

A Practical Protocol for Titrating "Optimal" PEEP in Acute Lung Injury: Recruitment Maneuver and PEEP Decrement

This study was conducted to evaluate the effectiveness and safety of a practical protocol for titrating positive end-expiratory pressure (PEEP) involving recruitment maneuver (RM) and decremental PEEP. Seventeen consecutive patients with acute lung injury who underwent PEEP titration were included in the analysis. After baseline ventilation, RM (continuous positive airway pressure, 35 cmH₂O for 45 sec) was performed and PEEP was increased to 20 cmH₂O or the highest PEEP guaranteeing the minimal tidal volume of 5 mL/kg. Then PEEP was decreased every 20 min in 2 cmH₂O decrements. The "optimal" PEEP was defined as the lowest PEEP attainable without causing a significant drop (>10%) in PaO₂. The "optimal PEEP" was 14.5 ± 3.8 cmH₂O. PaO₂/F_iO₂ ratio was 154.8 ± 63.3 mmHg at baseline and improved to 290.0 ± 96.4 mmHg at highest PEEP and 302.7 ± 94.2 mmHg at "optimal PEEP", both significantly higher than baseline ($p < 0.05$). Static compliance was significantly higher at "optimal" PEEP (27.2 ± 10.4 mL/cmH₂O) compared to highest PEEP (22.3 ± 7.7 mL/cmH₂O) ($p < 0.05$). Three patients experienced transient hypotension and one patient experienced atrial premature contractions. No patient had gross barotrauma. PEEP titration protocol involving RM and PEEP decrement was effective in improving oxygenation and was generally well-tolerated.

Key Words : Respiratory Distress Syndrome, Acute; Respiration, Artificial; Lung Injury, Acute; Positive-Pressure Respiration; Recruitment

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INTRODUCTION

Recent advances in the treatment of acute lung injury (ALI) have centered around the concept of ventilator-induced lung injury (VILI) and the need for lung recruitment (1). VILI is the theoretical basis for the recent trend of "lung-protective" strategy of mechanical ventilation in patients with ALI (2).

The "lung protective" strategy is mainly composed of two components. One is minimizing "volutrauma" by using small tidal volumes (3) and permitting hypercapnia (4). The other important strategy is lung recruitment: "open up the lung and keep the lung open" (5). It is now generally accepted that reducing tidal volume can improve outcomes (3) in these patients, however, it is not clear whether recruiting strategies can also improve outcomes.

The most popular way of keeping the lung open is to apply of positive end-expiratory pressure (PEEP). The best way to set PEEP in ALI has been a subject of intense debate. Traditional approach to titrating PEEP has been the "least" PEEP approach (6): smallest PEEP needed to achieve adequate oxygenation at a nontoxic concentration of oxygen. Other investigators have studied various methods to titrate PEEP (7-9),

but none has been shown to be superior. Recently, some investigators have advocated using the inspiratory limb of the pressure-volume curve to guide in setting PEEP levels in early ALI to minimized VILI (2). However, PEEP is a force which opposes derecruitment rather than the pressure that actually recruits the lungs. Therefore, titration of PEEP may be better accomplished by PEEP decrements after initial recruitment of collapsed lungs (10, 11).

This study was undertaken to assess effectiveness and safety of PEEP titration protocol using recruitment maneuver (RM) and titration of PEEP through PEEP decrement.

MATERIALS AND METHODS

Patients

The data of 17 consecutive patients with ALI who underwent the PEEP titration protocol between July 1999 and June 2000 at the medical intensive care unit (MICU) of Samsung Medical Center in Seoul, Korea were retrospectively reviewed. All patients met the American European Consensus defini-

tion for ALI (12) and had a $\text{PaO}_2/\text{FiO}_2$ (PF) ratio of less than 300 mmHg at PEEP of 8 cmH₂O. Patients with a history of treatment for chronic lung diseases, who had been on mechanical ventilator for more than 48 hr, with hypotension requiring vasopressors other than less than 20 $\mu\text{g}/\text{kg}/\text{min}$ of dopamine to maintain hemodynamic stability, and who were expected to die within 24 hr were excluded from the PEEP titration protocol.

