

Hyperoxemia in Mechanically Ventilated, Critically Ill Subjects: Incidence and Related Factors

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BACKGROUND: Excessive supplemental oxygen causes injurious hyperoxemia. Before establishing the best P_{aO_2} targets for mechanically ventilated patients, it is important to understand the incidence of hyperoxemia and related factors. We investigated oxygenation in mechanically ventilated subjects in our ICU and evaluated factors related to hyperoxemia ($P_{aO_2} > 120$ mm Hg) at 48 h after initiation of mechanical ventilation. **METHODS:** We retrospectively reviewed the medical records of patients admitted to our ICU from January 2010 to May 2013. Inclusion criteria were 15 y of age or older and administration of mechanical ventilation for > 48 h. Patients at risk of imminent death on admission or who had received noninvasive ventilation were excluded. We collected subject demographics, reasons for mechanical ventilation, and during mechanical ventilation, we collected arterial blood gas data and ventilator settings on the first day of intubation (T1), 48 h after initiation of mechanical ventilation (T2), and on the day of extubation (T3). Multivariable logistic regression analysis was performed to clarify independent variables related to hyperoxemia at T2. **RESULTS:** For the study period, data for 328 subjects were analyzed. P_{aO_2} statistically significantly increased over time to 90 (interquartile range of 74–109) mm Hg at T1, 105 (89–120) mm Hg at T2, and 103 (91–119) mm Hg at T3 ($P < .001$), coincident with decreases in F_{IO_2} of 0.4 (0.3–0.5) at T1, 0.3 (0.3–0.4) at T2, and 0.3 (0.3–0.35) at T3 ($P < .001$). Hyperoxemia occurred in 15.6% (T1), 25.3% (T2), and 22.4% (T3) of subjects. Multivariable logistic regression analysis revealed that hyperoxemia was independently associated with age of < 40 y (odds ratio 2.6, 95% CI 1.1–6.0), Acute Physiology and Chronic Health Evaluation II scores of ≥ 30 (odds ratio 0.53, 95% CI 0.3–1.0), and decompensated heart failure (odds ratio 1.9, 95% CI 1.1 to 3.5). **CONCLUSIONS:** During mechanical ventilation of critically ill subjects, P_{aO_2} increased, and F_{IO_2} decreased. One in 4 subjects were hyperoxemic at T2, and hyperoxemia persisted until T3. *Key words:* oxygenation; hyperoxemia; mechanical ventilation; oxygen toxicity; acute lung injury; critical care. [Respir Care 2015;60(3):335–340. © 2015 Daedalus Enterprises]

Introduction

Administration of oxygen is common and normally beneficial for mechanically ventilated patients. To maintain adequate P_{aO_2} , F_{IO_2} is usually set higher than O_2 in ambient

air.¹ Although several studies have provided epidemiological data for O_2 administration in critically ill subjects,¹⁻⁵ the evidence is insufficient for deciding the best target values for P_{aO_2} and optimal titration of F_{IO_2} during mechanical ventilation.

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The authors have disclosed no conflicts of interest.

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Recently, hyperoxemia was identified as an independent in-hospital mortality risk factor for ICU patients.³ Adverse outcomes of hyperoxemia were identified in patients after cardiac arrest⁶ and acute myocardial infarction⁷ and in extremely premature infants.⁸ Animal studies have demonstrated that high F_{IO_2} increases free radicals and causes an influx of inflammatory cells in the lung,⁹ pulmonary permeability, and endothelial cell injury.^{10,11}

Despite these concerns, hyperoxemia is accepted by many ICU physicians, who feel no need to adjust ventilator settings as long as F_{IO_2} is 0.4 or lower.^{4,12} To minimize risk, it is better to know the current levels of oxygenation in mechanically ventilated patients. In this retrospective cohort study, to guide future practice, we set out to determine how P_{aO_2} and F_{IO_2} change during mechanical ventilation in our ICU and to clarify which factors relate to hyperoxemia.

