Fluid loading responsiveness

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Chapter 10

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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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 positive end-expiratory pressure (PEEP) [1-3]. Furthermore, assessment of a reliable predictor prior to fluid loading would allow the physician to prevent harmful overloading. Ventilator-induced stroke volume variations (SVV) are commonly used to predict fluid responsiveness, i.e. an increase in cardiac output 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 respiratory rates and tidal volumes [4-8]. Passive leg raising can be used as a reversible, endogenous fluid challenge of about 250-300 ml and, if correctly performed, the cardiac output response correlates well to that upon exogenous fluid administration in predicting fluid responsiveness [4,9-20]. 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 cardiac output. 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 cardiac output to fluid loading, since an increase in PEEP is associated with an increase in CVP and a decrease in cardiac output, 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 cmH_2O and defined fluid responsiveness by the response in cardiac output 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 prior to surgery. Twenty consecutive patients undergoing elective cardiac surgery were enrolled into the study. During surgery, before admission to the ICU, each patient underwent pulmonary artery catheter insertion (Intellicath; Edwards Lifesciences; Irvine, CA, USA) to measure thermodilution cardiac output (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 $\mu g \cdot ml^{-1}$) 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 $ml \cdot kg^{-1}$ and a respiratory frequency of 12-14 $breaths \cdot min^{-1}$. The FiO_2 was 0.4 and baseline PEEP 5 cmH_2O. None of the patients suffered significant blood loss (> 50 $ml \cdot h^{-1}$) 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 5th intercostal space. CVP, mean arterial pressure (MAP) and heart rate (HR) were averaged over 30 second intervals. Bolus thermodilution CO was obtained, within 3 minutes 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 second 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 3 thermodilution measurements at the start of our protocol. All measurements were carried out following stabilization and within two hours of arrival on the ICU. During the observation period the patients remined supine and doses of sedative and vasoactive agents were unaltered. Measurements of CVP, SVV, CO, MAP and HR were made under five experimental conditions:

1) baseline 1;
2) PEEP increased with 10 cmH_2O (to a level of 15 cmH_2O);
3) baseline 2;
4) passive leg raising;
5) baseline 3;

Each condition was maintained for a five minute period and measurements were performed in the final three minutes of each period. Passive leg raising was performed by maintaining the patient supine position and raising the legs 30 degrees 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 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 showed that PLR from the supine position induces lower increase in CO than PLR from the semi-recumbent position [17]. Based on their results and those of Lafanachere 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 larger than 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%CI) 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 optimum cut-off value with the greatest combined sensitivity and specificity were computed, using baseline SVV, absolute values and changes in CVP [25]. AUC's 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<0.05 was considered statistically significant. Statistical calculations were performed by 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 by-pass surgery (CABG) and, eight received either a single valve replacement or a combination of CABG and valvular repair surgery. Table 2 shows that, compared to baseline, an increase with 10 cmH$_2$O PEEP decreased CO increased CVP and SVV, but had little effect on MAP and HR. Passive leg raising 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 (Figure 1), the change in CVP due to PEEP correlated best to the change in CO due to PLR (Figure 1). Changes in CO upon PEEP moderately correlated to changes in CO by PLR (r=-0.47, P=0.036).

Table 1 Patient characteristics (n=20).

Age	61 [range 35-80] years
Sex m/f	16 [80%]/ 4 [20%]
Body surface area	2.00 (0.21) m²
Type of surgery	
- coronary artery bypas grafting	11 [55%]
- valvular repair	9 [45%]
Dobutamine or dopamine	3 [15%]
Norepinephrine	2 [10%]
Tidal volume	752 (127) ml
Mean airway pressure	9 ± 1 cmH$_2$O
Positive end-expiratory pressure,	5 ± 0 cmH$_2$O
F$_1$O$_2$	0.4
P$_a$O$_2$	13.03 ± 0.13 kPa
P$_a$O$_2$/F$_1$O$_2$ ratio	31.0 ± 1.1

Data collected postoperative immediately before the study was performed. Data, except in the case of age, are shown as mean ± standard deviation

Table 2 Haemodynamics at baseline and after an increase in PEEP of 10 cmH$_2$O and after passive leg raising.

|	Baseline PEEP	+10 cmH$_2$O PEEP	Change	P	Baseline PLR	PLR	Change	P
CVP (mmHg)	9.2 ± 3.6	11.5 ± 3.2	2.4 ± 1.8	<0.001	9.2 ± 3.6	11.6 ± 3.6	2.3 ± 1.3	<0.001
SVV (%)	6.2 ± 3.8	10.6 ± 6.5	4.7 ± 3.7	<0.001	5.8 ± 3.5	3.9 ± 2.7	-1.9 ± 1.8	<0.001
CO (L·min⁻¹)	5.2 ± 1.3	4.6 ± 1.2	-0.6 ± 0.5	<0.001	5.5 ± 1.5	5.9 ± 1.7	0.4 ± 0.3	<0.001
MAP (mmHg)	83 ± 13	80 ± 14	-3 ± 10	0.054	84 ± 16	92 ± 14	8 ± 10	0.003
HR (min⁻¹)	79 ± 13	78 ± 12	-1 ± 1	0.400	79 ± 12	77 ± 12	-2 ± 3	0.259

PLR is passive leg raising; CVP is central venous pressure; SVV is stroke volume variation; CO is cardiac output by thermodilution; MAP is mean arterial blood pressure; HR is heart rate. Baseline PEEP is the group average of the values before and after the PEEP-challenge; baseline PLR the group averaged value before and after PLR. The results are shown as mean (SD).

