Published in final edited form as:

Am J Med. 2017 February ; 130(2): 207–213. doi:10.1016/j.amjmed.2016.09.029.

High Positive End Expiratory Pressure is Associated with Improved Survival in Obese Patients with Acute Respiratory Distress Syndrome

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Abstract

Background—In acute respiratory distress syndrome, minimizing lung injury from repeated alveolar collapse and reopening by applying a high positive end expiratory pressure improves oxygenation without influencing mortality. Obesity causes alveolar atelectasis thus suggesting that a higher positive end expiratory pressure might be more protective among the obese. We hypothesized that the effect of applying a high positive end expiratory pressure on mortality from acute respiratory distress syndrome would differ by obesity status.

Methods—This was a retrospective analysis of 505 patients from the Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury Trial, a multicenter randomized trial that compared a higher versus a lower positive end expiratory pressure ventilatory strategy in acute respiratory distress syndrome. We examined the relationship between positive end expiratory pressure strategy and 60-day mortality stratified by obesity status.

Results—Among obese patients with acute respiratory distress syndrome, those assigned to a high positive end expiratory pressure strategy experienced lower mortality compared to those assigned to a low strategy (18% vs 32%; $p = 0.04$). Among the non-obese, those assigned to high positive end expiratory pressure strategy experienced similar mortality with those assigned to low strategy (34% vs 23 %; $p = 0.13$). Multivariate analysis demonstrated an interaction between obesity status and the effect of positive end expiratory pressure strategy on mortality ($p < 0.01$).

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Author Contributions:

Christian Bime, Mallorie Fiero, Cristine E. Berry, Zhenqiang Lu, Eyal Oren, Sairam Parthasarathy, Joe G.N. Garcia – All participated in making substantial contributions to the conception or design of the work, the acquisition of the data from <https://biolincc.nhlbi.nih.gov/home/>, the analysis and interpretation of data for the work, the drafting and revision of the manuscript.

Conclusions—Ventilation with higher levels of positive end expiratory pressure was associated with improved survival among the subgroup of patients with acute respiratory distress syndrome who are obese.

Keywords

ARDS; PEEP; obesity; adult; survival; mortality

INTRODUCTION

For nearly half-a-century, use of mechanical ventilation has contributed to increased survival among patients with acute respiratory distress syndrome (ARDS)^{1,2}. However, a well-recognized complication of mechanical ventilation is ventilator-induced lung injury (VILI)^{3–5}. Possible mechanisms for VILI include over-distention of the alveoli by high transpulmonary pressures, shear forces produced by repetitive alveolar collapse and reopening, and oxygen toxicity^{3,5,6}. It has been hypothesized that additional positive end expiratory pressure (PEEP) protects against VILI by stabilizing alveoli, thus preventing repeated cycle of alveolar opening and closing during tidal ventilation⁷. In animal models of acute lung injury, the application of additional PEEP reduces lung injury and improves oxygenation^{7,8}. However, in human studies, three large multicenter randomized controlled trials demonstrated that the application of additional PEEP to a lung protective ventilation strategy was associated with improved oxygenation but without mortality benefit^{9–11}. A subsequent meta-analysis of individual-patient data from these trials showed that a high PEEP ventilatory strategy was associated with improved survival in a subgroup of patients with severe ARDS as defined by a baseline value of 200mm Hg or less for the ratio of partial pressure of oxygen (PaO₂) to fraction of inspired oxygen (FiO₂) concentration¹².

Obese patients are more prone to alveolar derecruitment as a consequence of the weight of the chest wall and increased intra-abdominal pressure, features that result in decreased respiratory system compliance and low lung volume respiration^{13–19}. As a result, obese patients with ARDS may benefit from a higher PEEP to counteract these effects. On the other hand, among patients with ARDS who are not obese, additional PEEP might cause increased VILI by over distension of normal alveoli. We hypothesized that in the subgroup of ARDS patients who are obese, mechanical ventilation with a higher PEEP strategy would confer improved survival compared to a low PEEP strategy. To investigate this hypothesis, we performed a post-hoc analysis using data from the Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury (ALVEOLI) Trial (NCT00000579)⁹.

