

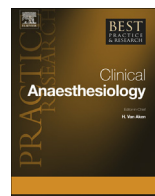


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Renal replacement therapy and anticoagulation



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Today, up to 20% of all intensive care unit patients require renal replacement therapy (RRT), and continuous renal replacement therapies (CRRT) are the preferred technique. In CRRT, effective anticoagulation of the extracorporeal circuit is mandatory to prevent clotting of the circuit or filter and to maintain filter performance. At present, a variety of systemic and regional anticoagulation modes for CRRT are available. Worldwide, unfractionated heparin is the most widely used anticoagulant. All systemic techniques are associated with significant adverse effects. Most important are bleeding complications and heparin-induced thrombocytopenia (HIT-II). Regional citrate anticoagulation (RCA) is a safe and effective technique. Compared to systemic anticoagulation, RCA prolongs filter running times, reduces bleeding complications, allows effective control of acid–base status, and reduces adverse events like HIT-II. In this review, we will discuss systemic and regional anticoagulation techniques for CRRT including anticoagulation for patients with HIT-II. Today, RCA can be recommended as the therapy of choice for the majority of critically ill patients requiring CRRT.

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Introduction

Acute kidney injury (AKI) occurs in up to 50% of all critically ill patients in intensive care units (ICUs). Today, approximately 10–20% of all ICU patients require renal replacement therapy (RRT) [1]. The optimal RRT for those patients is still a matter of debate. However, continuous renal replacement therapy (CRRT) is preferred over intermittent therapies because of improved hemodynamic stability and better volume control [2].

During CRRT, effective anticoagulation of the extracorporeal circuit is mandatory to prevent clotting of the circuit or filter and to maintain filter performance. Clotting of blood within the circuit reduces solute clearance and may cause blood loss. In addition, a short filter lifetime increases workload and overall treatment cost [3].

Until recently, the most common mode of anticoagulation was systemic application of unfractionated heparin (UFH) or other anticoagulants. It is obvious that with any systemic anticoagulant, the dose required to prevent clotting in the extracorporeal circuit will also impair coagulation of the patient. Thus, systemic anticoagulants increase the risk of bleeding in general and even more in critically ill patients who frequently have impaired coagulation and decreased platelet counts. Bleeding complications may at worst be lethal but in any case increase transfusion requirements and risk for transfusion-related adverse effects [4].

Thus, patients with systemic anticoagulation move between “Scylla and Charybdis,” i.e., the risk of excessive anticoagulation and bleeding versus inefficient anticoagulation, repeated filter clotting, and delivery failure. The most threatening risk of cause is bleeding and after individual risk assessment, many patients do not receive any anticoagulation. As expected, filter running times in those are short [4].

Today, new strategies targeting at anticoagulation restricted to the extracorporeal circuit are available. There is regional heparin–protamine anticoagulation (RHPA) but the most promising approach is regional citrate anticoagulation (RCA). In this review, we will discuss the most relevant anticoagulation strategies for CRRT with a focus on RCA.

CRRT with systemic anticoagulation

Unfractionated heparin

UFH is a glycosaminoglycan built of repetitive sulfated disaccharides of glucosamine and iduronic acid. It is synthesized by endothelial cells, mast cells, and basophil granulocytes. Heparin increases the activity of the enzyme inhibitor antithrombin III (AT III), thereby enhancing the ability of AT III to inhibit the activity of factor Xa (Stuart–Prower factor), IIa (thrombin), IXa, Xa, and XIIa.

Nowadays heparin is a standard drug for anticoagulation in critically ill patients. Its main advantages include low costs and the widely available possibility of monitoring its effects by laboratory tests (prothrombin time, aPTT) and bedside tests (activated clotting time, ACT). Furthermore, heparin can be instantly antagonized by the administration of protamine. For these reasons, heparin has been the most commonly used anticoagulant in CRRT for decades.

Though being implemented in clinical practice, systemic heparin anticoagulation in CRRT exhibits some major and minor adverse effects including bleeding events, heparin-induced thrombocytopenia (HIT-II), proinflammatory effects, and ineffective anticoagulation due to heparin resistance.

Bleeding events

During critical illness, patients are at increased bleeding risk (e.g., prior surgery, trauma, coagulopathy). Therefore, systemic anticoagulation with heparin enhances the risk of bleeding in these patients. With systemic heparin in CRRT, bleeding events occur in 5–40% of patients, and lethal bleeding complications have been described [5–11]. When compared to RCA, bleeding events occur more frequently under systemic heparin anticoagulation [12]. The frequency of bleeding events derived from studies comparing heparin versus RCA has been summarized in Fig. 1.

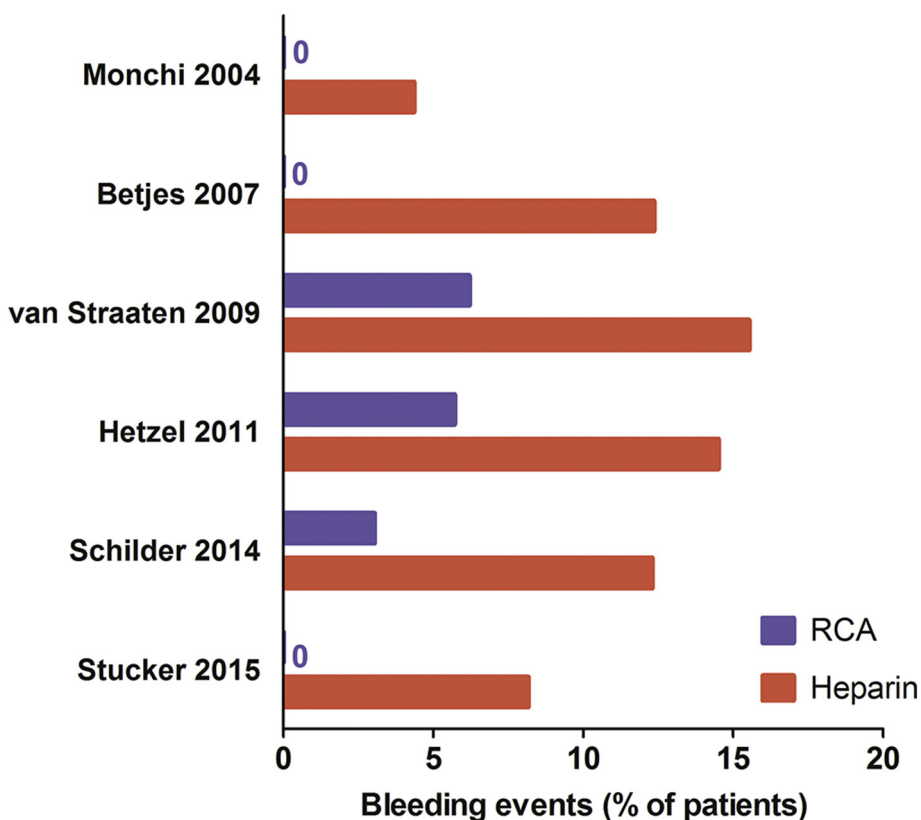


Fig. 1. Bleeding events during systemic heparin compared to regional Citrate anticoagulation.

