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Use of VO2 vs Static Compliance for Determination of Optimal PEEP in ARDS Patients

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Abstract

Background: Protective ventilation strategies using low tidal volume, limiting plateau pressure and manipulating FiO_2-PEEP combination to reach target oxygenation are standard for treatment of ARDS patients. However, the appropriate PEEP level for ventilating such individuals has not been established.

Aim of Study: The study investigated the effect of VCO_2 guided PEEP vs static compliance guided PEEP on oxygenation, CO_2 elimination, alveolar ventilation and static compliance in ARDS patients.

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 static compliance and Group B, where PEEP was titrated using VCO_2, once it failed to recover to baseline, the preceding PEEP value was considered optimum.

Results: Both groups received comparable values of PEEP applied ($p \leq 0.499$). This resulted in a significant increase in SpO_2, PaO_2, PaO_2/FiO_2, VA and static compliance from baseline ($p \leq 0.001$ in both groups), with no significant difference between the two groups. Mean and standard deviation of VCO_2 showed a significant increase from baseline (221.37±44.582 vs 225.10±46.42; $p \leq 0.004$) in Group B with no significant difference between two groups. Two cases in Group A had a decrease in VCO_2 from baseline and one showed both a decrease in VCO_2 from baseline and MAP below 65mmHg. Despite that mean and standard deviation of MAP doesn't significantly change from baseline (90.00± 17.76 vs 89.50± 17.57; $p \leq 0.5006$ and 86.83 ± 16.47 vs 85.27± 17.43 $p \leq 0.1577$) in both groups, and showed no significant difference between the two groups.

Conclusion: Using VCO_2 to determine optimum PEEP associated with comparable improvement in oxygenation and lung compliance, while resulting in a significant improvement in CO_2 elimination compared with optimum PEEP determined by static compliance in ARDS patients. It was, also, associated with no complication in terms of hemodynamic stability in contrast to optimum PEEP determined by static compliance which was associated with incidence of hemodynamic instability.

Key Words: *Hypoxia – ARDS – Optimal PEEP – VCO_2.*

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Introduction

ACUTE Respiratory Distress Syndrome (ARDS) is a major cause of acute respiratory failure. Its development leads to high rates of mortality, as well as short-and long-term complications, such as physical and cognitive impairment. Therefore, early recognition of this syndrome and application of demonstrated therapeutic interventions are essential to change the natural course of this devastating entity [1].

Protective ventilation strategies, low circulating volumes and elevated PEEP levels have been introduced and evaluated in different clinical studies. As a result, this strategy has become a standard for treatment of such patients. However, the appropriate PEEP level for ventilating such individuals has not been established [2].

Optimal PEEP levels are those that maximize oxygenation of the tissues without causing overdistention of alveoli or affecting patient's hemodynamics. Optimal PEEP determination can be done using different strategies as ABG's, cardiac output measurements, A-V O_2 content differences or mixed venous PO_2 [3]. Among these, several studies has suggested the use of static compliance in determination of optimal PEEP and argued the clear benefit of its use in assessment of lung recruitment [4].

VCO_2 obtained from volumetric capnogram is a noninvasive, fast, reliable and safe bedside monitoring tool, but monitoring and analysis of changes in VCO_2 to determine optimum PEEP have not been tested so far. Therefore, in the present study we hypothesized using CO_2 production (VCO_2) obtained from volumetric capnogram to determine optimum PEEP by using VCO_2 value as a guide for early detection of side effect of increasing PEEP on cardiac output. The present study assumed that failure of VCO_2 level to recover to baseline after application of certain PEEP level higher than optimal value, will be observed earlier than any change in MAP and can be used as an indicator of decreased cardiac output. Optimal PEEP detection using static compliance was used as a control group.

The primary outcome of the study is to collect and compare data about PaO_2/FiO_2 while the secondary outcome is collect and compare data about PEEP, oxygenation (SpO_2, PaO_2), VCO_2, alveolar ventilation (VA) and static compliance and monitor complications as hemodynamic instability and pneumothorax.

Patients and Methods

This was a prospective randomized study. The collected data was conducted during the period from March 2016 to March 2017. After approval from Institutional Ethics Committee, an informed consent from all participants' relatives was obtained. All patients' data was confidential with secret codes and private files for each patient. All given data were used for the current medical research only.

Sample size:

The sample size was calculated using Epi-Info software statistical package created by World Health organization and center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002. The sample size was calculated at N=30.

