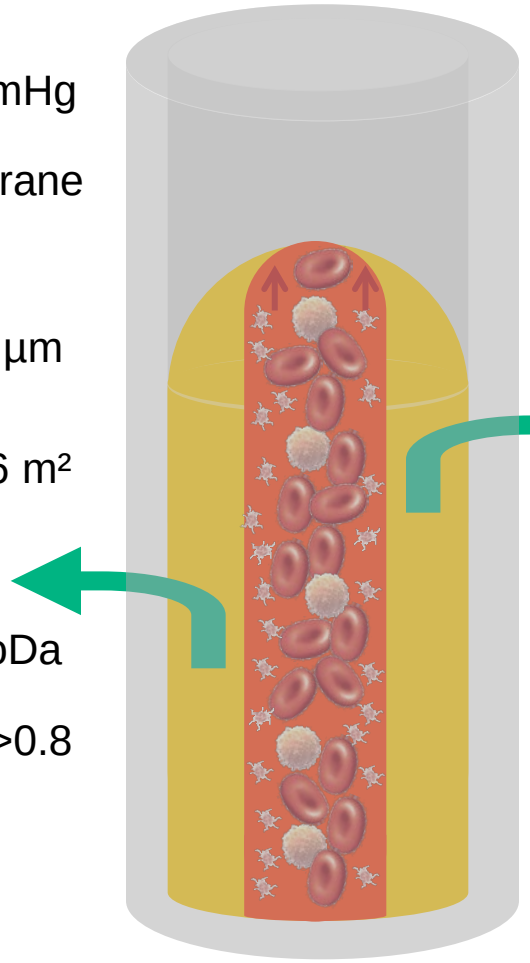
Secondary Membrane

Pore Size 0.2-0.6 µm

Surface 0.13-0.6 m²

Cut-off 3 MioDa

Sieving Coefficient >0.8

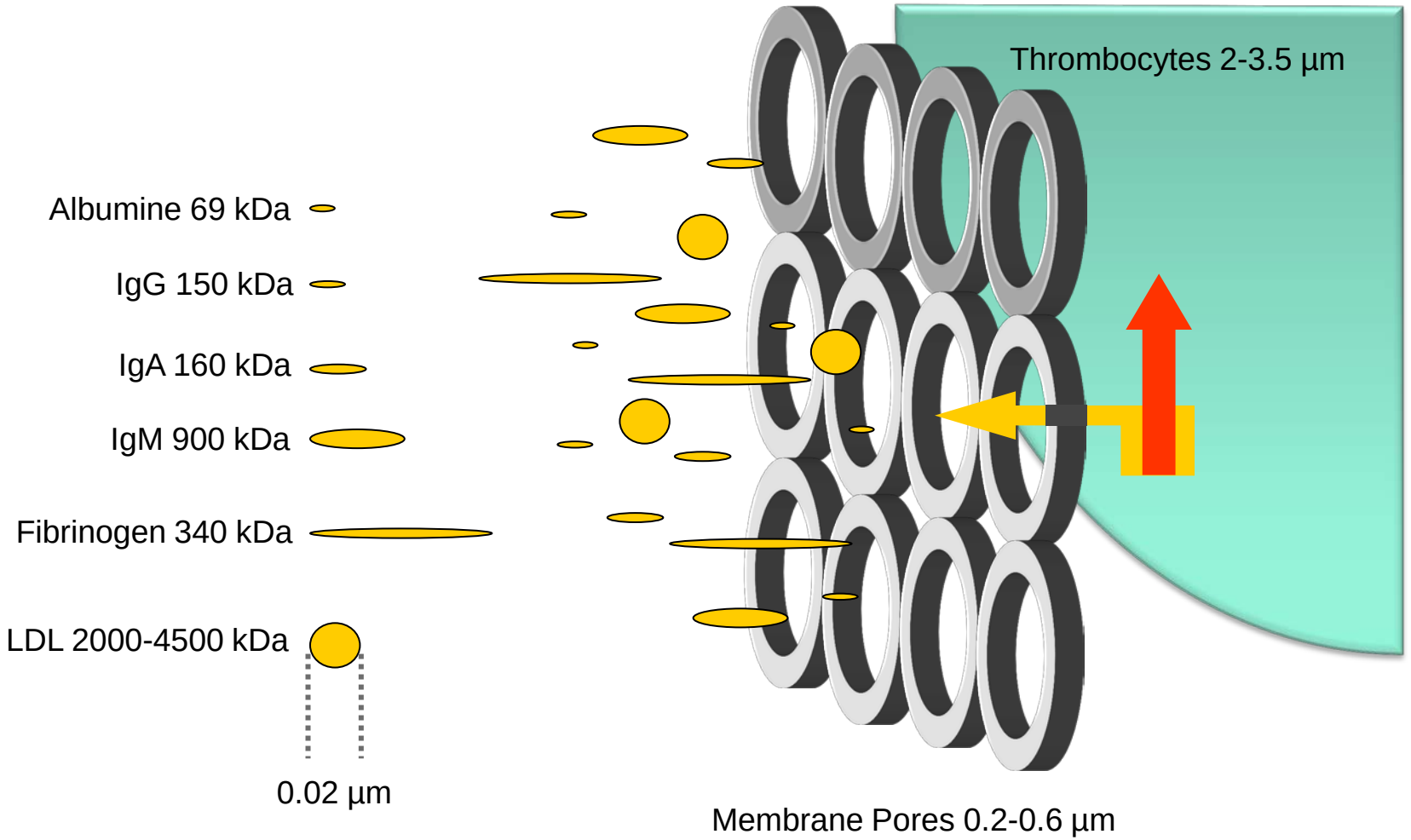


Hemocompatibility

Sterilisation:
ETO
Steam
Gamma

Filtration Rate <1/3
of Blood Flow Rate

Material:
Polypropylen
Polysulfon
Cellulosediacetat


Thrombocytes 2-3.5 µm
Albumine 69 kDa
IgG 150 kDa
IgA 160 kDa
IgM 900 kDa
Fibrinogen 340 kDa
LDL 2000-4500 kDa
0.02 µm
Membrane Pores 0.2-0.6 µm

