Practice of Excessive F_{IO_2} and Effect on Pulmonary Outcomes in Mechanically Ventilated Patients With Acute Lung Injury

Sonal Rachmale MD, Guangxi Li MD, Gregory Wilson RRT, Michael Malinchoc MSc, and Ognjen Gajic MD MSc

BACKGROUND: Optimal titration of inspired oxygen is important to prevent hyperoxia in mechanically ventilated patients in ICUs. There is mounting evidence of the deleterious effects of hyperoxia; however, there is a paucity of data about F_{IO_2} practice and oxygen exposure among patients in ICUs. We therefore sought to assess excessive F_{IO_2} exposure in mechanically ventilated patients with acute lung injury and to evaluate the effect on pulmonary outcomes. METHODS: From a database of ICU patients with acute lung injury identified by prospective electronic medical record screening, we identified those who underwent invasive mechanical ventilation for > 48 hours from January 1 to December 31, 2008. Ventilator settings, including F_{IO_2} and corresponding S_{pO_2}, were collected from the electronic medical record at 15-min intervals for the first 48 hours. Excessive F_{IO_2} was defined as $F_{IO_2} > 0.5$ despite $S_{pO_2} > 92\%$. The association between the duration of excessive exposure and pulmonary outcomes was assessed by change in oxygenation index from baseline to 48 hours and was analyzed by univariate and multivariate linear regression analysis. RESULTS: Of 210 patients who met the inclusion criteria, 155 (74%) were exposed to excessive F_{IO_2} for a median duration of 17 hours (interquartile range 7.5–33 h). Prolonged exposure to excessive F_{IO_2} correlated with worse oxygenation index at 48 hours in a dose-response manner ($P < .001$.). Both exposure to higher F_{IO_2} and longer duration of exposure were associated with worsening oxygenation index at 48 hours ($P < .001$), more days on mechanical ventilation, longer ICU stay, and longer hospital stay ($P = .004$). No mortality difference was noted. CONCLUSIONS: Excessive oxygen supplementation is common in mechanically ventilated patients with ALI and may be associated with worsening lung function. *Key words: oxygen; hyperoxia; acute lung injury; mechanical ventilation; ICU.* [Respir Care 2012;57(11):1887–1893. © 2012 Daedalus Enterprises]

Introduction

Titration of supplemental oxygen is important, but not adequately practiced. Hypoxia and hyperoxia both produce detrimental effects at a cellular level.[1-3] Healthcare practitioners are well aware of the catastrophic effects of hypoxia, and this has led to the "more is better" culture of oxygen supplementation. Adverse effects of hyperoxia in healthy adults have been documented since the 1940s.[4] Prolonged high F_{IO_2} in patients requiring mechanical ventilation worsens gas exchange, decreases ciliary efficacy, and produces hyperoxic bronchitis and atelectasis.[5] Studies have shown adverse effects associated with hyperoxia

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in various conditions such as COPD, after acute myocardial infarction, and after resuscitation from cardiac arrest.[6-8] Acute lung injury (ALI) presents initially with hypoxemia, which might lead to mechanical ventilation and use of high F_{IO_2}. If oxygen is continually supplemented without titration, it may inadvertently perpetuate ALI. The microscopic changes from hyperoxia are undifferentiated from those seen in ARDS.[5,9]

Although there is increasing awareness of the potential harms of high F_{IO_2}, this has not translated to change in routine practice. There are reports of unregulated oxygen use in the emergency room and pre-hospital emergency care environment.[7,10] The literature on the practice of oxygen supplementation in the ICU is sparse. ICUs harbor critically ill patients, with most requiring mechanical ventilation; thus oxygen titration becomes critical in this setting. In this study we describe F_{IO_2} practice within ICU in patients with ALI, and evaluate the association of excessive F_{IO_2} and pulmonary function.

QUICK LOOK

Current knowledge

Hyperoxemia has been reported to be a common condition in patients on mechanical ventilation when the set F_{IO_2} is ≤ 0.40. The literature on the effect of hyperoxemia on lung function and outcomes is contradictory.

What this paper contributes to our knowledge

Excessive oxygen supplementation is common in mechanically ventilated patients with acute lung injury, and may be associated with worsening lung function at 48 hours. The use of the lowest possible F_{IO_2} to maintain normoxemia may be warranted.