Heparin-induced thrombocytopenia

As an adverse effect of systemic heparin therapy, the complex of heparin and platelet factor 4 (PF4) can trigger the production of antibodies against these complexes. In medical and surgical patients, the occurrence of this antibody production varies between 8% and 17% [13]. The antibodies against the heparin–PF4 complex can bind to FcγRIIA receptors located in the plasma membrane of platelets. This binding activates platelets, causing a release of procoagulatory particles [14]. Subsequently this leads to a prothrombotic state with potentially life-threatening thrombosis or thromboembolism. Several studies have shown that HIT-II occurs more frequently in patients treated with systemic heparin when compared to RCA [10,11,15].

Heparin and inflammation

AT III exerts anti-inflammatory effects by preserving microvascular integrity in septic conditions and thereby protects from subsequent organ dysfunction [16]. By heparin binding, the protective effect of AT III is diminished [17].

Besides AT III-mediated effect of heparin on inflammation, heparin itself has pro-inflammatory and anti-inflammatory effects. Whether or not the use of heparin especially in septic patients is protective or harmful remains controversial.

Heparin resistance

There is a large variability of heparin response among patients. The term “heparin resistance” has been suggested to be used when a total dose of more than 35,000 IU of intravenous UFH per day is required to prolong the aPTT 1.5–2 times from normal mean [18]. Heparin resistance can occur

mediated by AT III deficiency. While congenital AT III deficiency is rare (1:2000–1:5000, [19]), many clinical conditions (e.g., perioperative bleeding, shock, liver cirrhosis, hemodialysis itself) can lead to decreased AT III levels and finally to inefficient anticoagulation by heparin with reduced filter life span.

Heparin resistance can also develop independently from AT III. Causes are the binding of heparin to a variety of heparin-binding molecules such as PF4, collagen, growth factors, or enzymes such as elastase [19]. Furthermore, especially in cardiosurgical patients, elevated levels of factor VIII are observed frequently. Then, binding of heparin to factor VIII can contribute to the development of heparin resistance [20]. Heparin resistance may cause an inefficient anticoagulation in CRRT and contribute to a reduced filter life span.

Clinical practice

During CRRT, heparin can be infused through a separate line or directly into the extracorporeal circuit. In most cases, a direct infusion into the arterial limb of the CRRT circuit is chosen. The rationale is that the highest heparin concentration is present at the prefilter site and thus at the location where the coagulation system is activated predominantly. A distinct advantage of this application mode, however, has never been proven. The heparin effect can be controlled through aPTT measurements or as point-of-care test through the ACT. The target range is prescribed under consideration of the patient's bleeding risk and may vary widely.

Low-molecular-weight heparin

Low-molecular-weight heparins (LMWH) are bound to heparin-binding proteins to a lesser extent than UFH. Additionally, they bind more predominately to factor Xa than IIa when compared to UFH [21]. LMWH are eliminated through the kidneys and their biological half-life is prolonged in patients suffering from renal failure. Thus, the risk of overdosing is high [22]. During CVVH, most LMWH are not removed to a clinically relevant extent [23]. Therefore, monitoring of the anticoagulatory effect of LMWH by daily measurement of anti-Xa activity is essential. The recommended range of anti-Xa activity is between 0.25 and 0.35 IU/ml [24]. The anti-Xa test is expensive and in many hospitals not generally available 24 h a day. Therefore, a tight control of anticoagulation using LMWH is not feasible. Furthermore, LMWH cannot be completely antagonized by protamine.

Only a few studies have investigated the efficacy of LMWH in CRRT. Joannidis et al. showed that with enoxaparin compared to UFH no difference in bleeding events occurred. Of note, anti-Xa activity was controlled daily and the dose of enoxaparin was adjusted accordingly. Although the filter lifetime for enoxaparin was significantly prolonged compared to heparin (22 vs. 31 h; $p < 0.017$), the overall lifetime for both techniques was short and disappointing [25]. In another study, filter life span in the LMWH and UFH group was identical, while costs were higher in the LMWH group [26]. As there is little data on LMWH in CRRT, a final recommendation for or against its use cannot be made.

Direct thrombin inhibitors

Argatroban is a direct inhibitor of factor IIa (thrombin). It is a small molecule derived from L-arginine with a molecular size of 500 Da [27]. It is metabolized in the liver and secreted biliary [27]. Argatroban has a half-life of 45 min so that its anticoagulatory effect fades 2–4 h after cessation of continuous infusion [28].

Argatroban can be applied as anticoagulant in CRRT in patients with HIT-II. In a study by Link and colleagues in 30 HIT-II-positive patients, argatroban was used as anticoagulant for CRRT. Minor bleedings occurred in two patients, but no patient showed major bleeding. Overall mean filter patency, however, was short with only 24 h [29].

Another direct thrombin inhibitor is recombinant hirudin, which is also approved for the treatment of HIT-II. Hirudin is eliminated through the kidneys. The normal half-life of 1–2 h is prolonged up to 50 h in patients with renal insufficiency [30]. Hirudin has a molecular weight of 6980 Da and is thus neither removed by hemodialysis nor reliably with hemofiltration. An antidote does not exist. The anticoagulatory effect of hirudin cannot be estimated reliably through the aPTT because the relation is not linear. The ecarin clotting time (ECT) is more reliable; however, the ECT is not available in most hospitals.

Hirudin is infused continuously during CRRT, but filter running times are short and bleeding complications occur in up to 38% of all patients [31]. To date, there is only one prospective randomized controlled trial (RCT) comparing argatroban with hirudin for CVVHD in HIT-II patients. Filter running times were not different, i.e., 32 h with argatroban and 27 h with hirudin [32]. In this trial, but also in other observational studies, relevant bleeding occurred more frequently with hirudin (OR 3.9). In addition, hirudin antibodies are produced in some patients and further increase the bleeding risk [32,33].

In conclusion, for HIT-positive patients who require anticoagulation, argatroban is the anticoagulant of choice in CRRT. Of note, RCA alone is not sufficient because HIT-II requires effective anticoagulation to stop the coagulation activation and to prevent thrombosis and thromboembolism. In this context, it is noteworthy that RCA is often not sufficient to prevent hemofilter clotting in patients with HIT-II. Repeated filter clotting during RCA-CRRT can thus be an early clinical sign of HIT-II. It should trigger a diagnostic workup to exclude HIT-II in such patients [34].

Regional anticoagulation

The most widely used anticoagulation mode for CRRT is systemic heparin. However, in recent decades, a variety of anticoagulation strategies have been tested. A major focus was to develop techniques to anticoagulate the circuit only, but not the patient. The latter techniques are referred to as regional anticoagulation techniques. Here we describe RHPA and RCA.

Heparin–protamine anticoagulation

RHPA is achieved by infusion of UFH into the arterial line of the extracorporeal circuit followed by a constant postfilter infusion of protamine. The dose of protamine must be effective to bind the prefilter infused UFH. The approach requires measurement of the aPTT in the circuit and systemically. The circuit aPTT should be doubled, while the systemic aPTT should be within the normal range [35]. In clinical practice, some handling problems occur. The heparin–protamine complexes are taken up by the reticuloendothelial system and broken down. Both substances are then released into the systemic circulation and are reactivated. The elimination half-lives of heparin and protamine differ substantially [36,37]. Thus, the ratio of heparin–protamine infusion is not constant but must be adjusted frequently. The calculation of the postfilter dose of protamine required to antagonize the prefilter infused heparin is difficult. In addition, protamine can exert serious adverse effects, including vasodilation and hypotension, release of complement factors, histamine, and other inflammatory mediators. Protamine may cause pulmonary hypertension and right heart failure. Most importantly, it may also impair coagulation itself [38].

