Conservative Oxygen Therapy in Mechanically Ventilated Patients: A Pilot Before-and-After Trial*

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Objectives: To assess the feasibility and safety of a conservative approach to oxygen therapy in mechanically ventilated ICU patients.

Design: Pilot prospective before-and-after study.

Setting: A 22-bed multidisciplinary ICU of a tertiary care hospital in Australia.

Patients: A total of 105 adult (18 years old or older) patients required mechanical ventilation for more than 48 hours: 51 patients during the "conventional" before period and 54 after a change to "conservative" oxygen therapy.

Interventions: Implementation of a conservative approach to oxygen therapy (target Spo_2 of 90–92%).

Measurements and Main Results: We collected 3,169 datasets on 799 mechanical ventilation days. During conservative oxygen therapy the median time-weighted average Spo_2 on mechanical ventilation was 95.5% (interquartile range, 94.0–97.3) versus 98.4% (97.3–99.1) ($p < 0.001$) during conventional therapy. The median Pao_2 was 83 torr (71–94) versus 107 torr (94–131) ($p < 0.001$) with a change to a median Fio_2 of 0.27 (0.24–0.30) versus 0.40 (0.35–0.44) ($p < 0.001$). Conservative oxygen therapy decreased the median total amount of oxygen delivered during mechanical ventilation by about two thirds (15,580 L [8,263–29,351 L] vs 5,122 L [1,837–10,499 L]; $p < 0.001$). The evolution of the Pao_2/Fio_2 ratio was similar during the two periods, and there were no difference in any other biochemical or clinical outcomes.

Conclusions: Conservative oxygen therapy in mechanically ventilated ICU patients was feasible and free of adverse biochemical, physiological, or clinical outcomes while allowing a marked decrease in excess oxygen exposure. Our study supports the safety and feasibility of future pilot randomized controlled trials of conventional compared with conservative oxygen therapy. (*Crit Care Med* 2014; 42:1414–1422)

Key Words: anoxia; critical illness; hyperoxia; lactic acid; oxygen inhalation therapy

Oxygen is the most widely prescribed therapy in mechanically ventilated ICU patients. The goal of oxygen therapy is to prevent or correct hypoxemia. The rationale for such intervention is that hypoxemia carries significant risk (1). However, the prevention or treatment of hypoxemia may induce hyperoxemia, which may also be injurious (2, 3). For example, a high Fio_2 may impair the innate immune response (4), cause lung injury, and induce interstitial fibrosis, atelectasis, tracheobronchitis, alveolar protein leakage, and infiltration by neutrophils (5–7). Systemically, hyperoxemia can increase vascular resistance, decrease cardiac output (7–10), and generate free radicals in various organs (11). Clinical adverse outcomes of hyperoxemia have also been reported in patients with acute exacerbations of chronic obstructive pulmonary disease (12), after cardiac arrest (13), after abdominal surgery (14), and in critical illness (15).

Although there is increasing awareness of the potential harms of hyperoxemia, this concern has not translated to change in routine practice. Substantial excess oxygen delivery is frequent in mechanically ventilated patients (16), and ventilator settings are not adjusted in most hyperoxemic cases (17). A recent study showed that most episodes of hyperoxemia occurred at low Fio_2 and with average Spo_2 levels of greater than 98%, implying that further decreases in Fio_2 could be safely implemented (18). However, no studies have shown the feasibility and/or safety of an approach to oxygen

*See also p. 1553.

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therapy deliberately targeting an oxygen saturation level between 90% and 92%.

Accordingly, we conducted a pilot prospective before-and-after trial of conservative oxygen therapy. We tested the hypothesis that a conservative approach to oxygen therapy (target Spo_2 of 90–92%) is feasible and safe in mechanically ventilated critically ill patients and can reduce exposure to excess oxygen.

MATERIALS AND METHODS

Study Design

We performed a prospective before-and-after pilot study in the 22-bed multidisciplinary ICU of the Austin Hospital, a tertiary care hospital affiliated with the University of Melbourne. The study was conducted from March 14, 2012, to June 27, 2012 (conventional oxygen therapy period), followed by a phase-out period (from June 28, 2012, to October 15, 2012) and a conservative oxygen therapy period (October 16, 2012, to January 17, 2013). The study was approved by the human research ethics committee of the Austin Health with a waiver for informed consent because this was a practice change that applied to all admissions expected to require mechanical ventilation (MV) for greater than 48 hours (approval no. H2011/04252). The study is registered at ClinicalTrials.gov (NCT01684124).

Patients were eligible if they were adult (18 years old or older) and required 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). During the conventional period, oxygenation goals for each patient were prescribed at the discretion of bedside clinicians. All clinicians were kept strictly unaware of the study during this period. Following a phase-out period that included education and preparation of all ICU staff, the intervention period commenced with screening of all consecutive admissions. If a patient was eligible for the trial, clinicians now prescribed an Spo_2 level between 90% and 92% using the lowest possible Fio_2.

