

Airway Pressures and Early Barotrauma in Patients with Acute Lung Injury and Acute Respiratory Distress Syndrome

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The determinants of barotrauma in mechanically ventilated patients with acute lung injury or acute respiratory distress syndrome (ALI/ARDS) have not been clearly established. Using data from ARDS Network randomized controlled trials, we retrospectively examined the association between airway pressures and the risk of early barotrauma in a cohort of 718 patients with ALI/ARDS and no baseline barotrauma. We studied airway pressures at three exposure intervals: baseline, one day preceding the barotrauma event (one-day lag), and concurrent with the barotrauma event. During the first four study days, the cumulative incidence of barotrauma was 13% (95% confidence interval [CI] 10.6 to 15.6%). In a forward stepwise Cox proportional hazards analysis using time-dependent variables, higher concurrent positive end-expiratory pressure (PEEP) was associated with an increased risk of early barotrauma (relative hazard [RH] 1.67 per 5-cm H₂O increment; 95% CI 1.35–2.07). Once concurrent PEEP was selected into the model, no other airway pressure was related to barotrauma, including plateau pressure. In the multivariate analysis, higher concurrent PEEP was also related to a greater risk of barotrauma (RH 1.93; 95% CI 1.44–2.60), controlling for age, ventilator group (6 versus 12 ml/kg), baseline PEEP, baseline plateau pressure, baseline tidal volume, Acute Physiology and Chronic Health Evaluation score, vasopressor use, serum albumin, hepatic failure, and coagulopathy. When one-day lagged values of PEEP were analyzed, higher PEEP was associated with a greater risk of barotrauma (RH 1.38 per 5-cm H₂O increment; 95% CI 1.09–1.76). Controlling for the covariates, higher PEEP was related to an increased risk of barotrauma (RH 1.50; 95% CI 0.98–2.30). In conclusion, higher PEEP may increase the likelihood of early barotrauma in ALI/ARDS.

Keywords: acute lung injury; adult respiratory distress syndrome; mechanical ventilators

The determinants of barotrauma in mechanically ventilated patients with acute lung injury or acute respiratory distress syndrome (ALI/ARDS) have not been clearly established (1–3).

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Previous observational studies have found an association between high inspiratory airway pressures or positive end-expiratory pressure (PEEP) and barotrauma (1, 4, 5), whereas others have found no relationship (6–8). More recently, clinical trials of lung-protective ventilation that targeted lower peak inspiratory or plateau pressures have found no reduction of barotrauma risk (9–11). The results of these intervention studies challenge the conventional view that high airway pressures cause barotrauma in patients with ALI/ARDS.

The relation of inspiratory and expiratory airway pressures to the development of barotrauma remains uncertain because previous studies had small sample sizes, included a narrow spectrum of ALI/ARDS patients, or did not control for the confounding effects of acute illness severity (1, 4–6, 8). Most studies did not measure plateau pressure, which approximates alveolar pressure more closely than other inspiratory airway pressures (1, 4–6). In previous studies, the time interval between measurement of airway pressure and the barotrauma event was not clearly specified (1, 5, 8). Using data from patients enrolled in the National Heart, Lung, and Blood Institute (NHLBI) ARDS Network randomized controlled trials, we retrospectively examined the association between airway pressures and the risk of barotrauma in a large, clearly enumerated cohort of patients with ALI/ARDS of diverse etiologies.

METHODS

Detailed study methods are described in the online data supplement. In the present study, we used data from 902 patients participating in the NHLBI ARDS Network multicenter randomized controlled trials. The protocol was approved by the institutional review board at each hospital. The results of the traditional versus lower tidal volume ventilation trials have been previously reported (9–11). Briefly, intubated, mechanically ventilated patients were eligible if they met criteria for ALI or ARDS and were enrolled within 36 hours. For the present study, we excluded those with baseline evidence of barotrauma before assignment to ventilator group, leaving 718 patients for analysis.

Clinical data, including chest radiographs, were reviewed and recorded at baseline and on Days 1, 2, 3, 4, 7, 14, 21, and 28 between 6 and 10 A.M. At each time, airway pressures were recorded, including peak inspiratory pressure, mean airway pressure, and PEEP. Plateau pressures were measured with a half-second inspiratory pause.

The primary study outcome variable was defined as new onset of radiographic evidence of barotrauma or new chest tube placement. Radiographic evidence of barotrauma included pneumothorax, pneumomediastinum, pneumatocele, or subcutaneous emphysema. Because barotrauma in mechanically ventilated patients often presents as acute, life-threatening hypoxemia or hypotension, we reasoned that not all cases of barotrauma would have preceding documentation by chest radiograph before chest tube placement. As a consequence, we chose an inclusive definition of barotrauma that would capture most events.

