# Renal Aspects of Cardiac Intensive Care

# 4

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## 4.1 Assessment of Renal Function

### 4.1.1 Importance of Urine Output

Apart from the clinical assessment of the patient, monitoring of postoperative renal function is primarily focused on the determination of hourly urine output (diuresis). An (age-commensurate) normal urine output in the absence of diuretic substances indicates adequate organ perfusion.

Urine output should not fall *unnoticed* below a value of 2 mL/kg BW/h postoperatively, as this may indicate a deteriorating cardiovascular situation. Blood pressure, heart rate, CVP, $SvO_2$, BE, lactate, and urine output thus represent objective parameters that allow the clinician to gain a picture of the patient's systemic circulation. By definition, oliguria is referred to if urine output is reduced to the following cutoff levels:

- Premature neonates/neonates: < 2.0 mL/kg BW/h.
- Children <1 year of age: < 1.0 mL/kg BW/h.
- Adolescents: < 0.5 mL/kg BW/h.

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#### 4.1.1.1 Definition of Oliguria

With a daily production of substances excreted in the urine of about 10 mosmol/kg/day = 0.42 mosmol/kg/h and a renal concentrating capacity of about 1200 mosmol/kg = 1.2 mosmol/mL, at least 0.35 mL/kg/h urine is required to keep the system in balance. However, if more urinary excreted substances are produced (e.g., with increased metabolism, catabolism, tissue necrosis) or if the renal concentrating capacity is restricted (e.g., due to immaturity of the kidney, kidney diseases, and drugs), a correspondingly larger quantity of urine must be excreted.

Urine output plays a vital role in the patient's fluid balance. In the absence of an adequate output, the i.v. fluid supply usually required in the postoperative setting can quickly lead to an increasingly positive fluid balance. This may contribute to the formation of edema and effusion, as well as respiratory problems and electrolyte fluctuations. For example, for a 10 kg child, the calculated input via drips and infusors on the first postoperative day (intake) adds up to 1000 mL/$m^2$/day ≈ 2 mL/kg/h (or more). An hourly urine output of at least 2 mL/kg/h (≈ 50 mL/kg/day) is therefore necessary to maintain fluids in balance. A patient is mathematically in negative balance if his or her output is greater than his or her input.

On the *input* side, (mL/day) can be reckoned, e.g.:

- Fluid volume administrations (mL/24 h).
- Infusors (mL/h × 24 h).
- Parenteral nutrition (mL/h × 24 h).
- Volume of all antibiotics and drugs (mL/24 h).
- Transfusions (mL/24 h).
- Enteral nutrition (proportion of fluid in the nutritional solution/quantity: mL/24 h × approx. 0.7).

On the output side, (mL/day) can be reckoned, e.g.:

- Amount of urine (mL/24 h).
- Blood losses (mL/24 h).
- Gastric juice losses (mL/24 h).
- Drain losses (mL/24 h).

The balance also includes losses via insensitive perspiration (approximately 20–40 mL/kg BW/day, depending on the moistening of inhaled air, fever, room temperature, etc.) and the oxidation water produced in metabolism, but these are not directly measurable and therefore are not included in the mathematical balance.

*The daily body weight provides the clinician with the most accurate idea of the actual fluid balance (gain or loss). However, taking the body weight is often hardly possible in critical ill patients.*

### 4.1.2 Laboratory Tests

**In plasma**

- Creatinine ($Crea_P$):
  - Dependent on muscle mass.
  - Increase if glomerular filtration rate (GFR) < 50% of normal.
- Urea:
  - Dependent on metabolism (e.g., increased in catabolism).
  - Dependent on urine output (e.g., increased in oliguria).
  - Dependent on nutrition (e.g., intake of amino acids).
  - Increase if GFR < 25% of normal.
- Blood gas analysis.
- Electrolytes (including calcium and phosphate).
- Creatine kinase (CK) (see Sect. 4.5.2).
- Plasma osmolarity ($Osmo_P$):
  - Normal: 280–310 mosmol/L.

$$\text{Osmo-estimated}\left(\text{mosmol/L}\right) = 2 \times \text{Na}\left(\text{mmol/L}\right) + \text{urea}\left(\text{mg/dL}\right)/6 + \text{glucose}\left(\text{mg/dL}\right)/18.$$

**In urine**

- Urine sodium (NaU):
  - Normal: 20–250 mmol/L.
  - Dehydration/fluid volume deficiency with antidiuresis: < 20 mmol/L (concentrated urine).
  - Increased in diuretic administration, salt-losing nephritis, adrenal insufficiency, etc.
- Urine creatinine ($Crea_U$):
  - Normal: 20–130 mg/dL.
- Urine osmolarity ($Osm_U$):
  - Normal (spot urine): 200–1200 mosmol/L.
  - Dehydration/fluid volume deficiency with antidiuresis: > 800 mosmol/L (concentrated urine).

**Calculated Values**

Fractionated sodium excretion (FeNa):

- Estimation of tubular function or concentrating capacity:

$$\text{FeNa}\left(\%\right) = \left(\text{Na}_\text{U} \times \text{Crea}_\text{P}\right) / \left(\text{Na}_\text{P} \times \text{Crea}_\text{U}\right) \times 100$$

$Na_U$ and $Na_P$ in mmol/L; $Crea_U$ and $Crea_P$ in mg/dL

- Dehydration/fluid volume deficiency with antidiuresis: FeNa <1%.
- Tubulopathy (e.g., acute tubular necrosis): FeNa >3%.
- With the use of diuretics: FeNa not evaluable.
- Similarly, FeK as well as tubular phosphate reabsorption (TPR) and calcium/creatinine can also be used to estimate tubular function.

Creatinine clearance (CC):
- Amount of blood plasma cleared of creatinine per minute.
- Estimation by the Schwarz formula:

**Formula 35**
(Patient's height (cm) × factor) / Serum creatinine (mg/dL)

– Factor for adolescents 0.7 (see also sect. 17.6.2).
– Factor for children 0.55.
– Factor for infants 0.45.

- Measurement by urine collection (duration of collection of 6–8 h usually suffices).
  – Creatinine: 1 mg/dL × 88.5 = µmol/L.

## 4.2 Physiologic Bases of Renal Function

The following relationships between renal blood flow (RBF), renal perfusion pressure (RPP), GFR, and urine output should be known.

The amount of urine excreted (urine output) depends on:

- GFR.
- Hormonal effects:
  – Antidiuretic: aldosterone, ADH (vasopressin).
  – Diuretic: ANP (atrial natriuretic peptide), BNP (brain natriuretic peptide).

Also on:

- Osmotic factors (e.g., glucose, mannitol).
- Drugs (e.g., diuretics, dopamine, caffeine, alcohol, etc.)
- Tubule disorders.
- Impaired concentrating capacity.

*GFR* in turn depends on:

- RBF – the most important influencing factor: the greater the renal blood flow, the greater the GFR.
- Hydrostatic pressure in the glomerular capillaries:
  - The higher the hydrostatic pressure, the greater the GFR.
  - The hydrostatic pressure is normally relatively constant and is regulated by the interaction of afferent and efferent vascular resistance, i.e., vascular tone of the afferent and efferent arterioles, respectively.
- Oncotic pressure in the blood: increasingly counteracts the hydrostatic pressure at the end of the filtration distance.
- Filtration area (Kf): for example, catecholamines and angiotensin result in a reduction of Kf through mesangial contraction, so that GFR decreases.

Also on:

- Changes of the glomerular membrane (charge, pore size, thickness of the basement membrane, etc.)
- Number of functioning nephrons (decreases physiologically >40 years; reduced in renal failure).
- Hydrostatic and oncotic pressures in Bowman's capsule.

*RBF* depends on:

- Cardiac output: normally the kidney receives about 20% of CO (in adults about 1.2 L/min).
- Renal perfusion pressure (RPP).
- Intrarenal vascular resistance ($R_{Kidney}$): RBF = RPP/$R_{kidney}$.

*RPP* depends on:

- MAP = renal inflow pressure.
- CVP = renal outflow pressure:
  - Thus, $RPP = MAP - CVP$.
  - As CVP is normally small in relation to MAP, $RPP \approx MAP$.
  - With an MAP <60 mmHg, there is an impending threat of oliguria in adults (correspondingly lower perfusion pressures in neonates and infants).
  - A CVP >18 mmHg is critical in terms of RBF.
- If intra-abdominal pressure (IAP) exceeds CVP, then $RPP = MAP - IAP$:
  - An IAP > 15–20 mmHg is critical.
  - At IAP values >20 mmHg, there is the impending threat of abdominal compartment syndrome.

Intrarenal vascular resistance depends on:

- Tone of the afferent arterioles in the glomerulus (main component).
- Tone of the efferent arterioles.
- Various factors are involved here in the effect on arteriolar tone:
  - Intrinsic (myogenic): myogenic stretch.
  - Passive extension of the arteriolar wall is followed by a reactive vascular muscle contraction.
  - Extrinsic (paracrine, endocrine, neurogenic).
    Vasodilation: PGE, NO, and ANP (afferent arterioles > efferent arterioles), dopamine (low dose via D1 receptors: afferent = efferent arterioles), adenosine (systemic effect).
    Vasoconstriction: Noradrenaline/adrenaline (alpha-1 receptors: afferent = efferent arterioles), angiotensin II and endothelin (afferent < efferent arterioles), vasopressin (ADH), adenosine (local effect)
- Pathological factors such as:
  - Microthrombosis.
  - Endothelial swelling.
  - Interstitial edema (the kidney possesses a capsule, so that intracapsular pressure increases in interstitial edema).
  - Tubular obstruction.

A deeper insight into the regulatory principles of the kidney (with good pictures) can be found at http://legacy.owensboro.kctcs.edu/gcaplan/anat2/notes/APIINotes3%20urinary%20system.htm.

