Oxygen Exposure Resulting in Arterial Oxygen Tensions Above the Protocol Goal Was Associated With Worse Clinical Outcomes in Acute Respiratory Distress Syndrome*

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Objectives: High fractions of inspired oxygen may augment lung damage to exacerbate lung injury in patients with acute respiratory distress syndrome. Participants enrolled in Acute Respiratory Distress Syndrome Network trials had a goal partial pressure of oxygen in arterial blood range of 55–80 mm Hg, yet the effect of oxygen exposure above this arterial oxygen tension range on clinical outcomes is unknown. We sought to determine if oxygen exposure that resulted in a partial pressure of oxygen in arterial blood above goal (> 80 mm Hg) was associated with worse outcomes in patients with acute respiratory distress syndrome.

Design: Longitudinal analysis of data collected in these trials.

Setting: Ten clinical trials conducted at Acute Respiratory Distress Syndrome Network hospitals between 1996 and 2013.

Subjects: Critically ill patients with acute respiratory distress syndrome.

Interventions: None.

Measurements and Main Results: We defined above goal oxygen exposure as the difference between the fraction of inspired oxygen and 0.5 whenever the fraction of inspired oxygen was above 0.5 and when the partial pressure of oxygen in arterial blood was above 80 mm Hg. We then summed above goal oxygen exposures in the first five days to calculate a cumulative above goal oxygen exposure. We determined the effect of a cumulative 5-day above goal oxygen exposure on mortality prior to discharge home at 90 days. Among 2,994 participants (mean age, 51.3 yr; 54% male) with a study-entry partial pressure of oxygen in arterial blood/fraction of inspired oxygen that met acute respiratory distress syndrome criteria, average cumulative above goal oxygen exposure was 0.24 fraction of inspired oxygen-days (interquartile range, 0–0.38). Participants with above goal oxygen exposure were more likely to die (adjusted interquartile range odds ratio, 1.20; 95% CI, 1.11–1.31) and have lower ventilator-free days (adjusted interquartile range mean difference of −0.83; 95% CI, −1.18 to −0.48) and lower hospital-free days (adjusted interquartile range mean difference of −1.38; 95% CI, −2.09 to −0.68). We observed a dose-response relationship between the cumulative above goal oxygen exposure and worsened clinical

*See also p. 646.

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Dr. Aggarwal contributed to this article as an employee of Johns Hopkins University. The views expressed in this article are his own and those of Johns Hopkins University School of Medicine, and do not necessarily represent the views of the National Institutes of Health or the U.S. government.

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outcomes for participants with mild, moderate, or severe acute respiratory distress syndrome, suggesting that the observed relationship is not primarily influenced by severity of illness.

Conclusions: Oxygen exposure resulting in arterial oxygen tensions above the protocol goal occurred frequently and was associated with worse clinical outcomes at all levels of acute respiratory distress syndrome severity. (*Crit Care Med* 2018; 46:517–524)

Key Words: acute respiratory distress syndrome; clinical outcomes; oxygen therapy

Acute respiratory distress syndrome (ARDS) is a critical illness syndrome associated with a risk factor that induces acute hypoxemic respiratory failure with a partial pressure of oxygen in arterial blood (Pa_{O_2})/fraction of inspired oxygen (F_{IO_2}) less than or equal to 300 mm Hg while receiving positive end-expiratory pressure (PEEP) greater than or equal to 5 cm H_2O (1). Despite beneficial interventions, ARDS mortality remains high at 30–40% (2–6), suggesting that other variables may affect clinical outcomes. Oxygen is a first-line therapy for hypoxemia in ARDS, with the goal to achieve acceptable arterial oxygenation and to maintain tissue viability. However, it is not known whether targeting a specified oxygenation goal affects clinical outcomes in ARDS.

Mechanically ventilated patients are frequently exposed to higher F_{IO_2}s than necessary to achieve adequate arterial oxygenation, and often for prolonged periods. In an analysis of ARDS patients, Rachmale et al (7) found excessive oxygen use, defined as a F_{IO_2} greater than or equal to 0.5 when oxyhemoglobin saturation (Sp_{O_2}) was greater than 92%, in 74% of patients for a median 17 of the first 48 hours of ventilatory support. Similarly, de Graaff et al (8) reported that among mechanically ventilated patients with a Pa_{O_2} greater than 120 mm Hg, the F_{IO_2} was reduced in only 25% of instances over a 24-hour period.

