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Optimizing PEEP Using Carbon Dioxide Production (VCO_2) in Patients with ARDS

Mohamed Samir Abdelghafar* **and Zahretelwady Mohamed Salaheldin Mohamed**

Department of Anesthesiology and surgical intensive care, Tanta University Faculty of Medicine, Tanta, Egypt

***Corresponding author**: Mohamed Samir Abd elghafar, Department of Anesthesiology and surgical intensive care, Tanta University Faculty of Medicine, El geish street, Tanta, Egypt, Tel: 00201275959533; E-mail: mohamedghafar76@yahoo.com

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Abstract

Background: The use of PEEP is a corner stone in the management of ARDS. Several methods were investigated to determine the optimal PEEP. However, no method is considered gold standard. The study investigated whether the use of VCO_2 to determine optimal PEEP value in ARDS patients improves oxygenation, alveolar ventilation and static compliance compared to ARDSNet FiO_2-PEEP combination.

Patients and methods: This prospective randomized controlled study was conducted at a tertiary university hospital ICU including sixty mechanically ventilated ARDS patients. Patients were randomized between two groups; group A, where PEEP was titrated using FiO_2-PEEP combination and group B, where PEEP was titrated according to VCO_2. In this group, PEEP was increased in increments of 2 cm H_2O every 20 minutes with VCO_2 monitoring. Once it failed to recover to baseline, the preceding PEEP value was considered optimum.

Results: Group B received statistically significant higher values of PEEP 10.87 (± 2.35) *vs.* 9.20 (± 1.13) cm H_2O; p <0.001 and lower values of FiO_2 40 (± 0) *vs.* 57.00 (± 8.37) %; p <0.001, compared with group A. Significantly higher PaO_2/FiO_2 and static compliance were observed in group B compared with group A [216.27 (± 36.79) *vs.* 158.60 (± 42.65); p <0.001 and 57.80 (± 7.93) *vs.* 52.73 (± 4.98) mL/cm H_2O; p <0.04, respectively]. While VA improved in both groups there was no associated impact of both interventions on VCO_2 or MAP.

Conclusion: Optimum PEEP determination using VCO_2 resulted in improvement of oxygenation and lung compliance compared with FiO_2-PEEP combination in ARDS patients. Higher PEEP used was not associated with increase in complications.

Keywords: Anesthesia and intensive care; Hypoxemia; Acute respiratory distress syndrome (ARDS); Ventilation; Optimal PEEP

Introduction

Ue use of Positive End Expiratory Pressure (PEEP) is a corner stone in the management of Acute Respiratory Distress Syndrome (ARDS), and was linked to decreased mortality in patients with ARDS [1]. Optimum PEEP value can be considered as the one which improves lung recruitment and hence oxygenation as well as ventilation, without compromising patient's hemodynamics or inducing alveolar hyperinflation.

Several methods were investigated to determine the optimal PEEP value in ARDS patients, which reflects the heterogeneity in the pathology of ARDS. Uese methods include, but not limited to, the use of multiple pressure volume curves [2] measurement of lung volumes, [3] ARDS Clinical Network Mechanical ventilation protocol (ARDSNet) FiO_2- PEEP combination, [4] and others. However, there is no gold standard method for determining such optimal value.

Volumetric capnogram can be used to monitor VCO_2 during mechanical ventilation in ARDS patients. It is postulated that increments of PEEP values cause a decrease in VCO_2, which recover quickly to baseline if not associated with a compromise of the pulmonary perfusion (cardiac output). Optimum PEEP may therefore be considered the maximal PEEP value which was not associated with a decrease in cardiac output and hence CO_2 delivery and elimination which can be assessed by VCO_2 value. Uus, when a decrease in VCO_2 with failure to recover to baseline is observed, the preceding PEEP value can be considered as the optimum PEEP. Our study aimed at comparing the use of VCO_2 obtained from volumetric capnogram to detect optimal PEEP *vs.* traditional ARDSNet FiO_2- PEEP combination, through its e9ects on oxygenation, alveolar ventilation and static compliance.

