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Current oxygen management in mechanically ventilated patients: A prospective observational cohort study☆

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Abstract

Purpose: Oxygen (O_2) is the most common therapy in mechanically ventilated patients, but targets and dose are poorly understood. We aimed to describe current O_2 administration and titration in such patients in an academic intensive care unit.

Materials and Methods: In consecutive ventilated (>48 hours) patients we prospectively obtained fraction of inspired O_2 (F_{IO_2}), pulse oximetry O_2 saturation (Sp_{O_2}) and arterial O_2 tension (Pa_{O_2}) every 6 hours. We calculated the amount of excess O_2 delivery and the intensivists' response to hyperoxemia (Sp_{O_2} >98%).

Results: During 358 mechanical ventilation days in 51 critically ill patients, median calculated excess O_2 delivery was 3472 L per patient. Patients spent most of their time with their Sp_{O_2} >98% (59% [29-83]) and Pa_{O_2} between 80 and 120 mm Hg (59% [38–72]). In addition, 50% of all observations showed hyperoxemia and 4% severe hyperoxemia (Pa_{O_2} >202.5 mm Hg). Moreover, 71% of the calculated total excess 263,841 L of O_2 was delivered when the F_{IO_2} was 0.3 to 0.5. When hyperoxemia occurred with an F_{IO_2} between 0.3 and 0.4, for 88% of episodes, no F_{IO_2} adjustments were made.

Conclusions: Excess O_2 delivery and liberal O_2 therapy were common in mechanically ventilated patients. Current O_2 therapy practice may be suboptimal and further investigations are warranted.

1. Introduction

The administration of oxygen (O_2) is the most widely prescribed therapy in mechanically ventilated intensive care units (ICU) patients and can be life saving. However, excessive supplemental O_2 may also be injurious [1,2]. For example, a high fraction of inspired O_2 (F_{IO_2}) may cause lung injury, induce interstitial fibrosis, atelectasis, tracheobronchitis, alveolar protein leakage and infiltration by neutrophils [3-5]. Systemically, O_2 can decrease cardiac output [5-8] and generate free radicals in various organs [9]. Clinical adverse outcomes of hyperoxemia have been also reported in patients with acute exacerbations of chronic obstructive pulmonary disease [10], after cardiac arrest [11] and in critical illness [12].

Despite the above concerns, many ICU clinicians believe that levels of F_{IO_2} up to 0.4 are not harmful [13]. When

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surveyed about O_2 administration practice, most Australian and New Zealand intensivists were less concerned about high F_{IO_2}-induced lung injury than barotrauma [14]. However, beyond such self-reported impressions, there is little knowledge, let alone understanding, of current practice in the field of O_2 therapy in mechanically ventilated ICU patients. In particular, no prospective studies have yet investigated this issue. Accordingly, we conducted a prospective observational study to assess the administration of O_2 therapy to a cohort of mechanically ventilated patients admitted to our tertiary intensive care unit. We hypothesized that hyperoxemia would be common (>50% of time) and that adjustments to correct it would be uncommon (<20% of observations).

2. Methods

We prospectively screened all patients admitted to our tertiary ICU between March and June 2012. Patients were eligible if they were adult (aged 18 years or greater) and required mechanical ventilation (MV) for more than 48 hours. Patients were ineligible if they were either considered at risk for imminent death by the treating medical team or required extracorporeal membrane oxygenation. All patients received MV with an Evita 4, Evita XL (Drägerwerk AG, Lübeck, Germany) or an AVEA ventilator (CareFusion, Yorba Linda, CA). The Human Research Ethics Committee of the Austin Hospital approved this study protocol (approval no. H2011/04252) and waived the need for informed consent.

2.1. Data collection

Using a standardized case report form, we collected information on age, sex, reason for ICU admission (surgical and non-surgical) and Acute Physiology and Chronic Health Evaluation (APACHE) III score. We recorded MV mode, positive end-expiratory pressure (PEEP) level, ventilator-derived minute ventilation, F_{IO_2}, pulse oximetry derived O_2 saturation (Sp_{O_2}) (Philips Healthcare, Eindhoven, The Netherlands), arterial oxygen saturation (Sa_{O_2}) and Pa_{O_2} as oxygenation-related variables. Simultaneously, we also collected arterial blood pH and arterial carbon dioxide tension (Pa_{CO_2}). Arterial blood gas analysis was performed with ABL800 FLEX (Radiometer, Copenhagen, Denmark). We collected these data following the commencement of MV until the patient was free of MV for greater than 24 consecutive hours. We obtained these data at 4 time points — 06:00, 12:00, 18:00, and 24:00, using the measurement closest to that time point. For patients who were readmitted to ICU and required MV ≥48 hours, only the index admission was considered. Oxygenation goals for each patient were prescribed at the discretion of bedside clinicians. To avoid a Hawthorne effect, clinicians were kept strictly unaware of the study.

