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The Value of PEEP and FiO₂ Criteria in the Definition the Acute Respiratory Distress Syndrome

Martin Britos, MD¹, Elizabeth Smoot, MS², Kathleen D. Liu, MD³, B.Taylor Thompson, MD⁴, William Checkley, PhD, MD⁵, Roy G. Brower, MD⁵, and National Institutes of Health, Acute Respiratory Distress Syndrome Network (ARDS Network) Investigators

¹Pulmonary and Critical Care Medicine, University of Maryland School of Medicine, Baltimore

²Biostatistics Center, Massachusetts General Hospital, Boston

³Nephrology and Critical Care Medicine, University of California, San Francisco

⁴Pulmonary and Critical Care Unit, Massachusetts General Hospital, Boston

⁵Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore

Abstract

OBJECTIVES: The criteria that define acute lung injury and the acute respiratory distress syndrome (ALI/ARDS) include PaO₂/FiO₂ but not positive end-expiratory pressure (PEEP) or FiO₂. PaO₂/FiO₂s of some patients increase substantially after mechanical ventilation with PEEP of 5-10 cm H₂O, and the mortality of these patients may be lower than those whose PaO₂/FiO₂s remain < 200. Also, PaO₂/FiO₂ may increase when FiO₂ is raised from moderate to high levels, suggesting that patients with similar PaO₂/FiO₂s but different FiO₂s have different risks of mortality. The primary purpose of this study was to assess the value of adding baseline PEEP and FiO₂ to PaO₂/FiO₂ for predicting mortality of ALI/ARDS patients enrolled in ARDS Network clinical trials. We also assessed effects of two study interventions on clinical outcomes in subsets of patients with mild and severe hypoxemia as defined by PaO₂/FiO₂.

DESIGN: Analysis of baseline physiologic data and outcomes of patients previously enrolled in clinical trials conducted by the National Institutes of Health ARDS Network.

SETTING: Intensive care units of 40 hospitals in North America.

PATIENTS: 2312 patients with ALI/ARDS.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Only 1.3% of patients enrolled in ARDS Network trials had baseline PEEP < 5 cm H₂O, and 50% had baseline PEEP ≥ 10 cm H₂O. Baseline PaO₂/FiO₂ predicted mortality, but after controlling for PaO₂/FiO₂, baseline PEEP did not predict mortality. In contrast, after controlling for baseline PaO₂/FiO₂, baseline FiO₂ did predict mortality. Effects of two study interventions (lower tidal volumes and fluid-conservative

Corresponding Author: Roy G. Brower, 1830 East Monument Street, Room 549, Baltimore, MD 21205, Phone: 410-614-0158, Fax: 410-955-0036, rbrower@jhmi.edu .

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hemodynamic management) were similar in mild and severe hypoxemia subsets as defined by $\text{PaO}_2/\text{FiO}_2$ ratios.

CONCLUSION: At ARDS Network hospitals, the addition of baseline PEEP would not have increased the value of $\text{PaO}_2/\text{FiO}_2$ for predicting mortality of ALI/ARDS patients. In contrast, the addition of baseline FiO_2 to $\text{PaO}_2/\text{FiO}_2$ could be used to identify subsets of patients with low or high mortality.

Keywords

Acute lung injury; Clinical trials, randomized; Ventilation, mechanical; Positive end-expiratory pressure

Introduction

The American-European consensus conference (AECC) criteria for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) include the acute onset of: (1) bilateral infiltrates on frontal chest radiograph, (2) $\text{PaO}_2/\text{FiO}_2$ less than or equal to 300 Torr (ALI) or 200 Torr (ARDS), and (3) absence of clinical indicators of left atrial hypertension (1). Many clinical studies of ALI/ARDS have used the AECC criteria to identify potentially eligible patients (2-8).