Patients and Methods

Uis prospective randomized controlled study was conducted in Anesthesia and Surgical Intensive Care Department of a university hospital during the period from March 2016 to March 2017. Uis is a tertiary hospital in a central catchment area covering an estimated population of 5 million citizens. Ue study was approved by the institutional review board of faculty of medicine and university hospitals, Tanta University with code: 30452/08/15.

Over the study period, all patients admitted to the surgical intensive care unit (SICU) who were mechanically ventilated via an oro-tracheal tube and were screened. Patients fulfilling Berlin definition [5] of ARDS were registered. Patients with known history of cardiac disease, acute coronary syndromes or low functional capacity; history of hepatic disease, alcohol intake or positive virology; history of chronic

kidney diseases or rising creatinine; with unstable hemodynamics in term of mean arterial blood pressure if less than 65 mm Hg or on vasopressors were excluded from the study. If a patient fulfilled the criteria, explanation to the family was done by the SICU doctor then a written informed consent from participants' legally authorized representative, according to national regulations, was obtained.

Ue patients were randomized into two groups, on a ratio of 1:1, using end-user computer-based randomization soIware. Samples, data input into ventilator and PEEP titration were done by the principal investigator.

Sixty patients who met the previous criteria were enrolled in the study. Patients were randomly allocated in equal proportions of 30 patients to each of the studied groups:

Group A

In this group, aIer baseline ventilation, optimum PEEP was determined using FiO_2-PEEP combination. Fraction of inspired oxygen (FiO_2) and PEEP were titrated based on the FiO_2-PEEP combination chart (Table 1) every 20 minutes. A minimum PaO_2 of 55-80 mmHg or SpO_2 88-95% was targeted as recommended by ARDSNet trials [4]. However, up titration was continued until reaching plateau oxygen saturation. Ue least combination that produces same oxygen saturation was considered optimal.

Group B

In this group, aIer baseline ventilation, the same oxygenation levels were targeted as recommended by ARDSNet trials. PEEP was increased in increments of 2 cmH_2O every 20 minutes and VCO_2 was monitored. Once it failed to recover to baseline, the preceding PEEP value was considered optimum.

Baseline ventilation, monitoring and PEEP titration protocol:

All patients were mechanically ventilated using Engström Carestations (General Electric, New York, USA). Basic monitoring for patients were done using BSM-2301K monitors (Nihon Kohden, Tokyo, Japan). A radial arterial catheter and triple-lumen central venous catheter were inserted for frequent sampling of arterial blood gas and central venous blood gas analysis, respectively using the AVL-988 multi-gas analyzer (Roche, Basel, Switzerland).

Adequate sedation of all patients (Richmond agitation sedation scale score -5) [6] was achieved with continuous infusions of midazolam 0.1 mg/kg/h. Bolus muscle relaxant injection of 3 mg cis-atracurium were injected as required during PEEP titration. Maintenance intravenous fluids were infused and fluid responsiveness was monitored regularly with passive leg raising test and bolus fluid infused as required. All patients were kept in supine position.

Ventilation settings were adjusted according to the ARDSNet protocol [5]. FiO_2 was initially set at 0.4 and PEEP at 5cmH_2O then recruitment maneuver in the form of a sustained application of PEEP at 40cmH_2O for 40 seconds was performed. PEEP was then titrated in steps of 2 cmH_2O according to method used in each group.

During the procedure, baseline hemoglobin level was obtained as well as arterial blood gas and central venous blood gas samples at each step as input data for volumetric capnogram module to calculate VA. In addition, patients were monitored for signs of hemodynamic instability in the form of hypotension with a mean blood pressure of less than 65 mmHg and/or pneumothorax.

Ue primary outcome was the PaO_2/FiO_2 while secondary outcome was: CO_2 production VCO_2, alveolar ventilation (VA), static compliance, MAP and complications if occurred with modulation of initial settings.

Ue sample size was calculated using Epi-Info soIware statistical package created by World Health organization and center for Disease Control and Prevention (Atlanta, Georgia, USA) version 2002. Ue sample size was calculated at N=24 and approximated to 30

Ue criteria used for sample size calculation were as follows:

95% confidence limit

80% power

Ue ratio between experimental and control groups is 1:1

Expected outcome in treatment group is double times better than control groups. (40-80% of optimal required) Statistical analysis was done by an independent statistician, who was blinded to allocation and methodology used in each group. Ue collected data were organized, tabulated and statistically analyzed, using SPSS (Statistical Package for Social Studies) version 19, created by IBM (Illinois, Chicago, USA).