2.2. Statistical analysis

Continuous data are reported as means (SD) or medians [interquartile range], depending on the underlying data distribution. Categorical data are reported as proportions. All analysis was performed by using JMP version 8.0.2 (SAS Institute, Cary, NC). A 2-sided P value of .05 was considered to be statistically significant. Throughout this study, hyperoxemia was defined as Sp_{O_2} >98% according to the British Thoracic Society guideline [15] and a recent review [16] that recommend target Sp_{O_2} of 94% to 98% for most acutely ill patients.

We calculated the time spent in predefined bands of the variables of interest (F_{IO_2}, Sp_{O_2}, and Pa_{O_2}) assuming a linear trend between individual measurements, and expressing the result as a proportion of the whole duration of MV. The band was defined as follows: F_{IO_2} was divided into 8 bands of 0.1: Sp_{O_2} above 92% was divided into 8 bands of 1%: Pa_{O_2} was divided into 4 bands (≤60, 60-80, 80-120, <120 mm Hg).

To avoid surveillance bias, we calculated the time-weighted averages of the oxygenation-related variables. The time-weighted value was determined by calculating the mean value between consecutive time points and multiplying it by the period of time between such points [18]. The sum of such time-weighted values is then divided by the total time to obtain the time-weighted average. We calculated the time-weighted average of all data for each patient as the time-weighted average during MV (TWA_{MV}). Similarly, we assumed the time-weighted average of 4 consecutive data sets of each day to be the time-weighted average for each 24-hour period (TWA_{24}). We excluded days when fewer than 12 hours of data were available for the day, for example, if patient was extubated, had a brief spontaneous breathing with a T-piece circuit, did not have arterial blood gas data, had surgery, or died.

When O_2 was delivered to a patient at an Sp_{O_2} >98% (hyperoxemia) and continued without a decrease in F_{IO_2} despite an Sp_{O_2} >98% at the following set of observations, we defined such therapy as "excess O_2 delivery" and calculated the amount. Excess O_2 delivery rate for each observation was determined as minute ventilation x (F_{IO_2} − 0.21) (L/min). Their time-weighted values provided calculated amount of excess O_2 delivery between consecutive time points.

We performed unadjusted univariate analysis with oxygenation-related variables for comparison between groups according to hospital survival status using the χ^2 test for proportions, Student t test for normally distributed outcomes, and Wilcoxon rank sum test for nonparametric data. In the same way, to investigate the clinical ramifications according to hyperoxemic status, patients were classified as having "hyperoxemia" and "non-hyperoxemia" using their TWA_{MV}-Sp_{O_2} (TWA_{MV}-related hyperoxemia and TWA_{MV}-related non-hyperoxemia, respectively). Moreover, patients who spent >50% of their mechanical ventilation time with hyperoxemia were classified as having "persistent hyperoxemia" and those who spent ≤50% of the time with hyperoxemia as "transient hyperoxemia." Additionally, we assessed trends over time in the variables of

interest for the first 7 days. Changes over time were determined using repeated measures mixed linear modeling with each patient treated as a random effect.

To assess differences in O_2 therapy according to O_2 target, we divided all data sets into 2 groups, hyperoxemia and non-hyperoxemia, and performed univariate analysis in the same way. In addition, to better describe the clinical features of hyperoxemia, we use another two different definitions of hyperoxemia: the first, Pa_{O_2} >108 mm Hg based on the reference range of Pa_{O_2} for healthy adults [19]; the second, Pa_{O_2} >120 mm Hg in accordance with a previous study [17]. Moreover, severe hyperoxemia was defined as Pa_{O_2} >202.5 mm Hg, a value derived as being greater than 2 SDs above the mean of hyperoxemic samples with F_{IO_2} of 0.21 to 0.4 in a previous study [17]. We used such data to investigate the incidence of hyperoxemia and severe hyperoxemia.

To investigate the intensivists' response to hyperoxemia, we assessed whether, in the subsequent data set, F_{IO_2} was adjusted after hyperoxemia was recorded. Finally, we assessed whether adjustments were more common during daytime hours (6:00-18:00) compared with after hours (18:00-6:00).

3. Results

We prospectively screened 678 admissions in 625 patients and recorded 1416 data sets on 358 MV days in 51 critically ill patients who needed MV for more than 48 hours. Table 1 shows the patients' baseline characteristics and oxygenation-related parameters. Mean age was 59 years, and mean Acute Physiology and Chronic Health Evaluation III score was 70. ICU and hospital mortality were 25% and 33%, respectively. Median TWA_{MV}-F_{IO_2} was 0.40, TWA_{MV}-Pa_{O_2} was 107 mm Hg and TWA_{MV}-Sp_{O_2} 98.4%, respectively. The median calculated total amount of excess O_2 delivery was 3472 L per patient.

Patients spent most of their time in a state of hyperoxemia (59% [29-83]) (Fig. 1A), a Pa_{O_2} between 80 and 120 mm Hg (59% [38-72]) (Fig. 1B) and an F_{IO_2} between 0.3 and 0.4 (24% [0-75]) or 0.4 and 0.5 (38% [8-71]) (Fig. 1C). Time spent at an Sp_{O_2} ≤92% and/or Pa_{O_2} ≤60 mm Hg was negligible. In total, patients received 263 841 L of excess O_2, 71% of which was delivered with an F_{IO_2} between 0.3 and 0.5 and 84% below 0.6. Of 51 patients, 32 (63%) were classified as the "TWA_{MV}-related hyperoxemia" group and 31 (61%) as the "persistent hyperoxemia" group. There was no difference in baseline demographic data and clinical outcomes according to hyperoxemic status (Appendix 1 and 2).

