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Early Titration of Oxygen During Mechanical Ventilation Reduces Hyperoxemia in a Pilot, Feasibility, Randomized Control Trial for Automated Titration of Oxygen Levels

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OBJECTIVES: Timely regulation of oxygen (Fio_2) is essential to prevent hyperoxemia or episodic hypoxemia. Exposure to excessive Fio_2 is often noted early after onset of mechanical ventilation. In this pilot study, we examined the feasibility, safety, and efficacy of a clinical trial to prioritize Fio_2 titration with electronic alerts to respiratory therapists.

STUDY DESIGN: Open-labeled, randomized control pilot trial.

SETTING: Medical ICU.

SUBJECTS: Adults requiring mechanical ventilation.

INTERVENTIONS: Protocolized oxygen titration was initiated one hour after initiation of mechanical ventilation. When Spo_2 exceeded 92% while on $Fio_2 \geq 0.5$, an electronic alert to respiratory therapists was triggered at 30-minute intervals. In the control arm, respiratory therapists titrated Fio_2 by standard physician's orders.

MEASUREMENTS AND MAIN RESULTS: The primary end point was to determine if early Fio_2 titration based on automated alerts was feasible in terms of reducing hyperoxemia. Secondary analyses included the number and frequency of alerts, mechanical ventilation duration, and ICU length of stay. Among 135 randomized patients, 72 were assigned to the intervention arm and 63 to the control arm. A total 877 alerts were sent. Exposure to hyperoxemia was significantly reduced in the intervention group by a median of 7.5 hours (13.7 [interquartile range (IQR), 2.9–31.1] vs 21.2 [IQR, 10.9–64.4]; $p < 0.0004$). Maximal Fio_2 titration during the first quartile resulted in significant reduction in mechanical ventilation duration and ICU stay. Minor hypoxemic events ($Spo_2 < 88\%$) represented 12% of alerts, 9% were transient and responded to a single Fio_2 increase, whereas 3% of alerts were associated with recurrent transient hypoxemia.

CONCLUSIONS: Our pilot study indicates that early Fio_2 titration driven by automated alerts is feasible in the ICU, as reflected by a statistically significant reduction of hyperoxemia exposure, limited consequential hypoxemia, and reduced ICU resource utilization. The encouraging results of this pilot study need to be validated in a larger ICU cohort.

KEY WORDS: electronic alerts; electronic medical records; hyperoxia; mechanical ventilation; oxygen

Supplemental fractional oxygen (Fio_2) is a core life-sustaining therapy in the ICU, used for over a million patients annually (1, 2). Precision in Fio_2 supplementation is necessary to prevent complications of hyperoxemia and hypoxemia. Detrimental effects of hypoxemia include cognitive deficits, tissue hypoxia, and, if extreme, anaerobic metabolism (3, 4). Hyperoxemia-related adverse effects include tracheobronchitis, absorption atelectasis, hyperoxia toxicity-associated lung injury (5, 6), and increased risk of ventilator-associated pneumonias (7, 8).

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Although the exact degree and duration of increased FIO_2 exposure required to cause hyperoxemia-induced free radical injury are not established, excessive supplemental FIO_2 during normoxia may contribute to higher morbidity and mortality in critically ill patients (9, 10). The deleterious impact of unnecessary FIO_2 exposure is well established in patients in the perioperative period, during reperfusion injury following cardiac arrest, resuscitation of septic shock, following acute myocardial infection, and after ischemic stroke (9–16). Although further research is warranted to determine optimal oxygen targets, hyperoxic exposure in the early hours after initiation of mechanical ventilation (MV) correlates with increased mortality in the ICU (17, 18). Therefore, time-sensitive measures to curtail excessive FIO_2 exposure are urgently needed.

Clinical practice guidelines continue to recommend targeted FIO_2 titration to avoid excessive or insufficient oxygen supplementation in acutely ill patients (19), yet excessive oxygen delivery is noted globally and is reflective of common hurdles to target oxygen titration (20–23). A bias toward liberal oxygenation is fueled by practitioners wishing to avoid real and perceived complications of hypoxemia along with a lack of awareness and concern of the risks of hyperoxic injury (24). Thus, avoidance of hyperoxemia, which is critical to the early hours of MV, may be best achieved using tools that are automated, and do not rely on minute-to-minute clinical decision-making. Workflow efficiency interventions utilizing electronic medical records (EMRs) to optimize oxygen titration can be effective for improving compliance to oxygenation protocols and reducing excessive FIO_2 administration, as shown by our group and others (25).