Methods

The study was approved by the Mayo Clinic institutional review board (IRB no. 06–005418). The inclusion criteria included all adult patients with ALI who had invasive mechanical ventilation for $>$ 48 hours at any of the ICUs at the Mayo Clinic, Rochester, Minnesota, from January 1 to December 31, 2008. Those who had a diagnosis of ALI, carbon monoxide poisoning prior to admission, withdrawal of care within 48 hours, or no research authorization were excluded.

A previously validated electronic surveillance tool (ALI Sniffer)[11] was used to screen all patients who received ICU services from 2004 to 2008. The ALI Sniffer has a negative predictive value ranging from 98–100%, and sensitivity of 96% (95% CI 94–98%), making it an excellent screening tool. The diagnosis of "sniffer positive" patients was confirmed or excluded by manual review by a team of critical care experts including clinical/research fellows and staff. The inter-observer variability between the reviewers for the year 2006 had a kappa value of 0.86. The criteria for identification of the patients by the ALI sniffer were the following within a single 24-hour period:

- Qualifying arterial blood gas analysis: P_{O_2}/F_{IO_2} $<$ 200 mm Hg for ARDS and $<$ 300 mm Hg for ALI. In case of multiple arterial blood gas values, the worst value during the 24 h window was selected.
- Qualifying chest radiograph report: free text Boolean query containing the words "edema" or "bilateral" and "infiltrate"
- Invasive mechanical ventilation for acute respiratory failure or duration of invasive mechanical ventilation $>$ 12 hours following an operative procedure

Mechanical Ventilation Protocol

Respiratory therapy guidelines in our institution suggest tidal volumes of 6–8 mL/kg predicted body weight for all patients with or at risk for ARDS. Predicted body weight charts are available on each machine. Oxygenation goals are not part of the protocol and are practiced at the discretion of bedside clinicians.

Data Collection

Utilizing a preexisting electronic database, the F_{IO_2} and the exact corresponding peripheral S_{pO_2} were noted. The F_{IO_2} and S_{pO_2} were collected through the first 48 hours of mechanical ventilation. These continuous F_{IO_2} values (recorded at each 15 min interval) and corresponding continuous S_{pO_2} values (also recorded at each 15 min interval) were used to define excessive oxygen exposure in the study patients. The first hour after endotracheal intubation was excluded (Fig. 1). In patients with a clinical diagnosis of shock and acute myocardial infarction, the first 6 hours after diagnosis were excluded.

Baseline Variables

Demographic data, along with admission Acute Physiology and Chronic Health Evaluation (APACHE) III scores were noted. Median F_{IO_2}, S_{pO_2}, P_{aO_2}, S_{pO_2}/F_{IO_2}, P_{aO_2}/F_{IO_2}, oxygenation index (OI), and risk factors for ARDS were recorded.

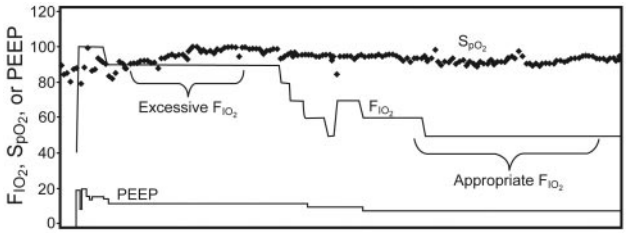

Fig. 1. F_{IO_2}, S_{pO_2}, and PEEP in an example patient.