For numerical values the range, mean, and standard deviations were calculated. Ue di9erences between mean values of the two studied groups were tested using student's t test. Di9erences of mean values at baseline and end of intervention were tested using paired t test. For categorical variables, the number and percentage were calculated and analyzed using chi square test. Ue level of significance was adopted at $p < 0.05$.

Results

Ue enrollment and allocation of patients are shown in Figure 1.

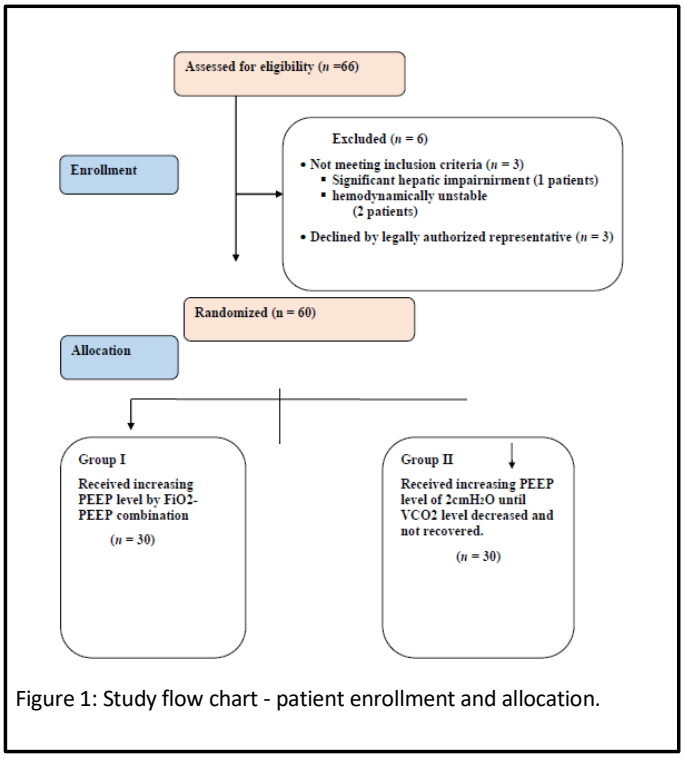

Figure 1: Study flow chart - patient enrollment and allocation.

Sixty patients who fulfilled the Berlin definition of ARDS [5] were enrolled. Demographic data and ARDS grade for each registered patient was collected (Table 1).

FiO_2 (%)	30	40	40	50	50	60	70	70	70	80	90	90	90	100
PEEP (cmH_2O)	5	5	8	8	10	10	10	12	14	14	14	16	18	20-24
FiO_2: Fraction of Inspired Oxygen; PEEP: Positive End Expiratory														

Table 1: FiO_2-PEEP combinations [5].

Significantly higher values of PEEP were applied in group B ($p < 0.001$), while significantly higher values of FiO_2 were applied in group A ($p < 0.001$). Both groups showed a significant increase in SpO_2 and PaO_2 from baseline ($p < 0.001$ in both groups), with no significant di9erence between the two groups. However, $PaO2/FiO_2$ values were significantly higher in group B compared with group A ($p < 0.001$). Ue static compliance in both groups showed a significant increase from baseline values ($p < 0.001$ in both groups) and was significantly higher in group B compared to group A ($p < 0.004$) (Table 2).

Category of patients	**Group A**	**Group B**	**x2**	**P**
ARDS grade				
Mild	12	12		
Moderate	17	18		
Severe	1	0	0	1
Sex				
Males	22	22		
Females	8	5	0.884	0.347
Age (years)			t	P
Range	18-62	18-57		
Mean (± SD)	34.47(± 14.12)	35.17(± 13.93)	0.193	0.848
Predicted body weight (kg)				
Range	54-81	51-79		
Mean (± SD)	69.90 (± 7.05)	66.13 (± 8.09)	1.92	0.06
ARDS: Acute Respiratory Distress Syndrome; SD: Standard Deviation				

Table 2: Comparison between demographic data and ARDS grade between the studied groups.