Excess oxygen is detrimental in several acute, life-threatening illnesses. A meta-analysis of critically ill patients following cardiac arrest, traumatic brain injury, stroke, and postcardiac surgery found that above normal arterial Pa_{O_2} values correlated with higher mortality (9), with the strongest association following cardiac arrest (10). Helmerhorst et al (11) found that ICU patients exposed to severe hyperoxia (Pa_{O_2} > 200 mm Hg) had higher mortality rates and fewer ventilator-free days (VFDs) when compared with mild hyperoxia (Pa_{O_2} 121–200 mm Hg) or normoxia (Pa_{O_2} 60–100 mm Hg). Potential mechanisms of damage induced by high levels of oxygen include an excessive proinflammatory response that can impede innate immunity (12) and augment lung injury (13), generation of reactive oxygen species that damage cells, and vasoconstriction to vital organs (14, 15). Preexistent lung damage in ARDS may impair antioxidant enzyme production and other adaptive responses, rendering patients particularly susceptible to oxygen-induced injury (16).

We analyzed if the cumulative effect of excess oxygen contributed toward worse clinical outcomes despite enrollment into ARDS clinical trials with a protocol targeting a Pa_{O_2} goal range (55–80 mm Hg). We quantified excess (i.e., above goal) oxygen exposure for any F_{IO_2} greater than 0.5 when the Pa_{O_2} was greater than 80 mm Hg.

METHODS

Description of Studies

We used data of ARDS patients enrolled in randomized clinical trials (RCTs) (17–25), excluding those assigned to receive targeted tidal volumes of 12 mL/kg of predicted body weight (17). All trials required that PEEP or F_{IO_2} be titrated to a common target of 55–80 mm Hg or Sp_{O_2} of 88–95%. When both Pa_{O_2} and Sp_{O_2} were available, Pa_{O_2} took precedence. Adults 18 years old or older were enrolled from 1996 to 2013 at participating hospitals, and were eligible if intubated, were receiving mechanical ventilation, and met criteria for acute lung injury (26). We included 10 trials enrolled participants within 36 (17, 22–24) or 48 hours (18, 21, 25) after inclusion criteria were met. Data collection followed common protocols (17–25). This analysis was approved by the institutional review board of the Johns Hopkins School of Medicine in Baltimore, United States.

Outcomes

The primary outcome was mortality prior to discharge home at 90 days (17–25). Secondary outcomes included VFDs and hospital-free days (HFDs) scores (27).

Assessment of Above Goal Oxygen Exposure

We defined above goal oxygen exposure a priori as any value above an F_{IO_2} greater than 0.5 among participants with a Pa_{O_2} greater than 80 mm Hg from altitude-adjusted morning arterial blood gases (ABGs) (17). With a Pa_{O_2} greater than 80 mm Hg and a corresponding F_{IO_2} greater than 0.5, excess oxygen (F_{IO_2}-days) was calculated as F_{IO_2} – 0.5. Using this definition, study participants with a higher relative F_{IO_2} at the same arterial oxygen tension had more above goal exposure for that time interval. We calculated a cumulative exposure as the sum of above goal oxygen exposures over the first 5 days because data points were collected each day during that interval. Participants may not have had an ABG during that 5-day interval either because it was not taken or because the participant was extubated or died. In those cases, we divided the cumulative above goal oxygen exposure by the number of days when an ABG was available and multiplied by 5, and conducted sensitivity analyses with subsets of data for participants with greater than or equal to 4 ABGs. The average number of ABGs per participant was 4.1, so we believe that this assumption is likely to have had a small effect on our analysis.

Definitions

We analyzed all participants with ARDS on the day of study entry and used Berlin criteria to define ARDS severity (1). We calculated tidal volumes by mL/kg PBW using standard equations (28) and static compliance as tidal volume/(inspiratory plateau pressure – PEEP).

