Chapter 1

General introduction and outline of the thesis

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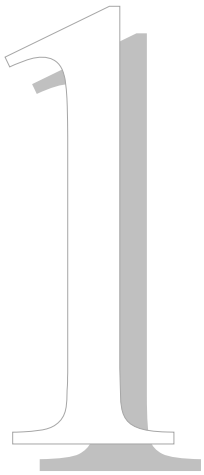

Acute kidney injury (AKI) is very common in the intensive care unit (ICU) and carries a high mortality risk. The incidence of AKI on the ICU across the world varies from 1-25% with a hospital mortality of 28-90%.[1-5] This great diversity is partly explained by the large number of definitions of AKI. Up until a decade ago there were more than 35 different definitions of AKI in the literature.[6] As there was need for a uniform definition, the Acute Dialysis Quality Initiative (ADQI), a consortium comprising nephrologists and intensivists specialized in AKI from around the world, formulated a consensus definition: the risk, injury, failure, loss and end-stage renal disease (RIFLE) classification for AKI. This classification consists of separate criteria for serum creatinine levels and urine output, and has been accepted by the medical community. Despite this uniform definition the reported incidence rate reported across the world still varied between 10.8% and 100%, which can be explained by the varying cohorts under study.[7] In approximately 5% of general ICU patients renal replacement therapy (RRT) is warranted.[3] In case of severe sepsis, AKI developed in roughly half of the patients of whom 11-20% needed RRT.[8,9] It is well known that even small changes in renal function without the need of RRT can affect outcome, even in the critically ill.[10] Renal function loss is a frequently occurring serious hazard and is considered an independent risk factor for morbidity and mortality. The management of AKI therefore remains one of the most challenging issues on the ICU.

The care surrounding patients with AKI consists of several basic principles:

1. *Prevention of AKI*. Prevention of AKI is of utmost importance. Primary prevention in the ICU is limited to those conditions in which the timing of injury is predictable such as major surgery or exposition to radiocontrast dye. AKI on the ICU is mostly the result of multiple insults and the primary insult is not predictable in the majority of cases. Therefore, prevention of AKI on the ICU often means prevention of a secondary insult in a patient who is at risk of developing renal function deterioration. The general principles of secondary prevention include the recognition of underlying risk factors predisposing patients to AKI (such as diabetes, hypertension, chronic kidney damage and age), maintenance of renal perfusion and avoidance of nephrotoxic agents.
2. *Identification of AKI.* To identify AKI, it is essential to find a tool to accurately assess renal function. In general renal function refers to the glomerular filtration rate that in clinical practice usually is considered to be reflected by serum creatinine and blood urea nitrogen levels. These parameters, however, are highly variable and depend on several factors such as the patients nutritional and hydration status, the presence of

catabolism and the use of drugs. On the ICU serum creatinine level lacks sensitivity and underestimates the degree of renal dysfunction. Furthermore, increases in serum creatinine substantially lag behind a reduction in glomerular filtration rate. A major increase in serum creatinine level, however, will certainly mean that significant renal failure has occurred. A substantial decrease in urine output can also be used to detect kidney injury. These two variables are therefore included in the RIFLE classification.

3. *Diagnosis*. Once AKI is established and recognized, its management must be focussed on reversing the process. Therefore the causative factor of AKI must be sought for and, if possible, eliminated. In the ICU, renal function deterioration associated with diminished renal perfusion, yet in the absence of tissue damage, is by far the most common cause of acute renal failure. If renal hypoperfusion is prolonged, tissue injury will eventually occur, causing acute tubular damage (resulting in apoptosis or necrosis and AKI). The most common causes of AKI include sepsis, major surgery, low cardiac output, hypovolemia and administered drugs.[11]
4. *Management.* Apart from attempts to reverse renal function deterioration, management must also be targeted at maintaining biochemical and physiological homeostasis as renal failure may result in azotemia, hyperphosphatemia, hyperkalemia, metabolic acidosis and fluid overload. Furthermore, the dosages of several administered drugs should be adjusted in case of renal function loss.
5. *Renal replacement therapy.* When in case of severe AKI conservative management is not sufficient to maintain biochemical and physiological homeostasis within acceptable limits, it can be necessary to initiate RRT. There are several modalities of renal replacement therapies but continuous venovenous hemofiltration (CVVH) is most often applied on the ICU. With RRT it is possible to restore homeostasis awaiting potential recovery of native kidney function. There are several technical and safety issues to consider when RRT is applied such as altered drug dosing, adequate vascular access, biocompatibility of dialyzers and anticoagulation.

