Does my patient need a fluid bolus?

Predicting fluid responsiveness in the critically ill patient

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Abstract

Intravenous fluid administration is a cornerstone of intensive care resuscitation. When considering fluid therapy, clinicians must attempt to answer two fundamental questions: (1) Is an increase in cardiac output likely to reverse or improve a hypoperfusion state? and (2) Is a fluid bolus likely to increase the cardiac output? Recent data on the potentially harmful effect of fluid overload in ICU patients have led intensivists to reconsider the sacrosanct practice of the “fluid challenge”. As such, various predictors of fluid responsiveness have been proposed as potential alternatives to inform clinicians on the best course of action. A better understanding of the largely ignored basic physiologic mechanisms that determine fluid responsiveness can inform the choice of available bedside maneuvers, interpretation of data, and use of available technologies in hypoperfused patients.

Predicting fluid responsiveness: overview of the clinical problem

Intravenous fluid administration is a cornerstone of intensive care resuscitation. In a preload responsive patient, i.e., a patient whose right and left ventricles operate on the steep portion of the Frank-Starling curve, additional volume will increase stroke volume and increase cardiac output[1]. That is not to say that all of these patients should receive a fluid bolus: euvolemic patients with normal cardiac function are also, by definition, fluid responsive. Rather, clinicians must attempt to answer two fundamental questions: (1) Is an increase in cardiac output likely to reverse or improve a hypoperfusion state? and (2) Is a fluid bolus likely to increase the cardiac output? While the former question is often difficult to answer, the latter has been the object of multiple clinical research studies in the past decade. Recent data on the potentially harmful effect of fluid overload in ICU patients have led intensivists to reconsider the sacrosanct practice of the “fluid challenge”[2,3,4,5]. As such, various predictors of fluid responsiveness have been proposed as potential alternatives to inform clinicians on the best course of action.

Fluid responsiveness is generally regarded as an increase in stroke volume (or cardiac output/index) by 10-15% after fluid administration (volumes vary), depending on technique[6]. While easily obtained static measures of volume status (central venous pressure [CVP] or pulmonary artery occlusion pressure [PAOP]) have been used for decades and are still routinely used, they have been shown to be reliably unreliable at predicting fluid responsiveness in critically ill patients[7,8,9,10,11]. There are many limitations to pressure measurements (such as CVP or PAOP) used as surrogates for a volume (preload, or right or left ventricular end-diastolic volume). For example, there is substantial inter- and intra-individual variability of cardiac compliance, and it is also important to emphasize that “low preload” does not necessarily equate with “preload responsiveness”. Critically ill patients often demonstrate perturbations of their circulatory system that prevent them from responding normally to fluid boluses, particularly when pathophysiologic conditions such as sepsis[7,10,12,13,14,15,16,17,18] or therapeutic interventions such as mechanical ventilation are present[6]. As mentioned above, fluid administration is not always a benign intervention: a positive fluid balance has been found to be independently associated with negative outcomes, including prolonged mechanical ventilation[4,5] and even increased mortality[2,3].

As such, routine decisions, such as ordering a fluid bolus, may have significant consequences in critically ill patients, and a thoughtful approach to fluid administration is warranted. A better understanding of the largely ignored basic physiologic mechanisms that determine fluid responsiveness will go a long way in understanding how available bedside maneuvers can assist clinical decision-making. Herein, we will briefly present the basic physiologic determinants of fluid responsiveness and provide a concise narrative review of the literature that provides guidance for clinicians faced with these “routine” but potentially consequential decisions. Ultimately, we will provide a practical approach for assessing fluid responsiveness in commonly encountered patient scenarios with unstable hemodynamics.