Biostatistical Methods

We evaluated the association between cumulative above goal oxygen exposure at 5 days after enrollment and in-hospital death at 90 days. We calculated octiles of cumulative above

goal oxygen exposure for values above zero and visually examined the dose-response relationship between categories of above goal oxygen exposure (no above goal exposure followed by octiles of cumulative oxygen exposure) and either the probability or log odds of in-hospital death. We used logistic regression to model the odds of in-hospital death at 90 days as a function of the cumulative above goal oxygen exposure at 5 days, age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) III score, PEEP, and baseline ARDS severity (14). We reported odds ratios (ORs) of mortality for observed values of the cumulative above goal oxygen exposure in the interquartile range. We conducted severity-stratified analyses to determine if baseline severity modified the association between cumulative above goal oxygen exposure and in-hospital death at 90 days, and we included indicator variables for each trial in our models to account for potential differences among trials. As sensitivity analyses, we modified the definition of above goal oxygen exposure for different thresholds of F_{IO_2} (0.3, 0.4, and 0.6) and Pa_{O_2} (85, 90, 95, and 100 mm Hg).

We also evaluated the association between cumulative above goal oxygen exposure at 5 days after enrollment and either VFDS or HFDS. We used linear regression to model free days as a function of the cumulative above goal oxygen exposure at 5 days, age, sex, APACHE III, PEEP, and ARDS severity at study entry. We used analysis of variance to compare means of continuous variables between subgroups and chi-square tests to compare proportions of dichotomous variables. We conducted analyses in R (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

RESULTS

Participant Characteristics

A total of 4,361 participants were enrolled in 10 RCTs in 1996–2013. Of these, 4,243 (97%) had at least one ABG in the first 5 days, 3,815 (87%) were managed with protocols that targeted tidal volumes of 6 mL/kg PBW, and 2,994 (69%) had an ABG on day 0 to define severity. Among 2,994 participants, average age ± SD was 51.3 ± 16.2 years, average APACHE III was 91.8 ± 29.9, and 54% were male. A total of 23% (687), 55% (1,659), and 22% (648) had mild, moderate, and severe ARDS on day 0, respectively. No differences in age (mean, 51.4 vs 52.6 yr; $p = 0.07$), sex (mean, 53.4% vs 52.3%; $p = 0.63$), or APACHE III (mean, 92.7 vs 91.5; $p = 0.40$) were found between participants who did not have a day 0 ABG and those who did; however, tidal volumes (7.1 vs 7.6 mL/kg PBW; $p < 0.001$) and PEEP (9.0 vs 9.4; $p < 0.01$) were lower. Static compliance was also not different (34.2 vs 33.1 mL/cm H_2O; $p = 0.23$).

We summarized differences in participant characteristics by categories of cumulative above goal oxygen exposure at 5 days (**Table 1**). Disease severity was greater with higher categories of above goal oxygen exposure, as evidenced by higher APACHE III, higher minute ventilation, higher plateau pressure, higher PEEP, lower pH, and lower systolic blood pressure.

Patterns of Above Goal Oxygen Exposure

A total of 1,549 study participants (48%) had a cumulative above goal oxygen exposure above 0. Among 2,994 participants, average ± SD cumulative above goal oxygen exposure at 5 days

