Volume Management in Continuous Renal Replacement Therapy

Josée Bouchard and Ravindra L. Mehta
Department of Medicine, University of California San Diego, San Diego, California

ABSTRACT

Volume management is an integral component of the care of critically ill patients to maintain hemodynamic stability and optimize organ function. The dynamic nature of critical illness often necessitates volume resuscitation and contributes to fluid overload particularly in the presence of altered renal function. Diuretics are commonly used as an initial therapy to increase urine output; however they have limited effectiveness due to underlying acute kidney injury and other factors contributing to diuretic resistance. Continuous renal replacement techniques (CRRT) are often required for volume management. In this setting, successful volume management depends on an accurate assessment of fluid status, an adequate comprehension of the principles of fluid management with ultrafiltration, and clear treatment goals. Complications related to excessive ultrafiltration can occur and have serious consequences. A careful monitoring of fluid balance is therefore essential for all patients. This review provides an overview of the appropriate assessment and management of volume status in critically ill patients and its management with CRRT to optimize organ function and prevent complications of fluid overload.

In critically ill patients, acute kidney injury (AKI) is common and these patients often suffer from concomitant fluid overload (FO). In a recent international survey of critically ill subjects with moderate and severe AKI, FO was present in 36.7% while oliguria and anuria occurred in 70.2% of patients (1). Several factors influence fluid balance, including hemodynamic, pulmonary, and renal parameters. Once kidney failure occurs, renal replacement is initiated for volume overload when management with fluid and diuretics is insufficient. In this setting, successful volume management depends on an accurate assessment of fluid status, adequate comprehension of the principles of ultrafiltration and clear treatment goals. These concepts are discussed further in this article.

Physiology of Fluid Status in Critically Ill Patients with Renal Impairment

Fluid balance can be simply defined as the difference between intake and output, although several parameters influence volume status. Fluid balance requires consideration of the total body water (TBW), its compartmental distribution and plasma composition. Intensive care unit (ICU) patients have a broad spectrum of physiological abnormalities that can contribute to impaired fluid regulation. For instance, increased vascular permeability is commonly encountered in sepsis and leads to albumin leakage into the interstitial compartment, reducing oncotic pressure and contributing to a decreased intravascular but expanded interstitial compartment. Fluid resuscitation further compounds this problem and, depending on the composition of the resuscitative fluids, acid-base and electrolyte abnormalities such as hypernatremia can ensue.

When kidney function is additionally compromised in AKI, urine output is variable, ranging from oliguria to normal or even above normal levels (2). Additionally, AKI is often superimposed on preexisting chronic kidney disease and often complicates other comorbidities. In acute tubular necrosis (ATN), tubular damage impairs the ability to reabsorb sodium and water, maintaining urine output. Urea osmotic diuresis and volume expansion may further contribute to preserve diuresis, as in chronic kidney disease (3,4).

Fluid balance is also adjusted by physicians in response to changes in hemodynamic and respiratory conditions. For example, patients in septic shock often receive large amounts of fluid to maintain hemodynamic status. In this setting, hypervolemia is frequent and seems to be independently linked with mortality (5). The net result of the disordered physiology is volume retention with altered compartmental distribution. A key aspect is that the condition is not static and is subject to evolution as the underlying illness changes. As vascular integrity returns, fluid shifts to the interstitium are minimized and intravascular volume overload is more manifest. Return of renal function permits a readjustment and return to normalcy.

Address correspondence to: Ravindra L. Mehta, MD, FACP, FASN, UCSD Medical Center, 200 W Arbor Drive, MC 8342, San Diego, CA 92103, Tel.: 619-543-7310, Fax: 619-543-7420, or e-mail: rmehta@ucsd.edu.

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Assessment and Optimization of Fluid Status in Critically Ill Patients with AKI

Assessment of fluid balance in critically ill patients should include the state of hydration (total body water), the compartmental distribution, and the composition (e.g., osmotic content). Several tools can be used, with various degrees of precision. In a single center study of 68 critically ill patients, where circulating blood volume (CBV) was assessed with [^{125}I] serum albumin, no single hemodynamic measure nor the spot urinary sodium concentration were good predictors of CBV (6). In addition, in contrast to common belief, only extreme values of central venous pressure (CVP $<$ 2 mmHg) seemed to predict hypovolemia. The authors justified this result by mentioning that considerable variation can occur in CVP measurement, especially in mechanically ventilated patients. Two small studies have shown contradictory results regarding the accuracy of external jugular or upper limb vein measurement as a predictor of CVP (7,8). In the study showing a poor correlation between the two parameters, serial peripheral measurements of the upper limb vein could still be useful to determine volume status and guide fluid therapy in critically ill patients (8). Osmotic content can be readily evaluated with serum and urine osmolality and osmolar gap measurements; however it is more difficult to ascertain compartmental volume. Bioimpedance techniques have been used in critically ill patients with variable results (9,10).