We, therefore, developed and tested a high-fidelity, bioinformatics-based EMR-derived electronic alert (e-alert) to be initiated within 1 hour of MV to facilitate prioritization of titration. The primary objective of this pilot study was to determine if time-sensitive automated, EMR-based, protocolized oxygen titration with pragmatic enrollment is feasible in the ICU setting, and secondarily to consider preliminary efficacy in objective reduction of hyperoxemia early during MV.

MATERIALS AND METHODS

Trial Design

This was a 1:1 randomized control, feasibility, open-labeled pilot study conducted at the Ohio State University (OSU) Wexner Medical Center and James Cancer hospital from August 2016 to January 2017. Since this was a pilot study to assess for feasibility, at the time of Initiation, it was not subject to Food and Drug Administration Amendments Act 801 for an applicable clinical trial.

Patients

All adult patients (>18 yr) requiring MV admitted to the medical ICU were included. We excluded prisoners, pregnant women, and those intubated only for procedural intent, such as bronchoscopy, esophageoduodenoscopy, and colonoscopy. Patients were enrolled within an hour of meeting eligibility criteria.

Consent

This study was carried out with deferred consent as approved by the OSU Institutional Review Board (Protocol 2014H0236). An explanatory script was placed outside the patient's room, and deferred consent was obtained at the earliest possible time from the patient or legal authorized representative. Deferred consent has been used in other oxygenation target studies (26), in neonatal, pediatric critical care, as well as emergency department patients (27–29). Procedures for deferred consent also discussed as Exception from Informed Consent are detailed by the Food and Drug Administration (30). In the event that the patient or the legal authorized representative refused consent, the patient was then withdrawn from the study, and no data were collected.

Data Collection

Data were collected from EMR by support staff blinded to the study intervention.

Intervention Arm. Subjects in the intervention arm had their FIO_2 levels titrated per e-alerts sent to phones carried by respiratory therapists. Levels of both FIO_2 and SpO_2 were transmitted from the bedside monitor and ventilator to an interim server connected to the EMR. The biomedical informatics team at OSU developed a real-time algorithm, which screened these values at specific time points (30-min intervals) and fired e-alerts on meeting criteria. See **Appendix 1** (http://links.lww.com/CCX/A999).

Alert Criteria. A 60-minute period delay was designed before the first alert to focus healthcare provider efforts on other essential time-sensitive patient

care duties (e.g., central catheters, arterial lines, and bronchoscopy). E-alerts were sent directly to respiratory therapists at 30-minute intervals if Spo_2 is greater than 92% and Fio_2 greater than or equal to 0.5 (or a monitor alarm if Spo_2 was <88%) along with decision support for Fio_2 titration. Fio_2 protocol and decision support (used for the intervention arm) are noted in **Figure 1**, ***A*** and ***B***. Any protocol deviations were documented.

Control Arm. Fio_2 titration was carried out per the routine ICU ventilator protocol (**Appendix 2**, http://links.lww.com/CCX/A999). Physicians placed orders for Fio_2 titration per the ICU ventilator protocol once at the beginning of MV. Management of positive end-expiratory pressure (PEEP) and other MV related parameters was carried per the ICU ventilator protocol in both arms (Appendix 2, http://links.lww.com/CCX/A999).