The lower limits of the 95% confidence intervals for TWA_{24}-Sp_{O_2} were above 96% (Fig. 2A) on each of the first 7 days of MV. Those for TWA_{24}-Pa_{O_2} were also above 80 mm Hg throughout the first 7 days of MV (Fig. 2B). TWA_{24}-F_{IO_2} on day 1 was significantly higher than during other days (Fig. 2C). After day 2, TWA_{24}-F_{IO_2} was maintained at around 0.4. TWA_{24}-P/F ratio did not show significant change over time (Fig. 2D). On 56% of study days, a TWA_{24}-Sp_{O_2} >98% was achieved with an F_{IO_2} of 0.3 or greater and showed no relationship with a TWA_{24}-F_{IO_2} (Fig. 3).

There were 1416 F_{IO_2} observations with a median value of 0.4 and a range from 0.21 to 1.0: 1287 Pa_{O_2} values with a

Table 1 Baseline characteristics and ventilation-related parameters of 51 critically ill patients

Variable	Total (N = 51)	Survivor (N = 34)	Non-survivor (N = 17)	*P*
Demographics				
Age	59 (17)	55 (17)	68 (12)	.006
Females	13 (25%)	11 (32%)	2 (12%)	.18
Surgical	10 (20%)	7 (21%)	3 (18%)	1.00
Emergency admission	50 (98%)	33 (97%)	17 (100%)	1.00
APACHE III score	70 (31)	61 (26)	86 (35)	.006
MV duration, h	125 [76-217]	113 [72-239]	138 [95-203]	.45
Length of ICU stay, d	6.5 [4.9-11.9]	8.0 [4.8-12.8]	6.0 [5.1-9.4]	.35
Length of hospital stay, d	15.3 [9-26.8]	20.1 [11.7-34.5]	9.4 [5.6-12.9]	<.001
Oxygenation-related variable				
TWA_{MV} Minute ventilation, L/min	8.6 [6.7-10.3]	8.1 [6.7-10.0]	9.4 [8.0-11.8]	.10
TWA_{MV} F_{IO_2}	0.40 [0.35-0.44]	0.40 [0.34-0.44]	0.44 [0.39-0.48]	.04
TWA_{MV} PEEP, cm H_2O	6.1 [5-7.5]	6.0 [5-7.1]	6.8 [5.4-9.4]	.10
TWA_{MV} Sp_{O_2}, %	98.4 [97.3-99.1]	98.6 [97.2-99.3]	98.3 [96.9-98.8]	.38
TWA_{MV} SaO_2, %	97.7 [96.6-98.5]	97.9 [96.7-98.9]	97.7 [96.2-98.2]	.14
TWA_{MV} Pa_{O_2}, mm Hg	107 [94-131]	113 [94-134]	103 [91-118]	.13
TWA_{MV} pH	7.44 [7.41-7.45]	7.44 [7.41-7.45]	7.43 [7.39-7.45]	.72
TWA_{MV} $PaCO_2$, mm Hg	40.3 [37-44.7]	41.9 [37.1-44.8]	38.9 [36.8-42.3]	.18
TWA_{MV} P/F ratio, mm Hg	283 (84)	299 (85)	251 (73)	.052
%time with hyperoxemia, %	59 [29-83]	63 [27-90]	56 [22-76]	.30
Total amount of excess oxygen delivery, L	3472 [1532-7178]	3049 [1307-6690]	3882 [1741-7358]	.71

P/F ratio, arterial oxygen tension/fraction of inspired oxygen ratio; %time with hyperoxemia, percentage of time spent with hyperoxemia.