In small studies RHPA was described as feasible but not superior to the comparator [39,40]. In one prospective randomized trial from the ANZICS group RHPA was compared to RCA. The study comprised 212 patients and 857 CRRT circuits. The RHPA and RCA groups were not different with regard to baseline demographic and clinical characteristics. The mean APACHE II score was 25, catecholamine therapy was required in 68%, and 73% of patients were mechanically ventilated. There was no statistically significant difference in any clinical outcome parameter between the RHPA and RCA groups. Hospital mortality was 29% and 31%, respectively. In patients with RHPA the OR for filter clotting was significantly increased compared to RCA (OR 2.03; [CI 1.36–3.03]). The median circuit life for RCA was 39.2 and 22.8 h with RHPA ($p < 0.0037$). There were significantly more serious adverse effects in the RHPA group (11 versus 3, $p = 0.011$) resulting in discontinuation of study treatment [15].

In conclusion and after summarizing the available data, regional heparin–protamine anticoagulation is a complex intervention with a high risk of adverse effects. It is not superior to other techniques and – in direct comparison – inferior to RCA. Therefore, RHPA cannot be recommended for clinical practice.

Regional citrate anticoagulation

Background and technical aspects

RCA for CRRT was first described in 1990 by Mehta et al. for continuous arteriovenous hemodialysis [41]. The group used a 4% sodium citrate solution as anticoagulant and applied a dialysate flow rate of 1 L per hour. The technical feasibility of RCA and a clear trend toward longer filter lifetimes

with citrate were shown. However, because of the small number of patients the difference was not significant.

Since then, RCA has been studied extensively. A PubMed search from July 2017 yields more than 670 papers on this topic. RCA protocols are available not only for continuous veno-venous hemodialysis (RCA-CVVHD) [42], continuous veno-venous hemofiltration (RCA-CVVH) [8], continuous veno-venous hemodiafiltration (RCA-CVVHDF) [43] but also for plasmapheresis and so-called liver dialysis therapies [44,45].

The basic principle of RCA is a reduction of ionized calcium (iCa) in the extracorporeal circuit. iCa is an essential cofactor of many steps of the clotting cascade. Citrate decreases iCa by chelating it in a reversible manner. Citrate is infused either separately into the extracorporeal circuit at a most proximal site, usually directly after the connection of the circuit to the vascular access. In CVVH, citrate is often included in the substitution fluid. The latter approach requires a predilution CVVH setting. The infusion rate of citrate, either separately or as part of the substitution fluid, is proportional to the blood flow rate and depends on the concentration of the citrate solution used. The target range of iCa in the dialysis circuit is 0.25–0.4 mmol/l, which requires a citrate concentration of approximately 4 mmol/l blood [46].

The citrate–calcium complex has a molecular weight of 300 Da. Thus, up to 50% of the infused citrate–calcium complexes are removed by the hemofilter during the first passage. To avoid a negative calcium balance and to compensate for these losses most but not all protocols recommend an infusion of calcium [47].

The citrate–calcium complexes that are not removed by the hemofilter enter the systemic circulation. There, these complexes dissociate and citrate is metabolized through the Krebs cycle mostly in liver cells [48]. At the end of the pathway one molecule of citrate yields some energy but also three molecules bicarbonate [49]. Most importantly, citrate thus acts both as anticoagulant and buffer base. This has to be taken into account when targeting acid–base control. Metabolic alkalosis can be an adverse effect of RCA [50,51].

The efficacy of anticoagulation should be controlled by measuring the level of iCa in the circuit, usually from a port located after the hemofilter. Target levels are 0.25–0.4 mmol/l because within this range, the plasmatic coagulation cascade is blocked almost completely.

There has been some concern with regard to the precision of iCa measurements with presently available blood gas analyzers. Modern blood gas analyzers are less precise when measuring iCa at very low concentrations, and in some cases, the measurements of iCa in postfilter samples may give misleading information in monitoring RCA [52]. Despite these concerns, most citrate protocols work well using these analyzers, but nevertheless, manufacturers should work on improving accuracy of their devices [53].

To maintain physiologic levels of iCa within the systemic circulation regular measurements of iCa from the patient's blood are recommended. The calcium substitution rate is then adjusted according to maintain a neutral calcium balance.

RCA and mortality

Despite proven positive effects of RCA on a variety of clinical parameters, until today, no reduction of mortality with RCA compared to systemic anticoagulation was shown. One small study showed a decreased mortality with RCA compared to nadroparin [8]. Unfortunately, the study was underpowered and the results were never confirmed [12,54]. To answer this question, a prospective RCT comparing RCA with systemic heparin anticoagulation and targeting >1000 patients is currently executed (clinicaltrials.gov NCT02669589).

RCA and filter lifetime

A number of observational but also some RCTs compared RCA with systemic anticoagulation modes. The most striking effect of RCA is a prolonged filter lifetime. In a recent meta-analysis, data from 11 RCTs with 992 patients were summarized. RCA reduced the risk for circuit loss compared to RHPA (HR 0.52, CI 0.35–0.77; $p = 0.001$) as well as to systemic heparin (HR 0.76, CI 0.59–0.98; $p = 0.04$) [54]. Although these observations in general are conclusive, there is heterogeneity between citrate protocols and whether circuit survival is prolonged depends on the quality of the protocol.

In one of the early studies, RCA was performed in postdilution CVVH and compared to LMWH, i.e., nadroparin. CVVH was performed with a blood flow of 220 ml/min and a filtrate flow of 4000 ml/h. Patients received nadroparin adjusted to body weight but without anti-Xa monitoring. The target dose of citrate was 3 mmol/l blood. The mean circuit survival time was 26–27 h in both groups without significant differences. This is not surprising because the citrate dose of 3 mmol/l is too low to decrease iCa into the target level. As the protocol did not include measurement of iCa in the extracorporeal circuit, no adjustment of the anticoagulant was feasible. This early citrate protocol therefore was not efficient to provide effective anticoagulation [8].

In another RCT using hemodiafiltration, a protocol with algorithms both to adjust systemic heparin and citrate was investigated. In patients receiving heparin, an aPTT was drawn every 6 h. Based on a predefined nomogram, the heparin dose was adjusted to maintain an aPTT of 40–45 s. Citrate infusion was adjusted also every 6 h to maintain postfilter iCa between 0.25 and 0.35 mmol/l. The first important observation was that with RCA, 17% of all circuits run up to 72 h, but none of the heparin anticoagulated ($p > 0.002$). Clotting was the cause for discontinuation of therapy in 82% of the heparin systems and in 31% on RCA ($p > 0.002$). The mean survival time of hemofilters was 15 versus 60 h ($p > 0.0001$) [55]. Thus, a protocol with an algorithm to adjust the citrate dose is superior to a fixed regimen [55].

RCA is also used for CVVHD. The “Berlin protocol” first published by Morgera gives clear recommendations to adapt the citrate dose following measurement of iCa in the circuit. In their first publication the authors described a median filter running time of 62 h [50]. Ongoing work showed excellent filter patency and effective metabolic control also in high-volume treatments [51]. In a recent multicenter trial in 120 patients with different degrees of liver dysfunction, finally, the clotting-free 72-h filter survival was 96% [56].

