

The effect of positive end-expiratory pressure on pulse pressure variation

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Abstract

Objectives: To determine the effect of different levels of positive end-expiratory pressure (PEEP) on pulse pressure variation (PPV).

Design: An observational study.

Setting: Operating theatres of a tertiary training hospital.

Subjects: Ventilated patients who required intra-arterial blood pressure monitoring.

Outcome measures: PPV during different levels of PEEP.

Method: Patients were anaesthetised by means of a standard technique and ventilated with a tidal volume of 9 ml/kg ideal body mass. The PPV was calculated at PEEP levels of 2, 5, 8 and 10 cmH₂O. PPV was compared at the various PEEP levels.

Results: PPV at a PEEP of 8 cmH₂O and 10 cmH₂O was significantly larger than that at 2 cmH₂O (p-value < 0.001). PPV at a PEEP of 10 cmH₂O was significantly larger than that at 8 cmH₂O (p-value < 0.001). PPV at a PEEP of 8 cmH₂O was larger than that at 5 cmH₂O (p-value = 0.002). PPV at a PEEP of 2 and 5 cmH₂O did not differ significantly (p-value = 0.194).

Conclusion: We have demonstrated that, in patients with normal lungs, PEEP has a significant influence on PPV. PPV may be overestimated if PEEP ≥ 8 cmH₂O is applied in patients who are ventilated with a tidal volume of 9 ml/kg. It is recommended that in patients with healthy lungs PPV should be measured at a standardised PEEP of ≤ 5 cmH₂O.

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Introduction

The first step in the management of circulatory failure is to differentiate between pump failure and hypovolaemia. The former is regarded as “volume unresponsive”, while the latter is regarded as “volume responsive”. Static indicators of preload, such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP), have been shown to be poor indicators of volume status.^{1,2}

Dynamic variables, such as systolic pressure variation (SPV), stroke volume variation (SVV) and pulse pressure variation (PPV), were introduced to distinguish between volume and inotropic deficit. It has been demonstrated that PPV predicts an increase in cardiac index more accurately than CVP, PAOP and SPV.³ PPV is defined as the maximum difference

between pulse pressures (PPs) during a ventilatory cycle divided by the mean PP.

The dynamic variables have their origin in the influence of heart-lung interactions on stroke volume during ventilation. The change in stroke volume is proportional to the slope of the Starling curve. If the heart functions on the steep ascending part of the curve, an increase in preload will lead to a significant change in left ventricular stroke volume, systolic arterial pressure and PP. If the heart functions at the flat portion (knee) of the Starling curve, identical increases in preload will result in little change in stroke volume.⁴

The PPV threshold that predicts fluid responsiveness varies between 8% and 17%. This figure varies in accordance with the study sample, namely type of surgery (cardiac surgery

and open or closed mediastinum), co-morbid disease (cardiac failure, septic shock, lung injury and hypovolaemia) and ventilator settings, including tidal volume (TV) and positive end-expiratory pressure (PEEP).

In cardiac surgery and septic shock patients, a PPV of 9.4%⁵ and 17%⁶, respectively, differentiates between fluid responders and non-responders with a high sensitivity and specificity (> 85%). Auler et al have demonstrated that a PPV threshold of 12% differentiates between fluid responders and non-responders with a sensitivity of 97% and a specificity of 95%.⁷

De Backer et al studied the effect of TV on PPV to predict fluid responsiveness in ventilated patients, including patients who suffer from acute respiratory distress syndrome (ARDS). Patients received various levels of PEEP. A PPV of 12% was the threshold that was used to differentiate between responders (a cardiac index increase of > 15%) and non-responders. Using a low TV (< 8 ml/kg, i.e. 7 ml/kg) or high TV (> 8 ml/kg, i.e. 9 ml/kg), they demonstrated that the threshold of 12% PPV had a sensitivity of 39%, a specificity 65% and a 51% correct classification with a low TV, but a sensitivity of 88%, specificity of 89% and an 88% correct classification with a high TV. The authors recommended a VT > 8 ml/kg when using PPV.⁸

PEEP improves intraoperative oxygenation.⁹⁻¹² PEEP decreases atelectasis (especially in obese patients following a recruitment manoeuvre),¹³ decreases airway closure and increases lung volume.^{14,15} However, high levels of PEEP may also impair oxygenation in non-obese patients.¹⁶ This may be due to lung stretching and decreased cardiac output.

