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The use of furosemide in critically ill patients

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Abstract

Critically ill patients are those with life threatening illness who, without adequate medical interventions, will suffer from severe morbidity and occasionally mortality. One of the most frequent cause of morbidity and mortality in critically ill patients is distributive or vasogenic shock. After liberal fluid resuscitation, an increase in microvascular hydrostatic pressure, fluid accumulation of interstitial compartment, and impaired organ function occur. Normally this phase, called ebb phase, will return to flow phase where inflammatory mediators homeostasis occurs, plasma oncotic pressure restored, diuresis, extravascular fluid mobilized and negative fluid balance occur. In certain group of patients, there is persistent systemic inflammation, plasma leakage, and failure to achieve flow phase spontaneously, which lead to fluid overload and global increased permeability syndrome (GIPS). GIPS causes venous resistance of organs within compartment, resulting in decreased perfusion pressure and organ failure. In this condition, it is necessary to remove the fluid actively and one of the drugs that can be used is furosemide. This literature review will describe what happens in critically ill patients, how furosemide works, what its benefits are in critically ill patients, what side effects and potential toxicities of furosemide.

Key words: Critical illness, fluid overload, furosemide.

Introduction

Critically ill patients are those with life threatening illness who, without adequate medical interventions, will suffer from severe morbidity and even mortality. (1,2) One of the most frequent cause of morbidity and mortality in critically ill patients is distributive or vasogenic shock. In this type of shock, clinician will perform standardized circulation resuscitation, after ensuring good airway and breathing, by giving a vast amount of fluid in a rapid manner, combined by vasoactive agent to ensure adequate perfusion. (3) However, even if an early resuscitation were successfully done, progressive organ failure will keep haunting a critically ill patient. (4) This was because acute inflammation will initiate a cascade of inflammatory mediators that will lead to microcirculation dysfunction and capillary leakage. (5,6) This was consistent with statement from Culbertson in 1942 about ebb phase, where there was a direct response caused by pro-inflammatory cytokines and initial stress hormone consisting of arterial vasodilatation, capillary albumin leakage, and decreased plasma oncotic pressure. (7) In that phase, complex reflex response of neuroendocrine system occurred, accompanied by renal dysfunction that leads to retention of sodium and water (fluid accumulation) with fluid overload. (6) Fluid overload (FO) is related to poor outcome and mortality. (6,8-10)

Cordemans, et al introduced the term of global increase permeability syndrome (GIPS), pointed the third hit of shock after acute injury and multiple

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organ dysfunction syndrome (MODS), marked by increasing capillary leak index (CLI), unreached goal of conservative late fluid management (CLFM), and progressive organ failure. (6) In case of GIPS, fluid removal intervention must be done to decrease or eliminate continuous organ dysfunction caused by congestion related to fluid overload after resuscitation of shock. (6,11) These interventions play an important role to restrict the formation of interstitial edema with compartment suppression, and furosemide would be used for that aim. (6,11,12)

Furosemide is a diuretic agent commonly prescribed in intensive care unit (ICU) and works by inhibit sodium-potassium-chloride transporter at thick ascending limb (TAL) of loop of Henle, thereby decreasing sodium, chloride, and water reabsorption, (13-16) along with direct effect on vascular beds. (17-20) In critically ill patient, furosemide offer a lot of benefit. If it is not used properly, side effects and even toxicities might occur. This review aims to unravel what really happens in critically ill patient, the pharmacokinetic and pharmacodynamic of furosemide, the benefit of furosemide in critically ill patient, and the side effects or the toxicities that should be prevented.

Critically ill patients

When critical illness has been present for more than 24 hour, there will be a change of body inflammatory response, which might cause organ dysfunction although early resuscitation was successfully done. (4) An acute inflammation in critically ill patient will initiate a cascade of inflammatory mediators that will lead to microcirculatory dysfunction, capillary leakage, and distributive shock. (5,6) Doig, et al reported that there was an increasing intestinal permeability in critically ill patient that would trigger hyperinflammation and MODS. (21) This inflammation explains why the critical condition of such patient still exists even though aggressive appropriate treatment has been given. (4)