# Sieving Coefficient

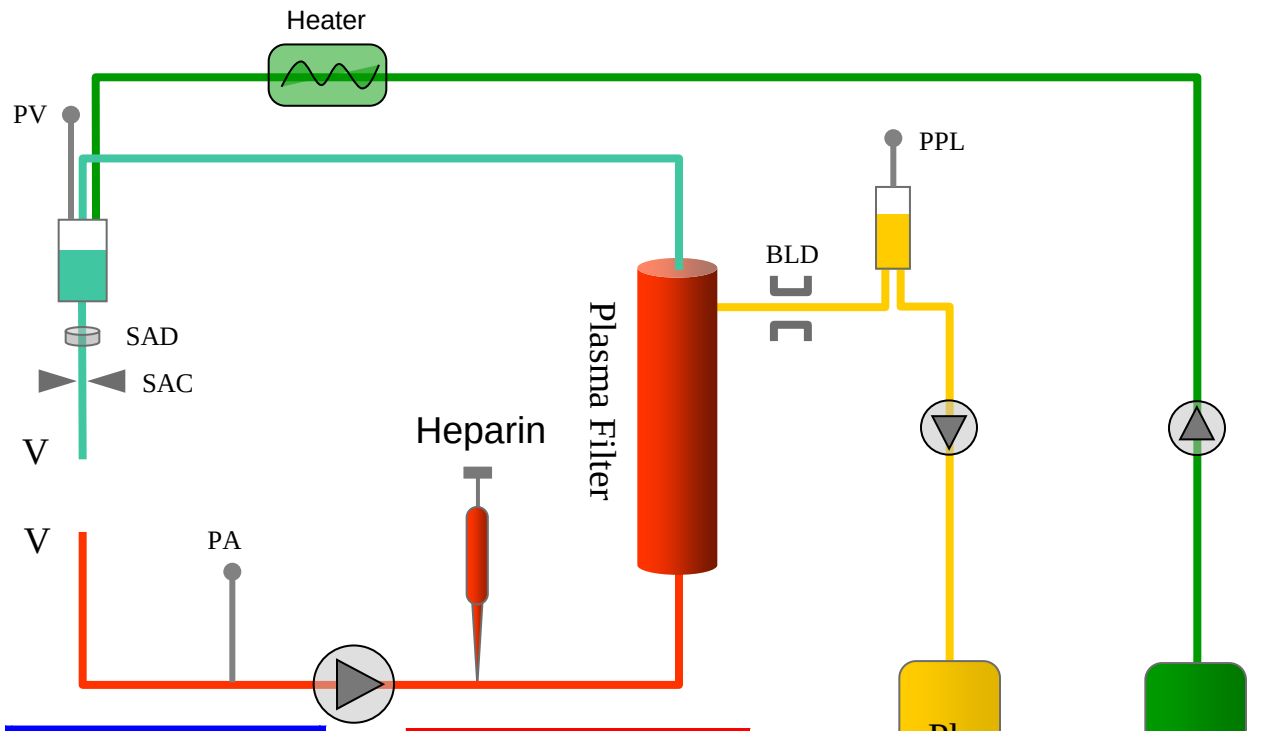
Concentration ratio of a certain component in
separated plasma to the Concentration in plasma before separation

| Plasma Component | Sieving Coefficient |
|---|---|
| Total Protein | 0.9 |
| Albumin | 0.95 |
| IgG | 0.9 |
| IgA | 0.85 |
| IgM | 0.8 |
| Fibrinogen | 0.95 |
| Cholesterol | 0.8 |

**optimal plasma separation**

1. plasma/blood flow 1/3
2. low TMP
3. high blood flow

# PEX - Therapeutic Plasma Exchange



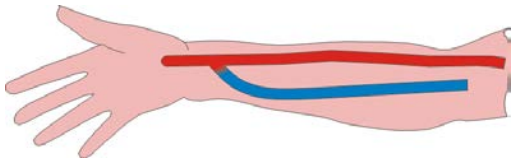

| Advantages |
| --- |
| rel. simple technic |
| bride spectrum of indication |
| rel. low costs |

| Disadvantages |
| --- |
| non-selective |
| substitution complications |
| no chronic application |