**Relationship of Flow, Pressure, and Resistance in Relation to Renal Hemodynamics**

- *RBF and vascular autoregulation*: The determining parameter for the kidney is RBF. Regulation of RBF is physiologically important as the main task of the kidney is filtration. To maintain GFR relatively constant over the course of the day (rest vs. activity), RBF must not vary excessively. If arterial pressure increases (expressed here as MAP), autoregulation prompts a rise in intrarenal vascular resistance due to vasoconstriction of the afferent arterioles, and RBF therefore increases only slightly (e.g., in an adult kidney with an increase in MAP from 100 to 150 mmHg, RBF increases by only 10%). The reverse is the case if MAP falls.
- *Critical RBF and RPP:* If MAP falls below a certain physiologic minimum (critical limit in adults, 60–80 mmHg), this can no longer be counteracted by autoregulation (maximum vasodilation is reached), and RBF subsequently falls pressure-passively. If RBF decreases by a half, GFR ceases. A further decline in RBF (to less than a 1/4 of normal) results in ischemic damage to the renal parenchyma (particularly the tubular cells). In the isolated adult kidney, RBF ceases at an RPP of 30 mmHg (closing pressure).

- *Dehydration* or *mild hypovolemia*: In moderate hypovolemia, GFR remains unchanged as a result of counterregulatory mechanisms (due in particular to angiotensin II; AT II). As AT II constricts the efferent arterioles more than the afferent ones, the filtration pressure in the glomerulus can initially be maintained despite the overall reduction in RBF. Concentrated urine is excreted.
- *Shock*: If MAP falls significantly as a result of a decrease in intravascular volume (e.g., hypovolemic shock) or low CO (hypovolemic or cardiogenic shock), activation of the sympathetic nervous system and other blood pressure-stabilizing hormonal feedback cycles (RAAS, ADH) occur. Autoregulation is suspended, and vasoconstriction of the afferent and efferent arterioles prevails under the effect of noradrenaline, angiotensin, and vasopressin. Because of the increase in renal vascular resistance in association with low renal perfusion pressure, RBF consequently decreases markedly (until the point when the kidney is literally "switched off" in the context of shock). The primary aim of the body in this situation is to preserve blood flow to the heart and brain (centralization of circulation) and prevent volume losses by diuresis. If the shock is not reversed in time, acute kidney injury occurs with tubular necrosis and renal cortical edema.
- Special situations:
  - Some patients have normal renal function or normal urine output despite very low blood pressure values (habitual hypotension). CO in these patients is usually normal. There is probably very low renal vascular resistance in these cases; as a result of which, RBF and hence GFR remain normal despite low RPP. If urine output is normal, pharmacologic "blood pressure cosmetics" should be avoided. However, intensive monitoring may be justified as physiologic reserves are sometimes small.
  - In long-term hypertension, the autoregulation range is shifted to higher values, i.e., higher MAPs are required for normal RBF.
  - Vasoplegic states (e.g., sepsis, post-CPB syndrome, liver failure, etc.) often result in a pathologically reduced peripheral vascular resistance with hypotension via systemic vasodilation (CO may be reduced, normal, or increased). At the same time, severe vasoconstriction can be present intrarenally (sympathetic activity, hormones, cytokines, mediators, etc.). In this case, autoregulation is usually impaired or abolished. Taken altogether, this results in a markedly reduced RBF and a fall in GFR, even with higher MAP values.
  - Drugs such as NSAIDs (inhibition of PGE2 synthesis), ACE inhibitors (AT II inhibition), dopamine (D1 receptor agonist), and theophylline (adenosine receptor-1 antagonist) have an effect on the vascular tone of the afferent or efferent arterioles. They may exert positive or negative effects, depending on the situation. In a situation of fluid volume deficiency, NSAIDs (abolition of afferent vasodilation) and ACE inhibitors (abolition of efferent vasoconstriction) in particular can cause a reduction in GFR and hence acute anuria.

**Conclusion for Clinical Practice**

- Normalization of CO and intravascular volume is the most important measure in terms of the treatment of oliguria.
- If MAP does not increase as a result, the restoration of adequate blood pressure is the second most important measure. This may require catecholamines.
- The concentration of urine (e.g., in connection with dehydration and fluid volume deficiency) means work for the kidney ($O_2$- and ATP-consuming processes in the tubules). The administration of isotonic volume replacement solutions (e.g., 0.9% NaCl, Ringer) reduces the concentrating work and therefore relieves the burden on the kidney (*Caution*: in patients with stiff LV, reduced pump function, or outflow obstruction, fluid replacement must be given under close monitoring). On the other hand, the developement of hyperchloremic acidosis should be avoided, for example, by using "balanced" electrolyte solutions, since renal function may be affected due to inappropriate intrarenal vasoconstriction.
- With reduced CO (e.g., cardiogenic or hypovolemic shock), the use of vasopressors to restore normal blood pressure can be counterproductive in respect of renal perfusion.
- By contrast, administration of noradrenaline in a situation of septic shock usually results in an increase in RBF and GFR.
- In manifest hypotension but with normal urine output, adequate organ perfusion may be assumed (no blood pressure therapy required).
- In the context of catecholamine therapy, evidence of adequate urine output can contribute to titration of blood pressure (although unfortunately there is generally a time lag between measure and effect, which means that the outcome frequently cannot be verified immediately).
- In chronic hypertension or diseases with intrarenal vasoconstriction, a higher than normal MAP should be targeted.

## 4.3 Pathophysiology in the Cardiac Patient

In cardiac patients, CO is often relatively fixed, i.e., it can be increased to only a limited extent. The development of oliguria is common following cardiac surgery (particularly within the first 24–72 h postoperatively).

The following points should be considered:

- Intravascular volume deficiency (e.g., hemorrhage, capillary leakage, effusion).
- Reduced CO: e.g., post-CBP stunning, myocardial edema, ischemia, downregulation of beta receptors, anatomic causes (residual defects), slow circulatory adaptation following corrective surgery.
- $O_2$ deficiency (R-L shunt with cyanosis, hypoxia, anemia), acidosis.
- Arterial hypotension (reduced RPP due to low MAP).
- Increased antidiuretic hormone levels (e.g., RAAS, catecholamines, ADH, etc.)
- Impaired autoregulation (e.g., pressure-passive behavior, intrarenal vasoconstriction).

- Drugs (e.g., NSAIDs, paracetamol, ACE inhibitors, catecholamines).
- Noxae (e.g., myoglobin, nephrotoxins, contrast agents, nephrotoxic drugs, cytokines, etc.)
- Reduced RPP as a result of a rise in back pressure due to increased intra-abdominal (IAP), intrathoracic, or right atrial pressure (CVP). Causes: ascites, pleural effusion or pulmonary edema, high ventilation pressures (or mean airway pressure), tamponade, PHT, RV failure, stiff RV.
- Post-CPB: ischemia-reperfusion injury, SIRS, vasoplegia, etc.

In a situation of low CO, GFR is reduced due to a reduction in RBF. In the presence of additional arterial hypotension, which is frequent after cardiac surgery, RBF and hence GFR decrease till further. Increased intrarenal vascular resistance from afferent and/or efferent vasoconstriction due to, e.g., high sympathetic tone or catecholamines may also complicate the situation. In addition, RAAS activation and increased ADH secretion occur postoperatively.

However, acute deterioration of renal function (AKI, acute kidney injury) may not just be hemodynamically induced but is often multifactorial in origin (see list above).

The therapeutic intention to stabilize renal function via normalization of CO, intravascular blood volume, and arterial blood pressure may be straightforward but cannot always be achieved immediately in the postoperative period (despite inotropic support, fluid volume administration, and vasopressors). It should be borne in mind that overly aggressive blood pressure therapy with vasopressors can be detrimental to organ perfusion in low cardiac output states.

If urine output remains insufficient despite optimization of all possible parameters or factors, furosemide should be administered in an attempt to increase it (see Sect. 4.4). This measure serves in the first place to maintain fluid balance, as the development of effusion and edema can contribute to a deterioration of the situation. However, acute kidney injury usually cannot be prevented by the use of furosemide.

Against the background of the relationships described above, the following questions therefore arise in the individual case:

- Can CO be increased?
- What does echocardiography reveal about cardiac function?
- Can catecholamines, fluid administration, rhythm control (e.g., cardiac pacing), etc. help?

Is intravascular filling sufficient?

- Are there any signs of centralization present (poor microcirculation, prolonged recapillarization time, or increased $\Delta T$)?
- Is CVP decreased (< 6 mmHg) or increased (> 12 mmHg)?
- Is compensatory tachycardia present?
- Does the arterial curve undulate (increased pulse pressure variation)?

Is the perfusion pressure sufficient to generate adequate urine output?

- Target MAP:
  - Neonates: 40 mmHg.
  - Infants: 45–50 mmHg.
  - Young/school children: 55–60 mmHg.
  - Adolescents: 60–70 mmHg.
- What dose of catecholamines and how much fluid are needed to achieve the target MAP?

Are there any signs of dysoxia (or reduced perfusion) present?

- Assessed on the basis of $SvO_2$, $avDO_2$, lactate, BE, microcirculation, and $\Delta T$.

**Very important** What other risk factors are present?

- For example, duration of CPB, nephrotoxins, previously known kidney diseases, and renal impairment.

Is rhabdomyolysis or hemolysis present (e.g., after CPB surgery)?

If urine output cannot be sufficiently stimulated despite optimization of CO and blood pressure, diuretics should be used in our opinion to try to increase urine production in an effort to avoid complications from a positive fluid balance (for explanation see below).

## 4.4 Furosemide Therapy

Furosemide is very suitable for increasing urine output postoperatively, as it can be given intravenously as an SD or drip (which usually requires a separate access) (see Table 4.1).

The aim of treatment is to maintain the patient's fluid balance and thus to prevent (prophylactically) or treat (therapeutically) effusion and edema formation.

If oliguria is present postoperatively with otherwise good circulatory conditions, urine output can frequently be "push-started" by a single dose of furosemide. However, the subsequent development of an intravascular volume deficiency must be avoided. The cause of the diminished urine output in this context is then usually residual intrarenal vasoconstriction or stress-related hormonal antidiuresis, and not a true "kidney problem."