Cuthbertson in 1942 introduced the concept of double metabolic response caused by bodily injury, such as ebb and flow phases. (7) In the ebb phase, there was production of proinflammatory cytokines and initial stress hormone, arterial vasodilatation and capillary albumin leakage, and decreased plasma oncotic pressure. Such distributive shock might cause systemic hypoperfusion and regional oxygen disturbance related to arterial underfilling, microcirculatory dysfunction, and secondary interstitial edema. (6) After liberal fluid resuscitation, e.g. early goal directed therapy (EGDT), in case of septicemia, (22) there was an increasing microvascular hydrostatic pressure, interstitial fluid accumulation, and organ dysfunction. (23) In this phase, there was a complex neuroendocrine reflex response along with renal dysfunction that might cause sodium and water retention with resultant a positive fluid balance. (6)

Positive fluid balance might be a sign of fluid accumulation. Fluid overload is associated with poor prognosis, and even death. (6,8-10) The relationship between fluid overload and patient prognosis was found in critically ill children that was given continuous renal replacement therapy (CRRT). (3) This study showed that fluid overload percentage more than 10-20% in CRRT initiation would increased the risk between 3 to 8 times of mortality. However, Goldstein, et al said such formulation, which is used to count fluid overload percentage, has its own weakness because it did not include the insensible water loss, wound loss, and visceral mass of long-stayed ICU patient. (3)

In distributive shock, treatment of fluid resuscitation was aimed to increase the venous return by increasing stress blood volume and gradient between mean systemic filling pressure (MSFP) and central venous pressure (CVP), and increase cardiac output. However, there was a group of patients that did not reach adequate cardiac output after fluid challenge (non-responders). (12) In the responders group, 30-60 minutes after fluid was given, the cardiac output will decrease again to starting point because of the redistribution of fluid to interstitial space.

Shock-free patients would have achieved homeostasis of inflammatory mediators in the next three days, followed by flow phase when there was a restoration of plasma oncotic pressure, diuresis, extravascular fluid mobilization, and negative fluid balance. (6) In contrast, in patient with persistent systemic inflammation, plasma leakage still happened and never reached the flow phase with continuous fluid accumulation that leads to increased positive fluid balance. (6)

In GIPS event, there was an increasing pressure in 4 main body compartments, including head, chest, abdomen, and extremities, related to interstitial edema that leads to organ venous distention along with decreased perfusion pressure continued by organ failure. (6) Study by Chen, et al showed similar results where there was venous congestion marked by peripheral edema and increased CVP related to acute kidney injury (AKI) event of the critically ill patient. (24)

Cordemans, et al stated that shock mechanism was

started by first hit (6 h), followed by second hit (48-72 h), and third hit (after 72 h). (6) During the first hit, there was acute inflammation, systemic inflammatory response syndrome (SIRS), microcirculation dysfunction, and distributive shock (ebb phase). During the second hit there was MODS, including acute lung injury, acute bowel injury, acute kidney injury, liver dysfunction, and nervous system dysfunction. During the third hit there was shock reversal that went to flow phase, or unresolved shock that became GIPS. In the latter, the given fluid was harmful; therefore, fluid removal (diuretics, albumin, renal replacement therapy [RRT]) should be done with monitoring of mean arterial pressure (MAP) and lactate level.

Inflammation might cause fluid overload, and endotoxin translocation through congested intestinal wall, even splanchnic ischemia. (25) Moreover, an inflammation based on fluid overload could occur because of pro-inflammatory effect of tissue sodium triggered by T-helper cell. (25)

Furosemide pharmacokinetic

Furosemide is a loop diuretic agent first approved by Food and Drug Administration (FDA) in 1966. Furosemide (4 chloro-N-[2-furyl methyl]-5-sulfamyl-anthranilic acid) is a potent and effective diuretic agent, and could be given orally or intravenously. (26) Furosemide has bioavailability range of 10-100% (mean=50%) and is affected by foods. (15) Onset of action is 30-60 minutes if given orally and 5 minute via intravenous administration. (15) Drug metabolism is about 50% via liver conjugation. (15) Furosemide has half-life about 1.5-2 hours in normal condition, 2.8 hours in renal dysfunction, 2.5 hours in liver dysfunction, and 2.7 hours in cardiac failure. (15)