Measurements

The patients were ventilated with the Servo 900C ventilator (Siemens Elema, Lund, Sweden) and were sedated and paralyzed by continuous infusion of midazolam and bolus injection of 4 mg vecuronium bromide as needed during PEEP titration. A radial arterial catheter was inserted for blood sampling and monitoring of arterial pressure. Patient's arterial pressure, heart rate, and pulse oximetry were monitored with Hewlett-Packard Component Monitoring System (Hewlett-Packard GmbH, Boeblingen, Germany). Airway pressure and tidal volume (V_T) were monitored by using the ventilator display. Plateau pressure (P_{plat}) was measured by using the inspiration hold button for 3 sec on the ventilator. Effective tidal volume ($V_{T\text{eff}}$) was calculated by subtracting the compressive volume from the expiratory V_T . Static compliance (C_{st}) was calculated by dividing $V_{T\text{eff}}$ with the difference between P_{plat} and PEEP.

Baseline ventilation

The patients received pressure-limited time-cycled ventilation and the V_T was maintained between 5–7 mL/kg of actual body weight. P_{plat} was maintained below 35 cmH₂O at all times throughout the protocol. Fraction of inspired oxygen was set to maintain adequate oxygenation ($\text{PaO}_2 > 60$ mmHg) and maintained constant throughout the protocol. At baseline, PEEP was set at 8 cmH₂O, inspiratory to expiratory ratio of 1:2, and respiration rate was 20 per min. The baseline ventilation was maintained for 30 min.

PEEP titration protocol

After baseline ventilation, RM was performed by changing the ventilator setting to continuous positive airway pressure (CPAP) of 35 cmH₂O for 45 sec. After RM, PEEP was increased to 20 cmH₂O. If minimal V_T of 5 mL/kg could not be obtained at PEEP of 20 cmH₂O within the pressure limit of 35 cmH₂O, PEEP was gradually decreased by 2 cmH₂O decrements every min until minimal V_T could be guaranteed (highest PEEP).

After 20 min of ventilation at highest PEEP, PEEP was decreased by 2 cmH₂O every 20 min until PaO_2 was reduced by more than 10% compared to the previous level of PEEP. The lowest level of PEEP which did not cause significant

drop ($>10\%$ of previous value) in PaO_2 was defined as the "optimal" PEEP. PEEP was not decreased to lower than 8 cmH₂O, and 8 cmH₂O was designated as the "optimal" PEEP in these patients.

Ventilation after PEEP titration and weaning

After the determination of "optimal" PEEP, RM was performed again and PEEP was set at "optimal" PEEP. Ventilator disconnections were kept to a minimum by using a closed suction catheter. Although not strictly protocolized after the initial determination of "optimal" PEEP, decrement of PEEP was attempted at least twice a day, and if there was a significant drop in PaO_2 or SpO_2 , RM was performed and PEEP increased to the previous level. Other general management was performed by an attending physician as needed. There was no predetermined weaning protocol and weaning and extubation were performed according to the decision of the attending physician of MICU using the conventional criteria.

Analysis

Data are given as the mean \pm SD. Comparison of measurements at baseline, highest PEEP, and "optimal" PEEP was done using repeated-measures ANOVA. Differences between time points were performed by using paired-t test with Bonferroni correction. Analysis was performed using SPSS version 10.0 software (SPSS, Chicago, IL, U.S.A.). A p value <0.05 was considered statistically significant.

RESULTS

Clinical characteristics

Clinical characteristics are shown in Table 1. There were 7 male and 10 female patients with a mean age of 60.5 ± 15.6 yr. The patients had 2.7 ± 1.0 organ failures (13) and APACHE II and SAPS II score of 20.9 ± 5.7 and 48.4 ± 10.8 , respectively. There were 11 pulmonary and 6 extrapulmonary causes for ALI. Ventilator weaning was possible in 13 patients (76.5%) and survival to hospital discharge was possible in 52.9% (9 out of 17).

