



Continuous Renal Replacement Therapy: A Review

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ABSTRACT

Kidney is an important organ to maintain hemodynamic stability inside the human body. In patient with acute kidney injury (AKI) there was a decreased kidney function that could interfere hemodynamic stability which can lead to multi organ failure even death. Around 5-10% patients with AKI required renal replacement therapy (RRT) to support their decreased renal function. Continuous renal replacement therapy (CRRT) is one of RRT modality that commonly used for patients with AKI who are hemodynamically unstable or in critically ill conditions. CRRT could divided into 4 mode, slow continuous ultrafiltration (SCUF), continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD) and continuous veno-venous hemodiafiltration (CVVHDF). CRRT used based on renal and nonrenal indication. Several studies are still trying to prove nonrenal indication of RRT, to ascertain whether CRRT could be used as therapy effectively. Therefore the indication, the mechanism and the comparison of renal replacement therapy are very important to be understood.

Keywords. Acute Kidney Injury, Continuous Renal Replacement Therapy, Hemodialysis



Introduction

The incidence of Acute kidney injury (AKI) was estimated about 60% in critically ill patients. The mortality rates for ICU patients with AKI was around 20% to 50%, particularly the mortality rates of patients with severe AKI who need kidney replacement therapy was around 40% to 80%. The mortality rates in patients who require renal replacement therapy is related to low mean arterial blood pressure (MAP) and arterial pH.^{1,2}

In 2018, intermittent hemodialysis (IHD) was the most common type of renal replacement therapy provide in Indonesia (98%), where the other 2% using Continuous Ambulatory Peritoneal Dialysis (CAPD). While the number of continuous kidney replacement therapy (CRRT) provide is no longer obtained, in 2014 it was only used in one case.^{3,4}

CRRT is an important treatment for critically ill patients with AKI. CRRT is often used to manage solutes, acid base, and volume in critically ill patients and it is estimated that ~ 5% of patients in ICU require CRRT. Various problems about the application of CRRT has become the current research topic, including the optimal time for CRRT initiation and termination, selection of CRRT modalities, and the role of CRRT in sepsis.^{5,6}

Various undesirable conditions could occur in the implementation of CRRT. Vascular access with large catheters could lead to visceral trauma. Electrolyte disturbance, hypothermia and hypotension could occur during the treatment using CRRT.⁷

With this article, the author hopes to provide an understanding of the management of the RRT especially by using the CRRT modality, as well as various considerations in the practice of this therapy to reduce mortality and complications possibility.⁷

RRT Definition

Renal replacement therapy consists of several modalities that used to diminish metabolic waste products and excess fluids from the patient through the bloodstream and how this therapy works replicate the kidney's physiology. Modern types of the therapy have used extracorporeal circuits. Generally, the principle of RRT divided into four processes: ultrafiltration, hemodialysis, hemofiltration, and hemodiafiltration.⁷



RRT Classification

Various types of renal replacement therapy, include CAPD and extracorporeal therapy such as IHD and CRRT, could be applied for the treatment of AKI. IHD and CRRT use similar extracorporeal blood circuits. The main thing that distinguishes both is related to the duration of the therapy, which occurs because the differences in ultrafiltration and clearance rate.^{8,9}

Continuous Ambulatory Peritoneal Dialysis

Peritoneal dialysis is the first developed renal replacement therapy. The application of peritoneal dialysis gives patients more freedom and flexibility. This process can be applied with manual method (Continuous Ambulatory Peritoneal Dialysis (CAPD)) or by utilizing automatic machine (Automated Peritoneal Dialysis (APD)).^{9,10}

Intermittent Hemodialysis

IHD is operationalized by the insertion of venous catheters to dispose low molecular weight particles through the diffusion and osmosis mechanism. The implementation of IHD requires relatively short period of time (3 to 5 hours). IHD is the fastest therapy to efficiently control electrolytes and acids / bases compared to the other modalities, a lower cost than CRRT and take an anticoagulation at a lower dose.^{8,9}

