EGYPTIAN JOURNAL OF ANAESTHESIA
2020, VOL. 36, NO. 1, 31–37
https://doi.org/10.1080/11101849.2020.1741253

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Lung ultrasound- versus FiO_2-guided PEEP in ARDS patients

Mai S. Salem, Hesham S. Eltatawy, Ahmed A. Abdelhafez and Salah El-din I. Alsherif

Department of Anesthesia, Surgical Intensive Care and Pain Medicine, Tanta University Hospitals, Tanta, Egypt

ABSTRACT

Background: Although FiO_2-determined PEEP is the standard in ARDS management, previous trials failed to show agreement on outcomes. Based on heterogeneous ARDS pathology, we evaluated the effect of LUS-determined PEEP on oxygenation and outcomes.
Methods: In this prospective, controlled trial, we randomly assigned 60 patients into LUS-determined PEEP (group I) and FiO_2-determined PEEP (group II). LUS-determined PEEP was based on LUS aeration score. Primary outcome was P/F ratio, secondary outcomes were; static compliance, 28-day mortality, duration of MV and length of ICU-stay.
Results: P/F ratio was 266 ± 44.5 in group I, 233 ± 53.9 in group II. Static compliance was 54.8 ± 6.6 in group I, 45.9 ± 3.8 in group II. IQR of duration of MV was 4–6 with a median value of 5 in group I, 6–11.7 with a median value of 7.5 in group II. 28-day mortality was 6.7% in group I, 30% in group II. The relative risk of mortality in group II is more or less 5 times in group I (RR 4.87 with 95%CI of 1.492–15.893). IQR of organ dysfunction-free days was 16–19 with a median value of 18 in group I, 0–12 with a median value of 10 in group II. IQR of MV-free days was 22–24 with a median value of 23 in group I, 0–22 with a median value of 20 in group II.
Conclusion: LUS-guided PEEP showed improved oxygenation, compliance and decreased mortality, organ dysfunction, duration of MV and ICU compared with FiO_2-guided PEEP.

ARTICLE HISTORY
Received 13 November 2019
Accepted 10 February 2020

KEYWORDS
ARDS; optimal PEEP; oxygenation; 28-day mortality; lung ultrasound guided PEEP

1. Introduction

Applying the optimal level of Positive End Expiratory Pressure (PEEP) is the main component in the treatment of Acute Respiratory Distress Syndrome (ARDS) [1]. Optimal PEEP is the value that ensures the best lung recruitment, resulting in enhancement of oxygenation without lung hyperinflation or affection of hemodynamics [2]. There is no gold standard method for optimal PEEP determination [3].

Lung morphology varies among patients with ARDS, either focal ARDS in which dependent areas are usually affected, or diffuse ARDS in which both dependent and nondependent areas are affected [4].

The rationale of our study is based on the fact that LUS can easily evaluate the heterogeneous distribution of aeration loss in ARDS. So we hypothesized that LUS can be used to individualize titration of PEEP to produce the best lung reaeration.

Our study was conducted to evaluate the efficacy of setting PEEP level guided by LUS in comparison with that guided by FiO_2 in ARDS patients.

Determination of PaO_2/FiO_2 was the primary outcome. Secondary outcomes were; static compliance, haemodynamics (MAP and HR), the incidence of barotrauma and organ dysfunction, time spent on mechanical ventilation, length of stay in ICU, weaning categories, number of days free of organ dysfunction, number of days without ventilatory support and mortality at day 28.

2. Methods

This prospective, randomized, controlled study was carried out in University Hospitals of Tanta. An approval of ethical committee was obtained, code 31679/07/17. Informed written consent was obtained from the relatives of all patients. Enrolled patients were placed on a ventilator in ICU. Every patient had a secret code number. All data and results used for current research only. Our study included patients who aged 18 years or older and fulfilling Berlin definition to confirm the criteria of ARDS.