Highest PEEP and "optimal" PEEP

In 8 patients, PEEP titration could not begin from PEEP of 20 cmH₂O because the minimal tidal volume could not be maintained with a P_{plat} limit of <35 cmH₂O. Highest PEEP was 18 cmH₂O for 2 patients, 16 for 1 patient, and 14 for 5 patients with the mean highest PEEP being 17.6 ± 2.8 cmH₂O. The "optimal" PEEP was evenly distributed from 8–20 cmH₂O with a mean of 14.5 ± 3.8 cmH₂O (Table 1, 2).

Table 1. Individual clinical characteristics of the patients

No.	Age (yr)	Sex	Cause of ALI	No. of OF	SAPS	APACHE	"Optimal" PEEP	Weaning	Survival
1	58	F	DAD d/t bleomycin	3	43	22	8	+	+
2	65	F	Pneumonia	4	59	30	8	-	+
3	74	M	Sepsis	3	68	28	10	+	-
4	63	F	Sepsis	2	65	26	18	+	+
5	71	M	Pneumonia	3	45	14	12	+	+
6	51	F	Pneumonia	2	52	28	14	-	-
7	65	M	Pneumonia	3	46	22	14	-	-
8	66	M	Pneumonia	2	49	25	14	+	+
9	61	F	Sepsis	2	42	22	14	+	+
10	70	F	Sepsis	4	46	21	16	+	-
11	61	M	Alveolar hemorrhage	3	50	23	16	-	-
12	43	F	Sepsis	3	34	19	16	+	+
13	46	F	Sepsis	1	59	22	18	+	+
14	82	F	Sepsis	3	53	19	18	+	-
15	78	M	Aspiration pneumonia	4	62	23	20	+	-
16	81	M	Pneumonia	4	62	28	10	-	-
17	19	F	Acute lupus pneumonitis	1	29	6	20	+	+
Mean	62.0 ±14.7			2.7 ±0.9	50.8 ±10.8	22.2 ±5.8	14.5 ±3.8	13/17 (76%)	9/17 (53%)

ALI: acute lung injury; OF: organ failure; SAPS: simplified acute physiologic score; APACHE: acute physiology and chronic health evaluation; PEEP: positive end-expiratory pressure; DAD: diffuse alveolar damage; d/t: due to; M: male; F: female; NA: not applicable.

Table 2. Comparison of parameters at baseline, highest, and "optimal" positive end-expiratory pressure (PEEP)

	Baseline PEEP	Highest PEEP	"Optimal" PEEP
PEEP (cmH ₂ O)	8 ±0	17.6 ±2.8*	14.5 ±3.8* [†]
P/F ratio	154.8 ±63.3	301.2 ±97.8*	302.7 ±94.2*
PaO ₂ (mmHg)	97.3 ±38.0	206.5 ±109.0*	204.9 ±100.8*
PaCO ₂ (mmHg)	48.1 ±11.6	51.9 ±16.3	51.4 ±15.3
pH	7.34 ±0.13	7.31 ±0.15	7.31 ±0.15
Pplat (cmH ₂ O)	21.7 ±3.6	32.8 ±1.9*	27.7 ±5.3* [†]
Cst (mL/cmH ₂ O)	27.1 ±9.9	22.3 ±7.8	27.2 ±10.4 [†]
mBP (mmHg)	82.9 ±17.3	82.1 ±11.4	82.9 ±14.4
HR (/min)	120.9 ±21.2	123.7 ±20.5	124.6 ±20.6

Data are mean ± SD.

mBP: mean blood pressure; HR: heart rate; Pplat: plateau pressure; Cst: static compliance; P/F: PaO₂/FIO₂; Bwt: body weight.