The criteria used for sample size calculation were as follows:

- 95% confidence limit.
- 80% power.
- The ratio between experimental and control groups is 1:1.
- The outcome in the Group A is 55% while in the Group B is 88%.

Study population:

Inclusion criteria:

Over the study period, patients admitted to the surgical ICU on mechanical ventilation via an orotracheal tube and fulfilling Berlin Definition to confirm the criteria of ARDS, were registered. All patients who had ARDS and PaO_2/FiO_2 ratio <300 were selected then ARDS grade was classified.

Berlin definition of ARDS [5]:

- Acute onset within one week.
- Patients can be classified with either mild ($PaO_2/FIO_2 \leq 300$mmHg) moderate ($PaO_2/FIO_2 \leq 200$mmHg) and severe ($PaO_2/FIO_2 \leq 100$mmHg) disease with PEEP or Continuous Positive Airway Pressure (CPAP) $\geq$5cmH_2O [5].
- Bilateral lung opacities consistent with pulmonary edema on computered tomography or chest radiogram not explained by cardiac failure or fluid overload.

Exclusion criteria:

The study excluded patients suffering from (cardiac, hepatic, renal) disease or with unstable hemodynamic.

Study design:

Patients who met the previous criteria were enrolled in the study. The patients were randomized using closed envelop into two equal groups of 30 patients.

Patients were subdivided into:

Group A: PEEP was increased in steps of 2 cmH_2O every 20 minutes and changes in static compliance was calculated and monitored. The highest static compliance was considered to be the best PEEP. If at 2 different PEEPs the static compliance was identical, we chose the one with the lower PEEP.

Group B: PEEP was increased in steps of 2 cmH_2O every 20 minutes and changes in VCO_2 were monitored. If VCO_2 failed to recover to baseline value, the previous reading of PEEP was considered optimum PEEP.

Oxygenation goal: The oxygen goal was a minimum of PaO_2 55-80mmHg or SpO_2 88-95% as recommended by ARDS network trial [6].

Study intervention:

- *Baseline ventilation:* All patients were ventilated with Engström Carestation-GE ventilator, USA. The patients received volume controlled time cycled ventilation and the VT was maintained between (6-8ml/kg) of predicted body weight calculated in males as 50+0.91 [height (cm)-152.4] and females as 45.5+0.91 [height (cm)-152.4].

At baseline, fraction of inspired oxygen (FiO_2) was initially set at 40%, PEEP was set at 5cmH_2O and inspiratory to expiratory ratio at 1:2 while the plateau pressure (Pplat) and respiratory rate was set according to ARDSNET protocol [6].

- *Data collected:* Peak airway pressure and PEEP were collected using ventilator display. Plateau pressure was measured by using inspiratory hold button on ventilator for 3 seconds. Static compliance was calculated by measuring corrected tidal volume divided by (Plateau pressure-PEEP) and VA. VCO_2 from volumetric capnogram module readings of the ventilator by mainstream CO_2 sensor placed between the tracheal tube and ventilator tubing's was recorded.

- *Monitoring:* Patient's blood pressure was monitored by noninvasive blood pressure, Heart Rate (HR) and rhythm and SpO_2 using Nihon Kohden BSM-2301K, Japan monitor.

- *PEEP titration protocol:* Adequate sedation (Richmond agitation sedation scale score-5) [7] was achieved with continuous infusions of midazolam of 0.1mg/kg/h and paralyzed with bolus injection of 3mg cisatracurium as needed during PEEP titration and patient kept in supine position. A radial arterial catheter and triple-lumen central venous catheter (via the subclavian or internal jugular vein) was inserted for frequent sampling of arterial blood gas and central venous blood gas analysis respectively using the AVL-988.

After baseline ventilation, recruitment maneuver in the form of sustained application of PEEP at 40cmH_2O for 40 seconds then baseline hemoglobin level, arterial blood gas and central venous blood gas samples were obtained as input data for volumetric capnogram module.

- *Complications during study period:* Hemodynamic instability in the form of hypotension with a mean blood pressure value of less than 65mmHg was treated by incremental dose of 5mg ephedrine and PEEP change to previous level.

Weaning:

Weaning and extubation were done according to the preset weaning protocol of the SICU.

