Journal of Advances in Medicine and Medical Research

34(9): 26-34, 2022; Article no.JAMMR.85254
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Efficacy of Titrating Positive End Expiratory Pressure Recruitment Versus Extended Sigh Recruitment by Volumetric Capnography in Patients with Acute Respiratory Distress Syndrome

Ahmed Kamal Taha [a*≡], Mohammad Ali Abdallah [a≡], Ghada Fouad Elbaradey [a≡] and Sohair Mostafa Soliman [a≡]

[a] Surgical Intensive Care and Pain Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2022/v34i931345

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/85254

Original Research Article

Received 02 February 2022
Accepted 04 April 2022
Published 20 April 2022

ABSTRACT

Background: The rationale for recruitment maneuvers is to open the atelectatic alveoli, thus increasing end expiratory lung volume, improving gas exchange, and attenuating ventilator induced lung injury. The study aimed to assess the efficacy of titrating positive end expiratory pressure recruitment versus extended sigh recruitment by volumetric capnography in patients with acute respiratory distress syndrome.
Methods: Seventy patients were randomly allocated into two equal groups according to plan for ventilator management of ARDS by protective lung strategy according to ARDS network. Group I (n= 35) titrating PEEP recruitment, and Group II (n= 35) extended sigh recruitment. The primary outcome measure was mortality in the first 28 days wheras the secondary outcome measures were changes in static compliance, dead space to tidal volume ratio, ventilation / perfusion ratio, duration of mechanical ventilation, weaning outcomes, oxygenation and hemodynamic data.
Results: There was no statistically significant difference in 28^{th} day mortality in both groups in group 1, 10 patients were died (28.57%)**,** In group II, 12 patients were died (34.28%) (p value =0.607), wheras there was significant increase regarding static compliance ml/cm H_2O, ventilation /

[≡] *Anesthesiology*
**Corresponding author: E-mail: thesismse@gmail.com;*

perfusion ratio (p value =0.003. 0.001 respectively) and significant decrease regarding dead space to tidal volume ratio in group I compared to group II, 15 minutes after recruitment and significant decrease in duration of mechanical ventilation (days) in group I compared with group II (p value = 0.014, 0.04 respectively). There was a significant difference in weaning categories between both groups with better outcomes in favor of group I (p value = 0.034). The findings of this study presented that there were no significant difference regarding other measurements.

Conclusion: Titrating PEEP recruitment was better than extended sigh recruitment as regard weaning outcomes and duration of mechanical ventilation, which may be due to improvement in aerated lung volume, reflected on decreased dead space to tidal volume ratio, better ventilation perfusion ratio and static compliance.

Keywords: PEEP; lung recruitment; ARDS; volumetric capnography; oxygenation.

1. INTRODUCTION

Acute respiratory distress syndrome (ARDS) is an acute severe lung disease commonly encountered in intensive care units (ICU). The pathophysiology of ARDS is characterized by broncho-alveolar injury and atelectasis [1]. “Recruitment maneuver denotes the dynamic process of an intentional transient increase in trans-pulmonary pressure aimed at opening unstable airless alveoli” [2].

“The rationale for recruitment maneuvers is to open the atelectatic alveoli, thus increasing end expiratory lung volume, improving gas exchange, and attenuating ventilator induced lung injury (VILI). However, recruitment maneuvers may also contribute to VILI, with translocation of pulmonary bacteria and cytokines into the systemic circulation” [3].

Extended sigh (ES) is designed to achieve sufficient pressure and avoid excessive airway pressure in the lung with ARDS. It was designed to mimic the mechanistic scheme and physiologic effect in patients with ARDS. “It is capable of achieving an augmented recruiting pressure and time through a prolonged inflation on a gradually increased end-expiratory pressure” [4].

Volumetric capnogram measures carbon dioxide concentration plotted against expired volume. Therefore, volumetric capnogram can simultaneously measure both expired CO2 and tidal volume, dead space, V/Q (Ventilation / Perfusion), cardiac output (C.O.), alveolar ventilation and many other clinical application [5].

