Case report: central venous pressure-guided de-resuscitation in sepsis patients with fluid overload induced acute kidney injury

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Abstract

***Background*: Aggressive fluid resuscitation is commonly administered in septic patients as recommended by Surviving Sepsis Campaign. However, positive fluid cumulative balance resulting in fluid overload is correlated with various complications such as acute kidney injury, acute respiratory distress and delayed wound healing.**

***Case report*: This report presents four septic patients with fluid overload and acute kidney injury who underwent active de-resuscitation aiming central venous pressure between zero and two mmHg.**

***Discussion*: In all patients, central venous pressure guided de-resuscitation was associated with systemic oxygenation improvement (arterial lactate dropped from 8.3 to 0.8 mmol/l, from 5.3 to 0.3 mmol/l, from 3.5 to 0.5 mmol/l, and from 3.3 to 0.7 mmol/l) and acute kidney injury resolution without hemodynamic instability and elevated lactate level. Negative cumulative balance is associated with a significant reduction of norepinephrine dose.**

***Conclusion*: A de-resuscitation strategy based on the target of central venous pressure 0-2 mmHg is a safe and effective procedure that resulted in improvement in hemodynamics, serum lactate, renal function and also systemic oxygenation.**

Key words: Fluid overload, acute kidney injury, positive cumulative balance, sepsis, de-resuscitation.

Introduction

Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection. Despite of new advanced researches in diagnostic and biomolecular pathophysiology of sepsis, new therapeutic intervention, especially in fluid management is still limited and most empiric. The Surviving Sepsis Campaign recommends early goal directed therapy (EGDT) protocol that consists of aggressive fluid resuscitation during the first 24 hours of management and target of central venous pressure (CVP) 8-12 mmHg. This strategy has decreased sepsis mortality from 46% to 30.2% with total fluid given up to 13 liter in 72 hours. However, results of ProCESS, ARISE and PROMISE trials indicated that EGDT as defined by Rivers et al may be more invasive than what is actually necessary for patients in septic shock. Significant positive fluid balance result in this protocol leads to high CVP and clinical sign of fluid overload such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), myocardial damage, gastrointestinal dysfunction and delayed wound healing. (1-3) Boyd et al found that positive cumulative fluid balance occurring between the first 12 hours and 4 days was related to increased mortality. (4)

Fluid overload is defined as positive cumulative fluid balance with clinical signs of dyspnea or pulmonary congestion or peripheral edema. Several parameters might be used to diagnose fluid overload, such as N-terminal prohormone of brain natriuretic peptide (NT-proBNP), measurement of total body water with Bioelectrical Impedance Vector Analysis (BIVA) and CVP. (5-7) Although CVP has failed as a useful measure for assessment of preload and fluid responsiveness, a CVP>8 mmHg is independently associated with higher

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mortality and increased risk of AKI in patients with sepsis and heart failure. This suggests that the CVP component of the 6-hour resuscitation bundle as widely promoted by the Surviving Sepsis Campaign in EGDT may lead to harm since according to Guyton model normal CVP is close to zero and not to 8 to 12 mmHg. (8-10)

Legrand and colleagues found a linear relationship between increasing CVP and AKI in sepsis patients. A higher trend of CVP was associated with worse renal outcome for all levels of CVP>4 mmHg. A CVP of 15 mmHg being associated with 80% risk of new or persistent AKI compared to approximately 30% risk at a CVP of 6 mmHg. (10)

Correcting fluid overload and restoring fluid balance in AKI are important goals. Nevertheless, there is still no consensus about how much fluid must be removed or the safe de-resuscitation target in these patients. This is important because over aggressive diuresis may cause intravascular volume contraction, which results in organ hypoperfusion. The aim of this report is to present four septic patients with positive balance and AKI who underwent active de-resuscitation aiming CVP near zero mmHg, in accordance with the Guyton normal CVP theory, Piccoli study on BIVA and Legrand study, resulting in better hemodynamics, renal function and systemic oxygenation. This procedure is a safe fluid removal technique in the presence of vasopressor and inotropic drugs.