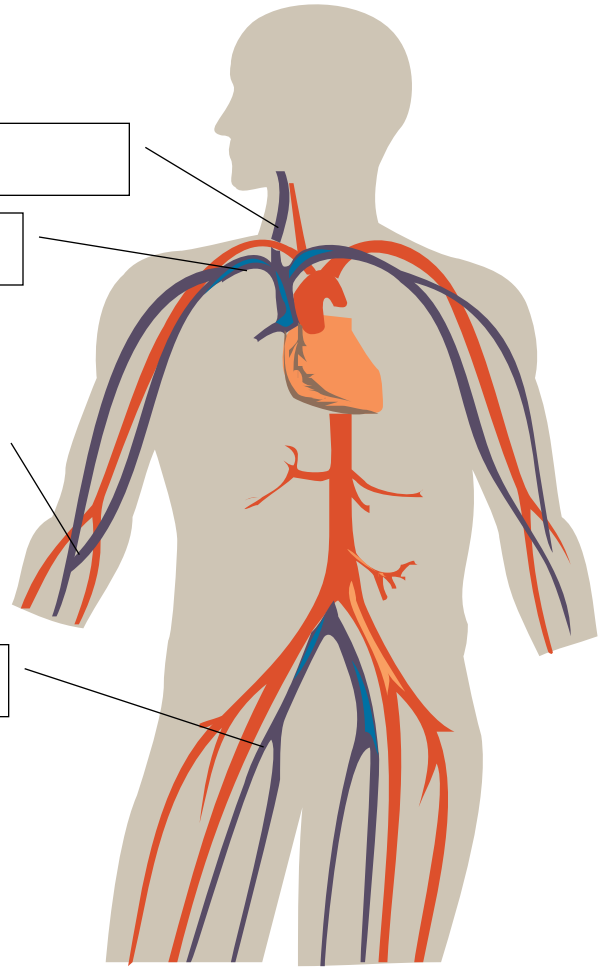
# Vascular Access

**Vascular Access**

- periferal vein
- arterio-venous fistula
- central-venous access



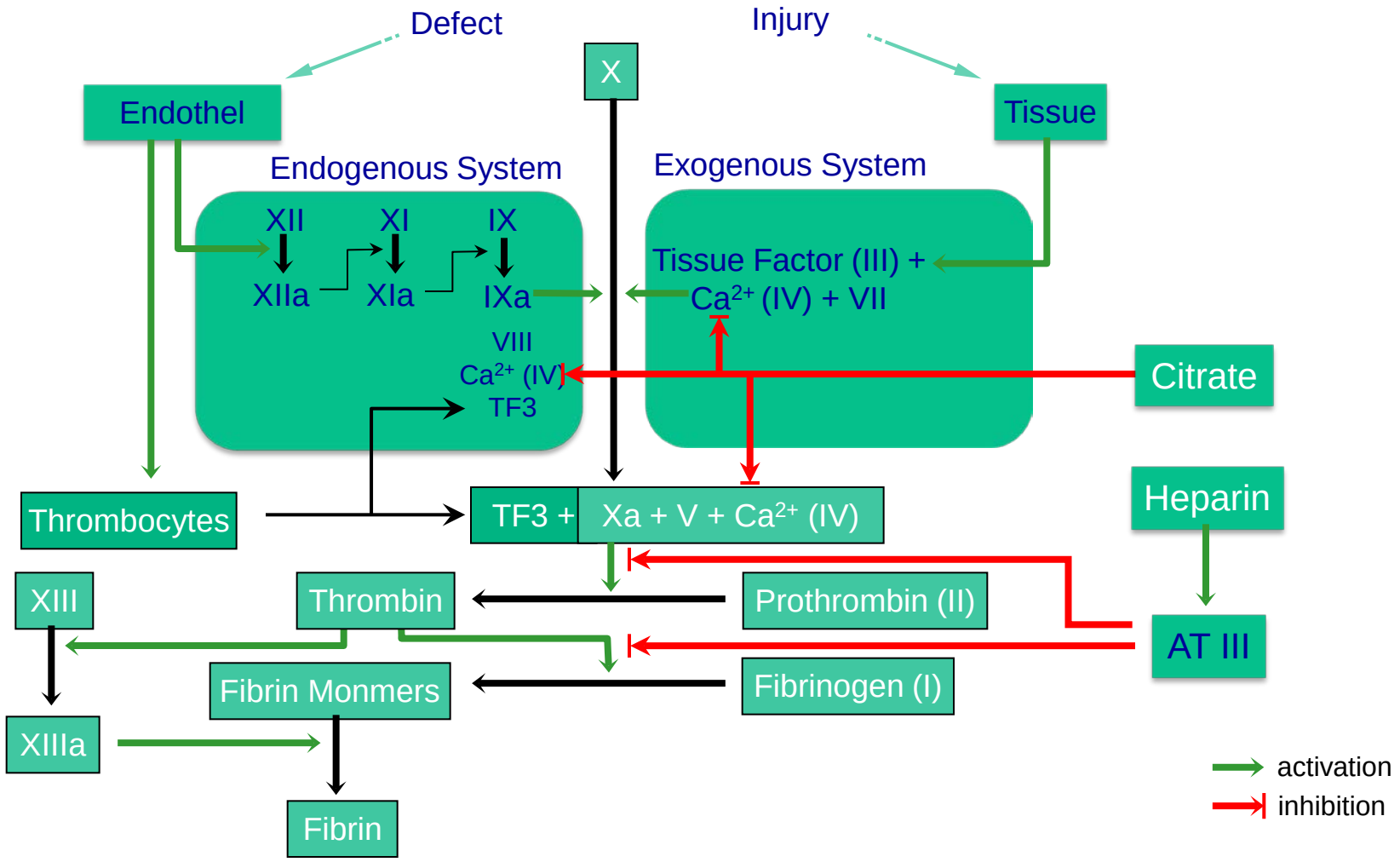
Cimino Fistula



# Anticoagulation

| | **initial** | **continuous** |
|---|---|---|
| Heparin | 40-60<br>IU/kg BW | 10-20 IU/kg/h |
| Citrate | 1000-3000<br>IU Heparin | 1:15-1:25<br>ACD/Blood |

# Coagulation Cascade



# Substitution

**Clinical Requirement**

- isovolemic, isotonic, isooncotic
- allergen and pyrogen free, sterile
- containing coagulation factors and immunoglobulins

# Substitution

| | Remarcs |
|---|---|
| 1. Plasma Expander | Dextrane, Hydroxyethylstarch (HES), Gelatine Preparation. Short Half Life Time |
| 2. Conserved Plasma Protein | Contain E'lytes, Albumine, Globulins. Expensive, Incompatibility Reactions |
| 3. Fresh Frozen Plasma (FFP) | AB0-Compatibility, Indication for TTP und Goodpasture Syndrome, Allergic Reactions, Viral Infections, Hypocalcemia |
| 4. Human Albumine Solution | Albumin + Hemofiltration Solutions with Lactate or Bicarbonate, Low Rate of Side Effects |

# Hemofiltration Solution

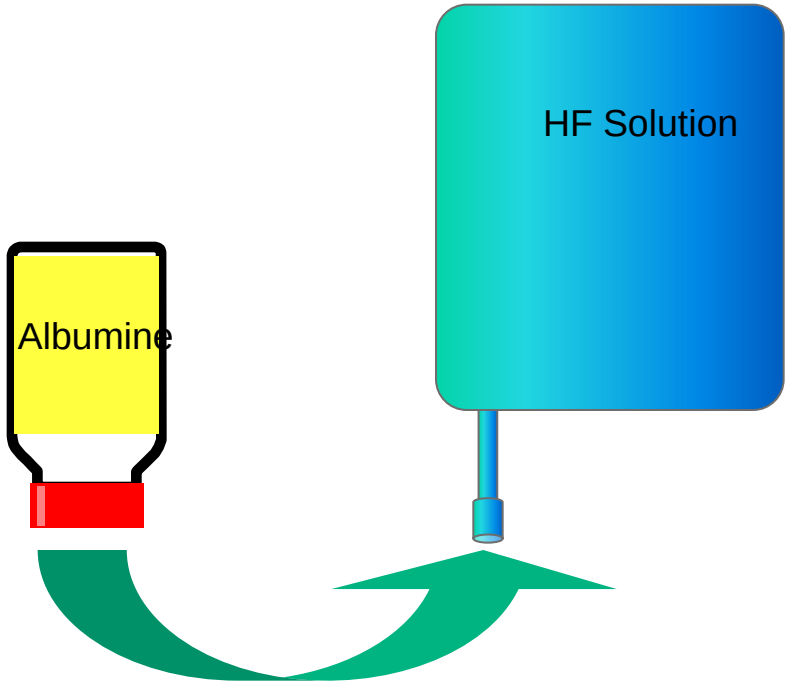
| $Na^+$ mmol/l | $K^+$ mmol/l | $Ca^{2+}$ mmol/l | $Mg^{2+}$ mmol/l | $Cl^-$ mmol/l | Lactate mmol/l | Glucose g/l | Osmol. mmol/l |
|---|---|---|---|---|---|---|---|
| 135-150 | 0-4 | 1.6-2.0 | 0.50-0.75 | 100-113 | 35-45 | 0-2.0 | 285-312 |

| $Na^+$ mmol/l | $K^+$ mmol/l | $Ca^{2+}$ mmol/l | $Mg^{2+}$ mmol/l | $Cl^-$ mmol/l | Bicarb. mmol/l | Glucose g/l | Osmol. mmol/l |
|---|---|---|---|---|---|---|---|
| 140 | 0-4 | 1.5 | 0.5 | 109-113 | 35 | 1.0 | 290-300 |

# Human Albumine Electrolyte Solution

| | **3% Solution** | **3.5% Solution** | **4% Solution** | **4.5% Solution** | **5% Solution** | **5.5% Solution** | **6% Solution** |
|---|---|---|---|---|---|---|---|
| HF-Solution (ml) | 850 | 825 | 800 | 775 | 750 | 725 | 700 |
| Human Albumine 20% (ml) | 150 | 175 | 200 | 225 | 250 | 275 | 300 |