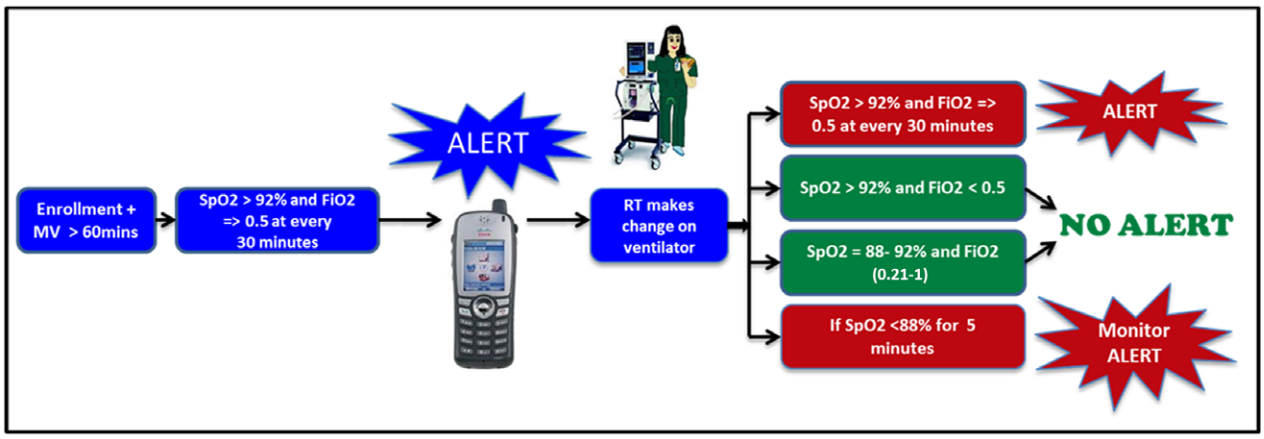
Education and Adherence

Respiratory therapists were educated prior to the onset of the study via two structured educational sessions. An electronic newsletter was sent, and an informational poster about the study was posted in the respiratory break room.

Statistical Analysis

Patient demographics and clinical characteristics were described using the median and interquartile range (IQR) for continuous variables or frequency and percent for categorical variables. Comparisons between intervention and control groups were performed using Wilcoxon two-sample test or Pearson chi-square test of independence. Since patients may differ in their total exposure to time of MV, we assessed both the duration in hours and percentage of overall time at different cutoffs

A



B

DECISION SUPPORT TOOL		
CONDITION	**CRITERIA**	**DIRECTIONS**
HYPEROXIA	FiO2 => 0.5 and SpO2 > 92% at 30 mins	If FiO2 < 0.7 then reduce FiO2 by 0.1 per alert
		If FiO2 => 0.7 then reduce FiO2 by 0.2 per alert
		PEEP management per ICU mechanical ventilation protocol
OPTIMAL FIO2 AND SPO2	SpO2 = 88-92%, SpO2 > 92% and FiO2 < 0.5	Make no change (There should be no alert)
HYPOXIA AFTER TITRATION	SpO2 less than 88% For atleast 5 minutes, FiO2 any value	Increase FiO2 by 0.2 → Inform MD → Next Steps per MD

Figure 1. Interventional arm workflow. **A**, Intervention arm-flow diagram: the process of oxygen titration in the intervention arm is shown. Alert notification starts only after an hour of intubation. When the criteria for Spo_2 and Fio_2 are met as noted above, then a pager/text alert is sent on the CISCO phone to the respiratory therapist (RT). Spo_2 and Fio_2 criteria for e-alert versus no e-alert are noted above. The bedside monitor will alarm if Spo_2 drops below 88% for 5 min. **B**, Decision support tool for intervention arm: the decision support tool used for oxygen titration in the intervention arm by the RT after receiving an alert is shown. *The first column* indicates the respective conditions for which an alert will be sent, and *the second column* defines the criteria. *The third column* indicates directions to be followed for each respective condition. MV = mechanical ventilation, PEEP = positive end expiratory pressure.

for hyperoxemia. We divided duration of MV into four quartiles, and e-alerts in each quartile were noted. Clinical outcomes were compared in patients with all alerts in the first quartile versus patients with e-alerts spread out through all the quartiles and also compared with control patients. Analyses were conducted using the JMP statistical software package (Version 14.0, SAS, Cary, NC) and R version 4.0.5 (31) with the ggplot2, Version 3.3.3, package (Springer-Verlag, New York) (32).

RESULTS

Over 6 months, 174 mechanically ventilated patients were screened consecutively for eligibility. Five patients were excluded during the preplanned refinement of screening algorithm in the first 2 weeks (alerts being tested and no actions taken). Six patients were excluded due to coenrollment in other studies, prisoner status, and transfer to other ICUs. One patient declined to participate in the study. Data for 32 patients who were enrolled and randomized were not available due to inability to consent. The most common reason for not being able to obtain deferred consent was unavailability of legal authorized representative, homeless status, patient transferred out of ICU or discharged on a weekend, and patient death or transfer to a long-term acute-care center prior to communication with a legally authorized representative.