Case reports

First case, a forty-six-year-old man admitted to Emergency Department with intra-abdominal sepsis, AKI and disseminated intravascular coagulation. After resuscitation and antibiotic administration, he underwent laparoscopic appendectomy and admitted to Intensive Care Unit (ICU). On arrival, he was sedated and ventilated, with positive cumulative fluid balance of 2800 ml, CVP 15 mmHg and signs of tissue hypoperfusion (anuria, lactate was 8.3 mmol/l). Circulation was supported by noradrenaline (0.12 ug/kg/min) and dobutamine (5 ug/kg/min). The patient had a low dynamic compliance of respiratory system (CRS value) 28 ml/cmH2O with a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) up to 120, dilated inferior vena cava (IVC) and significant B-lines. Furosemide infusion was started 2 hours later, aiming to achieve CVP of 0-2 mmHg (**Chart 1**). Sustained low-efficiency dialysis (SLED) was also initiated later due to hyperkalemia and AKI stage 3 (increasing serum creatinine [sCr] more than 4.0 mg/dl). SLED and furosemide infusion continued up to full stabilization of the renal function in the patient. The patient was discharged to the ward on the 5th day.

The second case was a 58-year-old man with cardiogenic shock complicating extensive anterior myocardial infarction. The circulation was supported by noradrenaline (0.5 ug/kg/min), nitroglycerine (5 ug/kg/min and dobutamine (5 ug/kg/min). At day 3, he developed acute shortness of breath, tachypnea, CVP 18 mmHg and oliguria. Workup included a chest X-ray demonstrating bilateral infiltrate, an echocardiography showing global hypokinetic, low ejection fraction 37%, aneurismatic left ventricle and bilateral B-lines. He was intubated and furosemide infusion was started. The day after, AKI stage 3 was developed (anuria for 15 hours and sCr was increased to 3.4) with positive cumulative fluid balance of 3200 ml. Because of unstable hemodynamic, continuous veno-venous hemofiltration (CVVH) was started with fluid exchange of 3000 ml/h and fluid removal 250-500 ml/h. The fluid removal strategy was aimed to achieve CVP 0-2 mmHg (**Chart 1**). This procedure was supported by albumin 20% infusion 50 ml/hr.

Third patient, a 12-year-old girl with a history of generalized peritonitis underwent uneventful laparotomy appendectomy under general anesthesia. On postoperative day 3, she was admitted to ICU due to acute respiratory failure, sepsis, AKI stage 2 (oliguria <0.5 ml/kg/h for 18 hours) with dilated IVC and CVP 13 mmHg. A chest X-ray showed bilateral infiltrate with cranialization. The laboratory results showed that the patient developed coagulopathy. Furosemide infusion was started with dosage of 2 mg/h targeting CVP 0-2 mmHg (**Chart 1**).

The fourth patient, a 10-year-old girl admitted to Emergency Department with a 5-day history of temperature of 39.4 °C to 40.5 °C and a 4-day history of severe bifrontal and intermittent headaches. Additional serum testing revealed the diagnosis of classic dengue fever. She was admitted to the ward for monitoring and intravenous hydration. On day 3, she was admitted to ICU due to dengue shock syndrome, thrombocytopenia 28×10^3/ul, pleural effusion, progressive dyspnea and AKI stage 2. Balance cumulative prior to ICU admission was positive 5040 ml. On arrival, she was sedated and ventilated, with CVP 8 mmHg and signs of tissue hypoperfusion (lactate was 3.3 mmol/l). Circulation was supported by noradrenaline (0.12 ug/kg/min). The patient had a low CRS value 30 ml/cmH2O with a PaO2/FiO2 ratio 105, dilated IVC and significant B-lines. Furosemide infusion was started at 3 mg/h. On day 5, she was extubated

