Pulse pressure variation as a guide to oxygen transport

Optimisation of cardiac output (CO), as a major determinant of systemic oxygen delivery, is an important task in the treatment of critically ill patients. Since, according to Frank-Starling's law, adequate cardiac preload is a prerequisite to maintain maximum stroke volume, fluid status should always be optimised before inotropics are applied. More and more clinicians are optimising intravascular volume by using 'dynamic parameters' of cardiac preload, such as systolic pressure variation (SPV), stroke volume variation (SVV) and pulse pressure variation (PPV). There is evidence that these parameters can predict whether a patient will respond favourably to fluid administration. Ideally, fluid management using PPV should lead to more stable organ function and improved final outcome in critically ill patients. The measurement of PPV is less invasive than that of many other parameters and several studies have shown its clinical value in practice. However, the limitations of using PPV need to be considered. In patients in whom respiratory changes are difficult to interpret, a passive leg raising manoeuvre should be considered for assessing fluid responsiveness. In conclusion, available results on PPV-guided therapy in high-risk surgical patients are promising; however, more data on critically ill patients are required in the future.

Optimisation of cardiac output (CO), as a major determinant of systemic oxygen delivery, is an important task in the treatment of critically ill patients. Since, according to Frank-Starling's law, adequate cardiac preload is a prerequisite to maintain maximum stroke volume (SV), fluid status has to always be optimised before inotropics should be applied.[1] Ideally, any marker of cardiac preload should be so reliable that it indicates fluid responsiveness a priori, which means that response to fluid loading is predictable, thereby excluding unnecessary fluid application which may be harmful in patients with capillary leakage e.g. those suffering from sepsis or ARDS. Over the last few years, it has clearly been demonstrated that cardiac filling pressures, i.e. central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) which in clinical practice are measured against the atmosphere, are unreliable indicators of cardiac preload in critically ill patients.[2] As pressure readings are influenced by compensatory physiological mechanisms that preserve pressure at the expense of flow, this may result in the inadvertent over- or under-administration of intravascular fluid. Unfortunately, when using these parameters, preload insensitivity will not be recognised until the fluid has already been administered. As a consequence, more and more clinicians optimise intravascular volume by using 'dynamic parameters' of cardiac preload. Systolic pressure variation (SPV) was suggested as one of these by Perel *et al.* in the 1980s.[3] SPV, stroke volume variation (SVV) and pulse pressure variation (PPV) are dynamic 'virtual' preload challenges, occurring each respiratory cycle, without the actual administration of fluid. There is evidence that these parameters can predict whether a patient will respond favourably to fluid administration. Ideally, fluid management using PPV should lead to more stable organ function and finally, improved outcome in critically ill patients. This review will focus on PPV as a dynamic preload variable and the possible benefit effected by a PPV-guided treatment.

PHYSIOLOGICAL BACKGROUND

There is a growing interest in the clinical value of the variations in blood pressure and CO that result from the interactions between the heart and lungs during ventilation. By analysing arterial pressure waveform beat-to-beat, systolic pressure variation (SPV), stroke volume variation (SVV) and pulse pressure variation (PPV) for each respiratory cycle can be measured and displayed at the patient's bedside. In general, mechanical ventilation in a controlled mode has been known to induce cyclic changes in arterial blood pressure. These changes come from cyclic modifications in systemic venous return and in right ventricular afterload related to changes in intrathoracic pressure and in transpulmonary pressure, respectively. Like SPV, PPV is also higher during mechanical inspiration and lower during expiration (Figure 1). Pulse pressure (PP) is calculated as the systolic minus the diastolic blood pressure which is higher during inspiration and lower during expiration.[4] In principle, PPV reflects changes in left ventricular stroke volume related to tidal ventilation. Because the left ventricle is directly filled from the pulmonary circulation, which is therefore its filling reserve, respiratory changes in left ventricular stroke volume, and thus PPV, are directly related to changes in the amount of blood in the pulmonary reservoir: during inflation, pulmonary vessels are emptied and blood is squeezed towards the left heart, whereas simultaneously a decrease in right ventricular ejection precludes its immediate re-filling. Two conditions have been described that prevent immediate re-filling of the pulmonary vasculature by the right heart, thereby inducing significant PPV: 1) hypovolaemia leading to a marked inspiratory decrease in right ventricular ejection related to a decreased venous return, and; 2) severe right ventricular dysfunction also leading to an inspiratory decrease in right ventricular ejection but due to an increase in right ventricular afterload. In the first case, the infused fluid reaches the pulmonary vessels and reduces PPV by optimised left ventricular preload and increased left ventricular stroke volume. In the second scenario, fluids do not reach the pulmonary vessels, do not correct PPV and will not increase left ventricular stroke volume.