After randomization, 72 patients were allocated to the intervention group and 63 patients to the control group. Alerts were not available or discontinued on seven patients in the intervention arm; however, they were included in the intention to treat analysis. Among those seven, e-alerts did not function in two patients due to electronic communication failure between EMR and that specific ventilator. Among the other five patients, e-alerts had to be discontinued by the study team due to recurrent hypoxemia after titration. Fio_2 data were not available in four patients in the intervention arm and five patients in the control arm due to technical issues with the electronic data (**Fig. 2**). Baseline characteristics including demographics, comorbidities, and etiology for ICU admission are noted in **Table 1**. All other ventilator-related variables were similar in both groups. During the study period, 877 alerts were sent for 72 patients in the intervention arm among which the majority (84%) were initiated in the initial half (first two quartiles) of MV, and the alert rate declined progressively (first quartile [56%], second quartile [28%], third quartile [8%], and fourth [4%]). See Appendix 1 and **Figure Appendix 1.1** (http://links.lww.com/CCX/A999).

Among alerts within the titration window, adherence was 55%. A total of 23% alerts were noted during a time titration could not be accomplished, that is, during bedside procedures or change to comfort care status. Episodic Spo_2 desaturation (<88%) that occurred within an hour of 30 alerts (9%) was reversible by increasing Fio_2 once without apparent adverse consequences. Alerts (n = 10, 3%) were stopped in five patients due recurrent hypoxemia after implementing titration per alerts. The most common reasons for not following the e-alerts documented by respiratory therapists were "care of another critical patient" or "inability to get to the patient in time." We could not validate 35 alerts for accuracy (**Appendix Fig. 1.2**, http://links.lww.com/CCX/A999).

Duration of hyperoxemia (time with $Fio_2 \geq 0.5$ when $Spo_2 > 92\%$) was reduced by a median of 7.5 hours in the intervention group (13.7 [IQR, 2.9–31.1] vs 21.2 [IQR, 10.9–64.4]; $p < 0.0004$), and exposure to severe hypoxemia ($Fio_2 \geq 0.7$ when $Spo_2 > 92\%$) was reduced by a median of 4.87 hours (3.1 [IQR, 1.9–6.5] vs 10.3 [IQR, 3.1–6.52]; $p < 0.002$) (**Table 2**). Consequently, the proportion of time spent in hyperoxemia during MV was significantly reduced in the intervention group versus the control group. ($Spo_2 > 92\%$ and $Fio_2 \geq 0.5$: 12% [3–25] vs 22% [6–40], $p < 0.05$; $Spo_2 > 92\%$ and $Fio_2 \geq 0.7$: 2% [0.03–5] vs 5% [1–15], $p < 0.05$) (**Fig. 3**, ***A*** and ***B***). Irrespective of the Spo_2 values, the intervention group, on average, was exposed to lower Fio_2 concentration, as reflected by a lower proportion of time at Fio_2 values greater than 0.5 (**Appendix Fig. 2**, http://links.lww.com/CCX/A999). Furthermore, a smaller cohort of patients (33), in whom all e-alerts were initiated within the first quartile of MV, showed a statistically significant reduction in both duration of MV and ICU stay compared with those who had titration alerts after the first quartile and compared with the control group (Table 2). There were no serious adverse events reported as a consequence of restricting the Spo_2 goals within the 88–92% range.

DISCUSSION

This pilot study demonstrates the preliminary efficacy of achieving time-sensitive Fio_2 titration in