Currently there are no specific standards for optimal volume levels in critically ill patients. Based on mortality rates from patients with severe sepsis or septic shock treated before admission to the intensive care unit, fluid and pressor administration should target a mean blood pressure $>$ 65 mmHg, central venous pressure $>$ 8–12 mmHg, urine output $\geq$0.5 ml/kg/hour, and central venous oxygen saturation (SvO_2) $\geq$70% (11,12). However, these studies did not focus on renal outcomes and the resuscitative strategies may not be applicable in critically ill patients with AKI. In ischemic ATN, autoregulation is lost and renal blood flow becomes linearly pressure-dependent. Subsequent hypotension and hypoperfusion can cause new kidney lesions (13,14). Therefore, maintaining adequate renal perfusion pressure is even more critical in ATN; however there are no definite measures to determine the optimal fluid and vasopressor therapies.

Complications Related to Fluid Overload

Over the last decade, there have been an increasing number of publications regarding the negative influence of fluid overload on morbidity and mortality in different clinical conditions. Fluid overload has been shown to increase complications in acute lung injury, acute respiratory distress syndrome (ARDS), acute pulmonary edema, and following surgery (15–19). In a randomized clinical trial of 1000 patients suffering from ARDS, a restrictive strategy of fluid management increased the number of ventilator-free days compared to a liberal strategy (14.6 $\pm$ 0.5 vs. 12.1 $\pm$ 0.5, $p < 0.001$). In a randomized trial of 172 patients undergoing colorectal resection, fluid excess increased cardiopulmonary (24% vs. 7%; $p = 0.007$) and tissue-healing complications (31% vs. 16%; $p = 0.04$) (15). Fluid overload may also contribute to gut and cerebral edema (20). In pediatric patients, fluid overload at dialysis initiation increased mortality in several observational studies (21–24). In the only prospective study so far, the percentage of fluid overload adjusted for body weight (%FO/BW) at dialysis initiation was significantly lower in survivors vs. nonsurvivors, even after adjustment for severity of illness (14.2 $\pm$ 15.9% vs. 25.4 $\pm$ 32.9%; $p < 0.03$). Cumulative fluid balance is also associated with increased mortality in septic patients, the odds ratio being 1.1 for every liter increase, despite adjustments for severity of illness (5).

In summary, optimal fluid and hemodynamic parameters are unknown for the management of AKI. Randomized data in other critically ill populations show that extra volume is probably detrimental. Fluid depletion should be corrected but extra volume should probably be avoided. Fluid management strategies in ICU patients should recognize not only the pathophysiologic events related to the underlying illness (e.g., sepsis) but also the effects of process of care, such as fluid resuscitation and the dynamicity of the process requiring alterations in the therapeutic strategy.

Volume Management with Continuous Renal Replacement Therapy

When considering optimal fluid management with any renal replacement therapy (RRT), three key factors come into play; when to initiate the therapy, how to prescribe and deliver the therapy and how to monitor for efficacy and avoid complications. The timing of initiation of RRT continues to be a matter of debate, since few studies have addressed this issue (25,26). In addition, these studies did not look at the timing of initiation with respect to fluid status. Observational studies in pediatric populations might favor earlier initiation of RRT in situations where %FO/BW is very high (21–24). However, randomized controlled trials are required to confirm these findings.

In order to prescribe and deliver the right amount of ultrafiltration (UF) in a critically ill patient, three aspects of knowledge are required: an adequate understanding of the process of ultrafiltration and the unique aspects of continuous renal replacement therapy (CRRT), the underlying clinical condition, and a close monitoring of cardiovascular response following UF. RRT techniques are designed to remove fluid from the intravascular compartment. Hemodynamic stability is then dependent on refilling of the intravascular volume from the interstitial compartment. Consequently the plasma refill rate (PRR) limits fluid removal. Due to limited time, rapid fluid shifts are inherent with intermittent hemodialysis (IHD) and increase the propensity for hemodynamic instability while CRRT permits a slower and more constant fluid removal that can be targeted to match the

PRR. In addition to fluid removal, the continuous nature and use of replacement solutions in CRRT permits its adaptation for fluid regulation.