# Albumine Solution

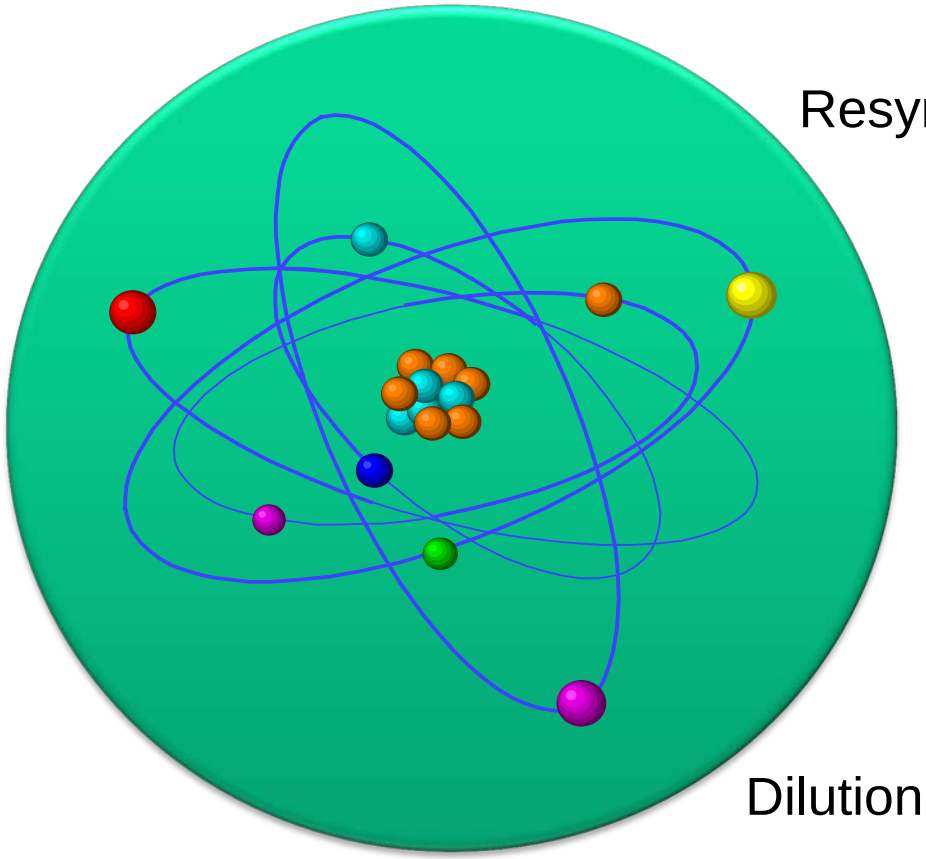



i.g. 2 Liters 4%-Solution = 400 ml Albumine 20% + 1600 ml HF Solution

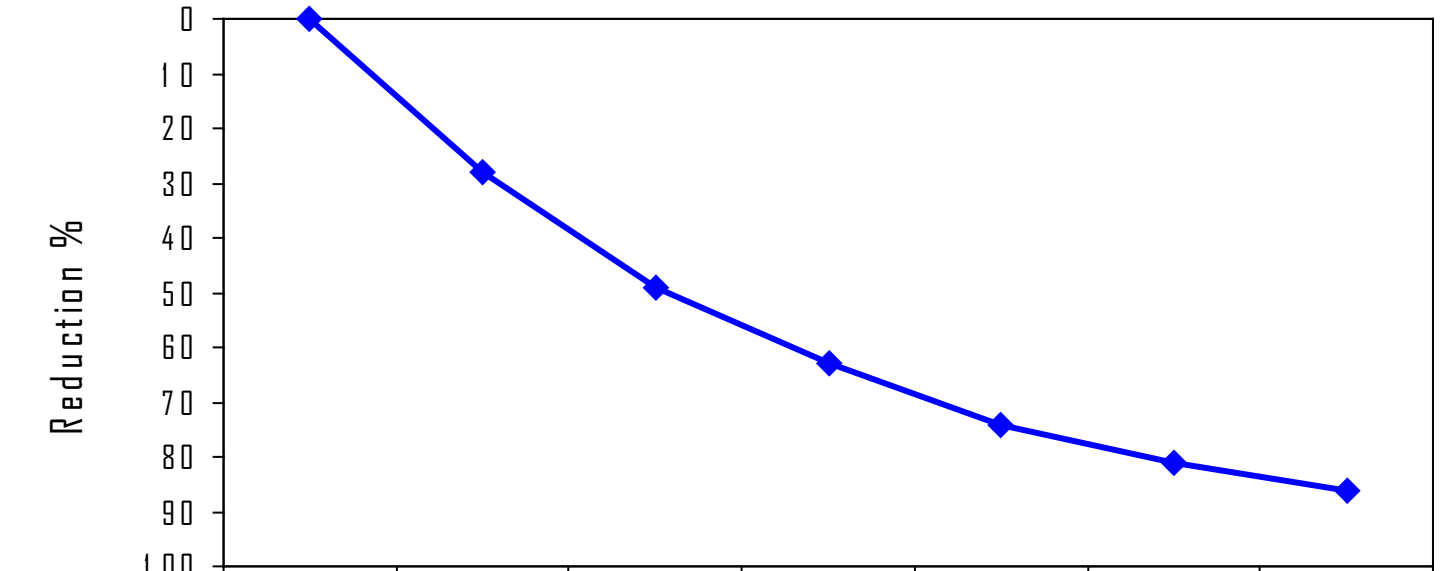
# Exchange Volume

| | |
|---|---|
| Plasma Volume | ½ - 2 PV |
| Ratio | 1:1 |
| Therapy Time | 1 – 3 h |
| Frequency | acute: 1x day for 3 days lang, then every 2 days<br>chronic: 1-4 monthly |