Cardiac output decreases during PEEP as the increased intrathoracic pressure impedes venous return.^{17,18} Michard et al studied the influence of PEEP on PPV in patients with acute lung injury or acute respiratory distress syndrome. PPV was higher and cardiac index lower when PEEP was adjusted from 0 cmH₂O to 10 cmH₂O. The increase in PPV correlated very well with the decrease in cardiac index.¹⁹

Previous studies on PPV have several shortcomings. Standardisation regarding TV and PEEP is lacking and subjects in several studies were drawn from populations with cardiac failure, pulmonary injury or sepsis. The amount of PEEP that is used in healthy patients intraoperatively usually varies from 2-5 cmH₂O, while TV follows the trend to ventilate with lower TV (6 ml/kg-8 ml/kg ideal body mass).

In this study, the effect of PEEP on PPV in healthy patients who received positive-pressure ventilation intraoperatively was determined while using a TV of 9 ml/kg. It was hypothesised that the level of PEEP would have no effect on PPV. Alternatively, it was hypothesised that PEEP would have a significant effect on PPV.

Method

The local ethics committee approved the study and informed consent was obtained from the participants.

Study design

This was an observational study.

Setting

The study was performed in an academic hospital.

Patient selection

American Society of Anesthesiologists grade I or II patients who were older than 18 years were selected with the use of convenience sampling. The sample comprised all patients who presented for elective surgery who required mechanical ventilation and intra-arterial blood pressure monitoring. Patients were excluded if they were pregnant, suffered from lung disease, had cardiac arrhythmias, were from intensive care units, required active resuscitation before or after induction of anaesthesia (fluid, inotropic or vasotropic support) to maintain haemodynamic stability, were scheduled for cardi thoracic surgery, or when cannulation of the radial arteries was contraindicated.

Anaesthetic technique and measurements

Patient age, gender, body mass and height were recorded. A 22G arterial cannula was inserted into the radial artery at the wrist of the nondominant hand after assessment of adequate collateral flow with the use of the Allen test. Monitoring also included an electrocardiogram, pulse oximetry and capnography. Intra-arterial blood pressure was measured at the midaxillary line at the level of the sternal angle with the use of a pressure transducer that was connected to an ADU S/5 anaesthetic unit (GE Health Care, Instrumentarium, Helsinki, Finland).

Patients were anaesthetised by means of a standard technique comprising sufentanil 0.15 µg/kg, lignocaine 1 mg/kg, propofol 1-2 mg/kg and vecuronium 0.1 mg/kg, followed by endotracheal intubation. Anaesthesia was maintained with sevoflurane in oxygen and air. Volume preloading was not carried out.²⁰ Patients were ventilated with a TV of 9 ml/kg ideal body mass and an inspiratory-expiratory ratio of 1:2.⁸ The respiratory rate was adjusted to maintain normocarbia (end-tidal CO₂ between 30 and 40 mmHg).

Measurements were taken after induction, intubation, and institution of positive-pressure ventilation, but before surgery started. PEEP was set at 2 cmH₂O (the minimum PEEP level of the ventilators used). The maximum and minimum systolic and diastolic blood pressures during a single ventilatory cycle were recorded three times. The PPV was calculated by using the maximum, minimum and mean

PPs (PP maximum, PP minimum and PP mean respectively) [PPV (%) = $100 \times (\text{PP maximum} - \text{PP minimum}) / [(\text{PP maximum} + \text{PP minimum}) / 2]$. The same measurements were taken at PEEP levels of 5 cmH₂O, 8 cmH₂O, and 10 cmH₂O. Before measurement of PPV at the different levels of PEEP, at least two minutes was allowed for stabilisation.