In some patients with bilateral infiltrates, $\text{PaO}_2/\text{FiO}_2$ s were lower than 200 while they received mechanical ventilation with zero or low levels of PEEP, but $\text{PaO}_2/\text{FiO}_2$ s then increased to greater than 200 or even 300 when low to moderate levels of PEEP were subsequently applied (9-12). In these patients, atelectasis could have been an important cause of hypoxemia rather than shunt from consolidation and pulmonary edema. In one study the mortality of these patients was considerably lower than those whose $\text{PaO}_2/\text{FiO}_2$ s remained below 200 after raising PEEP (10). Moreover, in many patients with bilateral infiltrates, $\text{PaO}_2/\text{FiO}_2$ s increased substantially when FiO_2 s were raised from moderate to high levels (11,13). This suggests that among patients with similar $\text{PaO}_2/\text{FiO}_2$ s, oxygenation failure is worse and risk of death is higher in those receiving higher FiO_2 s. Thus, without standardized or minimum PEEP and FiO_2 criteria, the AECC criteria could identify a heterogeneous group of patients, some of whom are at low risk of adverse outcomes such as death. If so, then use of the AECC criteria to identify patients for ALI/ARDS trials, without PEEP and FiO_2 criteria, could reduce the power of clinical trials because potential effects of new interventions may be smaller in patients with mild disease. Some investigators have speculated that the results of trials that enrolled ALI/ARDS patients using the AECC criteria without a minimum PEEP level were confounded by imbalances between study groups in patients with mild and severe lung injury that could not be detected without increasing PEEP (10). The National Institutes of Health ARDS Network used the AECC criteria as the inclusion criteria for most of its clinical trials since 1996 (2-5,14,15). Exclusion criteria reduced heterogeneity of the enrolled populations, but patients were not excluded if they were on zero or low PEEPs or low FiO_2 s. The primary purpose of the present study was to explore the potential value of adding PEEP and FiO_2 criteria to the AECC criteria to exclude patients with low risk of mortality. A secondary purpose was to address the concern that in patients with mild disease, potential effects of an intervention may be small or nonexistent. To address this concern we examined effects of two study interventions on subsets of ALI/ARDS patients with mild and severe hypoxemia. Parts of this study were presented previously in abstracts (16,17).

Materials and Methods

We reviewed existing data from 2,443 patients enrolled in 4 ARDS Network clinical trials from 1996 to 2005 (2-5). Etiologic causes of ALI/ARDS were listed as pneumonia (41%), sepsis (24%), aspiration (15%), trauma (9%), and other causes (11%). Baseline ventilator settings were set by clinicians and were available within 4 hours before the time of randomization. Baseline values usually occurred several or many hours after the criteria for ALI were initially met.

We created a frequency-distribution of baseline PEEP levels. To characterize the relationship between baseline PEEP and FiO_2 , we divided baseline FiO_2 into 10 subsets, each with FiO_2 range of 0.10, and then displayed distributions of PEEP within each interval. We calculated a correlation coefficient and corresponding 95% confidence interval to assess the relationship between baseline PEEP and FiO_2 .

We created tertiles of $\text{PaO}_2/\text{FiO}_2$, each containing approximately 770 patients. We used Cochrane-Armitage trend tests to determine if $\text{PaO}_2/\text{FiO}_2$ tertiles predicted mortality. We created three groups of baseline PEEP (≤ 5 , 6-10, and ≥ 11 cm H_2O) and baseline FiO_2 (≤ 0.50 , 0.50 – 0.69, and ≥ 0.70) within each $\text{PaO}_2/\text{FiO}_2$ tertile. We used Cochrane-Armitage trend tests to determine if differences in PEEP and FiO_2 within each $\text{PaO}_2/\text{FiO}_2$ tertile were associated with differences in mortality.