Data Collection

Using a standardized case report form, we collected information on age, gender, type of admission, Acute Physiology and Chronic Health Evaluation (APACHE) III score, renal replacement therapy (RRT) at baseline (defined as that started within 24 hr after enrollment), primary admission diagnosis, and reason for MV. We recorded positive end-expiratory pressure (PEEP), ventilator-derived minute ventilation, Fio_2, Spo_2 (Philips Healthcare, Eindhoven, The Netherlands), and Pao_2 as oxygenation-related variables. Simultaneously, we also collected blood pH, $Paco_2$, hemoglobin concentration, lactate concentration, and creatinine concentration from blood gas analysis. Blood gas analysis was performed with ABL800 FLEX (Radiometer, Copenhagen, Denmark). We collected these data at four time points—06:00, 12:00, 18:00, and 24:00, using the measurement closest to that time point and followed up from the commencement of MV until the patient was free of MV for greater than 24 consecutive hours, death, or up to 28 days after enrollment into the study (whichever occurred first). For patients who were readmitted to ICU and required MV for greater than 48 hours, only the index admission was considered.

To avoid surveillance bias, we calculated the time-weighted averages for the oxygenation-related variables and blood gas results. 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 (19). 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 four consecutive datasets 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 the patient was extubated, had a brief spontaneous breathing with a T-piece circuit, did not have arterial blood gas data, had surgery, or died.

Oxygen utilization rate for each observation was calculated as follows: Minute ventilation × (Fio_2 – 0.21)/0.79 (L/min) (20), where total inspired gas flows were regarded as minute ventilation if patient had a brief spontaneous breathing with a T-piece circuit. A sum of their time-weighted value was regarded as a total amount of oxygen use during MV. When oxygen was delivered to a patient at hyperoxemia (defined as Spo_2 > 98% according to the British Thoracic Society guideline (21) and a recent review (22) that recommend target Spo_2 of 94–98% for most acutely ill patients) and continued without a decrease in Fio_2 despite an Spo_2 greater than 98% at the following set of observations, we defined such therapy as "excess oxygen delivery" and calculated the amount. Excess oxygen delivery rate for each observation was determined as minute ventilation × (Fio_2 – 0.21) (L/min). A sum of their time-weighted values provided a total amount of excess oxygen delivery.

Outcomes

The primary outcome was change in Pao_2/Fio_2 ratio in the first 10 days. Secondary and tertiary outcomes included changes in lactate and creatinine levels in the first 10 days; laboratory test results; new nonrespiratory organ failure while the patient was in ICU; the prevalence of arrhythmias, infection (defined as positive bacterial culture in sputum, urine, or blood), and severe hypoxemia (defined as Pao_2 < 55 torr) (23) in the ICU; acquired RRT (defined as that started 24 hr after enrollment) in the ICU; use of antidelirium drugs (haloperidol, olanzapine, quetiapine, and dexmedetomidine) and packed RBC transfusions in the ICU; ventilator-, ICU-, and hospital-free days at 28 days; and hospital survival status at 28 days. New nonrespiratory organ failure was defined as a Sequential Organ Failure Assessment (SOFA) score (24) of at least 3 for any of the cardiovascular, renal, hepatic, or hematological systems after day 2 in patients who did not have such organ failure at day 1 (25). CNS (measured by the Glasgow coma score) was not considered because most patients received sedation.

Statistical Analysis

A minimum of 45 patients per group (90 patients total) were required to detect a difference of 0.6 SDs of relative change in Pao_2/Fio_2 ratio from baseline to the worst value between the two groups with 95% certainty at 80% power. Target recruitment was set at 50 patients per group.

Variables were assessed for normality. Baseline comparisons were performed using Fisher exact tests and reported as *n* (%). Continuous normally distributed variables were compared using Student *t* tests and reported as means (SD), while nonnormally distributed data were compared using Wilcoxon rank-sum tests and reported as medians (interquartile range). Changes over time were determined using repeated-measures mixed linear modeling with each patient treated as a random effect, and therapy group, time, and the interaction of therapy group and time as effect-fixed effects. Variables were log-transformed if appropriate in this model.

Trends over time in achieved Spo_2, Pao_2, and Fio_2 were assessed for the first 10 days. We calculated the time spent in predefined bands of the variables of interest (Fio_2, Spo_2, and Pao_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: Fio_2 was divided into eight bands of 0.1; Spo_2 above 89% was divided into 11 bands of 1%; and Pao_2 was divided into four bands (≤ 60, 60–80, 80–120, and > 120 torr).

To investigate the clinicians' response when Fio_2 was relatively low (< 0.5), we assessed whether, in the subsequent dataset, Fio_2 was adjusted according to Spo_2 levels. These frequencies were compared between groups by the chi-square test. Additionally, we evaluated adherence to the target Spo_2 in the conservative oxygen therapy group.

Changes in the relevant outcome variables (Pao_2/Fio_2 ratio, lactate, and creatinine) were expressed as relative percentage change from baseline. The first result after the commencement of MV was referred to as "baseline value." Changes from baseline to follow-up over the first 10 days, the worst value (%Δworst), TWA_{24} on day 1 (%Δ24 hr), and TWA_{24} on day 2 (%Δ48 hr) were assessed.