**p*<0.05 vs baseline PEEP; [†]*p*<0.05 vs highest PEEP.

Comparison of gas exchange

The PF ratio at baseline PEEP was 154.8 ±63.3 mmHg, which was significantly increased to 301.2 ±97.8 mmHg at highest PEEP (*p*<0.05). At "optimal" PEEP PF ratio was 302.7 ±94.2 mmHg, which was also significantly increased compared to baseline PEEP (*p*<0.05) (Table 2, Fig. 1). There were no significant differences in PaCO₂ between baseline, highest, and "optimal" PEEP (Table 2).

Fig. 2 shows individual trend in the PF ratio of 10 patients whose PF ratios at PEEP of 2 cmH₂O above ("optimal+2") and below ("optimal-2") "optimal" PEEP were both available. In two patients PEEP could be lowered to 8 cmH₂O without a significant drop in PaO₂ (no "optimal-2" PEEP)

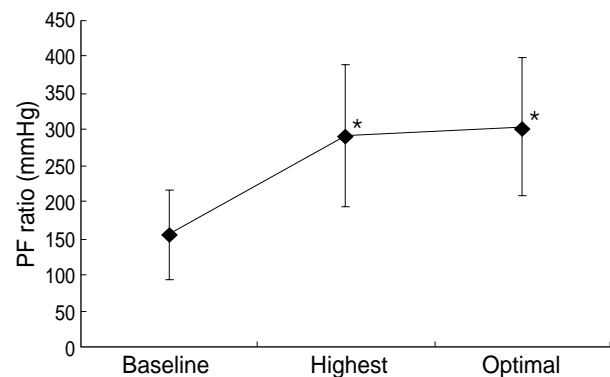


Fig. 1. Comparisons of PaO₂/FIO₂ (PF) ratios at baseline, highest, and "optimal" positive end-expiratory pressure (PEEP). The PF ratio was significantly increased at "optimal" PEEP and highest PEEP compared to at baseline PEEP. **p*<0.05 vs baseline PEEP.

and in 5 patients there was a significant drop in the PF ratio after the initial decrease in PEEP from highest PEEP (no "optimal+2" PEEP). PF ratios were 317.1 ±80.9 mmHg, 319.6 ±82.6 mmHg at PEEP of "optimal+2" and "optimal" respectively which dropped significantly to 255.4 ±71.5 mmHg at PEEP of "optimal-2". On average PF ratio fell 20.0 ±8.9% (range 11.8-38.3) when PEEP was lowered to "optimal-2" from "optimal".

Comparison of Pplat and Cst

Cst at baseline PEEP was 27.1 ±9.9 mL/cmH₂O and it decreased to 22.3 ±7.8 mL/cmH₂O at highest PEEP (*p*>0.05) (Table 2, Fig. 3). Cst at "optimal" PEEP was 27.2 ±10.4 mL/

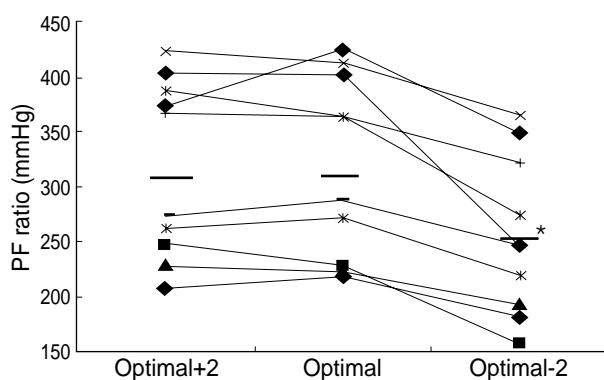


Fig. 2. Individual trend in the $\text{PaO}_2/\text{FiO}_2$ (PF) ratio of 10 patients whose PF ratio at PEEP of 2 cmH_2O above ("optimal+2") and below ("optimal-2") "optimal" PEEP were both available. PF ratio significantly dropped from 319.6 ± 82.6 mmHg at "optimal" to 255.4 ± 71.5 mmHg at "optimal-2". * $p < 0.05$ vs previous value.

cmH_2O which was significantly increased compared to that of the highest PEEP ($p < 0.05$). Pplat was 21.7 ± 3.6 cmH_2O , 32.8 ± 1.9 cmH_2O , and 27.7 ± 5.3 cmH_2O for baseline, highest, and "optimal" PEEP respectively which were all significantly different from each other (Table 2, Fig. 3) ($p < 0.05$).