In CRRT, the total ultrafiltrate is the amount of plasma water removed, total replacement is the amount of fluid delivered to the patient and net ultrafiltrate is the difference between total ultrafiltrate and total replacement. Replacement fluid can be administered either prefilter (predilution), postfilter (postdilution), or a mix of both. Predilution has the advantage of reducing filter clotting, but also decreases treatment efficiency. Postdilution provides higher clearances although it increases the filtration fraction (FF). The FF is defined as the ratio of ultrafiltration rate to plasma water flow rate and should be kept below 30%; otherwise filter clotting may occur (27).

$$\text{Filtration fraction} = \frac{\text{ultrafiltration rate}}{\text{plasma flow rate}}$$

As an example, for a patient with a hematocrit of 30%, if the blood flow rate is set at 150 ml/minute, the maximal ultrafiltration rate will be 1890 ml/hour (150 ml/minute × (100%–30%)/100% × 0.3 × 60 minutes/hour = 1890 ml/hour). Therefore, to avoid filter clotting when using high replacement fluid rates in postdilution CVVH, two options can be used: increase blood flow rate or add predilution.

It is important to differentiate fluid given prefilter (predilution fluid) from fluid administered postfilter either directly in the CRRT circuit or in a separate venous line (postdilution replacement). The intent of the former is to dilute blood going in and thereby reduce the filtration fraction whereas the latter replaces fluid removed from the patient. Total ultrafiltrate is the parameter reflecting treatment efficiency, or dose (28). Net ultrafiltrate is the parameter reflecting fluid balance. CRRT machines are designed to monitor and deliver fluids through their integrated pumps and achieve a "CRRT circuit balance" however, the machine has no knowledge of any other intakes and outputs outside the CRRT circuit. CRRT circuits thus account for the predilution and postdilution fluids to achieve the stated net ultrafiltration (fluid removal parameter) in the machine. However, overall patient fluid balance is determined by the difference in all intakes and outputs including the net ultrafiltration.

Current CRRT machines are designed to permit fluid removal or a zero fluid balance in the CRRT circuit. Consequently the effluent pump speed for all machines is set by the machine software and cannot be programmed directly. The components defining effluent pump speed (and thereby effluent volume) are the rates of predilution fluid, postdilution replacement fluid, dialysate flow rate (if used) and the net fluid balance (negative or positive) desired. Of these parameters the driving force is the net ultrafiltration. For instance, if a CVVHDF circuit is used and the dialysate, predilution, and postdilution flow rates are set at 1 l, 0.5 l, and 0.5 l/hour the effluent pump speed will range to a minimum of 2 l/hour (to achieve zero circuit balance) or higher to achieve a negative balance. In this scenario if a zero balance is desired the effluent pump speed will match the replacement fluid flow rate so the patient does not get any extra fluid. For any level of negative fluid balance the pump speed will exceed the total of the dialysate, predilution, and postdilution fluids by the desired amount. In no case can the CRRT machine be programmed to maintain a positive circuit fluid balance.

Prescription of Ultrafiltration

Given the inherent setup of all CRRT machines, three different levels of intervention can be used to prescribe ultrafiltration (20). In level 1, the main parameter utilized to achieve fluid balance is variation in the net ultrafiltration rate. Net ultrafiltration rates are adjusted to meet the anticipated needs for fluid balance over 8–24 hours. For instance, if the anticipated fluid intake is 4 l and the net loss desired is 2 l over a 24-hour period, the ultrafiltration rate is set as −250 ml/hour (4l + 2l/24 hours). The time interval where the adjustments are made can be more frequent, e.g., every 6 or 8 hours but the principle stays the same. The net ultrafiltration rate may not accommodate for unanticipated changes in fluid intake and therefore, the net ultrafiltrate may differ from the desired fluid balance at the end of the time period. Since the net ultrafiltration rates are not stable in this method, the effluent volume and the treatment dose may vary. It is worth mentioning that fluid balance often needs to be modified, as the underlying clinical condition may vary rapidly. Therefore, level 1 is not the most optimal method to use.

In level 2, CRRT is used to enable fluid regulation. This is achieved by utilizing the amount of postdilution replacement fluid administered to achieve fluid balance. A prerequisite is that the postdilution fluid is administered through a separate pump that is not part of the CRRT machine pumps. The hourly net ultrafiltrate is intentionally set to be greater than the hourly intake and is designed to contribute a predetermined amount of convective clearance in the effluent volume. Net patient fluid balance is therefore dependent on the hourly postdilution replacement rate. By manipulating the amount of postdilution replacement fluid rates almost any level of fluid balance can thus be achieved. Fluid removal occurs when the amount of postdilution replacement is adjusted to be less than all the output (including the net ultrafiltration), fluid repletion when the postdilution replacement is greater than all output net UF and a zero fluid balance is achieved when the two are equal. Level 2 allows one to precisely achieve almost any desired fluid balance in a few hours, unless the fluid removal capacity is exceeded.

