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Predicting the circulation's response to fluid resuscitation

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Abstract

Fluid resucitation plays a crucial role in pediatric resuscitation. Predicting fluid responsiveness is important as excessive fluid may decrease cardiac efficiency, and even induce overload. Various pathophysiology of shock suggest that fluid only benefit in optimizing preload. Various methods to assess fluid responsiveness includes measurement of static preload indices, dynamic indices to estimate volume status, and the use of protocols such as fluid challenge and passive leg raising technique. This paper highlights the mechanisms behind each measurements and summarized their use as predictor of fluid responsiveness in pediatric patients.

Key words: Fluid responsiveness, fluid resuscitation, pediatrics, hemodynamics.

Introduction

Fluid therapy is one of the modalities for resuscitation in critically ill patients. For years, it remains the principal therapy of choice in managing children in critical care settings. Acutely ill children may fall into shock of various pathophysiology. Every year, 3 to 7 out of 100 children suffer from shock. In developing countries, hypovolemic shock due to infectious gastroenteritis is the most common type, followed by septic shock. (1,2)

Unlike adults, children are more prone to shock, especially of hypovolemic origin. This is attributed to the higher percentage of extracellular fluid in children. (3) Furthermore, shock recognition in pediatric patients is challenging. The prevalence of pediatric shock in a study conducted in Kenya is found to be 1.5%. Septic shock is the leading cause of pediatric shock with around 57% of cases, followed by hypovolemic shock (24%), distributive shock (14%), and cardiogenic shock. (1)

Despite the importance of fluid in the management of critically ill children, excess fluid resuscitation may lead to dangerous complications. Studies have demonstrated that fluid overload disrupts oxygenation in patients and lead to organ dysfunction. (4-6) High volume of fluid resuscitation in patients with sepsis has also been shown to significantly increase mortality. (7-9) Negative effects of positive fluid balance in critically ill children have been well demonstrated. It has been shown to increase mortality, (4,9) result in tissue and lung edema, (10) and decrease oxygenation index. (11)

Given the importance of fluid resuscitation and the negative effects of positive fluid balance, clinicians should carefully titrate the amount of fluid administered based on individual response to fluid resuscitation. This calls for a reliable method to predict the patient's hemodynamic response to fluid resuscitation.

Hemodynamic changes during acute critical illness

Acute changes in critical illness that may precipitate shock include intravascular volume depletion (hypovolemic shock), impaired myocardial contractility (cardiogenic shock), and increased capillary permeability followed by abnormal fluid dis-

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tribution. (12) Commonly, these pathophysiologies of shock coexist.

Given various pathophysiologies of shock, the benefit of fluid administration only extends as far as optimizing venous return and preload, increasing stroke volume. This is true as according to the Frank-Starling principle, stroke volume increases following an increase in preload and plateaus as it reaches the preload-independent state. At this point, increased preload no longer increases stroke volume. Further increase in fluid volume beyond the capacity of ventricular contractility would even result in decreased cardiac efficiency which is detrimental. (10)

Consequently, being able to identify where the Frank-Starling curve flattens would be useful in guiding fluid resuscitation. There have been several methods used to predict the circulation's response to fluid resuscitation, this involves the use of both static and dynamic indices of preload, and the use of several protocols.

Static indices of volume status

Central venous pressure (CVP) is the most common parameter used to guide fluid resuscitation in clinical practice, especially in critically ill patients. CVP may arguably reflect venous return hence helpful in guiding fluid administration. CVP transducer is placed at a reference point in the right atrium, usually at the phlebostatic axis which provides the best consistency of CVP measurement. (13) CVP measurement is often used as a target in resuscitation guidelines, representing the preload as it resembles right atrial pressure. However, the technical limitations of CVP include, the static nature that is inferior to dynamic indices, and it is pressure measurement that is affected by surrounding pressure. (14) Similarly, pulmonary artery occlusion pressure (PAOP) or pulmonary artery wedge pressure (PAWP) represents left atrial pressure hence left ventricular function. (15)