Continuous administration compared with intermittent allows drug titration until expected effect. However, to make the drug reach the effective plasma level, it should be started by loading dose. (4) Yeh, et al compared continuous furosemide (loading dose of 10 mg intravenously followed by continuous infusion 2 mg/h, with an additional dosage could be given by clinician if needed) and an intermittently given (10 or 20 mg initial dosage, with an additional dosage could be given by clinician if needed). (27) The results were a significant difference in cumulative dose of furosemide but not for 24 h fluid balance, ICU length of stay, Ventilator free day (VFD), PaO2/FiO2 ratio (PFR), and even death. Systematic review and meta-analysis by Ng, et al showed continuously given furosemide therapy compared with intermittent intravenous administration in critically ill patient also had similar results where the continuous administration correlated with more total urine production (r=0.7; OR 811.19 [95%CI 99.84-1522.53]; p=0.03), although it did not had any difference on mortality rate (OR 1.15 [95%CI 0.67-1.96]; p=0.64). (28) Zangrillo, et al in their systematic review and meta-analysis showed that furosemide given continuously did not result in significant decreased death risk compared with intermittent bolus in critically ill patient, but the data to ascertain the best technique of furosemide administration was not enough. (29)

Albumin also affect the furosemide pharmacokinetic, where low level of albumin could increase distribution volume and might cause the transportation of the drug to renal tubules became inadequate. (4) However, this phenomenon still remains controversial. (14) Furosemide was eliminated by renal glomerular filtration and tubules secretion. (17) Loop diuretic secretion may decrease when there was a combined use with non-steroid anti-inflammatory drug or probenecid that may compete with low acidity secretion in proximal tubules. Metabolite of furosemide does not have any diuretic activity.

Furosemide pharmacodynamic

Furosemide works by inhibiting sodium-potassium-chloride transporter in the thick ascending limb (TAL) of loop of Henle, thereby decreasing sodium, chloride and water reabsorption. (13-16) Transporter, Na/K/2Cl (NKCC2 or NK2Cl), has been successfully copied and sorted for later mapped expression. (30,31) In addition to sodium, chloride and water, furosemide also increases the excretion of K^+, Mg^{2+}, H^+ and Cl^- through urine. (13) Loop diuretics including furosemide is the most effective diuretic available related to the magnitude of NaCl absorption capacity of TAL, and the drug action is not affected by acidosis, as in carbonic anhydrase inhibitor diuretic. (32) Cohort study by Huang, et al showed increased urine production, urinary sodium, potassium and chloride losses and the occurrence of hypochloremia and metabolic alkalosis following the usual dosage of 40 mg intravenous bolus. (33)

Furosemide also has an effect on the vasculature by altering vascular conductance. (18) Increased sodium and water retention in arterial blood vessel walls in patients with heart failure increase vascular stiffness and furosemide administration improve the condition rapidly within 24 hours and was associated with more diuresis instead of neurohormone inactivation. (18) However, 24-48 hours later, there is no further change of vascular

compliance and it suggests involvement of other factor which is neurohormone activation. (18) Figueras, et al performed studies on blood volume before and after furosemide therapy in patients with cardiogenic pulmonary edema. (19) After furosemide administration, intravascular volume is increased with the speed of replenishing fluid to intravascular exceeding volume of fluid excreted in urine. (19) Study conducted by Schuster, et al showed diuresis after furosemide administration did not reduce intravascular volume and even increased plasma volume. (20) Furosemide also has direct effect on blood flow through some vascular beds. (17) Blood flow to renal will be increased by furosemide through the action of prostaglandins in kidney vasculature. Before increased urine production can be measured, furosemide was found to decrease pulmonary congestion and left ventricular filling pressure in heart failure. (17)

The use of furosemide in critically ill patients

Furosemide is generally given for several indications such as reducing edema, improving gas exchange, correcting oliguria, reducing AKI, attaining venodilatory effects, and reducing pulmonary arterial wedge pressure. (3,18,34-37) In critically ill patients (with sepsis, inflammation, and heart failure), the oncotic pressure is often low, resulting in transcapillary fluid shift, increasing interstitial fluid volume in peripheral tissue and plasma volume reduction. (3) This condition causes increase in contra-regulator hormones such as angiotensin II, sympathetic hormones, and vasopressin resulting in sodium retention. (3) Therefore, plasma albumin administration may increase the effectiveness of diuretics due to increased oncotic pressure. (3)