A multivariable logistic regression analysis was performed to estimate the risk for various clinical outcomes with the conservative oxygen therapy, adjusting for APACHE III score, primary diagnosis, and reason for MV. A multivariable linear regression analysis was also conducted to assess the relationship between the conservative oxygen therapy and the relevant outcome variables. Because the magnitude of the increase in lactate and creatinine levels could be dependent on the use of RRT, the use of RRT during ICU (including both RRT at baseline and acquired RRT) was also included as an independent factor in this model. All analysis was performed using SPSS version 19.0 (SPSS, Chicago, IL). To account for multiple comparisons and further reduce the chance of a type I error, a two-sided *p* value of 0.01 was used to indicate statistical significance.

Sensitivity Analysis

Because several extra patients were enrolled in this trial in case of missing data, to assess the robustness of our results, all above analyses were repeated for the first 50 patients in each group. Furthermore, we carried out additional analysis using all available blood gas results from all study patients during the whole MV period to assess change in Pao_2/Fio_2 ratio and lactate and creatinine levels in the first 10 days. The blood gas results used here were stored electronically and retrieved.

RESULTS

Patient Characteristics

During the study period, there were 678 admissions from 625 patients during the before period and 498 admissions from 451 patients during the conservative oxygen therapy period.

We enrolled 51 patients with 1,409 datasets on 354 MV days in the conventional therapy group and 54 patients with 1,760 datasets on 445 MV days in the conservative oxygen therapy group. The two groups of patients had similar baseline characteristics (**Table 1**).

Conservative Oxygen Therapy and Treatment Effect

During the conservative treatment period, patients had a significantly lower time-weighted average Spo_2 (TWA_{MV}-Spo_2) (95.5% [94.0–97.3%] vs 98.4% [97.3–99.1%]; $p < 0.001$) and TWA_{MV}-Pao_2 (83 torr [71–94 torr] vs 107 torr [94–131 torr]; $p < 0.001$) with a significantly lower TWA_{MV}-Fio_2 (0.27 [0.24–0.30] vs 0.40 [0.35–0.44]; $p < 0.001$) compared with the conventional therapy period. There were no differences in minute ventilation, PEEP, pH, and $Paco_2$ between the groups (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A848).

Over the first 10 days, significantly lower levels of Spo_2, Pao_2, and Fio_2 were observed in the conservative group (**Fig. 1**). Conservative oxygen therapy decreased the total amount of oxygen delivered during MV by approximately two thirds (15,580 L [8,263–29,351 L] vs 5,122 L [1,837–10,499 L]; $p < 0.001$) and delivered much less excess oxygen (3,472 L [1,532–7,178 L] vs 192 L [0–1,184 L]; $p < 0.001$) (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A848).

The conventional oxygen therapy group spent 59% (29–83%) of the time in a state of relative hyperoxemia (Spo_2 > 98%) (**Fig. 2*A***) and Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A848). The Pao_2 was between 80 and 120 torr 59% (38–72%) of the time (**Fig. 2*B***) while the Fio_2 was mostly between 0.3 and 0.4 (24% [0–75%]) or 0.4 and 0.5 (38% [8–71%]) (**Fig. 2*C***). In the conservative oxygen therapy group, percentage of time spent with hyperoxemia significantly decreased (13% [2–36%]) (Fig. 2*A*; and Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A848). Patients in the conservative period spent a relatively short time in the target levels (3% [0–20%]) (Fig. 2*A*) often because their Spo_2 was greater than 92% while on 0.21 Fio_2. They spent most of the time at a Pao_2 between 60 and 80 torr (63% [21–76%]) (Fig. 2*B*) and at an Fio_2 below 0.3

TABLE 1. Baseline Characteristics of the Patients During the Conventional and Conservative Oxygen Therapy Periods

Variable	Conventional ($n = 51$)	Conservative ($n = 54$)
Demographics		
Age	59 (17)	56 (16)
Females (%)	13 (25)	22 (41)
Postoperative admission (%)	10 (20)	16 (30)
Unplanned admission (%)	50 (98)	48 (91)
Acute Physiology and Chronic Health Evaluation III score	68 (42–94)	62 (49–92)
MV duration, hr	125 (76–217)	125 (88–289)
Renal replacement therapy at baseline (%)	5 (10)	12 (23)
Primary diagnosis (%)		
Cardiovascular	14 (27)	10 (19)
Gastrointestinal	9 (18)	16 (30)
Neurological	7 (14)	14 (26)
Respiratory	13 (25)	6 (11)
Sepsis	4 (8)	3 (6)
Others	4 (8)	5 (9)
Reasons for MV (%)		
Pulmonary impairment	16 (31)	13 (24)
Hemodynamic instability	14 (27)	11 (20)
Neurological impairment	8 (16)	16 (30)
Surgical procedure	9 (18)	11 (20)
Others	4 (8)	3 (6)
Baseline		
F_{IO_2}	1 (0.8–1)	1 (0.75–1)
Spo_2, %	100 (98–100)	100 (98–100)
Pao_2, torr	225 (138–341)	229 (145–377)
Pao_2/F_{IO_2} ratio, torr	278 (137)	302 (142)
Lactate, mmol/L	1.6 (1–3.3)	1.75 (1.18–4)
Creatinine, μmol/L	89 (66–142)	109 (70–154)

MV = mechanical ventilation.

