Resident Journal Review:
Assessing Fluid Responsiveness in Resuscitation

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Fluid loading is the first step in the resuscitation of hemodynamically unstable patients. Adequate tissue or organ perfusion is the goal because under-resuscitation results in inadequate organ perfusion, while over-resuscitation increases the morbidity and mortality in critically ill patients. The traditional measurements used to assess resuscitation were based on cardiac filling pressures. They were static measurements such as central venous pressure (CVP) and pulmonary artery occlusion pressure. However, these measures are very invasive and have not been shown to predict fluid responsiveness. There are newer, dynamic tests of volume responsiveness based on the principles of the Frank-Starling curve. Each test uses a maneuver that changes the venous return (preload) and then measures the corresponding change in stroke volume as a marker of fluid responsiveness. Tests that assess changes in pulse pressure, stroke volume, and oximetric waveform are used in mechanically ventilated patients, while passive leg raise maneuvers are done in the spontaneously breathing patient. The role of ultrasound in determining fluid responsiveness has also been studied. In the end, the ultimate goal is to assess whether a critically ill patient’s stroke volume will be increased by the administration of a fluid bolus.


Fluid resuscitation is fundamental to the treatment of severe sepsis, particularly early in the course of the illness, in order to increase intravascular volume and maximize organ perfusion. However, there is some evidence to suggest that further administration of intravenous fluids following this initial phase may be detrimental to the patient.

The practice of early goal-directed therapy, which emphasizes early identification of septic patients and directs resuscitation efforts at maintaining a goal central venous oxyhemoglobin saturation (Scvo2) of ≥70%, has changed the way that many emergency physicians care for septic patients. However, the applicability of these guidelines to patients who are out of the initial 6-hour window or who are being cared for in an intensive care unit (ICU) setting is not known. In fact, a large study byGattinoni, et al., found no difference in morbidity or mortality among ICU patients randomized to three different treatment arms [normal cardiac index (CI), supranormal CI, or Scvo2≥70%]. While additional research is needed, it may stand that goals for treatment of early sepsis may not be relevant for patients later in the disease course.

Following initial resuscitation efforts such as intravenous fluids, antibiotics, vasopressor agents and, at times, blood transfusion, septic patients often have elevated CVP, CI, and Svo2. However, patients often remain hypotensive, have organ dysfunction, and/or have persistent lactic acido-sis. A common dilemma in the emergency room (ER) or ICU is whether to give additional IV fluid boluses, and if so, how much?

Administration of IV fluids is not an altogether benign intervention in the critically ill patient. Excess amounts of fluid can cause or worsen edema of the lungs, heart, intestine, brain, skin, and other tissues. This can lead to worsening respiratory status, abdominal compartment syndrome, and decompensated congestive heart failure, among other complications. For example, several studies have correlated positive fluid balance with increased mortality in ARDS and septic patients. It has also been associated with failure of weaning from mechanical ventilation. However, many of these studies included patients with pulmonary edema. Further research is needed which includes septic patients without pulmonary edema to ascertain whether similar results would be obtained.

The majority of septic patients in the ICU are continuously receiving antibiotics, enteral nutrition, vasoactive medications, sedatives, and gastrointestinal prophylaxis, among other fluid-containing agents. This results in significant fluid intake, even if the patient is not receiving separate “maintenance” fluids. The FACTT trial compared fluid management strategies in ICU patients with acute lung injury, which randomized patients to conservative and liberal fluid management strategies. The study found that, although there was no significant difference in mortality at 60 days, patients in the conservative fluid management arm had improved lung function and shortened duration of mechanical ventilation than those in the liberal fluid management arm. Therefore in most ICU patients who are mechanically ventilated, some degree of fluid restriction should be attempted.

When fluids are given, they are commonly administered as boluses. Although they are routine interventions in the ICU setting, there are no set criteria for how much and what type of fluid makes up a fluid bolus. In one study by Axler, et al., 159 boluses with a mean volume of 390mL were infused to ICU patients in medical and surgical ICUs. In part two of the study, 500mL of saline was infused in 13 patients, with hemodynamic monitoring. The authors found no change in MAP, heart rate, cardiac output (CO), CVP, Svo2, pulmonary artery pressure, oxygen delivery, oxygen consumption, or left ventricular end-diastolic area after the fluid bolus. In three patients who were oliguric, urine output after the bolus did not improve. This study highlights both the prevalence of fluid boluses in the ICU as well as their lack of effectiveness.

