Correlation between PCO_2 (arterial- end tidal) gradient and positive end expiratory pressure titration in mechanically ventilated patients with acute respiratory distress syndrome

Hassan A Abukhabar[1], Amr Abdallah[2], Mohammad El-Samman[3]

[1]Alexandria University, critical care medicine department, Alexandria, Egypt
[2]Alexandria university, critical care medicine department, Alexandria, Egypt
[3]Alexandria university, critical care medicine department, Alexandria, Egypt
habukhaber@yahoo.com; amrabdalla1971icu@gmail.com

Abstract: Positive end expiratory pressure (PEEP) is the cornerstone of hypoxemia treatment in patients with ARDS, but there is still some controversy over the optimum level to be used and how this should be determined. To reach to optimal PEEP, several studies on applied PEEP titration were performed over the last years according to physiologic measures; these studies included esophageal pressure, pressure volume (PV) curves, oxygenation and oxygen delivery. There is a debate about how to find optimal PEEP in the current literature. Our aim was to determine whether arterial minus end-tidal carbon dioxide ($PaCO_2$-$PetCO_2$) can be used for titration to find optimal PEEP in correlation with V_d/V_t in patients with acute lung injury or acute respiratory distress syndrome (ALI/ARDS).The present study included 20 adult patients of both sexes who fulfilled the inclusion criteria of ALI /ARDS. They were heavily sedated and mechanically ventilated with lung protective strategy. During this study PEEP was titrated from baseline (5 cmH_2O) by increments of 2 cmH_2O for 30 min till reaching the value of PEEP that corresponded to the least (P_aCO_2-$P_{et}CO_2$) gradient (PCO_{2grad}), least dead space fraction (Vd/Vt) and best oxygenation (PaO_2, Hypoxic index PaO_2/FiO_2, SaO_2). With each titration, the $PCO_{2\ grad}$, Vd/Vt, shunt fraction (Q_s/Q_t) and PaO_2 had been calculated. The $PCO_{2\ grad}$ and Vd/Vt decreased with each PEEP level elevation till the point that the $PCO_{2\ grad}$ and Vd/Vt started to increase (this point was taken as the highest PEEP), so the value preceding this highest PEEP by 2 cmH_2O was taken as the optimal PEEP (which corresponded to the least value of $PCO_{2\ grad}$). The value obtained before the optimal PEEP by 2 cmH_2O was taken as the pre-optimal PEEP. The mean value of PCO_{2grad} was 17.95±3.47 mmHg at baseline PEEP, and decreased significantly to 13.45±2.52 mmHg with pre optimal PEEP (12.3±3.06 cmH_2O), further decreased to 11.7±2.83 mmHg with optimal PEEP (14.3±3.06 cmH_2O) then increased to 15.3±2.47 mmHg at highest PEEP (16.3±3.06 cmH_2O). Vd/Vt follows the same course as the PCO_{2grad}, so the two variables were closely correlated. Highest and optimal PEEP significantly reduced shunt fraction in comparison to baseline and pre-optimal. There was no significant difference in shunt fraction (Q_s/Q_t) at highest and optimal PEEP. PCO_{2grad} was minimal when PaO2 was maximal. In patients with ALI/ARDS, the PCO_{2grad} is a good indicator of the efficiency of ventilation and PCO_{2grad} is directly proportional to the degree of alveolar dead space. So, PEEP titration using the $PCO_{2\ grad}$ is a useful and easily available bedside parameter to find the optimal PEEP in patients with ARDS.

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1. Introduction

ALI/ARDS are forms of high permeability pulmonary edema (pulmonary capillary leak syndrome)(1), characterized by: acute onset hypoxemia, bilateral pulmonary infiltrates on chest radiograph consistent with pulmonary edema and the absence of evidence of left atrial hypertension. The syndrome is called ALI when hypoxic index is ⩽300 and ARDS when ⩽200. Most patients with ALI progress to ARDS (2).

Two strategies designed to limit lung damage in the management of ARDS are low tidal volume ventilation (ARDS Network Lower-tidal volume strategy)(3) and open-lung ventilation, both of which may result in some degree of hypercapnia. The goals of both strategies are to maintain adequate oxygenation, while avoiding oxygen toxicity, hemodynamic compromise, barotrauma, or alveolar over-distention (4).

Carbon dioxide is produced in the tissues by aerobic and anaerobic metabolism, transported in blood to the lung by venous return (essentially equal to cardiac output (QT), and eliminated from the lung by minute ventilation(5).The fraction physiological dead space/tidal volume (Vdphy/Vt) is given by: $V_{dphy}/V_t = (PaCO_2 - PECO_2)/PaCO_2$, $PECO_2$ is the mixed expired PCO2(6). In turn, Vdphy is partitioned

into anatomic dead space (V_{dana}); conducting airways that do not participate in gas exchange) and alveolar dead space (V_{dalv}); ventilated alveolar units that are devoid of perfusion). V_{dalv}/V_{talv} = ($PaCO_2$ – $PACO_2$)/$PaCO_2$, where $PACO_2$ is the alveolar PCO_2, which can be estimated from end tidal PCO_2 ($PetCO_2$)(6). $PCO_{2\ grad}$ results from the presence of Vdalv or high alveolar ventilation-to-blood flow (VA/Q) lung regions. Relations between PEEP, alveolar dead space and exhaled CO_2 levels do exist. Excessive levels of PEEP would increase the dead space and dilute alveolar CO_2 by a larger volume, resulting in an increase in PCO_{2grad}(7). V_d/V_t can be assessed on the basis of exhaled CO_2 levels. In a series of 179 patients with early ARDS, the V_d/V_t was markedly elevated (mean 0.58) and there was a linear correlation between the degree of dead space ventilation and mortality; for every 0.05 increase in dead space fraction, the odds of death increased by 45 percent(8). V_d/V_t ratio is a standard measure of the contribution of lung units with high VA/Q, indicating the proportion of wasted ventilation per minute or the proportion of wasted volume of each breath. Because both Vd/Vt and PCO_{2grad} assess the contribution of high VA/Q lung regions, there should be a close relationship between the two variables(9).