However, changes in arterial blood pressure not only reflect changes in left ventricular stroke volume but are also related to the transmission of the intrathoracic pressure to the aorta.[5] Assuming that during controlled mechanical ventilation the intrathoracic pressure is transmitted similarly to the systolic and diastolic pressures, pulse pressure more accurately reflects left ventricular stroke volume. Accordingly, SPV have been shown to be slightly less valu-

SG Sakka MD, PhD,
Department of Anesthesiology and Intensive Care Medicine, University of Witten/Herdecke, Medical Center Cologne-Merheim, Cologne, Germany

able than PPV in detecting volume responsiveness.[6–8] For this reason, Michard *et al.* suggested not using SPV but rather PPV in clinical practice while they demonstrated that PPV could be a strong predictor of fluid responsiveness: the higher the PPV the greater the increase in stroke volume induced by fluid expansion.[7] In their paper, the authors described in 40 selected patients a specificity of 96% for PPV; however, patients with severe ARDS were excluded from the analysis.

CLINICAL APPLICATION OF PULSE PRESSURE VARIATION

Monitoring of PPV in critically ill patients may be helpful in various clinical scenarios to guide fluid therapy more adequately. In an animal model of haemorrhage and re-transfusion,[9] SVV, as measured by the pulse contour algorithm, and PPV, as calculated by the formula originally proposed, change gradually and consistently with decreasing blood volume, and reflect changes in stroke volume even during extreme hypovolaemia. In detail, correlations of SVV, SPV and PPV to SV throughout the study were -0.89, -0.91 and -0.91, respectively. The SPV correlated significantly with both, PPV and SVV (r=0.97 and 0.93 respectively). However, the PPV increased by more than 400% at 50% haemorrhage compared with increases of 200% and 120% for the SVV and SPV, respectively.

With respect to changes in cardiac afterload and their effects on preload parameters, Nouira *et al.*[10] found in an animal model of haemorrhagic shock that administration of norepinephrine was associated with a significant decrease in PPV and SPV. According to these authors, the value of these dynamic variables could be significantly reduced as they mask a true intravascular volume deficit possibly by shifting blood from unstressed to stressed volume.

However, even under controlled mechanical ventilation, pressure and volume controlled mode have different influences on PPV. In an animal model of haemorrhage, Fonseca[11] found that during removal of 15% of blood, both SPV and PPV significantly increased. However, at 30% of blood loss, volume controlled ventilation (VCV) led to a significantly higher PPV and SPV in comparison to pressure controlled ventilation (PCV). Thus, while VCV due to higher inspiratory airway pressures revealed fluid deficit with fluid responsiveness, PCV did not. According to the authors, it remains open whether to 'use' VCV in order to uncover fluid requirements and fluid responsiveness or to better apply PCV in hypovolaemic states because it provokes less haemodynamic interference.

Furthermore, data on PPV as a marker of fluid responsiveness are also available in assisted ventilatory support. In 30 patients,[12] PPV and SPV were measured during 20 minutes of pressure support ventilation with 3/min flow triggered synchronised intermittent mandatory ventilation (SIMV) breaths (tidal volume 10 ml/kg) and controlled mechanical ventilation (respiratory rate 12/min, tidal volume 10 ml/kg). Significant correlations were found between dynamic indices in SIMV during pressure support ventilation and those in controlled mechanical ventilation. The mean differences between two measurements were PPV 0.6 ± 2.8% (limit of agreement: -5.0 and 6.2) for PPV and 0.5 ± 2.3 mmHg (limit of agreement: -4.0 and 5.1) for SPV. According their findings, PPV and SPV could be accurately monitored in patients breathing with assisted respiratory assistance adding an imposed large enough SIMV breath.

Soubrier *et al.*[13] studied whether the respiratory changes in PP and SPV could predict fluid responsiveness in spontaneously breathing patients. Thirty-two patients with clinical signs of haemodynamic instability were subjected to a 500-ml volume expansion. In these patients, cardiac index increased by at least 15% after volume expansion in 19 patients (responders). At baseline, only dynamic indicators were significantly higher in responders than in non-responders (13 ± 5% *vs.* 7 ± 3% for PPV and 10 ± 4% *vs.* 6 ± 2% for SPV). Moreover, both parameters significantly decreased after fluid loading (11 ± 5% to 6 ± 4% for PPV and 8 ± 4% to 6 ± 3% for SPV). Sensitivity and specificity according to receiver operating characteristics (ROC) statistics were described by an area under the curve for PPV and SPV of 0.81 and 0.82, respectively. According to this study, a PPV ≥12% predicted fluid responsiveness with high specificity (92%) but poor sensitivity (63%). The forced respiratory manoeuvre (re)producing a dyspnoeic state decreased the predictive power of these parameters. Due to their lack of sensitivity and their dependence to respiratory status, PPV and SPV were found to be less reliable to predict fluid responsiveness in spontaneous breathing compared to mechanically ventilated patients. However, when the baseline value is high without acute right ventricular dysfunction in a participating patient, a positive response to fluid was mentioned to be likely.