Most barotrauma events occurred during the first four study days. No new episodes of barotrauma were recorded at Days 7 or 14, and

only 19 barotrauma events were recorded at Day 28. As a consequence, we focused the analysis on early barotrauma, occurring during the first four days following study entry (corresponds to first 4–6 days after ALI/ARDS onset).

Data analysis was conducted with SAS 8.1 (SAS Institute, Cary, NC). We used Cox proportional hazards regression analysis to study the relationship between airway pressures (peak inspiratory pressure, mean airway pressure, plateau pressure, and PEEP) and the incidence of barotrauma during the first four study days. In this analysis, barotrauma was considered a failure event. Patients were censored at the time of death, liberation from mechanical ventilation, or at the first barotrauma event. As a consequence, once a person developed barotrauma, they no longer contributed person-time to the analysis.

The time interval between exposure to airway pressure and development of barotrauma has not been well defined (6). As a consequence, we performed two sets of Cox proportional hazards analyses. First, we evaluated the association between baseline airway pressures and subsequent barotrauma risk. Second, we used extended Cox proportional hazards regression analysis with time-dependent variables for concurrent airway pressures (measured on the same day as barotrauma assessment) and the one-day lagged value (measured on the day preceding barotrauma assessment).

For both sets of analyses, we first examined the unadjusted association between each airway pressure and the incidence of barotrauma. Forward stepwise Cox models were then used to evaluate which of the airway pressures were most strongly related to the subsequent risk of barotrauma. Those airway pressures that were significantly associated with barotrauma were then entered into a multivariate proportional hazards regression analysis to control for age, ventilator group (6 versus 12 ml/kg), baseline markers of acute illness severity (vasopressor use, APACHE III [Acute Physiology and Chronic Health Evaluation] score, hepatic failure, coagulopathy, and serum albumin), and baseline acute respiratory illness severity (baseline tidal volume, baseline plateau pressure, and baseline PEEP). Because oxygenation and compliance are related to PEEP level (by protocol and formula, respectively), they were not included in the primary multivariate analysis. In a subsequent multivariate analysis, we tested the impact of adding these additional indicators of lung injury severity.

RESULTS

During the first four study days, 93 patients developed early barotrauma (13%). There were no apparent differences in demographic characteristics or baseline clinical characteristics by barotrauma status, including age, etiology of ALI/ARDS, APACHE III score, vasopressor use, and proportion assigned to low tidal volume ventilation ($p > 0.10$) (Table 1).

Among patients without evidence of baseline barotrauma, the cumulative incidence of barotrauma more than doubled during the first four study days (Table 2). On Day 1, the incidence of barotrauma was 5.8% (95% confidence interval [CI] 4.3 to 7.8%). By Day 4, 13% of patients developed barotrauma (95% CI 10.6 to 15.6%). Table 3 shows the distribution of barotrauma by side and type.

In the unadjusted analysis evaluating the association between airway pressure and the incidence of barotrauma, plateau pressure was related to the risk of developing early barotrauma (Table 4). There was no significant relationship between peak inspiratory pressure, mean airway pressure, or driving pressure (plateau pressure – PEEP) and barotrauma. For plateau pressure, higher baseline and one-day lagged values were associated with a greater risk of barotrauma (relative hazard [RH] 1.35 per 10-cm H₂O increment; 95% CI 1.04–1.74 and RH 1.28 per 10-cm H₂O increment; 95% CI 1.03–1.59, respectively). Concurrent plateau pressure was related to barotrauma risk, but the confidence interval did not exclude any association (RH 1.21 per 10-cm H₂O increment; 95% CI 0.99–1.48).

Forward selection and multivariate Cox proportional hazards regression using time-dependent variables were applied

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS WITH ACUTE LUNG INJURY/ACUTE RESPIRATORY DISTRESS SYNDROME AND DEVELOPMENT OF EARLY BAROTRAUMA: DAYS ONE THROUGH FOUR