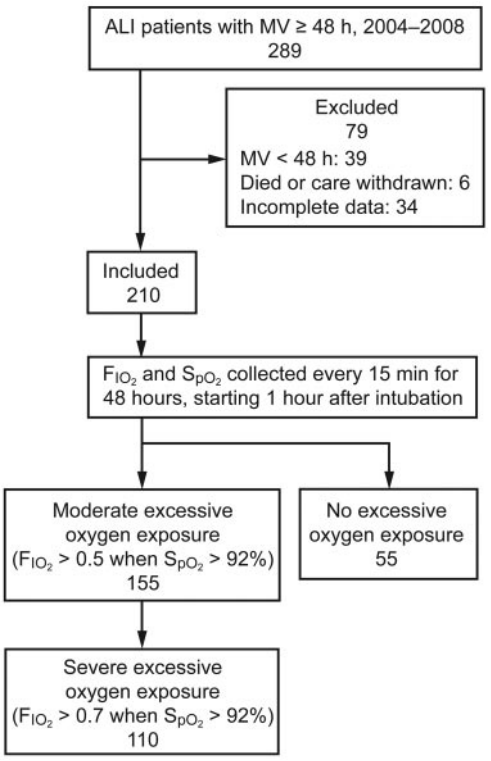

Fig. 2. Outline of the study. MV = mechanical ventilation.

Outcome Variables

The primary outcome variable was duration of exposure to excessive inspired oxygen for each patient during the initial 48 hours of mechanical ventilation. Excessive F_{IO_2} was defined as an $F_{IO_2} > 0.5$ on mechanical ventilation while maintaining a corresponding $S_{pO_2} > 92\%$ (Fig. 2).[12] Appropriate exposure to F_{IO_2} was defined as, if $S_{pO_2} > 92\%$, then $F_{IO_2} < 0.5$ or any F_{IO_2} with $S_{pO_2} < 92\%$ during mechanical ventilation.

The secondary, exploratory outcome variables were evolution of pulmonary failure (mean change in OI at 48 hours, compared to baseline), and ICU stay (ventilator-free days at day 28 in the ICU, or 28-day mortality, whichever occurred earlier).

Statistical Analysis

Continuous and categorical variables were compared using the Wilcoxon rank sum test and the chi-square test. Univariate and multivariate linear regression were performed to investigate the relation between F_{IO_2} and mean OI at 48 hours. Association between the mean change in OI and duration of exposure was evaluated by multivariate linear regression. Initial OI was added in the model for multivariate analysis in both cases. A P value of .05 was considered significant. Statistics software (JMP 6.0, SAS Institute, Cary, North Carolina.) was used for all data analysis.

Results

Screening of electronic medical records identified 289 patients with ALI, and 210 met the inclusion criteria (Table 1). Over the initial 48 hours of mechanical ventilation, excessive oxygen exposure ($F_{IO_2} > 0.5$, $S_{pO_2} > 92\%$) was identified in 155 (74%) patients, and, among them, 110 (53%) were exposed to $F_{IO_2} > 0.7$ ($F_{IO_2} > 0.7$, $S_{pO_2} > 92\%$) (see Fig. 2). Baseline characteristics, APACHE III scores, and risk factors for ALI/ARDS were similar between patients with and without excessive F_{IO_2} exposure. The initial OI, S_{pO_2}/F_{IO_2}, and P_{aO_2}/F_{IO_2} at admission were similar in both groups. Both groups were ventilated with comparable tidal volumes (7.2 vs 7.6 mL/kg predicted body weight, $P = .30$) and initial PEEP (5 vs 6.5 cm H_2O, $P = .20$) (Table 2). The nadir hemoglobin was similar in both groups (9 vs 9.2 g/dL, $P = .40$). Mean cardiovascular Sequential Organ Failure Assessment scores in the exposed and non-exposed groups were noted to be 3 versus 2.5 ($P = .80$). Use of sedation in both groups was as per the pre-designed protocol for the ICU. The median duration of excessive oxygen exposure was 17 hours (interquartile range [IQR] 7.5–33 h). Ninety six (62%) patients were exposed to excessive F_{IO_2} for 12 hours or more, and about half among them had exposure for > 30 hours. When considered for $S_{pO_2} > 95\%$, the median duration of excessive exposure was 11 hours.

At 48 hours, the exposed group had higher median OI (13.3 vs 5.1, $P < .001$.) and a higher mean change in OI (4.6 vs −1.5, $P < .001$.). Figure 3 reflects change in OI for each patient from baseline to 48 hours with severe ($F_{IO_2} > 0.7$), moderate ($F_{IO_2} > 0.5$), or no excessive F_{IO_2} exposure. At least 12 hours of excessive F_{IO_2} exposure was required for a significant increase in OI from baseline (2.26 vs 0.4, $P < .001$.). Thereafter, further exposure was linearly associated with a higher OI at 48 hours. This persisted even after adjusting for initial OI and severity of illness (Fig. 4, Table 3). Correlation between excessive exposure and worsening OI remained significant regardless of definition of excessive exposure ($F_{IO_2} > 0.5$ or > 0.7) (see the supplementary material at http://www.