and cumulative balance was +124 ml (**Chart 1**).
During the fluid removal, we measured hemodynamic variables such as mean arterial pressure (MAP), CVP, cardiac index (CI) and norepinephrine (NE) dose, kidney function (serum creatinine and urine output), ventilation parameter (PaO2/FiO2 ratio) and arterial lactate for systemic oxygenation. A negative fluid balance was reached after fluid removal strategy initiation, resulting in a decrease of CVP (from 16 to 2 mmHg, from 18 to 4 mmHg, from 13 to 0 mmHg, and from 8 to -1 mmHg, respectively) (**Chart 1**). We observed improvement in hemodynamics (decreased norepinephrine infusion from 0.28 to 0.02 ug/kg/min, from 0.8 to 0.03 ug/kg/min, from 0.18 to 0.01 ug/kg/min, and from 0.12 to 0.03 ug/kg/min) and ventilation (improvement in CRS and PaO2/FiO2 ratio). We also observed improvement in systemic oxygenation (arterial lactate dropped from 8.3 to 0.8 mmol/l, from 5.3 to 0.3 mmol/l, from 3.5 to 0.5 mmol/l, and from 3.3 to 0.7 mmol/l) and decreased serum creatinine level in all patients (**Charts 2 and 3**). Dobutamine support was not changed and cardiac index elevated during the procedure. Spontaneous diuresis occurred during the third day following SLED in the first patient and during the fifth day following CVVH initiation in the second one. The fluid removal strategy was continued up to full stabilization of the renal function in all patients.

Discussion

Increased capillary permeability, decreased colloid osmotic pressure, compromised splanchnic perfusion, and high volume of fluid resuscitation to treat hemodynamic instability resulted in positive cumulative balance. A significant positive fluid balance leads to a high CVP and clinical sign of fluid overload (FO) in our patients. (8-10)
According to Guyton model, venous return is determined by the gradient between CVP and mean circulatory filling pressure (MCFP). MCFP is regarded as the driving pressure that determines venous return and is considered synonymous with the effective circulatory blood volume. The MCFP is normally in the range of 8 to 10 mmHg and CVP is near zero mmHg. An increase in CVP or a fall in MCFP will reduce venous return, stroke volume and cardiac output. (8-10) Active de-resuscitation strategy applied to our patients, was targeted to achieve CVP of 0-2 mmHg. Lowering CVP with furosemide will increase venous return by increasing the gradient pressure between CVP and MCFP (**Figure 1**).
After resuscitation and optimization phase, we started active de-resuscitation for two main reasons. First, continuing fluid accumulation had deleterious effects if the patients did not passively excrete the excess amount of water and electrolytes. We used diuretics as adjunctive therapy in AKI to treat FO, or with an early renal replacement therapy, when diuretics could not control the fluid overload. (9) Secondly, if CRRT was initiated, we expected some favorable effect on the restoration of capillary permeability due to decrease in pro-inflammatory mediators such as interleukin-6. Pulmonary edema that occurred in our third patient was a common trigger for fluid removal, but it was a late and potentially lethal consequence of fluid overload.
In all patients, we found that active de-resuscitation targeting CVP of 0-2 mmHg was an effective and safe procedure. It was not only associated with systemic oxygenation improvement (significant arterial lactate reduction) but also AKI resolution (decreased ureum and serum sCr). We did not observe any hemodynamic instability and elevated lactate level during the de-resuscitation procedure. On the contrary, negative cumulative balance is associated with a significant reduction of norepinephrine dose.
To achieve a safe fluid removal in the presence of vasopressor and inotropic drug, we considered some factors, such as fluid removal rate and diuretics dose. Either with dialysis or diuretics, the fluid removal rate should be titrated to avoid under-filling. During active de-resuscitation, fluid will be removed from intravascular compartment to urine. The fluid mobilization rate from interstitial tissue such as peripheral edema or lung edema to replenish the intravascular fluid loss will determine the degree of intravascular volume contraction. If the rate of fluid removal is higher than the rate of interstitial to intravascular movement, there will be under-filling and hypoperfusion.

