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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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Abstract

Objective—High FiO_2s may augment lung damage to exacerbate lung injury in patients with ARDS. Participants enrolled in ARDS Network Trials had a goal PaO_2 range of 55–80 mmHg, 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 PaO_2s above goal (>80 mmHg) was associated with worse outcomes in patients with ARDS.

Design—Longitudinal analysis of data collected in these trials.

Setting—Ten clinical trials conducted at ARDS Network hospitals between 1996 and 2013.

Subjects—Critically ill patients with ARDS.

Measurements and Main Results—Each day, if the PaO_2 >80 mmHg and FiO_2 > 0.5, we determined above goal oxygen exposure, defined as the difference between the administered FiO_2 and 0.5, and summed these values over the first five days. We determined the effect of a cumulative five-day above goal oxygen exposure on mortality prior to discharge home at 90 days. Among 2994 participants (mean age 51.3 years, 54% male) with a study-entry PaO_2/FiO_2 that met ARDS criteria, average cumulative above goal oxygen exposure was 0.24 FiO_2-days (interquartile range 0 to 0.38). Participants with above goal oxygen exposure were more likely to die (adjusted

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interquartile-range OR=1.20, 95% CI 1.11 to 1.31), and have lower ventilator-free days (adjusted interquartile-range mean difference of −0.83, −1.18 to −0.48) and lower hospital-free days (adjusted interquartile-range mean difference of −1.38, −2.09 to −0.68). We observed a dose-response relationship between the cumulative above goal oxygen exposure and worsened clinical outcomes for participants with mild, moderate, or severe ARDS, 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 ARDS severity.

Keywords

ARDS; oxygen therapy; clinical outcomes

INTRODUCTION

ARDS is a critical illness syndrome associated with a risk factor that induces acute hypoxemic respiratory failure with a $PaO_2/FiO_2 \leq 300$ mmHg while receiving PEEP≥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 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 FiO_2s than necessary to achieve adequate arterial oxygenation, and often for prolonged periods. In an analysis of ARDS patients, Rachmale *et al* found excessive oxygen use, defined as a $FiO_2 \geq 0.5$ when $SpO_2 > 92\%$, in 74% of patients for a median 17 of the first 48 hoursof ventilator support (7). Similarly, De Graaf *et al* reported that among mechanically ventilated patients with a $PaO_2 > 120$ mmHg, the FiO_2 was reduced in only 25% of instances over a 24-hour period (8).

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 post-cardiac surgery found that above normal arterial PaO_2 values correlated with higher mortality (9), with the strongest association following cardiac arrest (10). Helmerhorst *et al* found that ICU patients exposed to severe hyperoxia ($PaO_2 > 200$ mmHg) had higher mortality rates and fewer ventilator-free days when compared to mild hyperoxia (PaO_2 121–200 mmHg) or normoxia (PaO_2 60–100 mmHg) (11). Potential mechanisms of damage induced by high levels of oxygen include an excessive pro-inflammatory 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). Pre-existent lung damage in ARDS may impair anti-oxidant enzyme production and other adaptive responses, rendering patients particularly susceptible to oxygen-induced injury (16).

We analyzed if cumulative effect of excess oxygen contributed towards worst clinical outcomes despite enrollment into ARDS clinical trials with a protocol targeting a PaO_2 goal

range (55–80 mmHg). We quantified excess (above goal) oxygen exposure for any FiO_2>0.5 when PaO_2>80 mmHg.

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 PBW (17). All trials required that PEEP or FiO_2 be titrated to a common target of 55–80 mmHg or SpO_2 of 88–95%. When both PaO_2 and SpO_2 were available, PaO_2 took precedence. Adults aged ≥18 years were enrolled from 1996–2013 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, USA.

Outcomes

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

Assessment of excessive oxygen exposure

We defined above goal oxygen exposure *a priori* as any value above a FiO_2>0.5 among participants with a PaO_2>80 mmHg from altitude-adjusted morning ABGs (17). With a PaO_2>80 mmHg and a corresponding FiO2>0.5, excess oxygen (FiO_2-days) was calculated as $FiO_2 - 0.5$. Using this definition, study participants with a higher relative FiO_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 five days because data points were collected each day during that interval. Participants may have not 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 five, and conducted sensitivity analyses with subsets of data for participants with ≥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 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 five 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 (ranging from none to octiles of cumulative 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 five days, age, sex, APACHE III, PEEP, and baseline ARDS severity [14]. We reported odds ratios 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 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 FiO_2 (0.3, 0.4, 0.6) and PaO_2 (85, 90, 95,100 mmHg).