To aid in the resuscitation of critically ill patients, static measures to predict fluid responsiveness have been developed. Central venous pressure is one of the most commonly used parameters for determining whether or not to administer IV fluids. However, many studies have proven CVP to be a poor predictor of fluid responsiveness. Historically, pulmonary artery occlusion pressure (PAOP) has also been used as a surrogate for determining left ventricular preload. On the other hand, studies have also shown PAOP to be a poor predictor of fluid responsiveness, even when its use is combined with the stroke volume index. Using a modified

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pulmonary artery catheter, the right ventricular end-diastolic volume index (RVEDVI) can also be measured from the RV ejection fraction. While some studies have shown that RVEDVI may be a better predictor of fluid responsiveness than PAOP, others found no difference in baseline RVEDVI in fluid responders versus non-responders. Left ventricular end-diastolic volume (LVEDA), which is measured by transesophageal echocardiography, has also been studied as a static measure of fluid responsiveness with little success. Finally, global end-diastolic volume (GEDV) can be used to estimate the maximum four-chamber volume of the heart, though it too was found to be only modestly accurate in predicting fluid responsiveness.

In contrast to static preload measures, which rely on hemodynamic values at a given point in time, dynamic predictors have increasingly gained favor for predicting fluid responsiveness. The first such parameter is measurement of right atrial pressure. In a study which included medical and surgical ICU patients, some of whom were mechanically ventilated but actively inspiring, a decrease of $\geq 1$ mmHg in right atrial pressure accurately predicted responsiveness after a fluid bolus. Additional dynamic parameters which are gaining popularity are pulse pressure variation (PPV) and systolic pressure variation (SPV). Both have been studied in septic patients as well as in those with hemorrhagic shock and found to be superior to several static measures of fluid responsiveness such as LVEDA and PAOP. Several studies indicate that a threshold value of PPV of 13% (calculated as maximum pulse pressure minus minimum pulse pressure divided by the average and converted to a percentage) had excellent specificity and sensitivity in discriminating fluid responders from non-responders. PPV, however, is limited by accuracy only with tidal volumes of at least 8mL/kg (which is on the higher end of standard lung protective tidal volume of 6mL/kg), patients with regular cardiac rhythms and with passive ventilation only.

Another dynamic measure that has been studied is peak aortic blood flow velocity variation, which is measured by transesophageal echocardiography (TEE). Though it has been shown to accurately predict fluid responders, peak aortic blood flow velocity variation has limited utility as a dynamic measurement due to the need to measure it using TEE, an invasive procedure. However, monitoring arterial flow variation in other vessels, such as the brachial artery, may be used as a surrogate. As opposed to measurement of peak aortic blood flow velocity variation, measurement of respiratory variation in inferior vena cava (IVC) diameter can be easily performed at the bedside and has been shown to be highly accurate in predicting fluid responsiveness. Finally, the passive leg raise (PLR) has been studied as a substitute for volume challenge due to its ease of performing the maneuver at the bedside and lack of side effects such as volume overload. During the maneuver, Doppler echocardiography is used to measure cardiac output (aortic blood flow or PPV). It has been shown to be a good predictor of volume responsiveness.


Central venous pressure measurements are utilized in many ICUs, emergency departments, and operating rooms throughout the world to assess the fluid status of patients and to aid in decisions regarding administration of fluids or diuretics. Guidelines and textbooks have taught us that CVP correlates with intravascular volume, and that a low CVP suggests volume depletion, and vice versa.

This systematic review addressed CVP monitoring and its ability to predict fluid responsiveness. The researchers searched MEDLINE, Embase, and the Cochrane Database for articles published from 1966 to June 2007. Clinical trials that reported either of the following were included in the study: (1) the correlation between CVP and measured blood volume, or (2) the correlation between CVP or change in CVP and change in stroke index/cardiac output following a fluid challenge. An increase in the stroke index or CO $>10\text{-}15\%$ was used as a marker for fluid responsiveness.

Out of 206 citations initially obtained, 24 studies were selected which included 830 patients. Five of the studies compared CVP with measured blood volume and 19 of the studies assessed changes in CVP and cardiac performance following a fluid challenge. Of the five trials that addressed CVP and its relation to the measured blood volume, the pooled correlation coefficient was 0.16. The correlation coefficient measures the strength of the linear association between two variables. A value of zero indicates no linear association between both variables whereas a value of one indicates a perfect linear association. The pooled correlation coefficient between change in CVP and change in CI following a fluid challenge was 0.11, which reflects a poor correlation.

Marik, et al., also calculated the pooled area under the receiver operator characteristic (ROC) curve for the studies addressing CVP and fluid responsiveness. The area under the curve (AUC) of 0.5 indicates the true-positive rate equals the false-positive rate. Ideally, the AUC should be between 0.9 to 1 to show that the true-positive rate is much higher than the false-positive rate. The pooled AUC that was calculated was 0.56, which suggested that at any given CVP measurement the ability to predict fluid responsiveness was only 56%.