Volumetric capnography is a promising, non-invasive, inexpensive and breath by breath measurement that used as bedside monitoring tool for mechanically ventilated critically ill patients, allowing for improved monitoring for ventilatory interventions as lung recruitment and positive end expiratory pressure titration [6]. This prospective study suggested that the effect of titrating PEEP in reducing values of dead space fraction, the percentage of non-aerated tissue, and increased percentage of normally aerated tissue.The aim of this study was to assess the efficacy of titrating positive end expiratory pressure recruitment versus extended sigh recruitment in ARDS by using volumetric capnography.

2. METHODS

This prospective randomized study was carried out at surgical intensive care unit (SICU) in Tanta University Hospitals for a period of 18 months from Marsh 2020 to Septemper 2021. Every relative was receiving an explanation of the purpose of the study, and the photos applied only to the research, and had a secret code number to ensure privacy to participants and confidentiality of data.

Criteria of study inclusion were as follows : adult patients (≥18 years) that admitted to the surgical ICU on mechanical ventilation and fulfilling Berlin Definition [7] to confirm the criteria of ARDS with moderate to severe grade of ARDS

Patient with congestive heart failure, valvular or ischemic heart diseases, patients with uncontrolled respiratory morbidity such as severe bronchial asthma or COPD, patients with renal and endocrine disorders, patients with hepatic dysfunction or with history of cerebrovascular disease and patients with haemodynamic instability were excluded from the study.

Patients were randomly allocated into two equal groups according to plan for ventilator management of ARDS through the aid of

computer generated software of randomization introduced into sealed opaque envelope: Group I (n= 35) (Titrating PEEP recuritment) & Group II (n= 35) (Extended sigh recruitment).

2.1 Initiation of Mechanical Ventilation

All the Patients included in the study were managed by protective lung strategy according to ARDS network by (CARESCAPE R860 – GE, USA) ventilator using volume assist-control mode, with tidal volume (TV) 4 to 8 mL/kg, predicted body weight (PBW). Reduce Vt by 1 ml/kg at intervals ≤ 2 hours until Vt = 6ml/kg PBW. Initial respiratory rate (RR) was set to approximate baseline minute ventilation (not > 35 cycle/min). Tidal volume Vt and RR were set to achieve pH (Goal: 7.30-7.45) and plateau pressure (Goal: ≤ 30 cm H2O). Fraction of inspired oxygen (FiO2) at base line was set to maintain adequate oxygenation (PaO2 60-80 mmHg or SpO2 90-95%).Adequate sedation according to Richmond agitation sedation scale score (-5) was achieved with continuous infusions of midazolam 0.1 mg/kg/h and fentanyl 1 □g/kg/hr. Patients were paralyzed with bolus injection of 0.03mg/kg cis-atracrurium during PEEP titration.

Group I: (Titrating PEEP) Recruitment maneuver (RM) was performed as following :changing mode of ventilation to pressure controlled ventilation (PCV) and keeping the driving pressure (plateau pressure – PEEP) ≤ 15 cmH_2o and escalating of PEEP by 2 cmH_2O every 2 breaths and till peak inspiratory pressure not exceed 40 cmH_2O then deescalating PEEP by 2 cmH_2o every 2 breaths.After application of this recruitment maneuver, derecruitment was prevented by applying a PEEP level achieving maximum dynamic respiratory compliance plus 2 cmH2O above this PEEP value.

Group II: (Extended sigh) Recruitment maneuver (RM) was performed on volume control mode with pressure limit 40 cmH_2O then applied as following : The V_t (ml/kg) - PEEP(cmH_2O) values will be changed to 6-15, 4-20, and 2-25, each step being 30 seconds (inflation phase). After V_t-PEEP 2-25, the mode switched to CPAP of 30 cmH_2O for a duration of 30 seconds (pause), after which the baseline setting resumed following the reverse sequence of inflation (deflation phase). This maneuver, which is called extended sigh, performed twice with one minute of baseline ventilation in between.After application of this recruitment maneuver, derecruitment was prevented by applying a PEEP equal to the lower inflection point (LIP) determined in P-V curve + 2 cmH_2O. If the LIP couldn't be determined, the PEEP was set at 10 cmH_2O.