TABLE 1. Participant Characteristics by Categories of Above Goal Oxygen Exposure

Characteristic or Factor	Cumulative Above Goal Oxygen Exposure at 5 d				*p*
	None	0.02–0.24	0.25–0.49	0.5–2.50	
Sample size	1,549	527	330	588	
Age (yr), mean (SD)	52.4 (16.4)	50.4 (15.6)	51.2 (15.6)	49.4 (16.7)	< 0.001
% male (n)	55 (847)	54 (286)	55 (181)	50 (292)	0.20
Acute Physiology and Chronic Health Evaluation III, mean (SD)	87.8 (29.7)	90.9 (29.0)	96.4 (28.5)	100.5 (30.0)	< 0.001
Body mass index (kg/m^2), mean (SD)	29.0 (7.6)	29.5 (8.8)	28.8 (8.1)	28.9 (8.6)	0.57
Tidal volume/kg predicted body weight, mean (SD)	7.6 (1.9)	7.7 (2.0)	7.5 (2.0)	7.5 (2.2)	0.21
Minute ventilation (L/min), mean (SD)	11.6 (3.8)	12.1 (3.6)	12.4 (4.0)	12.6 (3.9)	< 0.001
Plateau pressure (cm H_2O), mean (SD)	25.2 (7.0)	26.1 (6.7)	27.5 (7.1)	28.3 (7.9)	< 0.001
Positive end-expiratory pressure (cm H_2O), mean (SD)	8.5 (3.5)	9.7 (3.5)	11.0 (4.1)	11.6 (4.4)	< 0.001
pH, mean (SD)	7.38 (0.08)	7.37 (0.09)	7.36 (0.08)	7.34 (0.10)	< 0.001
Fraction of inspired oxygen, mean (SD)	0.54 (0.17)	0.63 (0.11)	0.73 (0.13)	0.87 (0.16)	< 0.001
Partial pressure of oxygen in arterial blood (mm Hg), mean (SD)	79.6 (18.3)	92.7 (26.1)	99.3 (33.8)	110.2 (46.5)	< 0.001
Systolic blood pressure, mean (SD)	115.3 (20.8)	113.0 (20.3)	112.0 (20.3)	110.8 (20.3)	< 0.001
90-d mortality (%)	25	23	29	37	< 0.001
Ventilator-free days score, mean (SD)	15.2 (14.2)	14.2 (10.1)	12.6 (10.6)	10.4 (10.5)	< 0.001
Hospital-free days score, mean (SD)	30.6 (21.6)	29.8 (20.5)	26.9 (21.4)	23.4 (21.7)	< 0.001

was 0.24 ± 0.41 FIO_2-days. Daily mean excess among all participants decreased from 0.09 (± 0.16) on day 0 to 0.02 (± 0.09) on day 4, and the proportion of above goal oxygen exposure decreased from 32% on day 0 to 10% on day 4. We summarized the distribution of cumulative above goal oxygen exposure at 5 days stratified by ARDS severity (**Fig. 1**). Participants with mild ARDS had a larger proportion of at goal oxygen exposure days when compared with participants with moderate or severe ARDS (71% vs 46% vs 46%; $p < 0.001$). Cumulative above goal oxygen exposure in severe ARDS was higher at any percentile when compared with those with moderate ARDS, followed by those with mild ARDS (Fig. 1). Average cumulative above goal oxygen exposure increased ($p < 0.001$) but the proportion of participants with severe ARDS decreased over the time period of eligible clinical trials ($p < 0.001$) (**e-Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D79).

Association Between Above Goal Oxygen Exposure and Clinical Outcomes

In-hospital mortality at 90 days was greater with higher categories of above goal oxygen exposure (**Fig. 2**). The distribution across categories of cumulative above goal oxygen exposure, ranging from 0.1–0.2 to 1–2.5, was fairly even. The slope of the relationship between cumulative above goal oxygen exposure and the log odds of mortality was approximately linear, thus supporting the use of a single slope in our regression analyses to model this relationship.

We summarized regression results for clinical outcomes by cumulative above goal oxygen exposure and other a priori selected variables (**Table 2**). Participants with cumulative above goal oxygen exposure were more likely to die in-hospital (adjusted interquartile range [AIQR] OR, 1.20; 95% CI, 1.11–1.31) have a lower VFDS (AIQR mean difference of –0.83; 95% CI, –1.18 to –0.48) and HFDS (AIQR mean difference of –1.38; 95% CI, –2.09 to –0.68). In sensitivity analyses, modifying the FIO_2 threshold to a lower (0.3 or 0.4) or higher value (0.6) did not affect the direction of the association and, in most cases, the statistical significance (**e-Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D79). Modifying the PaO_2 threshold to a higher value (85, 90, 95, or 100 mm Hg) also did not affect the direction of the association; however, the magnitude of the association was weakened (**e-Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/D79). The relationship between above goal oxygen exposure and mortality does not appear to be affected by residual confounding after accounting for potential differences in hospital mortality by clinical trial (AIQR OR, 1.21; 95% CI, 1.11–1.32). In subset analyses, the association between cumulative above goal oxygen exposure and mortality was not different for participants with either greater than or equal to 4 ABGs (AIQR OR, 1.34; 95% CI, 1.19–1.52) or 5 ABGs (AIQR OR, 1.25; 95% CI, 1.09–1.44).