We excluded pregnant patients and those suffering from haemodynamic instability, barotrauma, and organ/s dysfunction at presentation.

3. Study design

All patients fulfilling the criteria were enrolled in our study and ventilated using volume control mode. Tidal volume (TV) was set at 4 to 8 mL/kg, calculated on predicted body weight. Throughout the study, plateau pressure was kept less than 30 cmH_2O by reducing TV in 1 ml/kg steps to levels as low as 4 ml/kg. FiO_2 level was set to maintain accepted oxygenation (SpO_2 88–95% or PaO_2 60–80 mmHg). At first, FiO_2 was initially set at 40% and then increased if target oxygenation was not met. PEEP was set at 5cmH_2O, while the respiratory rate was set to maintain adequate minute

CONTACT Mai S. Salem Dr_mai.s.salem91@hotmail.com Faculty of Medicine, Department of Anesthesia, Surgical Intensive Care and Pain Medicine, Tanta University Hospitals, Tanta, Gharbya 35128, Egypt

ventilation and to keep the arterial pH >7.25 to 7.44. Inspiratory to expiratory ratio was 1:2. Patients received sedation using continuous infusion rate of midazolam of 0.1 mg/kg/h, and paralyzed with a bolus injection of 3 mg cisatracurium as needed during PEEP titration, and kept in a supine position.

The patients were randomized using closed envelope into LUS group (group I) and FiO_2 group (group II), 30 patients in each of them. In group I, optimum PEEP was determined by values obtained using lung ultrasound score of aeration as follows;

Examination of the anterior area of the chest wall was done using PEEP value of 5 cmH2O. When it revealed normal ultrasound pattern that reflects a focal aeration loss, cases were managed by using PEEP values equal to 10 cmH_2O or less. When lung ultrasound examination of the anterior chest wall showed abnormal ultrasound pattern that signified a diffuse loss of aeration, cases were managed by PEEP values equal to 12 cmH_2O or more. The LUS score was calculated as follows;

Each hemithorax was divided into six regions. For each region, points were calculated according to the worst observed pattern.

Normal ultrasound pattern = 0, well-separated B-lines pattern = 1, coalescent B-lines pattern = 2, and consolidation pattern = 3.

The score was calculated by the sum of points in each region and ranged from 0 to 36 [5].

Any increase in the score obtained, indicated a decrease in lung aeration [6].

At each value of PEEP, lung reaeration was evaluated by LUS score of aeration, and the value that produced the highest recruitment, considered optimal and used. While in group II Optimum PEEP was determined using FiO_2-PEEP combination, the oxygenation goal was a minimum of PaO_2 60–80 mmHg or SpO_2 88–95% as recommended by ARDS network trial, by considering the use of incremental FiO_2/PEEP combination [7]. Titration was continued till reaching the plateau oxygen saturation and the least combination which produces the same oxygen saturation was considered optimal (Table 1).

4. Data collection

For all registered patients, the following data were collected; demographic data (age and gender), cause and severity of ARDS, PaO_2/FiO_2, static compliance, mean arterial pressure (MAP), heart rate (HR), any adverse events and organ dysfunction.

Duration of ventilatory support, duration of stay in ICU, weaning categories, 28-day mortality, number of days free from organ dysfunction and number of days without assisted breathing at the day 28 were also recorded.

5. Sample size calculation

It was calculated using Epi–Info software statistical package that was 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 following criteria used for calculation of sample size:

Power of the study was 80%, 95% confidence interval limit, the ratio between experimental group and control group was 1:1. The outcome of the control group (oxygenation PaO_2/FiO^2) was 55% while in the experimental group was 88%.

Quantitative normally distributed variables were expressed by mean ±SD and compared using the student test and non-normal distribution variables were expressed by median and interquartile range and then compared by Mann Whitney test, while qualitative variables were presented by percentages and compared by Chi-Square test. The Kaplan-Meier analysis was used to compare 28-day survival between the two groups.