Routine monitoring of heart rate &rhythm by ECG, non-invasive blood pressure (NIBP), peripheral oxygen saturation (Spo2) using pulse oxymeter and volume of carbon dioxide (VCO_2) were performed.

2.2 Outcome Measures

The primary outcome measure was mortality in the first 28 days wheras the secondary outcome measures were changes in static compliance, dead space to tidal volume ratio, ventilation / perfusion ratio, duration of mechanical ventilation, weaning outcomes, oxygenation and hemodynamic data.

Incidence of mortality at 28^{th} day in both groups. Haemodynamic parameters as Heart rate, mean arterial blood pressure, SPO_2, and the dead space to tidal volume ratio (Vd/Vt) were recorded before the beginning of the alveolar recruitment and at 15 minutes after the end of alveolar recruitment.

Arterial blood gas was analyzed as regarding arterial PaO_2, and (PaO_2 / FiO_2) ratio, and The static compliance of the respiratory system (Cstatic) were recorded before the beginning of the alveolar recruitment and 15 minutes after the end of alveolar recruitment.

Ventilation /perfusion ratio (V/Q ratio %) was recorded before the beginning of the alveolar recruitment and 15 minutes after the end of alveolar recruitment. V is ventilation of the air that reaches the alveoli wheras Q is perfusion of the blood that reaches the alveoli via the capillaries. It is a derived data calculated by dividing alveolar ventilation by cardiac output which obtained from the output data of volumetric capnography through the metabolic module.

Weaning categories were recorded [8]. Duration of mechanical ventilation in days (patients who died early during their management, their data were recorded till death)in both groups.

2.3 Statistical Methods

2.3.1 Sample size

The calculation of sample size using the Epi-Info software statistical package (version 2002)

created by World Health Organization (WHO) and Center for Disease Control (CDC) and Prevention, Atlanta, Georgia, USA. The number of patients in the sample size was calculated at N = 35 in each group as a result of 95% confidence interval (CI), power of the study 80%, group 1 : group 2 ratio is (1: 1). Five patients were added in each group to prevent drop out.The primary outcome was (incidence of mortality at 28th day).

2.3.2 Statistical analysis

Data were analysed using SPSS Version 24 (IBM Corporation, Armonk, NY). Categorical variables were presented as absolute numbers and percentages. Continuous variables were presented as mean values with standard deviations or median with an interquartile range. To compare data between groups, the chi-square test or the student t-test or the Mann-Whitney test were used to analyse to variable data as appropriate. A paired t-test or the Wilcoxon test was used for intragroup comparison as appropriate. The statistically significant difference was less than 0.05 of a 2 tailed P value.

3. RESULTS

In this study, 105 patients were assessed for eligibility, 30 patients did not meet the criteria and 5 patients' relatives refused to participate in the study. The remaining 70 patients were randomly allocated into two groups (35 patients in each one). All patients were followed-up and analyzed statistically (Fig. 1).

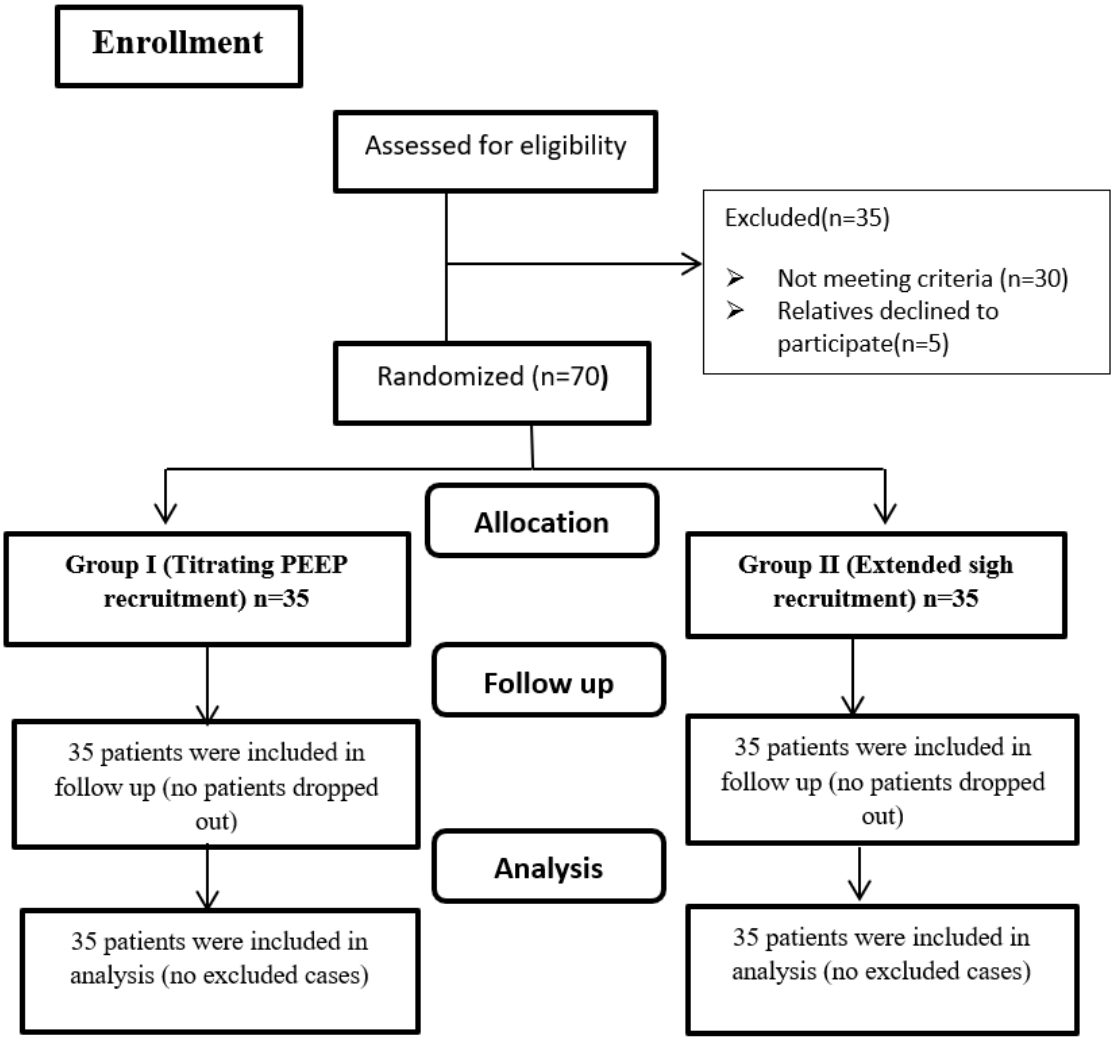

Fig. 1. Consort flowchart of the study groups

There were no significant difference regarding demographic data (age, weight and sex) (Table 1), heart rate (b/m) (p value = 0.706), mean arterial pressure (mmHg)) (p value =0.255) Fig. (2, 3), peripheral oxygen saturation % (Spo2 %) (p value = 0.879), partial arterial oxygen tension Pao2 (mmHg)) (p value = 0.916), Pao2 / Fio2 ratio) (p value = 0.452) (Table 2), incidence of 28th mortality day in both groups In group I, 10 patients were died (28.57%) and the day of mortality ranged from 4th to 10th with (Mean ± SD) 6.3 ± 2.06, In group II, 12 patients were died (34.28%) and the day of mortality ranged from 4th to 11th with (Mean ± SD) 6.75 ± 2.38 (Fig. 4).

Table 1. Demographic data of the studied groups

	Group I	Group II	P value
Age (years) (mean ± SD)	45.6 ± 12.08	42 ± 11.55	0.207
Body Weight (Kg)	69.69 ± 7.22	72.54 ± 6.02	0.076
Gender (F/M)	15 /20	18 /17	0.147

Data are presented as mean ± SD

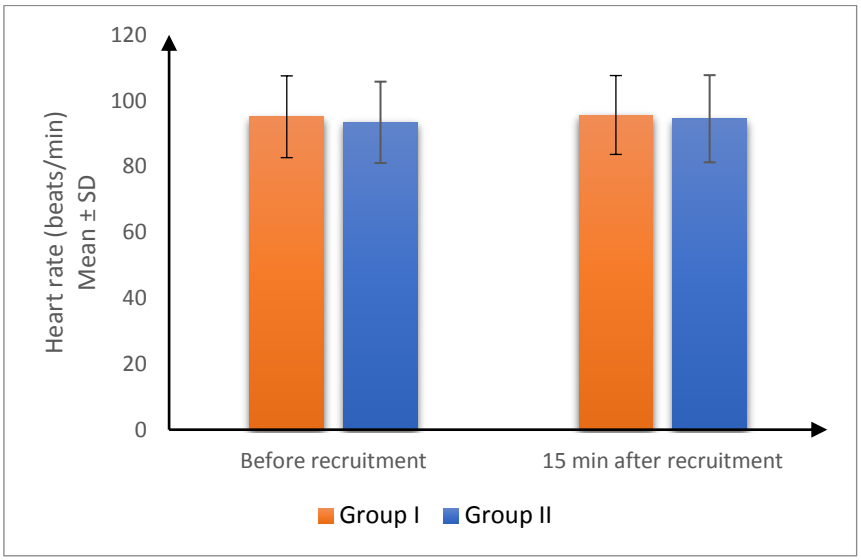

Fig. 2. Heart rate (b/ min) in both groups

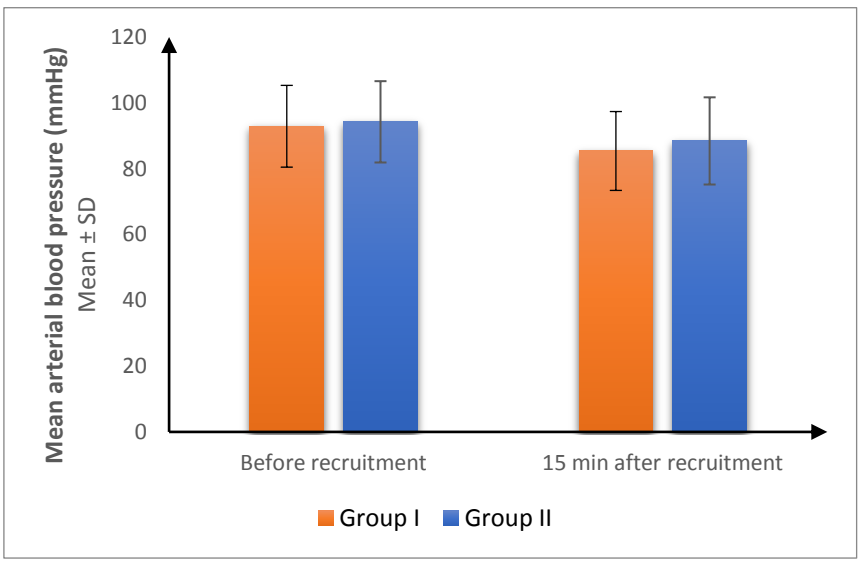

Fig. 3. Mean arterial blood pressure (mmHg) in both groups

There was significant increase regarding static compliance (Cstatic) ml/cm H2O and ventilation / perfusion ratio (V/Q ratio) in group I compared to group II 15 minutes after recruitment (p value =0.003 and 0.001 respectively) (Table 2).

There was significant decrease regarding dead space to tidal volume ratio (Vd / Vt ratio) in group I 15 minutes after recruitment and there was significant decrease in duration of mechanical ventilation (days) in group I compared with group II (p value = 0.014, 0.040 respectively) (Table 2).

There was a significant difference in weaning categories between both groups with better outcomes in favor of group I (p value = 0.034) (Table 3). There were no recorded complications as pneumothorax and hemodynamic instability in both groups.

Table 2. Oxygenation, static compliance, dead space to tidal volume ratio (Vd/Vt), ventilation / perfusion ratio (V/Q ratio) and duration of mechanical ventilation