In conclusion, not all citrate protocols are equally effective. However, if a clear target range for postfilter iCa levels is defined and algorithms to adjust citrate dose following iCa measurements in the circuit are present, RCA is superior to heparin with regard to filter lifetime and a reduced rate of filter or circuit clotting (Fig. 2).

Bleeding and transfusion requirements

The most obvious advantage of RCA is to avoid systemic anticoagulation in patients with bleeding risk. Numerous observational studies and RCTs studied whether bleeding complications and blood transfusions are reduced in RCA compared to systemic anticoagulation. Of note, in all RCTs, patients with an increased bleeding risk were excluded so that the true effect of RCA on bleeding and transfusion most likely is underestimated.

One of the first prospective RCTs to compare the efficacy and safety of UFH versus RCA in CVVH was published in 2004. Patients were randomized to systemic heparin or RCA, and those eligible for a second CVVH run received the other study medication in a cross-over design until the fourth circuit. The number of analyzed circuits was 49. Major bleeding occurred during heparin anticoagulation only. Transfusion rates (units of packed red cells/day of CVVH) were 0.2 with citrate and 1.0 with heparin ($p = 0.0008$) [6].

In an RCT with 215 patients, systemic anticoagulation with LMWH was compared to RCA in CVVH. Adverse effects needing discontinuation of the study drug were more frequent with nadroparin ($p < 0.001$). Bleeding complications were nonsignificantly lower with RCA (6/97) compared to nadroparin (16/103). The median number of red blood cell units transfused per CVVH day was 0.27 for RCA and 0.36 for LMWH (n.s.) [57].

In a prospective RCT using hemodiafiltration, RCA was compared to systemic heparin in 46 patients. The protocol provided strict algorithms to adjust anticoagulation. At least four coagulation checks per day were mandatory. The target aPTT was 40–45 s. Despite these tight controls and adjustments, bleeding was a major complication in the heparin group and occurred in 61.5% of patients compared to 15% in RCA ($p < 0.01$). The most important bleeding site was gastrointestinal, but there was also intracranial hemorrhage [57].

At present, there is only one nonrandomized observational study to investigate RCA in cardiac surgery patients with high bleeding risk. The study group consisted of 33 patients who were switched from hemofiltration with no anticoagulation or systemic heparin to RCA. Of note, switching to RCA

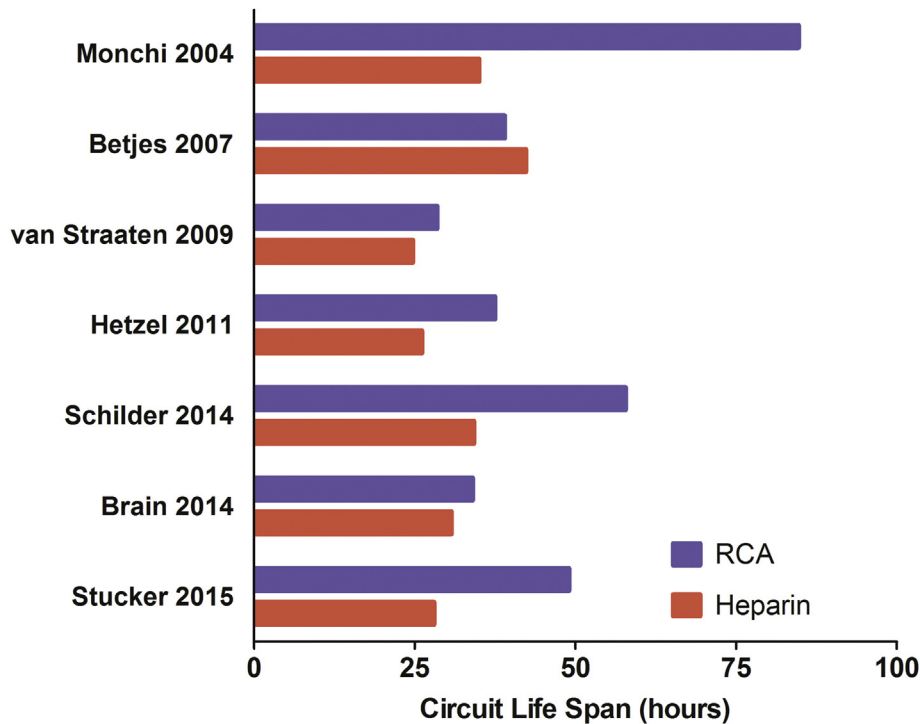


Fig. 2. Circuit life span.

significantly reduced transfusion requirements by more than 50% compared to both systemic heparin and no anticoagulation [58].

In recent meta-analyses, the data on bleeding complications have been aggregated. Unfortunately, in all meta-analyses, only bleeding complications have been analyzed, but not transfusion requirements [12,54,59]. Data now derive from 1134 patients and 14 studies. Compared to any systemic anticoagulation, RCA decreased the risk of bleeding with a hazard ratio of 0.31 (CI 0.19–0.51, $p < 0.01$) [12].

Blood losses and need for transfusion of red cells during CRRT can be caused by other reasons than overt bleeding. An often underestimated cause for blood loss is filter or circuit clotting. Clotting of the circuit often occurs suddenly with no opportunity to retransfuse the blood within. By and large, the filling volume of tubing system and hemofilter can sum up to 200 ml. A clotted system with no retransfusion, therefore, is equivalent to the loss of approximately one unit of packed red cells. In patients with frequent filter clotting and filter running times below 24 h, which are often described with systemic anticoagulation, a substantial transfusion demand can thus occur even without serious bleeding complications.

In conclusion, RCA significantly reduces bleeding risk and most likely transfusion requirements compared to systemic anticoagulation (Fig. 1).

Metabolic control

The major targets of any RRT are to provide effective volume control, a sufficient solute clearance, and electrolyte and pH control while avoiding adverse effects.

Volume control can be achieved independent of dialysis dose but solute clearance is a function of the delivered dialysis dose. RCA prolongs filter running time and decreases downtime and thus can help to deliver an effective dialysis dose. The overall solute clearance with RCA is sufficient in all studies and will not be discussed in detail here. However, in most studies investigating treatment protocols

with systemic anticoagulation, there is a relevant gap between prescribed and delivered dialysis dose [60]. The most important reason is unexpected downtime caused by circuit malfunction and clotting. Only one study using RCA for CVVHD showed that no difference between prescribed and delivered dose occurred. This is a unique observation until today and the explanation is the reliable and prolonged filter running time [51].

Control of pH and compensating renal metabolic acidosis is another important target. In conventional CRRT, the substitution or dialysis fluids contain a high concentration of bicarbonate (usually 32–35 mmol/L) to compensate metabolic acidosis. These solutions have been designed at a time when dialysis doses were much lower than today, i.e., 1.0 or 1.5 l/h only. With today's recommendations targeting at higher dialysis doses, after some days of treatment, overcompensation of acidosis may occur [61].

In RCA, citrate is metabolized to bicarbonate and is used as a buffer substance. The buffer capacity during RCA depends on the citrate load given to the patient, the concentration of buffer base in the dialysis or substitution fluid, and the turnover of dialysis or substitution fluid.

An essential component of any RCA protocol therefore is to provide a comprehensive algorithm to control acid–base status by adjusting flow rates of the different components. Given the high number of protocols available today, a full analysis of every protocol is beyond the scope of this review. However, it is obvious that not all protocols or solutions are effective. In a study on 33 patients with RCA, acidosis was not compensated and an additional bicarbonate infusion was required in 27/33 patients [58]. Similar results were shown in an RCA-CVVH trial with a dialysis dose of 32 ml/kg/h. Despite this high dose, the acidosis was resolved by an additional continuous infusion of bicarbonate only [62].