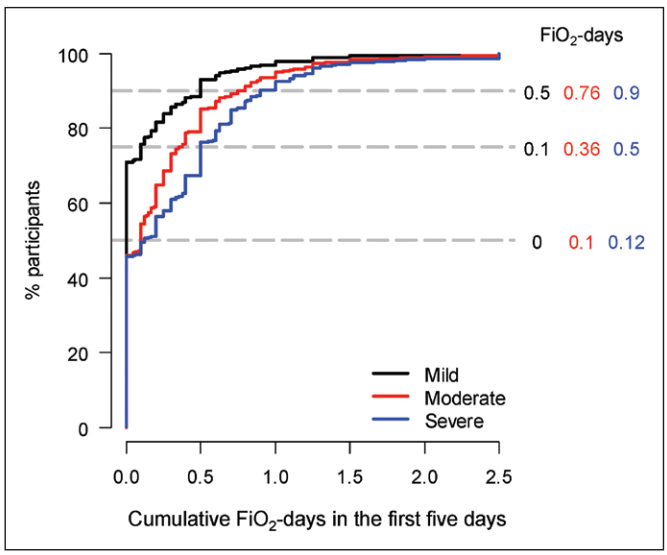

Figure 1. Empirical cumulative distribution of above goal oxygen exposure at 5 d stratified by severity of acute respiratory distress syndrome (ARDS). The 50th, 75th, and 90th percentiles of cumulative above goal oxygen exposure are shown by the *horizontal dashed lines*. Exposures of fraction of inspired oxygen (FIO_2)-days for each of these percentiles are indicated to the right of the *horizontal dashed lines* according to ARDS severity.

Effect Modification by Severity of ARDS

We assessed if above goal oxygen exposure was associated with hospital mortality at 90 days among different strata of ARDS severity (**Fig. 3**). We also calculated the percentage of participants who met or exceeded each of the thresholds of cumulative above goal oxygen exposure (0.1, 0.25, and 0.5 FIO_2-days). At least 10% of participants in each stratum of ARDS severity were exposed to at least 0.5 FIO_2-days (i.e., an average of 0.1 FIO_2 excess each day), and within the 0.5 FIO_2-days above goal oxygen exposure group, the OR of death was increased similarly in mild ARDS as in either moderate or severe ARDS. We found a dose-response relationship between cumulative above goal oxygen exposure at 5 days and greater mortality at 90 days, and this relationship held true for mild, moderate, or severe ARDS.

DISCUSSION

In our analysis of participants enrolled in 10 RCTs, we found a positive and dose-dependent association between oxygen exposure above the protocol goal and higher mortality, and lower VFDS and HFDS. Above goal oxygen exposure was associated with higher mortality irrespective of severity of ARDS at enrollment, suggesting that this association is less likely affected by reverse causality. As little as 2% of above goal oxygen exposure per day was sufficient to influence clinical outcomes. Observation of higher mortality with lower VFDS in the group with above goal oxygen exposure suggests the possibility that excess oxygen can exacerbate lung injury and thus prolong the need for mechanical ventilation. Although only correlative in humans, experimental animal models have also demonstrated synergistic lung injury using hyperoxia and ventilation with larger tidal volumes (29).

Other studies support the concept that above goal oxygen exposure may have adverse effects in acute respiratory failure. de Jonge et al (30) found a positive association between hospital mortality and higher FIO_2 values in the first 24 hours of mechanical ventilation, including the subset of