Data analysis

Continuous variables are reported as means, standard deviations (SD) and 95% confidence intervals (CI). The levels of PEEP were compared with respect to PPV using an analysis of variance for repeated measures, using random effects generalised least squares regression. For pair-wise comparisons, the higher levels of PEEP were compared with the 2 cmH₂O level in three contrasts. Hochberg's step-down approach was adopted to interpret the pairwise comparisons and also to address multiplicity: PPV at a PEEP of 10 cmH₂O was compared with PPV at a PEEP of 2 cmH₂O. If this difference was significant, PPV at a PEEP of 8 cmH₂O was compared to PPV at a PEEP of 2 cmH₂O and finally, if the latter was also significant, PPV at a PEEP of 5 cmH₂O was compared with PPV at a PEEP of 2 cmH₂O. Furthermore, a test for trend over escalating PEEP was also performed. Post hoc, results were confirmed with the use of Dunnett's method. Testing was carried out at the 0.05 level of significance. The sample size was determined with nQuery Advisor[®]. Stata[®] 11 software was used for analysis.

Sample size

Michard et al found a mean PPV of 9% with a standard deviation of 7%¹⁹ at a PEEP of 0 cmH₂O. If a conservative standard deviation of 7% for PPV at a PEEP of 2 cmH₂O is assumed, a clinically relevant increase in PPV would be 3.5% (that is a significant PPV threshold of approximately 12.5% minus 9%), since the expected PPV at a PEEP of 2 cmH₂O is 9%. A PPV in excess of 12% suggests hypovolaemia. Hence, a sample of 31 patients had a power of 85% to detect this elevation when testing one-sided at the 0.05 level of significance.

Results

Thirty-two participants completed the study: 15 women and 17 men. These 32 patients included four patients with hypertension and four smokers, but without clinical lung disease. Five patients were excluded due to haemodynamic instability. This necessitated administration of fluid and/or a vasoconstrictor after induction of anaesthesia. The following procedures were performed: major vascular surgery following trauma, major surgery involving the airway, major orthopaedic surgery, major cancer surgery, reconstructive surgery and other major abdominal procedures. Descriptive statistics are presented in Table I.

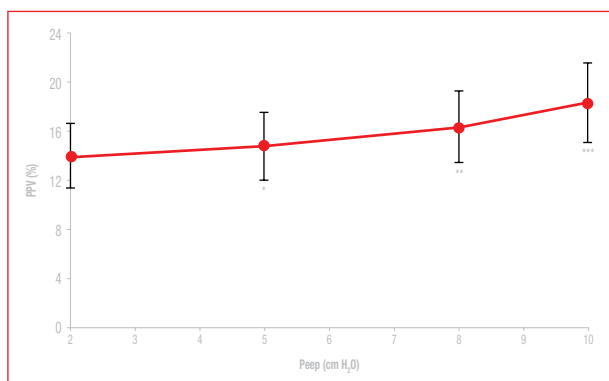
Table I: Descriptive statistics

Variable	Mean (SD)	95% CI
Age (years)	42.8 (12.6)	38.3, 47.4
Length (m)	1.7 (0.1)	1.7, 1.7
Real body mass (kg)	75.4 (15.2)	69.6, 81.2
Body mass index (kg/m ²)	26.1 (5.0)	24.3, 28.0
Ideal body mass (kg)	68.6 (9.8)	65.1, 72.2
Preoperative blood pressure (mmHg) and heart rate (per minute)		
BPS	118.1 (15.2)	112.7, 123.6
BPD	68.5 (14.2)	63.4, 73.6
BPM	85 (13.9)	80.0, 90.1
Heart rate	84.8 (15.6)	79.1, 90.4
Blood pressure and heart rate at PEEP 2 cmH ₂ O		
BPS	107.6 (23.8)	99.0, 116.1
BPD	62.4 (13.1)	57.7, 67
BPM	77.7 (14.2)	72.6, 82.8
Heart rate	83.8 (19.1)	77.0, 90.7
Blood pressure and heart rate at PEEP 5 cmH ₂ O		
BPS	105.0 (14.2)	100.0, 110.1
BPD	58.6 (11.4)	54.5, 62.7
BPM	74.1 (12.9)	69.4, 78.7
Heart rate	82.9 (18.7)	76.1, 89.6
Blood pressure and heart rate at PEEP 8 cmH ₂ O		
BPS	103.2 (14.4)	98.0, 108.4
BPD	57.9 (11.3)	53.8, 61.98
BPM	71.9 (11.7)	67.7, 76.1
Heart rate	80.2 (17.1)	74.0, 86.3
Blood pressure and heart rate (min ⁻¹) at PEEP 10 cmH ₂ O		
BPS	99.0 (22.3)	90.7, 106.8
BPD	59.2 (10.5)	55.4, 63.0
BPM	72.3 (11.5)	68.2, 76.5
Heart rate	80.8 (18.4)	74.1, 87.4
Pulse pressure variation (%)		
PEEP 2 cmH ₂ O	14.0 (7.4)	11.4, 16.7
PEEP 5 cmH ₂ O	14.7 (7.9)	11.9, 17.6
PEEP 8 cmH ₂ O	16.2 (8.1)	13.3, 19.1
PEEP 10 cmH ₂ O	18.1 (9.1)	14.8, 21.4

