Some light in the grey zone?

J. Bickenbach and G. Marx*

Department of Intensive Care, RWTH University Hospital, Aachen, Germany

*Corresponding author. E-mail: gmarx@ukaachen.de

Treatment of shock is not a new concern in intensive care medicine. The highest priority in patients with shock is the restoration of oxygen delivery. Fluid resuscitation is the very first goal of increasing cardiac output and oxygen delivery in patients with acute circulatory insufficiency. First, based on the simple physiology of the Frank–Starling mechanism, fluid loading should increase cardiac output (CO) by increasing preload and subsequently increasing left ventricular (LV) stroke volume.[1] However, fluid overload, especially in patients with pre-existing or developing cardiac failure, can end in only a fractional increase of stroke volume and negative effects like pulmonary venous congestion can predominate. It is therefore a daily task for each intensivist to identify those patients who will respond to and benefit from volume expansion (e.g. acute shock) and to avoid fluid overload in those who are no longer fluid responsive but are at risk for increased mortality by further fluid therapy (e.g. protracted sepsis, acute respiratory distress syndrome, acute kidney injury). Thus the therapeutic conflict between hypovolaemia and hypervolaemia needs to be addressed wisely. Consequently, precise monitoring of preload could be helpful in this clinical scenario (Fig. 1).

What about central venous pressure (CVP) monitoring? Although this static marker of preload is still used more often than dynamic indices (36% versus 22%, respectively),[2] its predictability for fluid responsivity is doubtful, as shown by a large meta-analysis of Marik and Cavallazi.[3] In an analysis of 43 studies, no correlation between baseline CVPs and changes in stroke volume index or cardiac index could be shown. CVP use seems more like an old habit, but it is no longer be recommended in guidelines.[4]

Dynamic markers for preload, such as systolic pressure variation (SPV), pulse pressure variation (PPV) and stroke volume variation (SVV), have proven to be superior to traditionally used static indices. However, the first and easiest way to predict the effects of increasing preload on cardiac output is the passive leg raise (PLR) manoeuvre. It mimics fluid loading of ∼300 ml by positioning the lower body above the trunk without infusing any volume. Effects of volume overloading are therefore avoided. The PLR is considered positive when an increase in cardiac output of ≥10% is observed. It can be repeated at any time and allows a fast and diagnostic check for further volume responsivity. A systematic meta-analysis considering PLR-induced changes in cardiac output showed a sensitivity of 0.85 and a specificity of 0.91.[5]

Could the PLR answer our questions regarding fluid resuscitation in critically ill patients? Maybe not all, as limitations for positioning occur in neurosurgical or trauma patients. Besides, raising the patient's legs can result in pain, discomfort or other stimuli that could trigger adrenergic stimulation and thus lead to misinterpretation of an increased cardiac output. Moreover, PLR is only a short-term test for preload responsiveness, and although easy to repeat, the decision for further fluid loading needs to be pondered cautiously. Conversely, a negative PLR should lead to consideration of ending fluid loading.

The most widely used dynamic marker for preload is the PPV. Based on intrathoracic and transpulmonary pressure changes during mechanical ventilation that decrease venous return, and thus right ventricular (RV) preload, reduced filling conditions and decreased stroke volume of the RV occur. In parallel, increased pressure in the alveolo-capillary units during inspiration with increased left ventricular (LV) stroke volume is seen.[6 7] The decreased RV stroke volume sustains reduced LV filling after two to three heart beats, depending on the pulmonary transit time.[8] Thus cyclic changes of intrathoracic pressures during mechanical ventilation lead to changes in LV stroke volume, which is highest during inspiration and lowest during expiration, and which indicates preload dependency of both ventricles.

PPV is a good predictor of preload responsiveness, and high values are associated with preload responsiveness and vice versa. This was shown in a large meta-analysis where 22 studies were analysed. Sensitivity for predicting fluid responsiveness of 88% with a specificity of 89% was shown. The median threshold of PPV was 12% (interquartile range 10–13%).[9] These results were received with great interest; however, no physician would expect to observe only one specific value for PPV in clinical scenarios.
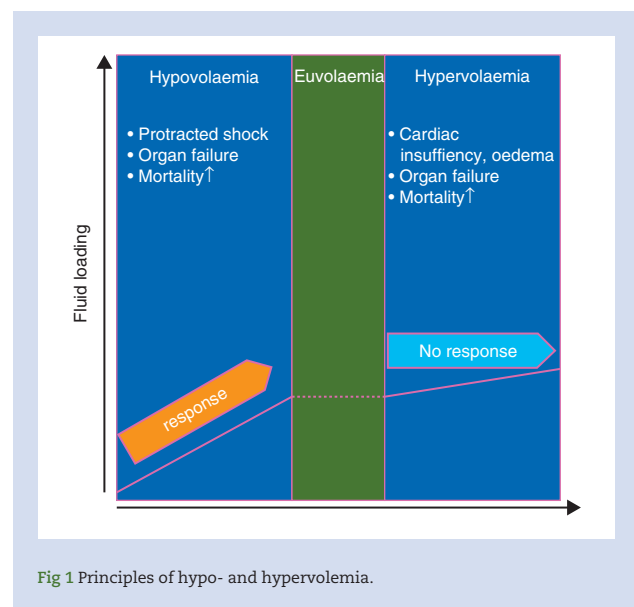

Fig 1 Principles of hypo- and hypervolemia.