Variable	No Barotrauma (n = 625)	Any Early Barotrauma (n = 93)
Demographic and clinical variables		
Age (yr), mean (SD)	52.0 (17.0)	53.2 (19.2)
APACHE III score, mean (SD)	84.3 (28.2)	88.5 (24.7)
Vasopressor use, n (%)	205 (33)	35 (39)
Hepatic failure, n (%)	144 (25)	25 (28)
Coagulopathy, n (%)	150 (25)	24 (26)
Serum albumin (g/L), mean (SD)	2.2 (0.6)	2.2 (0.5)
Direct pulmonary risk factor for ALI/ARDS*	370 (60.3%)	59 (63.4%)
Respiratory variables		
Randomized to low tidal volume, n (%)	317 (52)	51 (55)
Tidal volume (ml), mean (SD)	669 (123)	654 (131)
Peak inspiratory pressure (cm H ₂ O), mean (SD)	36.7 (9.0)	36.9 (9.7)
Plateau pressure (cm H ₂ O), mean (SD)	29.8 (7.6)	31.3 (8.0)
Mean airway pressure (cm H ₂ O), mean (SD)	16.1 (9.0)	17.9 (11.5)
PEEP (cm H ₂ O), mean (SD)	8.3 (3.7)	8.8 (4.2)

Definition of abbreviations: ALI/ARDS = acute lung injury/acute respiratory distress syndrome; APACHE = Acute Physiology and Chronic Health Evaluation; PEEP = positive end-expiratory pressure.

Clinical and respiratory variables were recorded before assignment to ventilator group.

* Direct pulmonary risk factor = pneumonia or aspiration (versus nonpulmonary = sepsis, trauma, or other).

to examine the independent impact of each airway pressure on the risk of barotrauma. Taken together, these analyses indicated that PEEP was the only airway pressure associated with a greater incidence of barotrauma (Table 5). The first step of the forward stepwise proportional hazards analysis identified concurrent PEEP, one-day lagged PEEP, and concurrent plateau pressure as significantly associated with the risk of barotrauma (data not shown). However, once concurrent PEEP was selected into the model, no other airway pressure was related to barotrauma ($p > 0.30$). For every 5-cm H₂O concurrent PEEP increment, the RH of developing barotrauma increased by 1.67 (95% CI 1.35–2.07) (Table 5). In the multivariate analysis, higher concurrent PEEP was also related to a greater risk of barotrauma (RH 1.93; 95% CI 1.44–2.60), controlling for age, ventilator group (6 versus 12 ml/kg), baseline PEEP, baseline plateau pressure, baseline tidal volume, APACHE III score, vasopressor use, serum albumin, hepatic failure, and coagulopathy (Table 5). Controlling for lung compliance and alveolar–arterial oxygen gradient did not appreciably affect these results (data not shown). Although PEEP and plateau pressures were moderately correlated ($r = 0.42$, $p = 0.001$), there was no evidence of statistical interaction between these airway pressures in multivariate analysis ($p = 0.56$).

TABLE 2. CUMULATIVE INCIDENCE OF EARLY BAROTRAUMA IN 718 PATIENTS WITH ACUTE LUNG INJURY/ACUTE RESPIRATORY DISTRESS SYNDROME

Study Day	Number of New Barotrauma Events (n)	Cumulative Incidence of Barotrauma (n) (%)	95% Confidence Interval
Day 1	42	42 (5.8)	4.3–7.8
Day 2	16	58 (8.1)	6.2–10.3
Day 3	16	74 (10.3)	8.2–12.3
Day 4	19	93 (13)	10.6–15.6

Of the original 902 patients, this analysis includes 718 patients without baseline barotrauma.

TABLE 3. DISTRIBUTION OF INCIDENT EARLY BAROTRAUMA AMONG PATIENTS WITH ACUTE LUNG INJURY/ACUTE RESPIRATORY DISTRESS SYNDROME

Radiographic Finding	Right	Left	Bilateral	Total
Pneumothorax	16	15	1	32
Pneumatocele	3	27	5	35
Pneumomediastinum	N/A	N/A	N/A	8
Subcutaneous emphysema	N/A	N/A	N/A	14
Chest tube only*	9	5	6	20

Definition of abbreviation: N/A = not applicable.

* Barotrauma was defined by chest tube only without reported evidence of radiographic barotrauma. See METHODS for further details.

To further examine the association between PEEP and barotrauma, we examined different time intervals between exposure to PEEP and the development of barotrauma. There was no significant relationship between baseline PEEP and the risk of barotrauma in forward selection or multivariate analysis (Table 5). When one-day lagged values of PEEP were analyzed in time-varying models, higher PEEP was associated with a greater risk of barotrauma (RH 1.38 per 5-cm H₂O increment; 95% CI 1.09–1.76). Controlling for the covariates, higher PEEP was related to an increased risk of barotrauma (RH 1.50; 95% CI 0.98–2.30). In this analysis, the 95% confidence interval did not exclude any relationship. Because baseline PEEP is correlated with one-day lagged PEEP, including both in the same multivariate analysis could reduce statistical precision. When baseline PEEP was omitted from the multivariate model, the CI excluded no association (RH 1.43; 95% CI 1.02–2.00). There was no statistical relationship between any other one-day lagged airway pressure and barotrauma in forward selection or multivariate analysis. Repeating these analyses excluding the tidal volume covariate did not appreciably affect the results (data not shown).