Overview of venous system physiology and limitations of static measures of fluid responsiveness

Because the venous side of the human circulatory system is significantly more compliant than its arterial counterpart, small changes in blood volume may only minimally change venous pressure measurements (i.e. CVP)[19]. The venous system consists of two volumes of blood, the unstressed volume and the stressed volume. The unstressed volume is the volume of blood present in a vein when the transmural pressure is equal to zero[19] ; it typically accounts for about 70% of the venous blood

volume. The stressed volume, consequently, is the volume of blood responsible for a positive transmural pressure, and typically accounts for approximately 30% of total venous blood volume. The stressed venous volume is the main determinant of the mean circulatory filling pressure (MCFP), which is the mean pressure in the vasculature if cardiac output stops and pressure is redistributed equally[19]. Furthermore, the pressure gradient between MCFP and CVP is the primary factor regulating venous return, and thus, a key contributor to stroke volume so long as the heart is functioning on the steep portion of its function curve. Therefore, in order for an increase in CVP to be accompanied by an increase in venous return, the MCFP must increase more than the increase in CVP. This requirement is met when the stressed venous volume is increased, either by volume administration or vasopressors[19], the latter shifting volume from the unstressed portion to the stressed portion of the venous system.

During spontaneous breathing, a decrease in intrathoracic pressure lowers CVP without decreasing MCFP, resulting in an increase MCFP-CVP gradient and increased venous return. While mechanical ventilation with positive pressure increases intrathoracic pressure and CVP, downward displacement of the diaphragm in euvolemic patients also compresses the intraabdominal vasculature, which, along with neurohormonal (antidiuretic hormone and renin-angiotensin-aldosterone system) and reflex-mediated splanchnic arterial venoconstriction, increases the MCFP and maintains the gradient between MCFP and CVP, and therefore, venous return[19]. In hypovolemic patients with reduced MCFP, the increased intrathoracic pressure generated by mechanical ventilation may result in such a reduction in the MCFP-CVP pressure gradient that the venous return is compromised. Consequently, the cardiac output decreases and hypotension ensues.

MCFP, given its intimate relationship with stressed venous volume, would therefore be the ideal parameter to aid in assessing the volume status, but it is not possible to measure it clinically. Classic surrogates of MCFP such as CVP and PAOP have been repeatedly shown to fail to accurately identify volume-responsive patients[7,8,9,10,20,21,22,23] likely because of the other factors contributing to these surrogates, such as venous resistance[19]. Essentially, CVP itself represents a surrogate for PAOP, itself a surrogate for left atrial pressure, and therefore left ventricular end-diastolic pressure (LVEDP), which is used as surrogate for the left ventricular preload, i.e. the left ventricular end-diastolic volume (LVEDV). It is therefore not surprising that PAOP does not correlate reliably with LVEDV, as measured by radionuclide left ventricular ejection fraction, especially when positive end-expiratory pressure is applied[24]. Additional technical factors impeding accurate PAOP measurements further limit its usefulness as a surrogate for LVEDP (and by extension LVEDV), including among others catheter location (i.e. placement outside West zone III), transducer placement and calibration, system dampening, respiratory artifact, valvular heart disease and altered left ventricular compliance[24].

In health, dramatic changes in MCFP and CO are seen with exercise but result in minimal changes in CVP[19,25]. It logically follows that CVP should not be expected to represent a reliable marker for fluid responsiveness in disease, yet historically, it is the most commonly reported factor used by intensivists to guide decision making in fluid management[26]. In fact, the predictive power of CVP for fluid responsiveness was no better than a coin-flip with a cutoff of < 5 mm Hg in patients receiving mechanical ventilation (positive predictive value 47%)[7]. When evaluated in sepsis, PAOP performed only marginally better, with a positive predictive value for fluid responsiveness of 54% using a PAOP threshold of < 12 mmHg[7]. Right atrial pressure (i.e. CVP) and PAOP also failed to predict fluid responsiveness in spontaneously breathing patients[20]. Right ventricular end-diastolic volume index (RVEDVI), as calculated from a pulmonary artery catheter using the right ventricular ejection fraction, has yielded variable results in its ability to predict fluid responsiveness as well[27,28], though it outperforms PAOP for this purpose[29]. Perhaps CVP is most valuable when its value is > 15 mm Hg, as this cutoff was successful in predicting no response to fluids[7]. Other static measures, such as left ventricular end-diastolic area, have yielded similarly disappointing results[30,31,32].