Conclusion

Although CVP has received discredit as a guide to fluid loading, it might be an easy adjunct for active de-resuscitation strategies. A de-resuscitation strategy based on the achievement of CVP 0-2 mmHg and negative fluid balance is a safe and effective procedure that results in improvement in hemodynamics, serum lactate, renal function and also systemic oxygenation.

Chart 1. Cumulative balance and central venous pressure (CVP) during active de-resuscitation strategy

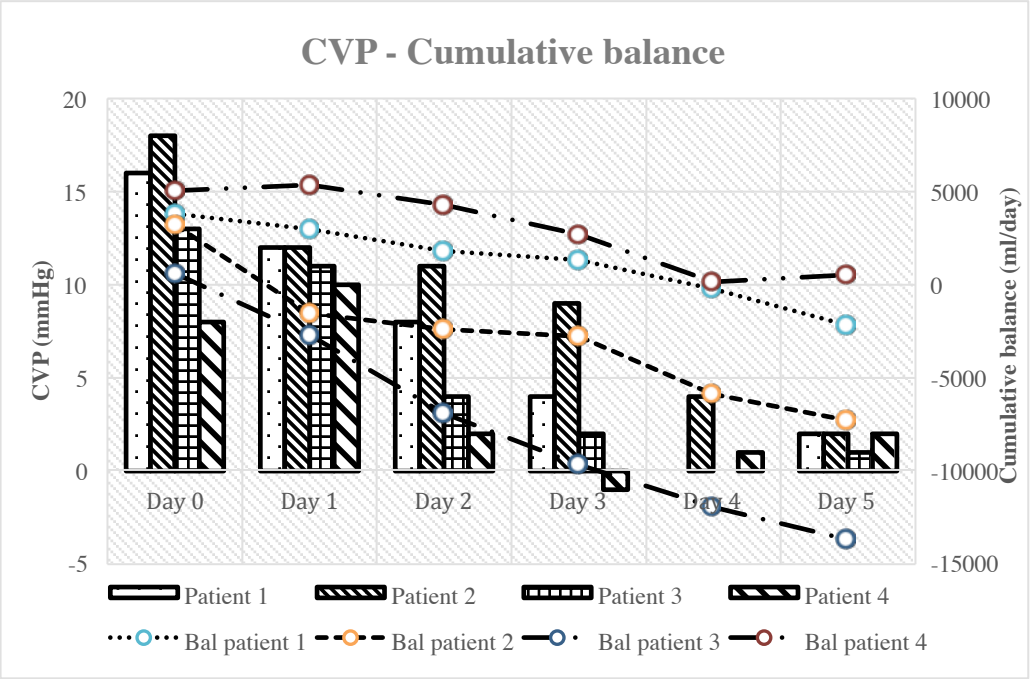


Chart 2. Cumulative balance and serum lactate during active de-resuscitation strategy