Over the last few years, several commercially available systems have been developed which enable monitoring of PPV continuously at the bedside. For instance, Umbrello *et al.*[14] described an online system which they found to be accurate when compared to an offline technique. In ten patients treated with a PEEP of 6 cmH_2O and tidal volume 10 ml/kg, PPV measured with the online technique on the monitor was 5.5 ± 2.3%, and with the offline method was 5.9 ± 2.3%. According to their results, PPV can be derived reliably by such a system. Also, Auler *et al.*[15] reported an online monitoring of PPV by automatic calculation and real-time monitoring using standard bedside monitors. In 59 mechanically ventilated patients after cardiac surgery, fluid administration increased cardiac output by at least 15% in 39 patients (66% responders). Before fluid administration, responders and non-responders were comparable with regard to right atrial and pulmonary artery occlusion pressures. In contrast, PPV was significantly greater in responders than in non-responders (17 ± 3% *vs.*

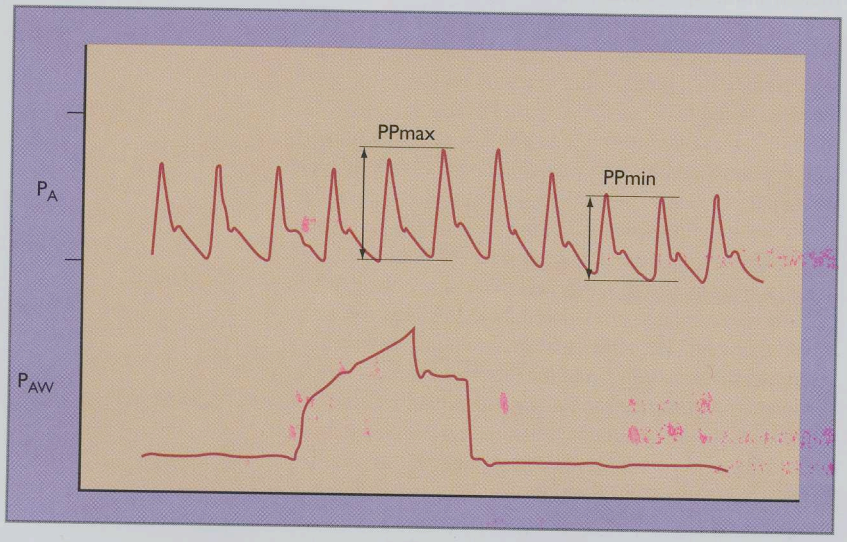

Figure 1. Respiratory changes in arterial pressure during mechanical ventilation. The pulse pressure (PP = systolic minus diastolic pressure) is minimal (PP_{min}) three heart beats after its maximal value (PP_{max}). The respiratory change in pulse pressure (pulse pressure variation, PPV) can be calculated as the difference between PP_{max} and PP_{min}, divided by the mean of the two values, and expressed as a percentage: $PPV(\%) = 100 \times (PP_{max} - PP_{min})/([PP_{max} + PP_{min}]/2)$.

9 ± 2%). A cut-off value of PPV of 12% allowed identification of responders with a sensitivity of 97% and a specificity of 95%. The authors concluded that automatic real-time monitoring of PPV is possible using a standard bedside monitor and was found to be a reliable method to predict fluid responsiveness after cardiac surgery.

INFLUENCE OF VENTILATOR SETTINGS ON PPV

As the concept of PPV is increasingly applied in critically ill patients with mechanical ventilation, the influence of end-expiratory pressure (PEEP) on PPV needs to be addressed. In patients with acute lung injury or ARDS, PPV was found to be useful to predict PEEP-induced haemodynamic instability – the higher the PPV on zero end-expiratory pressure, the greater the decrease in cardiac output when PEEP is applied. Consequently, some clinicians use PPV before applying PEEP or performing recruitment manoeuvres in patients with ARDS.[16] It has also been described that PEEP does increase PPV which may be surprising since applying PEEP does not increase the cyclic variation in airway and pleural pressures (from end-expiratory to end-inspiratory values) during a single mechanical breath. As an explanation, by increasing mean airway and pleural pressures and hence by decreasing mean cardiac preload, PEEP actually induces a leftward shift on the Frank-Starling curve. Therefore, a patient operating on the flat portion of the Frank-Starling curve on zero end-expiratory pressure (i.e. a fluid non-responsive patient) may move to the steep part of the curve during PEEP, and become fluid responsive. In other words, if PEEP does affect PPV, it does not affect its physiologic or clinical value: PPV is still a marker of the position on the Frank-Starling curve and logically an accurate predictor of fluid responsiveness.[17]

Also, tidal volume exerts influence on PPV and may thus have an impact on the usefulness of PPV for assessing fluid responsiveness. Tidal volume is the main determinant of respiratory variations in pleural pressure and cardiac preload which are responsible for significant PPV in patients operating on the steep portion of the Frank-Starling curve.[18] Without any significant change in pleural pressure and cardiac preload, a PPV cannot be observed even in fluid responsive patients (e.g. during apnoea, PPV equals zero even in patients operating on the steepest part of the Frank-Starling curve). Charron *et al.*[19] studied the influence of tidal volume in patients of whom 43% were responders to intravascular volume expansion. In their study,[19] percentage change in PPV was higher in responders compared with non-responders, that is, predictive values of %PP were similar and higher than that of left ventricle cross-sectional end-diastolic area at the appropriate level of tidal volume. A noteworthy point is that %PP was slightly correlated with norepinephrine dosage. In conclusion, %PP increased with the increase in the level of tidal volume, both before and after intravascular volume expansion, contrasting with an unexpected stability of aortic velocity time integral as a marker of stroke volume. De Backer *et al.*[20] have confirmed in 60 patients that PPV is less accurate in predicting fluid responsiveness when tidal volume is <8 ml/kg than when it is >8 ml/kg. In patients with ARDS, ventilated with a mean tidal volume of 6.4 ± 0.7 ml/kg (PEEP 13.9 ± 1.4 cmH_2O), Huang *et al.*[21] observed that a PPV cut-off value of 12% discriminates between fluid-responders and non-responders with a specificity of 100% and a sensitivity of 68%. Among the various baseline preload indicators, only baseline PPV showed a positive correlation with volume expansion induced absolute changes in cardiac index (Figure 2). It has been suggested that acute cor pulmonale – the incidence of which has been significantly lowered by the currently recommended use of low tidal volumes[22] – may be responsible for large PPV in patients non-responding to fluid loading (false positive).[4] The specificity of 100% reported by Huang *et al.* supports the notion that such a phenomenon (high PPV values in non-responders) is actually very uncommon.

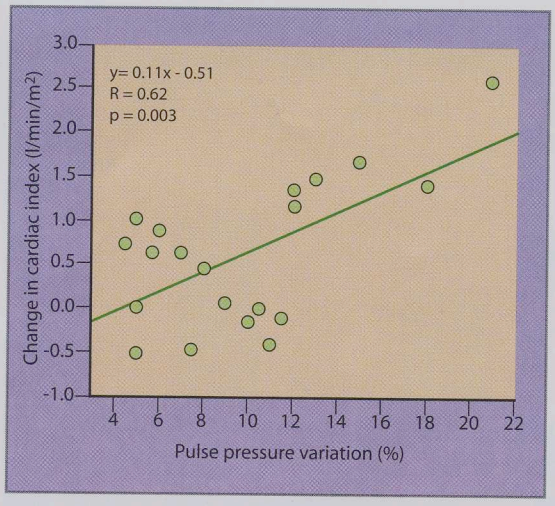

Figure 2. Linear correlation between baseline pulse pressure variation and absolute changes in cardiac index at end of volume expansion (modified from Kramer *et al.*[8]).

However, the sensitivity of 68% indicates that false negatives may be observed (roughly one-third of responders were not properly detected by PPV). As explained above, this phenomenon is likely related to small respiratory variations in pleural pressure and cardiac preload in patients ventilated with low tidal volumes (<8 ml/kg).

In summary, in ARDS patients ventilated with low tidal volume (and at any level of PEEP), a high PPV is almost always indicative that the patient will be responsive to fluid administration. However, a low PPV does not exclude the possibility of a positive response. In this clinical situation, it is wise to perform a passive leg raising manoeuvre while monitoring cardiac output continuously. Such a manoeuvre is reversible, mimics the effects of fluid loading, and has been shown to be very accurate in predicting fluid responsiveness.[23] If a significant increase in cardiac output is observed during the passive leg raising manoeuvre, the patient should respond to fluid loading. If there is not a significant increase in cardiac output, the patient should be a non-responder and giving fluid would most likely be a mistake.

PULSE PRESSURE VARIATION DIRECTED THERAPY

Guiding treatment by PPV as a dynamic preload parameter may be associated with more stable organ function in different pathophysiological states. With respect to intra-abdominal hypertension, Bliacheriene *et al.*[24] investigated the effects of pneumoperitoneum and hypovolaemia on PPV and SPV in an animal model. In detail, pneumoperitoneum was induced by application of CO_2 and hypovolaemia by controlled haemorrhage. While SPV was modified by haemorrhage but also influenced by pneumoperitoneum, PPV in contrast was modified only by haemorrhage. Their findings suggest that PPV should be used preferentially instead of SPV to detect hypovolaemia and guide fluid therapy during laparoscopy.

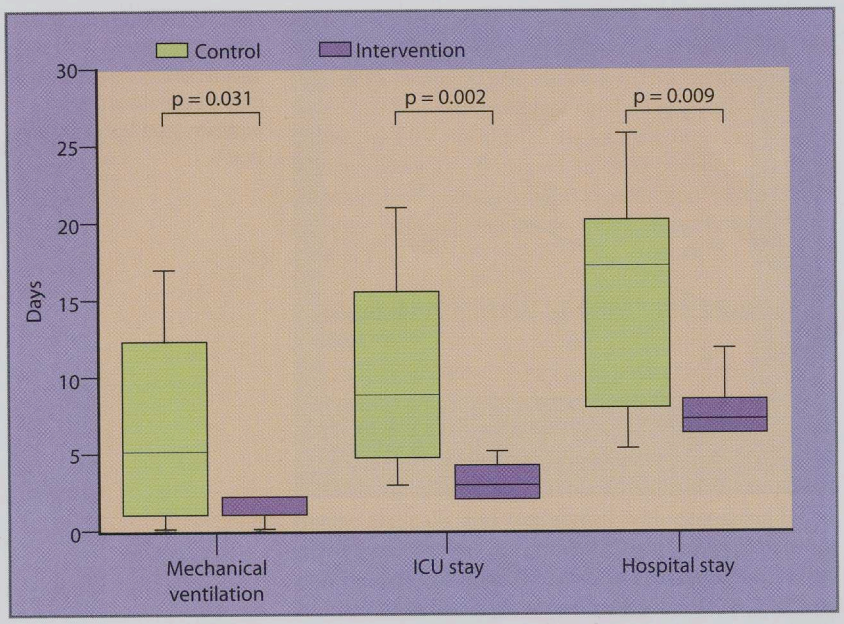

Figure 3. Guiding intra-operative fluid therapy by pulse pressure variation (PPV) in high-risk surgical patients. Box-and-whiskers representation of the duration (days) of mechanical ventilation (MV), stay in the intensive care unit (ICU), and stay in hospital in the control and intervention groups. The line inside a box denotes the median, the limits of the box denote the 75th percentile of the data, and the whiskers represent the 90th percentile of the data (modified from Lopes *et al.*[27]).

More recently, Renner *et al.*[25] found in a similar animal model of increased intra-abdominal pressure (IAP) that PPV, SVV, and global-end-diastolic volume (GEDV) were the only variables that showed a significant correlation with SV independent of changes in IAP. With respect to fluid loading, PPV, SVV, and GEDV significantly correlated with percentage change in SV before IAP was increased. After elevation of IAP up to 25 mmHg, this correlation remained nearly unchanged for PPV and GEDV, whereas for SVV it was abolished. ROC statistics revealed that PPV had the greatest area under the curve (estimate of sensitivity and specificity) of 0.92 during baseline and 0.89 during pneumoperitoneum (for comparison: SVV: 0.91 and 0.62, GEDV: 0.90 and 0.83). Transferring those data to critically ill patients, PPV may be of particular relevance for patients with intra-abdominal compartment syndrome.

In critically ill patients, Michard *et al.*[7] found that PPV was even better than SPV at predicting a response to fluid administration, but both were better than CVP or PAOP. A threshold value of a PPV <13% allowed discrimination between responding (cardiac index increasing by >15% to volume expansion) and non-responding patients.

Kramer *et al.*[8] studied the response to a volume challenge in postoperative cardiac surgical patients (6 responders and 15 non-responders). Baseline CVP and PAOP were no different between these two groups. In contrast, the %SPV and the %PPV were significantly higher in responders than in non-responders. ROC curve analysis suggested that the PPV was the best predictor of fluid responsiveness. The ideal PPV threshold for distinguishing responders from non-responders was found to be 11%. A PPV value of >11% predicted an increase in CO with 100% sensitivity and 93% specificity. According to these authors, PPV and SPV can be used to predict whether or not volume expansion will increase CO in postoperative CABG patients. PPV was superior to SPV at predicting fluid responsiveness while both were far superior to CVP and PAOP.

With respect to fluid therapy guided by dynamic parameters, our group studied 80 patients undergoing elective major abdominal surgery who were randomly assigned to a control or SPV group in which intra-operative fluid management was guided by SPV (trigger: SPV 10%).[26] Duration of surgery was comparable (5.8 *vs.* 5.4 hours); however, infusion volume was slightly higher in the SPV group (median 4865 ml *vs.* 4330 ml). Hepato-splanchnic blood flow, as assessed by indocyanine green plasma disappearance rate, lactate, and central venous oxygen saturation were not different between both groups. Only, vasopressor support was intermittently slightly lower in the control group. However, in comparison with routine care, intra-operative SPV-guided treatment was associated with slightly increased fluid administration whereas organ perfusion and function was similar. Unfortunately, we did not assess PPV which, however, has been shown to be correlated with SPV.

Very few data are available so far with particular respect to PPV on the benefit for guiding fluid therapy. In 2007, Lopes *et al.*[27] studied 33 patients undergoing high-risk surgery who were randomised either to a control group (n=16, PPV was not measured) or to an intervention group (n=17). In the intervention group, PPV was continuously monitored during surgery by a multi-parameter bedside monitor and minimised to 10% or less by volume loading. A noteworthy point is that none of the patients received continuous vasoactive support during surgery. While both groups were comparable in terms of patient demographics and type of surgery, the intervention group received significantly more fluid than the controls (4618 ± 1557 ml *vs.* 1694 ± 705 ml) and PPV significantly decreased from 22 ± 7% to 9 ± 1% or less at the end of the surgical procedure in all but four patients (range 7 to 11) in the intervention group. On admission to the ICU, mean arterial pressure was significantly greater in the intervention group; 24 hours after ICU admission fewer patients required vasoactive support in the intervention group, and blood lactate was lower in this group. Fewer patients developed complications in the intervention group (7 patients [41%] *vs.* 12 patients [75%]). Five patients died (on days 7, 11, 18, 19, and 26) in the control group, whereas two patients died (on days 7 and 22) in the intervention group (P=0.171). In control patients, cause of death was septic shock and ARDS in four cases (pneumonia n=1, abdominal sepsis n=2, pneumonia and urosepsis n=1), and acute pulmonary oedema in one case. In the intervention group, the cause of death was unexplained cardiac arrest in one case, and acute respiratory failure in one case (tracheostomy complication). Because death does influence the duration of mechanical ventilation, the duration of stay in the ICU, and the duration of stay in hospital, these parameters were also analysed considering only survivors (n=26). The median duration of mechanical ventilation, stay in the ICU, and stay in hospital was 1 *vs.* 5 days (P=0.29), 3 *vs.* 9 days (P=0.014), and 7 *vs.* 17 days (P=0.024) in survivors of the intervention group (n=17) and control group (n=16), respectively (Figure 3).

LIMITATIONS AND PITFALLS

As in every concept, PPV for prediction of fluid responsiveness, which is indisputably helpful in patients receiving mechanical ventilation, has its limitations. Principally, it may come to predict falsely positive infusion of fluid in the presence of a falsely high PPV in the absence of hypovolaemia and false negative results, i.e. low PPV despite fluid responsiveness. The major point is that particularly in right heart dysfunction false positive prediction by PPV may be encountered. Most patients with false positive PPV results are described in acute cor pulmonale.[20,28]

Furthermore, PPV has a lower reliability in patients with

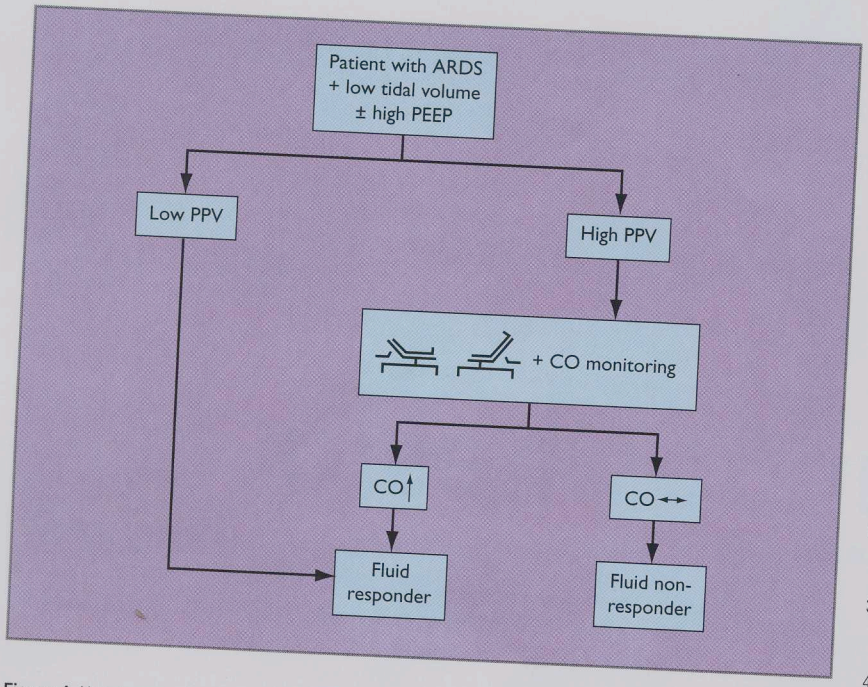

Figure 4. How to use pulse pressure variation in patients with acute respiratory distress syndrome (ARDS) ventilated with a low tidal volume (at any level of PEEP).
CO: cardiac output; PPV: pulse pressure variation; PEEP: positive end-expiratory pressure.
(modified from Teboul and Monnet[31])