Dynamic methods of predicting fluid responsiveness

Respiratory changes in CVP and IVC diameter

Given the shortcomings of CVP and other static measures of fluid responsiveness in critically ill patients, several dynamic methods have been proposed and extensively studied in various populations. Simple ultrasound imaging of inferior vena cava (IVC) diameter changes with mechanical ventilation has been shown to be predictive of fluid responsiveness in multiple studies [12,33]. Methodological issues include the different thresholds proposed for predicting fluid responsiveness (12% vs. 18% change in diameter with inspiration), and the optimal location for making these measurements, calling into question the generalizability of these results. These studies were not performed in spontaneously breathing patients (i.e. patients triggering ventilator breaths) and tidal volumes on average were more than 8 mL/kg ideal body weight in both groups. A subsequent small study in mechanically ventilated patients on vasopressors, a portion of whom also had sepsis, showed that a change in IVC diameter = 12% had a sensitivity of 100% but a specificity of only 53% for predicting fluid responsiveness, perhaps further supporting uncertainty as to the best cutoff threshold[34].

The utility of IVC diameter changes has been studied in spontaneously breathing patients as well. In one group of spontaneously breathing patients, respiratory variation in IVC diameter had only a fair sensitivity of 70% and specificity of 80% for predicting fluid responsiveness when a large variation (>40%) in diameter was present[35]. In a recent small study, vena cava collapsibility index (difference in maximum and minimum diameters divided by the maximum diameter) > 15% had a positive

predictive value of only 62%, but negative predictive value of 100%[36]. If a cutoff > 50% was used, the positive predictive value was 75% and negative predictive 80%[36]. The IVC was imaged in M mode just proximal to junction of hepatic veins, about 0.5 cm to 3 cm from the ostium of the right atrium[36]. Taken together, if a variation of at least 15% is not present, the patient seems unlikely to respond, but there is still considerable uncertainty for those with variation more than 15%.

The observed variability in findings between mechanically ventilated patients and those spontaneously breathing highlight the different factors that contribute to IVC diameter change, namely intrathoracic and intraabdominal pressures, CVP and compliance of the IVC, and the different physiologies seen in positive-pressure versus spontaneous (negative-pressure) ventilation. In positive-pressure ventilation, IVC distension during inspiration is a reflection compliance and potentially “preload reserve”, because intrathoracic pressure increases more than intraabdominal pressure on a positive-pressure breath[37]. Conversely, IVC collapsibility with negative-pressure breaths may be secondary to low CVP, but could also be the result of vigorous inspiratory effort and substantial decrease in intrathoracic pressure[37]. IVC diameter change has been correlated with CVP[38], but we have already discussed the unreliability of CVP as a predictor of fluid responsiveness[7,9,11].

The location chosen to make these measurements along the IVC also seems to matter, at least in spontaneously breathing patients, as diameter variation near the inlet to the right atrium did not correlate with variations at other locations in healthy patients during quiet respiration[39].

A recent meta-analysis of 8 studies using IVC diameter change to predict fluid responsiveness, with most patients mechanically ventilated, concluded that using IVC collapsibility to predict fluid responsiveness has value (pooled sensitivity of 76% and specificity of 86%), though more so in mechanically ventilated patients than in spontaneously breathing patients, with a diagnostic odds ratio of 30.8 versus 13.2, respectively[40]. However, this analysis provides no definitive answer as to what threshold we should use at the bedside[40]. The lack of specificity in spontaneously breathing patients and the lack of definitive threshold represent the biggest limiting factors for using respiratory changes in IVC diameter. Using a lower percentage change in mechanically ventilated patients, such as 12%, likely increases the false positive rate[34].