MATERIALS AND METHODS

Original Study and Oversight

We obtained data on the ALVEOLI Trial through the National Heart, Lung, and Blood Institute (NHLBI) clinical database repository <https://biolincc.nhlbi.nih.gov/home/>. The study details have been previously described elsewhere⁹. Briefly, between October 1999 and February 2002, 549 patients with ARDS were enrolled at 23 hospitals participating in the NHLBI ARDS Network (ARDSNet) to assess the effect of a high versus low PEEP

ventilatory strategy (in addition to low tidal volume ventilation) on ARDS mortality. The protocol for this secondary (post hoc) analysis of ALVEOLI data was approved by the protocol committee of ARDSNet and by the Institutional Review Board of the University of Arizona.

Definitions and Study Population

Baseline demographic, physiological, and radiographic characteristics were available for patients randomized to one of two strategies for adjusting PEEP (high versus low). The lower PEEP strategy was based on the PEEP titration table used in the original ARDSNet study that showed a mortality benefit of low tidal volume ventilation compared to traditional (higher) tidal volume ventilation for the management of patients with ARDS²⁰. The higher PEEP strategy was based on a study in which high PEEP levels and low tidal volumes were associated with a mortality benefit compared to low PEEP and high tidal volumes²¹. In the ALVEOLI trial, the ventilator procedures had two different strategies for adjusting PEEP and FiO₂ in discrete steps to maintain an arterial oxyhemoglobin saturation of 88 to 95 percent or PaO₂ of 55 to 80 mm Hg⁹. The details of the allowable combinations of PEEP and FiO₂ for the high and low PEEP strategies have previously been published⁹. The actual mean PEEP levels ($\pm$ standard deviations) for each study group during the first 28 days following randomization in the ALVEOLI study are shown in Figure 1. The patients were followed until day 90 or until they were discharged home while breathing without assistance for 48 hours⁹. The ALVEOLI study was stopped after the second interim analysis, when 549 of the planned 750 patients had been enrolled, on the basis of a pre-specified futility stopping rule⁹. In this post-hoc analysis, we used data from 505 patients to test the hypothesis that obesity status is an effect modifier in the association between PEEP strategy and ARDS survival while adjusting for important prognostic factors. Forty-four patients were not included in this analysis because of missing data on height and/or weight.

Endpoints

The primary outcome was the proportion of patients who died before hospital discharge within 60 days after enrollment (60-day in hospital mortality). Secondary outcomes included the proportion of patients who achieved unassisted breathing by day 28 and barotrauma anytime during hospitalization (defined as any new pneumothorax, pneumomediastinum, subcutaneous emphysema, or formation of a pneumatocele of >2 cm diameter after randomization).

Statistical analysis

In our primary analysis, we assessed whether obesity status modified the effect of PEEP strategy on 60-day in-hospital mortality using a multivariate logistic regression model examining the interaction between obesity status and PEEP strategy. The independent covariates were; obesity status (obese [Body Mass Index (BMI) ≥ 30 kg/m²] versus non-obese [BMI < 30 kg/m²]), PEEP strategy, the interaction between obesity status and PEEP strategy, age, gender, and Acute Physiology and Chronic Health Evaluation (APACHE) III score at baseline. All covariates were selected a priori and entered into the regression model. In our secondary analyses, we explored whether obesity status modified the effect of PEEP strategy on; the proportion of patients who achieved unassisted breathing by day 28 and

rates of barotrauma. The same preselected adjustment covariates described for the primary analysis were included for the secondary analyses. In our logistic regression model, we used BMI as a categorical variable (obese versus non-obese) so as to best define a particular subgroup likely to benefit from the high PEEP strategy. Other investigators exploring the effect of obesity status on ARDS survival have also used BMI as a categorical variable^{22,23}. Additionally, to graphically illustrate the effect of BMI on each PEEP strategy, we built a simple unadjusted logistic regression model for each outcome with BMI (as a continuous variable), PEEP strategy and their interaction term. Predicted 60-day in hospital mortality rate, unassisted breathing rate and barotrauma rates were computed from each model respectively. Statistical analyses were performed using R version 3.1.2. (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