BPD: diastolic blood pressure, BPM: mean blood pressure, BPS: systolic blood pressure, CI: confidence interval, PEEP: positive end-expiratory pressure, SD: standard deviation

A PPV of > 12% at a PEEP of 2 cmH₂O occurred in 16 of the 32 patients. At PEEP 10 cmH₂O, 23 of 32 had a PPV of > 12 %.

PPV at a PEEP of 10 cmH₂O was significantly larger than that at 2 cmH₂O (p-value < 0.001; CI of difference 2.97, 5.18). The PPV at a PEEP of 8 cmH₂O was also significantly larger than at a PEEP of 2 cmH₂O (p-value < 0.001; CI of difference 1.12, 3.33). PPV at a PEEP of 2 cmH₂O and 5 cmH₂O did not differ significantly (p-value = 0.194; CI of difference -0.37,



Error bars depict 95% confidence intervals.

* No significant difference between pulse pressure variation at PEEP of 2 cmH₂O and 5 cmH₂O

** Significantly larger than at PEEP at 2 cmH₂O

*** Significantly larger than at PEEP of 2 cmH₂O

Figure 1: PPV at different levels of PEEP

1.83) (Figure 1). There was a significant difference between PPV at PEEP of 5 cmH₂O and 8 cmH₂O (p -value = 0.002; CI of difference 0.60, 2.40). PPV at a PEEP of 10 was also significantly larger than at a PEEP of 8 (p -value < 0.001; CI of difference 0.91, 2.79). Post hoc, these results were confirmed with the use of Dunnett's method.

All intraoperative mean blood pressure (MBP) was significantly lower than preoperatively (p -value < 0.001). Intraoperatively, MPB at 2 cmH₂O was significantly higher than at the higher levels of PEEP (p -value < 0.014), while MBP at 5, 8 and 10 cmH₂O did not differ significantly from each other (p -value > 0.05).

The heart rate at 8 cmH₂O PEEP was significantly lower than it what it was preoperatively (p -value = 0.035), while the heart rates at the other levels of PEEP did not differ significantly from the preoperative heart rate (p -value > 0.05). Intraoperatively, the heart rate at 2 cmH₂O did not differ significantly from heart rates at the higher levels of PEEP (p -value > 0.05). The heart rates at 5, 8 and 10 cmH₂O did not differ significantly from each other (p -value > 0.05).

The PPV at a PEEP of 10 cmH₂O was 29.3% larger than at a PEEP 2 cmH₂O. PPV at a PEEP of 8 cmH₂O was 15.7% larger than at a PEEP 2 cmH₂O, while the PPV at 5 cmH₂O was 5% larger than at 2 cmH₂O.

Discussion

The study confirmed the alternative hypothesis, that PEEP has a significant effect on PPV when healthy patients are ventilated with a TV of 9 ml/kg ideal body mass. The PPV at a PEEP of 8 cmH₂O and 10 cmH₂O was significantly larger than at a PEEP 2 cmH₂O. There was a significant difference between PPV at a PEEP of 5 cmH₂O and of 8 cmH₂O. PPV at a PEEP of 2 cmH₂O and at a PEEP of 5 cmH₂O did not differ significantly. If a difference of approximately 15% is regarded as clinically significant, a PEEP level of at least

8 cmH₂O could be expected to have a clinically significant influence on PPV at a TV of 9 ml/kg ideal body mass.