Oxygenation index (OI) combines mean airway pressure (mPaw) with $\text{PaO}_2/\text{FiO}_2$: $\text{OI} = \text{mPaw} \times 100 \times \text{FiO}_2/\text{PaO}_2$. Many studies suggest that OI is useful to assess severity of oxygenation failure and risk of death in individual ALI patients (18-20). To compare the value of $\text{PaO}_2/\text{FiO}_2$ and OI for predicting mortality, we calculated areas under the curve for receiver operating characteristics for both $\text{PaO}_2/\text{FiO}_2$ and OI.

In previous studies, mechanical ventilation with lower tidal volumes reduced mortality (2), and a fluid-conservative hemodynamic strategy was associated with greater ventilator-free days (4). To test the hypothesis that the effects of these interventions were greater in patients with more severe illness, we compared the effects of the interventions in patients with mild and severe baseline hypoxemia. First, we ranked patients in the tidal volume hemodynamic strategy trials according to baseline $\text{PaO}_2/\text{FiO}_2$. We then divided the patients in each trial into baseline $\text{PaO}_2/\text{FiO}_2$ quartiles. Patients with mild and severe hypoxemia were defined as those in the highest and lowest $\text{PaO}_2/\text{FiO}_2$ quartiles, respectively. We compared the effects of study interventions in the highest and lowest $\text{PaO}_2/\text{FiO}_2$ quartiles.

In the ARDS Network trial of higher versus lower PEEP (3), patients in the higher PEEP study group received PEEPs of at least 12 cm H_2O after randomization. To assess effects of approximately 12-18 hours of mechanical ventilation with these higher PEEP levels, we compared frequency distributions of $\text{PaO}_2/\text{FiO}_2$ at baseline and on day 1 after randomization. We calculated mortality rates for patients with $\text{PaO}_2/\text{FiO}_2$ ratios < 200 , 201-300, and > 300 on the day after randomization. Patients or their surrogates gave informed consent for the original clinical trials. The institutional review board of Johns Hopkins Medicine approved this study of existing data with a waiver of the requirement for informed consent.

Results

Complete physiologic and outcomes data were available on 2312 patients enrolled in the 4 clinical trials. Of these, 77% had $\text{PaO}_2/\text{FiO}_2 \leq 200$; mortality in this group was 31.4%. Of the remaining 23% with $\text{P/F} > 200$, mortality was 21.9% ($P < 0.0001$ for the comparison of mortalities).

The distribution of baseline PEEPs for all subjects is shown in Figure 1. The most frequently used baseline PEEPs were 5 and 10 cm H₂O. Very few patients (1.3%) had baseline PEEPs less than 5 cm H₂O. Approximately 50% of all patients had baseline PEEPs of 10 cm H₂O or greater.

The relationship between the clinician-set baseline PEEP and FiO₂ levels is shown in Figure 2. Most clinicians selected PEEPs of 5, 8 or 10 cm H₂O. When FiO₂ was 50% or less, most clinicians selected either 5 or 8 cm H₂O. When FiO₂ was above 50%, most clinicians selected 10 cm H₂O. There was substantial variability in how baseline PEEPs and FiO₂s were combined. However, there were relatively few patients with high baseline PEEP combined with low baseline FiO₂. Levels of baseline PEEP and FiO₂ were positively and significantly correlated ($\rho = 0.47$, 95% CI 0.42 to 0.51; $P < 0.001$). Thus, although individual approaches varied, clinicians as a whole had apparently adjusted PEEP and FiO₂ in concert.

In univariate analyses, lower baseline PaO₂/FiO₂ predicted 60 day mortality (Table 2). Higher baseline PEEP levels also predicted higher 60 day mortality. Within each PEEP range (≤ 5 , 6-10, > 10 cm H₂O) mortality increased with decreasing PaO₂/FiO₂ (Table 2). However, within each PaO₂/FiO₂ tertile mortality did not increase significantly with increasing PEEP. Like higher PEEP, higher FiO₂ also predicted higher 60 day mortality (Table 3). However, unlike higher PEEP, within each PaO₂/FiO₂ tertile mortality increased significantly with increasing FiO₂.