Based on the findings above, Marik, et al., concluded that there was no association between CVP and blood volume, and that CVP did not predict fluid responsiveness. This is clinically important as aggressively hydrating a patient with a low CVP measurement and presumed volume depletion may in fact cause volume overload and pulmonary edema. Also, in a volume depleted patient with a falsely normal to high CVP measurement, fluid restriction or administration of diuretics may be detrimental to the patient as it would exacerbate the volume depletion.

The researchers were only able to find one study that showed the utility of CVP in predicting volume status but emphasized that it was conducted on seven horses undergoing controlled hemorrhage. Marik and his team commented on the use of CVP in the landmark article by Rivers, et al., for early goal-directed therapy. They recommended revision of the guidelines as his review found no correlation with CVP and volume status.
Fluid loading is considered the first step in resuscitating hemodynamically unstable patients. Therefore, determining various methods of assessing intravascular volume is especially important. Clinical studies demonstrated that only 50% of hemodynamically unstable critically ill patients are volume-responsive. So, how do we determine which patients should receive fluids? The key is to identify which patients will increase their stroke volume in response to a fluid bolus. Using the Frank Starling Principle, as the preload increases, left ventricular stroke volume increases until the optimal preload is achieved at which point the stroke volume remains relatively constant. Traditional CVP measures the right atrial (RA) pressure and thus right ventricular (RV) filling, which is assumed to be indicative of RV preload and indirectly, the left ventricular (LV) preload. However, in critically ill patients there is poor correlation between CVP and RV end diastolic volume. Furthermore, there are multiple studies that demonstrate there is NO RELATIONSHIP between the CVP and fluid responsiveness in various clinical settings.

In mechanically ventilated patients, the pulse pressure variation (PPV) using the arterial waveform, the stroke volume variation (SVV) from pulse contour analysis, and the variation of the amplitude of the pulse oximeter plethysmographic waveform has been shown to be HIGHLY PREDICTIVE of fluid responsiveness. These techniques are based on the simple physiology of positive pressure ventilations. Insufflation decreases RV preload, increases RV afterload and these changes lead to decreased RV stroke volume, which are at the minimum at end inspiration. The LV stroke volume is at the minimum at end expiration. The cyclic changes in RV and LV stroke volumes are greater when the ventricles are on the sloped portion of the Frank-Starling curve. A variation of greater than 12% is highly predictive of volume responsiveness.

The “Pleth Variability Index” (PVI) is an automated measurement of the “Perfusion Index” (PI) which reflects the amplitude of the pulse oximeter waveform. The PVI correlates with the respiratory induced variation and can be used to predict fluid responsiveness noninvasively in mechanically ventilated patients. There are limitations on PPV and PVI, such that tidal volume needs to be at least 8ml/kg (which is the higher end of standard lung protective tidal volumes of 6-8ml/kg) and it cannot be accurately used in patients with arrhythmias or those who are spontaneously breathing. Ultrasound is another tool for hemodynamic monitoring in the ventilated patient. Ventilator-induced variation in descending aortic blood flow measured by esophageal Doppler monitoring and measuring the cyclic changes in superior or inferior vena cava diameter by echocardiography can predict fluid responsiveness.

In ventilated patients, mechanical insufflation occluded during end inspiration for 15 seconds can increase arterial pulse pressure and pulse contour cardiac output. An increase of more than 5% accurately predicted fluid responsiveness. This test was able to be performed in cases of cardiac arrhythmias and of low tidal volume, conditions where PVV and SVV are unreliable.

While in the spontaneously breathing patients, passive leg raising (PLR) is the technique of choice. The patient starts in a semirecumbent position and is then changed to a supine position with legs raised to 45 degrees by use of the automatic motion of the bed. Blood transferred to the heart during PLR increases cardiac preload and is considered a reversible “autotransfusion”; it serves as a test of preload responsiveness. The response of aortic blood flow measured by esophageal Doppler, velocity time integral measured by transthoracic echocardiography, and femoral artery flow measured by arterial Doppler in response to PLR are helpful in predicting the response to volume administration. There are two devices (PICCO™ system and FloTrac-Vigileo™) that measure stroke volume and determine the hemodynamic response to PLR. Additionally, NICOM™ is noninvasive and uses bioreactance through electrode stickers on the skin to measure cardiac output during PLR.

Cardiac output (CO) is an important measurement for the management of critically ill patients. Bolus thermodilution has historically been the gold standard for determining cardiac output, however it is invasive as it requires a pulmonary artery catheter. This review article describes a variety of noninvasive cardiac output devices that could become useful in critical care medicine.

One example of a device that calculates cardiac output without a pulmonary artery catheter is the carbon dioxide (CO₂) partial rebreathing technique. This method compares the end-tidal CO₂ partial pressure obtained during a non-rebreathing period with that of a subsequent rebreathing period. The ratio of change can then be used to estimate pulmonary capillary blood flow, and thus CO. One major limitation is that the calculated pulmonary capillary blood flow must be corrected for both intrapulmonary and anatomic shunted blood. This calculation has proven inaccurate in approximating total CO, and should not be used to guide fluid or vasopressor therapy.