Fluid balance is increasingly recognized as a 'complementary vital sign' or biomarker in critically ill patients. (3,36,38) Cordemans, et al stated patients with GIPS require fluid removal and one of the drugs that can be used is furosemide. (6) It is similar to study conducted by Malbrain M, et al, which showed positive cumulative fluid balance was associated with intraabdominal hypertension (IAH) and other unfavorable outcomes. (12) The purpose of actively removing the fluid is to obtain negative fluid balance by mobilizing fluid that accumulates through late goal directed fluid removal (LGFR) or also known as de-resuscitation. (12)

Fluid removal often begins with the stabilization or de-escalation phase after resuscitation in all patients at risk of or with excess fluid accumulation. Careful management of fluid administration includes reducing all non-essential fluids. (3) No studies have prospectively evaluated clinical, physiological, biochemical, and/or specific organ damage parameters to guide the initiation and cessation of active fluid removal or to evaluate time-based relationship between fluid removal and organ function, undesirable events, and survival. (3) Goldstein, et al defined fluid balance trajectory as a safe physiological endpoint during fluid removal and suggest those target should be monitored. (3) Nevertheless, the guidelines are subjective and difficult to understand or apply. Assessment of excess fluid and its effect on target organs includes transcardio-pulmonary thermodilution (TPTD), bioelectrical impedance (BIA), PFR, extravascular lung water (EVLWI), pulmonary vascular permeability index (PVPI), intraabdominal pressure (IAP), abdominal perfusion pressure (APP), extracellular water (ECW), intracellular water (ICW), total body water (TBW), and volume excess (VE). (12) Malbrain M, et al used EVLWI through TPTD to estimate the number of capillary leaks and fluid overload. (12)

During fluid removal, tissue perfusion monitoring may be performed using LiMON (Pulsion Medical Systems, Feldkirchen, Germany), gastric tonometry (Datex Ohmeda, Helsinki, Finland), microdialysis, hepatosplanchnic perfusion monitoring and microperfusion with ScvO2, indocyanine green plasma disappearance rate (ICG-PDR), etc. (12) Yeh, et al showed that target of fluid removal in furosemide administration is net negative fluid balance 100-300 ml/4 hour. A safe limit to discontinue furosemide are persistent hypotension (defined as MAP<60 for more than 30 minutes), tachycardia (defined as increased heart rate 20% from baseline), administration of vasopressor or fluid bolus in the last 12 hours, myocardial infarction (electrocardiogram or troponin changes), acute renal failure (oliguria with creatinine >3.0 or oliguria with creatinine <3.0 but urine examination result indicates acute renal failure), refractory hypokalemia or cardiac arrhythmia induced by impaired electrolyte balance, metabolic acidosis (HCO3<18), and doctor's/nurse's consideration. (27)

A case report by Dewi NL, et al suggested CVP may be used as a target for the treatment of septic patients with AKI induced by fluid overload. (39) Fluid overload is defined as a positive cumulative fluid balance with clinical signs of pulmonary congestion or edema. Fluid overload can be assessed with several parameters such as N-terminal prohormone of brain natriuretic peptide (NT-proBNP), total body water (TBW) measurement by bioelectrical impedance vector analysis (BIVA), and CVP. (39) In four cases of septic patients with positive

fluid balance and AKI who had fluid removal aiming CVP target near zero was carried out safely by administration of vasopressor and inotropes. (39) High CVP is associated with organ dysfunctions (24,40,41) because it limits venous return and back pressure of all extrathoracic organs. (41) CVP can indicate fluid overload or increased total body water. (42,43) Legrand, et al reported that CVP value, other than cardiac output (CO), may be used as a guide when conducting fluid removal. (11) Legrand, et al in a retrospective observation analysis study also showed CVP was the only significant indicator for AKI. (40) In the study, CVP value >4 mmHg increased the risk of AKI. We created our own algorithm of fluid de-resuscitation in GIPS guided by CVP value (**Figure 1**).