6. Results

In our study 70 patients assessed for eligibility, 10 of them were excluded (Figure 1):

(1) Patients not meeting the inclusion criteria.
(2) Patients with brain insult at the time of presentation.
(3) Three patients with hypotension.
(4) Three patients whose relatives declined to participate.

Sixty included patients in our study were classified into two groups.

PEEP in group I was determined using LUS while in group II using FiO_2-PEEP chart (Table 1).

ARDS patients in the LUS group were classified into 70% with focal ARDS and 30% with diffuse ARDS (Table 2).

LUS score of aeration showed a statistically significant decrease at the end of mechanical ventilation (MV) in the LUS group (Table 2).

Table 1. FiO_2/PEEP combinations [7].

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 Pressure.

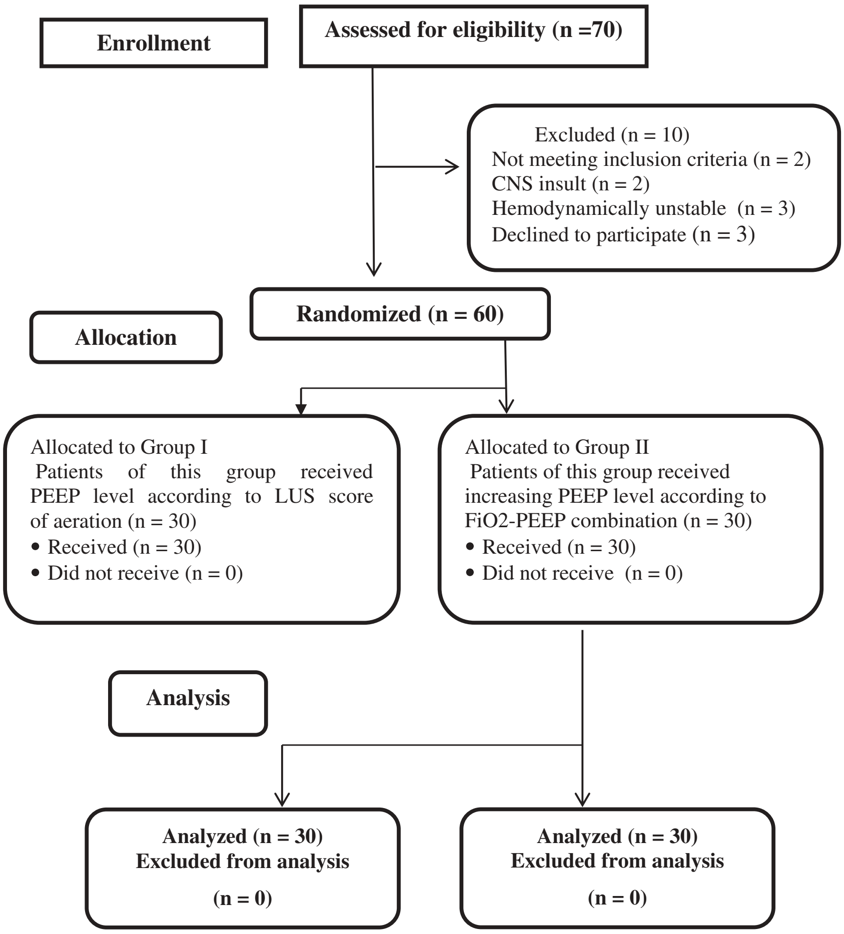

Figure 1. Patient flowchart summarizing enrollment, allocation, follow-up and analysis in the study protocol.

Table 2. LUS classification and score of aeration in group I.

Variables			P value
LUS classification			
Focal	21 (70%)		
Diffuse	9 (30%)		
Score of aeration	**Baseline**	**End**	
Median	12.5	2	<0.001*
IQR	12–18	2–3	

*significant if P < 0.05.
LUS: Lung ultrasound.
IQR: Interquartile range.