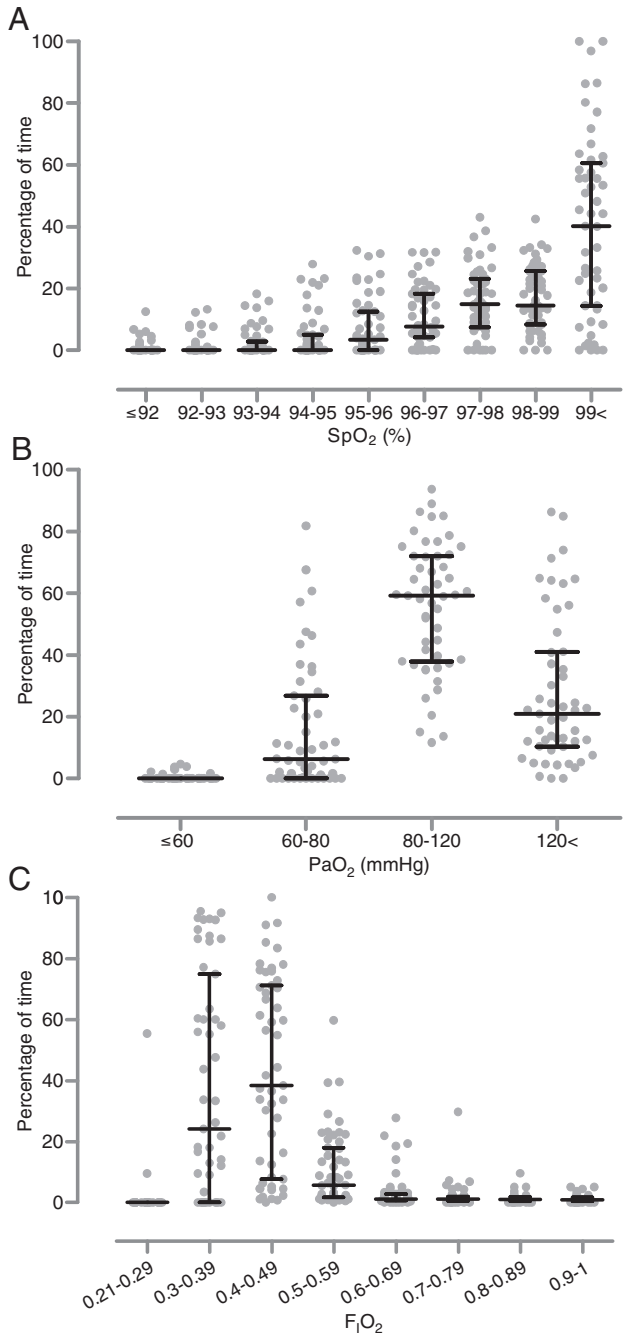

Fig. 1 Percentage of time spent in each band of Spo_2 (A), Pao_2 (B), and Fio_2 (C) for all study patients. Horizontal lines represent medians; error bars represent interquartile range; dots represent the study patients.

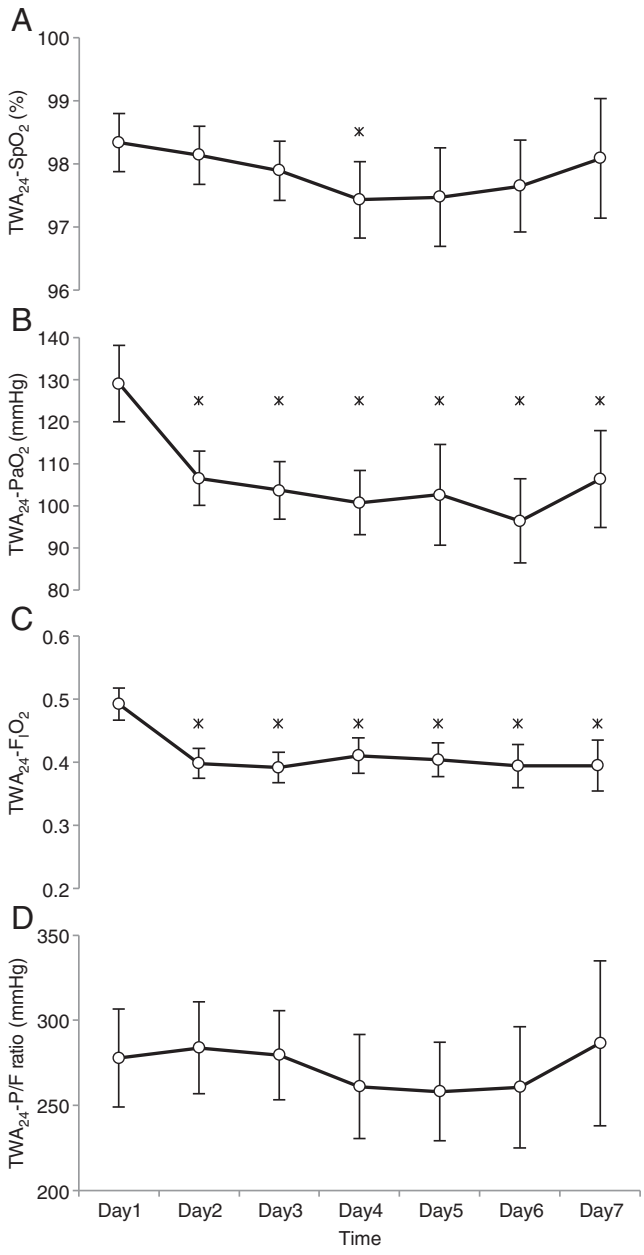

Fig. 2 Change in TWA_{24} for Spo_2 (A), Pao_2 (B), Fio_2 (C), and Pao_2/Fio_2 ratio (P/F ratio) (D) over time in the first seven days. Error bars indicate the 95% confidence intervals. *$P < .05$ vs. Day 1 (Tukey-Kramer adjustment for multiple comparisons).

median of 100 mm Hg and a range from 52 to 564 mm Hg, and 1416 Spo_2 observations with a median of 98% and a range from 87 to 100% (Table 2). Overall, 75% of observations occurred when the Fio_2 ranged from 0.3 to 0.4. In contrast, only 1% of observations were recorded with an Fio_2 between 0.21 and 0.29 (Table 2). Importantly, 50% of all observations showed hyperoxemia. Observations without hyperoxemia occurred under conditions of greater lung dysfunction as suggested by higher PEEP, higher Fio_2, higher minute ventilation and higher $PaCO_2$ despite normal pH (Table 2 and Fig. 4). On the other hand, in the hyperoxemia group, Fio_2 was mostly between 0.3 to 0.4 (Table 2 and Fig. 4). If hyperoxemia was defined as a Pao_2 >108 mm Hg and Pao_2 >120 mm Hg, the incidence of hyperoxemia was 39% and 26%, respectively. In addition, if severe hyperoxemia was defined as Pao_2 >202.5 mm Hg, 4% of observations were in the severe hyperoxemic range.