Furosemide also has a protective effect in patients with acute lung injury (ALI) possibly related to positive fluid balance reduction. (38) Cordemans, et al used combination of high levels of positive end-expiratory pressure (PEEP), small volume resuscitation with hyperoncotic albumin, and fluid removal with furosemide (Lasix®) or CRRT (PEEP albumin Lasix® [PAL] technique). (10) Fluids and Catheters Treatment Trial (FACTT) study showed that dry lung through conservative fluid restriction strategy and improved fluid excretion in patients with ALI and acute respiratory distress syndrome (ARDS) is more effective compared to those with wet lung or liberal fluid strategy. (44,45) In conservative strategy group, diuresis was used to maintain filling pressure target less than 8 mmHg in patients with pulmonary artery catheter, and CVP value less than 4 mmHg in patients with central venous catheter that would ultimately reduce pulmonary edema and improve gas exchange. (44) This strategy significantly reduced the length of stay and mechanical ventilation use without an increase in 60-day mortality or 28-day non-pulmonary organ failure. (44)

Teixera, et al found that patients with AKI who died were those with higher mean fluid balance. (46) European Society of Intensive Care Medicine strongly recommends controlling fluid resuscitation using crystalloids and avoid fluid excess. (43) For the prevention of AKI and renal function protection at intensive care unit, they also suggested giving diuretics to patients with good response and not simply to prevent AKI. (43)

Some arguments and theories support the use of furosemide to prevent or overcome acute renal failure because of its potential to flush cellular debris and casts which block the renal tubules and improve renal medullary oxygenation as it selectively reduces tubular oxygen utilization through inhibition of active transport and renal vasodilation. (47) However, in patients who did not respond favorably to furosemide, there was an increased risk of death in the hospital by 68% and an increased of death odds ratio or failure to achieve improvement in renal function by 77%. (47) Similar to that study, Mehta, et al showed the use of furosemide was associated with significantly increased risk of death or unfavorable renal function. (48)

Furosemide stress test (FST), can be used to predict severity of AKI. (49,50) In this test, 1 or 1.5 mg/kg furosemide was administered and urine production 2 hours later was assessed. Dose of 1 mg/kg was administered to patients who have not previously received furosemide and 1.5 mg/kg in those who have received it. The ideal cut off value of 2-hour urine volume to predict progressive AKI is <200 ml (100 ml/hour) with 87.1% sensitivity and 84.1% specificity. Patients with early stage of AKI (Kidney Disease Improving Global Outcome [KDIGO] stage I or II) who were given single-dose furosemide (1-1.5 ml/kg) to assess their response to furosemide was regarded as marker of AKI severity and worsening AKI predictor (KDIGO stage III). (3) Nevertheless, this FST does not delay definitive treatment with RRT. Patients with symptomatic fluid excess and AKI stage III plus indication of conventional RRT initiation such as hyperkalemia, uremia, acidosis or complications of fluid overload itself and those who are less likely to respond favorably to pharmacotherapy should get RRT immediately. (3)