If postoperative low cardiac output syndrome is the reason for oliguria to occur, which usually occurs 6–48 h after surgery, urine output should be maintained by means of repeated or, preferably, continuous furosemide administration *after optimization of all hemodynamic parameters or factors*. In our experience, this can

**Table 4.1** Information on furosemide

| | |
|---|---|
| Possible benefits | Increase in RBF<br>Tubular rinsing<br>Reduced tubular $O_2$ consumption |
| Possible disadvantages | Hypovolemia<br>Hence: decrease in CO<br>Electrolyte imbalance<br>Metabolic alkalosis |
| Mechanism of action | Is actively secreted in the proximal tubule<br>Acts from the luminal side<br>Inhibition of the Na-K-2Cl transporter<br>Inhibition of reabsorption of about 25–30% of filtered Na<br>Excretion of semi-isotonic to isotonic urine<br>Increase in fractional excretion of Na, K, Cl, Ca, and Mg |
| Pharmacokinetics | Oral availability very variable (10–90%)<br>Onset of action within minutes<br>Short duration of action (half-life 1–2 h)<br>High albumin binding (> 95%)<br>Elimination: 50% unchanged in urine<br>In renal impairment: higher dose<br>In neonates: higher dose (immature tubular function) |
| Benefits of a drip | Better efficacy (more effective urine excretion)<br>Less toxicity<br>Fewer electrolyte problems |
| Adverse effects | Hypokalemia, hypomagnesemia, hypocalcemia<br>Hyper- or hyponatremia<br>Metabolic alkalosis<br>Ototoxicity (rare)<br>Loss of water-soluble vitamins<br>Allergic reactions<br>Interstitial nephritis |

control the usually temporary impairment of excretory function until the low cardiac output is corrected or overcome (improvement usually within the first 3 days postoperatively). Patients whose urine production ceases completely without furosemide usually recover considerably more slowly, even if peritoneal dialysis (PD) is ultimately initiated. In our view, the general rule should therefore be *urine output should never be allowed to drop off*. Postoperative PD, a treatment which in our view seems considerably more invasive, is only very rarely necessary with this approach.

We start with multiple doses of furosemide (e.g., 4–6 × 0.2–1.0 mg/kg). If the total dose of 4–6 mg/kg/day is reached, a furosemide drip is used (max. 0.3–0.5 mg/kg/h). As shown in Table 4.1, a drip has various advantages (see Table 4.1), so that it should be considered at an early stage.

Theophylline (0.2 mg/kg/h) can be added to the furosemide drip. Theophylline acts as an adenosine-1 receptor antagonist and can increase RBF. However, in the prevention of AKI (acute kidney injury), the scientific evidence to support the use of theophylline is lacking. The same applies to the use of "renal dose dopamine."

**Table 4.2** Furosemide dosage

| | "Push starting" of urine excretion | Inadequate urine output (after or during optimization of circulation) | Inadequate urine output despite single furosemide doses | Prophylactic or therapeutic furosemide administration in special situations with risk of volume overload, e.g., Glenn, TCPC, ECMO (without hemofiltration) |
|---|---|---|---|---|
| | Dose absolute | Dose absolute | Drip (mg/kg BW/day) | Drip (mg/kg BW/day) |
| Neonates | 1–2 mg | 6 × 1–4 mg | 3–6 mg/kg BW/day | 3–6 mg/kg BW/day |
| Infants | 2–3 mg | 4–6 × 1–6 mg | 3–6 mg/kg BW/day | 3–6 mg/kg BW/day |
| Young children | 3–5 mg | 4–6 × 2–10 mg | 3–6 mg/kg BW/day | 3–6 mg/kg BW/day |
| Older child | 5–10 mg | 4–6 × 5–20 mg | 2–6 mg/kg BW/day | 2–6 mg/kg BW/day |

A further option for stimulating urine output with loop diuretics involves the administration of ethacrynic acid (Reomax®, Hydromedin®). This usually enables an additive diuretic effect to be achieved despite maximum furosemide therapy (dose, 1–2 mg/kg BW/day in 1–3 SD). The additional use of thiazide diuretics and spironolactone appears useful theoretically for selective nephron blockade (inhibition of the compensatory increase in Na absorption in distal tubular segments) but is generally not used in the acute treatment of oliguria. Stimulation of urine output with mannitol (0.25–1.0 g/kg BW) or dopamine (renal dose, 1–3 mcg/kg/min) is also not a routine measure. For the dosage of furosemide, see Table 4.2.

If, despite pharmacological support, urine output cannot be stimulated sufficiently to achieve an equilibrated fluid balance, i.v. fluid intake (particularly of "free water", i.e., low-percentage glucose solutions) must be reduced no later than the first postoperative day. Infusions, drugs, and enteral intake should be reviewed for their nature, composition, and the need for them. In this context we recommend using individually customized parenteral solutions rather than industrially pre-prepared solutions, including drugs in the balance calculations (draw up drugs, e.g., antibiotics, in the smallest possible volume), and discussing with nursing staff how to spare fluids.

A maxim of chronic diuretic therapy is that Na restriction increases the effectiveness of treatment. However, this usually cannot be achieved in an acute situation since losses of ECS (extracellular space), for example, should be offset by isotonic electrolyte solutions. Furthermore, additional noxious substances that can further impair renal function must be avoided in the phase of oliguria (or renal impairment).

## 4.5 Nephrotoxins

Many potentially nephrotoxic drugs are used in postoperative intensive care therapy. Table 4.3 provides an overview of possible nephrotoxic factors associated with cardiac surgery.

**Table 4.3** The main nephrotoxins in the intensive care unit

| Nephrotoxic drugs | Current risks | Preexisting risks |
|---|---|---|
| Antibiotics/antifungals: aminoglycosides, vancomycin/teicoplanin, beta-lactam AB, amphotericin B<br>Acyclovir, ganciclovir | CPB with fluid volume deficiency<br>CPB with DHCA<br>Prolonged CPB<br>ECMO<br>Hemolysis<br>Rhabdomyolysis<br>Abdominal compartment | Morphological kidney injury<br>Cyanotic heart defect<br>Syndromal diseases<br>Urine transport disorders<br>Recurrent pyelonephritis<br>Neonatal asphyxia<br>UVC<br>Status post-cardiac surgery with renal injury |
| Cyto-/immunostatics<br>CsA, tacrolimus<br>Cyclophosphamide<br>Cisplatin | | |
| Other:<br>Contrast media, NSAID, ACE inhibitors, ATR blockers, HES? | | |

*DHCA* deep hypothermic circulatory arrest, *UVC* umbilical venous catheter

### 4.5.1 Dosage of Drugs in Renal Impairment (Critical Reduced GFR)

If there are signs of renal impairment (decrease in GFR and/or increasing creatinine levels), the doses of drugs that are primarily eliminated by the kidneys may need adjustment. The repeated determination of plasma levels (trough levels) can be helpful in this respect, e.g., with aminoglycosides. Even in renal failure, the initial dose should normally be chosen to obtain effective levels. However, dose and/or interval must be adapted accordingly for all following administrations to prevent toxic levels from occurring. GFR-related dosage recommendations can be found at https://kdpnet.kdp.louisville.edu/drugbook/pediatric/ (for estimating GFR, see above).

### 4.5.2 Rhabdomyolysis

Following the death of muscle cells, larger quantities of myoglobin are released. This can happen if the muscle is damaged:

- By trauma (e.g., accident, electrical current, excessive muscle activity, pressure lesions in the case of immobility).
- By ischemia (e.g., thromboembolic, compartment syndrome, shock).
- By inflammation (e.g., myositis, necrotizing fasciitis).
- By hyperthermia (e.g., malignant hyperthermia).
- By drugs (e.g., statins, cocaine).
- Disturbance of the internal environment (e.g., hypokalemia, hypophosphatemia).

Rhabdomyolysis can follow an asymptomatic course but can also result in life-threatening acute kidney injury. The most sensitive indicator of muscle damage in the blood is creatine kinase (CK, normal, < 250 IU/L). In the

absence of cardiac or cerebral infarction, CK levels >5000 IU/L indicate severe muscle damage (increase within about 12 h after muscle damage, maximum after 1–3 days, fall about 2–3 days after muscle damage; half-life of CK about 1.5 days).

The myoglobin released in rhabdomyolysis (molecular weight, 17 Da(ltons); half-life, 2–3 h) is converted in the liver to bilirubin and is excreted as such or directly as myoglobin via the kidney; at urinary concentrations of > 100 mg/dL (normal, < 0.3 mg/dL), the urine is colored brown. However, three factors must be combined for acute kidney injury to occur: hypovolemia, acidosis, and formation of myoglobin conglomerates in the renal tubules. The combination of intrarenal vasoconstriction, tubular obstruction, and directly cytotoxic effects ultimately culminates in oliguria/anuria. This explains why there is no clear serum myoglobin cutoff value above which AKI occurs. Serum values as low as >500 ng/mL can be critical (or urinary myoglobin >10 mg/dL). There is also no 100% correlation between CK levels and serum myoglobin.

At serum myoglobin levels >500–1000 ng/mL (or serum CK >5000–10,000 IU/L), forced dialysis with urinary alkalinization is recommended for prophylaxis of AKI (if urine output is maintained). The main effect is adequate hydration. It is disputed whether diuretics or alkalinization contributes additionally to the prevention of AKI. Hemofiltration (HF) should be considered at values >5000 ng/mL, particularly in the presence of oliguria (myoglobin is eliminated better by hemofiltration than by hemodialysis).

Procedure of Forced Diuresis

Hyperhydration:

- 1.5–2 × Intake (= about 2–3 L/m$^2$/day)
- With 0.9% NaCl or half electrolyte solution.
- Target urine output: > 4 mL/kg/h.

Diuretics:

- Mannitol:
  - Benefit: no acidic urine.
  - 0.25–1 g/kg i.v. over 20 min every 4–6 h
- Furosemide:
  - Disadvantage: acidic urine.
  - 0.5–3–6 mg/kg/day in 4–6 SD
  - Drip: 0.1–0.3 mg/kg/h.