From these above points PCO_{2grad} can be used as a non-invasive method of titrating PEEP(10), in correlation with alveolar dead space. However, this method is still in need to be properly investigated.

2. Materials and Methods

This work was designed to study the value of use of PCO_{2grad} as end point in titration of PEEP and to find optimal PEEP in mechanically ventilated patients with ALI and ARDS, and to correlate between PCO_{2grad}, and PEEP titration.

This study was conducted on 20 adult patients of either sex with ALI/ARDS, admitted to the Department of Critical Care Medicine of Alexandria Main University Hospital, Egypt. Consents for inclusion in the study were taken from patients or their surrogates and Local Ethical Committee. The inclusion criteria for ALI/ARDS were as follows (a) acute onset of the disease, (b) PaO_2/ FiO_2< 300, (c) bilateral diffuse infiltrates on chest X-ray, (d) absence of signs of high left atrial pressure, (e) existence of evidence or risk factor of lung injury, such as aspiration, sepsis and massive transfusion.

The exclusion criteria include haemodynamic instability, hepatic or renal disorders and cardiogenic pulmonary edema.

Patient selection

All patients were initially subjected to full medical history, complete physical examination, arterial and mixed venous blood gases measurements, 12 lead electrocardiography, laboratory studies, chest radiography and Lung injury score (Murray score) calculation.

Patient preparation

Patients were in need for ventilatory support, so they had been intubated and mechanically ventilated after fulfillment of the inclusion criteria.

All patients were heavily sedated with midazolam loading i.v. dose 0.05- 0.1 mg/kg, maintenance dose 1-5 mg/h, or propofol (loading i.v dose 0.25-1 mg/kg, maintenance infusion 25-75 ug/kg/min) to restrict spontaneous movement and breathing throughout the study. Ventilator settings: according to protective lung strategy(3), were: Assist control ventilation (ACV), using Evita 2 dura Dräger ventilator, RR 16-25 breaths/min, to keep $PaCO_2$ around 35-45 mmHg, maintain PH (7.33-7.46) and to maintain baseline minute ventilation; Tidal volume (VT): we started with VT 8 mL/kg and adjusted according patient requirements to 6 mL/kg; FiO_2: was 0.6 during the study; Inspiratory flow rate (IFR): 40-50 L/min, rectangular constant wave; I:E ratio was 1:3, up to 1:1. PEEP added as 5 cmH_2O baseline, then titration done during the study.

In all selected patients the following had been done: A central venous catheter was inserted using Seldinger technique in a subclavian or internal juglar vein, for assessment of the fluid status, sampling of venous blood (PvO_2) (taken as mixed venous)(11,12) and measurement of central venous pressure (CVP). A capnograph sensor was placed between the Y-piece and the endotracheal tube main stream, to monitor and measure the end tidal PCO_2 ($PetCO_2$) and arterial blood was drawn from radial artery after insertion of arterial line for ABGs determination.

Technique of PEEP titration

In all patients after stabilization and sedation, PEEP was titrated from baseline (5 cmH_2O) by increments of 2 cmH_2O for 30 min till reaching the value of PEEP that corresponded to the least (P_aCO_2-$P_{et}CO_2$) gradient (PCO_{2grad}), least dead space fraction (V_d/V_t) and best oxygenation (PaO_2, Hypoxic index PaO_2/FiO_2, SaO_2). With each titration, the $PCO_{2\ grad}$, V_d/V_t, shunt fraction (Q_s/Q_t) and PaO_2 had been calculated. The $PCO_{2\ grad}$ and Vd/Vt decreased with each PEEP level elevation till the point that the $PCO_{2\ grad}$ and V_d/V_t started to increase (this point was taken as the highest PEEP), so the value preceding this highest PEEP by 2 cmH_2O was taken as the optimal PEEP (which corresponded to the least value of PCO_{2grad}). The value obtained before the optimal PEEP by 2 cmH_2O was taken as the pre-optimal PEEP. After that, optimal PEEP was applied for 24 hours in all patients. V_d/V_t ratio was kept between 0.3-0.6 with each PEEP level. The study was terminated if the patient became de-saturated,

hypotensive or the PCO_2 grad increased again with higher level of PEEP and if Vd/Vt exceed 0.6.

Measurements

The following measurements were done at baseline, preoptimal, optimal and highest PEEP level: Heart rate (HR(bpm)), Mean Arterial Pressure (MAP (mmHg), incidence of arrhythmias (all were measured by Viridia 24C, Hewellt Packard) and CVP (cmH_2O); Plateau pressure (Pplat), Static compliance (C_{st} = V_t / (P plat – PEEP) ml / cmH_2O and auto PEEP (all were measured by Evita 2 dura, Dräger); pH, PaO_2, $PaCO_2$ and PvO_2 (using Ciba Corning blood gas analyzer); and end tidal CO_2 ($PetCO_2$) as measured by the infrared CO_2 analyzer (Viridia 24C, Hewlett- Packard). Values of $PetCO_2$ at several breaths over duration of 30 sec, were averaged then PCO_{2grad} ($PaCO_2$-$PetCO_2$) and V_d/V_t (= ($PaCO_2$-$PetCO_2$) / $PaCO_2$) were calculated(13).Shunt fraction, hypoxic index and index of oxygenation were then calculated using the following equations:

1. Alveolar Oxygen Tension
   $P_AO_2 = [(PB – 47) FiO_2] – (PaCo_2 /RQ)$(13)
   (PB is the barometric pressure = 760 mmHg, RQ is the respiratory quotient = 0.8, 47 mmHg is the partial pressure of water vapour) to calculate CcO_2
2. Shunt fraction **$Q_S/Q_T = (CcO_2 – CaO_2) / (CcO_2 – CvO_2)$.**
   - **CcO_2** is the pulmonary capillary oxygen content [**CcO_2** = hemoglobin in g/dl x 1.39 x 1 + 0.003 x P_AO_2].
   - **CaO_2** is the arterial oxygen content [**CaO_2** = hemoglobin in g/dl x 1.39 x arterial oxygen saturation (SaO_2) + 0.003 x PaO_2].
   - **CvO_2** is the mixed venous oxygen content [**CvO_2** = hemoglobin in g/dl x 1.39 x mixed venous oxygen saturation (SvO_2) + 0.003 x mixed venous oxygen tension (PvO_2)](12).
3. Hypoxemic index HI = P_aO_2 / F_iO_2)
4. Index of oxygenation IO_2 = (P_aO_2 / P_AO_2).

C_{st}, PEEP, HI and pulmonary infiltrates and Murray score (LIS) were measured and/or calculated before the study and after 6 and 24 hours from application of optimal PEEP.

Statistical Analysis

SPSS version 13.0 software was used for data entry and analysis. All data were presented as range and mean ± SD. The paired t test was used for comparisons of measurements at baseline, preoptimal, optimal and highest PEEP levels and between before the study and after 6 and 24 hours form optimal PEEP application. The correlation coefficient was used to correlate between PCO_{2grad} and **V_d/V_t** and between PCO_{2grad} and (P_vCO_2-P_aCO_2). Changes were considered significant if $P<0.05$.

3. Results

Demographic data and etiology

This study included 22 patients in the period from January to June 2009. Two from 22 patients didn't tolerate **F_iO_2** of 0.6 with baseline PEEP 5cmH_2O, they become de-saturated, so they had been excluded from the study. There were 11 male (55%) and 9 female (45%) patients their age ranged between 24 and 60 with a mean of 48.0± 9.97 years.

Eleven patients had ARDS due to abdominal sepsis, pancreatitis and septic shock, five patients had ARDS due to severe pneumonia, two patients had ARDS due to lung contusion, one patient due to massive blood transfusion (up to 10 units packed RBCs and 6 units plasma) and one patient due to systemic lupus erythromatosis (SLE) and pneumonitis. So, seven out of twenty patients (35%) had pulmonary causes of ARDS while thirteen patients (65%) had extra-pulmonary causes.

Pre-optimal, Optimal and Highest PEEP

Baseline PEEP for all patients was 5, pre-optimal ranged between 7-17 with a mean of 12.3±3, optimal PEEP ranged between 9 and 19 with a mean of 14.3±3 and highest PEEP ranged between 13 and 21 with a mean of 16.3±3 cmH_2O.

Effects of PEEP titration on PCO_{2grad} and V_d/V_t (Table 1, Figures 1, 2)

The mean value of PCO_{2grad} was 17.95±3.47 mmHg at baseline PEEP, and decreased significantly to 13.45±2.52 mmHg with pre-optimal PEEP, further decreased to 11.7±2.83 mmHg with optimal PEEP, and increased to 15.3±2.47 mmHg at highest PEEP but still lower compared with baseline. The mean value of V_d/V_t was 0.500±0.053 at baseline PEEP, and decreased significantly to 0.349±0.052, and to 0.297±0.056 with pre-optimal and optimal PEEP, respectively then increased to 0.390±0.067 with highest PEEP. Optimal PCO_{2grad} and V_d/V_t mean values were significantly lower than baseline, preoptimal and highest PEEP. $PCO_{2\ grad}$ and V_d/V_t at highest PEEP were significantly higher than optimal, preoptimal but lower than baseline PEEP.

Effects of PEEP titration on oxygenation (Table 2)

All preoptimal, optimal and highest PEEP levels improved oxygenation parameters (PaO_2, SaO_2, PaO_2/FiO_2, PaO_2/PAO_2,Q_s/Q_t) significantly from baseline values, except preoptimal PaO_2/PAO_2. Highest PEEP produced significant improvement in all oxygenation parameters in comparison to preoptimal. Optimal PEEP produced significant improvement on preoptimal SaO_2 and Q_s/Q_t. Highest PEEP did not differ significantly from optimal except its effect on SaO_2, other parameters were comparable between the two PEEP levels.

Effects of PEEP titration on lung mechanics and hemodynamics (Table 3, Figures 3,4)

AutoPEEP, MAP, HR and CVP were stable during PEEP titration. Significant effects on baseline P_{plat} and C_{st} were observed only with optimal and highest PEEP, while preoptimal PEEP had no effect on these parameters.

In comparison to baseline, optimal and highest PEEP elevated P_{plat} significantly from 25.75± 1.83 to 28.25± 1.02 and 31.6±1.27 cmH_2O, respectively. This significant elevation in P_{plat} was associated with significant improvement in C_{st} which increased form 22.3±3.11 at baseline PEEP to 38.6±3.33 and 35.35±3.54 ml/ cmH_2O, respectively. However, Optimal PEEP produced more significant rise in C_{st} than highest PEEP (38.6±3.33 versus 35.35±3.54 ml/ cmH_2O) at a lower cost of P_{plat} (28.25± 1.02 versus 31.6±1.27 cmH_2O).