To examine the impact of our definition of barotrauma on study results, we repeated key analyses, using a more restrictive definition that required radiographic evidence of barotrauma. In the forward stepwise Cox regression analysis using time-dependent variables, concurrent PEEP remained the only airway pressure associated with a greater risk of barotrauma (RH 1.71 per 5-cm H₂O increment; 95% CI 1.39–2.12). In the multivariate model, higher PEEP was related to a greater risk of barotrauma (RH 1.86 per 5-cm H₂O increment; 95% CI 1.36–2.54).

DISCUSSION

In a large cohort of patients with ALI/ARDS of diverse etiologies, higher levels of PEEP were associated with a greater risk of

early barotrauma. In contrast, other airway pressures, including plateau pressure, did not appear to influence the development of barotrauma. After controlling for markers of acute and chronic disease severity, higher PEEP levels remained a risk factor for developing early barotrauma.

The present study is the first to evaluate plateau pressure in a large cohort of patients with ALI/ARDS (4–6). Plateau pressure provides the best clinically available estimate of alveolar pressure, which is one important determinant of alveolar distension (3). In a smaller study of 42 patients with ARDS, plateau pressure was not related to risk of barotrauma (8). Because the present analysis was based on an intervention trial that purposefully manipulated tidal volume and plateau pressure, patients had a broad range of plateau pressures. As a consequence, the observed lack of relationship indicates that plateau pressure is probably not a clinically important determinant of early barotrauma in ALI/ARDS, even though plateau pressure limitation reduces mortality as part of a low tidal volume strategy (9–11). Conceivably, ventilation with higher plateau pressures than commonly observed in this study could result in a higher likelihood of barotrauma.

Our results differ from the largest previous observational study of barotrauma, which found no relationship between any airway pressure and barotrauma (6). This study included only patients with sepsis-related ARDS, which could account for different findings. For example, ALI/ARDS directly related to pulmonary disease may differ from that due to extrapulmonary causes, such as sepsis (12). Patients with ARDS resulting from pneumonia appear to have lower lung compliance than those with extrapulmonary etiologies (12). Alternatively, different methods to ascertain exposure to airway pressures may account for disparate findings. In the study by Weg and colleagues, they chose the highest airway pressure at any time during the study for patients who did not develop barotrauma (6). This could have attenuated differences between patients with and without barotrauma, leading to bias toward the null. To avoid this problem, we used survival analysis techniques to compare airway pressures at comparable time periods for those with and without barotrauma. Moreover, we explicitly tested different exposure intervals, including baseline, one-day lagged, and concurrent airway pressures.

The observed association between higher PEEP levels and increased risk of barotrauma could reflect confounding results by severity of lung injury, rather than a causal effect. Both higher PEEP levels and greater barotrauma risk could both result from more severe underlying lung injury. If this were true, higher PEEP levels would be a marker of disease severity and not a causal factor. However, the observed association persisted after controlling for baseline PEEP and plateau pressure, which

TABLE 4. RELATIONSHIP BETWEEN INSPIRATORY AND MEAN AIRWAY PRESSURES AND THE RISK OF BAROTRAUMA AMONG 718 PATIENTS WITH ACUTE LUNG INJURY/ACUTE RESPIRATORY DISTRESS SYNDROME

Airway Pressure	RH of Barotrauma (95% CI)*		
	Baseline Measurement	Concurrent Measurement	One-Day Lagged Measurement
Peak inspiratory pressure	1.09 (0.89–1.35)	1.09 (0.89–1.34)	1.05 (0.85–1.30)
Plateau pressure	1.35 (1.04–1.74)	1.21 (0.99–1.48)	1.28 (1.03–1.59)
Mean airway pressure	1.11 (0.96–1.29)	1.08 (0.98–1.20)	1.04 (0.91–1.20)
Driving pressure (plateau pressure – PEEP)	1.17 (0.65–1.61)	1.01 (0.80–1.28)	1.18 (0.43–1.51)

Definition of abbreviations: ALI/ARDS = Acute lung injury/acute respiratory distress syndrome; PEEP = positive end-expiratory pressure; RH = relative hazard.

* RH from unadjusted Cox proportional hazards model (i.e., no covariates included). RH per 10-cm H₂O increment.

None of these airway pressures were significantly associated with the risk of barotrauma in the forward selection proportional hazards regression analysis after PEEP was selected into the model (see Table 5).