Though in clinical practice the *prevention*, *identification* and *diagnosis* of AKI are hardly points of debate, there is an ongoing search for novel biomarkers (such as cystatine C and neutrophil gelatinase-associated lipocalin) to detect AKI earlier as preventive interventions may be more effective when initiated sooner. The *management* of AKI and especially several aspects of *renal replacement therapy*, however, are topics that are highly controversial. As numerous clinical studies were performed with sometimes conflicting data, it has proven

challenging to compose universal and generally accepted guidelines for RRT and the management of AKI.

Indication and timing of start RRT

When renal function deteriorates, at some point it may be necessary to initiate RRT. Except for some clear indications such as severe hyperkalemia, diuretic resistant fluid overload or uremic complications such as pericarditis or encephalopathy, there is still great controversy concerning the appropriate timing of initation of RRT. Should it be initiated based on the severity of metabolic acidosis, the height of serum levels of urea and, creatinine, or on severe reduction in urinary output? These questions are still unanswered and clinical trials on this issue are scarce. In one trial, the effects of the initiation time of CVVH were studied in critically ill patients, developing early oliguric acute renal failure.[12] Thirty five patients were treated by early high volume hemofiltration (72-96 L per 24 hrs) and 36 patients received late and low volume hemofiltration (24-36 L per 24 hrs). Early start was defined as a initiation within 12 hrs after a 6 hr period of oliguria (< 30 mL per hr) and late start when patients fulfilled the conventional criteria for RRT, including a plasma urea level > 40 mmol/L, potassium > 6.5 mmol/L or severe pulmonary edema. Survival at 28 days and recovery of renal function did not differ between the two groups. Data from an observational study, however, suggested that mortality of patients starting RRT with a urea less than 27 mmol/L was lower than in patients with a urea of more than 27 mmol/L. It cannot be excluded that these results were confounded by severity of illness, however.[13] One major concern of starting RRT early is that spontaneous recovery of renal function in about 10% of patients is not awaited for and overtreatment may cause harm.[12]

Modality of RRT

The emergence of RRT on the ICU was one of the major advances in critical care medicine. Initially this support was intermittent at best and carried its own morbidity. The introduction of continuous renal replacement therapy (CRRT) at the end of the seventies was promising as it simulated the continuous function of the natural kidney. The CRRT technique, originally through an arteriovenous access and later through a venovenous methodology, slowly improved but also gained complexity in the following decades. Last three decades there has been a tremendous development in CRRT and nowadays it is the leading form of RRT worldwide in the ICU's. There are, however, still many ICU's which are not equipped to apply CRRT and in which intermittent hemodialyis (IHD) is the prevailing RRT modality. In

theory, CRRT does have some major advantages as compared to IHD. However, its superiority has never been proven in clinical trials. There are few randomized trials showing no differences in outcome between CRRT and IHD.[14,15] One large, prospective, randomised multicenter study has been performed comparing continuous venovenous hemodiafiltration with IHD for acute renal failure in patients with multi-organ dysfunction syndrome: the rate of survival at 60 days was similar.[16] In a multicenter observational study on AKI, CRRT even seemed to be associated with an increased mortality as compared to IHD.[17] Several meta-analyses performed on this topic, however, could not demonstrate convincing benefits of one method over the other with regard to mortality and/or recovery of renal function.[18-20] Taken together, so far there are no data proving benefits of CRRT as compared to IHD in the critically ill.