Urinary alkalinization:

- Sodium bicarbonate 8.4%: 0.25 mmol/kg/h.

Duration of forced diuresis: 24 to max. 72 h (depending on fall in serum myoglobin)

### 4.5.3 Possible nephroprotective substances

The following substances had positive or protective effects on renal function in experimental situations:

- L-thyroxine (5 µg/kg BW/day).
- Theophylline (5 mg/kg BW/day).
- N-acetylcysteine (NAC/ACC; 30–45 mg/ kg BW/day).

However, a general recommendation about the use of these substances cannot be given, since the clinical evidence for their effectiveness is lacking.

## 4.6 Definition of Renal Failure (see Table 4.4) and Indication for Renal Replacement Therapy (RRT)

The cause of acute postoperative renal failure is usually multifactorial (hemodynamic factors, ischemia-reperfusion, nephrotoxins, etc.). A clear distinction between prerenal and renal disorders is frequently difficult in postoperative intensive care medicine (postrenal disorders other than catheter obstruction or preexisting urinary tract disease can generally be ruled out). If there is a further decrease in urine output (anuria) despite optimization of hemodynamics, avoidance of nephrotoxic substances, and pharmacological diuretic therapy, renal function can be temporarily replaced by a renal replacement therapy (e.g., PD or hemodialysis). The argument for starting RRT in the postoperative period is often the increasingly positive fluid balance rather than a precise laboratory parameter (e.g., creatinine or BUN values). However, the clinical dynamics of the renal failure must also be taken into account.

The indication for a renal replacement procedure is usually established in:

- *Hyperhydration with effusions* (*pleural effusion*, *ascites*) and *edema* (*lung*, *brain*).
- Hyperkalemia (K > 6.5 mmol/L or symptoms).
- Cardiac volume overload (CVP > 18 mmHg).
- Anuria and AKI > 2 days.
- Increasing metabolic acidosis (pH < 7.0).
- Urea >200 mg/dL (> 35 mmol/L).
- Rhabdomyolysis (myoglobin >5000–10,000 ng/mL) *and* oliguria.

**Table 4.4** Network definition and staging of AKI – acute deterioration of renal function

| Stage | Serum creatinine criteria | Urine output criteria |
|---|---|---|
| 1 | Increase ≥0.3 mg/dL or increase to more than 150–200% from baseline | < 0.5 mL/kg/h for more than 6 h |
| 2 | Increase to more than 200–300% from baseline | < 0.5 mL/kg/h for more than 12 h |
| 3 | Increase to more than 300% from baseline or increase ≥4.0 mg/dL with an acute increase of at least 0.5 mg/dL | < 0.3 mL/kg/h for 24 h or anuria for 12 h |

## 4.7 Treatment of Transient Renal Failure by PD

### 4.7.1 Principles

In peritoneal dialysis, the peritoneum serves as a large, well-perfused (semipermeable) membrane through which both fluid and substance exchange occurs. By introducing an osmotically active fluid into the peritoneal cavity, water can thereby be removed from the blood. In addition, urinary excreted substances diffuse concentration- and time-dependently into the peritoneal dialysis fluid, resulting in these substances being cleared from the body.

By analogy with hemodiafiltration, it can be said that:

- The peritoneum is the dialysis filter (surface, permeability).
- The perfusion of the peritoneum corresponds to the blood flow in hemodialysis.
- The composition of the dialysis fluid, the quantity of dialysate, and the contact time determine the exchange factors.

### 4.7.2 Contraindications

There are only a few contraindications to PD:

- Abdominal surgery <5–7 days or abdominal drains.
- Abdominal wall defects.
- Communication between abdomen and thorax (e.g., congenital diaphragmatic hernia).
- Extensive abdominal adhesions.
- VP shunt (ventriculoperitoneal shunt) = relative contraindication.

Gastrostomy (PEG, percutaneous endoscopic gastrostomy), ileostomy, vesicostomy, and prune-belly syndrome are not contraindications for PD.

### 4.7.3 Benefits and Disadvantages of PD

See Table 4.5.

### 4.7.4 Procedure

#### 4.7.4.1 Insertion of a PD Catheter

- By the Seldinger technique:
  - PD catheter without cuff, straight (e.g., 8.5 F Cook® PD catheter).
  - Tenckhoff catheter with one cuff, straight or curled (e.g., 9.5 F Cook®-Tenckhoff catheter).

**Table 4.5** Benefits and disadvantages of PD

| Benefits | Disadvantages |
|---|---|
| No vascular access<br>No systemic heparinization<br>No blood contact with foreign surfaces<br>Ease of handling<br>Gentle substance and fluid exchange<br>Also possible in circulatory instability | Less effective in:<br>Intoxication<br>Hyperkalemia<br>Metabolic diseases (e.g., hyperammonemia)<br>Massive volume overload (e.g., acute pulmonary edema)<br>Bowel damage possible on catheter insertion (rare)<br>Inflammation with peritonitis possible<br>Increased intra-abdominal pressures with impairment of respiratory situation possible (IAP during PD normally <10 mmHg) |

  - Pigtail catheter (e.g., 8 F Cook® pleural/pneumopericardial drainage set); one or (if necessary) two catheters can be used.
  - Puncture site: e.g., left or right lower abdomen, on a line between the umbilicus and the superior iliac crest, half way along, puncture more or less vertical to the table beneath – ultrasound-guided.
  - Complications: injury to the bowel or other abdominal organs, bleeding, infection, mechanical obstruction of the catheter, leakage.

- By pediatric surgery in OR:
  - Usually Tenckhoff catheter with two cuffs, straight or curled (e.g., 9.5 F Cook®-Tenckhoff catheter).
- PD catheter size:
  - ≤ 3 kg: e.g., 8.5 F, 8 cm
  - 3–20 kg: e.g., 9–11 F, 15 cm
  - ≥ 20 kg: e.g., 11–15 F, 20 cm.

#### 4.7.4.2 Choice of PD Fluid

- Frequently used PD solutions (Fresenius):
  - High glucose solution (4.25% glucose): for maximum water removal (CAPD = continuous ambulatory peritoneal dialysis).
  - Intermediate glucose solution (2.5% glucose): at steady state, gentle to the peritoneum.
  - Low glucose solution (1.5% glucose): Standard solution, more rarely used for acute dialysis.
  - All three solutions contain lactate (35 mmol/L).
- Additives:
  - Heparin 200 IU/L (200 to max. 1000 IU/L).
  - In hypokalemia: 7.45% KCl max. 4 mmol/L *(never more).*
  - In infection: antibiotics (cefuroxime, cefazoline, ceftazidime 125 mg/L; vancomycin, 30 mg/L; teicoplanin, 20 mg/L; tobramycin, 8 mg/L; gentamicin, 8–10 mg/L).

- Use of a closed catheter system (change of system every 48 h).
- Bicarbonate-buffered solutions are probably more beneficial in circulatory shock than lactate-buffered solutions as they may support lactate clearance.

#### 4.7.4.3 Prescribing PD

Examples of prescribed dialysate amounts and PD cycles (duration and number) are given in Table 4.6.

Smaller dialysate volumes are used to begin with to prevent leaks from the catheter entry site (avoidance of increased intra-abdominal pressures while peritoneal compliance still remains low). Usually this can be increased to the target volume over the course of a few days (depending on tolerability and dialysis requirement).

The best water elimination can be obtained with frequent short cycles (30–60 min.) (A negative water balance is usually the main aim initially.) This requires the choice of a more highly concentrated glucose solution. Conversely, urea and creatinine clearance are better with longer cycles (>60 min.). Therefore, lower-concentrated glucose solutions are used at steady state (also because they cause less osmotic irritation of the peritoneum). The cycles can be extended over several hours as required.

Rule of thumb:

Frequent, short cycles, high glucose concentration→ increased elimination of water.
Longer cycles→ better elimination of substances normally excreted in the urine.

#### 4.7.4.4 Monitoring

- Vital parameters: EKG, BP, $SpO_2$, temperature.
- Daily laboratory tests:
  - In blood: differential blood count, CrP, creatinine, urea, protein, electrolytes, BGA.
  - In the dialysate: protein and cells and prophylactic microbial examination (if stable, only every 48–72 h, where necessary).
- Repeated blood glucose: can vary considerably with high glucose solutions.

**Table 4.6** Prescribing PD – recommendations

| | Amount of dialysate (mL/kg BW) | | Cycle |
|---|---|---|---|
| | Start | Aim | |
| Neonates | 10–20 | 20–30 | Inflow: about 5–10 min (depending on flow resistance)<br>Dwell time, 30 + X min; initially, 30–45 min; later, 45–60 min; in hyperkalemia or hypervolemia, if necessary 20–30 min<br>Outflow: 10–30 min (depending on flow resistance)<br>Number of cycles/day; initially, usually without interruption (e.g., 24–36 cycles/day); then, 6–12–24 cycles/day, according to need; after target dialysate volume achieved, 2–4 cycles/day |
| Infants/ young children | 15–20 | 40–50 | |
| > 25 kg BW | 15–20 | 30–40 | |

#### 4.7.4.5 Complications

Losses via the dialysate:

- Protein loss: about 0.3–0.5 g/kg BW/day.
- Phosphate and electrolyte loss.
- Losses should accordingly be replaced through the diet.

Leakage from the catheter outlet port:

- Discontinuation for 24–48 h.
- Smaller volumes, more frequent cycles.
- Where applicable, try to seal the leak (fibrin glue, cerclage), otherwise surgical reinsertion.