CVP is a poor predictor of fluid responsiveness as a static measure, but it has also been assessed as a dynamic measurement, perhaps with more value. One study in post-cardiac surgery patients who were mechanically ventilated did show reliability of “CVP index” (CVP on expiration – CVP on inspiration/CVP on expiration x 100) = 5%, with a sensitivity and specificity of 89% and 91% when using pulse pressure variation > 13% (see below) as the reference standard[41]. Furthermore, inspiratory decrease in CVP = 1 mmHg in spontaneously breathing on positive pressure ventilation patients predicted fluid responsiveness had a positive predictive value of correctly in 16 of 19 responders (defined as increase cardiac output with = 250 mL/min after fluid challenge) and incorrectly in only one of 14 non-responders, with corresponding positive and negative predictive values of 94% and 81%, respectively[9]. However, these findings were not confirmed in a second group of actively inspiring mechanically ventilated patients[20].

The changes in pleural pressure during the respiratory cycle are also imposed on the superior vena cava (SVC), and the collapsibility of the SVC may be a better predictor of fluid responsiveness in septic shock[18]. Measuring cardiac index by Doppler and evaluating SVC collapsibility by transesophageal echocardiography (TEE), a collapsibility of 36% for the superior vena cava (maximum diameter on expiration minus minimum diameter on inspiration divided by the maximum diameter on expiration) distinguished fluid responders from nonresponders with a specificity of 100% and sensitivity of 90%[18]. However, imaging of the superior vena cava requires the use of TEE, limiting its widespread use.

Passive Leg Raise

Passive leg raise (PLR) is a safe and easy bedside maneuver that can provide valuable insight on the effect of a fluid challenge if a measure of cardiac output or stroke volume is available. PLR increases blood return from periphery to the central circulation and increases preload[42,43]. Furthermore, PLR-induced changes in stroke volume as measured by analysis of systemic arterial pressure waveform correlate with changes in stroke volume on transthoracic echocardiogram[44]. Data in mechanically ventilated patients with esophageal Doppler and arterial access demonstrated that an increase in aortic blood flow by 10% with PLR predicted a positive fluid response with a sensitivity of 97% and specificity of 94%[43]. However, specificity was markedly reduced (46%) when patients were spontaneously breathing[43]. Other studies in spontaneously breathing patients, including those with severe sepsis or acute pancreatitis, have shown good specificity (89-100%) but poorer sensitivity to predict fluid responsiveness [45,46,47]. These contradictions in supporting data bring into question the reliability and generalizability of PLR in spontaneously breathing patients. Furthermore, a measure of stroke volume, cardiac output or Doppler peak velocities must be utilized simultaneously when performing the maneuver. It is likely that PLR, as has been shown for the Trendelenburg position, results in some degree of vasoconstriction and increased systemic vascular resistance. As such, an increase in blood pressure during PLR may reflect vasoconstriction rather than an increase in cardiac output[48].

Lamia et al. used a more conventional noninvasive measurement, transthoracic echocardiography, to determine if PLR could predict fluid responsiveness in hemodynamically unstable patients, 75% of whom had sepsis[46]. They found that a PLR-induced increase in stroke volume of 12.5% or more (using the product of the velocity time integral of aortic blood flow and aortic valve area) predicted an increase in stroke volume by at least 15% after subsequent fluid administration, with a specificity of 100%

and sensitivity of 77%[46]. Furthermore, this study included patients on mechanical ventilation with active inspiration (58%) and those without mechanical support (42%), and 25% of patients were in atrial fibrillation, though with fairly regular ventricular rates, perhaps allowing better generalization of the results compared to most other tested methods[46]. As critical care ultrasound is becoming more available, this could represent an attractive option. However, the methodology used to calculate stroke volume may require technology and skills many intensivists do not currently possess, and reported sensitivities and specificities may be dependent on operator skill.

More recently, bioreactance technology, a noninvasive method to measure cardiac output using only four surface electrodes[49,50], has been evaluated with PLR to assess fluid responsiveness. In postoperative cardiac surgery patients, PLR-induced changes in cardiac output as measured by bioreactance had a sensitivity of 88% and a specificity of 100% for predicting fluid responsiveness[51]. In hemodynamically unstable patients, PLR and bioreactance had a sensitivity of 94% and specificity of 100% for predicting fluid responsiveness (defined as > 10% increase in stroke volume index)[52]. However, in another group of critically ill patients, all of whom had shock (83% septic, 10% hypovolemic and 7% cardiogenic), bioreactance was unable to accurately measure cardiac index when compared with transpulmonary thermodilution and failed to predict fluid responsiveness when coupled with PLR[53]. The proportion of patients with septic shock in the latter study was considerably higher than previous studies, which may have contributed to the discrepant findings. The noninvasive nature of bioreactance is highly attractive, but further research is necessary to help delineate the role of bioreactance as a means of assessing changes in cardiac output in the critically ill, especially those with sepsis.