The AUCs of the receiver operating characteristics for OI and PaO₂/FiO₂ were 0.58 and 0.57, respectively. Thus, the addition of mean airway pressure to PaO₂/FiO₂ did not improve mortality prediction.

We next compared the effects of the lower tidal volume and fluid-conservative hemodynamic management strategies on patients in the mildest and most severe quartiles of baseline hypoxemia as defined by PaO₂/FiO₂. Effects of tidal-volume reduction on mortality were similar in the mild and severe hypoxemia quartiles of the tidal volume trial (Figure 3). The interaction between study group and hypoxemia quartile was not significant ($P = 0.814$). Also, the interaction between study group and FiO₂ quartiles was not significant ($P = 0.259$). The effect of fluid-conservative management on ventilator-free days was similar in the mild and severe hypoxemia quartiles of the hemodynamic management trial (Figure 4). The interaction between study group and hypoxemia subset was not significant ($P = 0.106$).

Frequency distributions of PaO₂/FiO₂ at baseline and on the first day after enrollment in the higher PEEP and lower PEEP study groups of the ARDS Network PEEP trial are shown in Figure 5. The proportions of patients in the higher PEEP group with baseline PaO₂/FiO₂ < 200 , 201-300, and > 300 were 79%, 17%, and 4%, respectively. After approximately 12-18 hours of ventilation with PEEPs of at least 12 cm H₂O in the higher PEEP group, these proportions shifted to 50%, 36%, and 14%, respectively. The mortality rates of these groups, categorized according to PaO₂/FiO₂ after 12-18 hours of mechanical ventilation with higher PEEP, were 31, 28, and 13.5%, respectively.

Discussion

The AECC criteria were designed to identify a large group of patients who could be of concern to investigators and clinicians because of ALI or ARDS (1). Because these criteria are inclusive, the resulting population may be very heterogeneous in disease severity and clinical outcomes. Therefore, most clinical trials exclude many patients who meet the AECC criteria to reduce heterogeneity in the enrolled cohorts. ARDS Network trials did not exclude patients who had received zero or very low level PEEPs at baseline. However, only

1.3% of patients enrolled in ARDS Network trials had baseline PEEP levels less than 5 cm H₂O, and approximately 50% of patients had baseline PEEPs of 10 cm H₂O or more. Baseline PEEP alone predicted mortality, but after controlling for baseline PaO₂/FiO₂, PEEP did not predict mortality (Table 2). Moreover, effects of two effective study interventions were similar in quartiles of patients defined by the highest and lowest PaO₂/FiO₂ ratios, without knowledge of baseline PEEP. These results suggest that at ARDS Network hospitals, addition of a minimum level of PEEP to the PaO₂/FiO₂ ratio would not have improved the ability to identify patients at higher risk of death or patients more or less likely to benefit from a new intervention. However, substantial proportions of patients received PEEPs of less than 5 cm H₂O in some other studies of mechanically ventilated patients. Some of these could have had mild ALI/ARDS with low mortality rates (21-23). To avoid enrolling these patients in clinical trials, a minimum PEEP of 5 cm H₂O could be required in the eligibility criteria.