Continuous renal replacement therapy

CRRT was defined as an extracorporeal method for purifying blood over a long period of time, replacing the kidney function. Previously, CRRT was implemented using blood pressure to create a continuous arterial venous hemofiltration (CAVH) flow and transmembrane pressure gradient. Currently, the usage of venous lumen is assisted by an extracorporeal pump to reach transmembrane pressure gradient. CRRT has a more gradual fluid removal and clearance process with a longer duration.^{8,9}

Prolonged intermittent renal replacement therapy

PIRRT is the hybrid form of IHD and CRRT. It is characterized by treatment duration which generally ranges from 8 to 16 hours. PIRRT has a lower clearance and ultrafiltration rate compared to IHD but faster than CRRT. PIRRT usually operationalized by a similar equipment for IHD with a lower blood flow and dialysate rates.¹¹



RRT Modalities Consideration

Hemodynamic state is the most important terms for the selection of RRT modality. Continuous type of RRT is recommended in the state of body could not well tolerated on fluid balance shift and metabolic fluctuations. However, several randomized controlled trials have not shown the superiority of CRRT over IHD or PIRRT in reducing the mortality rate and optimizing the recovery of renal function.^{5,8}

There are two particular situations where CRRT is favored as a renal replacement modality. First, in patients with intracranial hypertension and/or head injuries. Then, the second is fluid removal and achieving fluid balance targets in patients with excess fluid, including patients with congestive heart failure or acute pulmonary edema. CRRT provides slow and continuous fluid drainage at least to adjust the fluid intake.^{5,8}

The Principles of CRRT

Several physical and chemical principles are involved in different CRRT modalities, which are responsible for removing toxins and water. The main principles of CRRT are ultrafiltration, diffusion, convection, and adsorption.⁹

Ultrafiltration

Ultrafiltration is the process of 'squeezing' the fluid in plasma through semi permeable membrane by utilizing the hydrostatic pressure gradient. Blood is pumped under positive pressure through semipermeable membrane, producing positive hydrostatic pressure.^{9,12}

Diffusion

Diffusion or dialysis is the transfer of solutes from greater concentration to lower concentration area through semipermeable membrane. The process conducted by flowing the electrolyte solution (dialysate) in the opposite direction to the bloodstream, generates diffusion process across the semipermeable membrane.^{9,12}

Convection

Convection occurs when the flow of large amounts of solute through the semipermeable membrane due to positive transmembrane pressure. This pressure is attained from the ultrafiltration stream. Solvents that pass through the membrane will carried away the solutes as long as membrane porosity allows the solutes to be filtered from the blood.^{9,13}

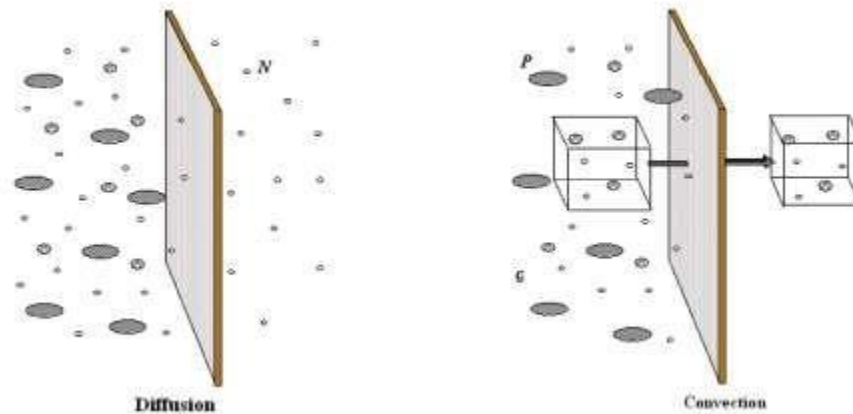


Figure 1. Diffusion and convection process scheme¹³

Adsorption

Adsorption process allows high molecular weight molecules attached to the synthetic membranes that utilized as the semipermeable membranes, but the capacity of filter adsorption tends to be full after a few hours of therapy.⁹

Mode of CRRT

Various mode of CRRT have been developed in recent years. When CRRT is utilized for fluid removal alone by applying the ultrafiltration solely, the technique known as slow continuous ultrafiltration (SCUF). Another mode of CRRT, such as continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), or hemodiafiltration (CVVHDF), applied for both solute clearance and volume reduction.⁸