# Kinetics

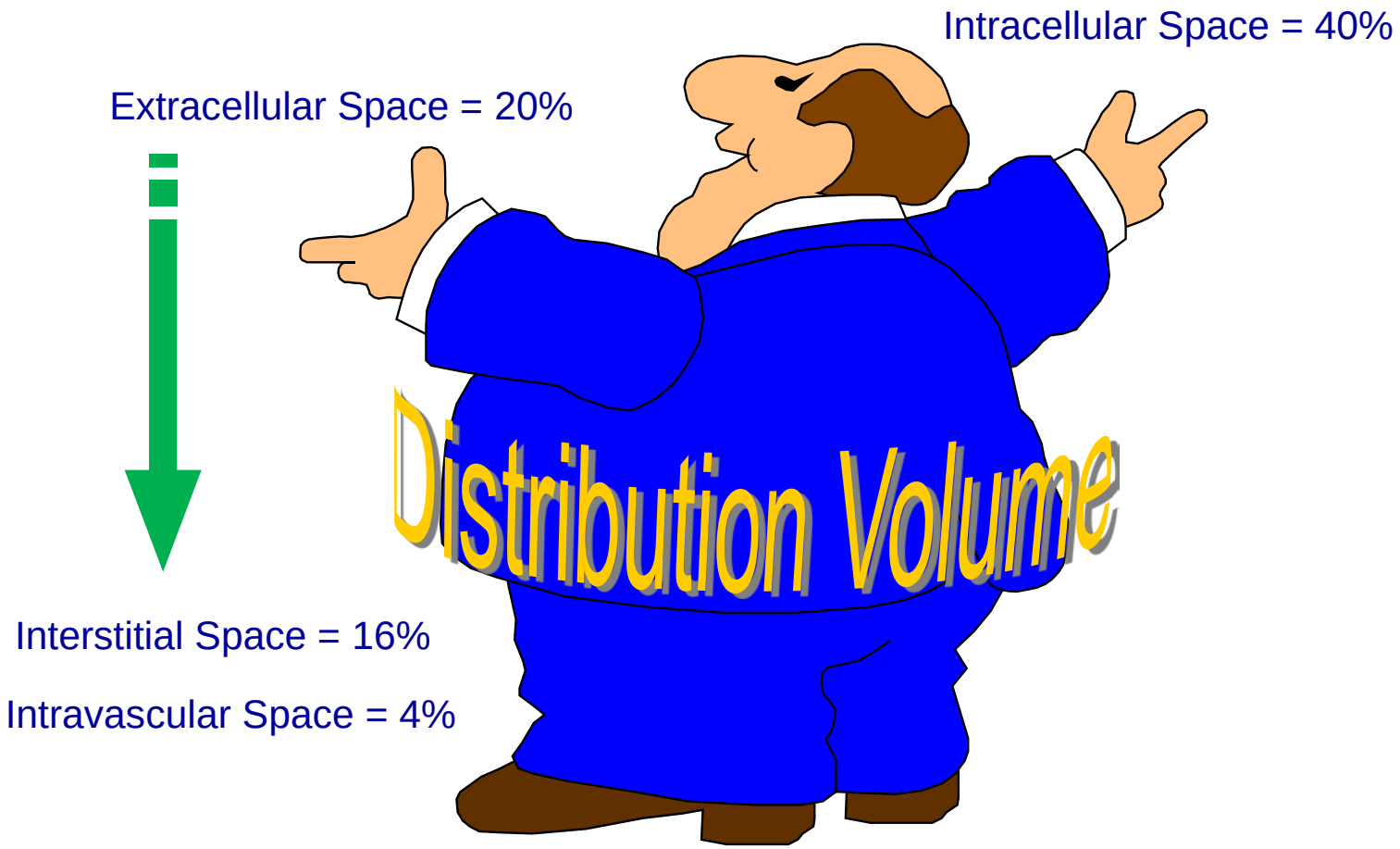

Redistribution
Resynthesis
Rebound
Return Rate
Distribution Space
Drugs
Dilution Effect

# Dilution Kinetics




| PV | 0 | 1/3 | 2/3 | 1 | 1 1/3 | 1 2/3 | 2 |
|---|---|---|---|---|---|---|---|
| Reduction % | 0 | 28 | 49 | 63 | 74 | 81 | 86 |

# Distribution Volume



# Distribution Volume

| Plasma Component | Molekular Weight Dalton | Intrav. Distribution % | Half Life Time Days | Normal value g/l |
|---|---|---|---|---|
| Albumine | 69 000 | 40 | 19 | 35-50 |
| IgG | 150 000 | 50 | 20-23 | 8-18 |
| IgA | 160 000 | 50 | 5-6 | 0.9-4.5 |
| IgM | 900 000 | 80 | 5-6 | 0.6-2.8 |

# Complications

| technical | medical |
|---|---|
| Access Problems | Hypotension |
| Plasma Filter Clotting | Allergy |
| Blood Leak | Fever |
| Hemolysis | Hypocalcemia |
| | Arrhythmia |
| | Edema |

# 8. TPE AND MEDICAL INDICATIONS OF PP THERAPIES

## HOW TO TREAT PLASMA DISEASES

# Indications for Plasmapheresis

| Disease (ASFA* Category) | |
|---|---|
| TTP/HUS (I) | Thrombotic Thrombocytopenic Purpura – Hemolytic Uremic Syndrome. Thrombocytopenia, hemolytic anemia, neurologic symptoms. Substitution of FFP is therapeutic desired. |
| Goodpasture Syndrome (I) | Rapid progressive glomerulonephritis and lungs bleeding. Prognostic important early indication to plasmapheresis in combination with Immunsuppressive therapy. |
| Guillain-Barré-Syndrome (I) | Acute inflammatory attack of myelin sheat in peripheral nerves and spinal ganglions through IgG-Antibodies and immuno-complexes. Ascending paralysis of extremities and trunk up to respiratory paralysis. |
| Myasthenia Gravis (I) | IgG-Autoantibodies against Acetylcholin rezeptors of skeletal muscles. Neuro-muscular symptoms. Myasthenic crises with respiratory paralysis. |
| Hyperviscosity Syndrome (I) | High blood viscosity e.g. in M. Waldenström, Myeloma, Cryoglobulinemia. Neurologic and hematologic disturbances, organ damage. |
| Cryoglobulinemia (I) | Immunglobulin complexis which precipitate in coldness. Skin bleeding closed to fingers and toes, articulation pain, glomerulonephritis. |
| Renal Transplantation (I) | In acute antibody-mediated rejection to remove anti-HLA antibodies. Also in desensitization for AB0-incompatible and hypersensitized patients before transplantation. |
| SLE (II) | Systemic Lupus Erythematodes. Autoimmuno desease of skin and vessels with deposition of immuno-complexes composed by DNA and DNA-Antibodies. |
| Multiple Myeloma (II) | Plasmacytoma. Plasma cell carcinoma which produce abnormal antibodies in bone marrow. The pathologic antibodies cause casts in Kidney. Changes in marrow cause bone damage and hypercalcemia. |
| Multiple Sclerosis (II) | Type of inflammation of CNS (inflammatory demyeliting disease) in which myelin sheath of brain and spine are damaged. Course of the disease can differ very much with wide range of neurologic symptoms. |
| Poisoning, Overdose (II) | Mushrooms, snakebite, cisplatin, digoxin |

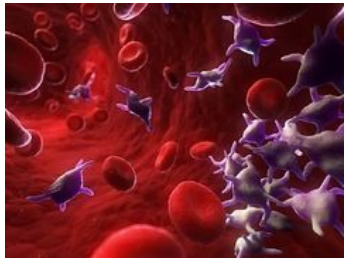
*ASFA = American Society for Apheresis

# TTP - Thrombotic Thrombocytopenic Purpura
# HUS - Hemolytic Uremic Syndrome

Both diseases are as **thrombotic microangiopathy** a combination of

1. intravascular thrombosis
2. thrombocytopenia and
3. hemolysis

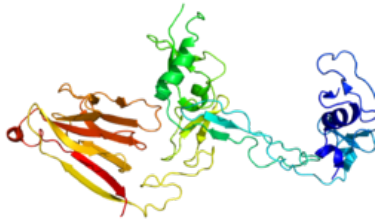
mainly in kidney and brain



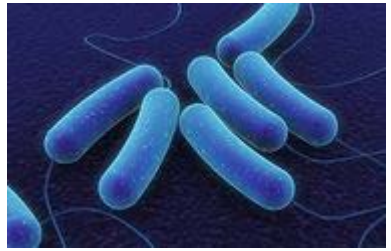
| | **Symptoms** | **Thrombocytopenia** | **SCr** |
|---|---|---|---|
| **TTP** | fiver, thrombocytopenia, microangiopathic hemolytic anemia, neurologic symptoms, kidney failure | severe | <1.3 mg/dl (<120 µmol/l) |
| **HUS** | AKI, microangiopathic hemolytic anemia, thrombocytopenia | mild | >2.2 mg/dl (>200 µmol/l |