Interestingly, a multicentre study by Cannesson and colleagues[10] examined the accuracy of prediction for PPV and its fluid responsiveness at lower values and identified a so-called grey zone for PPV values between 9% and 13% where no clear prediction of fluid responsiveness could be shown in the receiver operating characteristics curve analysis. These PPV values were seen in ∼25% of patients. However, patients included were ventilated with a small tidal volume (V_T) of $6\,ml\,kg^{-1}$ body weight, and it is known that PPV does not function well during mechanical ventilation with small V_Ts. This is a clear limitation of the technique, and a temporary increase of V_T could potentially lead to enhanced, more valid PPV values useful in predicting fluid responsiveness.

Min and colleagues[11] investigated the principle of augmented PPV in 38 adult patients requiring general anaesthesia. PPV was executed while higher V_Ts were applied. When patients were in the grey zone of PPV values between 9 and 13%, haemodynamic parameters [stroke volume index (SVI) and PPV] were computed at a V_T of $8\,ml\,kg^{-1}$ and then V_T was increased to $12\,ml\,kg^{-1}$ of ideal body weight, followed by a further measurement. After these two baseline measures, fluid loading ($6\,ml\,kg^{-1}$) with infusion of balanced crystalloid solution was performed, and again, haemodynamic variables were obtained at both V_Ts. Those patients with increased SVI of >10% after volume expansion were considered to be responders. For the 20 responders, increased V_T and augmentation of PPV led to significantly better predictability of fluid responsiveness. Yet, ventilatory parameters like driving pressure were significantly elevated during mechanical ventilation with high V_Ts.

This small clinical study in non-shock patients undergoing elective surgery underlines known physiological heart–lung interactions. However, what can we conclude from these data? We know that a V_T of $6\,ml\,kg^{-1}$ during mechanical ventilation in elective surgery is associated with better post-surgical outcomes than a V_T of $11\,ml\,kg^{-1}$.[11] For the sake of using physiological interactions, should we go back to unphysiologic V_Ts? Although the increases of V_T are only needed for the time of the measurement, it cannot be excluded that subjects with ventilatory compromise could deteriorate during these repeated procedures. Obviously these measures need to be done with great caution. Protocols could help to guide this process, as well as complementary multilayered approaches for haemodynamic monitoring (e.g. additional use of ultrasound).

Dynamic preload parameters provide an advance in haemodynamic monitoring of critically ill patients. The selection of parameters and techniques depends both on the physicians' experience and the patient's condition. They are restricted to mechanically ventilated, not spontaneously breathing, patients without cardiac arrhythmias. It should be stressed that the decision for fluid administration should not be made solely on the presence of preload responsiveness, but also on clinical signs of haemodynamic instability. Risks and benefits need to be evaluated cautiously.

The study of Min and colleagues[11] reveals an interesting approach. However, this study is only one brick in complex physiologic interactions and further data are required to enlighten the grey zone. Maybe innovative techniques are needed in this complex area addressing the daily worries of anaesthetists and intensivists regarding fluid challenge. Anaesthetists and intensivists should feel encouraged to use PPV (and other parameters) as components for a decision-making strategy of a more rational fluid management approach.

Authors' contributions

Both authors contributed equally to this manuscript.

Declaration of interest

None declared.

Funding

References

1. Meng L, Heerdt PM. Perioperative goal-directed haemodynamic therapy based on flow parameters: a concept in evolution. *Br J Anaesth* 2016 Dec; **117**(suppl 3): iii3–iii17
2. Cecconi M, Hofer C, Teboul JL, *et al.* Fluid challenges in intensive care: the FENICE study: a global inception cohort study. *Intensive Care Med* 2015; **41**: 1529–37
3. 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**: 1774–81
4. Marx G, Schindler AW, Mosch C, *et al.* Intravascular volume therapy in adults: Guidelines from the Association of the Scientific Medical Societies in Germany. *Eur J Anaesthesiol* 2016; **33**(7): 488–521
5. Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. *Intensive Care Med* 2016; **42**: 1935–47
6. Michard F, Teboul JL. Using heart lung interactions to assess fluid responsiveness during mechanical ventilation. *Crit Care* 2000; **4**: 282–9
7. Morgan BC, Martin WE, Hornbein TF, Crawford EW, Guntheroth WG. Hemodynamic effects of intermittent positive pressure ventilation. *Anesthesiology* 1966; **27**: 584–90
8. Jardin F, Farcot JC, Gueret P, Prost JF, Ozier Y, Bourdarias JP. Cyclic changes in arterial pulse during respiratory support. *Circulation* 1983; **68**: 266–74
9. Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. *Crit Care* 2014; **18**: 650
10. Cannesson M, Le Manach Y, Hofer CK, *et al.* Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a "gray zone" approach. *Anesthesiology* 2011; **115**: 231–41
11. Min JJ, Gil N-S, Lee J-H, Ryu DK, Kim CS, Lee SM. Predictor of fluid responsiveness in the 'grey zone': augmented pulse pressure variation through a temporary increase in tidal volume. *Br J Anaesth* 2017; **119**: 50–6