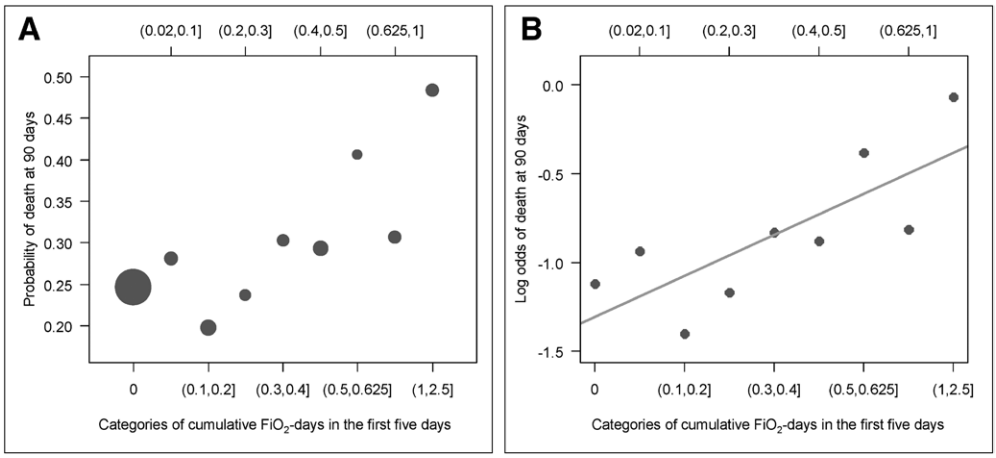

Figure 2. Probability (**A**) and log odds (**B**) of hospital mortality at 90 d by categories of cumulative above goal oxygen exposure at 5 d. In **A**, the sizes of *filled circles* are proportional to the sample size in each category. This graph could mean either that above goal oxygen exposure is detrimental or that participants with more severe acute respiratory distress syndrome are more likely to die and also receive more above goal oxygen exposure.

patients with high Pao_2s. In a study of mechanically ventilated ARDS patients, excess oxygen exposure was associated with longer ICU and hospital length of stays (7); however, lower PEEP levels in the excessive oxygen group may have confounded those results. In a single-center RCT, Girardis et al (31) compared controlled normoxia (goal Pao_2, 70–100 mm Hg) versus usual care oxygen therapy (goal Pao_2 up to 150 mm Hg) and found lower ICU mortality in the controlled normoxia group, although subjects with moderate or severe ARDS were excluded and the conservative oxygen group was healthier at baseline. When Asfar et al (32) randomized mechanically ventilated septic patients to nontitrated 100% oxygen for 24 hours versus oxygen titrated to an oxygen saturation of 88–95%, the trial was stopped due to a possible harm signal in the 100% oxygen group. However, not all studies suggest that exposure to high levels of oxygen is detrimental. Eastwood et al (33) did not find an association between higher than necessary oxygen exposure in the first 24 hours and higher hospital mortality.

TABLE 2. Single Variable and Multivariable Regression Analyses of Clinical Outcomes as a Function of Multiple Factors Including Cumulative Above Goal Oxygen Exposure

		In-Hospital Mortality at 90 d, OR (95% CI)		Ventilator-Free Days Score, Absolute Difference (95% CI)		Hospital-Free Days Score, Absolute Difference (95% CI)	
Factor	IQR or %	Single Variable	Multivariable	Single Variable	Multivariable	Single Variable	Multivariable
Age (yr), IQR	39–63	2.21 (1.95–2.52)	2.01 (1.75–2.31)	−2.72 (−3.28 to −2.16)	−2.13 (−2.68 to −1.58)	−6.06 (−7.18 to −4.93)	−4.34 (−5.45 to −3.23)
Being female (male is reference)	46	0.84 (0.71–0.99)	0.82 (0.68–0.97)	0.81 (0.03–1.58)	0.90 (0.19–1.62)	2.62 (1.06–4.18)	2.82 (1.37–4.27)
Acute Physiology and Chronic Health Evaluation III, interquartile difference	70–111	3.03 (2.67–3.44)	2.75 (2.41–3.15)	−5.24 (−5.74 to −4.74)	−4.31 (−4.82 to −3.79)	−10.7 (−11.7 to −9.7)	−9.30 (−10.34 to −8.26)
Cumulative above goal oxygen exposure at 5 d, IQR	0–0.38	1.25 (1.16–1.34)	1.20 (1.11–1.31)	−1.45 (−1.80 to −1.10)	−0.83 (−1.17 to −0.48)	−2.48 (−3.22 to −1.74)	−1.38 (−2.09 to −0.68)
Positive end-expiratory pressure (cm H_2O), IQR	5–12	1.14 (0.99–1.31)	0.89 (0.74–1.07)	−2.44 (−3.13 to −1.77)	−0.70 (−1.42 to 0.02)	−2.43 (−3.81 to −1.06)	0.61 (−0.85 to 2.06)
Severity (mild is reference)							
Moderate	55	1.43 (1.16–1.77)	1.25 (0.99–1.58)	−2.54 (−3.48 to −1.59)	−1.45 (−2.35 to −0.53)	−3.71 (−5.62 to −1.80)	−2.01 (−3.84 to −0.18)
Severe	22	1.98 (1.55–2.53)	1.51 (1.13–2.01)	−5.90 (−7.04 to −4.76)	−3.47 (−4.63 to −2.31)	−8.69 (−10.99 to −6.38)	−5.00 (−7.35 to −2.65)