However, the most reliable indicator of intravascular volume is transmural pressure, i.e. the difference between intravascular and extravascular pressure. Both CVP and PAOP only resemble intramural pressure, which is influenced by the respiratory cycle, cardiac cycle, as well as the anatomical and physiological characteristics of the heart. (15) A meta-analysis by Marik and Cavallazzi on 43 studies comparing CVP and stroke volume index/cardiac index to predict fluid responsiveness obtained area under the curve (AUC) of 0.56 (95% CI 0.54-0.58), with a correlation coefficient between baseline CVP to changes in stroke volume index (SVI) or cardiac index (CI) of 0.18 (95% CI 0.1-0.25). Hence, they recommended to abandon the approach of using CVP to predict fluid responsiveness. (16) Similarly, PAOP principally is the back-flow pressure of the pulmonary arterial flow, and is helps to identify pulmonary vascular resistance (and pulmonary edema). This, however, only represent a static value, which lack correlation to predict ventricular preload, subsequently fluid responsiveness. A study by Kumar, et al in normal healthy subjects undergoing pulmonary catheterization and volumetric echocardiography, receiving 3 L of normal saline infusion over 3 hours demonstrated neither CVP nor PAOP correlated to end-diastolic volume index and stroke volume index. (17) This study concluded that both static indices of preload have limited use to predict ventricular preload, moreover fluid responsiveness.

Furthermore, the use of CVP in measuring fluid responsiveness is actually counter intuitive. An increase in CVP may reflect increased preload, but not necessarily a response to fluid resuscitation. A good clinical response to fluid resuscitation should yield a minimal increase in CVP (with a large increase in cardiac output), while increase in CVP resembles poor cardiac compliance. (18) Hence the use of CVP alone, uncoupled with cardiac output measurement has little contribution to predict fluid responsiveness. In clinical practice, proper measurement of CVP may be useful to indicate right ventricular filling. Knowing the status of the preload may not predict fluid responsiveness. However, CVP measurement over time combined with the evaluation of cardiac output may be useful in guiding fluid administration.

As a surrogate of the right atrial pressure (Pra), CVP curve may be used to predict fluid responsiveness. Venous return is determined by the pressure gradient obtained by mean systemic filling pressure (Pmsf) minus Pra. Respiratory cycle affects Pra as follows: inspiration creates a drop in intrathoracic pressure and increases venous return due to a wider gradient between systemic filling pressure (Psf) and Pra. Conversely, upon expiration smaller pressure gradient yields a smaller venous return. (19) Based on Frank-Starling's theory, cardiac output is higher during inspiration as larger venous return creates larger sarcomere stretching and greater stroke volume. As the curve plateaus, a further increase in venous return is limited by the maximal length of the sarcomere, hence produces no further increase in stroke volume. Interestingly, this respiratory variation of Pra can be used to predict fluid responsiveness. Madger, Georgiadis, and Cheong tested their hypothesis on the use of inspiratory fall in Pra to predict fluid responsiveness

and obtained a significant increase in cardiac output in patients whom Pra decreased by ≥ 1 mmHg upon adequate inspiratory effort. (19) However, since many conditions have to be fulfilled before we can interpret fluid responsiveness based on Pra (respiratory swings in CVP), this method is rarely used in clinical settings.

Dynamic indices of fluid status

Since static indices have limited use as predictors of fluid responsiveness, dynamic indices have taken the spotlight as more reliable predictors. Popular dynamic indices for instance stroke volume variation (SVV) and pulse pressure variation (PPV), and inferior vena cava collapsibility (IVC). Using the understanding of heart-lung interactions during mechanical ventilation use, SVV can be measured using pulse contour analysis, while PPV from arterial waveform analysis using various measurements.

This is based on the physiological findings of changes in left ventricular stroke volume during the respiratory cycle. In spontaneously breathing individuals, blood pressure decreases on inspiration albeit the amplitude is less than 5 mmHg. Paradoxical to spontaneous respiration, the use of mechanical ventilation exerts cyclic changes on venous return, consequently aortic blood flow. On mechanical ventilation, inspiration decreases right ventricular preload and increases right ventricular afterload due to higher alveolar pressure than pleural pressure, creating gradient against right ventricular ejection. Meanwhile, left ventricular preload increases due to alveolar capillary squeezing and afterload decreases, hence stroke volume increases during inspiration. As previously described, inspiratory reduction in right ventricular ejection subsequently decreases stroke volume upon the next expiration (**Figure 1**).