In CVVH, the blood passes through semipermeable membrane by applying the ultrafiltration rate. The solute clearance achieved by convection process, and high ultrafiltration rate is needed to achieve sufficient clearance. Excessive ultrafiltration volume will be replaced by replacement solution. The replacement solution could be inserted before or after the hemofilter (pre- or postfilter). The prefilter replacement is utilized to decrease hemoconcentration, therefore the risk of clots and occlusion due to high ultrafiltration rates could be reduced.⁸

However, decreased hemoconcentration (hemodilution) due to prefilter replacements could inherit the effectiveness of solutes removal. Meanwhile, postfilter replacement is applied to maintain electrolytes serum that are wasted in the filtration process.⁸



Dialysate is a feature that utilized in CVVHD. The dialysate will be fused through the outer surface of the dialysis membrane, thereby solutes will get out of the blood into the dialysate as the impact of concentration gradients. Transport of these solutes achieved by diffusion process. The ultrafiltration rate applied is relatively low compared to CVVH, allowing fluid balance without using the replacement solution. Whereas, CVVHDF is a hybrid that combines CVVHD dialysate flow with a high ultrafiltration rate and the applied of replacement solution as in CVVH.⁸

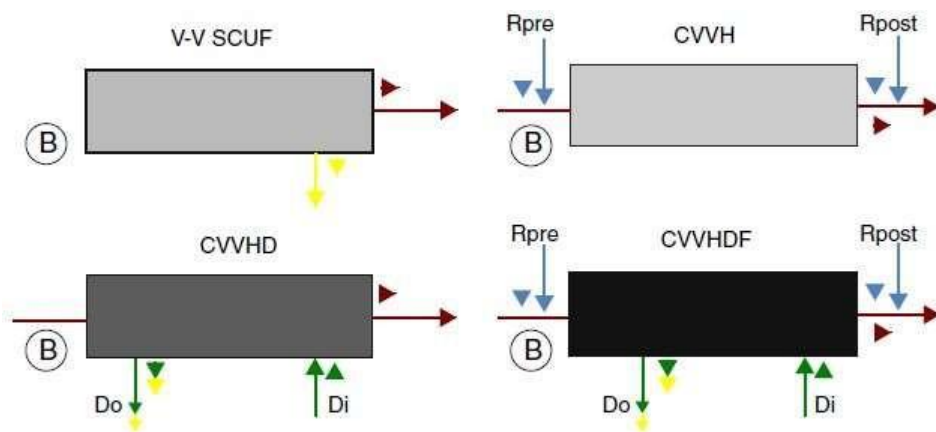


Figure 2. CRRT mode scheme. **Red arrows:** Veno-venous direction of blood flow **Blue arrow:** Replacement solution flow before (pre) or after (post) enters the blood circuit. **Green arrow:** Dialysate flow in (In) and out (Do). **Yellow arrows:** Effluent. **B:** blood pump, **D:** Dialysate, **R:** Replacement solution; **SCUF:** slow continuous ultrafiltration, **CVVH:** continuous veno-venous hemofiltration, **CVVHD:** continuous veno-venous hemodialysis, **CVVHDF:** continuous veno-venous hemodiafiltration.⁴

CRRT Indications

Renal Indications

The decision to start RRT is usually based on clinical signs such as excess volume and imbalance of molecules in the blood. However, the best approach to evaluating RRT initiation should be based on clinical symptoms, including the presence and degree of other organ dysfunction, rather than the biochemical markings of uremia. This approach is important for early intervention because it could improve the ability to control fluids and solutes, as well as stimulate the recovery of the kidney.^{5,14}

The benefits of CRRT depend on the balance between the burden currently on the kidneys and the ability of the kidneys to control the fluid and metabolic load. Thus, the



initiation of CRRT must be driven by the ability of the kidneys to meet the needs that are being replaced during therapy. Another important thing to note when applying early CRRT is that it could delay kidney recovery due to hemodynamic instability, bacteremia or sepsis.⁵