IQR = interquartile range, OR = odds ratio.

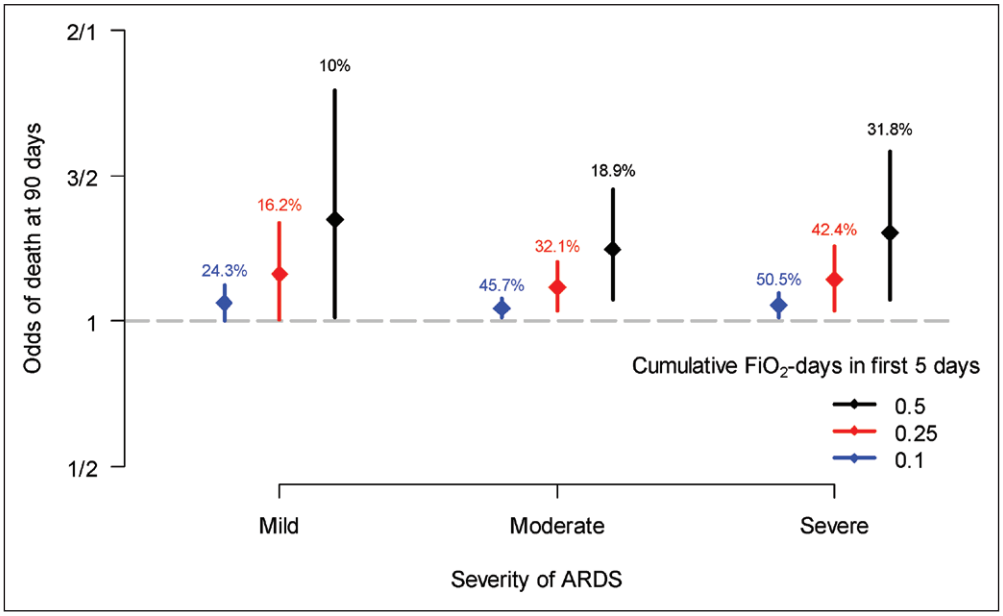

Figure 3. Odds of hospital mortality at 90 d by levels of cumulative above goal oxygen exposure at 5 d (0.1, 0.25, and 0.5, respectively) stratified by severity of acute respiratory distress syndrome (ARDS). The *diamonds* represent odds ratios, and the *vertical segments* are 95% CIs. The percentages above the vertical segments indicate the proportion of participants with values greater or equal to selected levels of cumulative above goal oxygen exposure. These data suggest that above goal oxygen exposure is detrimental even in participants with mild ARDS.

Our study demonstrates a dose-response association between above goal oxygen exposure and mortality in patients with mild, moderate, and severe ARDS, and it is important for the following reasons. First, we determined the cumulative dose of above goal oxygen exposure over a 5-day period, which integrates longitudinal data on oxygen exposure and contrasts single-exposure assessments in prior studies (9, 34). We found that above goal oxygen exposure was an important patient-related factor and a longitudinal variable for which the cumulative dose-effect was significant. Second, all of the analyzed data are from a large number of participants enrolled in trials where mechanical ventilation was managed using defined protocols with a prespecified target Pao_2 range. PEEP levels were also adjusted according to protocol, and unlike the findings by Rachmale et al (7), PEEP levels were higher in participants exposed to oxygen above protocol goals in our analysis. Yet, PEEP was not associated with any clinical outcomes. Third, because we analyzed data over 2 decades of multicenter ARDS Network trials, we are confident that above goal oxygen exposure was associated with worse outcomes. Interestingly, although the severity of ARDS at enrollment is somewhat reduced in trials conducted in recent years (2009–2013), cumulative above goal oxygen exposure increased. In early ARDS Network trials (22, 23), there was more focus on ventilator management rules with protocol-compliance reports provided to investigators. As such, investigators may have been more inclined to reduce Fio_2 when arterial oxygenation exceeded the goal range during early trials.