Peritonitis:

- Usually: staphylococci (60%), enterococci, and gram-negative intestinal bacteria (20%), fungi (< 5%).
- Symptoms (not always present): cloudy peritoneal fluid (>100 leukocytes/μL, >50% neutrophils), fever, abdominal pain.
- Antibiotics (systemic and intraperitoneal):
  - Vancomycin and ceftazidime.
  - Systemic dosage according to estimated GFR (and levels).
  - Intraperitoneal dosage (see above).
  - Duration: about 2–3 weeks.
- Antifungals (systemically only):
  - Amphotericin B not intraperitoneally (damages the peritoneum).
  - Liposomal Amphotericin B (AmBisome®) i.v.
- It is not absolutely necessary to interrupt PD in the presence of peritonitis. (PD is associated with rinsing of the abdominal cavity; where necessary, prolonged cycles, which increase exposure time to antibiotics, can be chosen.)
- PD should be interrupted in the case of uncontrollable (life-threatening) abdominal infections and *always* in fungal peritonitis.

Problems with inflow or outflow:

- Never “pump” in or “aspirate” out dialysate by syringe.
- Positional check of the catheter (X-ray), rinsing of catheter.
- Treatment of constipation and intestinal paralysis.
- Where applicable, increase dialysate volume.
- Change patient’s position.
- Where applicable, increase quantity of heparin in the dialysate; where applicable, catheter lysis.
- Where applicable, reinsertion elsewhere.
- Where applicable, surgical resection of the omentum.

If the PD is inefficient (insufficient control of fluid balance and retention values), a severe abdominal infection occurs, or the patient otherwise does not tolerate PD, switch to a hemodialysis procedure.

## 4.8 Hemodialysis

### 4.8.1 Practical Procedure in Continuous Venovenous Hemodialysis

Essentially four physical principles underlie hemodiafiltration (see also the Prismart lecture by Gambro-Hospal, which is available as a tutorial at http://www.Gambro.com). See Table 4.7 for the operating principle.

To be able to begin blood cleansing, the catheter access site and type of catheter must be chosen (see Table 4.8 and 4.9).

#### 4.8.1.1 Choice of Filter

The choice of filter (e.g., the Prismaflex filter from Gambro; see Table 4.10) can be made on the basis of the following rule of thumb: filter surface area ($m^2$) ≤ patient's body surface area ($m^2$). The filter consists of 6000–9000 hollow fibers, and the internal diameter of a hollow fiber is a few hundred µm with a wall strength of about 10–40 µm. Filter life-span (with heparin): about 72 h (in practice, as long as the filter is good).

**Table 4.7** Operating principles in substance elimination

| Diffusion | Osmosis | Ultrafiltration | Convection (solvent drag) |
|---|---|---|---|
| Equalization of the particle concentration across a semipermeable membrane along a concentration gradient<br>Effective diffusion only occurs for substances <1000 Da | Equalization of the particle concentration by liquid movement through the semipermeable membrane when particle balance is prevented | Compression of fluid (e.g., primary urine) through a semipermeable membrane due to a pressure gradient that exists across the membrane | Transfer of dissolved particles through a semipermeable membrane with the compressed ultrafiltrate (for molecules with an S = 1, the concentration in the ultrafiltrate corresponds to that of plasma)<br>Substances >1000 Da can also be eliminated according to their S. |
| Particularly in dialysis | | Particularly in filtration | Particularly in filtration |

Adsorption is utilized in hemoperfusion if noxious substances, e.g., in the charcoal filter, are adsorbed during circulation. Adsorption (e.g., proteins, cytokines) is also present to some extent with the filters used today

*S* sieving coefficient

**Table 4.8** Venous access

| Access site | Internal jugular vein (1st choice) | Subclavian vein | Femoral vein | Umbilical vein |
|---|---|---|---|---|
| | In children <5 kg, place catheter tip in RA | To be spared if there is a high risk of long-term dialysis due to danger of thrombosis or stenosis | Disadvantageous in "restless" patients due to risk of kinking; recirculation possible if high blood flows | In preemies and neonates in 1st WL |

*WL* week of life

**Table 4.9** Catheter for CVVHDF

| Weight | Catheter | Catheter flow rates[a] | Blood flows in CVVHDF[a] |
|---|---|---|---|
| < 3 kg | 2 × 4 F or 5 F (e.g., Cook®, single-lumen, 12 cm), also suitable for arteriovenous procedures | Up to 50 mL/min | 10–30 mL/min |
| 3–10 kg | 6.5 F (e.g., Joline®, double-lumen, 10 cm), 7 F (e.g., MedComp®) double-lumen, 10 cm) | Up to 75 mL/min | 3.0–5.0 kg: 10–50 mL/min<br>5.0–10 kg: 25–75 mL/min |
| 10–30 kg | 8 F or 9 F (e.g., Arrow®, double-lumen, 15 cm) | Up to 150 mL/min | 10–15 kg: 50–75 mL/min<br>15–20 kg: 75–100 mL/min<br>20–30 kg: 100–150 ml/min |
| > 30 kg | 12 F (e.g., Arrow®, double-lumen, 15 cm) | Up to 200 mL/min | 150–200 mL/min |
| > 50 kg | 14 F (e.g., Arrow®, double-lumen, 15 cm) | Up to 400 mL/min | 200–400 mL/min |

[a]All data are merely guide values

The occurrence of a bradykinin release syndrome (flush and arterial hypotension) with the use of AN69 filters is reported in the literature. However, we have not observed any such problems in the last approximately 15 years.

Examples of some sieving coefficients are given in Table 4.11.

#### 4.8.1.2 System Preparation and Filling (Priming)

The system (set and filter) is filled with 0.5–1.0 L 0.9% NaCl with 5 IU/mL heparin strictly as instructed by the dialysis machine (e.g., Prismaflex menu). The pressure sensor should be carefully vented (an air bubble at the top of the filter shows the existence of the shield and is therefore normal).

**Table 4.10** Prismaflex filters from Gambro

| Name | Membrane | Patients | Filter surface area | Volume | Min. blood flow |
|---|---|---|---|---|---|
| HF 20 | PAES hollow fiber | > 3 kg (see ref. [5]) 8–30 kg (according to Gambro) | 0.2 $m^2$ | Set: 60 mL; filter: 17 mL | 20 mL/min |
| M 60 | AN69 hollow fiber | > 10 kg | 0.6 $m^2$ | Set: 93 mL; filter: 42 mL | 50 mL/min |
| M 100 | AN69 hollow fiber | > 30 kg | 0.9 $m^2$ | Set: 152 mL; filter: 66 mL | 75 mL/min |
| M 150 | AN69 hollow fiber | > 50 kg | 1.5 $m^2$ | Set: 189 mL; filter: 105 mL | 100 mL/min |

**Table 4.11** Some sieving coefficients with M 60–150 filters (Sustance-filtrate/substance-plasma)

| Substance | Urea (60 Da) Creatinine (113 Da) Vitamin B12 (1355 Da) | Insulin (5200 Da) | Myoglobin (17,000 Da) | Albumin (68,000 Da) |
|---|---|---|---|---|
| Sieving coefficient | 1 | 0.95 | 0.55 | 0.01 |

*Priming* with red blood cell concentrate should be considered in children aged <1 year (or BW <10 kg) and low Hct (<30%), since in these cases purely crystalloid priming is associated with marked hemodilution (particularly at a priming volume >7–8 mL/kg, i.e., about >5–10% of the blood volume). We prime the Prismaflex system after a rinsing process by attaching a red blood cell concentrate in place of the rinsing solution and filling the filter system with blood via the manual rinse function.

#### 4.8.1.3 Dialysis/Replacement Solution

As *dialysis or replacement solution*, respectively, we use PhoXilium® (two-chamber system with NaHCO3), which has the following composition:

- Ca: 1.25 mmol/L.
- Mg: 0.6 mmol/L.
- Na: 140 mmol/L.
- K: 4.0 mmol/L.
- Cl: 115.6 mmol/L.
- HPO4: 1.2 mmol/L.
- HCO3: 30 mmol/L.
- Osmo: 293 mmol/L.

Bicarbonate-buffered solutions are generally to be preferred, particularly in the case of hepatic impairment after LTx (liver transplantation) in young infants or shock.

#### 4.8.1.4 Connection to the Patient

The red catheter limb (red clamp) is connected to the red dialysis line. Red means that the blood is conveyed from the patient to the filter (red = aspiration). The blue catheter limb (blue clamp) is connected to the blue dialysis line. Blue means that the blood is returned from the filter to the patient (blue = pressure). In practice, any limb (red or blue) can be tried for the best conditions of blood withdrawal from and return to the patient, respectively (trial and error!).

In children >10 kg with Hct >25–30% and without severe coagulation disorders, CVVHDF can be started after the dialysis lines have been connected and the three-way valves have been opened. Hemodilution due to the filling volume (usually <10 mL/kg) and an associated heparin dose (< 5 IU/kg) is usually tolerated without any problems. For children < 10 kg, see under "Priming" (above).

### 4.8.2 Anticoagulation

Anticoagulation is necessary to guarantee the life-span of the filter. If, however, the patient has a severe coagulation disorder with a high risk of bleeding, anticoagulation may be omitted initially (although the filter may then need to be changed more frequently).

Anticoagulation can be given systemically with heparin (i.e., patient and dialysis unit) or locally with citrate (i.e., dialysis unit only).

Alternatives to heparin in HIT include prostacyclin (Flolan), danaparoid (Orgaran), and hirudin.

Anticoagulation with unfractionated heparin as standard procedure:

- Initial heparin bolus: 50 IU/kg (10–100 IU/kg) i.v. depending on initial PTT (thromboplastin time).
- Maintenance dose by continuous infusion: Administration in dialysis machine before the filter or via CVC directly into the patient: Dose: 10–40 IU/kg/h, depending on PTT.
- Target PTT: 45–65 s (1.5–2.0 × normal); no test on lines through which heparin is given; where necessary, AT III determination and replacement.
- Target ACT: 140–180 s (see Table 4.12).

ACT (activated clotting time) is a relatively simple rapid general coagulation test suitable for point-of-care monitoring or in emergencies (trend measurement). This involves measuring the time in which native blood coagulates at 37 °C in the presence of an activator, such as kaolin (Hemo-Tec® ACT-II from Medtronic). Normal ACT is 120 ± 15 s – each patient usually has his or her own baseline (Medtronic values are on average 20–50 s lower than Hemochron values).