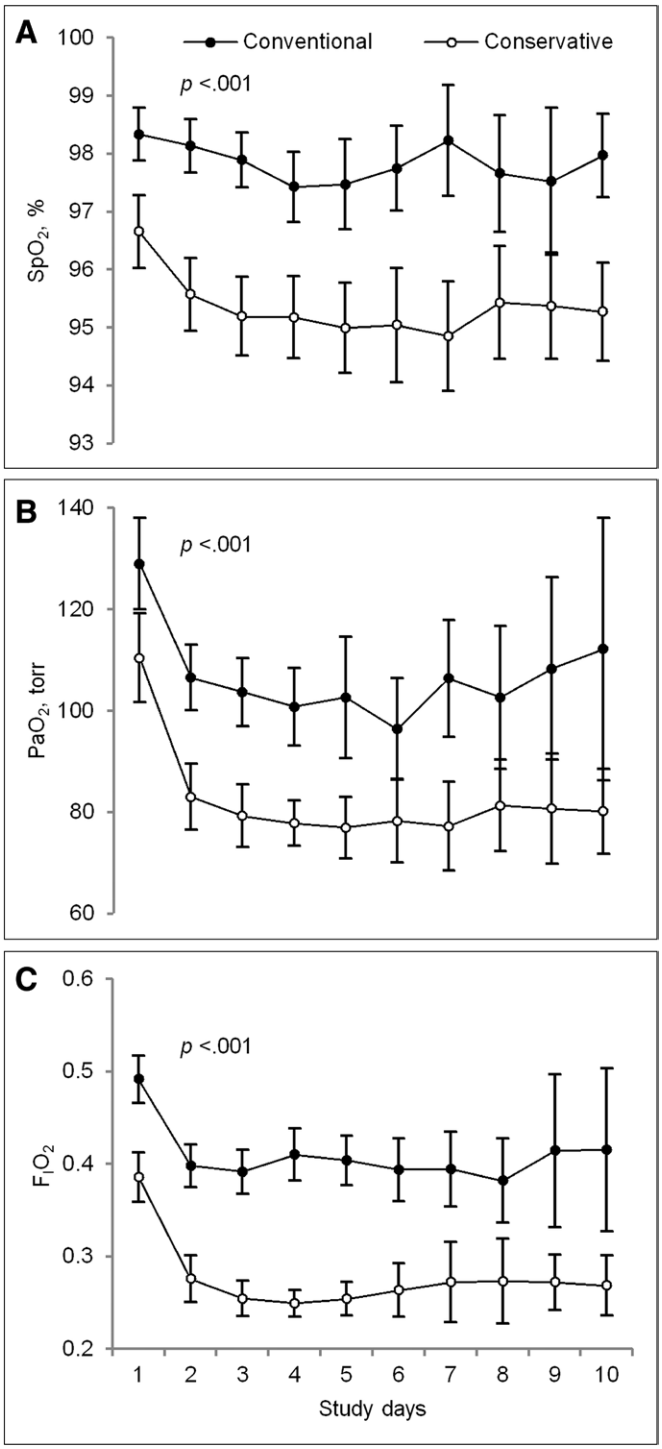

Figure 1. Changes in Spo_2 (**A**), Pao_2 (**B**), and F_{IO_2} (**C**) over time in the first 10 d. Conservative oxygen therapy achieved significantly lower Spo_2 and Pao_2 with lower F_{IO_2} compared with conventional oxygen therapy. *Error bars* indicate the 95% CIs. *p* value for comparison between groups with mixed linear model.

(81% [54–89%]) (**Fig. 3*C***). Importantly, while the conventional group essentially spent no time at an F_{IO_2} of 0.21 (0% [0–0%]), the conservative oxygen therapy group spent 33% (9–73%) of the time at an F_{IO_2} of 0.21 (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A848).

After excluding the first data of each patient and data observed while on an F_{IO_2} of 0.21, the distribution of Spo_2 peaked at 93% and a total of 21% of the observations were in the target range (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A848). Finally, when an Spo_2 was above the target levels with an F_{IO_2} below 0.5 (but not already 0.21), the F_{IO_2} was more frequently decreased in the conservative therapy group (**Table 2**).