Hemodynamic parameters

There were no significant differences in mean blood pressure and heart rate between baseline, highest, and "optimal" PEEP (Table 2).

Adverse events

Three patients experienced a transient decrease in blood pressure requiring therapeutic modification during the PEEP titration protocol; two patients needed administration of dopamine and one needed an increase in the dosage of dopamine from 15 to 20 $\mu\text{g}/\text{kg}/\text{min}$. One patient experienced frequent atrial premature contractions, however, there were no other significant arrhythmias. No barotrauma was documented on chest radiographs.

DISCUSSION

This study showed that PEEP titration by decremental PEEP after RM was effective in improving oxygenation and was generally well-tolerated. At "optimal" PEEP patients had significantly higher Cst compared to at highest PEEP while the improvement in oxygenation at highest PEEP was maintained at "optimal" PEEP.

With the emergence of VILI and "open lung" approach concept, the therapeutic role of PEEP has changed. Before the concept of VILI and "open lung" approach, PEEP was used mainly as an adjunct to improve oxygenation and decrease

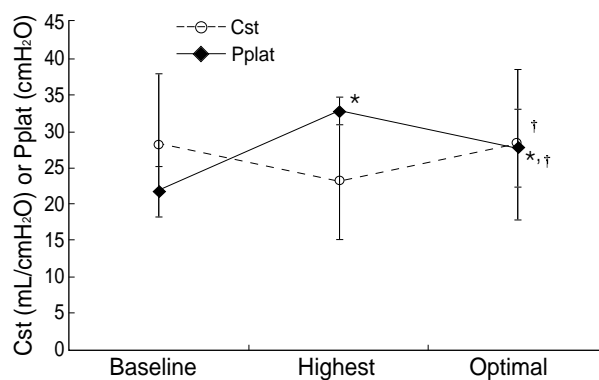


Fig. 3. Comparisons of plateau pressure (Pplat) and static compliance (Cst) at baseline, highest, and "optimal" PEEP. Pplat was increased significantly at highest PEEP compared to at baseline PEEP ($p < 0.05$) and was significantly decreased at "optimal" PEEP compared to at highest PEEP ($p < 0.05$). Cst significantly increased at "optimal" PEEP compared to at highest PEEP ($p < 0.05$). * $p < 0.05$ vs baseline PEEP, † $p < 0.05$ vs "optimal" PEEP.

work of breathing by shifting tidal breathing to a more compliant portion of the pressure-volume curve (14). Now PEEP is thought of as a means to recruit the lung and minimize injury associated with repeated opening and closure of atelectatic lung (15).

To this end, many investigators have recommended use of static pressure volume (PV) curves to set PEEP in early ARDS patients. Lower inflection point (LIP or Pflex) of the inflation limb of the static PV curve was thought of as the level of PEEP at which recruitment occurs and moves tidal ventilation to the linear portion of the PV curve (16). Using this approach to set a level of PEEP, a recent study reported survival benefit compared to a more traditional ventilatory strategy (2). However, there are several limitations in using LIP or Pflex to set PEEP in ARDS patients. In some patients LIP is not discernable (17). LIP is logistically difficult and technically demanding to measure (17). Chest wall mechanics may affect the shape of the PV curve (18), and there is large inter-observer variability in determining Pflex (19). More importantly, there is evidence that recruitment occurs well above Pflex both in experimental models (20) and in patients with acute respiratory failure (21).

It is well known that the inflation limb of the PV curve may depart significantly from the deflation limb of the same curve owing to the difference in opening and closing pressures of the lung units ("hysteresis") (22). Therefore, it may be theoretically more sound to use PEEP as an anti-derecruiting force that maintains open a substantial fraction of alveoli on the deflation limb of the PV curve after attempting as much recruitment as possible with a RM (11, 23). This is what we have attempted to do in this study. By performing RM and ventilating at a high PEEP, we attempted to recruit collapsed lung as much as possible and displace the lung mechanics of the patients toward the deflation limb of the PV curve. We

then decreased PEEP by 2 cmH₂O decrements to determine the pressure necessary to keep significant portion of the recruited lung open.