Table 1. Baseline Variables

	Excessive F_{IO_2} (n = 155)	No Excessive F_{IO_2} (n = 55)	P
Age, y	64 (52–79)	68 (51–81)	.70
Female, no. (%)	64 (41)	28 (51)	.22
White, no. (%)	148 (95.4)	53 (96.4)	.99
APACHE III score on admission	29 (20–47.3)	31 (16.5–49)	.80
P_{aO_2}/F_{IO_2} on admission	186 (128–260)	182 (112–321)	.20
S_{pO_2}/F_{IO_2} on admission	137 (99–166)	160 (98–245)	.20
Initial oxygenation index	7.5 (4.9–13.7)	6.4 (3.7–13)	.08
Initial P_{aO_2}, mm Hg	57 (44.7–64.2)	56 (46.2–67)	.80
Initial mean airway pressure, cm H_2O	13 (9.7–16.5)	12.5 (8.9–16)	.25
Initial static compliance, mL/cm H_2O	31 (21–45)	28 (19–42)	.50
Initial applied PEEP, cm H_2O	5 (5–10)	6.5 (5–10)	.20
Nadir hemoglobin, g/dL	9 (7.9–9.9)	9.2 (7.7–10.5)	.40
Cardiovascular SOFA score	3 (1–4)	2.5 (1–4)	.80
Risk Factors for ARDS, no. (%)			
Sepsis	41 (26)	20 (36)	.17
Shock	28 (18)	16 (29)	.08
Pancreatitis	4 (2.6)	1 (1.8)	> .99
High risk surgery	33 (21)	11 (20)	.84
Trauma	18 (12)	3 (5)	.29
Pneumonia	50 (32)	15 (27)	.49
Aspiration	32 (21)	5 (9)	.06

Values are median (IQR) except where otherwise noted.
APACHE = Acute Physiology and Chronic Health Evaluation
SOFA = Sequential Organ Failure Assessment

Table 2. Mechanical Ventilation Related Variables

	Excessive F_{IO_2} (n = 155)	No Excessive F_{IO_2} (n = 55)	P
F_{IO_2}	0.6 (0.5–0.7)	0.4 (0.4–0.5)	< .001
V_T over 48 h, mL/kg predicted body weight	7.2 (6.32–8.2)	7.6 (6.3–8.6)	.30
48 h applied PEEP	5 (5–10)	8 (5–10)	.02
48 h S_{pO_2}/F_{IO_2}	192 (138.5–240)	240 (160–250)	< .001
48 h P_{aO_2}/F_{IO_2}	207 (136.2–275)	267 (180–335)	< .001
48 h P_{aO_2}, mm Hg	92 (73–113)	87 (65–105)	.60
48 h mean airway pressure	15 (12–20)	13 (7.5–18.5)	.008
48 h static compliance	33 (22–54)	30 (10–63)	.40

Values are median (IQR).

rcjournal.com.). Over 48 hours the exposed group was found to have a higher median F_{IO_2} (0.6 vs 0.4, $P < .001$). The F_{IO_2} distribution over the study period in exposed and non-exposed groups is shown in the supplementary material. Both groups had similar P_{aO_2} values to begin with (57 vs 56 mm Hg, $P = .80$) and that improved in a comparable manner at 48 hours (92 vs 87 mm Hg, $P = .60$). The mean airway pressures were similar to begin with, but higher in the exposed group at 48 hours (15 vs 12 cm H_2O, $P = .008$). The exposed group had longer duration of mechanical ventilation and consequent ICU and hospital stay. There was no difference in the 28 day mortality between both groups (Table 4). When considering the association of overall F_{IO_2} to outcomes regardless of oxygenation, higher F_{IO_2} correlated with higher OI. In univariate analysis, F_{IO_2} was associated with higher hospital mortality, but when adjusted for severity of illness, the association was not significant.