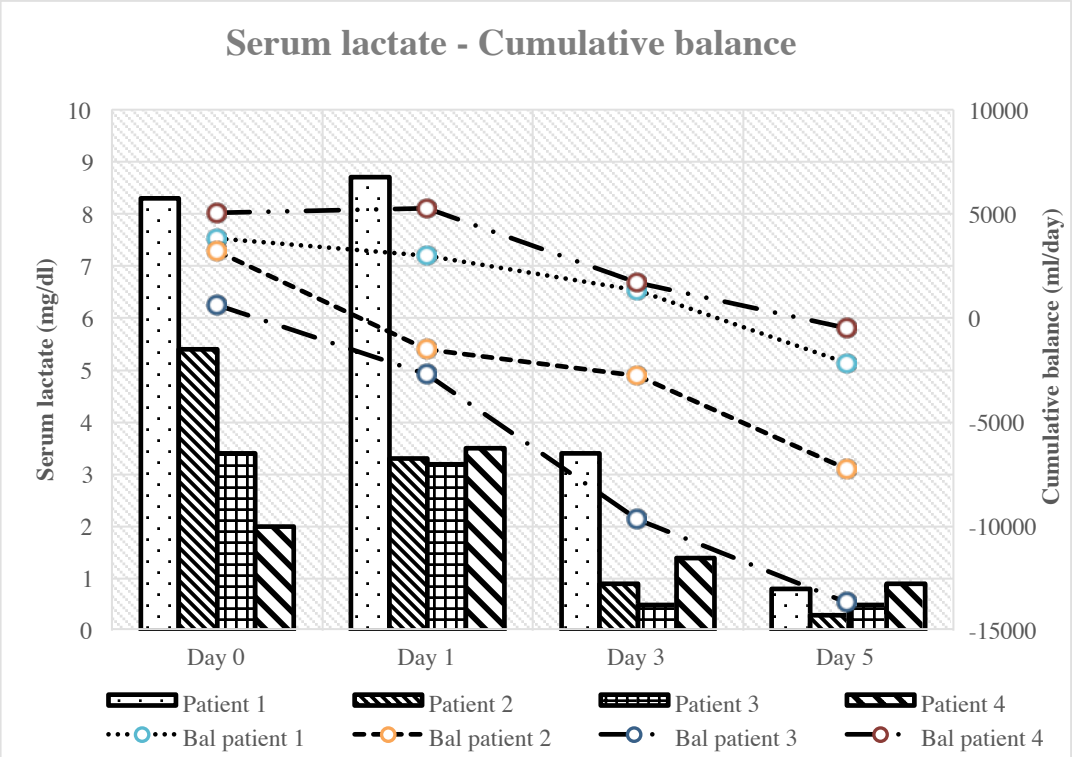


Chart 3. Cumulative balance and serum creatinine during active de-resuscitation strategy

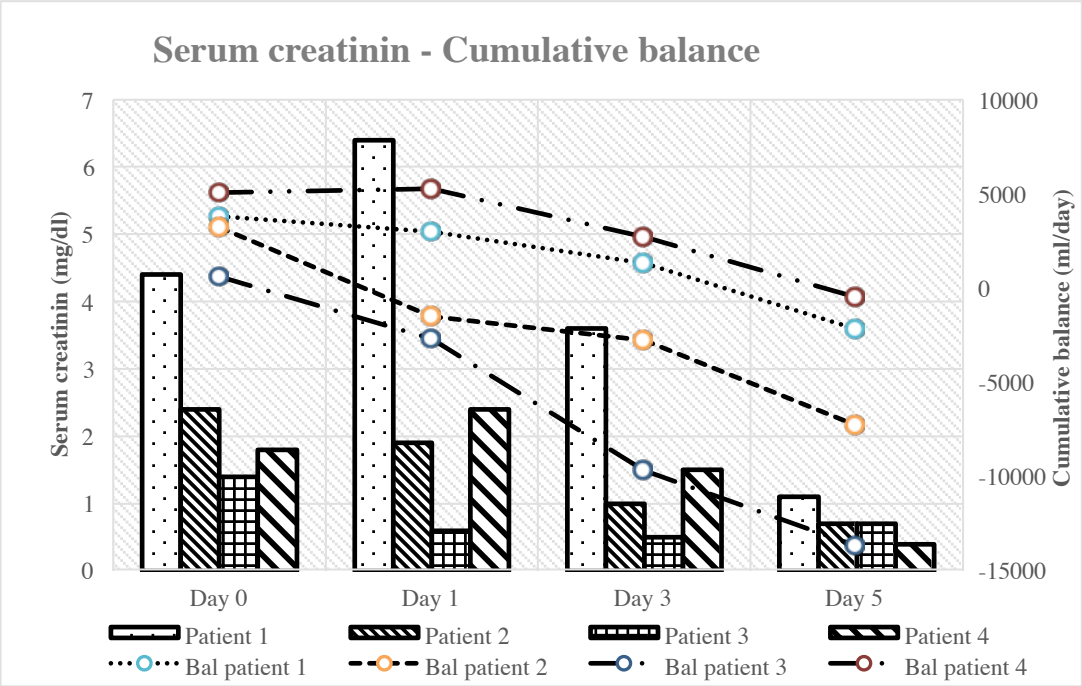
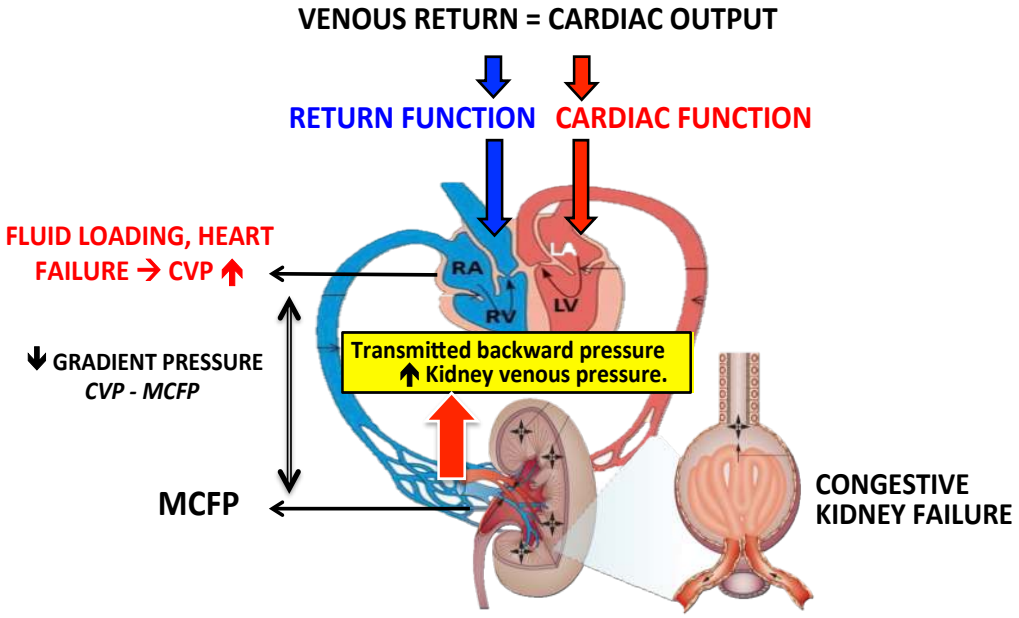