Side effects and toxicities

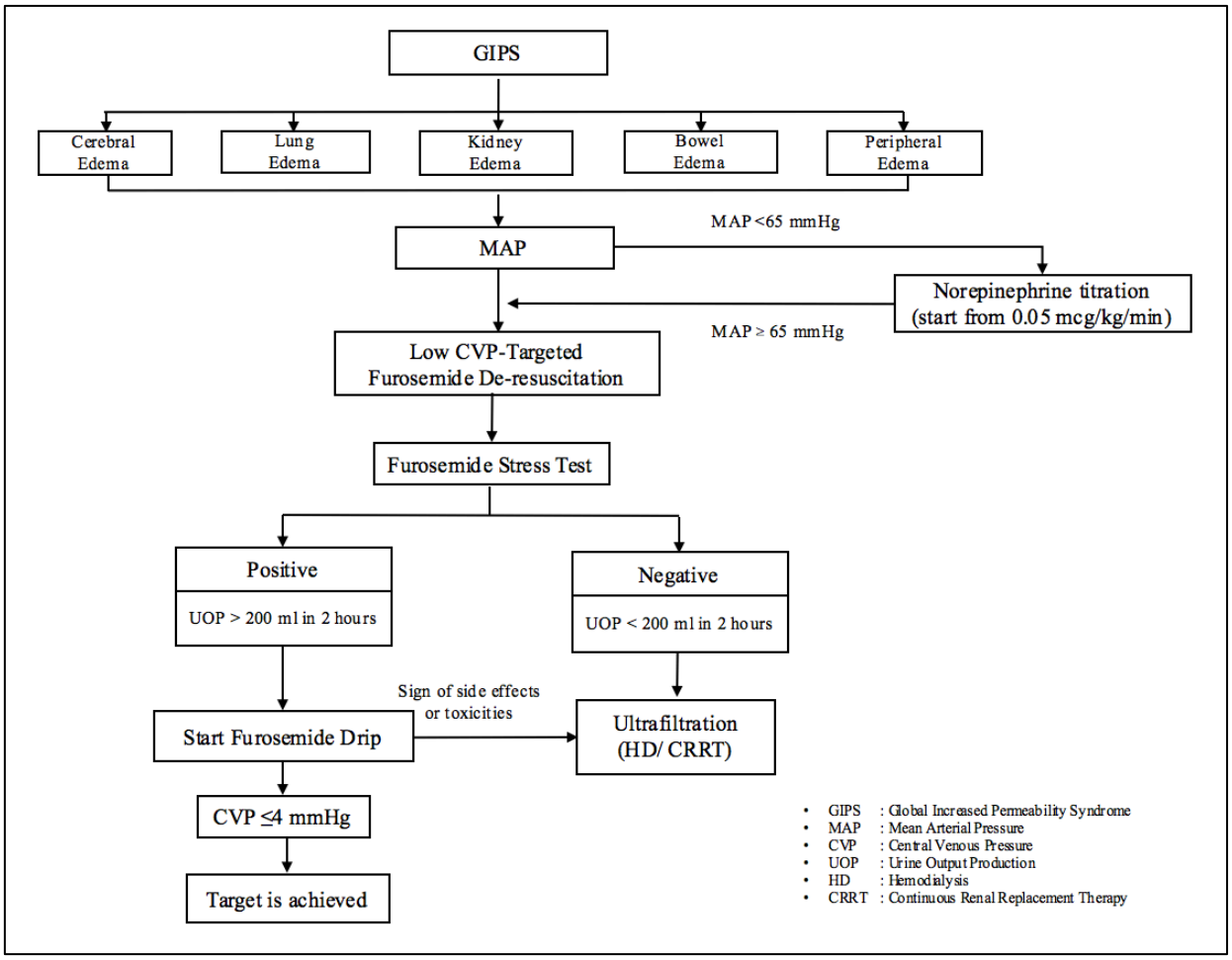
The most common side effects are fluid, electrolyte, and acid-base imbalance. (4) Fluid removal using furosemide without control would potentially lead to hypovolemia resulting in hypoperfusion and tissue hypoxia. (12) Nevertheless, previous studies have shown that furosemide increase blood volume due to fluid shift from interstitial to intravascular compartment more than urine production. (18-20) Electrolyte imbalances may vary. Hypokalemia can occur because of increased secretion of K^+ and H^+ through collecting duct. Because of increased excretion of Mg^{2+} and Ca^{2+}, in long term use, furosemide may cause hypomagnesaemia in some patients, especially those with magnesium deficiency. Generally, furosemide does not cause hypocalcaemia due to vitamin D-induced intestinal absorption and parathyroid hormone-induced renal reabsorption. In condition of hypercalcemia, we can give combination of loop diuretics and saline infusion to increase Ca^{2+} excretion. Furosemide can

also induce hypokalemic metabolic alkalosis. (17)
Furosemide toxicity may include muscle toxicity, hyperuricemia, allergic reactions, and other reactions. (17) The incidence of hearing loss, which is associated with loop diuretic, is usually reversible and most commonly occurs in patients with impaired renal function or taking other ototoxic drugs such as aminoglycoside. Furosemide can cause drug reactions such as skin rashes, eosinophilia and, more rarely, interstitial nephritis. Furosemide can also cause hepatic necrosis. (51) The use of diuretics excessively including furosemide may be harmful in hepatic cirrhosis, borderline renal failure, or heart failure. (17)

Conclusion

In critically ill patient, distributive shock due to acute inflammation will encourage clinician to give resuscitation in order to prevent MODS. Nonetheless, liberal fluid resuscitation may result in increased microvascular hydrostatic pressure, accumulation of interstitial fluid and impaired organ function or so called GIPS. Under condition of GIPS and fluid overload, fluid removal must be performed to reduce or eliminate further organ dysfunctions and one of drugs that can be used is furosemide.
During furosemide use as fluid removal agent, we can use various parameters as targets. One of the simplest and applicable parameters in clinical setting is CVP value. It is most important to perform fluid management strategies wisely, without or minimally cause fluid accumulation, and consequently, we may avoid GIPS.

Figure 1. CVP-guided fluid de-resuscitation



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