According to demographic data, no statistically significant difference was found between both groups (Table 3).

Classification and etiology of ARDS were stated in (Table 3).

Oxygenation (PaO_2/FiO_2 ratio) and static compliance (ml/cm H_2O) in the LUS group showed significantly higher values than those in FiO_2 group at the end of mechanical ventilation (Table 3).

No statistically significant difference was found between both groups concerning MAP and HR (Table 3).

SOFA score: Length of ICU stay and duration of MV values were significantly higher in FiO_2 group than LUS group (Table 3).

No statistically significant difference was recorded between both groups regarding the incidence of complication as hypotension and barotrauma (Table 3).

Organ dysfunction-free days and days with unassisted breathing at day 28 showed significantly higher values in the LUS group than the FiO_2 group (Table 3).

Survival rate was significantly higher in the LUS group compared with FiO_2 group (Table 3) (Figure 2).

Regarding weaning categories, no statistically significant difference recorded between both groups (Table 3).

7. Discussion

Our study demonstrated that lung ultrasound is a reliable method for optimal PEEP determination in ARDS patients. This came in agreement with Bouhemad et al. [6] who studied the role of LUS in the assessment of PEEP induced lung recruitment, they concluded that significant correlation was founded between LUS reaeration score and PEEP induced increase in oxygenation and this indirectly confirmed accuracy of LUS in the determination of PEEP induced lung recruitment.

Also, it is non-invasive, low cost, fast, repeatable and does not require patient transportation outside the ICU [8]. It is as reliable as CT as came in the study done by Algieri et al. [9] comparing transthoracic LUS and CT in the assessment of lung aeration, and found a good correlation between them.

Table 3. Patients' characteristics, oxygenation, and secondary outcomes.

Variables	LUS	FiO2-PEEP	P value
Sex			
Males	18(60%)	17(56.7%)	0.793
Females	12(40%)	13(43.3%)	
Age (years)	20–80	18–70	0.278
Classification			
Mild	10 (33.3%)	10 (33.3%)	0.892
Moderate	18 (60.0%)	17 (56.7%)	
Severe	2 (6.7%)	3 (10.0%)	
Causes			
Sepsis	7 (23.3%)	9 (30%)	0.993
Aspiration	7 (23.3%)	6 (20%)	
Pneumonia	3 (10%)	3 (10%)	
Drowning	1 (3.3%)	0 (0%)	
Toxins	2 (6.7%)	2 (6.7%)	
Pancreatitis	1 (3.3%)	2 (6.7%)	
Lung contusions	3 (10%)	2 (6.7%)	
TBI (traumatic brain injury)	3 (10%)	3 (10%)	
TRALI (transfusion related acute lung injury)	2 (6.7%)	2 (6.7%)	
Burn	1 (3.3%)	1 (3.3%)	
Optimal PEEP			
Median	10	8	0.035*
IQR	8–13.5	8–10	
PaO2/FiO2	266 ± 44.5	233 ± 53.9	<0.001*
Static compliance (ml/cmH2O)	54.8 ± 6.6	45.9 ± 3.8	<0.001*
MAP	74.86 ± 9.23	71.26 ± 7.18	0.1
HR	82 ± 7.57	83 ± 9.66	0.6
Side effects			
Barotrauma	0 (0%)	1 (3.3%)	1
Hypotension	2 (6.7%)	5 (16.7%)	0.78
SOFA score			
Median	1.5	3	<0.001*
IQR	1–2	2–4	
Duration of MV(days)			
Median	8	12	<0.001*
IQR	4–6	6–11.7	
Length of ICU(days)			
Median	8	10	<0.001*
IQR	6–16	0–12	
Organ dysfunction Free days			
Median	18	10	<0.001*
IQR	16–19	0–12	
Ventilator free days			
Median	23	20	<0.001*
IQR	22–24	0–22	
Weaning categories			
Simple	15 (50%)	13 (43%)	0.116
Difficult	12 (40%)	7 (23%)	
Prolonged	1 (3.3%)	1 (3.3%)	
No weaning	2 (6.7%)	9 (30%)	
28-day mortality	2 (6.7%)	9 (30.0%)	0.041*
Survival analysis			
Mean of survival	27	25.33	0.024*
Standard error	0.69	0.98	
95% CI for the mean	25.6–28.3	23.4–27.2	
Hazards ratio	4.87		
95% CI	1.49–15.89		

*significant if $P < 0.05$.
TBI: Traumatic brain injury.
TRALI: Transfusion-related acute lung injury.
IQR: Interquartile range.
SOFA: Sequential Organ Failure Assessment
MAP: Mean arterial pressure.
HR: heart rate.
MV: Mechanical ventilation.
CI: Confidence interval.

The necessity of recruitment detected by LUS is based on reaeration of lung regions, in which consolidations are transformed into coalescent B-lines in few cases, and sometimes rarely changed, coalescent B-lines are transformed into well-separated B lines or normal morphology and well-separated B-lines are transformed into normal morphology represented by A-lines (Figure 3).

In our study, relatively higher level of PEEP recorded in group I (LUS) compared to higher level of FiO_2 in group II (FiO_2-PEEP combination), resulting in improvement of oxygenation and static compliance, which came in agreement with Michelet et al. [10] who monitored the effect of PEEP on oxygenation index and lung mechanics in one-lung ventilation (OLV) of animal models during open-chest surgeries. They illustrated that the application of PEEP resulted in improvement of oxygenation. And also in a meta-analysis done by Breil et al. [11] regarding high versus low PEEP in ARDS, they collected and analyzed data from three clinical trials involving 2299 patients. They founded an improvement in lung aeration and clinical outcome by using PEEP values higher than those suggested by ARDS Network. Moreover, in the study done by Santuz et al. [12] and Stefanidis et al. [13], they observed that on increasing PEEP level, collapsed alveolar units became reinflated. Also by ultrasound assessment, the consolidation area was replaced gradually by B lines, which indicated reaeration of the lung. And in arterial gases, PaO_2/FiO_2 increased in correlation with the ultrasound changes.

The study conducted by Tang et al. [14] on 40 patients with ARDS, comparing PEEP titration by LUS and oxygenation method, found that after lung recruitment, the compliance and oxygenation index in LUS group were significantly higher than values in oxygenation group, suggesting that at the ultrasound endpoint, most of the alveoli were open after pulmonary recruitment. Thereby avoiding an arterio-venous shunt and improving oxygenation and lung compliance.

In the current study, there was one reported case developed pneumothorax in FiO_2 group.

In our study, there was a significant decrease in MAP and HR values in both groups from baseline but at the end of MV, no significant difference founded between both groups.

Organ dysfunction (SOFA) was higher in group II (FiO_2-PEEP combination) than group I (LUS) which came in agreement with the study done by Grasso et al. [15] who concluded that in 18 patients with a focal aeration loss, applying the ARDS Network protocol for PEEP selection induces alveolar hyperinflation and increased cytokine release. And also the study done by Aggarwal et al. [16] on ARDS patients using high FiO_2 levels to achieve normoxemia concluded that high FiO_2 may prevent neurocognitive dysfunction in survivors but high oxygen can be toxic to the lungs and ARDS patients are more susceptible to oxygen toxicity than others.