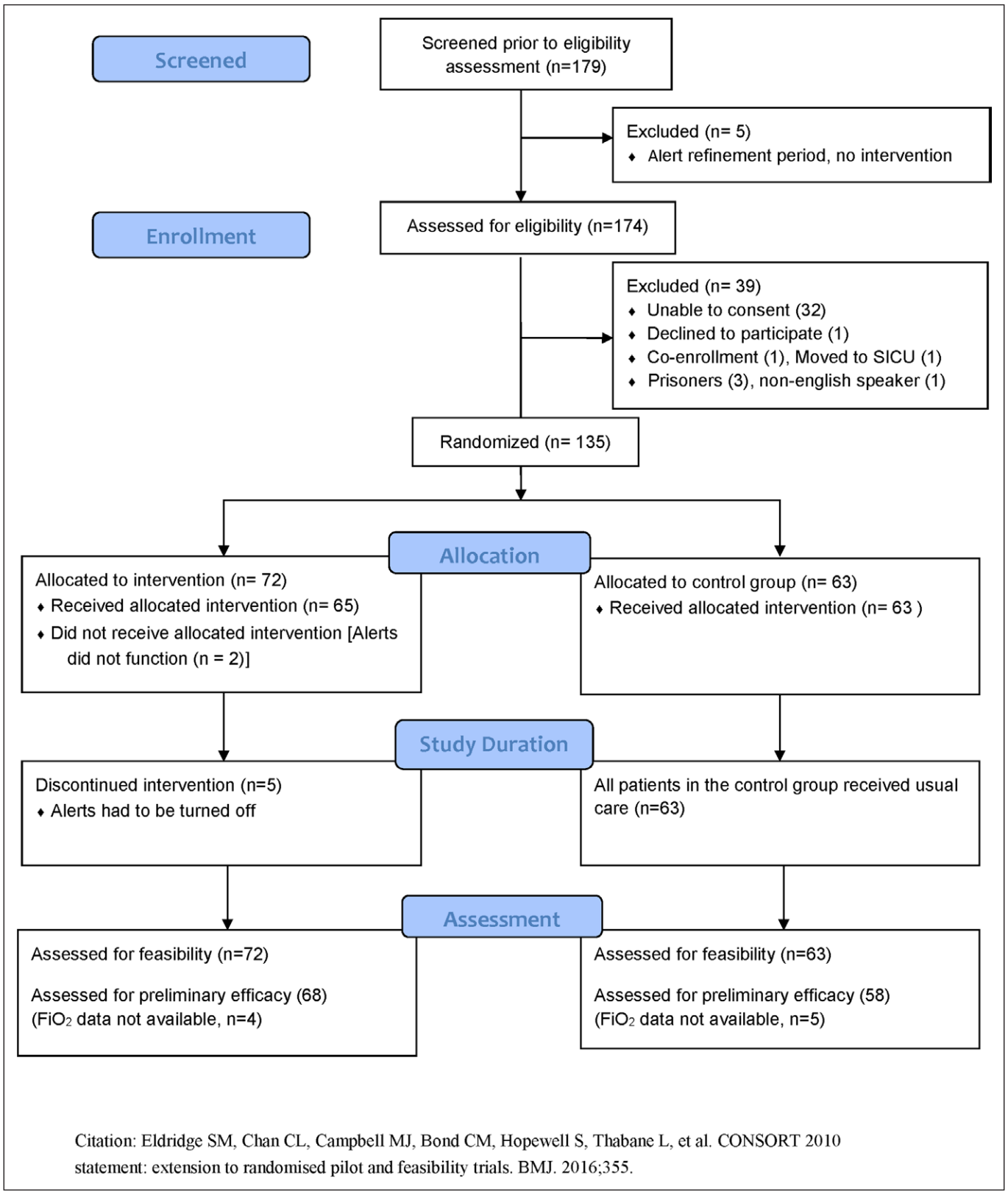


Figure 2. Consort flow diagram.

TABLE 1.
Patient Characteristics and ICU Course-Related Variables

Patient Characteristics	Intervention (*n* = 72)	Control (*n* = 63)
Age, yr	59 (49–70)	62 (53–67)
Sex, female, *n* (%)	39 (54)	22 (35)
Body mass index, kg/m^2	33.4 (26.8–44.4)	31.1 (24.7–33.9)
RR	20 (17–24)	20 (16–23)
Mean blood pressure	86 (78.8–92.5)	82 (77–92)
Heart rate	94 (85–101)	87 (80–102)
ICU diagnosis, *n* (%)		
Pneumonia	28 (39)	39 (62)
Sepsis	38 (53)	46 (73)
Shock	39 (54)	42 (67)
Aspiration	17 (24)	14 (22)
Gastrointestinal bleeding	10 (14)	3 (05)
Altered mental status	34 (47)	28 (44)
Liver failure	19 (26)	16 (25)
Cardiac arrest	8 (11)	10 (16)
Acute kidney injury	42 (58)	38 (60)
Comorbid conditions, *n* (%)		
Chronic obstructive pulmonary disease	24 (33)	20 (32)
ILD	2 (03)	1 (02)
CKD	15 (21)	14 (22)
CAD	16 (22)	19 (30)
Hematologic malignancy	7 (10)	12 (19)
Solid malignancy	24 (33)	29 (46)
Mechanical ventilation-related variables		
Vt/PBW, mL/kg	6.08 (5.9–6.7)	6.04 (5.9–6.3)
Positive end expiratory pressure, cm H_2O	6 (6–8)	6 (6–8)
Plateau pressure, cm H_2O	19 (16–23)	18 (17–22)
Mean airway pressure, cm H_2O	10 (9.5–14)	11 (10.5–15)

