Fluid loading responsiveness

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Chapter 14

Discussion; fluid loading responsiveness and how can we use it?

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A wide array of variables is available to the ICU and OR physician to assess the hemodynamic state of a patient. Urinary output, skin colour, capillary refill, mean arterial pressure, central venous pressure, heart rate, mixed venous oxygen saturation and pulse pressure are just a few of these variables and their number keeps rising [1,2]. However, it is still not possible to accurately detect hypovolaemia or hypervolaemia [3]. Overzealous fluid administration can increase the incidence of infections, anastomosal leakage, general and pulmonary oedema. This complicates hemodynamic management since unnecessary fluid loading can increase hospital stay and even mortality [4,5] Several strategies exist to decrease the likelihood of hypervolaemia and at the same time select patients that may require fluid loading, pharmacological support or both.

Fluid loading responsiveness

No gold standard exists to guide hemodynamic management. Fluid loading responsiveness (FLR) is a relatively novel strategy and has received wide attention. In general, fluid loading responsiveness can be described as the response of cardiac output (CO) on an intra-vascular administration of a certain amount of fluid. Responders are defined as those patients that increase their cardiac output above a threshold value after this volume loading [6]. It is assumed that increasing cardiac output will lead to an increase in flow and oxygen transport to vital organs consequently. Thus, FLR aims to optimize perfusion and oxygen delivery to vital organs like brain, heart and kidneys. FLR does not specifically lead to the diagnosis of strict hypovolaemia or normovolaemia. Fluid loading responsiveness is more likely to signal that a patient is functioning on or near the flat part of the Frank Starling curve. Identifying a responder with FLR indicates that fluid will likely cause an improvement of the hemodynamics of the patient with less chance of overfilling.

The working point of the circulation of an ICU patient can be described by the intersection of both the venous return curve and the Frank Starling curve. The venous return curve of a patient shifts upward during hypervolaemia and shifts parallel downwards during hypovolaemia. Whereas, the Frank Starling curve is influenced by neurological and humoral control mechanisms, vascular and cardiac function. Hence, the working point of the circulation changes continuously due to changes in the administration of parenteral fluids, airway pressure and changing renal, cardiac and vascular function [7]. This stresses the need for a continuous or repeated determination of fluid-requirements.

However, a practical consensus over the definition of fluid loading responsiveness is missing and therefore the definition of FLR differs widely in the available literature. Even more important is the ability to predict FLR, i.e. responders and non-responders without the administration of fluids. The idea behind predicting FLR is that overall fluid administration will decrease. To our knowledge no study exists to date that studies the impact of FLR or

prediction of FLR on outcome. Thus, more elaborate research is needed. But first we have to develop a uniform definition of FLR to be able to compare the results of FLR research. Second, we will need to come up with a workable algorithm to predict FLR and to guide fluid management in a patient followed by a study of its effect on outcome. In this manuscript we will discuss different dimensions to fluid loading responsiveness and its possible use in everyday practice.

Pitfalls in Determining Fluid Loading Responsiveness

No consensus exists how to assess FLR. The amount of fluid used to assess FLR varies between 7 ml·kg^{-1} [8] and 20 ml·kg^{-1} [9], or 250 ml [10] and 1000 ml [11]. It is easy to imagine that if instead of 250 ml 1000 ml is administered the change in CO can be expected to be larger. The amount of fluid administrated to determine FLR should be weight adjusted to allow for comparison of inter-individual and inter-study results. A 5 ml·kg^{-1} bolus should illicit a significant change in CO in responders. For instance this would be a 500 ml bolus in a 100 kg man or a 250 ml in a 50 kg fragile elderly lady.

Directly related to this, is the type of fluid that is used for administration. The composition of a fluid does not only determine the time that it will be present in the intravascular compartment but also the amount of fluid recruited from the extra-vascular compartment. Prather *et al*. [12] showed that colloids remain in the intravascular compartment for more than two hours and even attract fluids from the extravascular compartments where crystalloids tend to disappear within 80 minutes in dogs. Consequently, we have to point out the importance of the duration of the administration of fluid and timing of the measurement of CO. This directly influences the number of responders, i.e. the number of responders is expected to be larger if CO is measured directly after fluid bolus administration instead of 60 minutes after a 60 minute infusion. This issue will be less relevant when fluids are administered within 5 minutes and CO is measured within several minutes.