In contrast, some substitution fluids obviously contain too much citrate. In an RCT using such solutions after 72 h of treatment, serum bicarbonate had increased to 31 mmol/l and patients became hypercapnic. This complication did not occur when a solution with lower citrate content was used [63].

Another approach to RCA is RCA-CVVHD with a separate infusion of a 4% citrate solution. With this protocol, the citrate load is mainly a function of blood flow. The dialysis fluid is adapted and contains a reduced concentration of bicarbonate to compensate for the bicarbonate generated by metabolism of citrate. With this protocol, a regulation of pH in both directions, i.e., control of metabolic acidosis as well as alkalosis, is feasible by changing the ratio of blood to dialysate flow. The protocol recommends changes of 20% of either flow rate to yield a difference in serum bicarbonate of approximately 4 mmol/l. This protocol provided excellent acid–base control in the majority of patients [50]. This was also studied for high-volume treatments with a dialysis dose close to 50 ml/kg/h because there the risk of alkalosis might be higher. A tendency toward alkalosis was observed but could be compensated by following the recommended algorithm [51]. Unfortunately, up to date, no prospective RCT has compared this protocol to others.

A recent meta-analysis has finally resolved the issue of metabolic alkalosis. The analysis of six recent prospective RCTs showed that compared to systemic anticoagulation, the risk of alkalosis is not increased with RCA [54].

However, it must be kept in mind that “citrate anticoagulation” might have different metabolic effects depending on the protocol used. Therefore, it is mandatory to study the details of a given protocol carefully before starting the first treatments [64].

Calcium homeostasis

With RCA, a significant influence on serum levels of calcium and calcium homeostasis can occur. At first glance, the risk of serum hypocalcemia after infusion of citrate into the extracorporeal circuit seems obvious. In the majority of studies, hypocalcemia is described as adverse effect. However, the hypocalcemia is usually mild and can be adjusted by increasing the calcium substitution rate or a single calcium bolus.

Some RCA protocols can be applied even without additional calcium supplementation either because a calcium-containing substitution or dialysis fluid is used or because the total citrate dose is low [47]. From a physiological point of view, the risk of severe hypocalcemia is low. The blood flow rates during CRRT are in the range of 100–200 ml/min. This blood mixes in the vena cava with a blood volume equivalent to the cardiac output, i.e., 4–5 L/min, with normal calcium levels. Considering the

mass balance, a level of iCa close to normal will be restored immediately even if the blood returning from the circuit has a very low iCa level. Nevertheless, all meta-analyses clearly show that the risk of hypocalcemia is increased with RCA [12,54,59].

With RCA, a significant amount of calcium is removed as citrate–calcium complex through the hemofilter. It is mandatory to maintain a neutral calcium balance during therapy because continuous calcium losses and a negative calcium balance will activate the parathyroid gland and increase levels of parathyroid hormone. Then, calcium is released from bones and a slow but continuous decalcification occurs. This process cannot be detected by conventional blood analysis because iCa and total calcium will be restored to normal by activation of the hormone system. Therefore, following prolonged therapy, bone fractures have been described [65]. In this context, a word of caution must be issued when aiming for serum levels of iCa between 0.8 and 1.1 mmol/l because then a negative calcium balance is likely and parathyroid hormone levels will rise. A prospective study in 30 patients with RCA-CVVD targeting a physiologic systemic iCa between 1.12 and 1.20 mmol/l showed that no significant changes in parathyroid hormone levels occurred [66]. Therefore, maintaining systemic iCa within the physiologic range is associated with stable parathyroid hormone levels and can avoid decalcification.

Citrate accumulation

Citrate is metabolized mainly in the Krebs cycle in liver cells. In the case of impaired metabolism, citrate may accumulate. It is therefore required to detect citrate accumulation early and to adjust RCA or switch to an alternative anticoagulation regimen if necessary.

In the case of decreased metabolism, citrate levels in the patient's blood increase. Then, the citrate-bound calcium remains chelated and is not released. The first sign of citrate accumulation is a decrease in systemic iCa and an increased demand of the calcium substitution to maintain iCa in the physiologic range. Most RCA protocols provide recommendations how to proceed in such cases. Some machines also show a warning on the display if the calcium substitution rate exceeds the predicted demand.

In patients with RCA, at least once daily the total serum calcium should be measured. In the case of citrate accumulation, the total calcium will increase because the citrate-bound calcium fraction is added to the iCa and the protein-bound calcium. If the ratio of iCa/total Ca exceeds 2.5, a citrate accumulation is likely. A small study with direct measurement of citrate in patient's blood confirmed that an increased total Ca/iCa was the best predictor for citrate accumulation compared to a variety of other parameters [67].

With ongoing accumulation and failing metabolism, less bicarbonate is generated. Therefore, another sign of citrate accumulation is metabolic acidosis.

Citrate is an intermediate of energy metabolism, it is not toxic itself, and its elevated levels have not been associated with adverse effects yet. Nevertheless, its accumulation and consecutive low iCa could decrease cardiac contractility or cause arrhythmias as well as other symptoms of systemic ionized hypocalcemia. In mild cases, a reduction of citrate load by decreasing citrate dose, i.e., decreasing the target citrate concentration in the blood and accepting higher iCa levels in the extracorporeal circuit, is sufficient and RCA can be continued. With ongoing accumulation and severe ionized hypocalcemia, RCA should be stopped.

The largest study on incidence and outcome of citrate accumulation analyzed the clinical course of 1070 unselected patients treated with RCA-CVVHD at Charite Hospital Berlin. Decreased systemic iCa, increased demand for calcium substitution, elevated total/iCa ratio, and metabolic acidosis were evaluated as signs for citrate accumulation. Metabolic signs of citrate accumulation occurred in 32 of 1070 patients (2.99%). All patients were seriously ill with an APACHE-II score of 34 ± 10 . Systemic iCa decreased to 1.01 ± 0.10 mmol/L despite an increase in the calcium substitution rate to $129\% \pm 26\%$ of the initial dose. The mean total/iCa ratio increased to 2.51 ± 0.54 . All 32 patients had resistant shock with severe lactic acidosis (pH 7.20 ± 0.11 , lactate 136 ± 61 mg/dL), and all patients died [68].

In another study on 208 patients with RCA, the total/iCa ratio was identified as an independent predictor for 28-day mortality after multivariate analysis. A total/iCa ratio >2.4 on day 3 of RCA independently predicted a significant increase in mortality. On day 28, none of these patients was alive. Of note, neither the efficacy of citrate anticoagulation determined by blood urea nitrogen and mean filter patency nor the safety evaluated by bleeding episodes were significantly different between patients with or without an elevated ratio [69].

In conclusion, in patients on RCA, an elevated total/iCa ratio >2.5 is indicative of citrate accumulation. The overall incidence of this adverse effect in unselected ICU patients is close to 3%. It is found in the most severely ill patients, mostly coincident with severe lactic acidosis, as a sign of significantly impaired cellular metabolism. The mortality of these patients in two large studies was 100%. Thus, a clinically relevant and persistent citrate accumulation obviously is an indicator of an irreversibly impaired metabolism following shock. It is thus more a prognostic tool than a disease entity itself.