In our study, duration of MV, duration of stay in ICU, days with unassisted breathing and days free from organ dysfunction were higher in the LUS group than the FiO_2 group and survival rate was

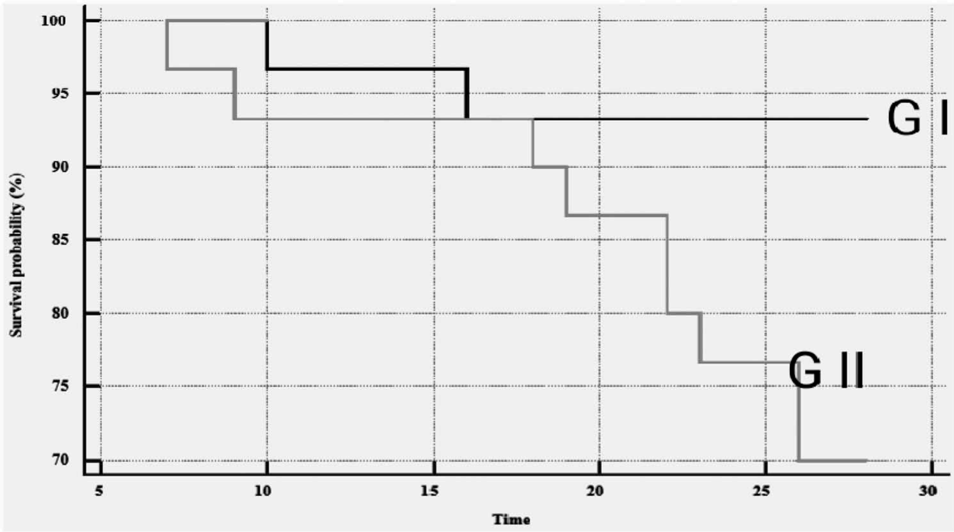

Figure 2. Kaplan-Meier curve for survival analysis.