Discussion

In this retrospective study we found that excessive oxygen exposure through mechanical ventilation was prevalent at a tertiary care center. Prolonged excessive F_{IO_2} exposure may be associated with worsening pulmonary function, in a dose-response manner. In this study mortality was not associated with excessive F_{IO_2} exposure.

Our methodology aimed to determine "excessive F_{IO_2} exposure" in ALI patients who had improving oxygenation, for which we have used S_{pO_2} as a surrogate. We defined excessive F_{IO_2} exposure when S_{pO_2} was > 92% and F_{IO_2} continued to be > 0.5. When S_{pO_2} was > 92% and the F_{IO_2} is appropriately titrated to ≤ 0.5, or in situations where S_{pO_2} remained < 92%, receiving F_{IO_2} > 0.5 was categorized as "appropriate exposure" to F_{IO_2}. While we used S_{pO_2} levels in conjunction with F_{IO_2} for monitor-

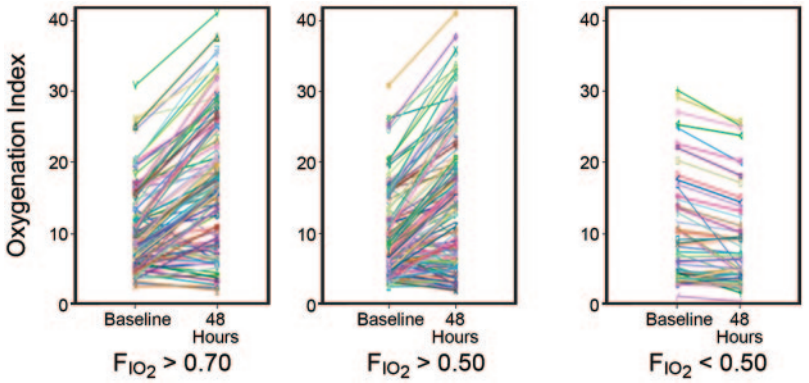

Fig. 3. Change in oxygenation index from initiation of mechanical ventilation (baseline) to 48 h after intubation, versus F_{IO_2}.

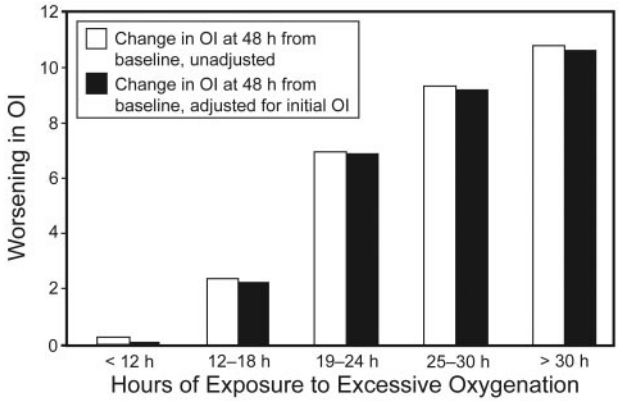

Fig. 4. Mean worsening of oxygenation index 48 h after initiation of mechanical ventilation (baseline), versus hours of excessive F_{IO_2}.

Table 3. Multivariate Linear Regression Analysis for Change in Mean Oxygenation Index at 48 Hours by Hours of Exposure

Hours of High F_{IO_2}	Mean OI Change at 48 h*	*P*
0–12	0.40	.30
12–18	2.26	< .001
18–24	6.91	< .001
24–30	9.22	< .001
> 24	10.6	< .001

* Model adjusted for initial oxygenation index (OI).

Table 4. Outcome Variables

	Excessive F_{IO_2} (n = 155)	No Excessive F_{IO_2} (n = 55)	*P*
48 h oxygenation index	13.3 (5.8–20.1)	5.12 (3.33–11)	< .001
Duration of mechanical ventilation, d	6 (3–10.5)	2.8 (1–6)	.001
ICU stay, d	9.1 (5.4–14.3)	6.8 (2.1–9.7)	.001
Hospital stay, d	19.8 (10.5–32)	14 (6.5–21)	.004
Mortality, no. (%)	75 (48.4)	29 (54.5)	.40

All values except mortality are median (IQR).