Methods

Study Population

We retrospectively reviewed medical records of patients admitted to our ICU from January 2010 to May 2013. The study protocol was approved by the human ethics committee of Tokushima University Hospital. Because our study was retrospective and because individual subjects were not identified, the requirement for signed informed consent was waived. We included subjects who were older than 15 y and had received mechanical ventilation for > 48 h. Patients at risk of imminent death on ICU admission or treated by noninvasive ventilation were excluded.

Data Collection

We collected demographic data on age, gender, body mass index, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, reasons for ICU admission and mechanical ventilation, route of admission, and duration of mechanical ventilation. We also reviewed ICU/hospital stay and ICU/hospital mortality. Arterial blood gas analyses of pH, P_{aO_2} , P_{aCO_2} , and serum lactate levels and ventilator settings of PEEP and F_{IO_2} data were sampled at 3 time points: within 24 h after intubation (T1), ~48 h after initiation of mechanical ventilation (T2), and before extubation (T3). For T1 oxygen values, we used the worst arterial blood gas recorded during the first 24 h. For subjects who subsequently died before extubation, we analyzed only data sampled at T1 and T2. Extubation was defined as the last extubation not followed by re-intubation within 48 h.

QUICK LOOK

Current knowledge

Hyperoxemia in mechanically ventilated patients occurs frequently at inspired oxygen concentrations of < 0.50. The incidence of hyperoxemia appears to be higher in surgical, trauma, and neurosurgical patients. Studies on the consequences of hyperoxemia on pulmonary function and outcomes have provided conflicting results.

What this paper contributes to our knowledge

In this retrospective study of the incidence of hyperoxemia in mechanically ventilated subjects, despite decreasing F_{IO_2} , P_{aO_2} increased with the duration of ventilator support. Hyperoxemia 48 h after initiation of mechanical ventilation occurred in one quarter of subjects and was associated with age of < 40 y, APACHE II score of ≥ 30 , and decompensated heart failure.

Statistical Analysis

Defining hyperoxemia as P_{aO_2} of 120 mm Hg or higher and assessing single arterial blood gas data at each time point, we carried out analysis of variance of P_{aO_2} and F_{IO_2} data obtained during mechanical ventilation, which enabled us to evaluate related variables for hyperoxemia at T2. We compared data for hyperoxemic and non-hyperoxemic subjects using the Mann-Whitney *U* test for continuous variables and the chi-square test for nominal variables. Subject age, body mass index, APACHE II score, duration of mechanical ventilation, P_{aO_2} , pH, P_{aCO_2} , serum lactate level, F_{IO_2} , PEEP level, and ICU/hospital stay were analyzed as continuous variables. Nominal variables were age of < 40, 40–69, and ≥ 70 y; APACHE II scores of < 15, 15–29, and ≥ 30 ; gender; reason for admission; route of admission; reason for mechanical ventilation; and ICU/hospital mortality. To determine independent factors associated with hyperoxemia, we performed multivariable logistic regression analysis, which was carried out using variables that reached a significance threshold of 0.15 in univariate analysis. Statistical calculation was carried out using SPSS 11.0.1 (SPSS, Chicago, Illinois). Data are expressed as median with interquartile range. $P < .05$ was considered statistically significant.

Results

During the study period, 1,664 patients were admitted to our ICU. Of 340 subjects identified as meeting the inclusion criteria, 328 subjects were included in the final anal-

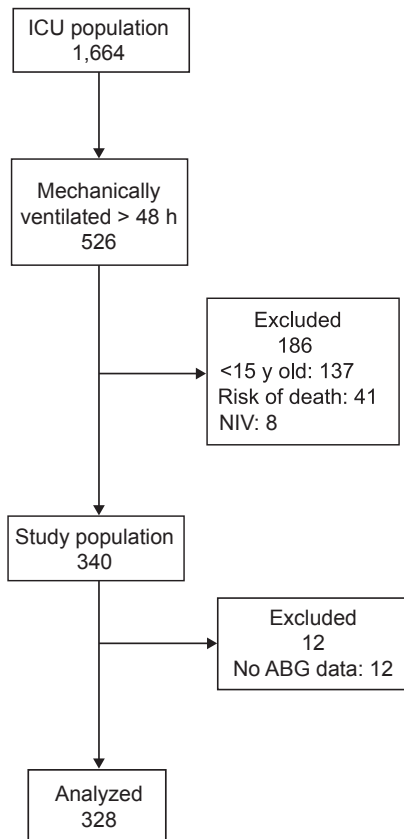


Fig. 1. Flow chart of study participants. NIV = noninvasive ventilation; ABG = arterial blood gas; risk of death = risk of imminent death at ICU admission.