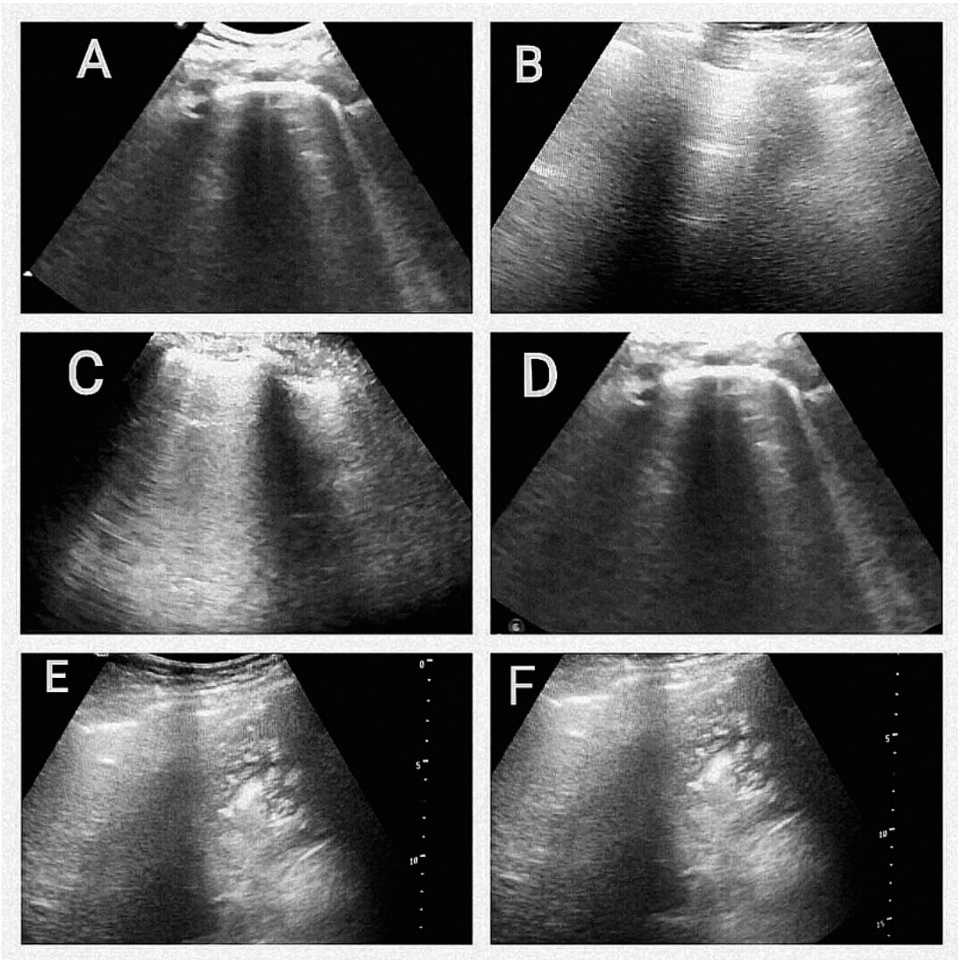

Figure 3. Illustration of PEEP induced lung recruitment detected by ultrasound.

(a) ARDS with well-separated B-lines and after PEEP, the same lung regions appear normally aerated (b). (c) Multiple coalescent B-lines are visible and after PEEP, the same lung regions appear more aerated with well-separated B-lines (d). (e) Lung consolidation has tissue-like echotexture and after PEEP, consolidation remained unchanged (f).

significantly higher in the LUS group than the FiO_2 group, which came in agreement with the study done by Rachmale et al. [17] on ARDS patients using high FiO_2, they founded that prolonged exposure to high FiO_2 levels was associated with worsening in oxygenation index, increased duration of MV, ICU and hospital stay.

Thus, concluded that excessive oxygen supplementation may lead to oxygen toxicity and worsening in lung function.

A meta-analysis done by Briel M. [11], comparing higher versus lower PEEP levels in ALI, found a significant decrease in ICU mortality in patients of the high PEEP group, also patients treated with higher PEEP levels achieved earlier successful unassisted breathing, which came in agreement with our study.

Oba et al. [18] compared high and low PEEP levels in ARDS and found a significant mortality benefit of high levels than low levels of PEEP, which come in agreement with our study.

In disagreement with our study, came the study, done by Bouhemad et al. [6] on ARDS patients. They found that LUS cannot differentiate complete reaeration from hyperinflation and suggested that PEEP titration should be done using different methods. Also, Gardelli et al. [19] reported a limitation in using LUS in PEEP titration, based on the fact that parenchymal abnormalities near the visceral pleura are only seen. But it could be a limitation in intrapulmonary causes of ARDS only. As in some cases, parenchymal abnormalities may lead to an asymmetrical, randomly localized alveolar damage. In contrast, it may not be a problem in extrapulmonary causes of ARDS, as there is generalized symmetrical consolidation.

So individualized PEEP levels by LUS depending on the distribution of aeration loss, allow determination of the optimal PEEP without PEEP related side effects. This results in improved oxygenation and static compliance, increased organ dysfunction-free days and days with unassisted breathing on day 28. Also results in a reduction of the timing of MV, duration of stay in ICU and improved survival. While in FiO_2 group, with each increase in PEEP and FiO_2 even if associated with increased oxygenation, it causes unnecessary distension of the healthy open pulmonary units in focal ARDS. This results in local inflammation with systemic inflammatory mediator release and yielding in organ injury. Also, high FiO_2levels used in group II may induce oxygen toxicity.

8. Limitations

It is a single-center trial.

It is a non-blind technique.

The majority of included cases were mild to moderate ARDS.

9. Conclusion

Based on our results, we can conclude that the determination of PEEP guided by LUS resulted in the improvement of oxygenation and lung compliance, as well as reduction in mortality, organ dysfunction and duration of MV and ICU stay in comparison with FiO_2 guided PEEP.

Author’s contribution

Mai S. Salem: Conduction of the study, collection of data and preparation of the manuscript.

Hesham S. Eltatawy: The design of the study and supervision of the conduct of the study.

Ahmed A. Abdelhafez: Supervising ultrasound work and revision of the manuscript.