Another technique for estimating CO is the esophageal Doppler technique. A Doppler transducer probe is placed in the esophagus and the CO is calculated based on the diameter of the descending aorta and the aortic blood velocity signal. There is a significant learning curve and poor positioning of the probe tends to underestimate the CO. Furthermore, a disproportionate percentage of the increase in CO from a fluid bolus in hemodynamically unstable patients is directed into the carotid arteries and may not correlate with an increase in blood flow velocity in the descending aorta. Another limitation of this technique is that it does not allow for continuous monitoring.

Cardiac output can also be estimated using the concept of pulse contour analysis, which is a technique based on the relationship between blood pressure, stroke volume, arterial compliance, and systemic vascular resistance. This method can calculate stroke volume from the arterial pressure waveform as long as both arterial compliance and systemic vascular resistance are known. It does not, however, correct for discrepancies between central and peripheral blood pressures, which can be large in conditions of intense vasoconstriction and can therefore result in a falsely low CO value.
Pulse contour analysis systems can be divided into three categories based on whether they require: (1) an indicator dilution CO measurement to calibrate the pulse contour, (2) patient demographic and physical characteristics for arterial impedance estimation, and (3) neither calibration nor preload data. Examples of two devices that require calibration are the LiDCO and the PICCO Systems. The LiDCO system uses a lithium indicator dilution for calibration while the PICCO system calibrates via transpulmonary thermodilution. Both of these systems have been shown to be at least as reliable as intermittent pulmonary artery catheter thermodilution over a broad range of CO in a variety of patients. The FloTrac System is an example of pulse contour analysis that does not require calibration, but instead estimates a patient’s vascular compliance based on variables such as sex, age, height, and weight. The system is operator independent and only requires a peripheral arterial catheter. Unfortunately, however, it has shown poor agreement when compared to intermittent thermodilution and has not been shown to accurately trend changes in stroke volume after a volume challenge or with vasopressors. The MostCare system estimates stroke volume by measuring the area under the curve of the arterial waveform and adjusts for factors such as wave morphology. The accuracy of this system, however, has not been proven consistent by independent studies.

Thoracic Electrical Bioimpedance (TEB) has also been used to calculate stroke volume. A high-frequency electric current of known amplitude and frequency is applied across the thorax and the voltage of the returning signal is measured and compared to that of the injected signal. The ratio between voltage and current amplitudes is a measure of transthoracic impedance, which varies in proportion to the amount of fluid in the thorax. Bioimpedance values have shown poor agreement, however, with invasively measured values and are sensitive to placement of electrodes, lung edema, body size, temperature, and humidity.

Another noninvasive example is the NICOM device, which estimates stroke volume by measuring the bioreactance across the thorax. Bioreactance refers to a phase shift in voltage, which can only occur from pulsatile flow. In the thorax, the overwhelming majority of pulsatile flow is from the aorta. Therefore, the NICOM device can estimate CO by measuring bioreactance. Multiple studies have shown a high correlation between CO measured by bioreactance to that measured by thermodilution and pulse contour analysis. In fact, one study by Raval, et al., showed the NICOM system to be more precise than thermodilution in accurately tracking changes in CO.\(^\text{10}\)

In summary, there are a number of noninvasive methods used to estimate the CO without placing a pulmonary artery catheter. An ideal device is easy to use, operator independent, reproducible, and accurate in measuring changes in CO secondary to fluid changes. Future studies are necessary to show that the placement of such noninvasive cardiac output monitors decrease rates of morbidity and mortality in critically ill patients.

Conclusion

Fluid administration has been a key component in the resuscitation of critically ill, hemodynamically unstable patients. Various methods for assessing volume status and fluid responsiveness have developed over time.

Static measures to predict fluid responsiveness include CVP, PAOP, RVEDVI, LVEDA, and GEDV; which have had poor to moderate accuracy in determining fluid responsiveness.

In contrast to static preload measures, which rely on hemodynamic values at a given point in time, dynamic predictors have increasingly gained favor for predicting fluid responsiveness. PPV and SPV have been found to be superior to several static measures of fluid responsiveness such as LVEDA and PAOP.

Other dynamic measures include peak aortic blood flow velocity variation (which is measured by TEE), measurement of respiratory variation in IVC diameter, and PLR; which have all shown to be good predictors of fluid responsiveness.

Cardiac output can be estimated using the concept of pulse contour analysis. These devices include the LiDCO system, the PICCO system, the FloTrac System, and the MostCare system.

The NICOM device is noninvasive and estimates the SV by measuring the bioreactance across the thorax. In the thorax, the majority of pulsatile flow is from the aorta which allows the device to estimate the CO.

Additional References: