Predicting cardiac output responses to passive leg raising by a PEEP-induced increase in central venous pressure, in cardiac surgery patients

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Editor’s key points

- Dynamic measures of circulatory filling such as stroke volume variation (SVV) with mechanical ventilation are generally considered more reliable than static measures such as central venous filling pressure (CVP).
- Drawbacks of SVV include dependence of the changes on tidal volume and ventilatory frequency.
- Change in CVP upon the application of increased PEEP is not subject to these limitations.
- In this small study in cardiac surgery patients, the change in CVP with PEEP performed similar to SVV as an indicator of fluid responsiveness.

Background. Changes in central venous pressure (CVP) rather than absolute values may be used to guide fluid therapy in critically ill patients undergoing mechanical ventilation. We conducted a study comparing the changes in the CVP produced by an increase in PEEP and stroke volume variation (SVV) as indicators of fluid responsiveness. Fluid responsiveness was assessed by the changes in cardiac output (CO) produced by passive leg raising (PLR).

Methods. In 20 fully mechanically ventilated patients after cardiac surgery, PEEP was increased +10 cm H₂O for 5 min followed by PLR. CVP, SVV, and thermodilution CO were measured before, during, and directly after the PEEP challenge and 30° PLR. The CO increase >7% upon PLR was used to define responders.

Results. Twenty patients were included; of whom, 10 responded to PLR. The increase in CO by PLR directly related (r=0.77, P<0.001) to the increase in CVP by PEEP. PLR responsiveness was predicted by the PEEP-induced increase in CVP [area under receiver-operating characteristic (AUROC) curve 0.99, P<0.001] and by baseline SVV (AUROC 0.90, P=0.003). The AUROC’s for dCVP and SVV did not differ significantly (P=0.299).

Conclusions. Our data in mechanically ventilated, cardiac surgery patients suggest that the newly defined parameter, PEEP-induced CVP changes, like SVV, appears to be a good parameter to predict fluid responsiveness.

Keywords: cardiac output, monitoring; cardiac surgery; central venous pressure; fluid loading responsiveness; passive leg raising

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Changes in central venous pressure (CVP) are probably more useful in guiding fluid treatment of mechanically ventilated hypovolaemic patients than absolute pressure values which are confounded by concomitant PEEP.¹–³ Furthermore, assessment of a reliable predictor before fluid loading would allow the physician to prevent harmful overloading. Ventilator-induced stroke volume variations (SVVs) are commonly used to predict fluid responsiveness, that is, an increase in cardiac output (CO) by fluid loading or passive leg raising (PLR). However, SVV is only applicable in mechanically ventilated patients without spontaneous breathing efforts and with a regular heart rhythm. Furthermore, SVV depends on ventilatory frequencies and tidal volumes.⁴–⁸ PLR can be used as a reversible, endogenous fluid challenge of about 250–300 ml and, if correctly performed, the CO response correlates well to that upon exogenous fluid administration in predicting fluid responsiveness.⁹ ¹⁹–²⁰ However, repeated PLR is not practicable in all patients and all settings. Another manoeuvre to predict fluid responsiveness is an end-expiratory hold which produces an increase in pulse pressure and CO. The magnitude of the change may be assessed by comparatively non-invasive pulse contour methods.¹⁹ However, it is likely that the change depends on inspiratory pressure and thus on tidal volume and the resultant impediment in venous return. Taken together, current dynamic methods to predict fluid responsiveness have limitations and may not prevent harmful fluid overloading in mechanically ventilated, critically ill patients.

We hypothesized that the change in CVP produced by a change in PEEP of short duration can be used to predict the response of CO to fluid loading, since an increase in PEEP is associated with an increase in CVP and a decrease in CO, dependent on volume status.¹ ²¹–²³ To test this hypothesis, we measured the changes in CVP due to an increase in PEEP of 10 cm H₂O and defined fluid
responsiveness by the response in CO to subsequent PLR. We compared the predictive value of the change in CVP with those of absolute CVP and SVV.

Methods

The study was approved by the Medical Ethics Committee of the Leiden University Medical Centre and written informed consent was obtained before surgery. Twenty consecutive patients undergoing elective cardiac surgery were enrolled into the study. During surgery, before admission to the intensive care unit (ICU), each patient underwent pulmonary artery catheter insertion (Intelicath; Edwards Lifesciences, Irvine, CA, USA) to measure thermodilution CO and CVP. A radial artery catheter was used to measure radial arterial pressure in all patients. In the ICU, anaesthesia was continued with propofol target control infusion (1.0 µg ml\(^{-1}\)) and sufentanil according to institutional standards. The lungs were mechanically ventilated in a volume-control mode with standard settings to achieve normocapnia with a tidal volume of 8–10 ml kg\(^{-1}\) and a respiratory frequency of 12–14 bpm. The F\(_{\text{IO}}\)\(_2\) was 0.4 and baseline PEEP 5 cm H\(_2\)O. None of the patients suffered significant blood loss (>50 ml h\(^{-1}\)) during the data collection period.

Protocol and measurements

Blood pressure transducers were referenced to the level of the intersection of the anterior axillary line and the fifth intercostal space. CVP, mean arterial pressure (MAP), and heart rate (HR) were averaged over 30 s intervals. Bolus thermodilution CO was obtained, within 3 min with an automated system under computer control, by the mean of triplicate measurements equally spread over the ventilatory cycle.\(^{24}\) SVV was determined from beat-to-beat CO values measured over 20 s intervals using the LiDCO (LiDCO Ltd, Cambridge, UK) radial artery pulse contour system. The system was calibrated by entering the mean value of the first series of three thermodilution measurements at the start of our protocol. All measurements were carried out following stabilization and within 2 h of arrival on the ICU. During the observation period, the patients remained supine and doses of sedative and vasoactive agents were unaltered. Measurements of CVP, SVV, CO, MAP, and HR were made under five experimental conditions: (i) baseline 1; (ii) PEEP increased with 10 cm H\(_2\)O (to a level of 15 cm H\(_2\)O); (iii) baseline 2; (iv) PLR; and (v) baseline 3. Each condition was maintained for a 5 min period and measurements were performed in the final 3 min of each period. PLR was performed by maintaining the patient in the supine position and raising the legs 30° by using the facility to raise the lower end of the bed. The thorax and head (i.e. the heart and baroreceptors) were maintained at the same position through all of the study periods and the pressure transducers did not have to be re-referenced.

Statistical analysis

Usually, fluid responsiveness is characterized by an increase of 10–15% in CO after rapid fluid loading with 500 ml.\(^2\) Recently, Jabot and colleagues\(^{17}\) showed that PLR from the supine position induces smaller increases in CO than PLR from the semi-recumbent position. On the basis of their results and those of Lafanechere and colleagues,\(^{15}\) we reasoned that in responders, PLR from the supine position should result in an increase of CO >7%. Our thermodilution technique with automated triplicate measurements equally spread over the respiratory cycle has a precision of 3.5%.\(^{24}\) Therefore, this technique should detect changes in CO induced by PLR >7% accurately, thereby allowing identification of responders. All data were normally distributed (Kolmogorov–Smirnov test \(P>0.05\)). The effects of PEEP and PLR were evaluated by subtracting the mean of the baseline value before and after the challenge from the value found during the challenge. Comparisons of different experimental conditions were performed using the paired t-test. The Pearson correlation coefficient was used to relate baseline variables to increases in CO upon PLR. Receiver operating characteristic (ROC) curves and 95% confidence intervals (95% CIs) for the area under the curve (AUC) were computed. A \(P\)-value for the difference between the AUC and the reference value of 0.5 (i.e. prediction of responders and non-responders by chance) is calculated. From the ROC curves, the optimal cut-off value with the greatest combined sensitivity and specificity was computed, using baseline SVV, absolute values, and changes in CVP.\(^{25}\) Areas under the curve of the ROC curves (AUROC) of baseline SVV and PEEP-induced change in CVP were compared. Data are summarized by mean and standard deviation (SD). A \(P\)-value of <0.05 was considered statistically significant. Statistical calculations were performed using SPSS for Windows (V12; SPSS Institute, Chicago, IL, USA), and MedCalc (V9, Mariakerke, Belgium).

Results

Twenty patients were included in the study; patient characteristics are tabulated in Table 1. Twelve patients underwent coronary artery bypass surgery (CABG), and eight received either a single-valve replacement or a combination of CABG and valvular repair surgery. Table 2 shows that, compared with baseline, an increase of 10 cm H\(_2\)O in PEEP decreased CO, increased CVP and SVV, but had little effect on MAP and HR. PLR increased CO, CVP, and MAP but decreased SVV. All variables returned to baseline after the PEEP and PLR challenges. Whereas baseline CVP and baseline SVV related to the percentage change in CO due to PLR (Fig. 1), the change in CVP due to PEEP correlated best to the change in CO due to PLR (Fig. 1). Changes in CO upon PEEP moderately correlated to changes in CO by PLR \((r=-0.47, P=0.036)\).

There were 10 PLR responders and 10 non-responders. CO values before and after the PEEP challenge were 5.1 (1.2) and 5.3 (1.5) litre min\(^{-1}\), in responders and non-responders (ns),
respectively. CO values around PLR were 5.5 (1.6) and 5.5 (1.5) litre min⁻¹ in responders and non-responders (ns), respectively. Baseline CVP values before and after the PEEP challenge were 7.1 (2.8) and 11.3 (3.1) mm Hg in responders and non-responders, respectively (P = 0.003). Baseline SVV values around the PEEP challenge were 8.7 (3.2)% and 3.5 (2.1)% in PLR responders and non-responders, respectively (P = 0.001), but the PEEP-induced change in SVV did not differ. The PEEP-induced increase in CVP was less in non-responders to PLR than in responders: 1.1 (0.4) and 3.6 (1.8) mm Hg or 9 (7)% and 62 (42)% (P = 0.001). Baseline values of CVP for responders and non-responders were 11.3 (3.1) and 7.1 (2.8) mm Hg (P = 0.006), respectively. Also, the decrease in CO upon the application of PEEP was less in PLR non-responders than responders [6 (7)% vs 16 (10)%, P = 0.014].

The results of ROC curves analyses are shown in Figure 2. For baseline CVP, the AUC was 0.85 (95% CI 0.68 and 1.00, P = 0.008) and the optimum cut-off value of 9.8 mm Hg had a sensitivity of 80% and a specificity of 80% to predict PLR responsiveness. The AUC for baseline SVV was 0.90 (95% CI 0.76–1.00, P = 0.003), and a baseline SVV cut-off of 7.3% had a sensitivity of 70% and a specificity of 100% to predict PLR responsiveness. For the predictive value of the CVP response (change) to PEEP, the AUC was 0.99 (95% CI 0.94–1.00, P < 0.001) and a cut-off value of an increase of 1.5 mm Hg had a sensitivity of 100% and a specificity of 90% for PLR responsiveness. The AUC of baseline SVV was not significantly different from the AUC for CVP response to PEEP (P = 0.299), suggesting that baseline SVV and the CVP response to PEEP can be used equally to predict responders and non-responders to fluid loading.

**Discussion**

Our study shows that with higher baseline SVV values, lower baseline CVP values, and greater increases in CVP upon a PEEP challenge, the response of CO on an endogenous fluid loading by PLR can be predicted. Of these predictors, the increase in CVP with PEEP seems most robust for predicting fluid responsiveness with least risk for confounding by ventilatory conditions.

We based our study on the simplified Guytonian model of the circulation (Fig. 3). We consider the effects of PEEP and of PLR in the hypo- and normovolaemic state. Many authors demonstrated that the venous return curve, that is, the relationship between CO and CVP, moves up in parallel with increased blood volumes (Fig. 3, lines hypo- and normovolaemia). We have previously constructed venous return curves using prolonged inspiratory hold manoeuvres in cardiac surgical patients and showed that the slopes were equal in hypo-, normo-, and hypervolaemic conditions. Magder and colleagues have shown that application of PEEP shifts the cardiac function curve to the right, altering the intersection with the venous return curve to a lower CO and a higher CVP (Fig. 3, change from point A to point B). In patients with hypovolaemia, the increase in CVP and decrease in CO (dCVP1 and dCO1) are larger than in patients with normovolaemia (dCVP2 and dCO2), in line with experimental data. Thus, the PEEP-induced change in CVP and the change in CO describe in which part of its function curve, the heart operates. Fluid loading by PLR will move up the venous return curve (Fig. 3, dashed lines). In patients with hypovolaemia and in those with normovolaemia, the intersection with the cardiac function curve will move towards its plateau. Fluid loading in these two volaemic conditions results in an increasing change in CVP (Fig. 3b, plateau).
from dCVP1 to dCVP2) and a decreasing effect on CO (Fig. 3B, from dCO1 to dCO2). Thus, with PEEP, dCVP and dCO should change inversely but proportionally, depending on the volume status, whereas with fluid loading, reverse effects of dCVP and dCO are predicted. We used PLR as a surrogate for fluid infusion since it correlates well with responsiveness to exogenous fluids. Moreover, the use of PLR obviates unnecessary and potentially harmful fluid loading in non-responders.

We found, as predicted by the model, that the increase in CVP by PEEP directly relates to the increase in thermodilution CO by PLR (dCO, PLR) is shown ($r=-0.63$, $P=0.003$); in the second graph (a), the relationship between baseline SVV and dCO, PLR ($r=0.67$, $P=0.002$). In the third graph (c), the relationship between the PEEP-induced change in CVP (dCVP, PEEP) and dCO, PLR is depicted ($r=0.77$, $P<0.001$). Baseline values of CVP and SVV were the averaged results of baseline measurements before and after the PEEP challenge. dCVP is the change in CVP due to PEEP compared with the averaged baseline value. The horizontal dashed line in the graphs indicates the cut-off between responders and non-responders.

Figure 1 In the first graph (A), the relationship between Baseline CVP and change in thermodilution CO by PLR (dCO, PLR) is shown ($r=-0.63$, $P=0.003$); in the second graph (B), the relationship between baseline SVV and dCO, PLR ($r=0.67$, $P=0.002$). In the third graph (C), the relationship between the PEEP-induced change in CVP (dCVP, PEEP) and dCO, PLR is depicted ($r=0.77$, $P<0.001$). Baseline values of CVP and SVV were the averaged results of baseline measurements before and after the PEEP challenge. dCVP is the change in CVP due to PEEP compared with the averaged baseline value. The horizontal dashed line in the graphs indicates the cut-off between responders and non-responders.
responders than in responders (normo- vs hypovolaemia). Our results imply that the predominant mechanism of the decrease in CO with PEEP is diminished venous return and a decrease in right ventricular preload, which in turn may limit the increase in CVP. We cannot judge from our data the effect of abnormal lungs and altered airway pressure transmission on the circulatory response to PEEP. Another limitation of the model is that it does not take circulatory control mechanisms into account. Therefore, we measured the effects of PEEP between 2 and 5 min after its application. Changes in myocardial contractility may change the position and shape of the heart function curve. Therefore, a deterioration of cardiac function may lead to a decrease in SVV and a decrease in the change in CVP produced by PEEP and also a less fluid-responsive patient. This was not examined in this study. The fact that baseline CVP was also associated with changes in CO can be explained by the relatively low PEEP we used in our patients, but changes in filling pressures to guide fluid treatment are less confounded by PEEP than absolute levels. The observation that the CO response to PEEP was of less predictive value than the CVP response for the CO increase upon PLR can be explained by a lesser decrease in CO for a given PEEP-induced increase in CVP in hypo- than in normovolaemic conditions, as shown in animal experiments. We should also keep in mind that the PEEP challenge moves the work-point of the cardiac function and venous return curves downwards to the steep part of the curve (larger change in CO), whereas PLR moves the work-point upwards into the flat part of the curve (smaller change in CO, Fig. 3). This may help explain why the PLR response of CO was of less predictive value for the PEEP-induced decrease in CO.