ALVEOLI Cohort analyzed

Five hundred and five total participants were included in this analysis. BMI was approximately normally distributed with a mean BMI of 27.4 kg/m², a median of 26.7 kg/m² and a range of 14.7 kg/m² to 53.3 kg/m². Majority of the participants were non-obese (70%). Most of the baseline characteristics were similar between the non-obese and the obese (Table 1). Female participants were more likely to be obese than non-obese ($P < 0.01$). The mean APACHE score was significantly higher among the non-obese compared to the obese ($P = 0.02$).

For all study participants, the overall 60-day in hospital mortality was 28% (143/505). Inhospital mortality did not differ by obesity status; 30% (105/355) in the non-obese, and 25% (38/150) in the obese ($P = 0.33$).

Effect Modification by Obesity Status on Death Prior to Discharge

There was significant effect modification by obesity status on the association between PEEP strategy (low versus high) and mortality even after adjusting for age, gender, and APACHE III score. In non-obese patients (BMI < 30 kg/m²) [$n = 355$], there were 58 (34%) deaths among those assigned to a high PEEP strategy and 40 (23%) deaths in those assigned to the low PEEP strategy (adjusted RR, 1.52; 95%CI, 0.88–2.6; $P = 0.13$). In obese patients (BMI ≥ 30 kg/m²) [$n = 150$], there were 14 (18%) deaths among those assigned to the high PEEP strategy and 22 (32%) in those assigned to the low PEEP strategy (adjusted RR, 0.42; 95%CI, 0.18–0.98; $P = 0.04$) [Table 2, Figure 2].

In a logistic regression model with BMI (as a continuous variable) and PEEP strategy (high versus low) as the predictive variables, we found that with increasing BMI, the PEEP strategy assignment had the opposite effect on the patient's predicted 60-day in hospital mortality (Figure 3A). For a patient with a BMI of 20 kg/m², the predicted 60-day in hospital mortality if assigned to low PEEP strategy was 24.3% versus 36.8% if assigned to high PEEP strategy ($P < 0.01$). Similarly, for a participant with BMI of 40 kg/m², the predicted 60-day in hospital mortality if assigned to the low PEEP strategy was 30.8% versus 20.1% if assigned to high PEEP strategy ($P < 0.01$) (Figure 3A). Figure 3A also

revealed a BMI of 30 kg/m² to be the point at which predicted death rates were the same for both PEEP strategies.

Unassisted Breathing by Day 28 and Barotrauma

There was no effect modification by obesity status on the association between PEEP strategy assignment and rates of unassisted breathing by day 28 [Table 2, Figure 2].

However, a novel observation was that with increasing BMI, PEEP strategy assignment exhibited opposing effects on the likelihood of achieving unassisted breathing by day 28. There was a negative association between BMI and rates of unassisted breathing by day 28 for patients assigned to the low PEEP strategy (Beta = -0.037). Conversely, there was a positive association between BMI and rates of unassisted breathing for patients assigned to the high PEEP strategy (Beta = 0.027) [Figure 3B].

We observed a significant effect of BMI on incidence rate of barotrauma for patients receiving high PEEP ($p = 0.03$) [Figure 3C]. However, there was no effect modification by obesity status on the association between PEEP strategy assignment and rates of barotrauma [Table 2, Figure 2].

DISCUSSION

Our analysis of the ALVEOLI study dataset showed that among ARDS patients who are obese, a high PEEP ventilatory strategy is associated with decreased 60-day in-hospital mortality. The effect of PEEP strategy on rates of barotrauma or proportion of patients who achieved unassisted breathing by day 28 did not differ by obesity status.