TABLE 5. POSITIVE END-EXPIRATORY PRESSURE AND THE RISK OF BAROTRAUMA AMONG 718 PATIENTS WITH ACUTE LUNG INJURY/ACUTE RESPIRATORY DISTRESS SYNDROME

PEEP Measurement	RH of Barotrauma (95% CI)	
	Forward Selection Model	Multivariate Model, Controlling for Other Covariates*
Baseline PEEP	1.20 (0.92–1.56)	1.20 (0.84–1.74)
Concurrent PEEP	1.67 (1.35–2.07)	1.93 (1.44–2.60)
One-day lagged PEEP	1.38 (1.09–1.76)	1.50 (0.98–2.30) [†]

Definition of abbreviations: PEEP = Positive end-expiratory pressure; RH = relative hazard from Cox proportional hazards model (RH per 5-cm H₂O increment of PEEP).

In forward selection model, only PEEP was significantly associated with the risk of barotrauma.

* Controlling for age, ventilator group (6 versus 12 ml/kg), baseline PEEP, baseline tidal volume, baseline plateau pressure, APACHE III score, vasopressor use, serum albumin, hepatic failure, and coagulopathy (includes all variables in model).

[†] When baseline PEEP is omitted from Cox model, RH 1.43 (95% CI 1.02–2.00).

reflect severity of lung injury. Because PEEP and F_IO₂ were jointly determined by protocol (i.e., a PEEP–F_IO₂ scale), oxygenation does not provide an independent marker of lung injury severity. Compliance is also not an independent marker of severity because PEEP is an element of the formula for lung compliance. Even so, addition of alveolar–arterial gradient and lung compliance to the multivariate analysis did not appreciably affect our results. The effect of PEEP also remained after controlling for nonpulmonary markers of illness severity such as APACHE III score and vasopressor use. Although our analysis does not suggest that the relation between PEEP and barotrauma is mediated by lung injury severity, we cannot fully exclude this possibility on the basis of observational data.

Because plateau pressure was manipulated by study protocol, statistical control for tidal volume group could have masked an effect of plateau pressure on barotrauma. However, repeating the analyses while excluding the tidal volume group had no appreciable effect on study results.

We chose an inclusive definition of barotrauma that required either radiographic evidence of air leaks or chest tube placement. This definition was used to capture acute events that would not necessarily have precedent radiographic documentation before chest tube placement. However, these criteria could result in classifying chest tube placement for other reasons, such as pleural effusion, as barotrauma. These alternative indications for tube thoracostomy are probably uncommon, relative to barotrauma events. If this misclassification occurred, it would likely be nondifferential with respect to airway pressures. As a consequence, the impact on study findings would be conservative, attenuating the association between airway pressures and barotrauma. Furthermore, we found similar results after using a more restrictive barotrauma definition that required radiographic evidence of barotrauma.

The present study focuses on early barotrauma, during the first 4–6 days after onset of ALI/ARDS (patients were enrolled within 36 hours of onset). This time period was chosen because daily airway pressure and chest radiographic data were collected, with longer data collection intervals thereafter. Later barotrauma was also rare, with only 19 events occurring after Day 4. Despite the generally held view that most barotrauma occurs late in the course of ALI/ARDS (3, 5), Gammon and colleagues observed that the majority of barotrauma occurred within six days after onset of ALI/ARDS, the time period of our study (8). As the pathophysiology of early and late ALI/ARDS differs (5, 13) with progression to lung fibrosis over time, our results may not be generalizable to later barotrauma.

Given our results, should critical care clinicians use lower levels of PEEP to prevent barotrauma? Although barotrauma is clearly undesirable, it comprises an intermediate health outcome. The most important goal of therapy for ALI/ARDS is to reduce mortality. In the ARDS Network randomized controlled trial, low tidal volume ventilation reduced mortality by 22% without influencing the incidence of barotrauma (9). Low tidal volume ventilation also reduced interleukin-6 levels and nonpulmonary organ failure, suggesting that the beneficial effects of this strategy include attenuation of the systemic inflammatory response to lung injury (9). On theoretical grounds, higher PEEP could further decrease lung injury from repetitive opening and closing of lower compliance lung regions (2, 3). A clinical trial of 53 patients has provided indirect support for this beneficial effect of PEEP (14). Currently, the ARDS Network is conducting a large-scale randomized controlled trial of higher PEEP as a lung-protective strategy, in conjunction with low tidal volume (15). This trial will provide critical information about the effects of PEEP on barotrauma and mortality. Until these trial results are available, we do not suggest that clinicians change their use of PEEP in ALI/ARDS.

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APPENDIX

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