We also evaluated the association between cumulative above goal oxygen exposure at five 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 five 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 (www.r-project.org).

RESULTS

Participant characteristics

4361 participants were enrolled in 10 RCTs in 1996–2013. Of these, 4243 (97%) had at least one ABG in the first five days, 3815 (87%) were managed with protocols that targeted tidal volumes of 6 mL/kg PBW, and 2994 (69%) had an ABG on day 0 to define severity. Among 2994 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% (1659), and 22% (648) had mild, moderate, and severe ARDS on day 0, respectively. No differences in age (mean 51.4 vs. 52.6 years; p=0.07), sex (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 five 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

1549 (48%) study participants had a cumulative above goal oxygen exposure above 0. Among 2994 participants, average±SD cumulative above goal oxygen exposure at five days 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 five days stratified by ARDS severity (Figure 1). Participants with mild ARDS had a larger proportion of at goal oxygen exposure days when compared to 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 to those with moderate ARDS, followed by those with mild ARDS (Figure 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; Online Supplement, e-Figure 1).

Association between above goal oxygen exposure and clinical outcomes

In-hospital mortality by 90 days was greater with higher categories of above goal oxygen exposure (Figure 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 to 1.31), have a lower VFDS (AIQR mean difference of −0.83, −1.18 to −0.48) and HFDS (AIQR mean difference of −1.38, −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 (Online Supplement, e-Table 1). Modifying the PaO_2 threshold to a higher value (85, 90, 95, or 100 mmHg) also did not affect the direction of the association; however, the magnitude of the association was weakened (Online Supplement, e-Table 2). The relationship between above goal oxygen exposure and mortality do 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 to 1.32). In subset analyses, the association between cumulative above goal oxygen exposure and mortality was not different for participants with either ≥4 ABGs (AIQR OR=1.34, 95% CI 1.19 to 1.52) or 5 ABGs (AIQR OR=1.25, 95% CI 1.09 to 1.44).

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 (Figure 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 odds ratio 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 five

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* found a positive association between hospital mortality and higher FiO_2 values in the first 24 hours of mechanical ventilation, including the subset of patients with high PaO_2s (30). 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* compared controlled normoxia (goal PaO_2 70–100 mmHg) versus usual care oxygen therapy (goal PaO_2 up to 150 mmHg), and found lower ICU mortality in the controlled normoxia group (31), although subjects with moderate or severe ARDS were excluded and the conservative oxygen group was healthier at baseline. When Asfar *et al* randomized mechanically ventilated septic patients to non-titrated 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 (32). However, not all studies suggest that exposure to high levels of oxygen are detrimental. Eastwood *et al* did not find an association between higher than necessary oxygen exposure in the first 24 hours and higher hospital mortality (33).

Our study demonstrates a dose-response association between above goal oxygen exposure and mortality in patients with mild, moderate, and severe ARDS, and is important for the following reasons. First, we determined the cumulative dose of above goal oxygen exposure over a five 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 is from a large number of participants enrolled in trials where ventilation parameters were managed using defined protocols with a pre-specified target PaO_2 range. PEEP levels were also adjusted according to protocol, and unlike the findings by Rachmale *et al* (7), 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 two decades of multi-center 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 $FiO_2 \leq 0.6$ (35), as was demonstrated by Suzuki *et al* when they assessed physician responses to $SpO_2 \geq 99\%$ (36). 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* implemented training and feedback protocols regarding conservative oxygen thresholds, resulting in less hyperoxia, reduced mechanical ventilator time and hospital mortality compared to pre-implementation ICU data (39).