CAD = coronary artery disease, CKD = chronic kidney disease, ILD = interstitial lung disease, PBW = predicted body weight, RR = respiratory rate. Variables are presented as median and interquartile range or count and percentage if not stated otherwise.

mechanically ventilated patients in the ICU setting. Feasibility of enrollment and initiation of the titration protocol in critically ill patients within an hour of MV are novel and are shown successfully by our pilot study. This pilot study indicates the possibility of early reduction of hyperoxemia directly affecting meaningful patient outcomes and resource utilization, which we plan to confirm with our definitive clinical trial. Furthermore, there were no serious adverse events reported. The results of this study have provided substantial information of our following clinical trial (*N* = 315) and will inform future studies designed to optimize respiratory interventions in the ICU setting to improve patient outcomes.

Prioritization of F_{IO_2} Titration in a Time-Sensitive Manner-Reduced Hyperoxemia Duration and Exposure to Excessive F_{IO_2}

We believe that the net reduction of hyperoxemia in the intervention group was due to early prioritization of titration. Presence of hyperoxemia (and its severity) early after initiation of MV has been shown to be directly associated with ICU mortality (34). Association of hyperoxemia to worse clinical outcomes has been

TABLE 2.
Primary and Secondary Outcomes

Primary Outcomes			
Outcome Variables	**Intervention ($n = 68$[a])**	**Control ($n = 58$[a])**	***p***
Duration of hyperoxemia (hr)	13.7 (2.9–31.1)	21.2 (10.9–64.4)	0.004
Duration of highly excessive oxygen ($Fio_2 > 0.7$) exposure (hr)	3.1 (1.9–6.5)	10.3 (3.1–6.52)	0.002
Spo_2, %	95 (94–97)	97 (96–98)	< 0.001
Fio_2, %	40 (35–40)	50 (40–56.9)	< 0.001
Outcomes Based on E-Alert Clustering			
Outcome Variables	**All E-Alerts in the First Quartile of MV ($n = 34$)**	**Patients With Spread Out E-Alerts + Control ($n = 101$)**	***p***
MV duration, d	2 (1–4)	3 (2–5)	0.02
ICU LOS, d	9.5 (5–25.7)	15 (9–23)	0.002
Ventilator-free days	22.5 (0–26)	18 (0–24)	0.5

MV = mechanical ventilation.

Variables are presented as median and interquartile range or count and percentage if not stated otherwise.

[a]Fio_2 values were missing due to technical issues in EMR data extraction in four subjects in the intervention arm and five subjects in the control arm.

noted consistently in observational analysis but not consistently in some randomized clinical trials. Even though recent randomized clinical trials Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen Therapy and handling oxygenation targets in the intensive care unit comparing liberal versus conservative oxygenation targets did not detect a significant mortality difference, they also did not report harm in their respective conservative oxygen arms (17, 33) Direct Fio_2 toxicity is both dose- and duration-dependent. Bronchoscopic evaluation after exposure to high Fio_2 bursts or prolonged moderate Fio_2 showed evidence of tracheal erythema, suppressed mucociliary clearance, increased profibrotic mediators, as well as products of lipid peroxidation (35). Tracheobronchitis and ventilation perfusion mismatch