		Group I	Group II	P value
Peripheral oxygen saturation (Spo_2) %	**Before recruitment**	92.00 **± 1.51**	91.97 **± 1.32**	**0.933**
	15 min after recruitment	94.03 ± 1.62	94.09 ± 1.52	0.879
	P value	< 0.001 *	< 0.001 *	
Partial arterial oxygen tension PaO_2 (mmHg)	Before recruitment	65.29 ± 5.1	64.74 ± 4.58	0.641
	15 min after recruitment	75.37 ± 9.32	75.6 ± 8.76	0.916
	P value	< 0.001*	< 0.001*	
PaO_2 / FiO_2	Before recruitment	144.09 ± 34.88	149.17 ± 29.18	0.511
	15 min after recruitment	166.80 ± 44.06	174.26 ± 38.31	0.452
	P value	< 0.001*	< 0.001*	
Static compliance of the respiratory system (Cstatic) mL/cm H_2O	Before recruitment	27.11 ± 3.68	27.23 ± 3.28	0.891
	15 min after recruitment	31.47 ± 3.78	29.06 ± 3.44	0.003*
	P value	< 0.001*	0.001*	
Dead space to tidal volume ratio (Vd/Vt)	Before recruitment	0.401 ± 0.024	0.393 ± 0.032	0.243
	15 min after recruitment	0.368 ± 0.027	0.386 ± 0.033	0.014*
	P value	< 0.001*	0.058	
Ventilation / perfusion ratio (V/Q ratio)	Before recruitment	51.94 ± 4.98	52.74 ± 5.08	0.508
	15 min after recruitment	71.77 ± 2.97	62.11 ± 4.86	<0.001*
	P value	< 0.001*	<0.001*	
Duration of mechanical ventilation (days)		7.31 ± 3.55	9.26 ± 3.55	0.04*

** significant as P value <0.05. Data are presented as mean ± SD*

Table 3. Weaning categories in both groups

	Group I (25 survivors)	Group II (23 survivors)	P value
Simple	10	5	
Difficult	8	3	0.034*
Prolonged	7	15	

** significant as P value <0.05*

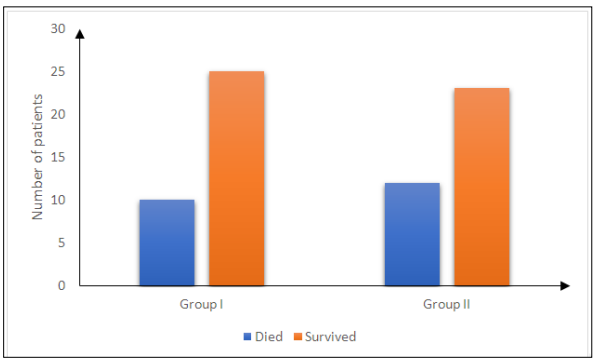

Fig. 4. Number of patients died and survived in both groups

4. DISCUSSION

Acute respiratory distress syndrome (ARDS) is a common life threatening condition in critically ill patients, associated with a high mortality" [9]. "Atelectasis formation in patients with ARDS can reduce the proportion of aerated lung available for ventilation and further exacerbate ventilation induced lung injury (VILI) by amplifying stretching forces at margins between aerated and atelectatic regions" [10].

"The non aerated lung volume can be separated into recruitable lung volume, which can be aerated, applying an appropriate level of pressure to the lung, and consolidated lung volume, which remains unrecruitable no matter the applied pressure" [11]. "Lung recruitment maneuver (LRM), which involves transient increase in transpulmonary pressure, aims to reopen recruitable lung units" [12]. "Along with the positive end expiratory pressure (PEEP), which helps to keep the lung units recruited and to reduce atelectasis, LRM has been used to manage ARDS by opening alveoli and keeping them open" [13].

In accordance with our results, Fengmei et al [14] "found that arterial oxygenation values and functional residual capacity were increased gradually during PEEP increasing. They found that Vd/Vt was significantly lower at 12 cmH_2O, and compliance of the static respiratory system was significantly higher at pressure step 12/10 cmH_2O". Also, Fan et al.[12] used incremental PEEP recruitment and CPAP at 40 cmH_2O and found that oxygenation was significantly increased after RM. They demonstrated that LRMs were not associated with reduced 28th day mortality. Moreover, Cavalcanti et al.[15] found that lung recruitment maneuvers were effective in raising arterial oxygen tension and functional residual capacity. The recruitment manuovers were well tolerated hemodynamically.