Fig 2 ROC curve of baseline CVP (dotted line), baseline SVV (dashed line), and change in CVP (straight line) upon a PEEP challenge to predict responsiveness to PLR. The AUC is 0.85 (with a 95% CI of 0.68–1.00) for baseline CVP, 0.99 (with a 95% CI of 0.94–1.00) for changes in CVP, and 0.90 (with a 95% CI of 0.76 and 1.00) for baseline SVV.

Fig 3 A simplified model of the interaction of the heart function curve and venous return curve. The effects of (a) PEEP and (a) fluid loading by PLR on CVP and CO are indicated. From hypovolaemia (hypo) to normovolaemia (normo), the venous return curve (straight line) moves up and the intersection with the cardiac function curve (curved line) increases to a higher CO and CVP level. (a) Addition of PEEP shifts the heart function curve to the right (dashed line) altering the intersection with the venous return curve to a lower CO and a higher CVP. With the application of PEEP, the change in CVP (dCVP) and the change in CO (dCO) are larger during hypovolaemia (dCVP1 and dCO1) than during normovolaemia (dCVP2 and dCO2). This suggests that the value of dCVP is an indicator for fluid loading responsiveness. (a) Addition of PLR (dashed lines) results in an increase in CVP and CO. With fluid loading by PLR during normovolaemia, a greater dCVP (dCVP2) and a smaller dCO (dCO2) are observable than during hypovolaemia (dCVP1 and dCO1). dCO with PLR have been shown to be an indicator of fluid loading responsiveness. For further explanation, see text.
than vice versa (data not shown). The decrease in CO with PEEP may lead to an unacceptably too low CO for several minutes. Thus, when there are clear signs of hypovolaemia, the use of the PEEP challenge may not be appropriate.

Our proposed challenge resembles the end-expiratory occlusion test to predict fluid responsiveness but carries the relative advantage, of being independent of ventilatory conditions provided that PEEP can be increased by 10 cm H₂O. Since the PEEP challenge is easy to apply and CVP is measured routinely in the ICU, the PEEP-induced change in CVP may provide the physician with a robust and easy-to-use tool to assess fluid responsiveness. The drawback of the PEEP challenge is its dependence on maintenance of a steady state during the challenge and potential worsening of hypotension. An SVV of about 10% or above, derived from non-invasive arterial pulse contour algorithms, has been used to predict an increase of 10–15% in CO in response to 500 ml fluid loading. Our patients were subjected to a smaller preload challenge and the optimal cut-off to define responsiveness was somewhat lower. The SVV requires a regular HR and full mechanical ventilatory support, with predictive values dependent on ventilatory frequencies and tidal volumes. Again, we may speculate that our PEEP challenge is less dependent on these prerequisites. Even though SVV had a similar predictive value to the PEEP challenge, the latter may thus be preferable, particularly in the case of arrhythmias. One might also argue that performing a PLR and looking at the CO response would render our PEEP challenge redundant. However, PLR is not always feasible and necessitates some CO measurement, while our PEEP challenge does not. (In contrast, the PLR challenge does not require mechanical ventilation.) Finally, the relatively small changes in CVP evoked by PEEP can only be discerned at the bedside when accurately measured.

In conclusion, our data suggest that brief PEEP-induced increases in CVP predict fluid responsiveness at least and also absolute values of CVP and SVV, after cardiac surgery, and are less likely to be confounded by ventilatory conditions.

Conflict of interest
None declared.

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