Different parameters are used to define (non)responders; cardiac output, stroke volume, stroke volume index, left ventricular end-diastolic area index, cardiac index and aortic blood flow velocity. The effect of fluid loading can be described as a move of the working point to the right on the Frank-Starling curve. When the heart operates on the ascending part of the curve cardiac output will increase more in response to fluid loading (responder) than if the heart already operates near the flat part of the curve. We advocate the use of the change in cardiac output to determine (non)responders since it is one of few parameters likely to correlate to (vital) organ perfusion, it is a robust parameter, and CO is one of two factors to describe the Frank-Starling curve. The Frank Starling principle is based on the fiberlength-contractility relationship within the ventricle. If ventricular end-diastolic volume (preload) is increased ventricular fiberlength is also increased, resulting in an increased 'tension' of the

muscle and an increased contraction length.

Another factor directly influencing the number of responders is the cut-off value. The cut-off to discriminate between responders and non-responders after a fluid challenge varies between 5% and 25% change in CO [10,13]. Since the precision and accuracy of cardiac output measurement technique directly determines the clinical significance, we would like to relate the technique to measure CO to the cut-off value and the amount of administered fluid [14]. Previously, Critchley and Critchley [15] concluded that a new method was allowed to replace the gold standard when repeatability was within twice the standard deviation (2SD) of the gold standard method. Cecconi *et al.* discussed that the coefficient of variance (CV) was to be used [16]. They advised only to use a new CO method clinically when CV is below 10% (or clinically significant in their words). However, studies on the accuracy of different CO methods to determine changes (after an intervention) are scarce or lacking. Moreover, it is disputable that the assessment of agreement of CO methods as put forth by Critchley and Cecconi can be used for this purpose. Data by de Wilde and co-workers suggest that pulse contour methods (Modelflow and possibly LidCO) track changes in thermodilution cardiac output more accurately than suggested by earlier repeatability data [17]. We found that a 4.3% change in Modelflow CO after 100 ml fluid administration accurately predicts fluid loading responsiveness.

Jansen *et al*. reported a precision of 3.5% for thermodilution cardiac output to determine (genuine) CO [18]. Henceforth, a cut-off for triplicate thermodilution CO would be between 3.5% and 7%. Thus, our data indicates that lower cut-off values can be used (or more fluid has to be administered than with thermodilution) than the previously used 20%. We, therefore, advocate the use of different cut-off values based on the methods used to assess CO and their accuracy to track changes in cardiac output. We also advocate the use of a limited number of CO measurement techniques in FLR research. Only those measurement techniques that (have) prove(n) to be precise and accurate can be used.

Prediction of FLR

The aim of predicting FLR is to achieve the most adequate or optimal cardiac output with the least amount of fluids. In the prediction of FLR three major shortcomings are to be solved. First, an unambiguous definition of FLR is needed (see the discussion above). Second, errors related to the calculation and use of various predictors like LVEDA, SVV, PVV and changes on challenges like PLR and PEEP need to be quantified. Third, patient characteristics have to be taken into consideration to select a suitable parameter for FLR prediction. Forth, reliability of statistical analysis to compute the sensitivity, specificity and the threshold value to define responders and non-responders must be defined.

Echographic and Dynamic Parameters to Predict FLR

In theory, echographically determined volume parameters of the heart are supposed to be highly reliable predictors of FLR. The volume changes within the heart or vena cava are directly linked to cardiac function; when wall movement is limited inotropic assistance is warranted. And when filling of the ventricles is not optimal, fluid administration is indicated. Study results are very promising [19]. Several factors may, however, frustrate these results. Operator-related factors, like level of experience, changes in probe position and intermittent application, greatly influence the reliability and robustness of echographic monitoring [20]. The predictive value for FLR of echographic parameters in patients receiving mechanical ventilation seems to outscore the results for these parameters in spontaneously-breathing patients [21].

These operator- and patient-bound factors influence the accuracy to predict FLR. We highlight the results of the most studied parameters here; results for left ventricular end-diastolic area (LVEDA) [22-26] vary with sensitivity reported to be between 60 to 89%, specificity between 58 and 91% and the AUC of the ROC curve between 0.24 ± 0.11 and 0.78 (95% CI between 0.59 and 0.97) [23,26]. For global end-diastolic volume index (GEDVI) [13,27-29] the AUC of the ROC curves is between 0.23 and 0.70 (0.46-0.94) [28,29].