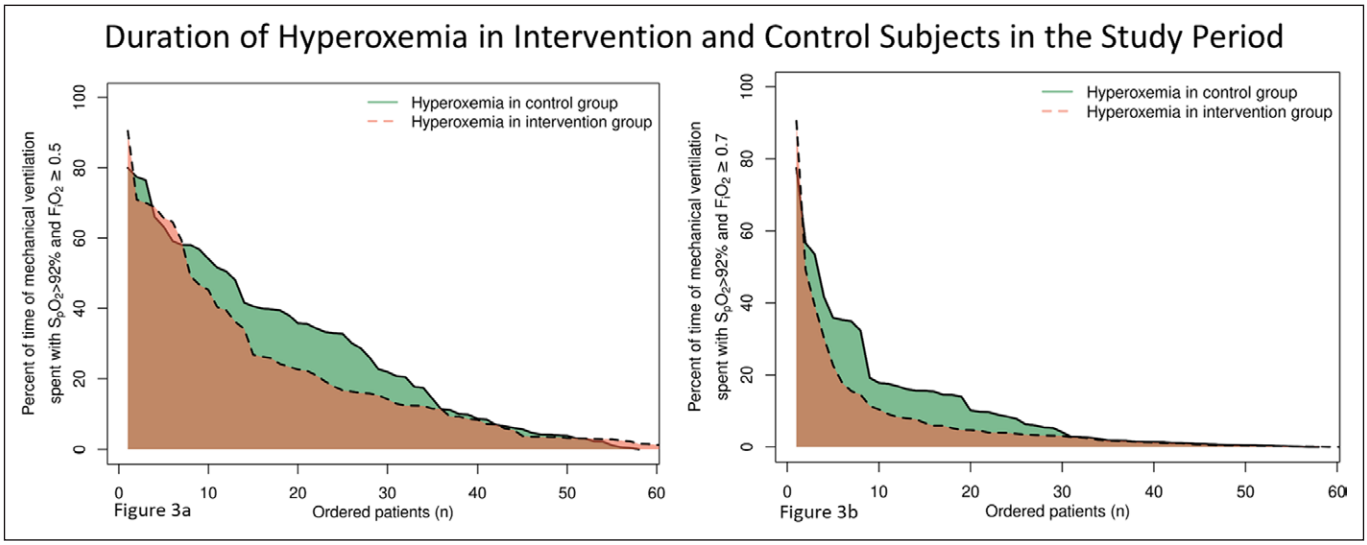


Figure 3. Hyperoxemia duration in intervention and control arms. Relative time spent on mechanical ventilation with $Spo_2 > 92\%$ and (**A**) $Fio_2 \geq 0.5$ or (**B**) $Fio_2 \geq 0.7$. The $n = 58$ control and $n = 68$ intervention patients are ordered from the highest to the least percentage of time in hyperoxemia. Based on two-sample Wilcoxon tests, we find the expected percentage of time spent in hyperoxemia was lower for the intervention group in both (A; $p = 0.02$) and (B; $p = 0.01$).

related to atelectasis from nitrogen washout are noted clinically (36–38). Hyperoxia augments ventilator-induced lung injury in the presence of high tidal volume ventilation and ventilator-associated pneumonias by altering lung microbiome in multiple animal models (5, 6, 8, 39). Through the production of reactive oxygen and nitrogen species, hyperoxia amplifies oxidative stress in critically ill patients in the presence sepsis, acute lung injury, aspiration, drug overdose, and other comorbid conditions (40–42). Furthermore, indirect hyperoxemia may counteract any increase in oxygen delivery by inducing vasoconstriction, thereby diminishing blood flow in critical vascular (heart and brain) possibly due to reduced vasodilator signaling (43, 44). Our study led to decrease in more extreme elevations of Fio_2 percentages exceeding 0.7, which may have biological implications by reducing pulmonary oxygen toxicity. In the absence of prioritization in the form of alerts or alarms, this study further demonstrates that hyperoxemia is a common occurrence in mechanically ventilated ICU patients, as reported in other studies and is proposed to contribute to worse hospital outcomes toxicity (22, 45–47). The causal relationship of high Fio_2 exposure with mortality remains controversial because effective Fio_2 titration is difficult to achieve. The current study provides a roadmap for standardizing Fio_2 titration to more reliably determine the benefits of lower oxygen exposure.