Evidence from numerous preclinical studies suggests that ventilation at low lung volumes and low end-expiratory pressures, below the lower inflection point on the pressure volume curve, increases the risk of lung injury in ARDS^{7,8,24-27}. The physiologic rationale underlying the ALVEOLI study and other similar studies was that application of additional PEEP above the lower inflection point attenuates the type of lung injury induced by repeated opening and closing of alveoli⁹⁻¹¹. These studies failed to show a survival benefit in favor of applying additional PEEP in patients with ARDS who are already on a low tidal volume ventilatory strategy⁹⁻¹¹. It has previously been suggested that because of the heterogeneous nature of the ARDS phenotype, the application of a higher PEEP might only benefit subgroups of patients with ARDS¹². Briel and colleagues conducted a meta-analysis of individual patient data from the ALVEOLI⁹, EXPRESS¹¹, and LOVS¹⁰ trials, and concluded that applying additional PEEP in patients with ARDS was associated with a survival benefit in patients with moderate or severe ARDS (baseline PaO₂:FiO₂ ratio ≤ 200 mmHg) but not among those with mild ARDS (baseline PaO₂:FiO₂ ratio > 200 mmHg)¹². In a similar effort, we identified another subgroup of ARDS patients, the obese (BMI ≥ 30 kg/m²), who might also benefit from a high PEEP strategy. Our results fuel speculation that prior studies assessing the efficacy of high PEEP strategies may have failed to demonstrate a beneficial effect due to the lack of consideration of BMI effects. The benefits of a higher PEEP strategy among obese patients could have been negated by potential harm among non-obese patients. The finding that a high PEEP strategy might be harmful to non-obese patients with

ARDS is intriguing given that severe VILI manifests clinically in the form of barotrauma. However, our analysis failed to identify a significant effect modification by obesity status on the rates of barotrauma by PEEP strategy although ARDS subjects with a BMI of less than 20–22 had greater predicted barotrauma rates (Figure 3C). The lack of significance in these findings might reflect inadequate sample size and the reduced total number of patients with barotrauma in our study. It could also reflect the complexity of the ARDS phenotype, further compounded by the effects of obesity on lung physiology especially in the context of increased permeability pulmonary edema.

It is well established that obesity affects several aspects of respiratory system mechanics and gas exchange, especially in the supine posture^{13–16,18,19}. In several studies conducted in sedated, paralyzed morbidly obese patients and compared with normal weight patients, Pelosi and colleagues showed that obesity causes several physiologic derangements in the respiratory system including: a reduction in respiratory system compliance with a greater reduction of lung compliance than chest wall compliance, an increase in lung resistance, a reduction in the functional residual capacity, and a reduction in alveolar oxygenation^{13–15}. Furthermore, they demonstrated that application of PEEP improved respiratory mechanics and oxygenation among obese patients but not in normal weight patients¹⁶. The effects of obesity on the respiratory system mechanics are further compounded by ARDS. Gattinoni and colleagues showed that in ARDS, the distribution of lung injury is uneven with areas of extreme injury and atelectasis and other areas with preserved lung architecture^{28,29}. Therefore, the amount of distending pressure applied to various regions of the lung varies depending on the degree of atelectasis or inflammation²⁹. Barotrauma during mechanical ventilation in patients with ARDS is believed to be caused by over-distension and subsequent injury to previously normal parts of the lung or by the repeated opening and closing of the atelectatic parts of the lung^{29,30}. The application of additional PEEP during positive ventilation in patients with ARDS is supposed to stabilize the collapsed alveoli and prevent atelectorauma^{9–11}. However, such a “one size fits all” approach fails to account for the effects of obesity on the respiratory system and the heterogeneity of atelectasis in the lung in ARDS. The submission that only certain subgroups of ARDS patients might benefit from a higher PEEP strategy is in line with recent findings by Amato and colleagues that driving pressure was more predictive of survival in ARDS than the tidal volume and PEEP³¹. The appropriate driving pressure and optimal PEEP setting for each patient with ARDS is best determined by bedside measurement of lung and chest wall mechanics. For example, in a single center pilot study of 61 patients with ARDS, Talmor and colleagues measured esophageal pressure as a surrogate for pleural pressure to guide the PEEP setting for each patient with ARDS³². They targeted a transpulmonary pressure during end-expiratory occlusion of 0 to 10 cm H₂O and transpulmonary pressure during end-inspiratory occlusion of less than 25 cm H₂O³². When compared to a strategy equivalent to the low PEEP arm of the ALVEOLI study, the esophageal pressure-guided strategy was associated with improved oxygenation and respiratory system compliance³². An interesting finding was a lower 28-day mortality (albeit not statistically significant) among patients randomized to the esophageal pressure-guided strategy compared to the control group (17% versus 39%; *P*=0.055)³². The value of this approach is currently being tested in a phase II clinical trial to determine if the use of a transpulmonary guided ventilation strategy in ARDS would