Figure 1. Increased central venous pressure (CVP) effect



Legend: The effect of increased CVP: 1) An increase in the CVP or a fall in the mean circulatory filling pressure (MCFP) will reduce the CVP-MCFP gradient. As a result, venous return, stroke volume and cardiac output will decrease; 2) A high CVP is transmitted backwards, increasing venous pressure that leads to increased renal subcapsular pressure, lowered renal blood flow and glomerular filtration rate (GFR).

References

1. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, et al. A randomized trial of protocol-based care for early septic shock in. N Engl J Med 2014; 370:1683-93.
2. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, Bellomo R, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014;371:1496-506.
3. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 2015;372:1301-11.
4. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality increase mortality. Crit Care Med 2011;39:259-65.
5. Larsen TR, Singh G, Velocci V, Nasser M, McCullough PA. Frequency of fluid overload and usefulness of bioimpedance in patients requiring intensive care for sepsis syndromes. Proc (Bayl Univ Med Cent) 2016;29:12-5.
6. Samoni S, Vigo V, Reséndiz LIB, Villa G, De Rosa S, Nalesso F, et al. Impact of hyperhydration on the mortality risk in critically ill patients admitted in intensive care units: Comparison between bioelectrical impedance vector analysis and cumulative fluid balance recording. Crit Care 2016;20:1-8.
7. Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol Rev 1955;35:123-9.
8. Velingga NA, Ince C, Boerma EC. Elevated central venous pressure is associated with impairment of microcirculatory blood flow in sepsis: a hypothesis generating post hoc analysis. BMC Anesthesiol 2013;13:17.
9. Malbrain M, Marik PE, Witters I, Cordemans C, Kirkpatrick AW, Roberts DJ, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther 2014;46:361-80.
10. Marik PE. Fluid Responsiveness and the Six Guiding Principles of Fluid Resuscitation. Crit Care Med 2016;44:1920-2.