In previous studies of ALI/ARDS, some patients with PaO₂/FiO₂ ≤ 200 had PaO₂/FiO₂s that were greater than 200 or even 300 after mechanical ventilation with PEEPs of 5-10 cm H₂O or greater (9-12). In three of these studies, the mortality rates of the patients with higher PaO₂/FiO₂ ratios after ventilation with PEEP were substantially lower than those whose PaO₂/FiO₂ ratios remained below 200 (9-11). For example, in one of the previous studies, patients were ventilated for 24 hours with PEEP of at least 10 cm H₂O before categorizing by PaO₂/FiO₂. Mortality rates for cohorts with PaO₂/FiO₂ < 200, 201-300, and > 300 were 45.5, 20, and 6.3%, respectively (10). However, some of the patients included in these studies had received PEEPs of less than 5 cm H₂O before the standardized ventilator settings. In contrast, only 1% of patients enrolled in ARDS Network trials had received PEEPs of less than 5 cm H₂O before enrollment. Moreover, patients enrolled in the ARDS Network studies had received mechanical ventilation for at least several hours and frequently for more than 24 hours before the baseline AECC data were recorded. Thus, the baseline ventilator settings and arterial oxygenation of the patients enrolled in ARDS Network trials may have been more similar to those of the patients in the previous studies *after* ventilation with standardized PEEP than to the initial measurements recorded in the previous studies *before* ventilation with standardized PEEP.

In single variable analyses, baseline PEEP and baseline PaO₂/FiO₂ both predicted mortality. However, some clinicians had apparently used higher PEEP in conjunction with higher FiO₂ (or lower PEEP with lower FiO₂), presumably to achieve arterial oxygenation goals (Figure 2). Therefore, baseline PaO₂/FiO₂ conferred additional information about baseline PEEP. After controlling for baseline PaO₂/FiO₂, the addition of baseline PEEP did not predict mortality. Moreover the addition of mPaw to PaO₂/FiO₂ (in the OI) did not increase the predictive value of PaO₂/FiO₂. Clinicians' manipulations of PEEP probably caused similar changes in mPaw.

The ARDS Network trials also did not use FiO₂, independent of PaO₂/FiO₂, to exclude patients at low risk of adverse outcomes. In contrast to the findings with PEEP, FiO₂ did predict mortality after controlling for PaO₂/FiO₂. However, in each of the PaO₂/FiO₂ tertiles, the range of mortality between the lowest and highest FiO₂ ranges was approximately 10%, and the lowest mortality (in the subset with the highest PaO₂/FiO₂ and lowest FiO₂) was still substantial at 21%. A subset with substantially lower mortality (with even lower FiO₂s and higher PaO₂/FiO₂s) could probably be identified, but this subset would be quite small.

Our results and interpretations are from analyses of the cohorts of patients enrolled in the trials, which includes patients with several etiologic causes of ALI. Effects of PEEP may be different in groups of patients with direct versus indirect lung injury (24). If so, then PEEP

could add to the predictive value of $\text{PaO}_2/\text{FiO}_2$ in one of these subsets but not the other. However, more recent studies did not demonstrate different effects of PEEP in direct versus indirect lung injury (25,26).

In this study, mortality was lower in patients whose $\text{PaO}_2/\text{FiO}_2$ ratios were greater than 200 than in those whose $\text{PaO}_2/\text{FiO}_2$ ratios were lower than 200. The difference in mortality was similar to but not as marked as in the previous studies (9-11) in which patients received standardized ventilator settings with 5-10 cm H_2O PEEP for up to 24 hours before determination of $\text{PaO}_2/\text{FiO}_2$. This difference between our study and the previous studies may be attributable to higher levels of PEEP received by some patients in our study at baseline than in the previous studies before patients received standardized ventilator settings for up to 24 hours. Patients with $\text{PaO}_2/\text{FiO}_2$ ratios greater than 300 at the time of screening were not eligible for enrollment in ARDS Network trials, and their $\text{PaO}_2/\text{FiO}_2$ ratios and ventilator settings would not be available in our dataset.

Eligibility criteria for clinical trials are frequently designed to avoid enrollment of patients who are unlikely to benefit from a new study intervention, such as those with very low mortality rates, especially if the intervention carries substantial risk. Mortality was significantly lower in patients with higher $\text{PaO}_2/\text{FiO}_2$ ratios in our cohort (Table 2). However, the effects of lower tidal volume and fluid-conservative hemodynamic management were similar among groups of patients with very low and high baseline $\text{PaO}_2/\text{FiO}_2$ ratios. Thus, inclusion of patients with mild hypoxemia at baseline did not diminish the power of the trials. On the other hand, by including patients with higher $\text{PaO}_2/\text{FiO}_2$ ratios, the trial results are applicable to a greater proportion of ALI/ARDS patients. Perhaps we could identify a subset with milder impairment in arterial oxygenation in which mortality was even lower; the effects of useful interventions could be less or absent in this subset. However, this subset would probably be small.