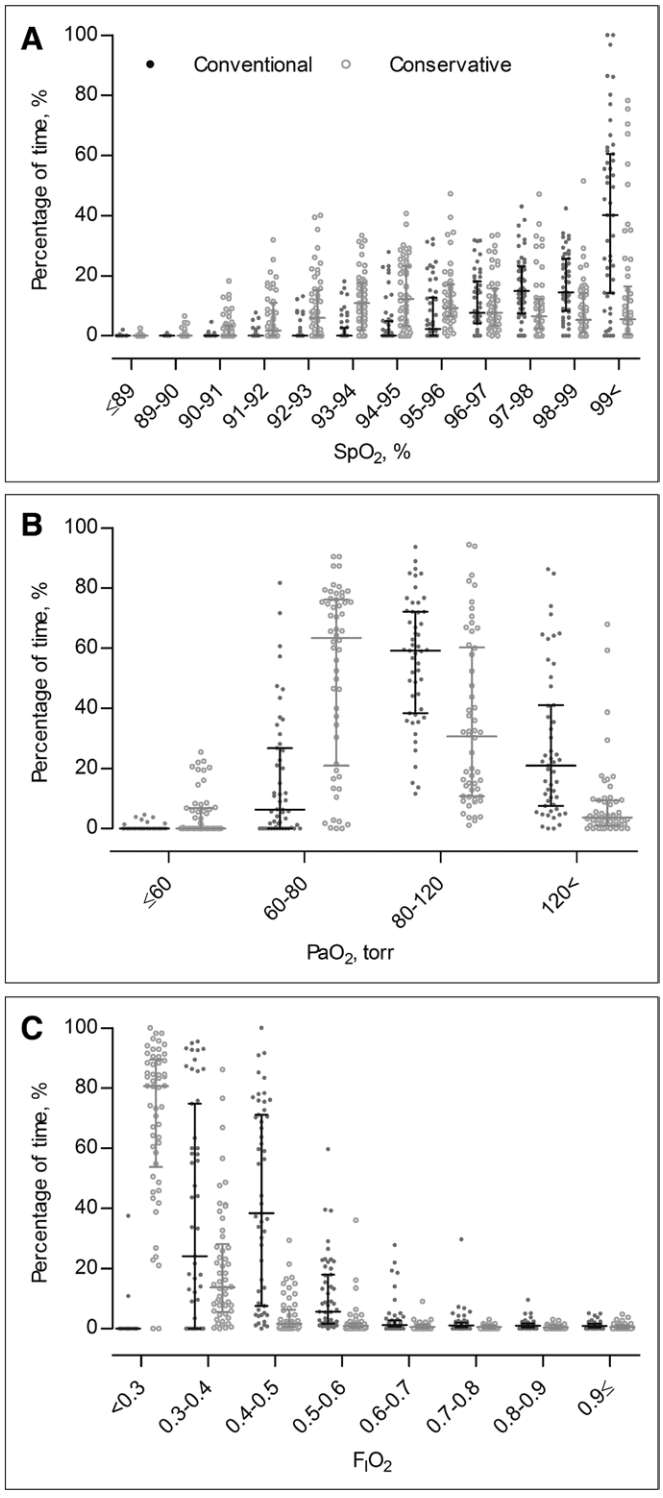

Figure 2. Percentage of time spent in each band of Spo_2 (**A**), Pao_2 (**B**), and Fio_2 (**C**) for all study patients. The conventional oxygen therapy group spent most of their time at an Spo_2 greater than 98%, a Pao_2 between 80 and 120 torr, and an Fio_2 between 0.3 and 0.5. Conversely, in the conservative oxygen therapy group, patients spent in a wide range of Spo_2 values, a Pao_2 between 60 and 80 torr, and an Fio_2 below 0.3. *Horizontal lines* represent medians; *error bars* represent interquartile range; *dots* represent the study patients.