Changes in Murray score and its components (Table 4)

Baseline mean values of HI (103.6±16.39) and C_{st} (21.75±6.19 ml/cmH_2O) increased significantly after 6 hours (233.9±48.7 and 37.5±4.39 ml/cmH_2O, respectively) and 24 hours (236.8±48.19 and 37.1±5.42 ml/cmH_2O, respectively) from optimal PEEP (14.3±335 cmH_2O). From 20 patients 12 (60%) had 3 quadrants infiltrates in chest X ray, 7 (35%) had 4 quadrants and only one patient (5%) had 2 quadrants. After 6 hours, optimal PEEP had no significant effect on pulmonary infiltrate, however a significant reduction appeared after 24 hours as 8 (40%) patients had 2 quadrants, 10 (50%) had 3 quadrants and 2 (10%) had 4 quadrants infiltrates**.** Baseline mean value of LIS (2.97±0.323) improved significantly late after 24 hours from optimal PEEP application to reach a lower mean value of 2.825±0.2.

Correlations (Table 5, Figures 5, 6)

With titration of PEEP incrementally, $PCO_{2\,grad}$ and Vd/Vt decreased, when correlation done between these two variables a significant positive correlation (R=0.713, P=0.001) was recorded. In addition, a significant positive correlation was found between PCO_{2grad} and ($PvCO_2$ - $PaCO_2$) gradient (R=0.523, P=0.001).

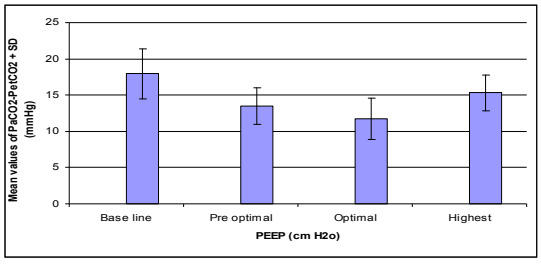

Figure 1. Mean values of PCO_{2grad} (mmHg) associated with titration of PEEP.

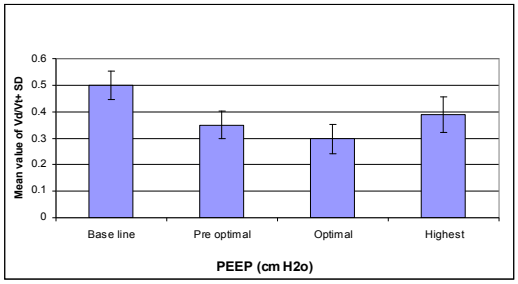

Figure 2. Mean values of V_d/V_t associated with titration of PEEP (cmH_2O).

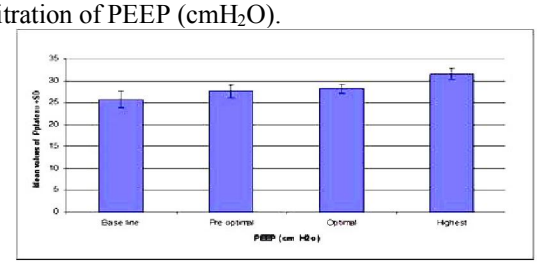

Figure 3. Changes in Pplat (cmH_2O) associated with titration in PEEP (cmH_2O).

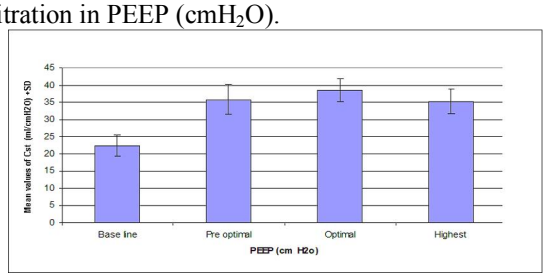

Figure 4. Changes in Cst (ml/cmH_2O) associated with titration in PEEP (cmH_2O).

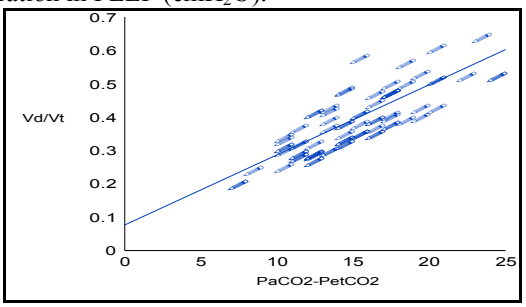

Figure 5. Correlation between $PCO_{2\,grad}$ (mmHg) and V_d/V_t.

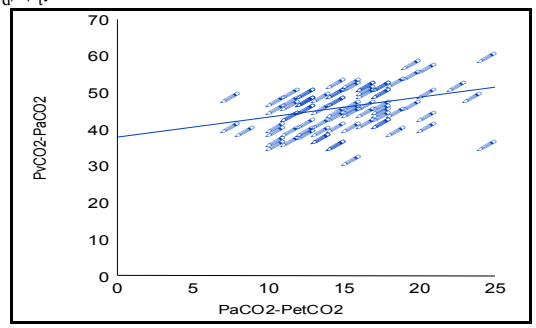

Figure 6. Correlation between PCO_{2grad} and $PvCO_2$ - $PaCO_2$.

Table (1): Changes in PCO_2gradient (mmHg) and associated with PEEP (cmH_2O) titrations.

	Base line PEEP	Pre optimal	Optimal	Highest
$PCO_{2\ grad}$:				
Range	12-24	10-19	7-19	11-20
Mean±SD	17.95±3.47	13.45±2.52	11.7±2.83	15.3±2.47
P1		**0.000**	**0.000**	**0.004**
p2			**0.0230**	**0.0123**
p3				**0.000**
Vd/Vt:				
Range	0.414-0.639	0.29-0.471	0.2-0.4	**0.32-0.61**
Mean±SD	0.500±0.053	0.349±0.052	0.297±0.056	**0.390±0.067**
P1		**0.000**	**0.000**	**0.000**
p2			**0.002**	**0.018**
p3				**0.000**

P1: Comparison between pre-optimal, optimal and highest Vs baseline PEEP; P2: Comparison between optimal and highest Vs pre-optimal PEEP; P3: comparison between highest Vs optimal PEEP. P is significant if P <0.05.