Ue baseline values of VCO_2, VA and MAP were comparable in both groups. VA values were significantly improved in both groups ($p < 0.001$ in both groups), with no significant di9erence between the two groups. Neither VCO_2 nor MAP significantly changed from baseline in both groups, with no significant di9erence between the two groups (Table 3).

	Group A	**Group B**	**p**
Optimum PEEP			
Baseline	5 (± 0.0)	5 (± 0.0)	
End	9.27 (1.23)	10.93 (± 2.38)	
P	0.001*	0.001*	0.001*
FiO_2			
Baseline	40 (± 0.0)	40 (± 0.0)	
End	56.67 (± 8.02)	40 (± 0.0)	
P	0.001*		0.001*
VA			
Baseline	3.55 (± 0.65)	3.77 (± 1.04)	0.393
End	3.81 (± 0.60)	4.07 (± 1.05)	0.237
P	0.001*	0.001*	-
VCO_2			
Baseline	219.30 (± 38.9)	224.93 (± 46.52)	0.613
End	220.53 (± 38.58)	226.87 (± 47.87)	0.575
P	0.061	0.054	-
SPO_2			
Baseline	93.56 (± 2.18)	93.77 (± 2.08)	0.717
End	96.13 (± 1.80)	96.013 (± 1.74)	0.999
P	0.001*	0.001*	-
PaO_2			
Baseline	73.27 (± 12.89)	74.03 (± 12.51)	0.816
End	86.93 (± 13.45)*	85.83 (± 13.48)*	0.753
P	0.001*	0.001*	-
PaO_2/ FiO_2			
Baseline	182.63 (± 32.86)	185.33 (± 31.27)	0.746
End	158.70 (± 42.53)*	216.43 (± 36.59)*	0.001*
P	0.001*	0.001*	-
Static compliance			
Baseline	44.63 (± 4.82)		-
End	52.83 (± 5.00)*		-

P	0.001*		-
MAP			
Baseline	91.53 (± 16.81)	91.70 (± 18.53)	0.971
End	92.87 (± 16.48)	91.37 (± 17.73)	0.736
P	0.088	0.659	-

SD: Standard Deviation, PEEP: Positive End Expiratory Pressure in cmH_2O; FiO_2: Fraction of Inspired Oxygen Expressed as %; VA: Alveolar Ventilation in L/min; VCO_2: Volume of Carbon dioxide in ml/min; SPO_2: Peripheral Oxygen Saturation in %, PaO_2: Partial Arterial Oxygen Tension in mmHg, Static Compliance in mL/cm H_2O and MAP: Mean Arterial Blood Pressure in mmHg

Table 3: Comparison between measured data between the studied groups at baseline and end of intervention. Values are expressed as mean (± SD).

Discussion

Ue use of fixed PEEP levels based on FiO_2 values according to ARDSNet protocol does not consider the heterogeneity of ARDS pathology among di9erent patients [7]. Despite its criticism, it has been used successfully in all ARDSNet trials [8] and hence it was used in the current study. However, the current study targeted higher SPO_2 than recommended by ARDSNet trials. Uis modification was based on Villar et al. [9] who reviewed publications from the last 2 years and the current guidelines dealing with ARDS. Uey recommended a target SPO_2 of 90–97%. Uis higher target was also suggested by Bein et al. [10].

Application of PEEP in ARDS patients to open potentially recruitable alveoli does not only improve oxygenation, but also augments CO_2 elimination. Ue approach of the current study to detect optimal PEEP depended on monitoring e9ect of PEEP on CO_2 elimination rather than oxygenation which better reflects PEEP related hemodynamic compromise. Measuring VCO_2 is a simple bedside tool, with superiority over end-tidal CO_2 in evaluation of CO_2 elimination [11,12].

Our findings showed that determination of optimum PEEP by monitoring VCO_2 is associated with improvement of oxygenation as well as lung compliance, without hypotension or pneumothorax, compared with use of FiO_2-PEEP combination in ARDS patients.

PEEP application is known to improve oxygenation in ARDS patients [13]. Ue higher values of PEEP used in group B in combination with lower values of FiO2, resulted in higher values of PaO2/FiO2, compared with group A.