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 five days following enrollment, necessitating an approximation to determine the cumulative five-day exposure. Since above goal oxygen exposure was similar each day, we likely did not over- or under-estimate 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 mmHg) that was not adjusted for severity. While 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). Moreover, it was not clear if 80 mmHg was an appropriate threshold to define above goal oxygen exposure; however, our findings were robust across a range of PaO_2 thresholds (80 - 100 mmHg). Moving the threshold of PaO_2 to 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, Mikkelson *et al* found an increased incidence of long-term cognitive impairment in ARDS survivors who had a lower average PaO_2 (71 vs. 86 mmHg) during the study period (41). 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 vs. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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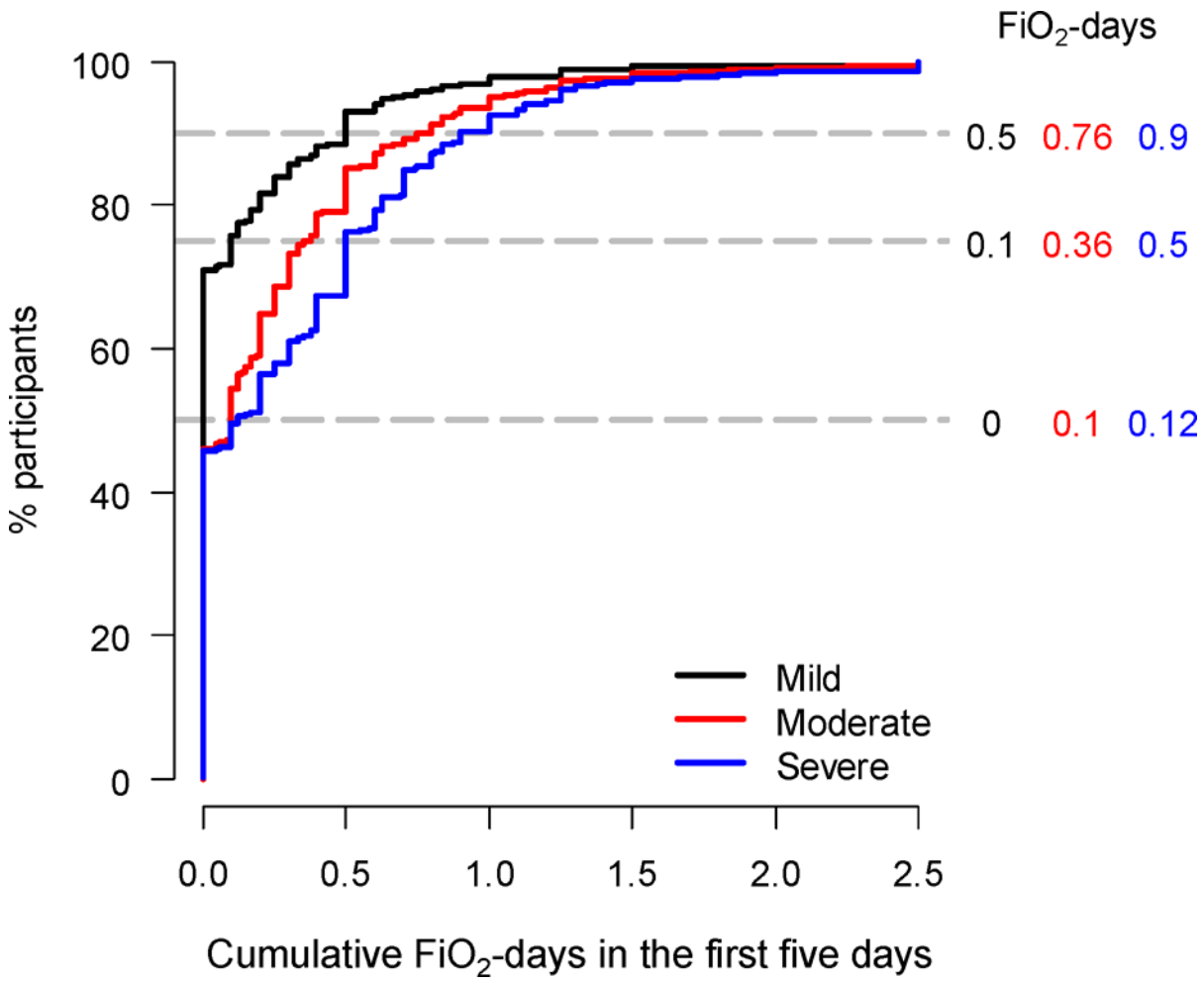

Figure 1.

Empirical cumulative distribution of above goal oxygen exposure at five days stratified by severity of ARDS. The 50th, 75th, and 90th percentiles of cumulative above goal oxygen exposure are shown by the horizontal dashed lines. Exposures of FiO_2-days for each of these percentiles are indicated to the right of the horizontal dashed lines according to ARDS severity.