In most hyperoxemic observations with an Fio_2 of 0.6 or greater, Fio_2 were decreased at the next time point (Fig. 5). In contrast, at lower Fio_2 levels, adjustments in Fio_2 in

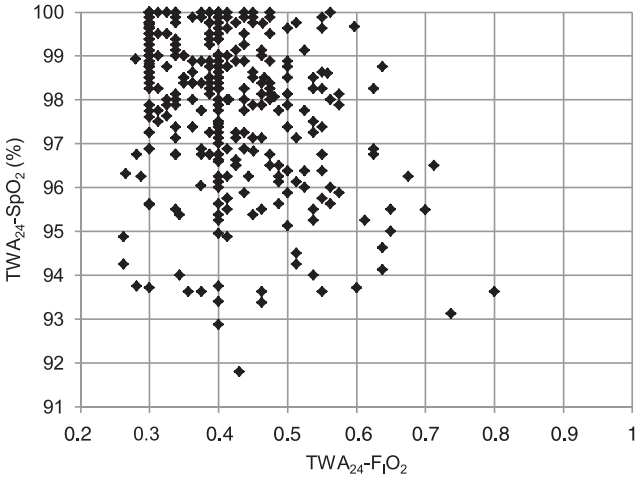

Fig. 3 Scatter plot of TWA_{24} for Spo_2 vs FIO_2 (n = 358).

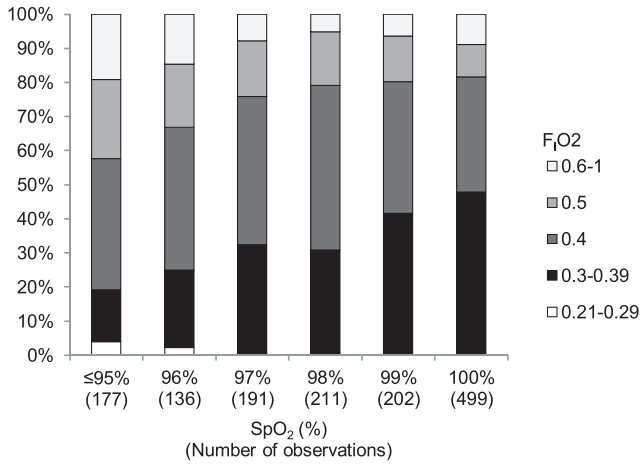

Fig. 4 Percentage of different FIO_2 levels according to Spo_2 (n = 1416).

response to hyperoxemia were made less frequently. In particular, in 88% of cases of hyperoxemia with an $FIO_2 \leq 0.4$ no adjustment was made (Fig. 5). Of 664 observations obtained during day time hours, 197 (30%) were followed by FIO_2 adjustments and 181 (26%) of 701 observations after hours were followed by FIO_2 adjustments in the subsequent data set ($P = .12$).

4. Discussion

4.1. Key findings

We conducted a prospective observational study of patients who required MV for at least 48 hours to assess O_2 administration practice in the setting of an Australian tertiary ICU. We found that patients spent most of their time with an FIO_2 between 0.3 and 0.5 and had a relatively high Spo_2 and Pao_2. Overall, about half of observations were in the hyperoxemic range, with most of them occurring while FIO_2 was low. More than two thirds of excess O_2 delivery occurred at low FIO_2. Adjustments to FIO_2 were rare, especially when hyperoxemia occurred at low FIO_2.

4.2. Relationship to previous findings

Some previous studies have discussed intensivists' self-reported practice on O_2 therapy. Among Canadian intensivists,

Table 2 Comparison of oxygenation-related variables between observations with hyperoxemia ($Spo_2 > 98\%$) and without hyperoxemia ($Spo_2 \leq 98\%$)