**Table 4.12** Target anticoagulation values in normal CVVHDF with heparin

| | ACT (s) | Platelets (10^9/μL) | PTT (s) | AT III (%) |
|---|---|---|---|---|
| Normal operation | 140–180 | 80–200 | 45–65 | > 80 |

**Table 4.13** Heparin management after ACT

| Current ACT | Heparin bolus (IU/kg BW) | Increased heparin infusion |
|---|---|---|
| ACT <100 s | 100 | Test first, then increase |
| ACT <130 s | 50 | Test first, then increase |
| ACT >130 s | No bolus | About 10–15% |
| ACT >150 s | No bolus | About 5–10% |
| ACT 170–200 s | No bolus | Monitor in 2–4 h |
| ACT >220 s | | Reduction by 10–15% |
| ACT >230 s | | Reduction by 20% |
| ACT >250 s | | Discontinue heparin for 1 h |

Interfering factors: prolonged in hypothermia and hemodilution, heparin (no linear dose-effect relationship), disseminated intravascular coagulation (DIC); relatively resistant in respect of platelet disorders, prolonged in (severe) thrombocytopenia.

#### 4.8.2.1 Management of Heparin Dosage

Unfortunately, we cannot give a general rule for the heparin dosage, since both the patient's conditions (bleeding, platelet count, fibrinogen, hemolysis, etc.) and dialysis-related factors (pressures, filter problems, etc.) must be taken into consideration.

From experience, following the initial bolus, treatment can be continued with a heparin dose of about 12.5 IU/kg/h (= 300 IU/kg BW/day).

ACT is then tested before the bolus heparin dose and 30 min after the bolus. Anticoagulation is then guided by ACT (monitoring, e.g., every (1–4 h). See Table 4.13.

These are guide values, which may need to be modified in each individual case. In particular, active bleeding, hemolysis, thrombocytopenia, or thrombocytosis, as well as signs of DIC or hyperfibrinolysis have to be taken into consideration. Further laboratory tests as well as the determination of ACT will therefore also need to be undertaken regularly:

- Every 6–8 h: blood count, coagulation tests (PTT, prothrombin time (INR), fibrinogen).
- Every 12–24 h: additionally liver and kidney function tests, hemolysis parameters, AT III, D-dimers.

#### 4.8.2.2 Anticoagulation with Citrate (Prismaflex in CVVHF Mode) (See Table 4.14)

In citrate renal replacement therapy (RRT) with the Prismaflex, sodium citrate is administered via the "pre-blood pump" (PBP, for explanation see below) for extracorporeal anticoagulation. As soon as the blood has left the patient, it is mixed with the citrate solution (see Fig. 4.1). We use Prismocitrate®, which contains sodium, chloride, and also 18 mmol/L trisodium citrate. Citrate binds the Ca2+ in the blood,

**Table 4.14** Citrate dialysis with Prismaflex®

| | |
|---|---|
| Prismaflex® | |
| Parameters to be set: | |
| Mode | Preferably CVVHF (alternatively also CVVHDF) |
| Target citrate concentration (mmol/L) | 3.0–3.5 mmol/L |
| Blood flow rate (mL/min) | Age-dependent: 20–200 mL/min (see Table 4.15) |
| Dialysate rate (mL/h) | Not applicable in CVVHF mode (for CVVHDF see Table 4.15) |
| Replacement rate; post (mL/h) | Min. rate to be set: 5 mL/kg/h (according to manufacturer, min. 100 mL/h) |
| Removal (mL/h) | Depending on balance target |
| Nonadjustable parameters: | |
| PBP rate (ml/h) | Obtained from chosen citrate concentration and blood flow |
| "Bags" used: | |
| Prismocitrate® | On the PBP scale (white) |
| PhoXilium® | On the replacement scale (purple); in CVVHDF also on the dialysate scale (green) |
| Haemosol B0® or Prismosol 2.0® | In hyperkalemia instead of PhoXilium® |
| Rinsing process/priming: | |
| Rinsing | First pass always with 1000 mL 0.9% NaCl +5000 IU heparin (= 5 IU heparin/mL), and then if desired second pass with 1000 ml 0.9% NaCl only |
| Priming | Where necessary in children <10 kg; using the menu field "Manual rinse," fill the set with RBCC (by eye) |
| Target parameters: | |
| Ca2+ concentration (extracorporeal) | 0.3–0.4 mmol/L (if Ca2+ < 0.25 mmol/L, reduce citrate concentration; if Ca2+ > 0.45 mmol/L, increase citrate concentration) |
| Ca2+ concentration (in the patient) | 1.0–1.2 mmol/L |
| Effluent rate (= "dialysis dose") | 35–45–(60) mL/kg/h (can be adjusted to only a limited extent because of the relatively "fixed" PBP rate); in CVVHDF mode the dialysis rate must be reduced accordingly, where necessary |
| Filtration fraction (FF) | < 30–(40)% |
| Controls: | |
| Ca2+ concentration (extracorporeal) | Record from blue port (after the filter) |
| | Initially, every 1–2 h (for the first 4–6 h); if stable (for 2 h), every 4–6 h |
| Ca2+ concentration (in the patient) | Arterial (or also central venous) |
| | Initially, every 1–2 h (for the first 4–6 h); if stable (for 2 h), every 4–6 h |
| | If total Ca2+ > 3 mmol/l (> 12 mg/dL or Ca2+tot/Ca2+ion >2.5 risk of citrate intoxication (then if necessary reduce blood flow and/or citrate conc. (< 3.0 mmol/l); where necessary, replace Prismocitrate® temporarily by PhoXilium®) |

(continued)

**Table 4.14** (continued)

| Replacements: | |
|---|---|
| 10% Ca2+ gluconate IV | Into the patient via CVC (distant from dialysis catheter) |
| | Starting dose: 0.2–0.4 mL/kg/h (or 0.045–0.09 mmol/kg/h) |
| | Then, depending on value, increase/reduce by 10–20% |
| | *Caution!* When 10% Ca2+ chloride is used, twice as much ionized Ca2+ is released (for comparison: 10% Ca2+ gluconate: 1 mL = 0.225 mmol; Ca2+ chloride: 1 mL = 0.5 mmol) |
| Magnesium i.v. | 0.15–0.3 mmol/kg/day (or 0.01 mmol/kg/h) |
| 8.4% Na bicarbonate | 0.25–1.0 mmol/kg/h (in metabolic acidosis) |
| AA, trace elements, water-sol. vitamins | Increase intake (if necessary, double daily dose) |

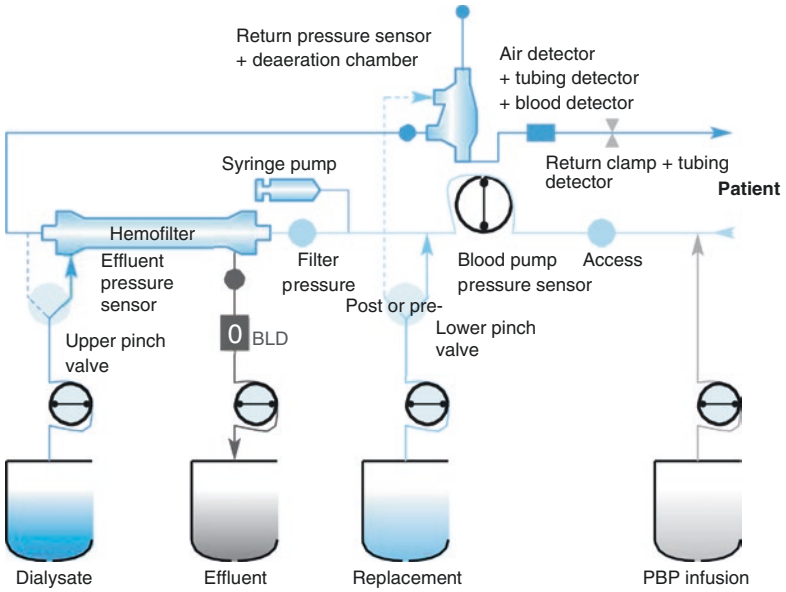


**Fig. 4.1** Prismaflex (Gambro) diagram

thereby inhibiting coagulation. In the machine, the ionized Ca2+ must be 0.3–0.4 mmol/L, which is usually achieved with a citrate concentration of 3–3.5 mmol/L. The target citrate concentration and the selected blood flow determine the PBP rate (which cannot be freely set). The coagulation efficiency of citrate administration is checked postfilter (blue port) by tests of calcium (BGA), and the citrate concentration is adjusted as necessary. To prevent citrate-induced hypocalcemia in the patient (and the associated adverse effects), continuous Ca2+ replacement or Ca2+ restitution is required (target serum Ca2+, 1.0–1.2 mmol/l). At the Giessen Pediatric Heart Center, we use 10% calcium gluconate for this, infused directly into the patient via a CVC (initial dose, about 0.2–0.4 mL/kg /h or 0.045–0.09 mmol/kg/h). In addition, patients receive Mg2+ replacement (e.g., 0.15–0.3 mmol/kg/day).

We use the Pho*X*ilium® solution as a dialysis and post-replacement solution in citrate RRT, even though it contains 1.25 mmol/L calcium ("Collin protocol"). This simplifies the performance of citrate RRT without the slight transmembrane transfer of calcium causing major problems (the citrate concentration must be increased slightly, where necessary).

Adverse effects with citrate RRT: Citrate is normally metabolized in the patient's liver to bicarbonate, which can cause metabolic alkalosis. By contrast, citrate-induced metabolic acidosis can occur in the event of citrate intoxication or reduced hepatic metabolism (e.g., in small patients due to still inadequate hepatic performance, hepatic impairment). Additive sodium bicarbonate replacement has proved helpful in this respect (targets in BGA: pH 7.3–7.4, HCO3– = 20–25 mmol/L).

Increased citrate values may also induce hypocalcemia (and hypomagnesemia) as well as a consequent coagulation disorder. An increased total plasma Ca2+ concentration of > 3 mmol/L usually indicates citrate intoxication (discrepancy between increasing total Ca2+ and decreasing ionized Ca2+). Low serum calcium values can also have a circulatory-depressant effect, particularly in neonates and infants (vasodilation, negative inotropism).