ysis (Fig. 1). Of this study population, 82 subjects (25%) died without being extubated. The median age was 68 (56–75) y, 206 subjects were male (62.8%), the body mass

index was 22 (20–25) kg/m², the APACHE II score was 25 (20–31), and total mechanical ventilation time was 153 (87–294) h. At the 3 time points (T1–T3), P_{aO₂} was 90 (74–109) mm Hg, 105 (89–120) mm Hg, and 103 (91–119) mm Hg, and F_{IO₂} was 0.4 (0.3–0.5), 0.3 (0.3–0.4), and 0.3 (0.3–0.35), respectively. The PEEP level was 6 (6–8) cm H₂O at all 3 time points. Figure 2 shows changes in P_{aO₂} and F_{IO₂} over time during mechanical ventilation. Despite a concurrent decrease in F_{IO₂} ($P < .001$), P_{aO₂} significantly increased over time ($P < .001$). Subsequently, significant differences were found in P_{aO₂} and F_{IO₂} between any 2 time points (all $P < .001$) except for P_{aO₂} between T2 and T3 ($P = .93$). Hyperoxemia occurred in 15.6% of subjects at T1, 25.3% at T2, and 22.4% at T3.

Table 1 shows the characteristics of hyperoxemic and non-hyperoxemic subjects at T2. Comparable values for each group were (hyperoxemia vs non-hyperoxemia): P_{aO₂}, 133 (124–145) versus 98 (84–108) mm Hg; F_{IO₂}, 0.3 (0.3–0.4) versus 0.3 (0.3–0.4); PEEP, 6 (6–8) versus 8 (6–8) cm H₂O; and duration of mechanical ventilation, 144 (72–387) versus 170 (105–325) h. The most frequent reasons for prolonged mechanical ventilation were altered mental status and airway obstruction. Hyperoxemia at T2 correlated with age of < 40 y ($P = .03$), serum lactate level ($P = .03$), and decompensated heart failure ($P = .04$). We entered variables including age of < 40 y, APACHE II score of ≥ 30 , decompensated heart failure, postoperative care, PEEP, and lactate level into the equation of the proportional odds model. Among them, hyperoxemia was independently associated with age of < 40 y (odds ratio 2.6, 95% CI 1.1–6.0) and decompensated heart failure (odds ratio 1.9, 95% CI 1.1–3.5). An APACHE II score of ≥ 30 was associated with lower incidence of hyperoxemia (odds ratio 0.53, 95% CI 0.3–1.0) (Table 2).

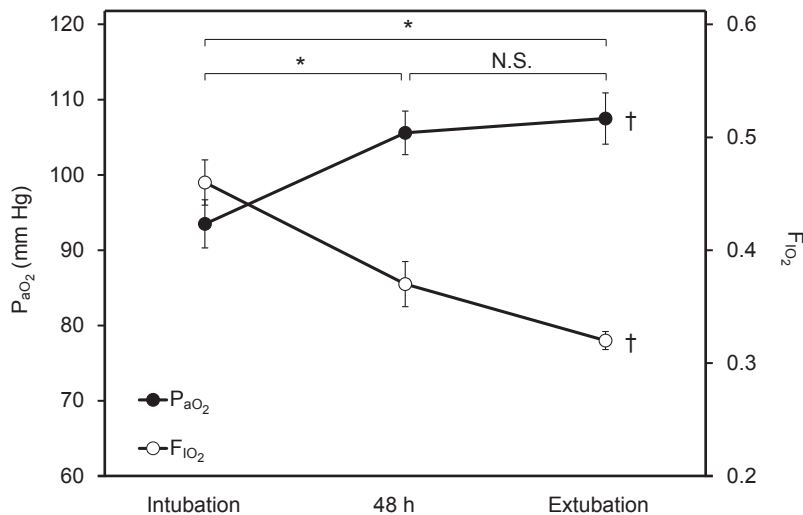


Fig. 2. Change in P_{aO₂} and F_{IO₂} over time during mechanical ventilation. Error bars indicate 95% confidence intervals. * $P < .001$; † $P < .001$ for trend. NS = not significant.