Table (2): Mean values of PaO_2, SaO_2, PaO_2/FiO_2, PaO_2/PAO_2, Q_s/Q_t at different PEEP levels.

		Baseline	Pre-optimal	Optimal	Highest
P_aO_2	Range	71-140	99-195	107-201	110-210
(mmHg)	Mean±SD	95.95±17	130±28	140.4±29	153.2±28
	P1		**0.00**	**0.000**	**0.000**
	P2			0.1292	**0.0064**
	P3				0.083
S_aO_2 (%)	Range	89-95	92-97	93-98	95-99
	Mean±SD	91.85±1.5	94.8±1.3	96.15±1.2	96.9±1.1
	P1		**0.00**	**0.000**	**0.000**
	P2			**0.0011**	**0.000**
	P3				**0.027**
P_aO_2/F_iO_2	Range	118.3-233	165-325	178-335	183-350
	Mean±SD	159.9±29	216.7±46	234±48	255.28±46
	P1		**0.00**	**0.000**	**0.000**
	P2			0.1299	**0.0065**
	P3				0.084
P_aO_2/P_AO_2	Range	0.189-0.358	0.26-0.52	0.29-0.737	0.29-0.56
	Mean±SD	0.25±0.04	0.343±0.07	0.391±0.1	0.403±0.07
	P1		0.439	**0.00**	**0.00**
	P2			0.0622	**0.0074**
	P3				0.34
Q_s/Q_t	Range	0.26-0.43	0.17-0.35	0.14-0.3	0.15-0.27
	Mean±SD	0.321±0.04	0.251±0.04	0.20±0.04	0.19±0.03
	P1		**0.00**	**0.00**	**0.00**
	P2			**0.0005**	**0.0001**
	P3				0.253

P_aO_2: partial pressure of O_2; **S_aO_2:** arterial O2 saturation**; P_aO_2/F_iO_2**: hypoxic index; **P_aO_2/P_AO_2**: arterial to alveolar partial pressure of O_2; **Q_s/Q_t:** shunt fraction.

Table (3): Mean values of Pplat, Cst, autoPEEP, MAP, HR and CVP at different PEEP levels.

		Base line	Pre optimal	Optimal	Highest
$P_{plateau}$	Range	22-28	24-30	25-29	29-34
(cmH_2O)	Mean±SD	25.75±1.8	27.6±1.5	28.25±1	31.6±1.2
	P1		0.246	**0.00**	**0.00**
	P2			0.062	**0.00**
	P3				**0.00**
C_{st}	Range	18-26	28-41	32-45	29-40
(ml/ cmH_2O)	Mean±SD	22.3±3.1	35.8±4.3	38.6±3.3	35.35±3.5
	P1		0.052	**0.00**	**0.00**
	P2			0.014	0.361
	P3				**0.002**
autoPEEP	Range	0-2	0-2	0-2	0-2
(cmH_2O)	Mean±SD	1.05±0.3	1±0.4	0.8±0.6	0.85±0.6
	P1		0.286	0.067	0.129
	P2			0.125	0.207
	P3				0.404
MAP	Range	61-90	60-92	62-91	64-94
(mmHg)	Mean±SD	76.5±10	77.35±11	76.9±11	78.5±10
	P1		0.495	0.454	0.275

	P2			0.4507	0.3719
	P3				0.320
HR	Range	75-111	77-115	77-110	79-110
(beats/min)	Mean±SD	98.65±11	97.5±11	97.3±11	95.9±9
	P1		0.476	0.353	0.200
	P2			0.4777	0.3131
	P3				0.332
CVP	Range	13-18	13-18	13-20	13-19
(cmH_2O)	Mean±SD	14.9±1.5	14.45±1.5	14.75±2	14.55±1.8
	P1		0.308	0.398	0.260
	P2			0.300	0.426
	P3				0.372

P_{plat}: plateau pressure**;** **C_{st}**: static compliance; **MAP:** mean arterial pressure; **HR:** heart rate**;** **CVP**: central venous pressure.

Table (4): Comparison between mean values of LIS, Cst, HI and pulmonary infiltrates at different periods.

		before study	6 h with optimal PEEP	24 h with optimal PEEP
LIS	Range	2.5-3.5	2.5-3.25	2.5-3.25
	Mean±SD	2.97±0.32	2.83±0.21	2.82±0.2
	P1		0 06	**0.04**
	P2			0.43
C_{st}	Range	11--32	30--45	24--48
(ml/cmH_2O)	Mean±SD	21.75±6.19	37.50±4.39	37.05±5.42
	P1		**0.00**	**0.00**
	P2			0.39
HI (P_aO_2/F_iO_2)	Range	74-130	178-335	170-340
	Mean±SD	103.6±16.3	234±48.73	236±48.1
	P1		**0.00**	**0.00**
	P2			0.43
Pulmonary infiltrates	Range	2--4	2--4	2--4
(quadrants)	Mean±SD	3.3±0.5	3±0.7	2.7±0.6
	P1		0.077	**0.002**
	P2			0.089
PEEP (cmH_2O)	Range	7-11	9-19	9-19
	Mean±SD	9.135	14.3±3.35	14.3±3.35

LIS: lung injury score**;** **Cst:** static compliance**;** **HI:** hypoxic index**.**

Table (5): Correlations between the studied parameters.