Pulse and Systolic Pressure Variation

Spontaneous inspiration causes a decline in intrathoracic pressure, and this pressure change is reflected in both CVP and PAOP, even when breathing efforts occur during mechanical ventilation. The presence or absence of active inspiration and the respective effects on pleural pressure during mechanical ventilation likely contributes to the observed inability of right atrial pressure changes to reliably predict fluid responsiveness[9,20,41,54].

Passive positive pressure ventilation increases pleural pressure on inspiration before returning to “baseline” values on end-expiration[55]. As a result of these cyclic changes, inspiration reduces right ventricular filling, and increases left ventricular filling and compliance, while lowering left ventricular afterload[6], resulting in an increase in left ventricular stroke volume and systolic blood pressure, promptly followed by a decrease in the same. As pulse pressure is directly proportional to stroke volume, its variability has been studied as a predictor for fluid responsiveness.

Pulse pressure variation (PPV), calculated as the difference between the maximum and minimum pulse pressures divided by the average of their sum and multiplied by 100, at a cutoff of > 13% outperformed right atrial pressure, PAOP, and systolic pressure variation in predicting fluid responsiveness, with a sensitivity and specificity of 94% and 96%, respectively[10]. This method has garnered substantial attention because while it does require arterial access, there is no requirement to measure stroke volume or cardiac output. All that is necessary is observing the minimum and maximum pulse pressure over a 30 second interval and performing the calculation.

PPV has been validated in different populations, but its general application has been hampered by several requirements defined in earlier studies[20,43,54,56,57]. First, the patient must be mechanically ventilated with tidal volumes 8-12 mL/kg ideal body weight, as PPV has not performed well with lower tidal volumes, including those with acute respiratory distress syndrome (ARDS) ventilated with a low tidal volume strategy[10,56,57,58]. One might reason that if alveolar volume change is important for the increase in left-sided filling with positive pressure ventilation, and a large percentage of the lung in an ARDS patient is derecruited, when small tidal volumes are utilized, the change in lung volume is insufficient to translocate enough blood from the lung to left atrium to substantially affect the stroke volume as measured by PPV. Next, the heart rhythm must be regular, to ensure the variability in stroke volume is not due to different filling times[54], which is a requirement many critically ill patients fail to fulfill. Finally, inspiration must be passive, which is achieved by adjusting ventilator settings or, more commonly, with heavy sedation with or without paralysis, as PPV’s ability to predict fluid responsiveness has limitations across populations of spontaneously breathing patients[10,20,43]. In a group of 59 elective thoracic surgery patients, PPV during spontaneous forced inspiration, but not tidal breathing, was able to predict fluid responsiveness when a cutoff of 13.7% was used, with a sensitivity of 90% and specificity of 87%[59]. However, in hemodynamically unstable patients, the sensitivity of PPV to detect fluid responsiveness was only 63% in one study (using a cutoff of 12%), though it did remain highly specific (92%)[60]. Forced expiration further decreased sensitivity, though specificity was preserved[60]. Therefore, the use of PPV cannot be recommended in spontaneously breathing patients with or without mechanical ventilation.

Similarly, systolic pressure variation demonstrated an outstanding ability to predict fluid responsiveness in sepsis-related hypotension requiring mechanical ventilation when a drop of more than 5 mmHg was used as a cutoff (positive predictive value of 95% and negative predictive value 93%)[17] and this performance was confirmed in a subsequent study of mechanically ventilated cardiac surgery patients[61].