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Table 1. Comparison of Characteristics of Hyperoxemic and Non-Hyperoxemic Subjects at 48 h After Initiation of Mechanical Ventilation

	Hyperoxemic Subjects (n = 83)	Non-Hyperoxemic Subjects (n = 245)	P
Age, y	65 (51–73)	69 (59–76)	.02
< 40 y, n (%)	11 (13.3)	14 (5.7)	
40–69 y, n (%)	42 (50.6)	114 (46.5)	
≥ 70 y, n (%)	30 (36.1)	117 (47.8)	
Males, n (%)	47 (56.6)	159 (64.9)	.18
BMI	22 (20–25)	23 (19–25)	.81
APACHE II score	23 (19–29)	26 (20–32)	.02
< 15, n (%)	10 (12.0)	16 (6.5)	
15–29, n (%)	55 (66.3)	148 (60.4)	
≥ 30, n (%)	18 (21.7)	81 (33.1)	
Reason for admission, n (%)			
Medical, emergency	56 (67.5)	181 (73.9)	.51
Surgical, emergency	6 (7.2)	16 (6.5)	
Surgical, planned	21 (25.3)	48 (19.6)	
Route of admission, n (%)			
Out-of-hospital	38 (45.8)	95 (38.8)	.26
In-hospital	45 (54.2)	150 (61.2)	
Reason for mechanical ventilation, n (%)			
Decompensated heart failure	24 (28.9)	45 (18.4)	.04
Infectious pneumonia	4 (4.8)	19 (7.8)	.37
Postoperative care	7 (8.4)	37 (15.1)	.12
Altered mental status	27 (32.5)	62 (25.3)	.20
Interstitial pneumonia	0 (0.0)	11 (4.5)	.05
Asthma	0 (0.0)	1 (0.4)	.56
Airway obstruction	27 (32.5)	62 (25.3)	.56
Neuromuscular disease	5 (6.0)	13 (5.3)	.80
Post-cardiopulmonary resuscitation	4 (4.8)	17 (6.9)	.50
ARDS	4 (4.8)	24 (9.8)	.16
Pulmonary embolism	1 (1.2)	0 (0.0)	.09
F _{IO₂}	0.3 (0.3–0.4)	0.3 (0.3–0.4)	.65
P _{aO₂} , mm Hg	133 (124–145)	98 (84–108)	< .001
P _{aO₂} /F _{IO₂}	408 (339–447)	280 (225–346)	< .001
PEEP, cm H ₂ O	6 (6–8)	8 (6–8)	.06
pH	7.46 (7.43–7.49)	7.45 (7.42–7.49)	.38
P _{aCO₂} , mm Hg	39 (35–42)	39 (35–43)	.34
Lactate, mmol/L	1.2 (0.9–1.6)	1.4 (1.0–1.9)	.03
Duration of mechanical ventilation, h	144 (72–387)	170 (105–325)	.16
ICU stay, d	8 (4–13)	8 (6–14)	.25
ICU mortality, n (%)	16 (19.3)	66 (26.9)	.16
Hospital stay, d	48 (26–85)	47 (28–79)	.81
Hospital mortality, n (%)	23 (27.7)	91 (37.1)	.13

Values are given as median (interquartile range).

BMI = body mass index

APACHE = Acute Physiology and Chronic Health Evaluation

Discussion

In this retrospective cohort study, we investigated current oxygen management and factors that contribute to hyperoxemia in mechanically ventilated subjects. P_{aO₂} significantly increased over time, with 25.3% of subjects presenting hyperoxemia at ~48 h after initiation of mechan-

ical ventilation. We discovered that age of < 40 y, APACHE II score of ≥ 30, and decompensated heart failure were independently associated with hyperoxemia.