Statistical analysis:

The collected data were organized, tabulated and statistically analyzed using SPSS Version 19 (Statistical Package for Social Studies) created by IBM, Illinois, Chicago, USA. For numerical values the range mean and standard deviations were calculated. The differences between mean values of the two studied groups were tested using student's *t*-test. Differences of mean values between mean values at baseline and end of intervention were tested using paired *t*-test. For categorical variable, the number and percentage were calculated. The level of significance was adopted at $p<0.05$.

Results

Sixty patients who fulfilled the Berlin definition of ARDS [8] were enrolled. Demographic data and ARDS grade for each registered patient were collected (Table 1).

There was no significant difference values of PEEP applied between two groups ($p \leq 0.499$). The baseline values of SpO_2, PaO_2 and PaO_2/FiO_2 were comparable in both groups. Both groups showed a significant increase in SpO_2, PaO_2 and PaO_2/FiO_2 from baseline ($p \leq 0.001$ in both groups), with no significant difference between the two groups (Table 2).

The baseline values of VCO_2, VA and MAP were comparable in both groups. VA values were significantly improved in both groups ($p \leq 0.001$ in both groups), with no significant difference between the two groups. VCO_2 showed a significant increase from baseline ($p \leq 0.001$) in Group B with no significant difference between two groups. Two cases in Group A had a decrease in VCO_2 from baseline while one showed both a decrease in VCO_2 from baseline and MAP below 65mmHg. Despite that mean and standard deviation of MAP doesn't significantly change from baseline in both groups, and showed no significant difference between the two groups (Table 2).

The static compliance in both groups showed a significant increase from baseline values ($p \leq 0.001$ in both groups) with no significant difference between the two groups (Table 2).

Table (1): Comparison between demographic data between studied groups.

	Group A	Group B	χ^2	*p*
Sex:				
Males	20	22	0.317	0.57
Females	10	8		
Age:				
Range	16-57	16-62	*t*	*p*
Mean ± SD	37.62±11.75	38.14±13.83	0.73	0.67
Predicted body weight:				
Range	61-80	59-77	1.54	0.57
Mean ± SD	62.42±10.32	63.63±9.50		

Table (2): Comparison between measured data between the studied groups at baseline and end of intervention. Values are expressed as mean (±SD).

	Group A	Group B	*p*
Optimum PEEP:			
Baseline	5 (±0.0)	5 (±0.0)	0.499
End	11 .33±2.23	10.93±2.31	
p	0.001*	0.001*	
SPO2:			
Baseline	92.27±2.65	92.83±2.55	0.402
End	96.33±1.69	96.26±1.78	0.882
p	0.001*	0.001*	
PO2:			
Baseline	73.63±11.73	73.27±12.23	0.906
End	87.80±11.42	87.53±11.74	0.929
p	0.001*	0.001*	
PaO2/FiO2:			
Baseline	184.08±29.34	183.17±30.58	0.906
End	219.84±28.84	219.00±29.49	0.912
p	0.001*	0.001*	
VCO2:			
Baseline	218.30±37.99	221.37±44.582	0.775
End	217.60±40.96	225.10±46.42	0.5096
p	0.751	0.004*	
VA:			
Baseline	3.53±0.88	3.73±1.05	0.427
End	3.73±0.93	4.09±1.02	0.152
p	0.001*	0.001*	
Static compliance:			
Baseline	46.16±5.94	45.00±6.04	0.453
End	60.13±7. 83	58.00±7.43	0.284
p	0.001*	0.001*	
MAP:			
Baseline	86.83±16.47	90.00±17.76	0.477
End	85.27±17.43	89.50±17.57	0.353
p	0.1577	0.5006	

*: Significant <0.05.
Where:
SD : Standard Deviation.
PEEP : Positive End Expiratory Pressure in cmH2O.
FiO2 : Fraction of Inspired Oxygen expressed as %.
VA : Alveolar Ventilation in L/min.
VCO2 : Volume of Carbon Dioxide in ml/min.
SPO2. : Peripheral oxygen saturation in %.
PaO2 : Partial arterial oxygen tension in mmHg, Static compliance in mL/cm H2O.
MAP : Mean Arterial Blood pressure in mmHg.

Discussion

It is argued that adjusting PEEP using lung mechanic [4] or alveolar ventilation and hence CO_2 elimination [9] is superior to oxygenation in assessment of lung recruitment. In the current study we compared the use of static compliance vs. VCO_2 in determination of optimal PEEP.