In two previous trials in ARDS patients, new therapeutic interventions appeared to be effective only in subsets of patients with severe disease (27,28). However, in the ARDS Network tidal volume and hemodynamic management trials, effects of the interventions were similar across the ranges of severity as defined by $\text{PaO}_2/\text{FiO}_2$. Thus, patients with mild and moderate ALI/ARDS, as defined by $\text{PaO}_2/\text{FiO}_2$, can benefit from some interventions that reduce mortality or time on mechanical ventilation. It is also possible that there is a level of severity above which outcomes are less modifiable by a new clinical trial intervention.

A strength of this study is the large number of patients with pertinent data and the large number of contributing hospitals and intensive care units. The data were collected during conduct of the ARDS Network trials, when patients were enrolled in clinical trials. Therefore the data are relevant to the concerns raised regarding the lack of a minimum PEEP in the eligibility criteria of these trials. A limitation of this study is that while our conclusions apply to the specific trials conducted and to the ARDS Network hospitals where they were conducted, they may not apply in other circumstances. Clinicians' practices for setting PEEP and FiO_2 are highly variable (22,29,30). It is possible that there is greater variability in how PEEP is used at other hospitals. Some clinicians prefer to use very low PEEP, even when FiO_2 has been raised to high levels. In such circumstances, a minimum PEEP criterion for eligibility in a clinical trial could help to avoid enrollment of patients with very mild disease. It is also possible that our analyses could not detect a small predictive value of baseline PEEP when added to baseline $\text{PaO}_2/\text{FiO}_2$ for predicting mortality because of inadequate sample size. Finally, since many patients with ALI/ARDS were excluded from ARDS Network trials, our analysis may not be applicable to those who were not included.

Conclusion

The addition of PEEP to the AECC criteria would have made little or no difference in the mortality of the patients enrolled in ARDS Network trials. In contrast, the addition of FiO₂ to the AECC criteria could be used to identify subsets of patients with relatively low or high mortality. However, our analyses do not support the concern that the effectiveness of interventions varies with the severity of oxygenation failure in subsets of ALI/ARDS patients.

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Figure 1. Frequency distribution of baseline PEEP. Numbers over bars indicate numbers of patients at each level of PEEP and percentages of all patients.

Figure 2. Relationship of baseline PEEP to baseline FiO₂. The width of each bar is proportional to the number of patients at each PEEP-FiO₂ combination. Red bars indicate median PEEP levels at each of the FiO₂ ranges.

Figure 3.

Effects on mortality of tidal volume reduction in mild and severe hypoxemia subsets in the ARDS Network clinical trial of mechanical ventilation with traditional versus lower tidal volumes (2). Effects of tidal volume reduction were not significantly different in the mild and severe hypoxemia subsets. Mortality rates in the lower and higher tidal volume study groups are represented by the light bars and dark bars, respectively. Values in parentheses are standard deviations.

Figure 4.

Effects on ventilator-free days of fluid-conservative versus fluid-liberal hemodynamic management in mild and severe hypoxemia subsets of the ARDS Network clinical trial of hemodynamic management strategies (4). Effects of hemodynamic management strategy were not significantly different in the mild and severe hypoxemia subsets. Ventilator-free days in the fluid-conservative and fluid-liberal study groups are represented by the light bars and dark bars, respectively. Values in parentheses are standard deviations.