In agreement with current study results, a meta-analysis by Breil et al. [14] involving 2299 patients reported that the use of PEEP values higher than suggested by ARDSNet trials was associated with improvement in lung aeration as well as clinical improvement, compared with lower values. Although statistically significant ($p < 0.001$), some may argue that PEEP di9erence between two groups may not be considered clinically significant (10.87 (± 2.35) in group B *vs.* 9.20 (1.13) in group A), yet the combination allowed the use of significantly lower FiO2 (57.00 (± 8.37) in group A *vs.* 40 (± 0.0) in group B; $p < 0.001$). A meta-analysis by Briots et al. [15] on 2312 patients previously enrolled in ARDSNet trials, recommended against the use of high FiO2 values in ARDS patients due to its association with high mortality rates.

Uere is no significant di9erence between both groups, as regard e9ect on VCO2 ($p= 0.552$), which is in agreement with Johnson et al. [12] who found no significant e9ect on VCO2 with application of PEEP value of 10 cmH2O in anesthetized patients.

Contrary to our findings, Tusman et al. [16] reported an increase of VCO2 with incremental increase of PEEP (2 cmH2O/min) as a part of recruitment maneuver in morbidly obese patients. Uis apparent disagreement may be explained by an increase of VCO2 in the early non-steady state and accelerated response of VCO2 by recruitment maneuver applied. In addition, the increase in VA from baseline value aler increasing PEEP, noted in our study in both groups, could be reflected on VCO2 if the period was longer than 20 minutes.

Ue increase of VA in response to an increase of PEEP values, as noticed in both groups in our study, is in agreement with Tusman et al. [16] However, the opposite was reported by them in their earlier animal study, [17] occurring aler 10 minutes. Uis di9erence in results may be due to their earlier measurement of VA which possibly didn't allow enough time for VA recovery and increase from initial level.

Ue lack of significant di9erence in VA between the two groups (p=) in the present study may be explained by the fact that Group A may also have benefited from recruitment maneuvers at the beginning of the study and increasing PEEP levels which were significantly higher than baseline ($p \leq 0.001$). It may, also, be due to inability of the current study to include severe ARDS patients, who could demonstrate maximum response to any interventions, which is considered one of the current study limitations.

Ue improvement of the static compliance with use of PEEP value determined by VCO_2 in our study was also observed by Maisch et al. [18] who reported that use of static compliance for optimal PEEP determination was superior to the use of PaO_2 in patients undergoing cardiac surgery. Uis can be explained by remodeling of worsened sigmoid volume-pressure relationship in ARDS by the e9ect of PEEP, which maintains alveoli open, and prevent flattening of volume-pressure curve, as reported by Coruh et al. [19].

No hypotension or pneumothorax was observed in the current study, even with the higher values of PEEP which were used in group B. Ue lack of detrimental hemodynamic e9ect may be explained by the work of Gattinoni et al. [20] who reported a decrease in pulmonary artery pressure with no significant adverse e9ect on the cardiac output, secondary to improvement of lung recruitment. Lung recruitment is accompanied by pulmonary vessels recruitment, which improves right ventricular function, and lel ventricular function consequently.

Uis could suggest that VCO_2 monitoring was useful to avoid the side e9ects of increasing PEEP on cardiac output. Changes in VCO_2 were observed earlier than any change in MAP.

In contrast, Chikhan et al. [21] reported that high PEEP values up to 20 cm H_2O improve arterial oxygenation, but can compromise oxygen delivery to tissues due to decrease in cardiac output. Uis may be explained by the e9ect of high rather than optimum PEEP value.

Limitations

Adding to the previously mentioned limitation regarding lack of recruitment of severe ARDS patients, the di9erent protocol of PEEP titration used in both groups made blinding not feasible. While that may reflect a potential bias, data processing and calculation were done electronically using the ventilator and the statistical analysis was

blinded. Another limitation is the inability to divide patients into subgroups according to their ARDS grade due to the small sample size which could otherwise deprive any results of statistical significance.

Conclusion

Based on our results, we conclude that optimum PEEP determined by volumetric capnogram (VCO_2 monitoring) is associated with improvement of oxygenation as well as lung compliance, compared with FiO_2-PEEP combination in ARDS patients without resulting in increased complications.

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