Variable	N	Total	N	Hyperoxemia	N	Non-hyperoxemia	*P*
Ventilator mode	1416		701		715		
VCV		156 (11%)		89 (13%)		67 (9%)	.051
SIMV		591 (42%)		287 (41%)		304 (43%)	.55
PSV		600 (42%)		296 (42%)		304 (43%)	.91
SB		69 (5%)		29 (4%)		40 (6%)	.22
Minute ventilation, L/min	1346	8.5 [6.9-10.6]	671	8.0 [6.4-10.0]	675	9.2 [7.4-11.1]	<.001
PEEP, cm H_2O	1347	5 [5-8]	672	5 [5-8]	675	7 [5-10]	<.001
≥10 cm H_2O		279 (21%)		93 (14%)		186 (28%)	<.001
FIO_2	1416	0.4 [0.3-0.4]	701	0.4 [0.3-0.4]	715	0.4 [0.3-0.5]	<.001
0.21-0.29 *		12 (1%)		0 (0%)		12 (2%)	<.001
0.3-0.39 †		506 (36%)		323 (46%)		183 (26%)	<.001
0.4		556 (39%)		246 (35%)		310 (43%)	.002
0.5		205 (14%)		75 (11%)		130 (18%)	<.001
0.6-1.0		137 (10%)		57 (8%)		80 (11%)	.06
Pao_2, mm Hg	1287	100 [82-121]	626	116 [101-136]	661	86 [74-100]	<.001
pH	1356	7.43 [7.39-7.47]	669	7.44 [7.4-7.46]	687	7.43 [7.39-7.47]	.38
$PaCO_2$, mm Hg	1356	40 [36-46]	669	39 [36-44]	687	42 [38-49]	<.001

VCV, volume control ventilation; SIMV, synchronized intermittent mandatory ventilation; PSV, pressure support ventilation; SB, spontaneous breathing.
* In 92% of this group $FIO_2 = 0.25$.
† In 98% of this group $FIO_2 = 0.3$.

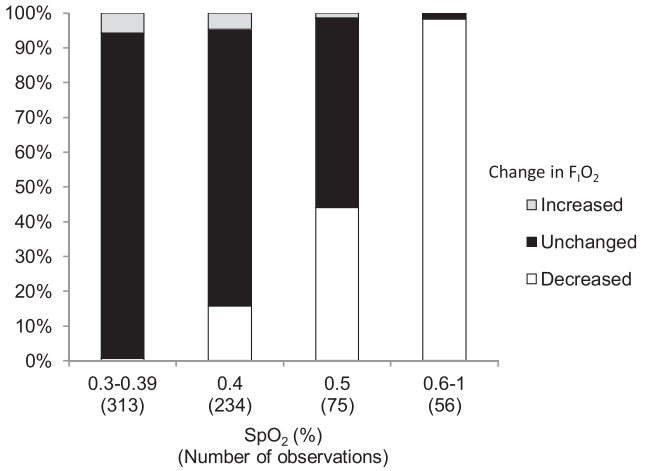

Fig. 5 Percentage of adjustments to F_{IO_2} according to last F_{IO_2}, when Sp_{O_2} was 99% or greater (n = 678). Gray bar = F_{IO_2} was increased; black bar = F_{IO_2} remained unchanged; white bar = F_{IO_2} was decreased.

half reported that they would decrease F_{IO_2} when Sp_{O_2} was 95% to 100% and F_{IO_2} between 0.21 and 0.4, and about 80% would decrease F_{IO_2} when Sp_{O_2} was 95% to 100% and F_{IO_2} 0.4 to 0.5 [13]. Half of Australian and New Zealand intensivists stated that an Sp_{O_2} of 90% in a ventilated patient with acute respiratory distress syndrome would be acceptable [14]. However, such self-reported behavior is contradicted by our study.

Previous studies of O_2 administration practice in patients receiving MV in ICU have all been retrospective. In a Dutch retrospective observational study, hyperoxemia (defined as Pa_{O_2} >120 mm Hg) was frequent (22%) and, even when the F_{IO_2} was 0.4 or lower, it was accepted in the majority of cases [17]. Rachmale et al found that 74% of MV patients at the Mayo clinic were exposed to excessive F_{IO_2} for a median duration of 17 hours [20]. These findings are consistent with our observations and suggest that liberal O_2 therapy is common in mechanically ventilated patients in ICU. To our knowledge, no other studies have been published that systematically assessed O_2 therapy in MV patients.

4.3. Clinical implications

Our findings that hyperoxemia was common that it often occurred when F_{IO_2} was relatively low and that it was not corrected by appropriate adjustment in F_{IO_2} are of concern. This is because even mildly elevated F_{IO_2} levels have been reported to exacerbate lung injury in an animal study [21], contribute to absorption atelectasis, and increase V/Q mismatch in patients with acute respiratory distress syndrome [22]. Adverse outcomes of hyperoxemia also have been reported in some other settings, such as in patients with acute exacerbations of chronic obstructive pulmonary disease [10], after cardiac arrest [11], and in critical illness [12]. Of even greater concern, a recent follow-up study of a randomized controlled trial revealed that patients randomized to 80% perioperative O_2 administration were more likely to die compared with those randomized to 30% O_2 [23]. Thus, hyperoxemia should probably be avoided whenever clinically indicated. Importantly, the observation in our study that most episodes of hyperoxemia occurred at low F_{IO_2} implies that further decreases in F_{IO_2} should likely be easily and safely implemented.

4.4. Strengths and limitations

Our study has several strengths. We prospectively identified eligible patients and used standardized data collection methods. Our clinicians were unaware of the study, which enabled us to assess current O_2 therapy in an unmodified clinical environment. To our knowledge, this is also the first study to prospectively assess all of the following: the calculated amount of excess O_2 delivery, duration of time spent in each particular F_{IO_2}, Sp_{O_2} and Pa_{O_2} level, and the clinical response to hyperoxemia.