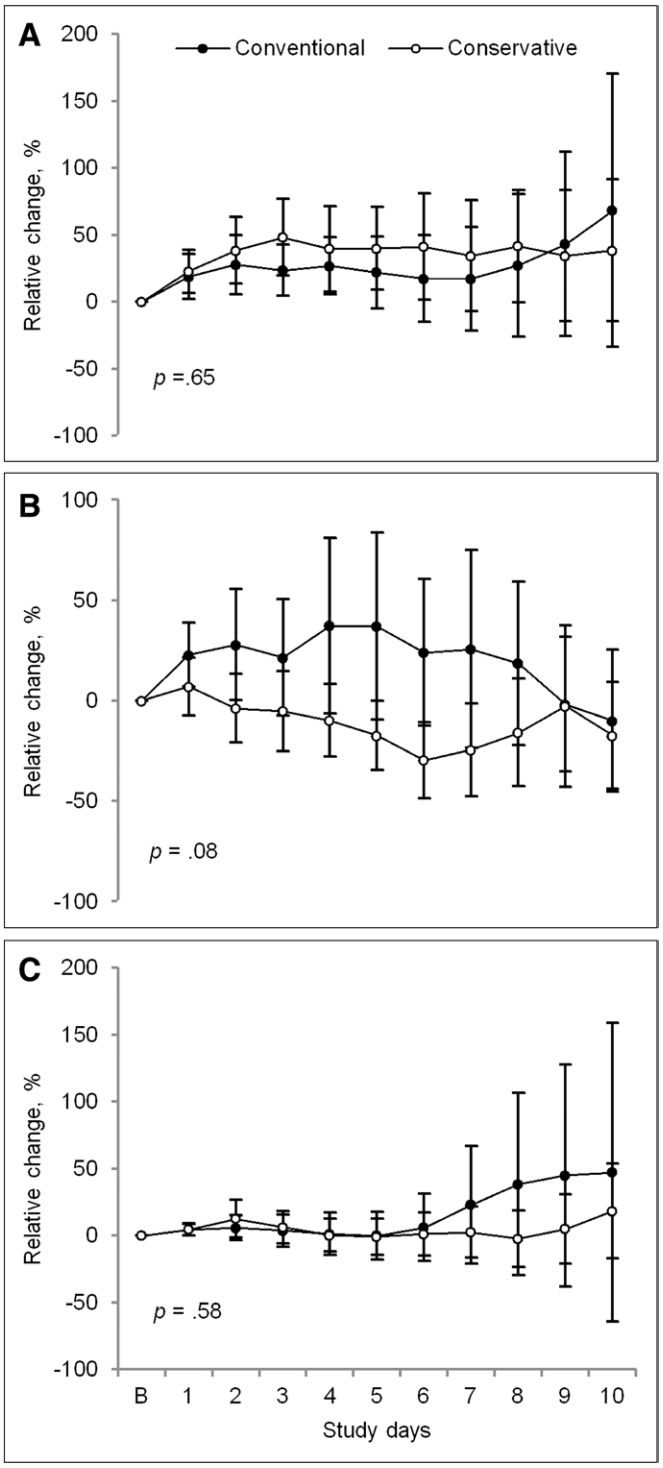

Figure 3. Relative changes in Pao_2/Fio_2 ratio, lactate, and creatinine level over time in the first 10 d. **A**, Relative changes in Pao_2/Fio_2 ratio were comparable between conservative and conventional oxygen therapy group. **B**, Conservative oxygen therapy group had a trend to decrease lactate from baseline. **C**, There was no difference in relative change in creatinine level between groups. *Error bars* indicate the 95% CIs. *p* value for comparison between groups with mixed linear model.

Outcomes

On univariable comparison, %Δworst, %Δ24 hr, and %Δ48 hr in Pao_2/Fio_2 ratio were not significantly different between groups, while lactate had a trend to decrease in the conservative oxygen therapy group (**Supplemental Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A848). Relative percentage changes between baseline

TABLE 2. Adjustments to Fio_2 According to Spo_2, When Fio_2 Was Less Than 0.5 (Excluding 0.21)

	Conventional			Conservative		
Spo_2	Decreased	Unchanged	Increased	Decreased	Unchanged	Increased
93%	1 (6%)	8 (50%)	7 (44%)	23 (21%)	65 (60%)	21 (19%)
94%	4 (13%)	19 (63%)	7 (23%)	32 (31%)	54 (52%)	18 (17%)
95%	4 (12%)	26 (79%)	3 (9%)	32 (33%)	54 (55%)	12 (12%)
96%[a]	2 (2%)	63 (75%)	19 (23%)	35 (36%)	55 (57%)	6 (6%)
97%[a]	4 (3%)	103 (76%)	29 (21%)	20 (30%)	41 (61%)	6 (9%)
98%[a]	13 (8%)	130 (81%)	17 (11%)	18 (30%)	40 (67%)	2 (3%)
99%[a]	8 (5%)	134 (88%)	10 (6%)	20 (38%)	31 (58%)	2 (4%)
100%[a]	31 (8%)	341 (87%)	19 (5%)	29 (49%)	26 (44%)	4 (7%)

[a]$p < 0.01$, for comparison between the conventional and conservative oxygen therapy group.

and follow-up in the first 10 days were also analyzed (Fig. 3). No differences were found in Pao_2/Fio_2 ratio (**Fig. 3*A***) and creatinine levels (Fig. 3*C*), but the conservative oxygen therapy group had a trend toward decreasing lactate levels over the first 10 days ($p = 0.08$) (**Fig. 3*B***). There were no significant differences in any other clinical outcomes (**Supplemental Table 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/A848).

On multivariable regression analysis, conservative oxygen therapy continued to show a trend toward decreases in lactate levels between baseline and the worst value and between baseline and day 2 (standardized coefficients of –0.18, $p = 0.093$ and standardized coefficients of –0.20, $p = 0.050$, respectively) (**Table 3**). There was a trend toward a decrease in the risk of new nonrespiratory organ failure in conservative oxygen therapy group (adjusted odds ratio, 0.32; 95% CI, 0.12–0.83;

TABLE 3. Multivariable Linear Regression Analyses With Conservative Oxygen Therapy as Independent Variable

Outcome	Estimates	SE	*β*	*p*
P/F %Δworst in the first 10 d[a]	5.66	4.60	0.12	0.22
P/F %Δ24 hr[b]	13.65	11.93	0.12	0.26
P/F %Δ48 hr[c]	21.51	17.04	0.13	0.21
Lac %Δworst in the first 10 d[a]	−47.04	27.67	−0.18	0.093
Lac %Δ24 hr[b]	−17.54	11.59	−0.16	0.13
Lac %Δ48 hr[c]	−33.30	16.78	−0.20	0.050
Cr %Δworst in the first 10 d[a]	−13.96	14.28	−0.097	0.33
Cr %Δ24 hr[b]	1.99	3.93	0.053	0.61
Cr %Δ48 hr[c]	7.28	8.77	0.081	0.41
Mechanical ventilation–free days at 28 d	1.45	1.82	0.075	0.43
ICU-free days at 28 d	0.65	1.80	0.036	0.72
Hospital-free days at 28 d	−2.94	1.45	−0.21	0.046

P/F = Pao_2/Fio_2 ratio, Lac = lactate, Cr = creatinine.