In recent years, new variables based on heart-lung interaction, i.e. respiratory-induced stroke volume variation (SVV) and pulse pressure variation (PPV) have been introduced in the ICU. Pulse pressure (PP) is defined as the beat-to-beat difference between the systolic and the diastolic pressure. PPV is the amplitude of cyclic changes induced by mechanical ventilation. The variations in PP and stroke volume induced by mechanical ventilation have been linked to volume status [30]. PPV is thought to be directly proportional to stroke volume variation [31]. The reliability for SVV and PPV varies from lower sensitivity and specificity of 70% to over 90% to predict FLR. Although SVV is a direct measure of variation in cardiac output, results for SVV show a wider spread [13,32,33]. Even though PPV is used as an indirect measure for SVV, results for PPV seem superior which may be especially true in septic patients [34], where vasoplegia is less likely to cause a reliable SVV measurement result. We need to consider that the calculation of SVV requires beat-to-beat SV measurements using a pulse contour analysis algorithm whereas PPV is measured directly from the arterial waveform. SVV will require an ongoing validation in clinic conditions as algorithms are developing with time [35]. In that context it is noteworthy that more recent publications report lower area under the ROC curves than older publications. Whether this depends on publication bias, a decrease in the accuracy of newer pulse-contour methods to determine SVV or more frequent improper use remains uncertain. Several restrictions apply to the use of dynamic parameters. Cardiac arrhythmias significantly decrease the reliability of SVV and PPV [20]. The use of these dynamic parameters has been validated in sedated and mechanically ventilated patients without

spontaneous breathing activity. Third, SVV, and probably PPV, is not only influenced by intravascular volume but also by the depth of the tidal volume used in mechanical ventilation of the lungs [26].

Patient Characteristics, Challenges and FLR

When FLR is assessed patient (co)morbidity is of importance to select the most reliable parameter. For SVV, PPV and LVEDA determinations the limitations are reasonably well described (see above). For several disease states, however, we do not know yet how they influence the reliability of a parameter to predict FLR. For instance, we do not know what the influence of right ventricular dysfunction has on the accuracy of dynamic variables to predict FLR. In these cases, the use of a challenge could be helpfull.

Reversible autotransfusion by passive leg raising (PLR) and a provocation method with the application of increased PEEP have also become the subject of intense interest. Particularly, the groups of Boulain, Monnet and Teboul studied the reliability of parameters during PLR to predict FLR [36,37]. The robustness and reliability of the "static parameters" during the challenge can be explained by the direct use of the Starling curve. The working point on the Frank Starling curve of each individual patient (with its own pathophysiological constitution) is determined and FLR can be assessed. The amplitude of the change in CO after the challenge can be used to predict FLR. These challenges are reversible, standardized and easily performed.

Statistical Testing

Overall receiver operating characteristics (ROC) are used to describe the precision of the prediction of fluid loading responsiveness. Sensitivity and specificity and threshold values to identify responders and non-responders on fluid loading are determined for several variables in a specific population. However, the application of ROC curves also requires secondary testing in a control population with the earlier found cut-off values in order to determine reproducibility in similar and different sub-populations. Since reproducibility is only rarely assessed, straightforward extrapolation of study results is not possible. This also hinders formulation of a department protocol for bedside use.

A second issue related to statistical analysis in FLR research is related to the size of the study populations; population size varies between 8 [38] and 60 [39] in reports up to 2010. However, no study reports on power analysis. Moreover, rarely the significance of the found area under the ROC curve (AUROC) is reported. Hanley *et al*. demonstrated the value of statistical testing between ROC curves [40]. We advocate the use of this test to compare AUROC with mathematical chance (Test: AUROC $\neq$ 0.500) and to allow comparison of ROC curves for different parameters, especially when power analysis are absent.

Conclusions

The restricted use of fluids in the intensive care and operating theatre reduces risk of complications like pulmonary edema. Targeted infusion strategies have shown to benefit patients. Fluid loading responsiveness is a novel strategy that aims to optimize perfusion and oxygen delivery to vital organs. This strategy is likely to signal that a patient is functioning on or near the flat part of the Frank Starling curve. Predicting fluid loading responsiveness is described as the use of a hemodynamic variable to predict the effect of a fluid bolus administration.

FLR research has shown promising results but no consensus exists on the exact definition of FLR. The amount of fluid, type of fluid, the parameter used to define responders, timing of the measurement of CO after fluid loading, the cut-off value to define responders and the cardiac output measurement technique vary widely. Based on these pitfalls and current knowledge, we propose to define FLR is the use of (a set of) baseline hemodynamic variables (or a change in a variable after a challenge manoeuvre) to predict a clinically significant change in cardiac output within 5 minutes after a 5 $ml \cdot kg^{-1}$ bolus of a crystalloid or colloid fluid is administered within 5 minutes. Moreover, the use of an accurate and precise cardiac output measurement technique to assess FLR is desirable. We advise a cut-off for triplicate thermodilution CO of 3,5% and for pulse contour CO around 5% change. Consequently, we can use this explicit classification to define responders and integrate results of different FLR studies. Until major morbidity and mortality studies have been performed into the LFR strategy, we advise the use of pulse pressure variation and challenges like passive leg raising to assess FLR in critically ill patients. Baseline PPV and changes in static filing pressure after PEEP and PLR challenges have repeatedly shown to predict FLR with high sensitivity and specificity in different patient populations. However, it remains important to recognize a patients specific pathophysiology to select the most reliable parameter to predict FLR.

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