When CVVH is applied as RRT, it is furthermore controversial what the optimal infusion site for the replacement fluid is. When the fluid is infused before entering the hemofilter (predilution), clearance may be limited because blood is diluted before it enters the filter. The latter, however, results in a lower blood viscosity which may retard coagulation, prolong filter life and thereby improve efficiency. The argument against postdilution is that the increase in blood viscosity leads to early filter coagulation and to a shorter filter life. Solute clearance, for a given blood flow and ultrafiltrate rate, however, may be higher as compared to predilution, in the absence of hemodilution.[21] Clinical evidence favouring one or the other concept is scarce, however, and the available data concerning this issue is limited.[22-24]

Dose of RRT

The dose of renal replacement is defined as the amount of blood purification achieved by RRT techniques per unit of time. In chronic dialysis urea clearance is used as a marker of small solute removal. In patients with end stage renal disease the correlation between dialysis intensity and mortality has been extensively studied and there is consensus that intensity really matters up to a certain level.[25] Ronco et al. and Saudan et al. demonstrated a strong association between CRRT dose and mortality in the critically ill with AKI.[26,27] Based on these trials a minimum dose, expressed as weight adjusted hourly effluent volume, of 35 ml/kg/h was advocated for several years. In more recent larger randomized trials, however, a dose-mortality association was not found.[28-30] The difficulty of all trials on intensity of RRT conducted so far, is that they are hard to compare with each other because, different RRT modalities were used, different endpoints studied and lacked stratified randomisation for sepsis. Nevertheless, it can be concluded based on the currently available data that high dose of RRT

(defined as an effluent rate of > 25 ml/kg/h) does not confer a survival benefit in critically ill patients with AKI. Another major drawback of the trials on AKI conducted so far, is that there was no distinction on underlying cause. It can be hypothesized that treatment strategy in patients with sepsis-induced AKI should be different from AKI without sepsis, as there are several observational trials suggesting a hemodynamic benefit of high dose hemofiltration in sepsis.[31-34] Whether high dose RRT in patients with sepsis-induced AKI indeed is beneficial, remains a topic of controversy. The IVOIRE (hIgh Volume in Intensive CarE) trial will probably clarify some issues (NCT00241228).

Non-renal indication of RRT

Non-renal indications of RRT concern the use of extracorporeal techniques to remove substances that cannot be removed by normal kidneys. These non-renal indications are based on the removal of pro-inflammatory mediators in sepsis or sepsis-like syndromes, the removal of fluid in chronic heart failure, the removal of endogenous toxins or the removal of drugs in case of intoxications. These indications are less well established as compared to the classic renal indications.

Sepsis is a syndrome in which pro-inflammatory mediators lead to a generalized inflammatory response overwhelming the anti-inflammatory response. It is a major cause of mortality in adult and paediatric patients worldwide. Of course the cornerstone of sepsis treatment is prompt and adequate eradication of the underlying infection together with appropriate antibiotic treatment as well as supportive therapy. Several decades ago, it was hypothesised that CRRT could play a role in attenuating the inflammatory response by the extracorporeal removal of harmful cytokines and other soluble middle molecular weight mediators.[35] The removal of these solutes during CRRT is partly by convection, but probably primarily due to absorption in the filter.[36] High-volume hemofiltration (HVHF) with frequent filter change has the potential of removal of inflammatory mediators by convection and absorption. At present, HVHF with or without AKI still remains an experimental therapy, though there are some promising data suggesting beneficial effects.[31-34] The aforementioned IVOIRE trial will probably also give some clarification regarding this issue.

In congestive heart failure, the decreased effective circulating volume results in the activation of several neurohumoral systems such as the sympathetic system and the renin-angiotensin-aldosteron system as well as in the release of vasopressin. In case of refractory congestive heart failure concomitant with a compromised renal function, ultrafiltration by CRRT can decrease neurohumoral activation by removal of fluid and sodium.[37] In patients

with heart failure resistant to diuretics, a continuous form of RRT is the best technique to restore dry body weight and improve diuresis together with heart function.