[a]%Δworst = (worst value – baseline)/baseline × 100.

[b]%Δ24 hr = (time-weighted average of day 1 – baseline)/baseline × 100.

[c]%Δ48 hr = (time-weighted average of day 2 – baseline)/baseline × 100.

The models for P/F-related variables and mechanical ventilation (MV)-, ICU-, and hospital-free days at 28 d were adjusted for Acute Physiology and Chronic Health Evaluation (APACHE) III score, primary diagnosis, and reason for MV; the models for Lac- and Cr-related variables were adjusted for APACHE III score, primary diagnosis, reason for MV, and use of renal replacement therapy.

These results must be interpreted with caution because data were not normally distributed.

TABLE 4. Adjusted Odds Ratio for Key Outcomes With Conservative Oxygen Therapy

Outcome	Number of Events (Conventional: Conservative)	Adjusted OR (95% CI)[a]	*p*
New nonrespiratory organ failure	22: 16	0.32 (0.12–0.83)	0.019
Arrhythmia	24: 16	0.56 (0.22–1.43)	0.23
Packed RBC	26: 27	0.65 (0.25–1.67)	0.37
Infection	28: 31	0.89 (0.36–2.22)	0.80
Use of antidelirium drugs	25: 27	1.52 (0.61–3.80)	0.38
Mortality at 28 d	16: 9	0.35 (0.12–1.06)	0.062

OR = odds ratio.

[a]Adjusted for Acute Physiology and Chronic Health Evaluation III score, primary diagnosis, and reason for mechanical ventilation.

Only results from outcomes that occurred 25 or more times are reported here. Results from the other outcomes are reported in **Supplemental Table 5** (Supplemental Digital Content 1, http://links.lww.com/CCM/A848).

$p = 0.019$) (**Table 4**). The direction of these results essentially remained unchanged when we performed sensitivity analysis in the first 50 patients in each group (**supplemental data**, Supplemental Digital Content 1, http://links.lww.com/CCM/A848) or used all available blood gas results collected from all study patients during their whole MV period (**Supplemental Fig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A848; and **Supplemental Table 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/A848).

DISCUSSION

Key Findings

We conducted a pilot feasibility and safety before-and-after trial of conservative oxygen therapy in mechanically ventilated patients in the setting of an Australian tertiary ICU. An oxygen therapy approach targeting an oxygen saturation of 90–92% achieved significantly lower Spo_2 and Pao_2 levels and marked oxygen exposure. The changes in Pao_2/Fio_2 ratio from baseline did not differ between conservative and conventional oxygen therapy. There was no significant difference between groups in any other secondary outcome although conservative oxygen therapy was associated with a trend toward the decrease in the risk for nonrespiratory organ failure and lactate concentrations.

Relationship to Previous Findings

Previous observational studies have shown that a "liberal" approach to oxygen therapy is dominant in mechanically ventilated patients in ICU. In a Dutch multicenter retrospective observational study involving thousands of patients, hyperoxemia (defined as $Pao_2 > 120$ torr) was frequent (22%) and, even when the Fio_2 was 0.4 or lower, the Fio_2 was decreased in only 6% of cases (17). Furthermore, 74% of MV patients at the Mayo Clinic were exposed to excessive Fio_2 for a median duration of 17 hours (16). Concern over such liberal use of supplemental oxygen has recently gained increased prominence (2, 3, 26, 27) arguing that avoidance of unnecessary exposure to hyperoxemia is likely to be desirable. To our knowledge, however, ours is the first study investigating the feasibility, safety, and physiological consequences of lower Spo_2 targets in mechanically ventilated ICU adult patients. Implementing a more conservative oxygen therapy protocol produced a clear separation in Spo_2, Pao_2, and Fio_2 compared with our standard preintervention liberal oxygen therapy group and also with previous observational studies of oxygen administration practice in patients receiving MV in ICU (16, 17).

The acute respiratory distress syndrome (ARDS) Network study comparing higher versus lower PEEP resulted in a statistically significant difference in Fio_2 and found no adverse association with such changes (28). The British Thoracic Society guideline (21) and a recent review (22) recommended target Spo_2 of 94–98% for most acutely ill patients even though the guidelines do not apply to mechanically ventilated patients, and evidence supporting such recommendations is lacking. Thus, for patients receiving MV, the optimal Spo_2 target levels remain unclear.

The greatest concern with conservative oxygen therapy in mechanically ventilated patients is the prevalence of severe hypoxemia and increased risk of tissue hypoxia which may cause the development of organ failure. Employing an Spo_2 target of 92% and 90% in mechanically ventilated patients led to 80% and 35%, respectively, of Pao_2 values being greater than or equal to 60 torr (23). In our conservative group, the percentage of time spent with a Pao_2 less than or equal to 60 torr was negligible. Furthermore, oxygen administration decreases cardiac output; systemic and coronary oxygen delivery (29); and cortical cerebral blood flow (30) while increasing oxidative stress (31). These factors may explain the trend we observed toward decreased risk for new nonrespiratory organ failure in the conservative therapy group.