spontaneous breathing activity and is not applicable in patients with arrhythmias.[17] In general, it may be hypothesised that, in patients with low lung compliance, the decreased transmission of alveolar pressure to the intrathoracic compartment could result in low PPV, even in cases of preload responsiveness. However, high PPV may be observed in patients with severe acute lung injury (and thus low lung compliance).[16] Importantly, low lung compliance is generally associated with high alveolar pressures, even in the case of reduced tidal volume. As a result, despite reduced pressure transmission, the respiratory changes in intrathoracic pressure should remain significant, thus leading to a certain amount of PPV in preload responsive patients. Overall, the potential role of lung compliance on PPV thus remains to be documented. Others have challenged this viewpoint by arguing that in patients with acute lung injury (in whom reduced tidal volume is recommended) low lung compliance is associated with cyclic changes in both transpulmonary pressure and intrathoracic pressure still high enough for PPV to keep its ability to predict fluid responsiveness.[29] Finally, arterial compliance per se and changes in vasomotor tone may modify the pulse wave itself and its amplification characteristics both by modifying the sites at which the pressure wave is reflected and by affecting pulse wave velocity. This may alter the relationship between aortic pulse pressure and peripheral pulse pressure, and the resulting effect on PPV remains to be clarified. Most recently, PPV and SVV were found to be able to predict fluid responsiveness under closed-chest conditions, whereas all static and dynamic preload indicators fail to predict fluid responsiveness under open chest conditions,[30] emphasising that the influence of intrathoracic pressure is of particular importance for interpretation.

In patients in whom respiratory changes are difficult to interpret, a passive leg raising manoeuvre should be considered for assessing fluid responsiveness. The appropriate utilisation of this test requires a real-time assessment of its effects on systemic blood flow. A practical way following this suggestion is summarised in Figure 4.[31]

CONCLUSION

Pulse pressure variation is a very promising clinical tool for management of fluid responsiveness in critically ill patients with circulatory failure and mechanical ventilation. The present body of evidence supports the incorporation of this parameter in standard monitoring devices. The measurement of PPV is less invasive than that of many other parameters and several studies have shown its clinical value in practice. However, limitations of the concept of PPV for assessing fluid responsiveness, especially present in an unselected population, need to be considered. Available results on PPV-guided therapy in high-risk surgical patients are promising; however, more data on critically ill patients are required in the future.

REFERENCES

1. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. *Crit Care Med* 1999; **27**: 639–660.
2. Osman D, Ridel C, Ray P, *et al.* Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med* 2007; **35**: 64–68.
3. Perel A, Pivoz R, Cotev S. Systolic pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. *Anesthesiology* 1987; **67**: 498–502.
4. Jardin F. Cyclic changes in arterial pressure during mechanical ventilation. *Intensive Care Med* 2004; **30**: 1047–1050.
5. Denault A, Gasior T, Gorcsan J, *et al.* Determinants of aortic pressure variation during positive-pressure ventilation in man. *Chest* 1999; **116**: 178–186.
6. Bendjelid K, Romand J. Fluid responsiveness in mechanically ventilated patients: a review of indices used in intensive care. *Intensive Care Med* 2003; **29**: 352–360.
7. Michard F, Boussat S, Chemla D, *et al.* Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med* 2000; **162**: 134–138.
8. Kramer A, Zygun D, Hawes H, Easton P, Ferland A. Artery pulse pressure variation predicts fluid responsiveness following coronary bypass surgery. *Chest* 2004; **126**: 1563–1568.
9. Berkenstadt H, Friedman Z, Preisman S, *et al.* Pulse pressure and stroke volume variations during severe haemorrhage in ventilated dogs. *Br J Anaesth* 2005; **94**: 721–726.
10. Nouira S, Elatrous S, Dimassi S, *et al.* Effects of norepinephrine on static and dynamic preload indicators in experimental hemorrhagic shock. *Crit Care Med* 2005; **33**: 2339–2343.
11. Fonseca EB, Otsuki DA, Fantoni DT, Bliacheriene F, Auler JOC. Comparative study of pressure- and volume-controlled ventilation on pulse pressure variation in a model of hypovolemia in rabbits. *Eur J Anaesth* 2008; **25**: 388–394.
12. Zaniboni M, Formenti P, Umbrello M, *et al.* Pulse and systolic pressure variation assessment in partially assisted ventilatory support. *J Clin Monit Comput* 2008; **22**: 355–359.
13. Soubrier S, Saulnier F, Hubert H, *et al.* Can dynamic indicators help the prediction of fluid responsiveness in spontaneously breathing critically ill patients? *Intensive Care Med* 2007; **33**: 1117–1124.
14. Auler JO Jr, Galas F, Hajjar L, *et al.* Online monitoring of pulse pressure variation to guide fluid therapy after cardiac surgery. *Anesth Analg* 2008; **106**: 1201–1206.
15. Umbrello M, Formenti P, Galimberti A, *et al.* On-line measurement of systolic pressure variation and pulse pressure variation on a multiparametric monitor. *Intensive Care Med* 2008; **34**: 386–387.
16. Michard F, Chemla D, Richard C, *et al.* Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. *Am J Respir Crit Care Med* 1999, **159**: 935–939.
17. Michard F. Changes in arterial pressure during mechanical ventilation. *Anesthesiology* 2005, **103**: 419–428.
18. Michard F. Volume management using dynamic parameters: the good, the bad, and the ugly. *Chest* 2005, **128**: 1902–1903.
19. Charron C, Fessenmeyer C, Cosson C, *et al.* The influence of tidal volume on the dynamic variables of fluid responsiveness in critically ill patients. *Anesth Analg* 2006; **102**: 1511–1517.
20. De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005, **31**: 517–523.
21. Huang CC, Fu JY, Hu HC, *et al.* Prediction of fluid responsiveness in acute respiratory distress syndrome patients ventilated with low tidal volume and high positive end-expiratory pressure. *Crit Care Med* 2008; **36**: 2810–2816.