Tumor lysis syndrome may result in AKI due to tubular obstruction by uric acid crystals or hyperphosphatemia with deposition of calcium phosphate crystals in the renal interstitium and tubuli. Preventive strategies include hyperhydration, and allopurinol or rasburicase. If despite such preventive measures AKI still develops, recovery depends on normalisation of plasma uric acid and phosphate. Hemodialysis is most effective in removal of these substances. However, CRRT has the advantage of preventing a rebound hyperphosphatemia. So, CRRT can also be used to prevent AKI due to tumor lysis syndrome.[38]

In case of intoxication rapid removal of the harmful agent may be beneficial.[39,40] As CRRT is characterized by its slow effects on blood purification, it has a limited role in case of intoxication. For this indication IHD seems the optimal blood purifying technique. There are, however, no randomized controlled trials addressing this issue.

Anticoagulation

One of the main disadvantages of CRRT is the necessity of continuous anticoagulation for maintenance of the integrity of the extracorporeal circuit. Inadequate anticoagulation results first in deterioration of filter performance and subsequently in filter clotting with blood loss. Excessive anticoagulation, however, may result in bleeding complications reported to occur in 5-26% of treatments.[41,42] Ideally, the anticoagulation is delivered regionally, which means that only the extracorporeal circuit is anticoagulated. As with intermittent hemodialysis, many anticoagulation methods have been pursued for continuous therapies including low dose heparin, low molecular weight heparin, prostanoids, mesylate and regional citrate anticoagulation.[43,44] Heparin continues to be the most commonly used anticoagulant for CRRT. It is inexpensive, relatively easy to use and monitor. Though it provides adequate extracorporeal anticoagulation, there is however a high risk of bleeding as well as the development of heparin induced thrombocytopenia and thrombosis.

Citrate acts as an anticoagulant through its ability to chelate calcium. Calcium has an essential role in activation of several clot factors (II, V, VII, VIII, IX, X, XIII) and in the conversion of fibrinogen to fibrin. Citrate given pre-filter will allow complete anticoagulation of the extracorporeal circuit. The anticoagulant effect is overwhelmed and neutralized when citrated blood from the extracorporeal circuit returns and mixes with central venous blood containing sufficiently amounts of calcium. Thus, citrate can be used to anticoagulate an extracorporeal circuit, without systemic anticoagulation, resulting in regional anticoagulation.

Eventually it is cleared by the tricarboxycyclic acid pathway in the liver, skeletal muscles and renal cortex producing bicarbonate. Citrate CRRT carries the potential risk of citrate accumulation that can occur either as free citrate accumulation or as accumulation of calcium citrate complexes. The main dangers of citrate as an anticoagulant are those of hypocalcaemia when insufficiently counteracted by calcium infusion after passage of blood through the filter or due to citrate accumulation. Also, metabolic alkalosis may develop when too much citrate enters the circulation. Citrate has been widely used for conventional hemodialysis and has been successfully adapted for use in CRRT.[45-59] Currently two methods of regional citrate anticoagulation which are being used. The first and most frequently used method employs intravenously prefilter administered concentrated trisodium citrate together with the use of hypotonic alkali-free replacement solution or dialysate. The second method employs citrate-containing replacement solution that is isotonic and has an adjusted concentration of citrate, so that the amount of bicarbonate equivalents is similar to that employed when lactate- or bicarbonate-buffered solutions are used. The experience with the latter method is limited.

CVVH with regional anticoagulation with citrate does have some major advantages compared to systemic anticoagulation with heparin including less bleeding risks and the avoidance of heparin induced thrombocytopenia. There may even be a survival benefit when patients are treated by CVVH with citrate. Two randomized trials on this issue, albeit with different citrate regimens, showed conflicting results. Here fore, more trials are needed to elucidate this topic.[58,59]

Outline of the thesis

In this thesis all basic principles in managing AKI are discussed. The objectives of the studies, however, are to explore strategies to optimize treatment by continuous venovenous hemofiltration as renal replacement therapy. In order to address the basic principles systematically, this thesis is divided in two parts.