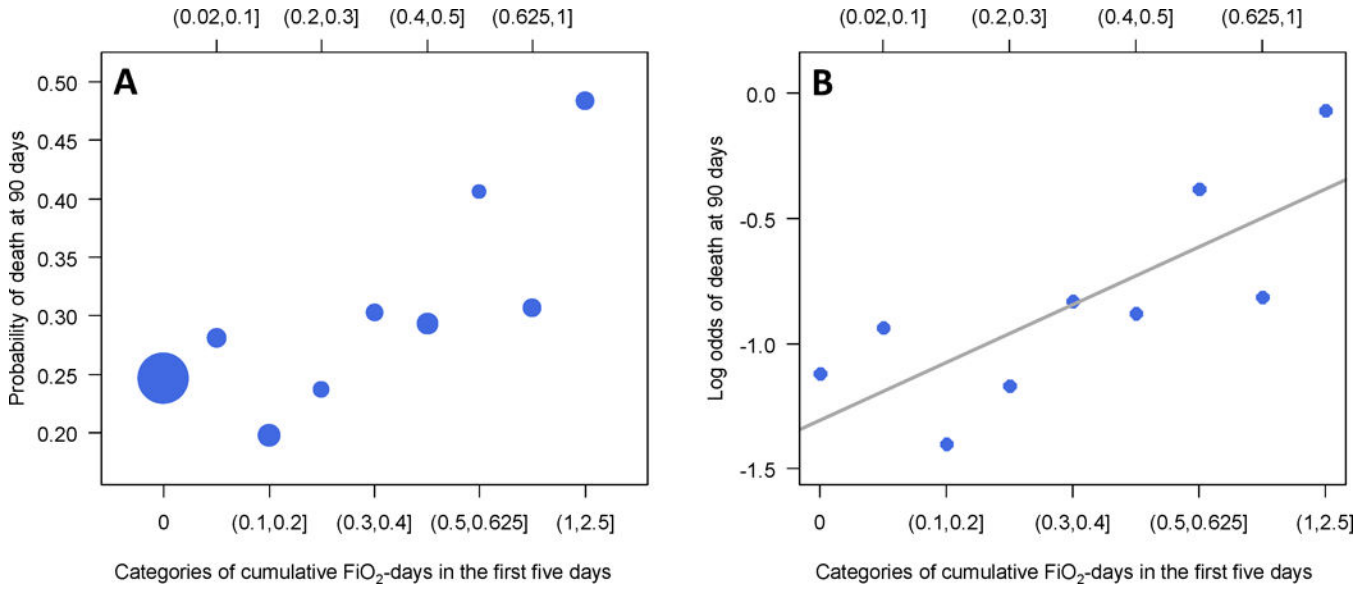

Figure 2.

Probability (Panel A) and log odds (Panel B) of hospital mortality at 90 days by categories of cumulative above goal oxygen exposure at five days. In panel 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 ARDS are more likely to die and also receive more above goal oxygen exposure.