To begin with, although not in ARDS patients, the comparability between combining VCO_2 and SPO_2 vs. dynamic compliance in detecting efficiency of gas exchange in obese patients undergoing recruitment to open collapsed lung was studied earlier by Tusman et al., [10]. Combining VCO_2 and SPO_2 demonstrated a high specificity to detect improvement in area of exchange during lung recruitment. However, in the study VCO_2 was not used to titrate PEEP and to the best of our knowledge was never used thereafter.

In the current study, determination of optimum PEEP by monitoring VCO_2 was associated with improvement of CO_2 elimination with comparable results regarding static compliance and oxygenation when compared with the use of static compliance in ARDS patients. It was not associated with hypotension or pneumothorax. On the other hand, while using static compliance to up-titrate PEEP, two case showed a decrease in VCO_2 with no recovery as early indicator of decrease cardiac output and one case developed manifest hypotension.

Improvement of oxygenation by using PEEP titration by VCO_2 was comparable to PEEP set according to static compliance. In both groups there was a significant increase ($p \leq 0.001$) in oxygenation parameters (SPO_2, PaO_2 and PaO_2/FiO_2) with no significant difference between two groups.

In agreement with the current study results, Tusman et al., [10] demonstrated an overall increase in oxygenation parameters while using static FIO_2 during recruitment set according to dynamic compliance. While VCO_2 was not used as a method for optimizing PEEP during recruitment, an increase in SPO_2 was also associated with increase in VCO_2.

In disagreement with the current study finding, a study by El-Baradey et al., [11] static compliance guided PEEP improved oxygenation but to a lesser extent than PEEP set according to Vd/Vt. A decrease in Vd/Vt although not measured in the current study, but can be reflected by changes in CO_2 elimination [12].

Pintado et al., [4] also, noted that although optimal PEEP determined by compliance had less organ dysfunction it has no significant effect on oxygenation.

Although improvement of oxygenation is targeted in ARDS patients, it was argued by Gattinoni et al., [9] that improved efficiency of alveolar ventilation and Hence, CO_2 elimination had better prognostic value of survival compared to PaO_2/FiO_2 ratio. Thus, in current study effect of PEEP on VCO_2 and VA were, also, analyzed.

Although there was no significant difference between the two groups at end of intervention, there was a significant increase in VCO_2 from baseline in Group B. In Group A three cases showed a decrease in VCO_2 with no recovery to baseline which may have contributed to the lack of significant difference in mean and standard deviation in this group from baseline.

In agreement with current study results, Tusman et al., [13] tabulated an overall increase in VCO_2 level by increasing PEEP from 6cmH $_2$O to 12 cmH$_2$O in lavaged lung animal.

In a human study later performed by Tusman et al., [10] they tabulated an increase in VCO_2 when compliance increase. This occurred in the current study in Group B but not Group A and could be explained by applying more than optimal PEEP in Group A which caused over-distention and/or a decrease in cardiac output and hence CO_2 delivery in some patients which decreased over all mean VCO_2.

The lack of significant increase in VCO_2 like in the current study in Group A was also, demonstrated in Ferrando et al study [14]. They found no significant difference in elimination of CO_2 when titrating PEEP according to dynamic compliance, which again may be explained by above optimal PEEP applied.

Both groups showed a significant increase in alveolar ventilation from baseline with no significant difference between two groups.

The current study finding of increased VA from baseline in Group A was in agreement with Tusman et al., human study [10]. They noted the effect of increasing PEEP levels (ascending limb of recruitment maneuver) on increasing alveolar ventilation taking VCO_2 as its marker.

In disagreement with current study finding, Tusman et al., [13] noted a decreased VA after 10 minutes of PEEP application in spite of the rise in VCO_2. This difference in results, however, cannot be explained as an increase in VCO_2 can only occur if alveolar ventilation increase and hence, CO_2 elimination. It may be due to the different timing of measuring VA. A ten minute window possibly didn't allow enough timing of VA recovery and increase from initial level.

Also, the current study findings were disagreement with Johnson et al., [15] results. They demonstrated a persistent decrease in VA after 20 minutes of PEEP application. This may be due to higher than optimal PEEP applied which cause a decrease in both VCO_2 and VA.

The lack of significant difference in VA between two groups in the present study may be explained by the fact that both groups benefited from comparable levels of PEEP and recruitment maneuvers at the beginning of procedure.

In the current study, the comparison of the static compliance resulting from optimal PEEP detection by two methods was done. This demonstrated a significant increase in the static compliance of both groups from baseline with no significant difference between two groups.