Because of the usually high "turnover" in citrate RRT (high PBP rate), small patients also tend to cool off more. This can be avoided (if not therapeutically required) by additional warming (e.g., Bair Hugger®)

### 4.8.3 Prescription or Setting of CVVHDF (See Table 4.15)

The CVVHDF mode is beneficial for combining the benefits of HF (hemofiltration) with those of HD (hemodialysis).

- In the first step, an appropriate blood flow is chosen:
  - < 10 kg: 3–10 mL/kg BW/min
  - > 10 kg: 2–5 mL/kg BW/min
- In the next step, the target clearance rate is defined:
  - Clearance rate = dialysis rate + replacement rate + removal rate.
  - Is shown by the Prismaflex on the display in mL/kg/h and is called "effluent rate"
  - For a simpler description: *Clearance rate = dialysis rate + replacement rate* (for removal see below)

**Table 4.15** Guideline values for basic setting, e.g., CVVHDF

| | Blood flow[a] (ml/min) | Fluid removal[a] (mL/kg BW/h) | Dialysate flow[a] (mL/h) | Replacement rate[a] (mL/h) |
|---|---|---|---|---|
| Neonates | 10–50 | 1–2 (max. 5) | 250 | 150 |
| Infants/young children | 30–75 | Ditto | 400 | 300 |
| Small children | 75–100 | Ditto | 500 | 450 |
| Adolescents/adults | 100–200 | Ditto | 1000 | 1000 |

[a]All data are merely guide values

Replacement rate in Table 4.15 = sum of PBP rate and the replacement rate in the Prismaflex

  - aim for:
    < 10 kg: 35–55 mL/kg BW/h
    > 10 kg: 25–45 mL/kg BW/h
  - Using the Prismaflex it has to be considered that the total replacement rate is the sum of the "PBP rate" plus the "replacement rate".

- Ratio of HF to HD:
  - Usually 50:50.
  - For elimination of substances >1000 Da, HF is superior to HD.
  - For elimination of substances <1000 Da, HD is superior to HF.

- Ratio pre- to postdilution:
  - Usually 50:50 (where applicable, 33:66).
  - With high Hct > 0.4, where applicable 100% predilution.
- With HF: max. replacement rate = blood flow × 0.2.
- Lastly, a balance aim is defined and removal is set:
  - Removal rate (mL/h) = *A* + *B*.
    *A* (ml/h) = input (e.g., oral nutrition × 0.7 + i.v. administrations).
    *B* (mL/h) = target negative fluid balance.

- Example for prescriptions on the display of the Prismaflex:
  - Modus CVVHDF, anticoagulation with heparin.
  - Weight of the child = **20 kg.**
  - Prismaflex filter = **M60** (min. blood flow = 50 ml/min).
  - Catheter = 9F Sheldon catheter.
  - **Blood flow = 80 ml/min** (range 50–100 ml/min).
  - Desired clearance dose, for example, = 40 ml/kg/h × 20 kg = **800 ml/h.**
  - If HD and HF are wished to be 50:50:
  - **Dialysate rate = 400 ml/h.**
  - Replacement rate = 400 ml/h.
  - In the Prismaflex, the "total" replacement rate of 400 ml/h must be further partitioned in:
  - **PBP rate**, for example, = **300 ml/h** (then predilution).
  - **Replacement rate** (at the display), then = **100 ml/h** (pre- or postdilution as desired).
  - The filtration fraction should not be larger than 30%.
  - Last, the **removal rate** is set at the rate to achieve the desired fluid balance (e.g., **40–60 ml/h**).

### 4.8.4 Start of CVVHDF

Hypotension can occur on starting CVVHDF (due to hemodilution, volume shifts, mediator release, etc.). The resultant volume deficit should be corrected in the case of low CVP (< 6–8 $cmH_2O$) and hypotension by fluid volume administration (e.g.,

10 mL/kg 0.9% NaCl) or adaptation of the catecholamine dose. For monitoring during hemodiafiltration, see Table 4.16.

### 4.8.5 Pressure and Pumps

See Figs. 4.1 and 4.2. The Prismaflex has 5 roller pumps:

The blood pump aspirates the blood from the vein (negative pressure before the pump), pumps it through the filter, and then back into the patient (positive pressure after the pump). Blood flow rates are between 6 and 450 mL/min (adjustable in steps of 2–10 mL/min).

The replacement pump is responsible for replacement of the ultrafiltrate and pumps replacement solution (e.g., Pho*X*ilium® solution). It can administer the replacement solution pre- or post-hemofilter (settings 0–8000 mL/h).

The dialysate pump pumps the dialysis fluid (e.g., Pho*X*ilium® solution) through the dialysis phase of the hollow filter on the countercurrent principle. Its setting corresponds to the dialysis rate (setting 0–8000 mL/h).

The removal pump conveys the ultrafiltrate and the dialysate to the effluent bag. The hydrostatic pressure across the membrane, and hence the amount of ultrafiltration, is regulated via the removal pump (see below under TMP): Amount of ultrafiltration = replacement + removal.

Fluid removal can be adjusted between 0 and 2000 mL/h (in steps of 5–10 mL/h).

**Table 4.16** Monitoring during hemodiafiltration

| Patient | Balance | Filter[a] | Flows[a] | Pressures[a] (mmHg) | Coagulation | Laboratory |
|---|---|---|---|---|---|---|
| Temperature | Input | Operating time, when change, if applicable | Blood flow rate (mL/min) | Access pressure | ACT every 1–4–8 h | Urea, creatinine every 12–24 h |
| Circulation (BP, HR, CVP, ultrasound) | Output | $\Delta P$, TMP | Dialysate rate (mL/h) | Effluent pressure | PTT every 6–12 h | BGA, electrolytes every 4–8 h |
| Weight | | | Replacement rate (mL/h) | Filter pressure | Platelets every 12–24 h | Protein every 24–48 h |
| | | | Predilution, postdilution | Return pressure | | Phosphate, magnesium, total calcium every 24 h |
| | | | Removal rate (ml/h) | TMP | | Drug levels |
| | | | | $\Delta P$ | | |

[a]All these informations are shown by the Prismaflex

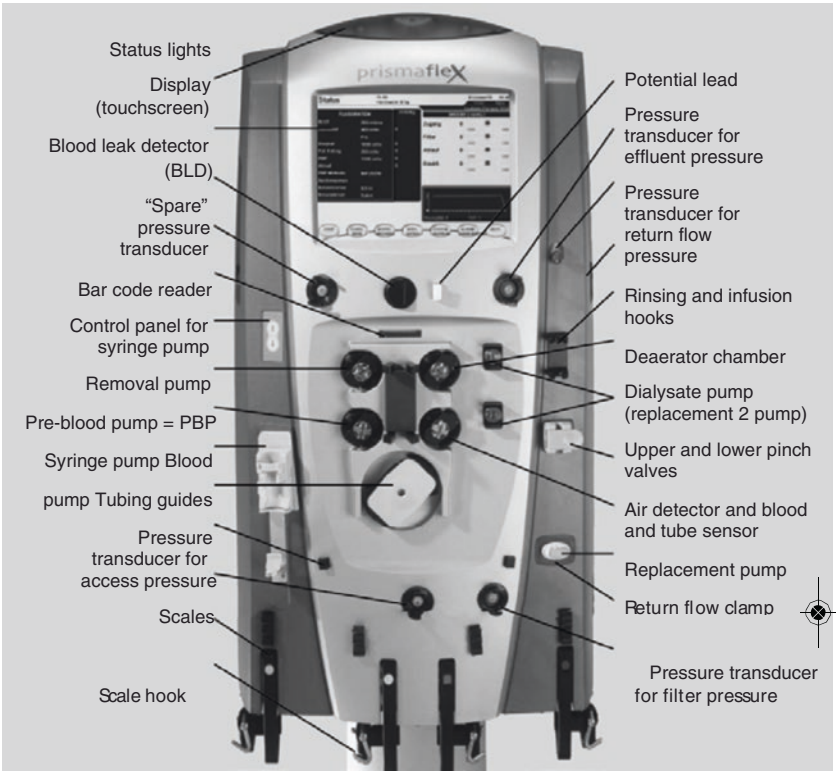


**Fig. 4.2** Prismaflex device (Gambro). Explanation of the individual components

The removal pump has an output of between 0 and 10,000 mL/h (dialysate and ultrafiltration are conveyed to the effluent bag via this pump).

The *pre-blood pump* (adjustable between 0 and 4000 mL/h) is responsible for the rate of predilution replacement (at 100% predilution it corresponds to the replacement rate, at 50% predilution to half the replacement rate). In citrate RRT, the PBP pumps Prismocitrate®, for example, as anticoagulant before the blood pump (before the filter). The rate of Prismocitrate® pumped is considered a "replacement rate" (= filtration) and therefore adds to the effluent rate (= clearance rate; see Sect. 4.8.3).

The Prismaflex displays six pressures:

The *access pressure* (mmHg) is taken before the blood pump and – with a venous access – is usually negative. In adults, the access pressure values are between −150 and −50 mmHg. In children with a relatively large Shaldon catheter, the pressures are less negative. If the Prismaflex sounds an alarm (disconnection alarm) because an adequate access pressure is not detected, there are options for canceling the alarm, increasing the blood flow or Hct or incorporating artificial resistance by means of a clamp. By contrast, with very negative pressures (in which case the catheter usually suctions), the catheter should be rinsed, the catheter lumen replaced, or

the catheter changed. If the lower pressure limit is exceeded, the machine switches off to prevent possible damage from suction (if necessary, fluid volume administration in the event of intravascular fluid volume deficiency).

The *filter pressure* (mmHg) is recorded after the blood pump and before the filter. It is always positive (highest pressure in the whole system). Normal values for filter pressure are +100 to +250 mmHg.