Table 1 Relative and absolute indications in CRRT⁵

Indication	Absolut	Relatif
Metabolic disorder	BUN>100 mg/dL	BUN >76 mg/dL
	Hyperkalemia > 6 mEq/L with abnormal ECG	Hyperkalemia >6 mEq/L
	Hypermagnesemia > 8 mEq/L with anuria and absent deep tendon reflexes	Hypermagnesemia > 8mEq/L
		Dysnatremia
Asidosis	pH <7.15	pH > 7.15
	Lactic acidosis related to metformin use	
Oliguria/Anuria		AKIN grade 1,2 or 3
<i>Fluid Overload</i>	Diuretic resistant	Diuretic sensitive

Excessive volume in AKI occurs due to impaired renal ability to maintain fluid balance when getting IV fluids, blood products, and / or other drugs needed for resuscitation and supportive care of critically ill patients and could occur even if the patient does not experience oliguria or anuria. There is no prospective data that sets a specific threshold for RRT. In the selection of RRT modalities, CRRT has several advantages over IHD. CRRT continuously and slowly releases fluid that is at least adjust the fluid intake, while the target for fluid removal in IHD must be achieved within 3 to 4 hours which may lead to temporary intravascular underfilling, intradialytic hypotension and recurrent kidney injury, thereby increasing the risk for kidney function could not be restored.^{5,8}

Metabolic acidosis in AKI develops due to reduced bicarbonate regeneration and failure to excrete ammonium ions. The use of CRRT is recommended in patients with severe metabolic acidosis that is not respond to medical therapy. In general, the standard limit for CRRT indications by pH level is less than 7.10 or 7.15. In most cases, CRRT could correct abnormal blood pH within 24-48 hours. RRT initiation may be needed earlier in patients with acute lung injury, because the severe acidemia results from a combination of metabolic and respiratory acidosis.^{5,15}



Various electrolyte abnormalities associated with AKI. Severe hyperkalemia can be life threatening because of the risk of bradycardia and even asystole due to disruption of heart conduction. Emergency intermittent hemodialysis is the treatment of choice for severe hyperkalemia because it could provide higher clearance than CRRT in shorter duration. CRRT could be applied for hyperkalemia in patients who cannot tolerate IHD or if hyperkalemia is not life-threatening.^{5,14,15}

Other electrolyte abnormalities, such as severe hyponatremia or hypernatremia and severe hyperphosphatemia, can accompany AKI and should be deciding as indication for RRT initiation. In patients with severe and chronic sodium disorders, rapid correction of hyponatremia could lead to osmotic demyelination or cerebral edema, so the target correction rate should not exceed 8 mmol / L within 24 hours. CRRT allows the slower and more controlled correction of sodium concentrations needed to prevent neurological sequelae due to osmotic demyelination.^{5,15}

The use of CRRT is recommended as a management of uremic syndrome with obvious symptoms, such as encephalopathy and pericarditis. Although this condition is a complication of AKI that occurs relatively late, early CRRT administration based on blood urea nitrogen (BUN) levels <60 mg / dL in patients with acute kidney injury has a better survival rate than in patients with BUN levels > 60 mg/dL.^{5,8}

Nonrenal Indication

The implementation of CRRT has been investigated for its effectiveness for a various conditions which could be applied as the indication for CRRT. Early CRRT implementation is known to prevent organ failure and further complications due to septic shock. Some inflammatory mediators such as cytokines can be removed by CVVH or CVVHDF methods. The adsorption process that occurs in these two methods has been known to have a significant role in reducing plasma cytokines especially in the first hour of CRRT administration.¹⁶⁻¹⁸

Polymethylmethacrylate membrane hemofilter, which has a very good adsorption capacity, in continuous hemodiafiltration (PMMA-CHDF) has been carried out for the treatment of severe sepsis or septic shock. PMMA-CHDF could effectively eliminate various pro-inflammatory cytokines such as tumor necrotizing factor (TNF), Interleukin-6 (IL-6) and IL-8 from the blood, which allows faster recovery. The utilization of CRRT as adjunctive therapy for sepsis patients with AKI remains controversial, but current data do not recommend the use of CRRT in septic shock patients without AKI.¹⁶⁻¹⁸