The effect of titrating PEEP by VCO_2 on static compliance was to the best of our knowledge never studied. An optimal PEEP improves static compliance. The current study suggest that VCO_2 guided PEEP improves static compliance, however, further studies are needed to confirm this finding.

Lastly, in current study, there was no reported cases developing pneumothorax. Mean arterial blood pressure showed no significant change from baseline in both groups and no significant difference between two groups. In spite that, one case in Group A developed hypotension and decrease in VCO_2 and two other cases showed a decrease in VCO_2 with no recovery to baseline which is an early indicator of decrease in cardiac output.

The deficiency of static compliance method in detecting over-distention of alveoli, hence causing complication was in agreement with El-baradey et al., [11] who concluded that static compliance guided PEEP is associated with an increase in Vd. Again since CO_2 elimination decrease if dead space decrease, the decrease in VCO_2 reported in group A, also suggest that static compliance guided PEEP cause over-distention of alveoli.

In disagreement with the current study finding, Pintado et al., [4] who compared compliance-guided PEEP group or an FIO_2-guided group concluded that using static compliance to detect optimal PEEP had no effect on patients' hemodynamics and resulted in more incidence of barotrauma and pneumothorax.

Conclusion:

Based on our results, we conclude that optimum PEEP determined by volumetric capnogram (VCO_2 monitoring) is associated with comparable improvement in oxygenation as well as lung compliance, while resulting is a significant an improvement in CO_2 elimination compared with optimum PEEP determined by static compliance in ARDS patients. It was, also, associated with no complication in terms of hemodynamic stability in contrast to optimum PEEP determined by static compliance which was associated with incidence of hemodynamic instability.

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إستخدام جهاز قياس حجم ثانى آكسيد الكربون فى تحديد ضغط نهاية الزفير الإيجابى الآمثل فى مرضى متلازمة الضائقة التنفسية الحادة

تعتبر متلازمة العسر التنفسى الحاد سببا رئيسيا للفسل التنفسى الحاد. ويؤدى تطورها إلى معدلات وفاة عالية، بالإضافة إلى مضاعفات قصيرة وطويلة الآجل، مثل الإعتلال الجسدى والإدراكى. ولذلك، فإن التمييز المبكر لهذه المتلازمة وتطبيق التدخلات العلاجية المثبتة يعتبر آساسيا لتغيير المسار الطبيعى لهذا الداء المدمر.

وقد تم تدابير عدة للتهوية الوقائية فى دراسات سريرية مختلفة فى السابق. وكنتيجة لذلك، آصبحت هذه التدابير قياسية لعلاج هؤلاء المرضى. على الرغم من هذا، فإن مستوى ضغط نهاية الزفير الآعلى المثالى لتهوية هؤلاء المرضى لم يتم تحديده بعد.

ومستويات ضغط نهاية الزفير الآعلى المثالية هيا تلك التى تحقق آقصى قدر من توصيل الآوكسجين للآنسجة دون آن تؤدى إلى تمدد زائد فى الحويصلات الهوائية آو تؤثر على الديناميكية الدموية للمريض. ويمكن تحديد مستوى ضغط نهاية الزفير الآعلى المثالى بإستخدام تدابير مختلفة ومن ضمنها إقترحت دراسات عديدة إستخدام المطاوعة الساكنة فى تحديد مستوى ضغط نهاية الزفير الآعلى المثالى وجادلت بالميزة الواضحة لإستخدامها فى تقدير تجنيد الرئة.

إن متابعة وتحليل التغيرات فى حجم ثانى آوكسيد الكربون الناتج لتحديد مستتوى ضغط نهاية الزفير الآعلى المثالى لم يتم إختياره حتى الآن. لهذا، فإننا فى الدراسة الحالة نضع فرضية إستخدامه لتحديد مستوى ضغط نهاية الزفير الآعلى المثالى، وذلك عن كمرشد للكشف المبكر عن الآعراض الجانبية لزيادة مستوى ضغط نهاية الزفير الآعلى على المخرج القلبى. وقد إفترضت الدراسة الحالة آن الفشل فى تعافى مستوى حجم ثانى آوكسيد الكربون الناتج إلى خط الآساس بعد تطبيق مستوى محدد لضغط نهاية الزفير الآعلى، آعلى من القيمة المثالية، سيتم ملاحظته مبكرا قبل إنخفاض المخرج القلبى. وقد تم تحديد مستوى ضغط نهاية الزفير الآعلى المثالى بإستخدام المطاوعة الساكنة فى مجموعة التحكم.