# TTP - Thrombotic Thrombocytopenic Purpura
# HUS - Hemolytic Uremic Syndrome

| | **Ethiology** | **Pathology** |
|---|---|---|
| **TTP** | idiopathic hereditary Secondary (pregnancy, medicine) | Lack or antibodies against enzyme ADAMTS13 which is necessary to brake the coagulation factor vWF |
| **HUS** | Typical (E. coli) Atypical: secondary or hereditary | E. Coli produces Shiga-like toxin which can so damage cells of glomerular endothelialium and can inactivates ADAMTS13 |



ADAMTS13



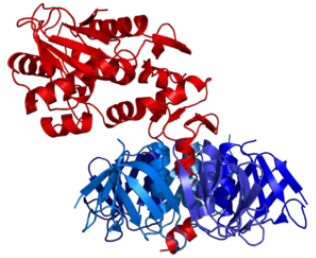
E. coli bacterium

# TTP - Thrombotic Thrombocytopenic Purpura
# HUS - Hemolytic Uremic Syndrome

| | Therapy | Prognosis |
|---|---|---|
| **TTP** | FFP, PEX<br>in case of Antibodies<br>immunosuppressive<br>therapy | PEX improved mortality<br>from 85-100% to 10-30% |

→ Anti-ADAMTS13
- Antibodies

| | Therapy | Prognosis |
|---|---|---|
| **HUS** | FFP (?), PEX (?)<br>HD, HF<br>immunosuppressive<br>therapy | PEX reduces mortality of<br>atypical HUS to 10-30% |



→ Shiga-like Toxin 1 with
subunit A (red, 32 kDal)
and
5xB (blue, each 7.7 kDal)

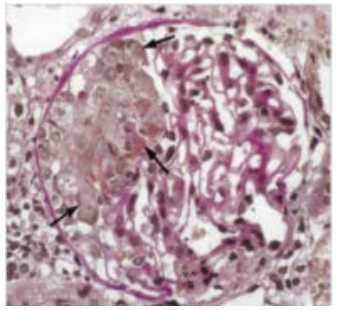
No replacement of Thrombocytes !!

# Goodpasture Syndrome

**Definition**
Autoimmune disease with antibodies against glomerular basemend membrane (anti-GBM disease) leading to rapid progressive glomerulonephritis (RPGN) and lungs bleeding.

**Symptoms/Clinic**

- Proteinuria, hematuria
- Coughing, Lung bleeding
- Anti-GBM antibodies
- Rapid progressive kidney failure
- **Renal biopsy** “half moon” in glomerulus*



**Prognosis**
important early indication to plasmapheresis (TPE or PA) in combination with Immunosuppressive therapy (Prednison, Cyclophasphamide).

**TPE (terapeutic Plasmaexchange)**

- 1.5 plasma volume every day for 2 weeks, or until anti-GBM antibodies not detectable