Salah El-din I. Alsherif: The idea of research and the final approval of the manuscript.

Disclosure statement

The authors report no conflict of interest.

References

[1] Aikawa P, Zhang H, Barbas CS, et al. The effects of low and high tidal volume and pentoxifylline on intestinal blood flow and leukocyte-endothelial interactions in mechanically ventilated rats. Respir Care. 2011;56 (12):1942–1949.

[2] Whitehead T, Slutsky A. The pulmonary physician in critical care• 7: ventilator induced lung injury. Thorax. 2002;57(7):635.

[3] Valentini R, Aquino-Esperanza J, Bonelli I, et al. Gas exchange and lung mechanics in patients with acute respiratory distress syndrome: comparison of three different strategies of positive end expiratory pressure selection. J Crit Care. 2015;30(2):334–340.

[4] Arbelot C, Ferrari F, Bouhemad B, et al. Lung ultrasound in acute respiratory distress syndrome and acute lung injury. Curr Opin Crit Care. 2008;14 (1):70–74.

[5] Soummer A, Perbet S, Brisson H, et al. Ultrasound assessment of lung aeration loss during a successful weaning trial predicts postextubation distress. Crit Care Med. 2012;40(7):2064–2072.

[6] Bouhemad B, Brisson H, Le-Guen M, et al. Bedside ultrasound assessment of positive end-expiratory pressure–induced lung recruitment. Am J Respir Crit Care Med. 2011;183(3):341–347.

[7] Thompson BT, Bernard GR. ARDS Network (NHLBI) studies: successes and challenges in ARDS clinical research. Crit Care Clin. 2011;27(3):459–468.

[8] Liang H-Y, Liang X-W, Chen Z-Y, et al. Ultrasound in neonatal lung disease. Quant Imaging Med Surg. 2018;8(5):535.

[9] Algieri I, Mongodi S, Chiumello D, et al. CT scan and ultrasound comparative assessment of PEEP-induced lung aeration changes in ARDS. Crit Care. 2014;18(1): P285.

[10] Michelet P, Roch A, Brousse D, et al. Effects of PEEP on oxygenation and respiratory mechanics during one-lung ventilation. Br J Anaesth. 2005;95(2):267–273.

[11] Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. J Am Soc Anesthesiologists. 2010;303(9):865–873.

[12] Santuz P, Bonetti P, Serra A, et al. Correspondence: ultrasound-guided lung recruitment in a young infant with ARDS. Pediatr Anesthesia. 2010;20(9):895–896.

[13] Stefanidis K, Dimopoulos S, Tripodaki E-S, et al. Lung sonography and recruitment in patients with early acute respiratory distress syndrome: a pilot study. Crit Care. 2011;15(4):R185.

[14] Tang K-Q, Yang S-L, Zhang B, et al. Ultrasonic monitoring in the assessment of pulmonary recruitment and

the best positive end-expiratory pressure. Medicine (Baltimore). 2017;96(39):e8168.

[15] Grasso S, Stripoli T, De Michele M, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. Am J Respir Crit Care Med. 2007;176(8):761–767.

[16] Aggarwal NR, Brower RG. Targeting normoxemia in acute respiratory distress syndrome may cause worse short-term outcomes because of oxygen toxicity. Ann Am Thorac Soc. 2014;11(9):1449–1453.

[17] Rachmale S, Li G, Wilson G, et al. Practice of excessive FIO2 and effect on pulmonary outcomes in mechanically ventilated patients with acute lung injury. Respir Care. 2012;57(11):1887–1893.

[18] Oba Y, Thameem DM, Zaza T. High levels of PEEP may improve survival in acute respiratory distress syndrome: a meta-analysis. Respir Med. 2009;103(8):1174–1181.

[19] Gardelli G, Feletti F, Gamberini E, et al. Using sonography to assess lung recruitment in patients with acute respiratory distress syndrome. Emerg Radiol. 2009;16(3):219.