Pulse pressure variation is directly proportional to the stroke volume, hence also produces stroke volume variation. As both are influenced by arterial compliance, for a given compliance, the amplitude of pulse pressure correlates to left ventricular stroke volume. During hypovolemia, PPV and SVV are greater. This is due to inspiratory decrease in right ventricular output, subsequently decrease in left ventricular output during the following expiration. In lower volume status, changes in stroke volume is more sensitive to preload status. In contrast, in hypervolemic conditions, PPV and SVV are smaller. (20)

Assessment of SVV can be done using echocardiography, while PPV can be done via arterial line. Successful measurements over at least one mechanical breath allow for determination of respiratory variation, with good predictor value of fluid responsiveness. A meta-analysis by Yi, et al concluded that SVV has a moderate predictive value of fluid responsiveness in children with a pooled sensitivity of 0.68, specificity of 0.65, and AUC of 0.81. (21) However, several conditions may not be suitable for PPV and SVV measurements, such as small tidal volume, spontaneous breathing, open chest (example during surgery), and sustained cardiac arrhythmia. (22) Consequently, as children have different and evolving cardiovascular and respiratory physiology such as higher heart rate, higher vascular compliance and higher thoracic wall compliance, (23) physicians have to be careful in interpreting these indices as their use is even more limited in smaller children.

Fluid responsiveness tests

Weil fluid challenge

Fluid challenge was first introduced by Weil and Henning back in 1979 to identify fluid responders. Weil and Henning's fluid challenge protocol involved carefully monitored fluid administration using CVP and PAWP. Fluid was administered until shock is corrected or preload indices indicate optimal preload has been achieved. (24) Since then, various protocols for fluid challenge exists, paired with many ways to determine fluid responsiveness.

Fluid challenge remains the gold standard for assessing fluid responsiveness in critically ill patients. Currently, there is no standardized protocol for fluid challenge. Principally, fluid challenge involves the administration of a specific amount of fluid intravenously to assess preload reserve and subsequent systemic hemodynamic response. In order to produce stroke volume increase, the volume of fluid administered must sufficiently increase right ventricular diastolic volume. (25) Using various techniques of hemodynamic measurement, it is generally assumed that fluid responders exhibit at least a 10-15% increase in stroke volume/cardiac output.

A study by Toscani, et al showed that a minimal or 4 ml/kg of crystalloid intravenous fluid was required to observe a 14% increment in mean systemic filling pressure. The dose of fluids affects the change in cardiac output (CO). Heterogenous method of hemodynamic measurement, and patient's illness also affects the response to fluid administration. (26) Fluid Challenges in Intensive Care (FENICE) study reported a median infusion of fluid challenge duration of 24 minutes. (27) This supports the understanding that rapid fluid admin-

istration increases venous return, while slower rate (>30 minutes) produces a lower increase in end-diastolic volume, hence fluid administered is less effective to produce stroke volume increase. The timing of hemodynamic assessment varies between different studies. It is generally accepted that assessment should be done before 10 minutes, as complete dissipation of hemodynamic impact of fluid assessment would have occurred by 10 minutes. (26)

In practice, fluid challenge is performed tailored to the patient's condition. The volume, type of fluid, duration of administration, and hemodynamic assessment should be adjusted to the patient's clinical condition, clinician's skill, and available tool for hemodynamic measurement.