There were 10 PLR responders and 10 non-responders. Cardiac output values before and after the PEEP challenge were 5.1 ± 1.2 and 5.3 ± 1.5 L·min⁻¹, in responders and non-responders (ns), respectively. Cardiac output values around PLR were 5.5 ± 1.6 and 5.5 ± 1.5 L·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 mmHg in responders and non-responders, respectively (P=0.003). Baseline SVV values around the PEEP challenge were 8.7 ± 3.2 and $3.5 \pm 2.1\%$ 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 mmHg 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 mmHg (P=0.006), respectively. Also, the decrease in CO upon the application of PEEP was less in PLR non-responders than responders (6 ± 7% versus 16 ± 10%, P=0.014).

Figure 1 In the first graph (i), the relationship between baseline central venous pressure (Baseline CVP) and change in thermodilution cardiac output (CO) by passive leg raising (dCO, PLR) is shown (r=-0.63, P=0.003); in the second graph (ii), the relationship between baseline stroke volume variation (Baseline SVV) and dCO, PLR (r=0.67, P=0.002). In the third graph (iii), relationship between the positive end-expiratory pressure (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 to the averaged baseline value. The horizontal dashed line in the graphs indicate the cut-off between responders and non-responders. Closed symbols refer to responders.
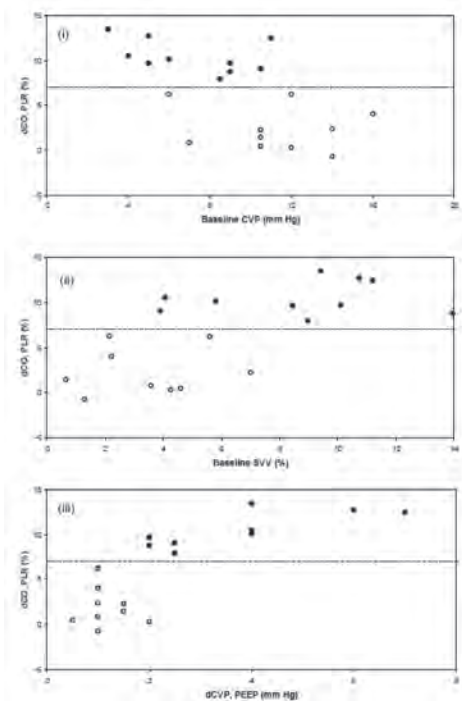
The results of ROC curves analyses are shown in Figure 2. For baseline CVP, the AUC was 0.85 (95%CI 0.68 and 1.00, P=0.008) and the optimum cut-off value of 9.8 mmHg had a sensitivity of 80% and a specificity of 80% to predict PLR responsiveness. The AUC for baseline SVV was 0.90 (95%CI 0.76 and 1.00, 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 and 1.00, P<0.001) and a cut-off value of an increase of 1.5 mmHg 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), indicating that baseline SVV and the CVP response to PEEP can be used equally to predict responders and non-responders to fluid loading.

Figure 2 Receiver operating characteristics (ROC) curve of baseline CVP (dotted line), baseline stroke volume variation (dashed line) and change in central venous pressure (straight line) upon a PEEP challenge to predict responsiveness to passive leg raising. The area under the curve is 0.85 (with a 95% CI of 0.68 and 1.00) for baseline CVP, 0.99 (with a 95% CI 0.94 and 1.00) for changes in CVP and 0.90 (with a 95% CI 0.76 and 1.00) for baseline SVV.

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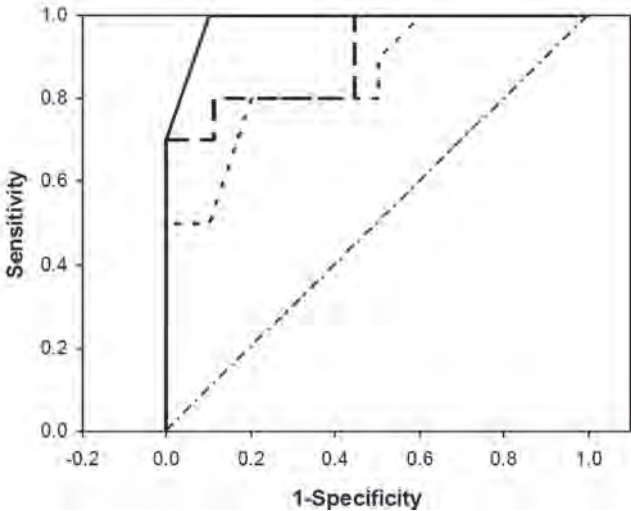
Discussion