Lim et al.[4] devised a new form of sigh (extended sigh) capable of achieving an augmented recruiting pressure x time through a prolonged inflation on a gradually increased end expiratory pressure in patients with ARDS. They demonstrated that major hemodynamic and respiratory complications were not noted during the study as compared with pre extended sigh and Pao2 was increased in post extended sigh. Furthermore, Huh et al [16]. demonstrated that initial oxygenation improved more in the decremental PEEP titration group and 28th mortality days did not differ significantly between both groups. Also, Bhattacharjee S et al [17] found that use of recruitment maneuver by PEEP titration does not provide any benefit in terms of mortality, length of ICU, and hospital stay in ARDS patients.

In addition, Yu et al.[18] who evaluated "the efficacy and safety of protective lung ventilation strategy combined with lung recruitment maneuver (RM) in the treatment patients with acute respiratory distress syndrome (ARDS) in totally 74 patients.They found that PaO2 and PaO2/FiO2 of RM group were significantly higher than those of non-RM group". Also Hodgson et al.[19] who examined the effectiveness and safety of a novel open lung strategy, which includes staircase recruitment manoeuvres (SRM) and low airway pressure with PEEP titration. They found that PaO2/FIO2 was higher in the treatment group than the control group over seven days, but in disagreement with our study no difference in duration of mechanical ventilation between both groups. Moreover, Goligher et al.,[20] who conduct "a systematic review and meta-analysis of randomized trials including 1423 patients comparing mechanical ventilation strategies with different. They reported that the rate of hemodynamic compromise was not significantly increased with LRMs, but in disagreement to our results, They demonstrated that LRMs in combination with a higher PEEP ventilation strategy reduce mortality".

In contrast to our results, Campagna and Carter [21] showed "another assumption is that the sigh manoeuvre may precipitate a similar pattern in intrathoracic pressure as the valsalva manoeuvre, hence producing reduction in heart rate and as opposed to the previous findings, Lim et al. [4]reported an increased heart rate, perhaps reflecting just a sympathetic response to the lengthy recruitment procedure" which lasted for 3.5 minutes and the study done by Dan stieper karbing et al.[22] in which there were "12 ARDS patients subjected to recruitment maneuvers followed by setting PEEP at 5 and then either 15 or 20 cmH2O. They found that increasing PEEP resulted in reduced values of pulmonary shunt and the percentage of non-aerated tissue. They concluded that improved lung aeration following an increase in PEEP is not always consistent with reduced shunt and V/Q mismatch". On the other hand, Goligher et al.,[20] who" conducted a systematic review and

meta-analysis of randomized trials. They demonstrated that LRMs in combination with a higher PEEP ventilation strategy reduce mortality".

This study has some limitations such as: Sample size was relatively small and may need further studies with increasing sample size. More randomized trials need to be conducted to verify the findings of our study. Lung recruitability was tested over a fixed changes in PEEP and lack of wider range of PEEP is a limitation to completely assess the potential for recruitment especially in extended sigh recruitment. Accurate identification of potentially recruitable lung volume is difficult and bedside tools as electrical impedance tomography, and lung ultrasound may be useful to guide the ventilation**.**

The concurrent study recommends using PEEP titration in patients with moderate and severe ARDS. Additional studies including a large number of patients are required for generalization of these results. Also, further studies assessment for recruitment as P/V Loop and Neurally adjusted ventilatory assist (NAVA) is a form of partial ventilatory support in the machine applies positive pressure to the airway opening throughout each inspiration. Further research is needed to define the diagnostic value and potential utility of Vcap for routine use in intensive care unit.

5. CONCLUSION

Although there was no difference between titrating PEEP recruitment and extended sigh recruitment as regard to oxygenation and mortality. Titrating PEEP recruitment was better than extended sigh recruitment as regard weaning outcomes and duration of mechanical ventilation which may be due to improvement in aerated lung volume, reflected on decreased dead space to tidal volume ratio (VD/VT), better ventilation perfusion ratio (V/Q) and static compliance.

Monitoring of VD/VT and (V/Q) % by volumetric capnography were useful tools for detecting lung collapse and for establishing optimal PEEP after a recruitment maneuver and monitoring of efficacy of gas exchange.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

After the institutional ethical committees' approval with registration number (**31550/05/17**), a written informed consent was obtained from all participants' relatives.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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