In previous large retrospective studies,^{1,3} when the worst P_{aO₂} values during the first 24 h of ICU admission were assessed, the incidence of hyperoxemia varied from 23% to 50%, with F_{IO₂} of 0.50–0.62. In our population, hyper-

Table 2. Multivariable Logistic Regression Analysis of Hyperoxemia

Variable	Odds Ratio (95% CI)	P
Age < 40 y	2.58 (1.10–6.01)	.03
APACHE II score \geq 30	0.53 (0.29–0.97)	.04
Decompensated heart failure	1.94 (1.08–3.49)	.03
Postoperative care	0.49 (0.19–1.15)	.12
PEEP (per 1 cm H ₂ O increase)	1.04 (0.94–1.15)	.47
Lactate (per 1.0 mmol/L increase)	1.08 (0.88–1.44)	.55

APACHE = Acute Physiology and Chronic Health Evaluation

oxemia was found in 15.6% of subjects on the first day of mechanical ventilation, less than in previous studies.

Despite setting the F_{IO_2} at lower levels, P_{aO_2} increased over time, which implies that it may be possible to further decrease F_{IO_2} during mechanical ventilation. Subsequently, we found no statistically significant differences between P_{aO_2} at T2 and T3. Suzuki et al² reported that P_{aO_2} remained unchanged after the second day of mechanical ventilation. For subjects in our study, we examined variables related to hyperoxemia detected at 48 h. On average, they continued to receive mechanical ventilation for another ~6 d after T2.

Hyperoxemia is known to be harmful, but how long it can be tolerated and the relationship of P_{aO_2} levels to physical harm have not been clarified. For example, even though 2 large cohort studies^{1,3} assessed the worst P_{aO_2} during the first 24 h of ICU admission, it is still not clear whether the risks of hyperoxemia outweigh the advantages of high P_{aO_2} for patients with pulmonary disease or injury.¹³

Interestingly, we found the highest incidence of hyperoxemia in younger subjects and with low APACHE II scores. The reasons for this are not clear, especially as younger and less sick subjects were considered to have good lung function. Decompensated heart failure was also an independent factor related to hyperoxemia. Pathological decompensated heart failure is caused by transient excessive capillary pressure without increased permeability.¹⁴ In a multi-center study of noninvasive ventilation in subjects with acute hypoxemic respiratory failure, Antonelli et al¹⁵ reported decompensated heart failure to be associated with the lowest failure rate of noninvasive ventilation. By improving alveolar diffusing capacity, PEEP works well for decompensated heart failure.

Our study has several limitations. First, this study was performed retrospectively in one center that could sample only 20% of the entire ICU population during the study period. Moreover, we cannot tell whether possible changes in our practice affected the oxygenation status. Second, we evaluated factors related to hyperoxemia at 48 h after initiation of mechanical ventilation. We speculated that oxygenation around this time point may represent that for the

remaining course because P_{aO_2} at T2 and T3 did not differ significantly (see Fig. 2). However, it is conceivable that the trajectory of care and changes in illness severity may have altered the clinical status of each subject at this time point. Third, the timing and frequency of arterial blood gas analyses differed among the subjects. Although, we monitored both S_{pO_2} and end-tidal CO_2 for all mechanically ventilated subjects, it is difficult to know how much oxygenation fluctuated between arterial blood gas analyses. To solve this problem, the research method using time-weighted averages of variables⁴ may be useful to determine the time patients spent in hyperoxemic ranges. Fourth, even though optimal oxygenation and critical hyperoxemia are still unknown, in line with previous studies, we arbitrarily defined hyperoxemia as P_{aO_2} of 120 mm Hg or higher. Finally, we selected subjects who required mechanical ventilation for > 48 h. These subjects may have been more critically ill and particularly susceptible to changes in oxygen demand and delivery given their illness severity; however, all patients need evaluation.

Conclusions

In our retrospective cohort study evaluating the incidence of hyperoxemia in mechanically ventilated subjects, despite decreasing F_{IO_2} , P_{aO_2} significantly increased during mechanical ventilation. We also found that hyperoxemia at 48 h after initiation of mechanical ventilation was particularly associated with age of < 40 y, APACHE II score of \geq 30, and decompensated heart failure.

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