	R value	P value
$PCO_{2\ grad}$ and Vd/Vt	0.713	**0.001**
$PCO_{2\ grad}$ and (P_vCO_2-P_aCO_2)	0.523	**0.001**

R: correlation coeffiecent; CVP: central venous pressure; Vd/Vt : dead space fraction.

4. Discussion

Recent advances in the treatment of ALI/ARDS have centered on the concept of ventilator induced lung injury (VILI) and the need for lung recruitment (14). The lung protective strategy is mainly composed of two components. One is minimizing volutrauma by using small tidal volumes (3). The other strategy is lung recruitment: "open up the lung and keep the lung open" (15).

The most popular way of keeping the lung open is to apply positive end expiratory pressure (PEEP). PEEP is the cornerstone of hypoxemia treatment in patients with ALI and ARDS, but there is still some controversy over the optimum level to be used and how this should be determined(16). An ideal level of applied PEEP that maximizes recruitment, maximizes oxygenation, and prevents injurious cyclic atelectasis without causing overdistention, decreased venous return, and impaired oxygen delivery has not been identified and probably varies from patient to patient (17).

In the present study patients with hemodynamic instability or shock were excluded till being stabilized to be able to tolerate applied PEEP titration. This is due to the fact that high levels of PEEP can impede the venous return by increasing the positivity of the intra-thoracic pressure which can decrease the cardiac output and compromise circulation, leading to a reduction in the blood pressure. Also, patients with cardiac diseases (like arrhythmias and ischemic heart disease) and chronic pulmonary diseases (like lung fibrosis and COPD) were excluded because of difficulty in clinical diagnosis of ALI or ARDS in these patients and they

may not tolerate the hemodynamic effects of high PEEP levels. In COPD patients, the presence of auto PEEP and dynamic hyperinflation will interfere with PEEP titration.

All patients in our study tolerated the PEEP titration protocol relatively well, with only four patient experienced a transient hypotension during PEEP titration around pre-optimal, optimal, and highest PEEP (MAP < 65 cmH_2O, which correspond to systolic blood pressure <90 cmH_2O, and diastolic pressure < 60 cmH_2O), these patients needed therapeutic modification during the PEEP titration protocol; two patients managed by fluid infusion and two patients needed small dose of dopamine as an inotropic agent. Two patients during PEEP titration experienced atrial premature beats which resolved spontaneously with no any harm effect on hemodynamics, another patient experienced supra-ventricular tachycardia which managed immediately by verapamil 5mg intravenous injection and resolved immediately within 5 minutes without any effect on hemodynamics. As regard hypoventilation and barotraumas, there is no documented adverse event on blood gases and chest X-ray respectively during PEEP titration.

In the present study we observed, with every PEEP elevation, a significant decrease in PCO_{2grad} ,V_d/V_t and Q_s/Q_t associated with significant increase in PaO_2, HI and SaO_2 to a certain PEEP level. The least PCO_{2grad} corresponded to the optimal PEEP provided all expected beneficial effects and did not cause harmful effects and this was taken as an end point for titration i.e. when oxygenation is at its best (optimal PEEP) PCO_{2grad} is least. After that PEEP level we observed that PCO_{2grad} and V_d/V_t started to increase again which corresponded to the highest PEEP. Also, the increase in PCO_{2grad} and V_d/V_t with highest PEEP was significant than pre-optimal and optimal PEEP.The explanation for this observation is that excessive levels of PEEP would increase ventilation to areas with high VA/Q and increase the dead space and dilute alveolar CO_2 by a larger volume, resulting in an increase in PCO_{2grad} again. In a study done in dogs by Coffey et al(18), the effect of PEEP on V_d/V_t was studied with multiple inert gas elimination technique and it was shown that the decrease in V_d/V_t was due to reductions in shunt and midrange VA/Q heterogeneity and the increase in V_d/V_t with higher PEEP levels was due to increased ventilation to high VA/Q regions and a larger anatomical dead space. We showed that the shunt decreased in our patients also. The mechanisms mentioned by Coffey et al can be extrapolated to play a role also in human patients.

In agreement, Murray IP et al (10) studied titration of PEEP by PCO_{2grad} in 10 adult mongrel dogs after oleic acid induced lung injury. In this study, the PCO_{2grad} was 7.3 ± 2.3 mm Hg before oleic acid increased to 18.3±6 mmHg ($p < 0.001$) 90 minutes after oleic acid injection. With the institution of 10 through 20 cmH_2O of PEEP, the mean value of PCO_{2grad} in the ten dogs returned to a level that did not differ significantly from control. At 25 cmH_2O of PEEP, the average PCO_{2grad} increased once again to a level that was significantly higher than the control values and the values at 10, 15, and 20 cmH_2O of PEEP ($p < 0.05$). PCO_{2grad} significantly deteriorated when oleic acid was injected into the pulmonary artery and application of PEEP to a certain level improved significantly PCO_{2grad} and additional PEEP beyond that level produced significant deterioration in PCO_{2grad}.