Allowing arterial oxygenation to exceed targets frequently leads to above goal oxygen exposure as we defined it for this study. This permissiveness may be due to a reluctance to titrate oxygen in critically ill patients to maintain a margin of safety against hypoxia, especially when the set Fio_2 less than or equal to 0.6 (35), as was demonstrated by Suzuki et al (36) when they assessed physician responses to Spo_2s greater than or equal to 99%. In our study, more frequent above goal oxygen exposure occurred in moderate and severe ARDS as compared to mild ARDS, supporting the hypothesis that ICU physicians tend to favor higher arterial oxygenation goals with increasing severity of disease. Recent prospective studies, however, suggest that targeting a lower arterial oxygen saturation goal is feasible and safe among mechanically ventilated patients (37, 38). Helmerhorst et al (39) implemented training and feedback protocols regarding conservative oxygen thresholds, resulting in less hyperoxia, reduced mechanical ventilator time, and lower hospital mortality compared to preimplementation ICU data.

Our analysis has some shortcomings. First, it was conducted retrospectively, and therefore cannot establish causal relationships. Second, some participants did not have an ABG on each of the 5 days following enrollment, necessitating an approximation to determine the cumulative 5-day exposure. Since above goal oxygen exposure was similar each day, we likely did not overestimate or underestimate the cumulative exposure. Third, we did not have any information on whether physicians titrated Fio_2 and PEEP according to the ARDS Network Fio_2/PEEP table. Fourth, we cannot determine if clinicians primarily used Spo_2 instead of Pao_2 to titrate Fio_2. In ARDS patients, a wide range of Pao_2 values can be measured for a given Spo_2 and vice versa (40). If clinicians also used Spo_2 to titrate Fio_2, it may have affected the actual above goal exposure time determined by daily Pao_2. Fifth, we used a fixed threshold of Fio_2 at 0.5 to define the amount of oxygen delivered when Pao_2 was above goal (> 80 mm Hg) that was not adjusted for severity. Although 0.5 may not be the best threshold for Fio_2, sensitivity analyses demonstrated that our findings were robust to the choice of Fio_2 threshold (between 0.3 and 0.6). Furthermore, it was not clear if 80 mm Hg was an appropriate threshold to define above goal oxygen exposure; however, our findings were robust across a range of Pao_2 thresholds (80–100 mm Hg). Moving the threshold of Pao_2 to a higher value may have weakened the association because higher Pao_2 values are likely reflective of a less sick study population. Finally, residual confounding or reverse causality due to severity

of illness may affect our results; however, above oxygen exposure effect sizes were similar regardless of ARDS severity.

In contrast to our findings of negative clinical outcomes associated with above goal arterial oxygen tensions, Mikkelsen et al (41) found a higher occurrence of long-term cognitive impairment in ARDS survivors who had a lower average Pao_2 (71 vs 86 mm Hg) during the study period. A study of preterm newborns demonstrated a higher risk of death in participants randomized to a lower oxygen saturation target of 85–89% (42). As such, there appears to be equipoise for a prospective, randomized study in adults with ARDS to determine the short- and long-term clinical impact of adjusting oxygen exposure to target a lower Pao_2 goal versus a higher Pao_2 goal.

In summary, above goal oxygen exposure was associated with worse clinical outcomes including death and length of stay in ARDS patients. This association was consistent across categories of ARDS severity and was robust to varying thresholds of oxygen exposure that could be considered unsafe. Future research needs to evaluate these associations in RCTs of oxygen management strategies and determine if they extend to the general population of mechanically ventilated patients.

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