Fluid Responsiveness and the Six Guiding Principles of Fluid Resuscitation

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The advanced life support technology, which is provided in the ICU, is intended to provide temporary physiologic support for patients with reversible organ dysfunction allowing homeostatic mechanisms to return the patients to their previous level of functioning (1). The introduction of the pulmonary artery catheter in the early 70s ushered in a style of critical care medicine that can best be characterized as "aggressive"; if some care is good, more care is even better. Aggressive fluid resuscitation titrated to the central venous pressure (CVP) or pulmonary artery occlusion pressure became regarded as the cornerstone of resuscitation. This approach ushered in an era of rigid protocolized care, where critically ill and injured patients received large amounts of crystalloids regardless of their hemodynamic status (2–4). However, an emerging body of evidence suggests that aggressive fluid resuscitation leads to severe tissue edema that compromises organ function and leads to increased morbidity and mortality (5, 6). A recent global cohort study that evaluated the approach to fluid resuscitation in 46 countries concluded that the "current practice and evaluation of fluid management in critically ill patients seems to be arbitrary… is not evidence-based and could be harmful." (7) This article presents a rational, physiological approach to fluid resuscitation, which is based on six fundamental principles. If one is considering giving a fluid bolus, I would recommend using dynamic rather than static measures to assess the patient according to the principles listed below.

1. FLUID RESPONSIVENESS: THE FOUNDATION OF FLUID RESUSCITATION

Fundamentally, the only reason to give a patient a fluid challenge is to increase their stroke volume (SV); if this does not happen, fluid administration serves no useful purpose and is likely to be harmful (8). A patient is considered to be fluid responsive if his/her SV increases by at least 10% following a fluid challenge (usually 500 cc of crystalloid) (8). Fluid administration will only increase SV if two conditions are met, namely 1) if the fluid bolus increases the stressed blood volume causing the mean circulating filling pressure to increase greater than the increase in CVP and thereby increasing the gradient for venous return (9, 10) and 2) if both ventricles are functioning on the ascending limb of the Frank-Starling curve (8).

Studies in heterogeneous groups of critically ill and injured patients and those undergoing surgery have reproducibly and consistently demonstrated that only about 50% of hemodynamically unstable patients are fluid responsive (5, 11, 12). This is a fundamental concept that is not widely appreciated (2, 3, 13) and challenges the widely accepted notion that fluid administration is the "cornerstone of resuscitation." (2, 3) These observations dictate that only patients who are fluid responsive should be resuscitated with fluid boluses. This concept represents a major paradigm shift and places 'fluid responsiveness" center stage in the management of critically ill and injured patients and those undergoing surgery.

2. CLINICAL SIGNS, THE CHEST RADIOGRAPH, THE CVP, AND ULTRASONOGRAPHY CANNOT BE USED TO DETERMINE FLUID RESPONSIVENESS

Although clinical signs, such as a hypotension, tachycardia, narrow pulse pressure, poor skin perfusion, and slow capillary refill, may be helpful for identifying inadequate perfusion, these signs are unable to determine volume status or fluid responsiveness (14). The CVP or change in CVP following a fluid challenge is no more accurate in predicting fluid responsiveness than flipping a coin and should be abandoned for this purpose (11). It should also be recognized that the change in the mean arterial pressure (MAP) following a fluid bolus is poorly predictive of fluid responsiveness (12, 15). Although widely recommended (4), ultrasonography of the vena cava and its respiratory variation are no more predictive than the CVP for assessing fluid responsiveness

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(16). Echocardiography has limited utility for assessing volume status and fluid responsiveness. Transthoracic measurements of left ventricular outflow tract velocities (VTI) for the estimation of SV require considerable expertise and are not easily obtainable or reproducible in ICU patients (17). Furthermore, the VTI is not ideal for detecting rapid changes in SV following a passive leg raising (PLR) maneuver or fluid challenge.

3. THE PLR MANEUVER OR A FLUID CHALLENGE COUPLED WITH REAL-TIME SV MONITORING IS THE ONLY ACCURATE METHOD FOR DETERMINING FLUID RESPONSIVENESS

Currently, there are only two techniques that are widely available, practical, easy to perform, and physiologically based, which can be used to determine fluid responsiveness with a high degree of accuracy, namely, the PLR maneuver and the fluid challenge (8, 18). These techniques are best coupled with minimally invasive or noninvasive cardiac output monitors, which can track changes in SV dynamically and in real time (8, 19). The PLR is simple to perform taking less than 5 minutes to complete. Beyond its ease of use, this method has the advantage of reversing its effects once the legs are returned to the horizontal position (18). A metaanalysis, which pooled the results of 21 studies, confirmed the excellent diagnostic value of the PLR to predict fluid responsiveness in critically ill patients with a global area under the receiver operating characteristic curve of 0.94 (12). The gold standard to determine fluid responsiveness is the change in SV following a fluid challenge (8). As crystalloids redistribute very rapidly, the fluid bolus should be given as quickly as possible and ideally within a 10–15 minute period. A bolus of between 200 and 500 cc is recommended. Large fluid boluses of 20–30 mL/kg, although still widely recommended (3, 4), are unphysiologic and likely to lead to marked volume overload with severe tissue edema (5, 6).