The *effluent pressure* (mmHg) is recorded at the effluent sensor, i.e., between filter and filtrate collection bag. It is positive to negative. The removal pump regulates the effluent pressure according to the requirements from blood, replacement, and dialysate flow, as well as filter function, so that the specified removal rate is obtained (normal values −150 to +50 mmHg).

The *return pressure* (mmHg) is recorded behind the filter in the blood flow and is always positive (drive force for the return of blood to the patient; normal, +50 to +150 mmHg). With the Prismaflex, it is at least 10 mmHg and increases in the event of an obstructed catheter lumen, increased blood flow, or small catheter lumen, for example.

Calculated pressures:

- TMP = transmembrane pressure = mean pressure difference between blood phase and dialysate phase of the filter.
  - TMP = effective filtration pressure.
  - Prismaflex: TMP = $(P_{filter} + P_{return} / 2) - P_{effluent}$.
  - $(P_{filter} + P_{return} / 2)$ = hydrostatic pressure of blood (always positive).
  - $P_{effluent}$ = hydrostatic pressure of ultrafiltrate (negative to positive).
  - Determines the amount of ultrafiltrate (i.e., the higher the TMP, the higher the ultrafiltration quantity – for a constant filter quality).
  - Normal: +100 to max. +350 mmHg.
  - Increased blood flow and/or replacement rate in predilution (higher hydrostatic pressure of blood) and an increase in removal rate (more negative pressure of ultrafiltrate) result in an increase in TMP.
  - TMP also increases with deterioration of filter quality (microthrombosis of the hollow fibers or clogging of the membrane pores), because increasingly higher pressures are needed to achieve the set aims (e.g., if filter pressure is very positive and effluent pressure very negative).
  - If TMP increases critically (> 250–300 mmHg), exchange the filter.

- *Filter pressure drop (ΔP)* – in the blood phase of the filter:
  - $\Delta P$ = (Pfilter−Preturn).
  - Corresponds to the pressure drop across the filter (on passage of the blood through the filter's hollow fibers).
  - Indication of the quality of the filter (i.e., $\Delta P$ rises with increased microclotting in the hollow fibers).
  - The $\Delta P$ profile during operation is the determining factor (e.g., at the beginning 10 mmHg, after 24 h 80 mmHg).

### 4.8.6 Management of Catheter Problems During Operation (e.g., Rinsing)

If suction by the machine or constantly increased return pressures recur frequently because of a catheter, it is better to allow the machine to circulate on its own for a short time. A short circuit between the inflow and outflow end of the catheter can be created for this purpose. Removal from the patient must then be turned back to 0 mL/h. The catheter can then be checked while the dialysis is running (i.e., lower risk of clotting). If this is freely aspirable (always begin with aspiration) and if the same problems occur after a further attempt at connection, each limb of the catheter must be rinsed with an arterial rinse (24 IU heparin/48 mL 0.9% NaCl) and if necessary changed.

### 4.8.7 Ending of CVVHDF Therapy

This is generally a clinical decision. Possible criteria are:

- Spontaneous urine output >0.5–1.0 mL/kg/h.
- GFR (kidney) > 20 mL/min.
- Clinical improvement of disease process.
- Stable urea and creatinine values despite interruption of RRT for 24–48 h.

Where applicable, pharmacological support is given (kidney initiation trial) with, e.g., furosemide and theophylline as a drip. After RRT is stopped, where possible the blood in the system is returned to the patient.

### 4.8.8 Appendix

#### 4.8.8.1 Ultrafiltration via the Filter (See Fig. 4.3)

The blood pump removes the blood from the patient and pumps it over the filter back to the patient. Pressure in the blood compartment is highest before the filter ($P_{filter}$) and decreases across the filter ($P_{return}$). This fall in pressure is described as $\Delta P$.

TMP exists across the filter membrane. It describes the mean pressure difference between the hydrostatic pressure of the blood compartment and that of the filtrate compartment. While the hydrostatic pressure in the blood compartment is defined by the pressures $P_{filter}$ and $P_{return}$ (i.e., by the set blood flow and the resistances in the system), the hydrostatic pressure in the filtrate can be regulated by the removal pump (which conveys the filtrate to the effluent bag). This provides control of the TMP and thus the quantity of fluid filtered (ultrafiltrate). Substance exchange occurs with the ultrafiltrate (convection) according to molecular

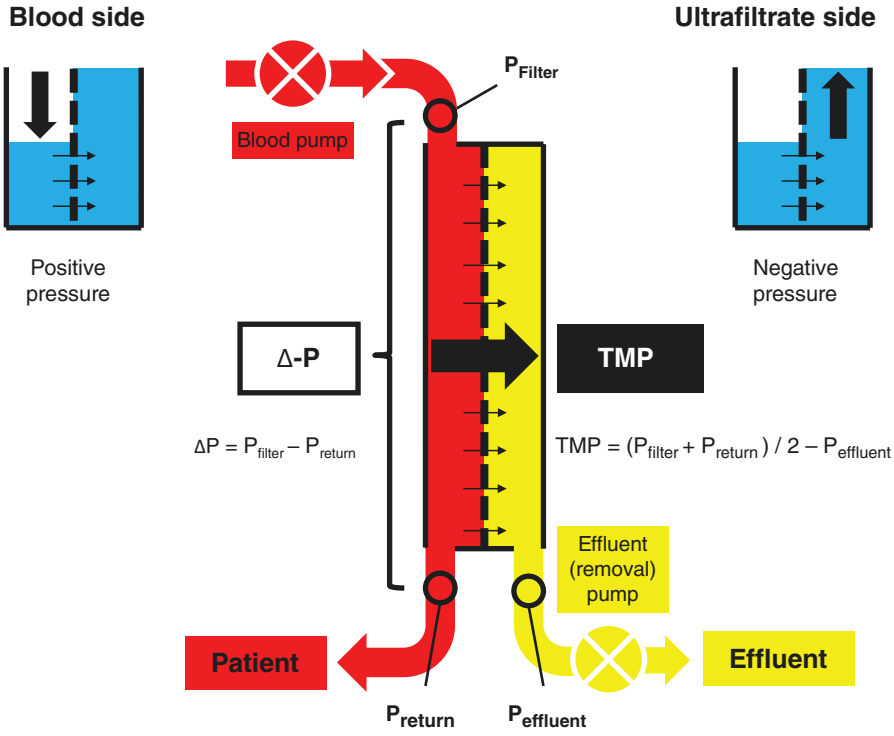


**Fig. 4.3** Ultrafiltration via the filter (diagram)

weight, sieving coefficient, and membrane properties. In hemofiltration, the proportion of the volume of the ultrafiltrate that should not be lost to the patient is replaced by a replacement solution (not depicted here). Therefore, replacement rate + removal rate = ultrafiltration rate. The replacement solution can be administered before the filter (predilution) or after the filter (postdilution) (not depicted here; see Fig. 4.1).

#### 4.8.8.2 Dialysis via the Filter (See Fig. 4.4)

The blood pump removes the blood from the patient and pumps it through the filter. The dialysate pump pumps the dialysate in the opposite direction through the filter (countercurrent principle). In pure dialysis, the exchange of substances occurs across the membrane as a result of the concentration gradient between the blood compartment and the dialysate compartment. Molecular weight, sieving coefficient, and membrane properties play a significant role in this process. The removal pump conveys the dialysate enriched with the eliminated substances to the effluent bag.

If additional fluid is removed from the blood in HD, the removal pump increases its rate relative to the dialysate pump; as a result of which, there is additional fluid filtration.

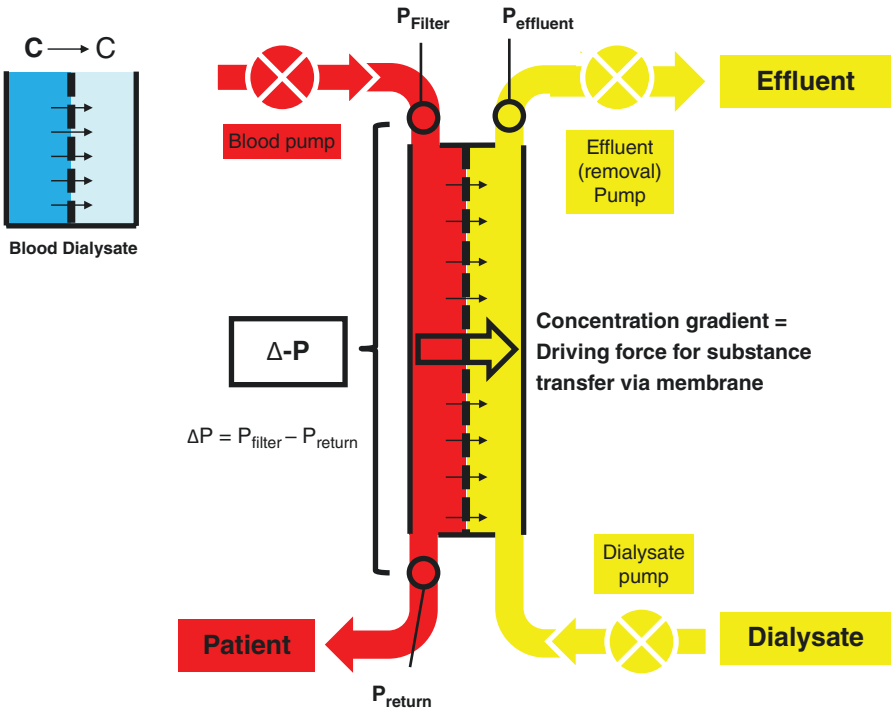


**Fig. 4.4** Dialysis via the filter (diagram)

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## Important Websites

1. http://www.dosing.de
2. http://legacy.owensboro.kctcs.edu/ gcaplan/anat2/notes/APIINotes3%20 urinary%20system.htm
3. http://lane.stanford.edu/portals/picu_ ppslides/Stanford_Prismaflex_ trainingPW.pdf (20.11.2012).
4. Further information on renal replacement therapy and prismafelx is available by contacting baxter international Deerfield IL, USA via: http://www.baxter.com/contact-and-support/contact.page