Liver dysfunction

Liver dysfunction or failure was originally considered a contraindication for RCA because citrate is metabolized predominantly in the hepatic citric acid cycle. Intensive care patients with liver dysfunction had a reduced citrate clearance [70]. Early clinical observations thus raised concerns about the safety and efficacy of RCA in the presence of liver failure [71]. However, coagulation is often impaired in liver dysfunction and bleeding risk is high. Thus, patients with impaired liver function (LF) might particularly benefit from RCA by avoidance of filter clotting and bleeding as well.

The incidence and clinical significance of citrate accumulation recognized by an elevated total/iCa ratio during RCA-CVVHD was studied retrospectively in 161 patients with liver failure compared to control groups. In patients with normal LF or mild hepatic dysfunction, no elevated total/iCa ratio was observed. In severe liver failure, defined as serum bilirubin >7 mg/dl, an elevated ratio of 3.4 occurred in 33%. However, in two-thirds of patients, RCA was well tolerated. The only independent risk factor for mortality was an increased total/iCa ratio, while liver failure without elevated ratio was not [72].

In a retrospective study, metabolic complications during RCA were evaluated in 697 patients with liver dysfunction. Patients were categorized into four groups according to their MELD scores (17–31, 32–37, 38–45, >45). The mortality was highest in group IV (MELD score >44). The authors observed a slightly lower pH, bicarbonate level, and serum iCa in group IV; however, the overall compensation was acceptable. Most importantly, none of the patients required discontinuation of RCA because of citrate accumulation or metabolic derangements [73].

The safety and efficacy of RCA-CVVHD was prospectively evaluated in 133 patients with different degrees of liver dysfunction. In a multicenter, prospective, observational study, end points for safety were severe acidosis or alkalosis (pH <7.2 or >7.55) and severe hypo- or hypercalcemia (iCa < 0.9 or 1.5 mmol/L). The endpoint for efficacy was filter lifetime. Patients were grouped according to their baseline serum bilirubin (normal LF < 2 mg/dl, mild LF 2–7 mg/dl, severe LF > 7 mg/dl). The frequencies of safety endpoints in all three groups were not different, and only three patients had impaired citrate metabolism. In two of those, RCA was continued with a reduced citrate dose and accumulation was reversed. The third patient had a severe graft-versus-host-reaction following stem cell transplantation. He died of multiorgan failure. This study confirmed preceding data that RCA can be safely used in patients with different degrees of liver dysfunction. It also demonstrated that in case of citrate accumulation, RCA must not be stopped immediately but can be continued with a reduced citrate dose in some patients [74].

Finally, RCA was used for anticoagulation in patients with AKI following liver transplantation. Saner et al. studied an RCA-CVVHD protocol in 68 patients. MELD score was 23, median treatment with RCA-CVVHD was 8 days, and all patients tolerated RCA without relevant metabolic side effects [75]. RCA has also been used safely for liver support treatments with MARS [45] and Prometheus [76].

Thus, liver failure per se is not a contraindication for RCA, and patients with liver disease can benefit from this technique. If citrate accumulation occurs, at first, a reduction of the citrate load is required. Nevertheless, patients must be monitored closely for signs of citrate accumulation, and in some cases, a switch to other anticoagulation techniques is necessary.

RCA and hypoxemia

The metabolic pathway of citrate is oxygen dependent. A severe hypoxemia thus might impair this cycle. A small study compared RCA in patients with liver dysfunction (serum bilirubin 21.5 mg/dl) to a group with severe hypoxemic ARDS. In patients with liver dysfunction the metabolic acidosis was well compensated with RCA and no hypocalcemia occurred. In those with hypoxemia (paO₂ <60 mmHg), metabolic acidosis worsened during RCA and hypocalcemia occurred in all [77]. This study clearly

shows that hypoxemia is a risk factor for citrate accumulation and RCA might not be tolerated, while elevated bilirubin as indicator of liver dysfunction is less relevant.

Treatment-associated cost and workload

RCA increases costs through citrate and calcium solutions and, in some protocols, because of more expensive substitution/dialysis fluids. On the other hand, costs for tubing systems and hemofilters and bleeding- and transfusion-associated costs will decrease. The most important cost reduction, however, is a decreased workload of staff. Shortage of ICU nursing staff is present in many countries, and time gained by not setting up a new circuit after clotting can be used for direct patient care. A general comparison of the overall costs is difficult because of different reimbursing systems in countries. However, several studies showed reduced costs with RCA compared to systemic anticoagulation, ranging from approximately 26\$ [78] up to 500\$ per treatment course [55]. A detailed analysis shows that this is mostly caused by a 50% reduction of costs for filter sets and nurse wages [10].

Conclusion

RCA is safe, effective, and cost-efficient and can be recommended as a standard for most patients. Patients with severe liver failure, severe hypoxemia, and shock with lactic acidosis are at risk for citrate accumulation. Citrate accumulation in those patients can be identified by careful and close monitoring. In some of these, RCA can be continued with modified settings, while in some, a switch to an alternative anticoagulation technique is required. For patients with HIT-II, taking into account the limited data, argatroban can be recommended.

Practice points

- Continuous renal replacement therapy requires effective anticoagulation of the extracorporeal circuit to avoid filter clotting and to assure the delivery of an effective dialysis dose.
- Different systemic anticoagulation modes are available, including systemic heparin anticoagulation. All systemic anticoagulation modes are associated with significant adverse effects. Most important are bleeding complications.
- For patients with HIT-II, at present, argatroban seems to be the mode of anticoagulation with lowest rate of adverse effects.
- Regional citrate anticoagulation is superior to systemic anticoagulation because it prolongs filter running time and reduces bleeding complications.
- Adverse effects of RCA are citrate accumulation and hypo-/hypercalcemia. Close and careful monitoring often allows the continuation of RCA with a reduced citrate dose.
- Patients at risk for adverse effects are those with hypoxemia, severe lactic acidosis, and shock. The majority of patients with liver failure can be treated with RCA successfully.
- Regional citrate anticoagulation can be recommended as the therapy of choice for the majority of critically ill patients requiring CRRT.

Research agenda

- There is need for prospective randomized trials to evaluate effects of different RRT techniques and anticoagulation modes on relevant outcome parameters, including mortality and recovery of renal function.
- Technological developments should target modifying surface structures of hemofilters and tubing systems to avoid activation of the coagulation system. This way, blood purification without any anticoagulation might become feasible.
- Modern technology should be used to develop an automated RCA with integrated sensors and closed-loop control and adjustment of citrate and calcium dose.

Conflicts of interest

TB, TS, TS, and DKM report no conflicts of interest.