4. THE HEMODYNAMIC RESPONSE TO A FLUID CHALLENGE IS USUALLY SMALL AND SHORT LIVED

Fluid boluses are most frequently administered to patients with hypotension (7). However, it is not widely recognized that the hemodynamic response to a fluid challenge is usually small and short lived. Nunes et al (20) evaluated the duration of the hemodynamic effect of a fluid bolus in patients with circulatory shock. In this study, 65% of patients were fluid responders whose cardiac index increased by 25% at the end of the infusion (30 min). However, the cardiac index had returned to baseline 30 minutes after the end of the infusion. Glassford et al (21) performed a systematic review that examined the hemodynamic response of fluid boluses in patients with sepsis. These authors reported that although the MAP increased by 7.8 ± 3.8 mm Hg immediately following the fluid bolus, the MAP had returned close to baseline at 1 hour with no increase in urine output. In a retrospective analysis of the ARDSnet Fluid and Catheter Treatment Trial, Lammi et el (22) examined the physiological effect of 569 fluid boluses in 127 patients. According to the protocol, fluid challenges were given for hypotension or oliguria. In this study, the MAP increased by 2 mm Hg following the bolus with no increase in urine output. These data indicate that fluid boluses are generally an ineffective treatment strategy for hypotension, circulatory shock, and oliguria.

5. FLUID RESPONSIVENESS DOES NOT EQUATE TO THE NEED FOR FLUID BOLUSES

Most healthy humans are normally fluid responsive and function on the ascending limb of the Frank-Starling curve; they have preload reserve and do not require fluid "to live" on the flat part of the curve to function optimally. Similarly, critically ill and injured patients and those undergoing surgery do not need to be pushed to the top of their Frank-Starling curve. Patients should only receive a fluid bolus if they are preload responsive and likely to benefit from the fluid bolus, that is, the potential benefits and risk should be evaluated prior to each fluid bolus. Patients should only continue to receive fluid boluses if the hemodynamic benefits are likely to outweigh the risks of an accumulating positive fluid balance. Patients should not receive repeated fluid boluses until they are no longer fluid responsive. As patients "ascend" the Frank-Starling curve, the adverse effects begin to outweigh the benefits as atrial pressures increase with increasing release of natriuretic peptides and increasing hydrostatic edema (**Fig. 1**). Because of the small and short lived effect of a fluid bolus, it may be preferable to treat the fluid responsive septic patient with norepinephrine (23). Norepinephrine will increase venous return, SV, and MAP, thereby increasing organ perfusion while limiting tissue edema (23).

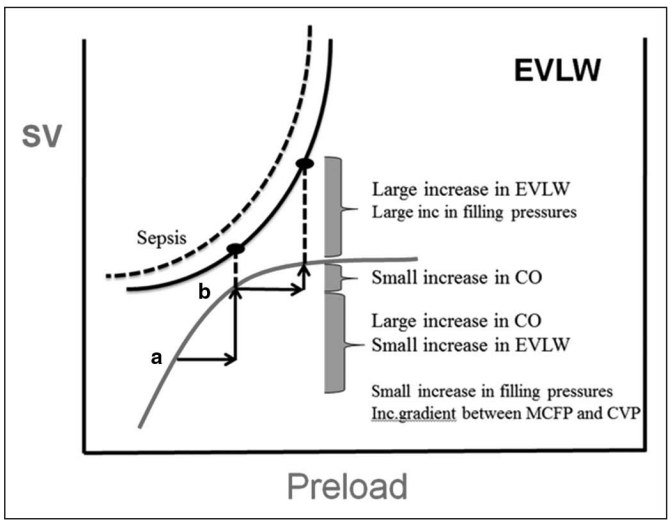

Figure 1. Superimposition of the Frank-Starling and Marik-Phillips curves demonstrating the effects of increasing preload on stroke volume (SV) and lung water in a patient who is preload responsive (a) and nonresponsive (b). With sepsis, the extravascular lung water (EVLW) curve is shifted to the left. CO = cardiac output, CVP = central venous pressure, MCFP = mean circulating filling pressure. Reproduced with permission from Marik and Lemson (24).

6. A HIGH CVP IS A MAJOR FACTOR COMPROMISING ORGAN PERFUSION

Organ blood flow is driven by the difference in the pressure between the arterial and venous sides of the circulation. The MAP minus the CVP is the driving force for organ blood flow. However, when the MAP is within an organ autoregulatory range, the CVP becomes the major factor determining organ and microcirculatory (5). The kidney is particularly affected by increased venous pressure, which leads to increased renal subcapsular pressure and lowered renal blood flow and glomerular filtration rate (25). Legrand et al (26) demonstrated a linear relationship between increasing CVP and acute kidney injury (AKI), with a high CVP being the only hemodynamic variable independently associated with AKI. In critically ill patients and those with heart failure, a CVP of greater than 8 mm Hg has been demonstrated to be highly predictive AKI. There are now compelling data that the primary hemodynamic goal in critically ill and injured patients and those undergoing surgery is an MAP of greater than 65 mm Hg and a CVP of less than 8 mm Hg. Remarkably, this CVP target contradicts current guidelines that recommend targeting a CVP of greater than 8 mm Hg (3, 4). Furthermore, fluid loading oliguric patients with a low CVP with the goal of achieving a CVP of greater than 8 mm Hg may paradoxically increase the risk of progression to AKI.