Passive leg raising

Passive leg raising (PLR) is a maneuver to predict responsiveness to fluid bolus, without administration of fluid. In PLR, fluid expansion is mimicked by passively elevating legs 45° to mobilize venous blood of the lower body, increasing preload. Subsequent hemodynamic change is then measured. Cardiac output is ideally measured within one minute as hemodynamic changes occur short term and transiently during PLR (**Figure 2**). The use of PLR is promising as it can replace the classic fluid challenge with no side effects. (28)

A previous study by Lukito, et al compared hemodynamic parameters following PLR and 10 ml/kg normal saline infusion over 15 minutes and obtained an increase in cardiac index by >10% in PLR was able to predict preload-dependency in critically ill pediatric patients with 55% sensitivity and 85% specificity (AUC 0.71, 95% CI 0.546-0.874). (29) A similar study by Lu, et al also demonstrated a promising predictor value of PLR, with 94% sensitivity to predict at least 7.5% increase in CI following 10 ml/kg normal saline over 10 minutes. (30) The diagnostic value was even higher in children above 5 years old. However, it should be noted that anatomical and physiological characteristics of smaller children are different from that of adults. Hence PLR may not contribute to a significant expansion in preload, and changes in cardiac output may not be as easily detectable as in adults (due to higher ventricular compliance and thoracic wall compliance).

Conclusion

Fluid resuscitation remains a key approach in pediatric shock. Carefully administered fluid with regards to fluid responsiveness status of the patient will improve the safety of fluid resuscitation. Various methods and variables may be used to predict fluid responsiveness. It is generally accepted that dynamic indices represent preload volume better than static indices. Physicians may choose any method best suited to their clinical practice settings. Since there is no standard reference value for each hemodynamic variable, the individual trend may be helpful in guiding fluid resuscitation. Hemodynamic monitoring should be done prior to, during, and after fluid administration, and best to be conducted in series to predict response to fluid administration. In the absence of advance hemodynamic monitoring, fluid administration is best to be administered in a less aggressive manner, closely titrated to clinical clues of cardiac output, and should be immediately discontinued upon any signs of volume overload.

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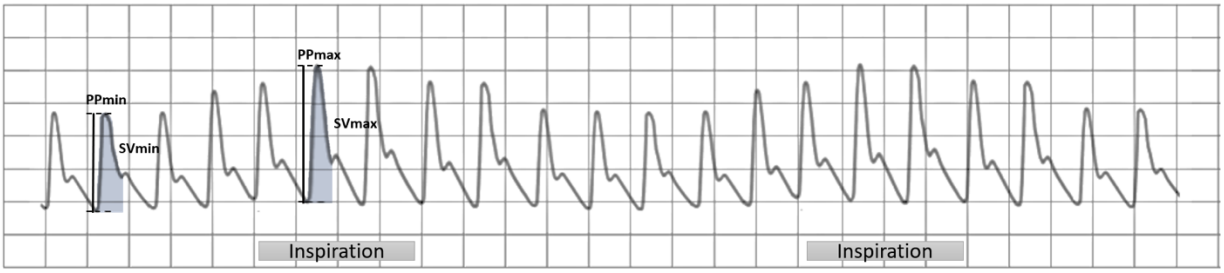
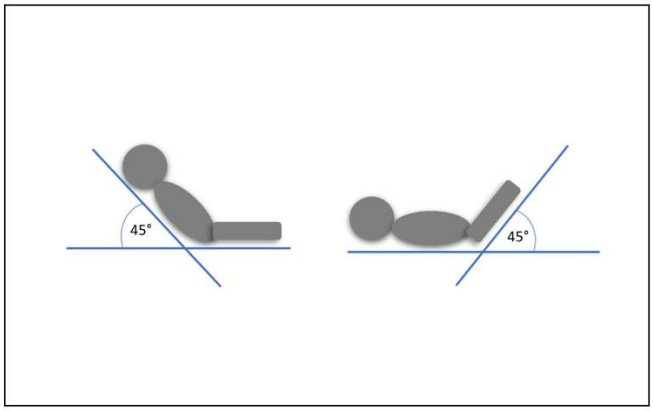
Figure 1. Cardiopulmonary relationship during mechanical ventilation use



Legend: Pulse pressure variation (PPV) and stroke volume variation (SVV) during respiratory cycle with positive pressure ventilation. Highest values or PPV and SVV are seen upon inspiration.

Figure 2. Schematic representation of passive leg raising maneuver to predict fluid responsiveness



Legend: Passive leg raising involves initially elevated upper torso of 45°, followed by passively inclined lower extremity of 45° while the upper torso is flattened parallel to the ground.

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