Hypercytokinemia has been reported to play an important role in pathophysiology of severe acute pancreatitis and acute respiratory distress syndrome (ARDS). The use of PMMA-CHDF has been investigated to eliminate cytokines as a treatment in severe acute pancreatitis. The mortality rate among patients who received PMMA-CHDF was significantly lower (6.1%) compared to controls (25%). Therefore, this technique is recommended for use in patients with severe acute pancreatitis.^{5,19}

Another multicenter study assessing the efficacy of using PMMA-CHDF in ARDS patients. The average survival rate of patients is 75.6%, with the highest survival rate reaching 95%. Thereby, PMMA-CHDF could utilize as the treatment for ARDS patients.^{5,20}

Dosing CRRT

The CRRT dose is determined based on the level of effluent flow, i.e. total of dialysate flow and ultrafiltration flow. Previously a higher effluent flow rate was hypothesized to be related with an increase of survival rate, but this relationship was disputed in two multicenter randomized control trial studies. The recommended target dose is 20-25 mL / kg per hour. To achieve this target dose, presently the recommended dose of the effluent dose is 25 to 30 ml / kg per hour to overcome the possibility of CRRT interruption due to circuit failure, fluid bag replacement or other procedures requiring CRRT termination. In addition, it is also important to know that the CRRT dose is a dynamic measure that may need to be higher over a certain period of time and adjusted for the patient's clinical needs.^{6,21}

Procedures in Providing CRRT

Vascular Access

Generally, vascular access for CRRT utilization could performed by placing a double lumen catheter into the internal jugular vein, femoral vein or subclavian vein. In adults, the design and position of the catheter must be adequate to maintain a blood flow rate of 200 to 300 mL / minute. Right internal jugular venous cannulation is generally preferred than the left, given the strait path to the right atrium. Femoral catheters are generally associated with higher levels of bacteremia than internal jugular catheters. Subclavian cannulation is generally avoided because of the higher risk of insertion complications and the risk of venous stenosis.⁸

Anticoagulants



Clotting on the extracorporeal circuit is the most common complication during CRRT. Several systemic and regional anticoagulant therapies for CRRT are currently available. Unfractionated heparin (UFH) is the most widely used anticoagulant worldwide. Nevertheless, all systemic therapies are accompanied by significant side effects, especially heparin-induced bleeding and thrombocytopenia (HIT-II). Regional citrate anticoagulation (RCA) is a safer and more effective technique compared to systemic anticoagulation. RCA extends filter life, reduces bleeding complications, enables effective control of acid-base and reduces side effects such as HIT-II. Currently, RCA is recommended as the treatment of choice as anticoagulant for critically ill patients who need CRRT.^{8,22,23}

Drug Dosage

Drug dosage regulation during CRRT is a challenge because several factors that could interfere, including nonrenal clearance, remaining kidney function and changes in volume distribution and protein binding. Errors in drug dosages could cause toxicity either because of reduced doses or due to therapy failure caused by lack of doses. Especially in administering antibiotic drugs for patients with AKI accompanied by sepsis.⁸

Nutrition Management

Patients with AKI who undergo CRRT usually experience high protein catabolic levels. In addition, CRRT causes the loss of amino acids and water-soluble micronutrients such as vitamins and other micronutrients. Calorie intake that needs to be given around 35 kcal / kg per day, with a target protein intake of 1.5 g / kg per day accompanied by water-soluble vitamin supplements.²⁴

Complications

Hemorrhagic and Catheter Related

Complications from CRRT have been largely preventable and have drastically reduced in the last decade. Insertion of a large central venous catheter could lead to vascular or visceral injury. The injury could lead to bleeding, pneumothorax, hemothorax, infection or thrombosis. The implementation of ultrasonography in catheter insertion significantly reduces this risk. In addition, hemorrhagic risk has been reduced by the usage of regional anticoagulants such as RCA.^{8,25}