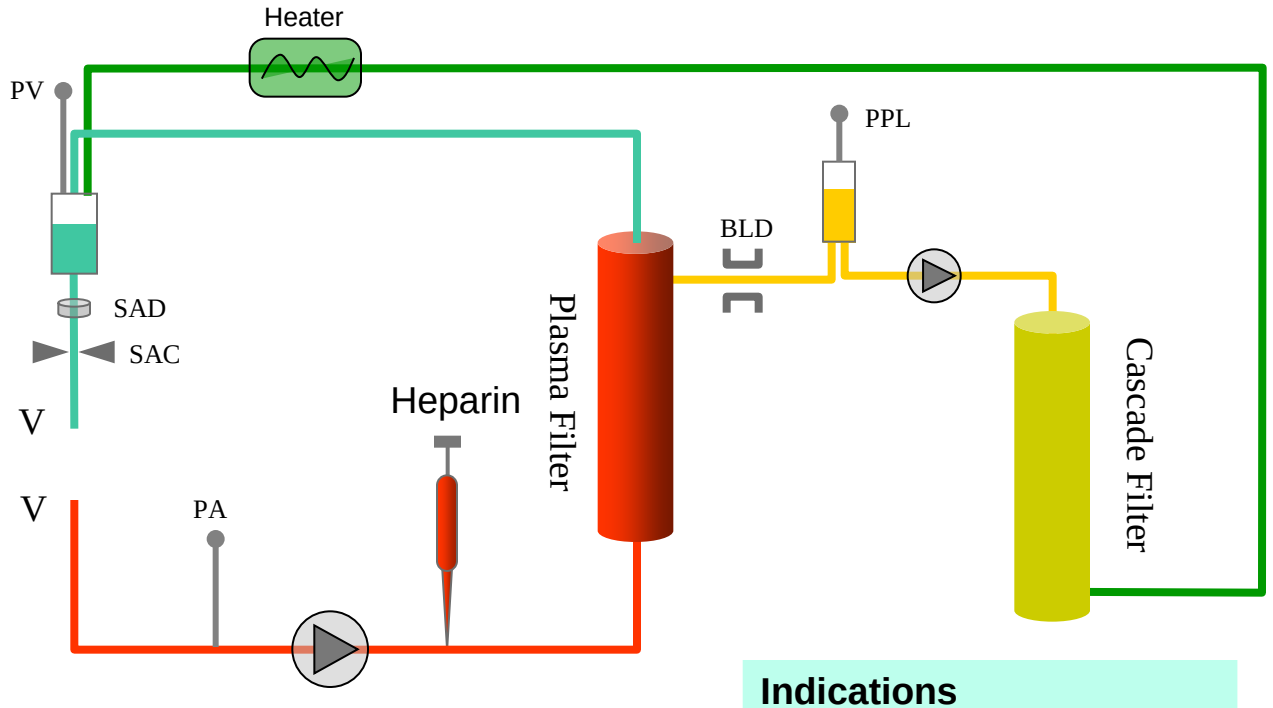
or

- 2 plsma volumes every day for 7 days, then every second day for 1 more week

## Remind

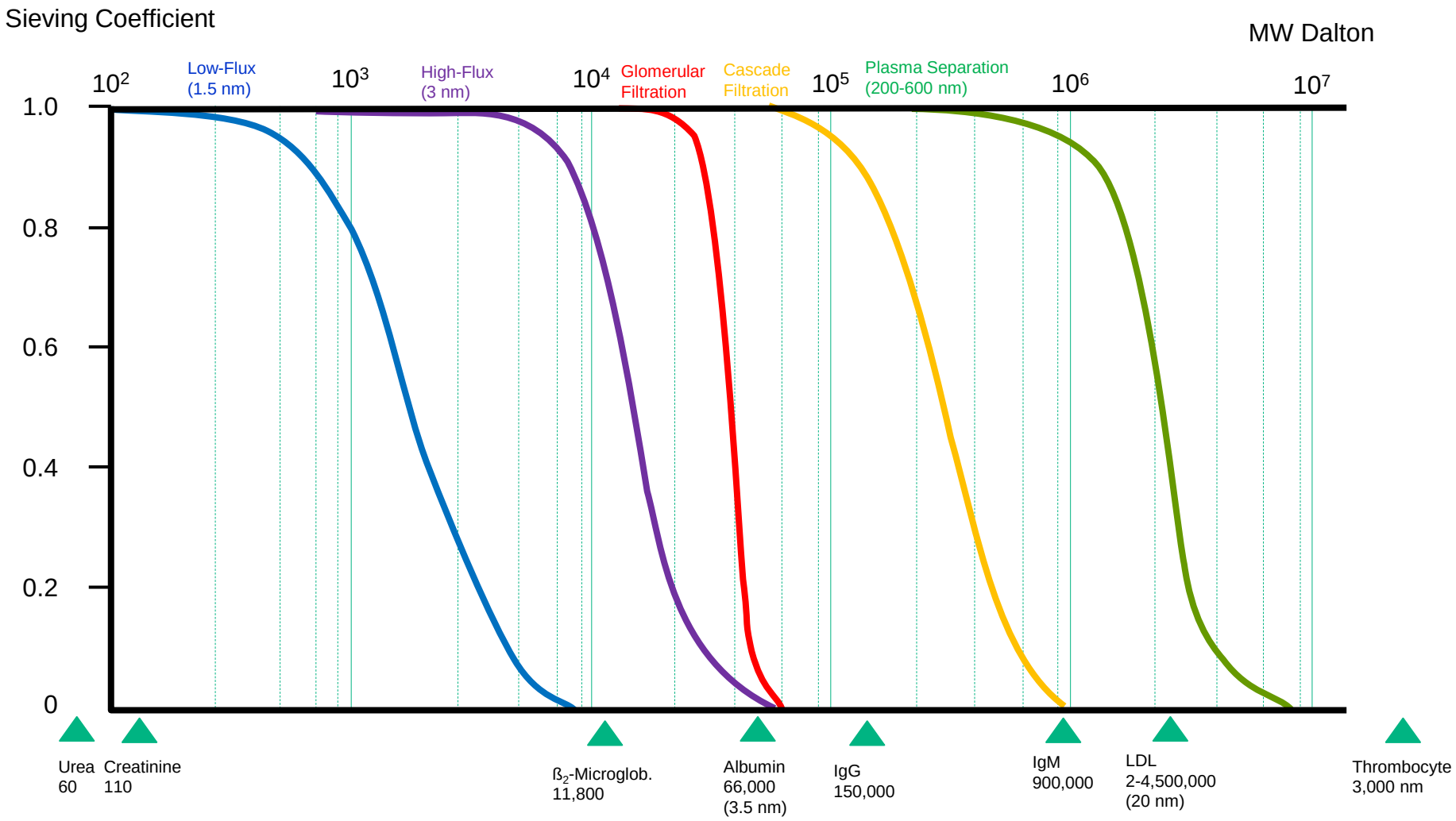
- Plasmapheresis is often a symptomatic therapy
- Plasmapheresis can cause a „Rebound-Effect“ by resynthesis and redistribution of pathogens
- Therefore plasmapheresis is regulary accompanied by an immuno-suppressive or cytostatic therapy

# CF - Cascade Filtration

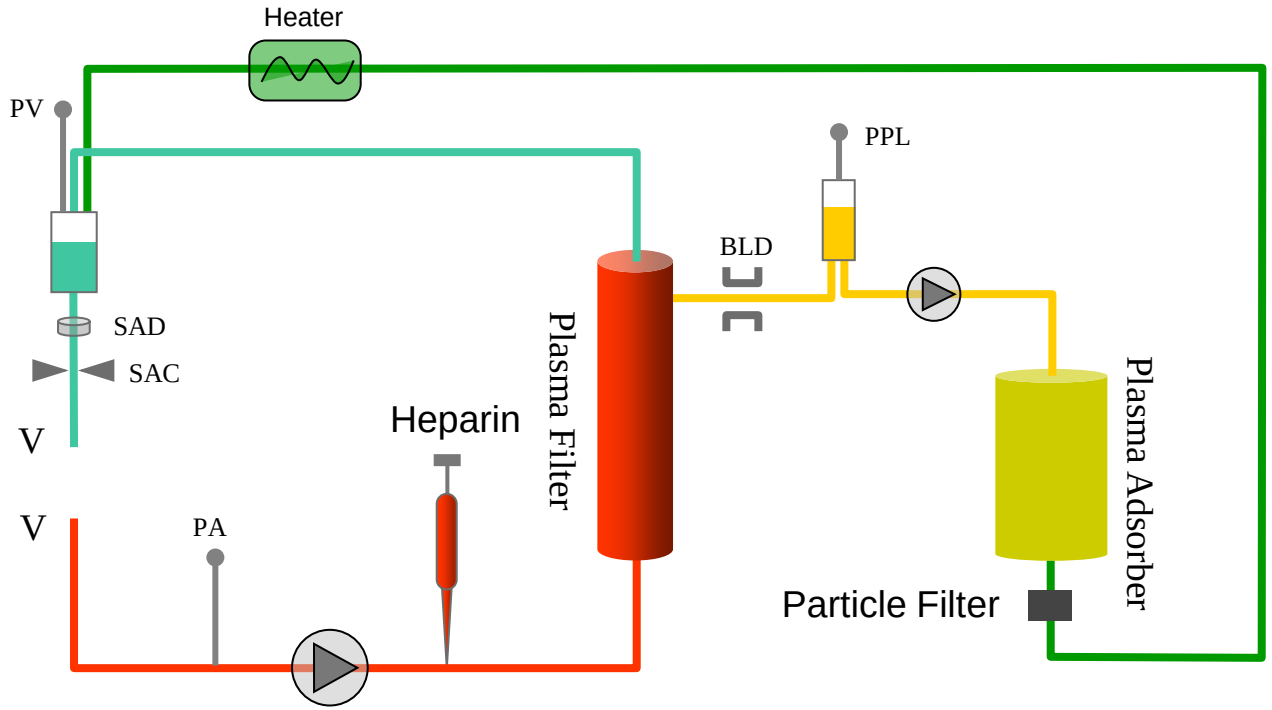



| **Indications** |
| --- |
| Hyperviscosity Syndrome |
| M. Waldenström (IgM) |
| Hypercholesterolemia |
| Cryoglobulinemia |