Our study also has some limitations. First, the sample size may be considered small. However, we were able to collect 1416 data sets on 358 MV days, related to patient O_2 therapy, and obtained a detailed picture of the O_2 administration in our patients, which revealed clinically important observations. Second, we studied patients in only one center, and our findings may not be generalizable. However, we note that our center and ICU have all the typical characteristics of a tertiary ICU in a developed country, suggesting a degree of external validity. This notion is supported by an incidence of hyperoxemia (if defined by Pa_{O_2} >120 mm Hg) similar to that reported in another large cohort study [17]. Third, we collected data during only 4 time points per day. More frequent measurements may have captured current practice in more detail. However, to avoid surveillance bias, we calculated the time-weighted averages of the variables of interest. Fourth, we used British Thoracic Society guidelines [15] to define hyperoxemia even though the guidelines do not apply to mechanically ventilated patients, and evidence supporting such recommendations is lacking. However, there is no evidence or consensus statements on the use of O_2 therapy in the care of the critically ill to use as reference points for the assessment of hyperoxemia. Finally, we enrolled only patients who required at least 48 hours of MV, and our study may have a selection bias towards a sicker cohort of patients. However, these are the patients where optimal O_2 therapy is likely to be particularly important.

4.5. Future studies

To confirm or refute our findings, similar studies should be performed in other hospitals and health care settings. Furthermore, our findings suggest the need for a prospective

clinical trial to explore the safety and feasibility of a more conservative approach to O_2 therapy in patients receiving MV.

4.6. Conclusions

We studied current practice in O_2 administration in a cohort of patients who were mechanically ventilated >48 hours. We found that substantial excess O_2 delivery and liberal O_2 therapy were common, that patients spent significant amounts of time with hyperoxemia, and that such hyperoxemia was not corrected despite relatively low F_{IO_2}. These results suggest that current O_2 therapy practice may be suboptimal and support the need for further investigations.

Appendix 1

Comparison of patients with hyperoxemia (TWA_{MV}-Sp_{O_2} >98%) and without hyperoxemia (TWA_{MV}-Sp_{O_2} ≤98%)

Variable	TWA_{MV}-related hyperoxemia (N = 32)	TWA_{MV}-related non-hyperoxemia (N = 19)	*P*
Demographics			
Age	58 (17)	61 (17)	.57
Females	10 (31%)	3 (16%)	.32
Surgical	6 (19%)	4 (21%)	1.00
Emergency admission	10 (31%)	5 (26%)	.76
APACHE III score	71 (30)	66 (34)	.59
MV duration, h	116 [73–200]	138 [92–250]	.38
Length of ICU stay, d	6.3 [4.9-10.9]	9.1 [5.3-12.3]	.76
Length of hospital stay, d	14.6 [9.7-34.8]	17.9 [8.1-24.6]	.53
Died in ICU	7 (22%)	6 (32%)	.51
Died in hospital	11 (34%)	6 (32%)	1.00
Oxygenation-related variable			
TWA_{MV} Minute ventilation, L/min	8.1 [6.5-10.3]	8.6 [7.7-11.1]	.29
TWA_{MV} F_{IO_2}	0.38 [0.34-0.43]	0.44 [0.40-0.50]	.01
TWA_{MV} PEEP, cm H_2O	5.9 [5-6.8]	7.1 [5.1-9.2]	.04
TWA_{MV} Sp_{O_2}, %	98.9 [98.5-99.3]	96.7 [95.4-97.4]	<.001
TWA_{MV} SaO_2, %	98.2 [97.8-98.8]	96.5 [95.4-97.0]	<.001
TWA_{MV} Pa_{O_2}, mm Hg	116 [104–134]	94 [83–105]	<.001
TWA_{MV} pH	7.44 [7.41-7.45]	7.43 [7.37-7.44]	.16
TWA_{MV} $PaCO_2$, mm Hg	40.1 [36.9-43.7]	42.3 [38.9-48.5]	.06
TWA_{MV} P/F ratio, mm Hg	317 (69)	227 (78)	<.001
%time with hyperoxemia, %	76 [61–92]	19 [8–32]	<.001

P/F ratio, arterial oxygen tension/fraction of inspired oxygen ratio; %time with hyperoxemia, percentage of time spent with hyperoxemia.