Hemodynamic



Implementation of CRRT could lead to hemodynamic disorders, especially hypotension. The hypotension occurs due to hypovolemia, myocardial dysfunction, cardiac arrhythmias or changes in vascular resistance. Hypovolemia occurs if the speed and/or amount of fluid discharged is not replaced properly by the volume of blood given to the patient, resulting in intravascular underfilling. Meanwhile, myocardial contractility is influenced by the buffer solution usage, therefore the selection of the right buffer solution is needed. Bicarbonate solution is preferred over acetate because it has better hemodynamic tolerance.²⁵

Metabolic Disorder

CRRT utilization could also lead to metabolic complications, especially related to the use of RCA. RCA could cause two different situations: citrate accumulation and excess citrate, which cause metabolic acidosis and metabolic alkalosis. When citrate is not metabolized adequately, it would act as a weak acid. Its accumulation induces metabolic acidosis with a normal chloride and lactate concentration. In this condition, chloride and lactate levels need to be assessed to rule out the possibility both causing the acidosis. Meanwhile, metabolic alkalosis is not directly related to the production of CO₂ and bicarbonate from citrate metabolism through the Krebs cycle. According to the Stewart model, an increase in bicarbonate concentration actually is a consequence and not a cause of metabolic alkalosis.²⁵

Electrolyte Imbalance

Electrolyte imbalance is a frequent CRRT complication. Giving dialysate or replacement solution with inadequate potassium concentrations could lead to iatrogenic hypokalemia. The implementation of RCA could also create the electrolyte imbalance in patient's body. The combination of cation by citrate causes hypocalcemia and hypomagnesemia if improper replacement is given. However, automatic pumps on CRRT could reduce metabolic disorders caused by RCA and calcium supplementation.²⁵

Hypothermia

Hypothermia in CRRT occurs because the dialysate and replacement fluid applied is usually not warmed. Loss of heat during CRRT action causes vasoconstriction and increases hemodynamic stability but could mask the emergence of fever. If more heat loss occurs, significant hypothermia could arise and requires aggressive external heating. Currently, this complication is more controlled.^{8,25}



Substance removal

Removal of substances that are not actually desirable during therapy remains a major problem with CRRT administration. Especially antibiotic therapy, micronutrients and vitamins which the intake must be adjusted during CRRT administration. Monitoring the dose of the drug is very important in the administering of antibiotics, because the concentration of this drug will determine the effectiveness of bactericidal and bacteriostatic. Numerous of the patients indicated CRRT also has sepsis, therefore the right antibiotic dose is very important.²⁵

Hypersensitivity

Finally, the risk of CRRT complications is also related to the utilization of extracorporeal circuit. Hypersensitivity reactions could arise due to the activation of cytokines that cause immediate allergic reactions or delayed allergic reactions. In addition, air embolization may arise when the catheter is installed or removed and any time during the treatment if the air enters the circuit beyond the air detector limit.⁸

Termination of CRRT

There are no specific criteria for terminating CRRT after the recovery of kidney function or the transition to other RRT modalities. The initial manifestation of kidney function recovery is an increase in urine output. In an observational study urine output > 400 mL / day without diuretic therapy is the predictor of success in terminating CRRT. In another study, urinalysis was performed when urine output > 750 mL / day. The RRT is continued if the creatinine clearance is < 12 mL / minute and stopped if > 20 mL / min, and a decision is given to the doctor's judgement if the creatinine clearance is measured between 12 to 20 mL / minute. Although this strategy could inform clinical decision making, appropriate criteria for stopping RRT are still unavailable.

Conclusion

CRRT has become the main management of AKI in critically ill patients. Although the use of CRRT can facilitate the management in patient with the hemodynamic instability, available data do not indicate that the implementation of CRRT provides improved survival or recovery of kidney function compared to other alternatives. CRRT could applied to patient based on renal or nonrenal indications, and more study still needed to explore another



indication and usability of CRRT. Based on large and multicenter studies, the addition of solute clearance with effluent flow > 20 to 25 mL / kg per hour is not related to the increase in results obtained. Recently, the complication of CRRT has been reduced by the application of RCA, modern CRRT device and more applicable regulation of CRRT. Thus, the role of CRRT needs to be considered in achieving overall management targets to not only maintain patient life, but also as a promising treatment.

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