CONCLUSIONS

Fluid resuscitation is the defining skill of intensivists, emergency medicine physicians, surgeons, and anesthesiologists, yet many of these clinicians have a poor understanding of the fundamental principles involved in fluid administration resulting in conflicting, inconsistent, and potentially harmful treatment strategies. Fluid administration should be guided by an assessment of fluid responsiveness combined with the determination of the potential benefits and harms of fluid administration. Large fluid boluses should be avoided.

REFERENCES

1. Guidelines for intensive care unit admission, discharge, and triage. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. *Crit Care Med* 1999; 27:633–38
2. Dellinger RP, Carlet JM, Masur H, et al; Surviving Sepsis Campaign Management Guidelines Committee: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873
3. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41:580–637
4. Surviving Sepsis Campaign; 6 Hour Bundle Revised. Available at: http://www.survivingsepsis.org/News/Pages/SSC-Six-Hour-Bundle-Revised.aspx. 2015. Accessed April 9, 2015
5. Marik PE: Iatrogenic salt water drowning and the hazards of a high central venous pressure. *Ann Intensive Care* 2014; 4:21
6. Kelm DJ, Perrin JT, Cartin-Ceba R, et al: Fluid overload in patients with severe sepsis and septic shock treated with early goal-directed therapy is associated with increased acute need for fluid-related medical interventions and hospital death. *Shock* 2015; 43:68–73
7. Cecconi M, Hofer C, Teboul JL, et al; FENICE Investigators and the ESICM Trial Group: Fluid challenges in intensive care: The FENICE study: A global inception cohort study. *Intensive Care Med* 2015; 41:1529–1537
8. Marik PE, Monnet X, Teboul JL: Hemodynamic parameters to guide fluid therapy. *Ann Intensive Care* 2011; 1:1
9. Guyton AC: Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev* 1955; 35:123–129
10. Marik PE. The physiology of volume resuscitation. *Curr Anesthesiol Rep* 2014; 4:353–359
11. Marik PE, Cavallazzi R: Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med* 2013; 41:1774–1781
12. Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: A systematic review and meta-analysis. Intensive Care Med 2015; In Press
13. Vincent JL, Pelosi P, Pearse R, et al: Perioperative cardiovascular monitoring of high-risk patients: A consensus of 12. *Crit Care* 2015; 19:224
14. Saugel B, Ringmaier S, Holzapfel K, et al: Physical examination, central venous pressure, and chest radiography for the prediction of transpulmonary thermodilution-derived hemodynamic parameters in critically ill patients: A prospective trial. *J Crit Care* 2011; 26:402–410
15. Monge García MI, Guijo González P, Gracia Romero M, et al: Effects of fluid administration on arterial load in septic shock patients. *Intensive Care Med* 2015; 41:1247–1255
16. Corl K, Napoli AM, Gardiner F: Bedside sonographic measurement of the inferior vena cava caval index is a poor predictor of fluid responsiveness in emergency department patients. *Emerg Med Australas* 2012; 24:534–539
17. Yong Y, Wu D, Fernandes V, et al: Diagnostic accuracy and cost-effectiveness of contrast echocardiography on evaluation of cardiac function in technically very difficult patients in the intensive care unit. *Am J Cardiol* 2002; 89:711–718
18. Monnet X, Teboul JL: Passive leg raising: five rules, not a drop of fluid! *Crit Care* 2015; 19:18
19. Marik PE: Noninvasive cardiac output monitors: A state-of the-art review. *J Cardiothorac Vasc Anesth* 2013; 27:121–134
20. Nunes TS, Ladeira RT, Bafi AT, et al: Duration of hemodynamic effects of crystalloids in patients with circulatory shock after initial resuscitation. *Ann Intensive Care* 2014; 4:25
21. Glassford NJ, Eastwood GM, Bellomo R: Physiological changes after fluid bolus therapy in sepsis: A systematic review of contemporary data. *Crit Care* 2014; 18:696
22. Lammi MR, Aiello B, Burg GT et al. Response to fluid boluses in the fluid and catheter treatment trial. *Chest* 2015; 148:919–926
23. Hamzaoui O, Georger JF, Monnet X, et al: Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. *Crit Care* 2010; 14:R142
24. Marik PE, Lemson J: Fluid responsiveness: An evolution of our understanding. *Br J Anaesth* 2014; 112: 620–622
25. Prowle JR, Kirwan CJ, Bellomo R: Fluid management for the prevention and attenuation of acute kidney injury. *Nat Rev Nephrol* 2014; 10:37–47
26. Legrand M, Dupuis C, Simon C, et al: Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: A retrospective observational study. *Crit Care* 2013; 17:R278