Murat Sungur et al(19) who performed PEEP titration by increments of 5, 10, 15 and 20 cmH2O in 8 sedated and paralyzed patients with ARDS showed that PCO_{2grad} was 11.0 mmHg (range 2.8-20.0) at 5 and decreased to 9.0 mmHg (range 1.2-20.0) with 10, further decreased to 7.0 mmHg (range 2.0-16.1) with 15 and then increased to 17.0 mmHg (range 4.6-22.0) with 20 cmH_2O PEEP. Q_s/Q_t was 0.4 (0.28-0.71) and 0.4 (0.19-0.45) with 5 and 10 cmH_2O of PEEP and decreased to 0.31 (0.11-0.71) with 15 cmH_2O of PEEP and to 0.30 (0.29-0.32) with 20 cmH_2O PEEP. VD/VT decreased to 0.21 (0.2-0.36) and 0.15 (0.6-0.36) with 10 and 15 cmH_2O of PEEP from 0.35 (0.05-0.41) at 5 cmH_2O of PEEP and increased to 0.31 (0.05-0.47) with 20 cmH_2O of PEEP. But these results were, in contrast to our results ,not significant. This discrepancy may be due to large number of patients in our study compared with their study (20 versus 8) and to the fact that they used PEEP titration by large interval i.e. at 5, 10, 15, 20 cmH_2O but in our study we used the PEEP titration by 2 cmH_2O increments from baseline PEEP.

Jardin et al (20) compared the PCO_2 grad with total static compliance measurements (Cst) to titrate PEEP in eleven patients in acute respiratory failure requiring controlled ventilation with PEEP, they found that with the best PEEP (9.3±1.6 cmH_2O), Cst improved significantly and an increase in FRC was obtained. Also, Q_s/Q_t was reduced significantly and PaO2 improved. With a higher level of PEEP (20.2±2.4 cmH_2O), FRC was increased further but Cst deteriorated. Despite deterioration in lung mechanics, Q_s/Q_t was reduced further and PaO_2 improved. No significant change in the PCO_{2grad} at any level of PEEP. The discrepancy in results between Jardin et al(20) and our study may be due to the fact that the former authors studied the PCO_{2grad} in a heterogeneous group of acute respiratory failure patients including cardiogenic pulmonary edema in

contrast to our study which studied PEEP titration in ARDS patients using the PCO_{2grad}.

Using $PetCO_2$ to determine the effectiveness of ventilation (estimating $PaCO_2$) is inappropriate in ARDS patients due to ventilation/perfusion mismatch, but that the difference between them, P (a-et) CO_2, could be used to assess the efficiency of ventilation. We anticipated that $PetCO_2$ and $PaCO_2$ would be greatly different in individual patients but that PCO_{2grad} and V_d/Vt would be closely related.

In the present study, we found significant positive correlation between PCO_{2grad} and V_d/V_t with PEEP titration, and reached its smallest value with optimal PEEP (r=0.713, P=0.001). This was anticipated and expected because both variables reflect the contributions of high VA/Q regions. Thus, either V_d/V_t or CO_{2grad} can be used as estimates of wasted ventilation. For example, V_d/V_t has been used retrospectively to predict ability to wean from mechanical ventilation, and PCO_{2grad} <8-10 mm Hg also was shown to be associated with successful weaning (21).

In agreement, Mark K et al (21) have performed comparison between PCO_{2grad} and V_d/V_t in 17 patients with respiratory failure and found correlation between both of them (r =0.80, p<0.05). Also, Shimada Y et al(22) who studied the evaluation of the progress and prognosis of ARDS found that V_d/V_t and PCO_{2grad} could be used as markers of severity, response, and prognosis in ARDS (large V_d/V_t and large PCO_{2grad} indicates severity of the disease and bad prognosis and vice versa).

Most authors found that V_d/V_t values in ARDS to exceed 0.5(8). Analysis of data obtained in our study revealed that 9 patients out of 20 had V_d/V_t < 0.5. Two reasons may be responsible for these low values; first, PaO_2/FiO_2 ratios of these patients did not show severe ARDS (PaO_2/FiO_2 ranged between150-233) and second, the formula we used requires mixed expired PCO_2 values, but we used $PetCO_2$ values(6) due to availability of capnography in ICU as a non invasive method for determining end-tidal PCO_2.

In the present study PaO_2, SaO_2, HI and Q_s/Q_t were used to evaluate effect of PEEP titration on oxygenation. Improvement in these parameters occurred at optimal and highest compared with baseline and pre-optimal PEEP without significant difference between highest and optimal PEEP.

In agreement, Murat Sungur et al(19) showed that with FiO_2 of 1.0, PaO_2 was 216 (range 54-315), 240 (range 61-391), 258 (range 76-284) and 214 (range 67-340) mmHg with 5, 10, 15 and 20 cmH_2O of PEEP respectively, this means improvement in PaO_2 with PEEP titration. Also, Intrapulmonary shunt decreased with increasing levels of PEEP and was minimal with 20 cmH2O of PEEP (significant difference between 5 and 20 cmH_2O of PEEP, P<0.05). Also, Murray IP et al(10) showed that the mean PaO_2 with FiO_2 of 0.5 was 233±39 mm Hg during the control period, decreased to 109±37mm Hg (P <0.001) 90 minutes after the administration of oleic acid; the mean PaO_2 at 10 mm Hg of PEEP returned to 214 ± 47 mm Hg and did not change further as PEEP was increased to 15, 20, and 25 mm Hg (p > 0.05). In the same study, the Q_s/Q_t calculated during the control period was 0.023 ±0.016. Ninety minutes after oleic acid injection, Q_s/Q_t increased to a mean of 0.176 ±0.151 (P< 0.001). At 10 mm Hg of PEEP, the mean Q_s/Q_t closely resembled the control Q_s/Q_t. The Q_s/Q_t continued to decrease by small increments as PEEP was increased to the 25 mm Hg level. Possible explanations are that PEEP causes improvement in ventilation-perfusion (VA/Q) relationships(23) and causes reduction in pulmonary blood flow including shunting regions(24). These changes account for improvement in PaO_2 with PEEP(25) especially the use of the proper level of maintenance PEEP which was determined by the PCO_2 grad. When the PCO_2 grad is minimal PaO_2 was also at the highest level. Intrapulmonary shunt also decreased with increasing levels of PEEP and was minimal with the optimal PEEP.