A Practical Bedside Approach

With an understanding of the principles and predictive power of the bedside tools available to assess fluid responsiveness, one can choose the most appropriate option for an individual patient. We agree with others[7,54] that given its poor predictive value for fluid responsiveness in a variety of patient populations, CVP should be abandoned as a predictor of fluid responsiveness in general[62,63,64] . For reasons outlined above, the same can be said of PAOP[7,24].

If a measure of cardiac output or stroke volume is readily available, passive leg raise paired with its measurement is the best method for predicting fluid responsiveness across different patient populations. PLR has robust predictive power in mechanically ventilated patients[43], and although it performs slightly worse in spontaneously breathing patients[45,46,47], the physiologic rationale of the technique is evident: if increasing preload using the patient's own blood volume (i.e. raising the legs) results in increased stroke volume, it is fair to assume that increasing the circulating volume with a fluid bolus will have a similar effect.

We recommend recording baseline values for stroke volume in the semi-recumbent position (i.e. head of bed elevated 30-45 degrees) and then position the patient supine. The legs should then be raised to a 45 degree angle and the stroke volume measurement recorded and compared with baseline values[43]. If the stroke volume increases by more than 12.5%, a fluid bolus is recommended. As discussed above, many options are available to measure stroke volume, some of which are non-invasive but require new technology or advanced echocardiographic skills, and the choice of which option is used depends on its availability and the expertise of the team caring for the patient.

Reliable prediction of fluid responsiveness can be achieved using pulse pressure variation in intubated patients with regular heart rate who are not triggering the ventilator and have an arterial line in place. Based on the available literature, we recommend increasing the tidal volume to at least 8 mL/kg ideal body weight, and perhaps 10 mL/kg if acceptable for the brief period of evaluation, in volume assist control mode. The respiratory rate can transiently be increased as well to ensure that patient triggering does not confound the test. Alternatively, sedation with or without paralysis to the same end is reasonable. Record the arterial pressure wave form for about 30 seconds, so that several breaths are present to include in the evaluation, and print the strip. Manually measure the pulse pressure maximum and minimum and insert the numbers into the formula: PPV = (maximum pulse pressure – minimum pulse pressure) / mean of maximum and minimum pulse pressure x 100%. If this value is greater than 13%, the patient is reliably fluid responsive[10].

For a spontaneously breathing patient free of mechanical ventilation with no central access or invasive measure of cardiac output, most circumstances would probably warrant empiric administration of a fluid bolus through a peripheral IV in the event of hypotension or signs of circulatory failure, unless a cardiogenic etiology is suggested by history and exam findings. This type of "fluid challenge" could be paired with serial lactate levels as a surrogate for increasing flow or reversing hypoperfusion[65]. PLR with assessment of stroke volume by transthoracic echocardiography as described by Lamia et al[46] or perhaps cardiac output by bioreactance are attractive options, but technical skills and availability of technology limit widespread application. We consider all other options to be of insufficient reliability to predict fluid responsiveness; however, assessing changes in IVC diameter using bedside ultrasonography likely offers the next best additional information.

Practically speaking, a longitudinal subcostal view utilizing M mode time recorded diameter changes in IVC diameter 2-3 cm from right atrium during inspiration appears to be add some insight[35,36]. If IVC collapsibility index ({maximum diameter – minimum diameter}/maximum diameter) is greater than 40%, the patient is very likely to respond to fluid challenge. A collapsibility index of less than 15% seems to reliably predict non-responders, but that leaves us with the large area between 15% and 40% where little additional predictive power is gained with this methodology[35,36]. It seems little value is added by the knowledge of CVP for those patients with a central venous catheter in place, other than those with very high CVP (i.e. > 15 mmHg) are unlikely to respond to fluid[7,20].

Conclusion

The "routine" decision of whether or not to administer fluid to a hemodynamically compromised patient remains a clinical challenge. Given the heterogeneity of critically ill patients, we may never have a "one size fits all" approach. However, with a sound knowledge of the physiology of heart-lung interactions and application of available maneuvers and technologies to the right patients, the decision can be more than just a flip of the coin.

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