Figure 5. Frequency distributions of PaO₂/FiO₂ ratio at baseline (light bars) and on the first day after enrollment (dark bars) in the ARDS Network clinical trial of mechanical ventilation with lower versus higher PEEP (3). Left: Higher PEEP study group. Right: Lower PEEP study group.

Table 1

ARDS Network trials used for the current study

	Number of Subjects	Enrollment Period	Baseline PaO ₂ /FiO ₂ [*]	Baseline PEEP [*]
Traditional versus Lower Tidal Volumes (2)	904 [#]	1996-1999	148 ± 69	8.4 ± 3.9
Higher versus Lower PEEP (3)	549	1999-2002	150 ± 68	9.5 ± 4.2
Fluids and Catheters ^{&} (4,5)	1000	2000-2005	152 ± 70	9.5 ± 4.0

^{*} Baseline PaO₂/FiO₂ and PEEP values (± SD) are for all patients enrolled in the trials

[#] 904 includes 861 patients randomized to traditional or lower tidal volumes and 43 patients who, after the tidal volume trial completed enrollment, were assigned to the lower tidal volume protocol during continued enrollment in another trial that had been combined with the tidal volume trial in a factorial design (14).

[&] Two trials were conducted together in a factorial design in the same patients.

Table 2Mortality rates according to PaO₂/FiO₂ tertiles and PEEP levels.

	PEEP ≤ 5 (n = 731)	5 < PEEP ≤ 10 (n = 999)	11 ≥ PEEP (n = 582)	Total^B
PaO ₂ /FiO ₂ > 175 (n = 771)	23.1 ± 5%	22.0 ± 6%	25.9 ± 18%	23.1 ± 2% (p > 0.70)
110 < PaO ₂ /FiO ₂ ≤ 175 (n = 763)	31.4 ± 9%	25.4 ± 5%	28.1 ± 13%	27.8 ± 3% (p > 0.37)
PaO ₂ /FiO ₂ ≤ 115 (n = 778)	35.7 ± 2%	35.2 ± 7%	38.2 ± 7%	36.5 ± 3% (p > 0.49)
Total ^A	27.8 ± 3% (p < 0.0001)	27.8 ± 2% (p < 0.0001)	33.3 ± 4% (p < 0.0001)	

Overall mortality was 29.2%. ± values are standard errors. Data analyzed using Cochran-Armitage trend test.

^A Within each PEEP range there is a highly significant increase in mortality with lower PaO₂/FiO₂ levels (p < 0.0001).

^B Within each PaO₂/FiO₂ tertile there is no significant difference in mortality with increasing PEEP levels.

Table 3Mortality rates according to PaO₂/FiO₂ tertiles and FiO₂ levels.

	FiO₂ ≤ 0.50 (n = 946)	0.50 < FiO₂ < 0.70 (n = 553)	0.70 ≤ FiO₂ (n = 819)	Total^B
PaO ₂ /FiO ₂ > 175 (n = 771)	21 ± 2% (n = 593)	26 ± 4% (n = 98)	33 ± 5% (n = 84)	23 ± 2% (p = 0.015)
115 < PaO ₂ /FiO ₂ ≤ 175 (n = 763)	25 ± 2% (n = 330)	26 ± 3% (n = 287)	36 ± 4% (n = 148)	28 ± 3% (p = 0.016)
PaO ₂ /FiO ₂ ≤ 115 (n = 778)	30 ± 10% (n = 23)	28 ± 3% (168)	39 ± 2% (n = 587)	37 ± 3% (p = 0.017)
Total ^A	23 ± 2% (p = 0.014)	27 ± 2% (p = .019)	38 ± 2% (p = 0.017)	

Overall mortality was 29.2%. ± values are standard errors. Data analyzed using Cochran-Armitage trend tests.

^A Within each FiO₂ range there is a significant increase in mortality with lower PaO₂/FiO₂ levels.

^B Within each PaO₂/FiO₂ tertile, there is a significant increase in mortality with increasing FiO₂ levels.