Armand MD et al(26) studied the effect of PEEP level changes in 85 patients without and 31 patients with patent foramen ovale shunting. In the group without PFO shunting, increasing the PEEP level from 9± 3 to 14± 2 cmH_2O induced PRO shunting in 8 (9%) patients. In the group with PFO shunting, lowering the PEEP from 11±5 to 3±2 cm H_2O abolished shunting in 4 (13%) patients. Although optimal (14.3±3) and highest (16.3±3) PEEP approaches these values, we did not found worsening of shunting in our patients at these PEEP levels. This could be attributed to the use of lower increments of PEEP applied over 30 minutes which have minimized this effect.

This study showed that PEEP titration using the PCO_{2grad} was effective in improving oxygenation as well as lung mechanics and was generally well-tolerated. At optimal PEEP, patients had significantly higher Cst compared with highest PEEP while the improvement in oxygenation at highest PEEP was maintained at optimal PEEP. These results clearly indicated that PEEP levels higher than optimal added no more to oxygenation but could produce reduction in Cst and increase P plat (from 28.25±1.02 to 31.6±1.27) beyond the safe limits that guard against barotraumas. This reduction in compliance produced by highest PEEP could be the result of overstretch of alveoli leading to reduction in surfactant activity.

To reach to optimal PEEP, several studies on applied PEEP titration were performed over the last years according to physiologic measures. These studies included: the least PEEP approach, esophageal pressure, PV curves, oxygenation and oxygen delivery.

In the present study we tested the hypothesis that optimal PEEP would improve the PCO_{2grad} and V_d/V_t in ALI/ARDS patients who have high VA/Q lung regions and accordingly this gradient can be used as a noninvasive measure for determination of optimal PEEP.

Traditional approach to titrate PEEP had been the least PEEP approach(27): smallest PEEP needed to achieve adequate oxygenation at a nontoxic concentration of oxygen. The lowest level of applied PEEP at which an adequate PaO2 is maintained (with the F_iO_2 is less than 0.6) is used for ongoing mechanical ventilation(28). However, improved oxygenation alone is insufficient to warrant a change in routine clinical practice because prior studies have not shown an association between survival and improved oxygenation, particularly when the latter is achieved with a potentially harmful mechanical ventilation strategy(29).

Esophageal pressure is an estimate of pleural pressure(28) and was used to calculate the trans-pulmonary pressure, which can then be adjusted by titrating applied PEEP, since airway pressure is related to the applied PEEP. This strategy was designed to maintain an arterial oxygen tension (PaO_2) between 55 and 120 mmHg, or oxy-hemoglobin saturation between 88 and 98 percent. The group, in whom applied PEEP was guided by esophageal pressure measurements was managed with significantly higher total PEEP than the control (18 versus 12 cmH_2O) and had a significantly higher PaO_2/F_iO_2 ratio (280 versus 191).

Some investigators used intrapulmonary shunt reduction as a target to titrate PEEP. They considered PEEP to be optimal and should be increased until the intrapulmonary shunt decreases below 15% of cardiac output (CO)(29). With this technique they reached PEEP levels as high as 40 or 50 cmH_2O to achieve their target.

Suter et al(30) pointed out that, changes in O_2 delivery (DO_2) should be used as the reference standard for titrating PEEP. They found that increases in PEEP caused an increase in DO_2 up to a certain point with improvement of total static compliance, and further increases in PEEP caused a decrease in DO_2 and worsen static compliance. Use of DO_2 and CO for PEEP titration can be helpful for finding optimal PEEP but it is clear that to measure DO_2, pulmonary artery catheter is required and this is an invasive procedure.

Another method was used for PEEP titration and determination of optimal PEEP is the lower inflection point (LIP). There are two methods of titrating applied PEEP that require a PV curve; the first method involves using a level of applied PEEP that is slightly above the lower inflection point(32). The second involves using a level of applied PEEP that matches the pressure at which lung compliance is maximized. This is determined from the PV curve (slope equals compliance) or by stepwise titration of applied PEEP with calculation of compliance at each step(33). There are significant limitations to using PV curves to identify the level of applied PEEP necessary for open lung ventilation. Among the limitations, the lower inflection point cannot be identified in some patients and neuromuscular blockade is generally required to accurately construct a PV curve (33,34).

Lung injury score (LIS) was used in the present study for further evaluation of severity of ARDS. LIS used before the study with the randomly preset PEEP, after 6 hours of the study with optimal PEEP and 24 hours after the study with optimal PEEP. Diagnosis of ARDS made when LIS was >2.5(31). There was significant improvement in LIS after 24hour of the study with optimal PEEP than before the study (P1=0.04). Also, chest X-ray showed significant improvement of the chest infiltrates within 24 hours of application of optimal PEEP than baseline (P1=0.002).

There are some 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 $PetCO_2$ instead of CO_2 elimination. Single breath CO_2 elimination technique needs relatively expensive equipment.

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Corresponding Author:
Dr. Amr Abdallah
Lecturer of Critical Care Medicine.
Critical Care Medicine Department.
Faculty of Medicine, University of Alexandria.
Raml station, PO box 21563- Alexandria- Egypt.
Cell Phone: 002- 0100106679
E-mail: amrabdalla1971icu@gmail.com

Authors
Dr. Hassan A Abukhabar

Professor of Critical Care Medicine
Critical Care Medicine Department
Faculty of Medicine, Alexandria University, Egypt
E-mail: habukhaber@yahoo.com

Dr. Mohammad El-Samman
MS of Critical Care Medicine.
Critical Care Medicine Department.
Faculty of Medicine , University of Alexandria.
Raml station, PO Box 21563, Alexandria- Egypt
Cell Phone: 002- 01224298514

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