ing excessive oxygen exposure, both S_{pO_2} and P_{aO_2} levels could be used for monitoring oxygenation. Although, P_{aO_2} levels are considered the gold standard for arterial oxygenation, they can be determined only by invasive blood gas measurements. It is neither feasible nor necessary to have multiple blood gas measurements for F_{IO_2} titration. Additionally, they can significantly vary over short periods with constant F_{IO_2}, due to agitation and positioning. The noninvasive nature and continuous measurements of peripheral oxygen saturation allow continuous F_{IO_2} titration at the bedside, a standard of care in most ICUs.[13] S_{pO_2} levels may have reduced accuracy in conditions of low cardiac output, methemoglobinemia, or skin color and artifacts. S_{pO_2}/F_{IO_2} shows good correlation with P_{aO_2}/F_{IO_2} in ALI.[14] Our cutoff for optimal saturation was 92%. In mechanically ventilated patients, employing a saturation of 92% has a positive predictive value of 80% for a $P_{aO_2} \geq 60$ mm/Hg (except in African-American patients, where S_{pO_2} of at least 95% is required to prevent hypoxia).[12] The ARDS Network study for lower tidal volumes in ARDS patients used an oxygenation goal of S_{pO_2} 88–95%.[15]

In our study 74% patients had excessive oxygen exposure for 41% of time within the first 48 hours of mechanical ventilation (see the supplementary material). We found that adherence to the ARDS Network maximum target S_{pO_2} values was also incomplete, as in the exposed cohort 90% of patients had S_{pO_2} values higher than 95% for a median duration of 2 hours (1.5–4 h). These findings are not completely surprising. The practice of high oxygen to ensure "safety" and hence "inattention" to timely oxygen titration has been noted in various healthcare settings across the world. A retrospective review of clinicians' response to F_{IO_2} changes after blood-gas analysis in mechanically ventilated patients in a Dutch ICU revealed that hyperoxia

(P_{aO_2} > 120 mm Hg) was frequent and led to down-titration of F_{IO_2} in only 25% of the arterial blood gas tests.[16] In a study of patients who were prescribed oxygen in the emergency room setting at a tertiary care hospital, oxygen prescription was either not required or excessive in 79% of evaluations, determined by peripheral oxygen saturation of 92% or greater.[10]

There could be various reasons for this practice of oxygen supplementation. Optimal F_{IO_2} titration requires frequent monitoring. Time constraints for intensivists could be a plausible explanation for inadequate titration in the ICUs. Setting up a protocol-driven titration by registered respiratory therapists might be a reasonable approach to minimize excessive oxygen supplementation. Similar ventilation protocols have been successful for weaning and neonatal ventilation.[17,18] The determinants of oxygen delivery include hemoglobin, cardiac output, and oxygen saturation. Therefore, clinicians may tend to hyperoxygenate in the presence of anemia or dysoxic states associated with hemodynamic compromise. In our cohort, the nadir hemoglobin levels were in the range of 9 g/dL and were similar between 2 groups; therefore, excessive F_{IO_2} provision to allow for liberal oxygenation should not have been necessary. Additionally, we chose to exclude the first 6 hours of shock and acute myocardial infarction, considering that these conditions are reflective of generalized and/or local tissue dysoxia. Higher oxygen may be needed to alleviate tissue hypoxia. The practice of using higher F_{IO_2} cannot be considered unreasonable under these settings. These high values could affect outcomes, but according to the contemporary clinical guidelines, they cannot be labeled as "excessive oxygen"; therefore, to stay on a conservative side, we choose to exclude these values. This question or dogma, however, should be explored in future studies

Prolonged F_{IO_2} exposure showed linear correlation with worsening OI. Also, the OI increased irrespective of F_{IO_2} (F_{IO_2} > 0.5 or > 0.7). This was associated with longer duration of mechanical ventilation and ICU stay. OI integrates airway pressure with oxygenation and has shown to be a reliable predictor of worsening lung function in ALI.[19-21] Decline in lung function related to duration and concentration of F_{IO_2} has been well defined in various animal studies.[22] Prolonged exposure even to moderately high F_{IO_2} (0.6) resulted in alveolar septal edema in baboons.[23] Wistar rats demonstrated dose dependent lung toxicity when exposed to higher F_{IO_2}.[24]