improve mortality and time off ventilator compared to a high-PEEP control group³³ (NCT01681225).

Even though our findings are interesting, there are several notable limitations. Firstly, given that we performed a post-hoc secondary analysis using primary data from a previously completed study, our results may represent effects due to chance and therefore can only be viewed as hypothesis generating. Our analysis was constrained by the available sample size from this study that was completed about 15 years ago. Additionally, we were missing BMI data in 44 patients with no available information on height or weight, which further limited our statistical power. However, despite these limitations, we were able to detect a significant effect modification by obesity status on the association between PEEP strategy (low versus high) and ARDS survival.

These results confirmed our stated hypothesis which was based on evidence from several previously published physiologic studies demonstrating the beneficial effect of PEEP on respiratory system compliance and respiratory function during mechanical ventilation of patients with severe obesity^{13–16}. However, there are several possible alternative explanations for our findings. For example, obese patients may sustain ARDS forms of a greater severity and therefore the observed survival benefit could represent the effect of disease severity as suggested by Briel and colleagues¹². Transpulmonary pressures were not measured and so the potential mechanism of benefit of a higher PEEP strategy among obese patients remains speculative. Nonetheless, our finding that the subgroup of ARDS patients who are obese might benefit from a higher PEEP strategy underscores the importance of a personalized physiologic approach to determining the optimal ventilatory strategy for each patient with ARDS.

Conclusion

The application of additional PEEP during positive ventilation was associated with decreased mortality in the subgroup of patients with ARDS who are obese. Among patients with ARDS who are not obese, additional PEEP might be harmful.

Acknowledgments

Support:

Christine Bime was supported for this work by the University of Arizona Health Sciences Center Career Development Grant

We wish to thank the National Heart, Lung, and Blood Institute (NHLBI) ARDSNet study investigators who conceived, designed, and executed the “Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury (ALVEOLI)” study.

We also thank the NHLBI <https://biolincc.nhlbi.nih.gov/home/> who made the original data available to us for analysis.

Special thanks to Dr. Dean Billheimer and Dr. Shannon M. Knapp from the Statistical Consulting Laboratory, BIO5 Institute, University of Arizona for assisting us with the advanced statistical analyses.

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Figure 1.
Average positive end expiratory pressure levels by group assignment during the first 28 days of the study

Figure 2. Obese vs non-obese – Odds Ratio of Mortality, Barotrauma, and Unassisted Breathing by day 28 for High PEEP group: All study patients, Obese (BMI ≥ 30 kg/m²), and Non-Obese (BMI < 30 kg/m²)

Figure 3.

Results of logistic regression models of each outcome (Death prior to discharge, Unassisted Breathing by day 28, Barotrauma) with BMI and positive end expiratory pressure group (high versus Low) as the predictive variables

Panel A - Predicted death rate was computed using logistic regression model with positive end expiratory pressure, BMI and interaction terms as predictor variables.

Panel B - Predicted rate of unassisted breathing was computed using logistic regression model with positive end expiratory pressure, BMI and interaction terms as predictor variables.