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References

- *[1] Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med* 2015;41:1411–23.
- [2] Rabindranath KS, Adams J, MacLeod AM, et al. Intermittent versus continuous renal replacement therapy for acute renal failure in adults (Review). *Cochrane Libr* 2009;(1).
- [3] Srisawat N, Lawsin L, Uchino S, et al. Cost of acute renal replacement therapy in the intensive care unit: results from the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study. *Crit Care* 2010;14:R46.
- [4] van de Wetering, Westendorp RG, van der Hoeven JG. Heparin use in continuous renal replacement procedures: the struggle between filter coagulation and patient hemorrhage. *J Am Soc Nephrol* 1996;7:145–50.
- [5] Kutsogiannis DJ, Gibney RT, Stollery D, et al. Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. *Kidney Int* 2005;67:2361–7.
- [6] Monchi M, Berghmans D, Ledoux D, et al. Citrate vs. heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized study. *Intensive Care Med* 2004;30:260–5.
- [7] Betjes MG, van Oosterom D, van Agteren M, et al. Regional citrate versus heparin anticoagulation during venovenous hemofiltration in patients at low risk for bleeding: similar hemofilter survival but significantly less bleeding. *J Nephrol* 2007;20:602–8.
- [8] Oudemans-van Straaten HM, Bosman RJ, Koopmans M, et al. Citrate anticoagulation for continuous venovenous hemofiltration. *Crit Care Med* 2009;37:545–52.
- [9] Hetzel GR, Schmitz M, Wissing H, et al. Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial. *Nephrol Dial Transpl* 2011;26:232–9.
- [10] Schilder L, Nurmohamed SA, Bosch FH, et al. Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial. *Crit Care* 2014;18:472.
- [11] Stucker F, Ponte B, Tataw J, et al. Efficacy and safety of citrate-based anticoagulation compared to heparin in patients with acute kidney injury requiring continuous renal replacement therapy: a randomized controlled trial. *Crit Care* 2015;19:91.
- *[12] Liu C, Mao Z, Kang H, et al. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: a meta-analysis with trial sequential analysis of randomized controlled trials. *Crit Care* 2016;20:144.
- [13] Amiral J, Peynaud-Debayle E, Wolf M, et al. Generation of antibodies to heparin-PF4 complexes without thrombocytopenia in patients treated with unfractionated or low-molecular-weight heparin. *Am J Hematol* 1996;52:90–5.
- [14] Arepally GM. Heparin-induced thrombocytopenia. *Blood* 2017;129:2864–72.
- *[15] Gattas DJ, Rajbhandari D, Bradford C, et al. A randomized controlled trial of regional citrate versus regional heparin anticoagulation for continuous renal replacement therapy in critically ill adults. *Crit Care Med* 2015;43:1622–9.
- [16] Leithauser B, Schumacher J, Lendemans S, et al. Antithrombin attenuates microvascular leakage and leukocyte-endothelial interaction in response to endotoxin. *Semin Thromb Hemost* 2002;28(Suppl. 1):87–94.
- [17] Warren BL, Eid A, Singer P, et al. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001;286:1869–78.
- [18] Hirsh J. Anticoagulant therapy in venous thromboembolism. *Bailliere's Clin Haematol* 1990;3:685–92.
- [19] Tait RC, Walker ID, Perry DJ, et al. Prevalence of antithrombin deficiency in the healthy population. *Br J Haematol* 1994;87:106–12.
- [20] Thota R, Ganti AK, Subbiah S. Apparent heparin resistance in a patient with infective endocarditis secondary to elevated factor VIII levels. *J Thromb Thrombolysis* 2012;34:132–4.
- [21] Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001;119:645–94S.
- [22] Palm M, Mattsson C. Pharmacokinetics of heparin and low molecular weight heparin fragment (Fragmin) in rabbits with impaired renal or metabolic clearance. *Thromb Haemost* 1987;58:932–5.
- [23] Oudemans-van Straaten HM, van Schilfgaarde M, Molenaar PJ, et al. Hemostasis during low molecular weight heparin anticoagulation for continuous venovenous hemofiltration: a randomized cross-over trial comparing two hemofiltration rates. *Crit Care* 2009;13:R193.
- *[24] Oudemans-van Straaten HM, Wester JP, de Pont AC, et al. Anticoagulation strategies in continuous renal replacement therapy: can the choice be evidence based? *Intensive Care Med* 2006;32:188–202.
- [25] Joannidis M, Kountchev J, Rauchenzauner M, et al. Enoxaparin vs. unfractionated heparin for anticoagulation during continuous veno-venous hemofiltration: a randomized controlled crossover study. *Intensive Care Med* 2007;33:1571–9.
- [26] Reeves JH, Cumming AR, Gallagher L, et al. A controlled trial of low-molecular-weight heparin (dalteparin) versus unfractionated heparin as anticoagulant during continuous venovenous hemodialysis with filtration. *Crit Care Med* 1999;27:2224–8.
- [27] Koster A, Fischer KG, Harder S, et al. The direct thrombin inhibitor argatroban: a review of its use in patients with and without HIT. *Biol Targets Ther* 2007;1:105–12.