A RM can be performed by sustaining high airway pressure for prolonged periods (2, 24) or sigh and its variations (25, 26). In this study we used CPAP of 35 cmH₂O which is similar to those in other reported series (2, 24). We started at 20 cmH₂O of PEEP because we felt that it was highest level of PEEP that could be applied in most ICUs. The pressures used in this study may not be high enough to fully recruit the lungs. In some patients, pressures up to 60 cmH₂O and PEEP of 25 cmH₂O may be needed to maximally recruit the lungs and keep the lungs recruited (23).

The "optimal" PEEP in our patients ranged from 8 to 20 cmH₂O. It could have been lower because in 2 patients PEEP could be decreased to 8 cmH₂O without losing gain in oxygenation at a higher level of PEEP. We did not lower PEEP below 8 cmH₂O, because we thought PEEP should be at least similar to the superimposed pressure of the dependent zone, which was estimated to be around 10 cmH₂O by Gattinoni and colleagues at the most dependent area (27) in the early ARDS patients. Also it could have been higher in some patients because we did not evaluate PEEP levels higher than 20 cmH₂O. It is not certain whether the PEEP titration method used in this study is superior to other methods of PEEP titration; for example best compliance method used by Suter and colleagues (9) because direct comparison with our data is not possible. Large scale randomized study measuring patient outcomes may be needed to better answer these questions.

High levels of PEEP have potential drawbacks. PEEP can decrease the cardiac output by decreasing preload by impairing venous return, however, this drop in cardiac output can be overcome by adequate volume repletion. All patients in our series tolerated the PEEP titration protocol relatively well, with only three patients experiencing a transient drop in blood pressure responsive to fluid infusion and increase in the dosage of dopamine. Indeed, other series using pressures comparable to ours did not find any lasting cardiovascular effects (24, 25, 27). Another problem with high PEEP is the danger of overstretching, especially in the well-aerated regions of the lung (28). In this study, although recruitment occurred as evidenced by improved oxygenation, compliance was lowest at highest PEEP. This suggests that overstretching did occur at highest PEEP which was minimized at by decreasing the PEEP level to "optimal" PEEP without losing the gain in oxygenation.

The compliance at "optimal" PEEP was similar to baseline PEEP. One possible explanation for this might be that to achieve optimal recruitment, some overstretching may be inevitable. Since acutely-injured lung is heterogeneous and different regions react differently to applied pressure (27), pressures needed to recruit one region may overstretch regions of already well-aerated lung. Another possibility is that less tidal recruitment (inspiratory inflation with end-expiratory collapse) occurred at "optimal" PEEP due to stronger anti-

derecruiting forces compared to baseline PEEP.

There are several limitations to this study. One is that, since we did not use a pulmonary artery catheter, cardiovascular effects of our protocol could not be rigorously studied. Another is that we used PaO₂ as a surrogate marker of lung recruitment instead of actual lung volume. There are many technical difficulties in measuring or estimating recruited lung volumes in ventilated patients (28, 29), and at present it is impractical to use these methods in everyday care of critically-ill patients. In this study we used PaO₂ because it is available in all intensive care units and is easy to measure, and an increase in PaO₂ shows good correlation with recruited lung volume (30). Thirdly, we did not measure intrinsic PEEP. Many ALI patients can have intrinsic PEEP (31) and it is possible that intrinsic PEEP may have affected both gas exchange and lung mechanics parameters of study. However, because we titrated PEEP in a decremental manner, the possible effect of intrinsic PEEP on oxygenation should have been minimal.

In conclusion, our practical PEEP titration protocol employing RM and decremental PEEP was effective in improving oxygenation and was generally well-tolerated.

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