# Sieving Coefficient

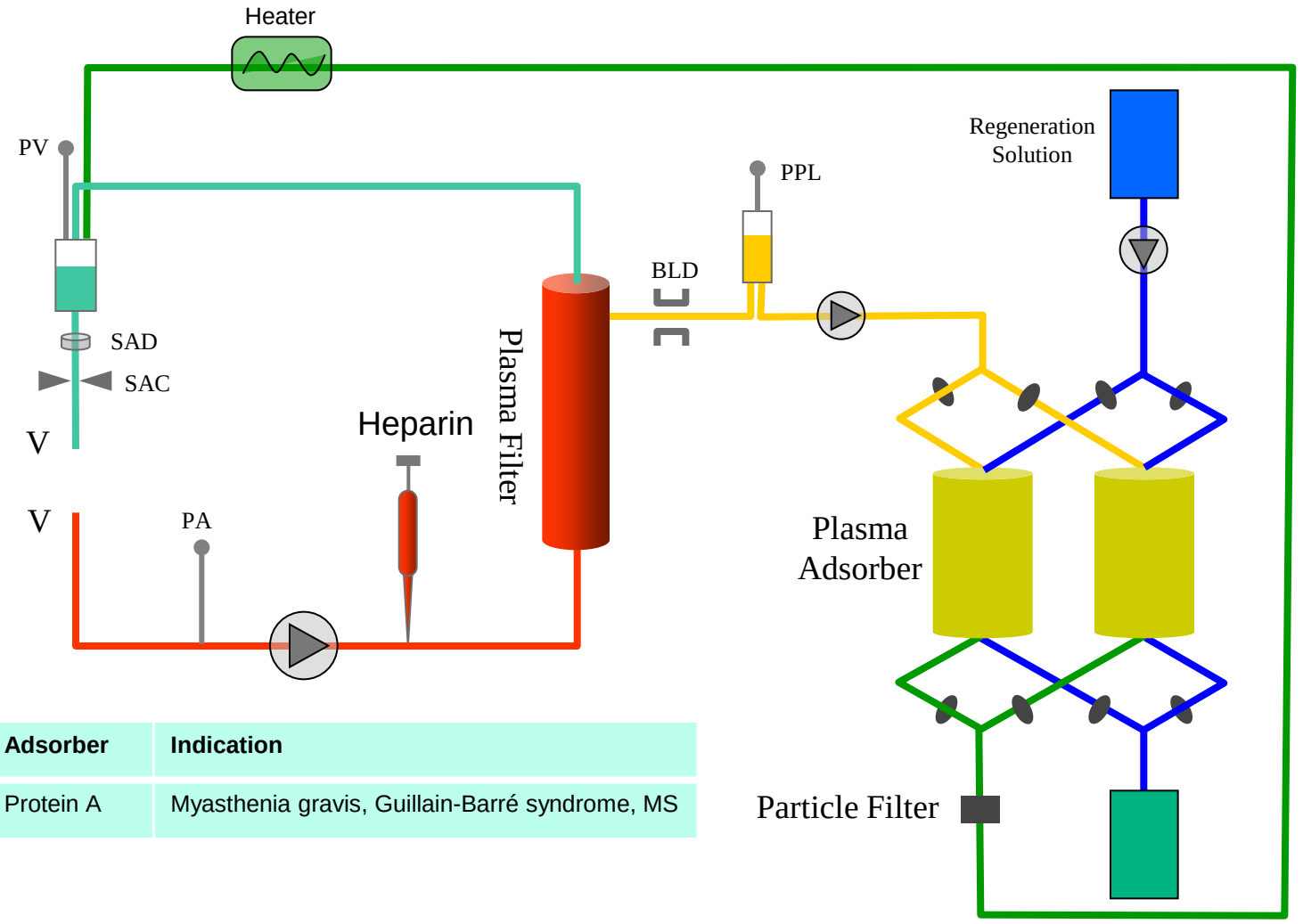


# PAP – Plasmaadsorption „single column“



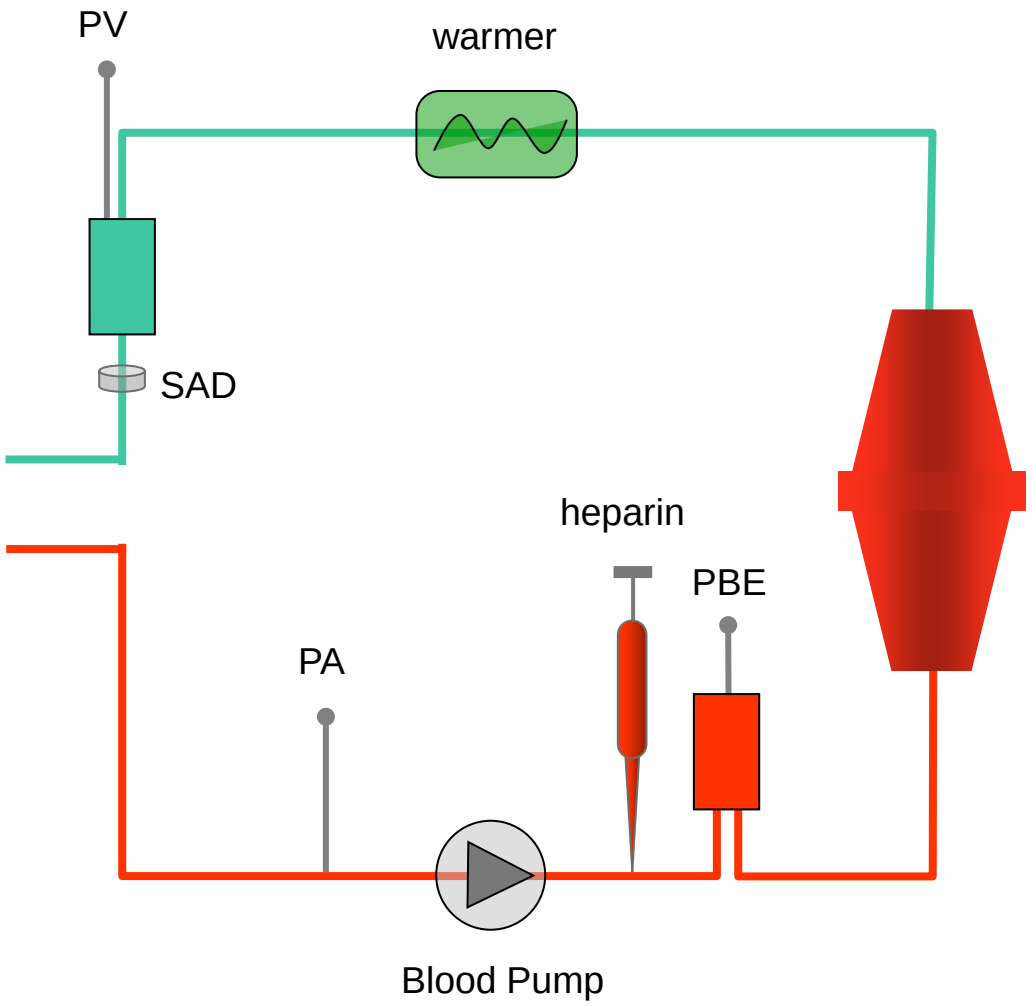

| Adsorber | Indication |
|---|---|
| SPA | Renal Transplant, dilated cardiomyopathy, SLE, pemphigus vulgaris |
| Antibody columns | SLE, myastenia gravis, Renal Transplant, dilated cardiomyopathy, |
| Phenyalanin | SLE, Malignant rheumatoid arthritis, Guillain-Barré syndrome, MS |
| Tryptophan | Myasthenia gravis, Guillain-Barré syndrome, MS |
| Styrenedivinylbenzene | Hyperbilirubinemia |

# PAP – Plasmaadsorption „double column“




| Adsorber | Indication |
|---|---|
| Protein A | Myasthenia gravis, Guillain-Barré syndrome, MS |

# HP – Hemoperfusion




| Adsorber | Indication |
|---|---|
| Activated Charcoal<br>Ion-exchange resin | Digoxin, Phenobarbital, paraquat, antimon, Mushrooms |

B BRAUN
SHARING EXPERTISE

# THANK YOU FOR YOUR ATTENTION!