We found a trend to greater relative decrease in lactate from baseline in the conservative oxygen therapy group. The lung is a substantial source of lactate during ARDS or endotoxemia (32–34) and in critically ill patients (35). Such lung lactate production is associated with lung injury score (32) suggesting that lactate generation was not attributable to lung tissue hypoxemia (36). Prolonged exposure to a high Fio_2 causes histopathological changes similar to those seen in ARDS and exacerbated ventilator-induced lung injury (2). Even a moderate

FIO_2 of 0.5 has been reported to cause lung injury and changes in lung tissue compared with air in experimental models (37). Additionally, ventilation with oxygen (6 hr) even at ambient air level (21%) increases tissue volumes, myofibroblast differentiation, and apoptosis in the sheep immature lung compared to nitrogen alone (38). On the other hand, in a recent study, a relatively low FIO_2 of 0.4 in mechanically ventilated patients without respiratory failure did not induce detectable inflammatory effects (39). However, inflammation may be a secondary event rather than a causal factor in lung injury (40) while the generation of reactive oxygen species may play a greater role in epithelial cell death and hyperoxemia-induced lung injury (40, 41). Thus, the effect of relatively low dose oxygen on lung remains uncertain.

Clinical Implications

Our findings suggest that an oxygen therapy protocol targeting an SpO_2 between 90% and 92% is feasible, can be safely implemented for mechanically ventilated patients in ICU, and leads to a marked decrease on oxygen exposure. These findings are important because a lower SpO_2 may be a potential therapeutic target for randomized controlled trials, particularly in patients with ARDS who die more often of multiple organ failure than hypoxemia (42). Our study also opens the door to phase II randomized controlled trials of conventional compared with conservative oxygen therapy.

Strengths and Limitations

To our knowledge, this is the first study to compare two different SpO_2 targets in mechanically ventilated patients in ICU. To make our findings robust, we additionally analyzed a total of 5,735 blood gas results in the study patients collected during the whole MV period as part of a sensitivity analysis.

However, our study has several limitations. Before-and-after design is subject to secular changes that may have led to independent improvements in care. Additionally, the two study periods enrolled patients during a different time of the year, and thus we could not exclude a seasonal effect. However, in our ICU, in the period after the intervention, there had been secular trends toward a greater use of RRT and stable hospital mortality (**Supplemental Table 6**, Supplemental Digital Content 1, http://links.lww.com/CCM/A848).

As we mentioned earlier, the median TWA_{MV}-SpO_2 achieved in the conservative group was above the target level. This is at least partially explained by the fact that 45% of the results in the conservative group were observed at an FIO_2 of 0.21 and further titration was impossible. However, after excluding such data and the first dataset for each patient, about 50% of the observations with the SpO_2 above the target levels failed to lead to adjustments in FIO_2. Because the peak of the distribution of SpO_2 among such observations was 93%, it appears that implementation was not complete and that clinicians and nurses tolerated an SpO_2 around the upper limit of the study target. Nonetheless, the prescribed approach markedly decreased the total amount of oxygen usage.

Although they were not statistically significant, there were imbalances in patient baseline characteristics such as primary diagnosis and reasons for MV. We therefore used multivariable analysis to control for potentially confounding effects.

Because PaO_2/FIO_2 ratio could conceivably be affected by FIO_2 when there is any significant degree of shunt (43), a change in PaO_2/FIO_2 ratio may not be insufficient in detecting pulmonary injury. However, PaO_2/FIO_2 ratio is frequently assessed and widely and easily understood and calculated in clinical practice; it is used in the Berlin definition of ARDS (44) and in several severity scoring systems such as SOFA score (24) and Simplified Acute Physiology Score II (45).

We did not collect data on tidal volume during the study period. Larger tidal volume is associated with the risk of development of lung injury in mechanically ventilated ICU patients (46). However, the typical target tidal volume in our unit is between 6 and 8 mL/kg and this was not changed during the study period.

The current study may be underpowered for all of secondary outcomes and multivariable analysis because the sample size calculation was based on PaO_2/FIO_2 and the number of the outcome events was small. Additionally, outcomes such as MV-, ICU-, and hospital-free days in multivariable linear regression analysis did not follow normal distributions and meet the assumptions required for this analysis. Therefore, these results must be interpreted with caution. Although there was a large CI, the adjusted odds ratio of acquired RRT in the conservative therapy group was 2.90. Renal adverse effect of conservative oxygen therapy cannot be excluded.

Our findings need to be confirmed or refuted in different healthcare systems and different ICUs. The feasibility and safety of more strict approaches to SpO_2 targeting (47, 48) may also require testing in future studies.

CONCLUSIONS

Our preliminary data suggest that implementing an oxygen therapy target of SpO_2 of 90–92% in mechanically ventilated ICU patients is feasible and not associated with major clinical or physiological adverse events. Our findings support the safety and feasibility of future randomized controlled trials of conservative versus conventional oxygen therapy.

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