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

Figure 3 A simplified model of the interaction of the heart function curve and venous return curve. On the left (A) the effects of positive end-expiratory pressure (PEEP) and on the right (B) the effects of fluid loading by passive leg raising (PRL) on central venous pressure (CVP) and cardiac output (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) rises to a higher CO and CVP level. Left panel, 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 ($dCVP^1$ and dCO^1) than during normovolaemia ($dCVP^2$ and dCO^2). Which suggest that the value of dCVP is an is an indicator for fluid loading responsiveness. Right panel, addition of PLR, dashed lines) results in an increase in CVP and CO. With fluid loading by PLR during normovolaemia a greater dCVP ($dCVP_2$) and a smaller dCO (dCO_2) is observable than during hypovolaemia ($dCVP^1$ and dCO^1). dCO with PLR have been shown to be an indicator of fluid loading responsiveness. For further explanation see text.
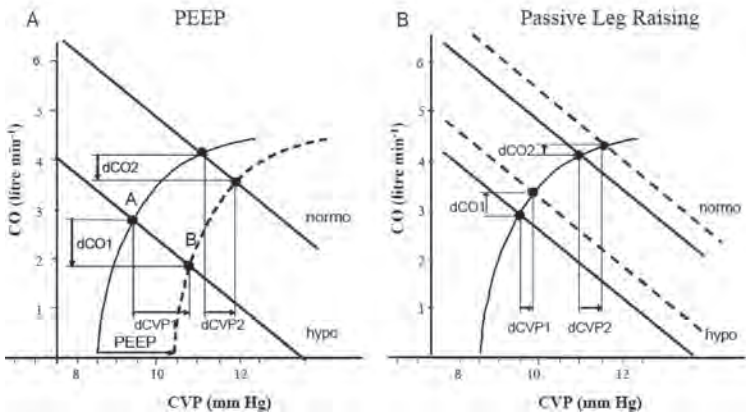
We based our study on the simplified Guytonian model of the circulation (Figure 3). We consider the effects of PEEP and of PLR in the hypo- and normovolaemic state. Many authors demonstrated that the venous return curve, i.e. the relationship between CO and CVP, moves up in parallel with increased blood volumes (Figure 3, lines hypo- and normovolaemia) [26-29]. 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 [29]. Magder has 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 (see Figure 3A, change from point A to point B) [1]. In patients with hypovolaemia, the increase in CVP and decrease in CO (dCVP1 and dCO1) is larger than in patients with normovolaemia (dCVP2 and dCO2), in line with experimental data [21]. Thus, the PEEP-induced change in CVP as well as the change in CO describes in which part of its function curve the heart operates. Fluid loading by PLR will move up the venous return curve (Figure 3B, dashed lines). In patients with hypovolaemia and in those with normovolaemia the intersection with the cardiac function curve will move towards its plateau [30]. Fluid loading in these two volaemic conditions results in an increasing change in CVP (see Figure 3B, from dCVP1 to dCVP2) and a decreasing effect on CO (see Figure 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 well correlates with responsiveness to exogenous fluids [4,9-20]. 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 CO by PLR and thus may be of value to predict fluid responsiveness (Figure 1); second, that PEEP increases CVP and decreases CO, but that the increase in CVP as well as the decrease in CO is less in non-responders than in responders (normo- versus 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, that in turn may limit the rise in CVP [1,21,22] We cannot judge from our data the effect of abnormal lungs and altered airway pressure transmission on the circulatory response to PEEP [22,23] 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 minutes 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 of in the change in CVP produced by PEEP as well as a less fluid-responsive patient. This was not examined in this study The fact that baseline CVP was also associated with changes in cardiac output 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 [3,22]. 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 rise in CVP in hypo- than in normovolaemic conditions, as shown in animal experiments [21]. 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 curve (smaller change in CO, Figure 3). This may help explain why the PLR response of CO was of less predictive value for the PEEP-induced fall in CO 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 areclear signs of hypovolaemia the use of the PEEP-challenge may not be appropriate.

Our proposed challenge resembles the end-expiratory occlusion test [19] to predict fluid responsiveness but carries the relative advantage, of being independent of ventilatory conditions provided that PEEP can be increased by 10 cmH$_2$O. 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. A SVV of about 10% or above, derived from non-invasive arterial pulse contour algorithms, has been used to predict an increase of 10% to 15% in CO in response to 500 ml fluid loading [4-8]. 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 heart rate and full mechanical ventilatory support, with predictive values dependent on respiratory rates and tidal volumes [7,8] Again, we may speculate that our PEEP challenge is less dependent on these prerequisites. Even though SVV had a similar predictive to the PEEP challenge, the latter may thus be preferable, particularly in 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 [14,18]. Finally, the relatively small changes in CVP evoked by PEEP can only be discerned at the bedside when accurately measured.

Conclusions

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

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