Panel C - Predicted barotrauma rate was computed using logistic regression model with positive end expiratory pressure, BMI and interaction terms as predictor variables.

Table 1

Baseline characteristics by obesity status

Characteristic	Non-obese (BMI < 30) (N = 355)	Obese (BMI ≥ 30) (N = 150)	P-value
Age, mean (SD)	51.0 (18.5)	52.0 (14.0)	0.52
Female, No. (%)	142 (40)	82 (55)	< 0.01
Race or ethnic group No. (%)			0.35
- White	257 (72)	115 (77)	
- Black	58 (16)	17 (11)	
- Other ¹	40 (11)	18 (12)	
Severity of illness at baseline			
APACHE III, mean (SD)	84.7 (21.2)	79.8 (19.9)	0.02
Baseline PaO ₂ :FiO ₂ , mean (SD) ²	186.8 (83.1)	184.5 (80.0)	0.79
ARDS severity ²			0.96
200 < PaO ₂ :FiO ₂ ≤ 300, No. (%)	118 (37)	50 (38)	
100 < PaO ₂ :FiO ₂ ≤ 200, No. (%)	160 (50)	65 (49)	
PaO ₂ :FiO ₂ ≤ 100, No. (%)	41 (13)	18 (14)	
Baseline Physiologic parameters			
Compliance (SD) ³	35.3(19)	30.3(23)	0.03
Tidal Volume ⁴	6.1 (0.8)	6.4 (0.9)	0.92
Cause of lung injury, No. (%)			0.32
- Pneumonia	152 (43)	57 (38)	
- Sepsis	74 (21)	39 (26)	
- Aspiration	57 (16)	15 (10)	
- Trauma	25 (7)	13 (9)	
- Multiple transfusions	21 (6)	5 (3)	
- Other	26 (7)	21 (14)	

¹ Other includes: Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native, Other² N = 452³ Compliance denotes static compliance of the respiratory system calculated as the calculated tidal volume /driving pressure⁴ Tidal Volume (mL/Kg Predicted Body Weight)

Table 2

Study Outcomes by Positive End Expiratory Pressure Assignment

Outcomes*	Non-Obese				Obese			
	High PEEP [£]	Low PEEP [£]	Adjusted OR Ψ (95% CI)	P value	High PEEP [£]	Low PEEP [£]	Adjusted OR Ψ (95% CI)	P value
Mortality [§] , %	34	23	1.52 (0.9, 2.6)	0.13	18	32	0.4 (0.18, 0.97)	0.04
Unassisted Breathing [¶] , %	74	76	1.02 (0.6, 1.8)	0.92	80	74	1.52 (0.65, 3.55)	0.34
Barotrauma, %	13	7	1.98 (0.9, 4.4)	0.09	3	6	0.35 (0.06, 2.04)	0.24

* Outcomes:

Primary Outcome:

[§] Mortality = defined as the proportion of patients who died before hospital discharge within 60 days after enrollment (60-day in hospital mortality)

Secondary Outcomes:

Unassisted Breathing = defined as the proportion of patients who achieved unassisted breathing by day 28,

Barotrauma = defined as the proportion of patients with any new pneumothorax, pneumomediastinum, subcutaneous emphysema, or formation of a pneumatocele of >2 cm diameter after randomization

Ψ Adjustment covariates include:

- Obesity status (obese [BMI ≥ 30 kg/m²] versus non-obese [BMI < 30 kg/m²]),
- PEEP strategy (high versus low),
- The interaction between obesity status and PEEP strategy,
- Age,
- Gender,
- Baseline ARDS severity (ratio of PaO₂/FiO₂)
- Acute Physiology and Chronic Health Evaluation (APACHE) III score at baseline

[£] The mean PEEP ($\pm$ SD) for those assigned to high PEEP strategy during the study was 11.8 ($\pm$ 5)

[¶] The mean PEEP ($\pm$ SD) for those assigned to low PEEP strategy during the study was 7.8 ($\pm$ 3.6)