22. Scherrer-Crosbie M, Streckenbach SC, Zapol WM. Acute cor pulmonale in acute respiratory distress syndrome: A dreaded complication of the past? *Crit Care Med* 2001; **29**: 1641–1642.
23. Monnet X, Teboul JL. Passive leg raising. *Intensive Care Med* 2008; **34**: 659–664.
24. Bliacheriene F, Machado SB, Fonseca EB, *et al.* Pulse pressure variation as a tool to detect hypovolaemia during pneumoperitoneum. *Acta Anaesthesiol Scand* 2007; **51**: 1268–1272.
25. Renner J, Gruenewald M, Quaden R, *et al.* Influence of increased intra-abdominal pressure on fluid responsiveness predicted by pulse pressure variation and volume variation in a porcine model. *Crit Care Med* 2009; **37**: 650–658.
26. Buettner M, Schummer W, Huettemann *et al.* Influence of systolic-pressure-variation-guided intraoperative fluid management on organ function and oxygen transport. *Br J Anaesth* 2008; **101**: 194–199.
27. Lopes MR, Oliveira MA, Pereira VOS, *et al.* Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomized controlled trial. *Critical Care* 2007, **11**: R100.
28. Magder S. Clinical usefulness of respiratory variations in arterial pulse. *Am J Respir Crit Care Med* 2004; **169**: 151–155.
29. Teboul JL, Vieillard-Baron A. Clinical value of pulse pressure variations in ARDS. Still an unresolved issue? *Intensive Care Med* 2005, **31**: 499–500.
30. de Waal EEC, Rex S, Kruitwagen CLJJ, Kalkman CJ, Buhre WF. Dynamic preload indicators fail to predict fluid responsiveness in open-chest conditions. *Crit Care Med* 2009; **37**: 510–515.
31. Teboul JL, Monnet X. Prediction of volume responsiveness in critically ill patients with spontaneous breathing activity. *Curr Opin Crit Care* 2008; **14**: 334–339.

CORRESPONDENCE TO:
Samir G Sakka MD, PhD
University of Witten/ Herdecke
Department of Anesthesiology and Intensive Care Medicine
Medical Center Cologne-Merheim
Ostmerheimerstr. 200
D-51109 Cologne
Germany
E-mail: sakkas@kliniken-koeln.de

Instructions to authors

International Journal of Intensive Care (IJIC) is published four times a year in English. The journal includes clinical reviews and original papers dealing with the whole field of intensive care and emergency medicine. In addition to such articles, *IJIC* publishes comments, case reports, meeting reports and letters to the editor.

Manuscript preparation: Presentation of manuscripts should conform to the updated Uniform Requirements for Manuscripts Submitted to Biomedical Journals (see http://www.icmje.org).

All manuscripts must be submitted electronically to the Commissioning Editor at Greycoat Publishing, t.tighe@greycoatpublishing.co.uk. If there has been previous contact with another Greycoat Publishing commissioning editor, the message and attachments should be copied to that address too. If any problems are experienced, please contact the office on +44 (0)20 7937 6233 or send mail to Greycoat Publishing Ltd, 106 Earl's Court Road, London W8 6EG, UK.

Prior publication and co-author approval: Authors submitting a paper do so on the understanding that neither the work nor any part of its essential substance, tables or figures have been or will be published by or submitted to another scientific journal or is being considered for publication elsewhere. This must be stated in the covering letter. This restriction does not apply to abstracts, but includes work published in any other language. All work must have been approved by all co-authors.

Copyright: Submission of the manuscript implies that if and when it is accepted for publication, the authors automatically agree to transfer the copyright to the publisher. The copyright protection implies that the publisher holds the exclusive right to reproduction in any form (including publication in another language) and distribution of any of the articles in the journal. Material published in *IJIC* may be stored on microfilm, video discs, in an electronic database or in any other electronic format, etc, and be reproduced photographically with prior written permission of the publisher. One copyright transfer form should be completed by the corresponding author on submission of any manuscript to *IJIC*.

Peer review: Each manuscript will be reviewed by the editor and/or one or more reviewers. Authors will be notified of any queries or requests for revision.

Statement of interest: Authors should acknowledge all financial support for the work and other personal connections to the work. A statement will then be added to the manuscript at publication.

Proofs: If the manuscript is accepted for publication, it will be edited and set in house style. A proof (pdf file) will be sent to the corresponding author, which may contain queries and/or requests for clarification. Corrections should be returned to the Production Department as promptly as possible by e-mail.

For more detail about guidelines for this journal and other publications, please visit www.greycoatpublishing.co.uk