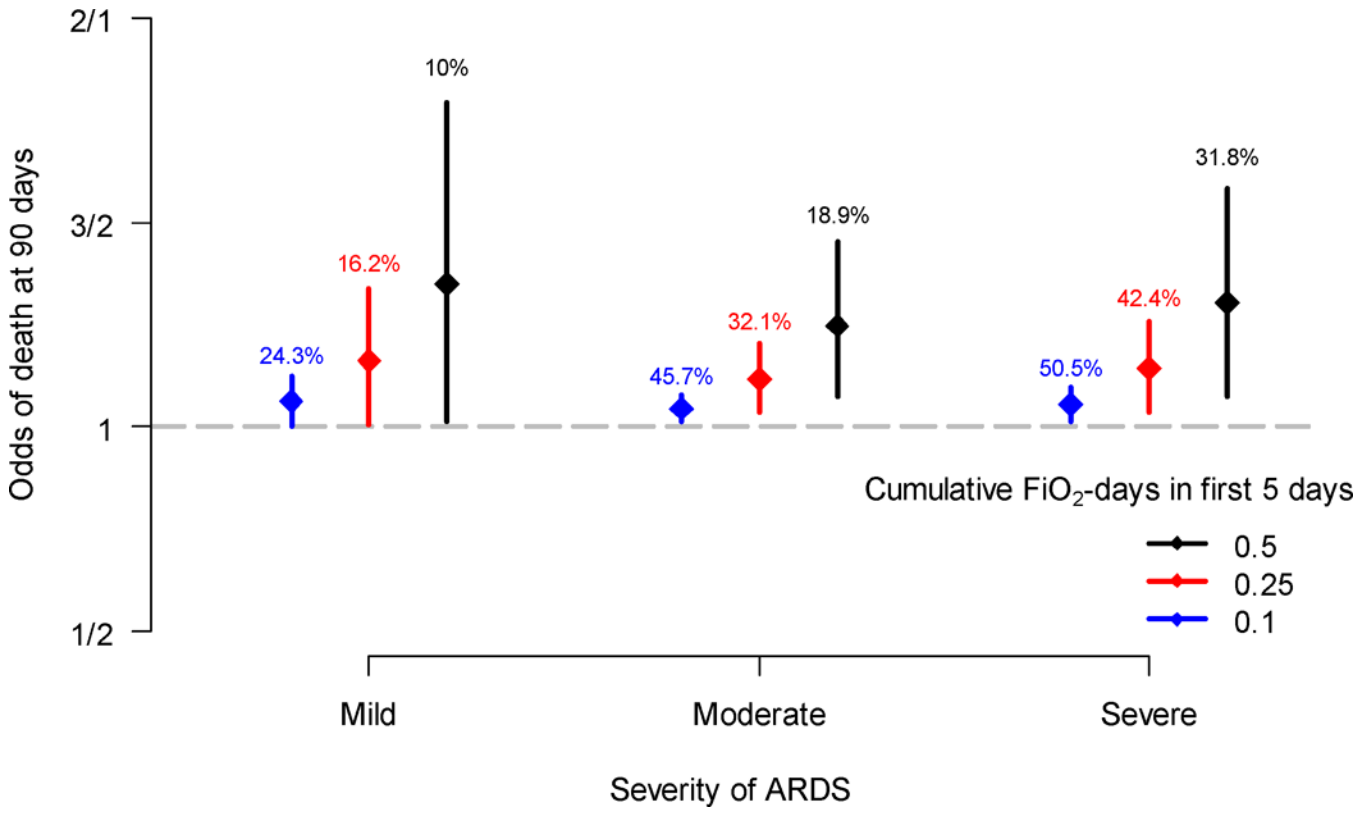

Figure 3.

Odds of hospital mortality at 90 days by levels of cumulative above goal oxygen exposure at five days (0·1, 0·25, and 0·5, respectively) stratified by severity of ARDS. The circles represent odds ratios, and the vertical segments are 95% confidence intervals. 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 patients with mild ARDS.

Table 1

Participant characteristics by categories of above goal oxygen exposure.

Characteristic or factor	Cumulative above goal oxygen exposure at five days				
	None	0·02 – 0·24	0·25 – 0·49	0·5 – 2·50	p-value
Sample size	1549	527	330	588	
Age in years, 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
APACHE III, mean (SD)	87·8 (29·7)	90·9 (29·0)	96·4 (28·5)	100·5 (30·0)	<0·001
Body mass index in 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 per kg PBW, mean (SD)	7·6 (1·9)	7·7 (2·0)	7·5 (2·0)	7·5 (2·2)	0·21
Minute ventilation in L/min, mean (SD)	11·6 (3·8)	12·1 (3·6)	12·4 (4·0)	12·6 (3·9)	<0·001
Plateau pressure in cm H_2O, mean (SD)	25·2 (7·0)	26·1 (6·7)	27·5 (7·1)	28·3 (7·9)	<0·001
PEEP in 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
FiO_2, mean (SD)	0·54 (0·17)	0·63 (0·11)	0·73 (0·13)	0·87 (0·16)	<0·001
PaO_2 in mmHg, 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-day 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

Table 2

Single variable and multivariable regression analyses of clinical outcomes as a function of multiple factors including cumulative above goal oxygen exposure.

Factor	Interquartile range or %	In-hospital mortality at 90 days, Odds ratio (95% CI)		Ventilator-free days score, absolute difference (95% CI)		Hospital-free days score, absolute difference (95% CI)	
		Single variable	Multivariable	Single variable	Multivariable	Single variable	Multivariable
Age in years, interquartile range	39 – 63	2·21 (1·95 to 2·52)	2·01 (1·75 to 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 to 0·99)	0·82 (0·68 to 0·97)	0·81 (0·03 to 1·58)	0·90 (0·19 to 1·62)	2·62 (1·06 to 4·18)	2·82 (1·37 to 4·27)
APACHE III, interquartile difference	70 – 111	3·03 (2·67 to 3·44)	2·75 (2·41 to 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 days interquartile range	0 – 0·38	1·25 (1·16 to 1·34)	1·20 (1·11 to 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)
PEEP in cm H_2O, interquartile range	5 – 12	1·14 (0·99 to 1·31)	0·89 (0·74 to 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 to 1·77)	1·25 (0·99 to 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 to 2·53)	1·51 (1·13 to 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)