Level 3 is similar to level 2 but also targets the hourly fluid balance to achieve a predefined hemodynamic parameter, such as a central venous pressure, mean arterial pressure or pulmonary arterial wedge pressure. For example, if central venous pressure needs to be maintained within 8–12 mmHg, then a scale is prescribed so that if CVP is within target values, net fluid balance is zero. Otherwise, if CVP is greater than desired, net fluid balance can be set at −50 or −100 ml/hour, depending

on the value of the CVP. This method takes full advantage of the flexibility of the CRRT for continuous fluid management.

Setting Goals for Volume Management with CRRT

As discussed earlier, critically ill patients have dynamic needs where fluid delivery and fluid removal need to be adjusted to optimize organ support. Consequently, fluid balance at any given time needs to meet three main objectives, i.e., (1) to remove excess fluid without compromising cardiac output and effective circulating volume, (2) compensate for increased fluid given to provide adequate nutrition and drugs, and (3) attempt to maintain urine output. The first goal is easier to monitor in critically ill patients who have invasive monitoring of their cardiac index or mixed-venous oxygen saturation (SvO_2), which is a surrogate for cardiac index measurement (29,30). Regarding the second goal, most ICUs do take into account fluid delivery in their prescription of fluid removal, as explained previously. Regarding urine output, there is no study to provide specific guidelines on this issue, although optimization of hemodynamic parameters seems intuitively related to a better preservation of kidney function.

Prevention and Management of Complications

Different types of errors related to ultrafiltration have been described. The prescription can be inadequate or the operator can deliver a different ultrafiltration than the prescription. If fluid removal is the goal, net UF rates need to be optimized to the PRR to minimize hemodynamic instability. When large net ultrafiltration rates are prescribed, UF may exceed the refilling capacity of compensatory fluid movement from the intracellular and interstitial compartments to intravascular compartment. Prompt recognition of signs of hypovolemia which include a drop in blood pressure, tachycardia and if more invasive monitoring is used, rapid drop in CVP or pulmonary arterial wedge pressure can be used to modify the prescription. We favor the use of level 2 or 3 UF strategies to optimize fluid removal at a rate commensurate with the clinical status.

A third type of error was recently recognized due to serious adverse events. Excessive ultrafiltration resulted when operators overrode safety alarms intended to limit UF when the gravimetric scales were being adjusted (31). In these cases, an alarm called "incorrect weight change detected" was overridden without identifying the underlying cause. These problems are inherent to all CRRT machines and resulted in significant changes in the software programs controlling fluid removal in CRRT machines (http://www.fda.gov/cdrh/safety/022706-gambro.html). As a result, prompt attention to ultrafiltration balance should always be a priority in patients treated with CRRT.

When administering large amount of dialysate and or replacement fluids, hypothermia may occur. One small randomized controlled trial has assessed the efficacy of fluid warmers on maintaining patients' temperature when using a total ultrafiltration rate equals or less than 3 l/hour (32). There was no significant difference in mean core temperature loss between circuits with or without a fluid warmer (−0.92°C vs. −1.11°C, $p = 0.34$). No data are available related to the efficacy of fluid warmers in preserving temperature in patients receiving larger amounts of dialysate and replacement fluids.

To prevent complications, simple but important measures should be undertaken. These include the use of standardized order sets for prescription of the therapy, flow sheets to record and monitor fluid balance, well-trained nursing personnel, and a sufficient nurse-to-patient staffing ratio. Often it is difficult to ascertain whether alterations in the clinical status are a result of fluid management or a consequence of the underlying illness. Hence, ongoing monitoring of fluid balance and adjustments to compensate for changes in clinical status are key to ensure patient safety (33).

Conclusion

In conclusion, volume management in critically ill patients undergoing CRRT is challenging, however certainly feasible. Although fluid depletion is commonly known to be harmful, several studies have also shown that fluid overload can also be detrimental in different clinical conditions. Randomized clinical trials should be undertaken to define the best timing of initiation of CRRT and the most appropriate techniques to achieve fluid regulation in these patients. In the meanwhile, physicians should utilize a standardized approach for the prescription and delivery of CRRT including careful monitoring of net ultrafiltration to enhance patient safety.

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