- [28] Di Nisio M, Middeldorp S, Buller HR. Direct thrombin inhibitors. *N Engl J Med* 2005;353:1028–40.
- [29] Link A, Girndt M, Selezan S, et al. Argatroban for anticoagulation in continuous renal replacement therapy. *Crit Care Med* 2009;37:105–10.
- [30] Fischer KG. Hirudin in renal insufficiency. *Semin Thromb Hemost* 2002;28:467–82.
- [31] Hein OV, von Heymann C, Diehl T, et al. Intermittent hirudin versus continuous heparin for anticoagulation in continuous renal replacement therapy. *Ren Fail* 2004;26:297–303.
- *[32] Treschan TA, Schaefer MS, Geib J, et al. Argatroban versus Lepirudin in critically ill patients (ALicia): a randomized controlled trial. *Crit Care* 2014;18:588.
- [33] Kern H, Ziemer S, Kox WJ. Bleeding after intermittent or continuous r-hirudin during CVVH. *Intensive Care Med* 1999;25:1311–4.
- [34] Lehner GF, Schopf M, Harler U, et al. Repeated premature hemofilter clotting during regional citrate anticoagulation as indicator of heparin induced thrombocytopenia. *Blood Purif* 2014;38:127–30.
- [35] Tolwani AJ, Wille KM. Anticoagulation for continuous renal replacement therapy. *Semin Dial* 2009;22:141–5.
- [36] Butterworth J, Lin YA, Prielipp R, et al. The pharmacokinetics and cardiovascular effects of a single intravenous dose of protamine in normal volunteers. *Anesth Analg* 2002;94:514–22 [Table of contents].
- [37] Bussey H, Francis JL, Heparin Consensus G. Heparin overview and issues. *Pharmacotherapy* 2004;24:103S–7S.
- [38] Carr JA, Silverman N. The heparin-protamine interaction. A review. *The J Cardiovasc Surg* 1999;40:659–66.
- [39] Morabito S, Guzzo I, Solazzo A, et al. Continuous renal replacement therapies: anticoagulation in the critically ill at high risk of bleeding. *J Nephrol* 2003;16:566–71.
- [40] van der Voort PH, Gerritsen RT, Kuiper MA, et al. Filter run time in CVVH: pre- versus post-dilution and nadroparin versus regional heparin-protamine anticoagulation. *Blood Purif* 2005;23:175–80.
- [41] Mehta RL, McDonald BR, Aguilar MM, et al. Regional citrate anticoagulation for continuous arteriovenous hemodialysis in critically ill patients. *Kidney Int* 1990;38:976–81.
- *[42] Morgera S, Scholle C, Melzer C, et al. A simple, safe and effective citrate anticoagulation protocol for the genius dialysis system in acute renal failure. *Nephron Clin Pract* 2004;98:c35–40.
- [43] Durao MS, Monte JC, Batista MC, et al. The use of regional citrate anticoagulation for continuous venovenous hemodiafiltration in acute kidney injury. *Crit Care Med* 2008;36:3024–9.
- [44] Morabito S, Pistolesi V, Tritapepe L, et al. Regional citrate anticoagulation for RRTs in critically ill patients with AKI. *Clin J Am Soc Nephrol* 2014;9:2173–88.
- [45] Faybik P, Hetz H, Mitterer G, et al. Regional citrate anticoagulation in patients with liver failure supported by a molecular adsorbent recirculating system. *Crit Care Med* 2011;39:273–9.
- [46] Ataullakhanov FI, Pohilko AV, Sinauridze EI, et al. Calcium threshold in human plasma clotting kinetics. *Thromb Res* 1994;75:383–94.
- [47] Broman M, Klarin B, Sandin K, et al. Simplified citrate anticoagulation for CRRT without calcium replacement. *ASAIO J* 2015;61:437–42.
- [48] Monchi M. Citrate pathophysiology and metabolism. *Transfus Apher Sci* 2017;56:28–30.
- [49] New AM, Nystrom EM, Frazee E, et al. Continuous renal replacement therapy: a potential source of calories in the critically ill. *Am J Clin Nutr* 2017;105:1559–63.
- *[50] Morgera S, Schneider M, Slowinski T, et al. A safe citrate anticoagulation protocol with variable treatment efficacy and excellent control of the acid-base status. *Crit Care Med* 2009;37:2018–24.
- [51] Kalb R, Kram R, Morgera S, et al. Regional citrate anticoagulation for high volume continuous venovenous hemodialysis in surgical patients with high bleeding risk. *Ther Apher Dial* 2013;17:202–12.
- [52] Schwarzler P, Kuhn SO, Stracke S, et al. Discrepant post filter ionized calcium concentrations by common blood gas analyzers in CRRT using regional citrate anticoagulation. *Crit Care* 2015;19:321.
- [53] Kindgen-Milles D, Ostermann M, Slowinski T. Ionized calcium measurements during regional citrate anticoagulation in CRRT: we need better blood gas analyzers. *Crit Care* 2015;19:427.
- *[54] Bai M, Zhou M, He L, et al. Citrate versus heparin anticoagulation for continuous renal replacement therapy: an updated meta-analysis of RCTs. *Intensive Care Med* 2015;41:2098–110.
- [55] Park JS, Kim GH, Kang CM, et al. Regional anticoagulation with citrate is superior to systemic anticoagulation with heparin in critically ill patients undergoing continuous venovenous hemodiafiltration. *Korean J Intern Med* 2011;26:68–75.
- *[56] Slowinski T, Morgera S, Joannidis M, et al. Safety and efficacy of regional citrate anticoagulation in continuous venovenous hemodialysis in the presence of liver failure: the Liver Citrate Anticoagulation Threshold (L-CAT) observational study. *Crit Care* 2015;19:349.
- [57] Oudemans-van Straaten HM. Citrate anticoagulation for continuous renal replacement therapy in the critically ill. *Blood Purif* 2010;29:191–6.
- [58] Morabito S, Pistolesi V, Tritapepe L, et al. Regional citrate anticoagulation in cardiac surgery patients at high risk of bleeding: a continuous veno-venous hemofiltration protocol with a low concentration citrate solution. *Crit Care* 2012;16:R111.
- [59] Wu MY, Hsu YH, Bai CH, et al. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy: a meta-analysis of randomized controlled trials. *Am J Kidney Dis* 2012;59:810–8.
- [60] Lyndon WD, Wille KM, Tolwani AJ. Solute clearance in CRRT: prescribed dose versus actual delivered dose. *Nephrol Dial Transpl* 2012;27:952–6.
- [61] Ronco C, Ricci Z. Renal replacement therapies: physiological review. *Intensive Care Med* 2008;34:2139–46.
- [62] Shum HP, Chan KC, Yan WW. Regional citrate anticoagulation in predilution continuous venovenous hemofiltration using prismatic citrate 10/2 solution. *Ther Apher Dial* 2012;16:81–6.
- [63] Anstey C, Campbell V, Richardson A. A comparison between two dilute citrate solutions (15 vs. 18 mmol/l) in continuous renal replacement therapy: the base excess and renal substitution solution study. *Blood Purif* 2016;42:194–201.
- [64] Jacobs R, Honore PM, Hendrickx I, et al. Regional citrate anticoagulation for continuous renal replacement therapy: all citrates are not created equal! *Blood Purif* 2016;42:219–20.

- [65] Klingele M, Seiler S, Poppleton A, et al. The gap between calculated and actual calcium substitution during citrate anticoagulation in an immobilised patient on renal replacement therapy reflects the extent of bone loss – a case report. *BMC Nephrol* 2014;15:163.
- [66] Raimundo M, Crichton S, Lei K, et al. Maintaining normal levels of ionized calcium during citrate-based renal replacement therapy is associated with stable parathyroid hormone levels. *Nephron Clin Pract* 2013;124:124–31.
- [67] Schultheiss C, Saugel B, Phillip V, et al. Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study. *Crit Care* 2012;16:R162.
- [68] Khadzhynov D, Slowinski T, Lieker I, et al. Evaluation of acid-base control, electrolyte balance, and filter patency of a Prismaflexbased regional citrate anticoagulation protocol for pre-dilution continuous veno-venous hemodiafiltration. *Clin Nephrol* 2014;81:320–30.
- [69] Link A, Klingele M, Speer T, et al. Total-to-ionized calcium ratio predicts mortality in continuous renal replacement therapy with citrate anticoagulation in critically ill patients. *Crit Care* 2012;16:R97.
- [70] Kramer L, Bauer E, Joukhadar C, et al. Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients. *Crit Care Med* 2003;31:2450–5.
- [71] Hetzel GR, Taskaya G, Sucker C, et al. Citrate plasma levels in patients under regional anticoagulation in continuous venovenous hemofiltration. *Am J Kidney Dis* 2006;48:806–11.
- [72] Meier-Kriesche HU, Gitomer J, Finkel K, et al. Increased total to ionized calcium ratio during continuous venovenous hemodialysis with regional citrate anticoagulation. *Crit Care Med* 2001;29:748–52.
- [73] Balogun RA, Turgut F, Caldwell S, et al. Regional citrate anticoagulation in critically ill patients with liver and kidney failure. *J Nephrol* 2012;25:113–9.
- *[74] Khadzhynov D, Schelter C, Lieker I, et al. Incidence and outcome of metabolic disarrangements consistent with citrate accumulation in critically ill patients undergoing continuous venovenous hemodialysis with regional citrate anticoagulation. *J Crit Care* 2014;29:265–71.
- [75] Saner FH, Treckmann JW, Geis A, et al. Efficacy and safety of regional citrate anticoagulation in liver transplant patients requiring post-operative renal replacement therapy. *Nephrol Dial Transpl* 2012;27:1651–7.
- [76] Senturk E, Esen F, Ozcan PE, et al. The treatment of acute liver failure with fractionated plasma separation and adsorption system: experience in 85 applications. *J Clin Apher* 2010;25:195–201.
- [77] Gong D, Ji D, Xu B, et al. Regional citrate anticoagulation in critically ill patients during continuous blood purification. *Chin Med J* 2003;116(3):360–3.
- [78] Gutierrez-Bernays D, Ostwald M, Anstey C, et al. Transition from heparin to citrate anticoagulation for continuous renal replacement therapy: safety, efficiency, and cost. *Ther Apher Dial* 2016;20:53–9.