Part one consists of two chapters (chapter 2 and 3) in which an overview is given on several topics on acute kidney injury and renal replacement therapy on the ICU. In **chapter 2** the difficulties of defining AKI are discussed as well as its clinical classification and pathogenesis. The basic principles of renal replacement and practical issues are outlined. Controversial topics as timing, dosing, modality and non-renal indication of RRT are discussed.

In **chapter 3** a general overview is given on patient safety during RRT. Issues like vascular access, drug removal, biocompatibility of dialyzers, anticoagulation, thermal and solute balance are addressed.

Studies we have performed on optimizing strategies on continuous venovenous hemofiltration are discussed in **part two** of this thesis. In **chapter 4** we studied two groups of a relatively large number of homogenous critically ill patients with systemic heparinsation treated by CVVH in pre- and postdilution mode, as the optimal entry site of replacement fluid still is an issue of debate. CVVH with the delivery of replacement fluid before entering the dialyzer can prolong filter life as compared to delivery after the dialyzer;[22] the delivered dose, however, is less which may result in decreased azotemic control.[23] In this study we hypothesized the equivalence of pre- and postdilution CVVH regarding filter life and azotemic control, in spite of a difference in delivered dose.

In **chapter 5** we describe the analysis a large cohort of patients with septic AKI treated by CVVH. The objective of this study was to retrospectively examine whether or not CVVH characteristics are associated with mortality in critically ill patients with sepsis-induced AKI. Issues like timing and dose were especially analysed. Our hypothesis is that dose rather than timing of CVVH is a determinant of outcome in septic AKI.
Chapter 6 considers a cohort of patients with non-septic AKI treated by CVVH. The objectives are similar to that of the prior study. In this study our hypothesis is that outcome in non-septic AKI is determined by both patient and CVVH characteristics.

In 1999 Palsson and Niles described a new technique of regional anticoagulation with replacement solution containing citrate (RCA).[51] As this fluid was not commercially available, few ICU's used this technique. We adopted this technique several years ago with some minor adjustments. The custom-made citrate-containing replacement fluid was fabricated by a pharmaceutical company. With this method, treatment by CVVH is per protocol in the predilution mode. In **chapter 7** a detailed description of the use of trisodium citrate as regional anticoagulation in CVVH as applied in our hospital is given.

We adopted the technique of CVVH with trisodium citrate as regional anticoagulation especially to be used in patients with an increased bleeding risk. This category of patients was historically treated by CVVH in predilution mode without anticoagulation. In **chapter 8** we

prospectively studied two cohorts of critically ill patients with acute renal failure and high bleeding risk treated by either predilution anticoagulant-free CVVH or RCA using a custom-made citrate-based replacement solution. We hypothesized that treatment with RCA prolongs filter life and improves azotemic control by less down-time without increasing costs.

Treatment with citrate as regional anticoagulant carries the potential risks of electrolyte and acid-base disorders. When applying CVVH with a citrate containing replacement solution, these risks theoretically are minimized. An often mentioned drawback of this technique, however, is that the buffer cannot be dosed separately from the substitution fluid, which can be a problem in severe acidosis. In **chapter 9** we describe a study performed on the metabolic effects of citrate-based versus bicarbonate-based replacement fluid in CVVH. Our hypothesis is that our mode of citrate-based replacement fluid corrects metabolic acidosis as rapidly and fully as bicarbonate-based treatment with comparable electrolyte control, during CVVH for AKI.

There is rather little experience with CVVH with citrate-containing replacement fluid worldwide. We adopted this treatment mode several years ago because of its potential beneficial effects and the positive experience in some ICU's.[51,52] In **chapter 10** we analysed a large group of patients treated by CVVH with this custom-made citrate-containing replacement solution. The focus was on issues like safety and efficacy.

Finally, **chapter 11** contains a summary and discussion of this thesis. Also suggestions for future research are made.

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