Our findings are in conjunction with some previous human studies. Nash et al, in the 1960s, provided the first detailed pathologic review of pulmonary changes after exposure to both higher concentration of oxygen and duration of therapy.[5] They found distinct pathological changes of interstitial edema progressing to fibrosis seen with prolonged duration of high F_{IO_2}. A pulmonary venous admixture study revealed worsening shunt fraction when F_{IO_2} was increased beyond 0.6.[25] Davis et al studied the effects of high F_{IO_2} (0.95) on humans after about 16 hours of exposure, and found increased "alveolar capillary leak," as well as evidence of induction of fibrosis, through bronchioalveolar fluid assessment.[26] Sevitt and colleagues worked to determine the threshold for hyperoxic lung injury.[27] They found changes of diffuse pneumonitis after 48 hours of exposure to F_{IO_2} of 0.6–1.0. Prolonged exposure of 7 days to F_{IO_2} of 0.40 was also detrimental, while no worsening was noted with F_{IO_2} < 0.40.

Based on our study results, we may contemplate that, in patients with ALI, further excessive F_{IO_2} may have resulted in some degree of alveolar damage, which reflected as worsening OI. Patients with ALI can be prone to effects of hyperoxia. Santos et al looked at the effects of high F_{IO_2} in ALI patients and found deterioration in pulmonary shunt, probably by collapse of unstable alveolar units.[28] Hyperoxia can also augment ventilator-induced lung injury in ALI in the presence of high tidal volumes, by activating signaling pathways.[29]

Excessive F_{IO_2} did not appear to influence mortality in our cohort. In another large retrospective study of mechanically ventilated ICU patients in the Netherlands, the hospital mortality was independently associated with the mean F_{IO_2} during ICU stay.[30] In the same study, high F_{IO_2} in the first 24 hours of admission was linearly related to hospital mortality, along with both high and low P_{aO_2} values. In an Australian pre-hospital setting, liberal oxygenation practices were prevalent in patients with COPD exacerbation, and appropriate titration showed reduction in mortality and hypercapnia.[7]

There are several limitations that have to be addressed in the interpretation of data obtained for this study. S_{pO_2} measurements may not have complete accuracy. Errors created by equipment, skin color, or artifacts from foreign objects on nails are possible. Our patient population is mostly white, and the results may not be generalizable to other settings. The S_{pO_2} cutoff value of 92% is not optimal for African-American patients and should be extended to 95%.

The association between worsened OI and high F_{IO_2} may not be necessarily causal. Although this association appeared to be independent of potential confounding covariates, it is possible that there might have been some differences in our patients that we may not have accounted for in our multivariate analysis. In addition, in this epidemiologic study, the OI was not obtained under standardized ventilator settings; however, this limitation affected both of the study groups. The OI correlates directly with the product of F_{IO_2} and the mean airway pressure, and inversely with P_{aO_2}. Considering this mathematical relationship, the increase in OI could partially be attributed to the high F_{IO_2} rather than to actual worsening in lung function.

In the exposed group, lower PEEP could have resulted in lower OI at 48 hours. However, the presence of higher

mean airway pressures at 48 hours, in spite of lower PEEP levels and improvement in arterial oxygen, may be indicative of worsening of OI, as a conjugate function of all the 3 variables, rather than only higher F_{IO_2}. Based on the retrospective nature of the study, we can only speculate that the group with excessive F_{IO_2} may have had a higher F_{IO_2} as a consequence of using lower PEEP. This may reflect inadequate use of PEEP in practice.

With the current study design we are unable to show the cutoff value for degree of $F_{IO_2} > 0.50$ that may be toxic to patients who continue to have prolonged hypoxemia (with $S_{pO_2} < 92\%$. This would help to clarify the targets of "permissive hypoxemia," which have not been well defined in the literature and need to be studied further.

Conclusions

Optimal oxygen titration is important and not adequately practiced in ICUs, resulting in substantial exposure to unnecessary excessive oxygen. There is a likely association between excessive oxygen and worsening lung function, which needs further study. Optimal titration needs close monitoring and may be a potential area for greater participation of respiratory therapists. The safety and efficacy of F_{IO_2} titration protocols needs to be evaluated in prospective studies.

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