This study addressed two factors that affected PPV that were neglected in previous studies. A TV was used that has been shown to have a significant influence on PPV, namely > 8 ml/kg,⁸ as well as on the impact of PEEP. The results are in agreement with those of a study undertaken by Michard et al. The latter investigated the influence of PEEP on cardiac index and PPV in patients with abnormal lungs, namely acute lung injury (ALI). PPV was higher and cardiac index lower when PEEP was adjusted from 0 cmH₂O to 10 cmH₂O. The increase in PPV correlated with the decrease in cardiac index ($r = -0.97$, p -value < 0.001).¹⁹

The study by Michard et al¹⁹ had limitations. The sample was very small. There were 14 patients and it included patients with abnormal lungs only. This limitation could have influenced the transalveolar pressure and therefore the impact of PEEP on cardiac index. This aspect could give their study greater validity, since high levels of PEEP are more likely to be applied in patients with abnormal lungs. However, the influence of PEEP on PPV has not been investigated in patients with normal lungs. Moreover, it is not uncommon for PEEP levels of more than physiological PEEP of 5 cmH₂O to be needed intraoperatively; even in patients with normal lungs.

Our study differs from that of Michard et al.¹⁹ They did not standardise TV, which varied from 7 ml/kg-12 ml/kg. The intrathoracic pressure changes with different TV, cardiac preload and cardiac output change. This could have led to inconsistencies in the PEEP-PPV relationship. However, in their study of 14 patients, only two patients were ventilated with a TV of < 9 ml/kg, while nine of the 14 patients were ventilated with a TV of > 9 ml/kg. We found a significant decrease in intraoperative blood pressures with increasing PEEP, but with a constant TV of 9 ml/kg. However, we do not regard the decreases of MBP at 2 cmH₂O and MBPs at the other levels of PEEP to be clinically significant. The maximum change was 8 cmH₂O: -5.8 mmHg (CI -3.9, -8.7).

Lefrant and De Backer addressed the reliability of PPV in patients with ALI or ARDS.²¹ The thickened alveolar walls limit the transmission of intra-alveolar pressure to the pleural and pericardial cavity. Since lung compliance in patients with a lung injury is reduced, the transmission of pressure is even lower if these patients are ventilated at low TV, which are currently recommended. However, at higher TV, the PPV is more reliable.

Currently, a large TV is not recommended in patients with ALI. Michard et al found a sound correlation between PEEP and PPV ($r = -0.79$). These findings suggest that even in patients with abnormal lungs (in their study, ALI), PEEP has an influence on PPV and the cardiac index.

Therefore, it appears that the use of PPV as an indicator of fluid status and its effect on cardiac index is valid for all patients who require mechanical ventilation, i.e. during general anaesthesia (microatelectasis) and intensive care (lung injury). The prerequisite in both types of patients is that the TV should be > 8 ml/kg (ideal body mass), as was demonstrated by Vallée et al.²² If a lower TV is used, a lower cut-off point of PPV should be used, i.e. 8% instead of the traditional 12%.⁸

In order to increase the sensitivity and specificity of PPV in patients with ARDS, Vallée et al suggested that the effect of the driving pressure (DP) of ventilation, i.e. the difference between plateau inspiratory pressure and PEEP, should be taken into account to adjust for changes in lung compliance. The adjusted PPV was calculated, namely as PPV/DP. In their total sample of 184 patients, PPV/DP increased the area under the receiver operating characteristic curve (AUC) from 0.71 for PPV to 0.81 for PPV/DP. In patients who were ventilated with a TV of ≥ 8 ml/kg, the AUC increased to 0.88. However, in those patients who were ventilated with a TV < 8 ml/kg, PPV/DP did not predict fluid responsiveness (AOC = 0.62). A PPV/DP ratio of > 0.9 predicted fluid responsiveness in patients who were ventilated with a TV of ≥ 8 ml/kg.²²

In this study, TV was calculated in accordance with ideal body mass, because lung capacity does not increase with an increase in the body mass index. Some of the quoted studies do not mention the way in which TV was calculated.