Appendix 2

Comparison of patients with persistent hyperoxemia and those with transient hyperoxemia

Variable	Persistent hyperoxemia (N = 33)	Transient hyperoxemia (N = 18)	*P*
Demographics			
Age	57 (18)	63 (15)	.24
Females	10 (30%)	3 (17%)	.34
Surgical	6 (18%)	4 (22%)	.73
Emergency admission	12 (36%)	3 (17%)	.20
APACHE III score	69 (31)	70 (33)	.89
MV duration, h	114 [74–196]	139 [102–250]	.27
Length of ICU stay, d	6.5 [4.9-10.8]	7.7 [5.1-12.4]	.91
Length of hospital stay, d	15.3 [9.9-37.4]	15.9 [7.6-25.0]	.40
Died in ICU	7 (21%)	6 (33%)	.50
Died in hospital	11 (33%)	6 (33%)	1.00
Oxygenation-related variable			
TWA_{MV} minute ventilation, L/min	8.0 [6.5-10.0]	9.4 [8.3-11.3]	.08
TWA_{MV} F_{IO_2}	0.37 [0.34-0.43]	0.44 [0.40-0.50]	<.001
TWA_{MV} PEEP, cm H_2O	5.8 [5–6.7]	7.3 [5.9-9.3]	.01
TWA_{MV} Sp_{O_2}, %	98.9 [98.5-99.3]	96.6 [95.3-97.4]	<.001
TWA_{MV} SaO_2, %	98.3 [97.8-98.9]	96.5 [95.3-96.8]	<.001
TWA_{MV} Pa_{O_2}, mm Hg	125 [108–135]	92 [83–96]	<.001
TWA_{MV} pH	7.44 [7.42-7.45]	7.42 [7.37-7.44]	.03
TWA_{MV} $PaCO_2$, mm Hg	40.1 [37.0-44.0]	42.1 [38.3-50.8]	.09
TWA_{MV} P/F ratio, mm Hg	325 (72)	208 (41)	<.001
%time with hyperoxemia,	74 [59–92]	19 [7–30]	<.001

References

[1] Altemeier WA, Sinclair SE. Hyperoxia in the intensive care unit: why more is not always better. Curr Opin Crit Care 2007;13:73-8.

[2] Capellier G, Panwar R. Is it time for permissive hypoxaemia in the intensive care unit? Crit Care Resusc 2011;13:139-41.

[3] Davis WB, Rennard SI, Bitterman PB, et al. Pulmonary oxygen toxicity. Early reversible changes in human alveolar structures induced by hyperoxia. N Engl J Med 1983;309:878-83.

[4] Jackson RM. Pulmonary oxygen toxicity. Chest 1985;88:900-5.

[5] Fracica PJ, Knapp MJ, Piantadosi CA, et al. Responses of baboons to prolonged hyperoxia: physiology and qualitative pathology. J Appl Physiol 1991;71:2352-62.

[6] Lodato RF. Decreased O_2 consumption and cardiac output during normobaric hyperoxia in conscious dogs. J Appl Physiol 1989;67: 1551-9.

[7] Harten JM, Anderson KJ, Angerson WJ, et al. The effect of normobaric hyperoxia on cardiac index in healthy awake volunteers. Anaesthesia 2003;58:885-8.

[8] Haque WA, Boehmer J, Clemson BS, et al. Hemodynamic effects of supplemental oxygen administration in congestive heart failure. J Am Coll Cardiol 1996;27:353-7.
[9] Zwemer CF, Whitesall SE, D'Alecy LG. Cardiopulmonary-cerebral resuscitation with 100% oxygen exacerbates neurological dysfunction following nine minutes of normothermic cardiac arrest in dogs. Resuscitation 1994;27:159-70.
[10] Austin MA, Wills KE, Blizzard L, et al. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. BMJ 2010;341:c5462.
[11] Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 2010;303:2165-71.
[12] de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. Crit Care 2008;12:R156.
[13] Mao C, Wong DT, Slutsky AS, et al. A quantitative assessment of how Canadian intensivists believe they utilize oxygen in the intensive care unit. Crit Care Med 1999;27:2806-11.
[14] Eastwood GM, Reade MC, Peck L, et al. Intensivists' opinion and self-reported practice of oxygen therapy. Anaesth Intensive Care 2011;39: 122-6.
[15] O'Driscoll BR, Howard LS, Davison AG. BTS guideline for emergency oxygen use in adult patients. Thorax 2008;63(Suppl. 6):vi1-vi68.
[16] Decalmer S, O'Driscoll BR. Oxygen: friend or foe in peri-operative care? Anaesthesia 2013;68:8-12.
[17] de Graaff AE, Dongelmans DA, Binnekade JM, et al. Clinicians' response to hyperoxia in ventilated patients in a Dutch ICU depends on the level of F_{IO_2}. Intensive Care Med 2011;37:46-51.
[18] Finney SJ, Zekveld C, Elia A, et al. Glucose control and mortality in critically ill patients. JAMA 2003;290:2041-7.
[19] The blood gas handbook. Brønshøj, Radiometer Medical ApS, 2011.
[20] Rachmale S, Li G, Wilson G, et al. Practice of excessive F (IO(2)) and effect on pulmonary outcomes in mechanically ventilated patients with acute lung injury. Respir Care 2012;57:1887-93.
[21] Sinclair SE, Altemeier WA, Matute-Bello G, et al. Augmented lung injury due to interaction between hyperoxia and mechanical ventilation. Crit Care Med 2004;32:2496-501.
[22] Downs JB. Has oxygen administration delayed appropriate respiratory care? Fallacies regarding oxygen therapy. Respir Care 2003;48:611-20.
[23] Meyhoff CS, Jorgensen LN, Wetterslev J, et al. Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: follow-up of a randomized clinical trial. Anesth Analg 2012;115:849-54.