The influence of PEEP on PPV may influence its usefulness in patients with chronic obstructive pulmonary disease (COPD). Therefore, the present study excluded patients who suffer from COPD and those who had a clinically detectable lung disease. One patient was older than 60 years. The lung undergoes COPD-like changes with increasing age.²³ The lungs of patients with COPD are subjected to auto-PEEP, which often contraindicates the use of additional PEEP during mechanical ventilation. This aspect has not been investigated, but the findings of this study, which used a relatively large TV of 9 ml/kg, suggest that PPV may be used in COPD patients if PEEP is kept ≤ 5 cmH₂O.

This study has important implications. Firstly, PEEP induces a pseudohypovolaemic or volume-responsive state. Secondly, if haemodynamic stability requires fluid loading during PEEP, a state of hypervolaemia may arise when PEEP is discontinued. This possibility calls for the judicious use of vasoconstrictors rather than fluid loading in patients in whom the sudden discontinuation of PEEP is foreseen.

Furthermore, PPV is influenced by PEEP of at least 8 cmH₂O at a TV of 9 ml/kg. The implication of this finding is not that patients should not be ventilated with a small

TV (< 9 ml/kg) at all in the course of the procedure during which PPV is measured, or that PEEP should not be used. It is recommended that TV should temporarily be adjusted to 9 ml/kg during measurement and that PEEP levels of < 8 cmH₂O should be used when measuring PPV. Therefore, the levels of PEEP that are often used in patients with normal lungs intraoperatively, i.e. 5 cmH₂O, do not affect the validity of PPV.

In this study, all patients were *nil per os* for at least six hours. Very often, the fasting period was overnight and therefore it was more than six hours. Therefore, dehydration following the period of fasting, as well as the cardiovascular effects of propofol and sevoflurane and the effects of positive ventilation, probably affected cardiac preload. These factors may explain the observation that the PPV at the minimum level of PEEP (2 cmH₂O) was already above the limit of fluid responsiveness, namely 14.4% (95% CI 13.1, 15.7). No volume load was given before the induction of anaesthesia, although a fluid bolus before induction might have influenced the findings. Although it is common practice to precede induction of anaesthesia with a fluid load, it does not reliably prevent hypotension.²⁰

The large PPV ($> 14\%$), even with low levels of PEEP (2 cmH₂O), demonstrates the effect of anaesthesia (anaesthetic drugs and positive-pressure ventilation) on cardiac filling. The effect would probably be more pronounced in patients with co-morbid cardiovascular conditions, including diastolic dysfunction and hypovolaemia. We did not exclude ASA II hypertensive patients. Since hypertension influences diastolic function, it may also influence PPV. At a PEEP of 2 cmH₂O, one of the four patients with hypertension (47 years old, BMI 35 kg/m²) had a PPV of $> 12\%$, namely 15.7%. The oldest patient was a 72-year-old male with hypertension. He had a PPV at 2 cmH₂O of 8.8%. At a PEEP of 10 cmH₂O, 23 of 32 patients had a PPV of $> 12\%$, which included three of the four patients with hypertension. The influence of hypertension on the effect of PEEP on PPV was not the research question, but should be investigated. Furthermore, the effect of fluid loading before induction of general anaesthesia needs further investigation. The study by Turner et al excluded patients with hypertension.²⁰

This was an observational study. However, a randomised study with a larger sample size that exposes different groups of patients to different levels of PEEP, and adjusting for different co-morbidities, including diastolic function, is needed.

Conclusion

This study demonstrates that in patients with normal lungs and who are ventilated with a TV of 9 ml/kg, PEEP has a significant influence on PPV. If PEEP levels of ≥ 8 cmH₂O

are used, PPV may overestimate fluid responsiveness in comparison with physiological levels of PEEP, namely ≤ 5 cmH₂O. In patients with normal lungs who are ventilated with a TV of 9 ml/kg, PPV should be interpreted at a PEEP of ≤ 5 cmH₂O.

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