Early Fio_2 Titration May Reduce Mechanical Ventilation Duration and ICU Length of Stay

We noted here that early intervention to mitigate hyperoxemia exposure may be beneficial both in terms of duration of MV and ICU stay. It is interesting to consider if early avoidance of hyperoxia fundamentally reduces lung damage to speed recovery. Alternatively, or perhaps additionally, early liberation may relate to earlier achievement of extubation criteria. This pilot study was not formally designed or powered to study these mechanisms. Improving compliance to guidelines, for example, low tidal volumes, through EMR is demonstrated to be effective (48, 49). "Reminders," both paper and electronic, are reported to enhance compliance by 73–78% by modifying healthcare provider behavior (50). Our approach of using reminders and decision support is supported by the normalization process theory for implementation of interventions guidelines (51–54). These e-alerts for Fio_2 titration directly to the CISCO phones of respiratory therapist are real time and do not rely on access to EMR, thereby providing "reminders" without increasing provider workload. Our ventilator protocol specifies spontaneous breathing trials at Fio_2 at 0.4, and as noted previously, e-alerts led to lower average Fio_2 values and, therefore, may have expedited readiness of MV liberation. The implications of earlier ventilation liberation are well established, including lower risk of ventilator-associated complications, such as pneumonia, mechanical injury, and reduced resource utilization.

Decisions to Use Spo_2 Range of 88–92 and Future Implications

Our target was directed to a pulse oximetry Spo_2 range of 88–92% only if Fio_2 is greater than or equal to 0.5 per our ICU protocol, which is a conservative oxygenation goal than reported in guidelines (55–57). This target was chosen to assure compliance with the institutional guidelines, based on expert opinion and in conjunction with ICU and respiratory therapy leadership. The safeguards integrated within the protocol to prevent rapid hypoxemia included protocol deference with clinical concerns, minimum of 30 minutes above target, utilizing PEEP as directed in the ICU MV protocol, and smaller Fio_2 changes for modest supplied Fio_2 (change of 0.1 instead of 0.2). The Spo_2 goal of 88–92% used for this study was reported to be achievable without adverse events in a multicenter pilot study at the time this study was conducted (58). In the absence of massive derangements, physiologically, the oxygen-sensing carotid body receptors would not be triggered to release vasoactive mediators in this range (59). Spo_2 value of 92% has shown an overall 80% positive predictive value for a Pao_2 greater than 60 mm Hg (60) and is further validated by positive correlations between Spo_2/Fio_2 and Pao_2/Fio_2 ratios in hypoxemic respiratory failure (61). Subsequently, the French Liberal or Conservative Oxygen Therapy trial also targeted an Spo_2 range of 88–92% in patients with acute respiratory distress syndrome (ARDS) but was terminated before completion due to increased mortality (and increased mesenteric ischemia) in the conservative group at 90 days (18). This trial was different in that it was restricted to patients with ARDS who were likely predisposed to and more vulnerable to severe hypoxemia than our population. In addition, recent

reports have highlighted skin tone variation with currently calibrated pulse oximeters resulting in occult hypoxemia in people of color amplifying racial and ethnic disparities (62, 63). Further data are required to confirm these findings. There are currently no rigorous clinical or research practices that we know of, designed to mitigate undetected hypoxemia based on Spo_2 inaccuracy. However, still taking this recent literature into account and our corroborative experience in this pilot trial, we believe that Spo_2 titration should be extended to a liberal range. This extended range maintains an arterial oxygen tension (Pao_2 within a physiologic range) while favoring oxygenation goals as supported by recent literature and clinical practice guidelines (10, 19, 64).

Limitations

There are some limitations to our pilot, which have been addressed by making modifications to the definitive trial. First, the study could not be practically blinded, and, as mentioned above, compliance with Fio_2 titration was limited because the algorithm did not pause alerts during procedures or when patients were transitioned to comfort care status. Likewise, it was impractical for the protocol to be followed when patients traveled outside the ICU for surgeries, procedures, or scans. We presume that noncompliance seen at upper values of both target ranges, Fio_2 (0.5 or 0.6) and Spo_2 (93–94%), may have been due to cognitive biases anchored to the perception that mild hyperoxemia is a low-risk condition (e.g., relative to hypoxemia). There is a growing trend toward reducing Fio_2 to the lowest clinically indicated Fio_2, but stronger data are needed to convince ICU practitioners. We intend to circumvent unintended bias at the ICU provider level by focusing on further stakeholder (ICU respiratory therapists and other bedside provider) engagement and education, emphasizing compliance with the Fio_2 titration algorithm. Future modifications of the algorithm to eliminate alerts that cannot be acted upon (e.g., during transport) will potentially further improve algorithm compliance by reducing "alarm Fatigue."

Based on our experience, the following modifications were made to the definitive clinical trial (Clinicaltrials.gov NCT04481581).

1) Alteration of target Spo_2 range and Fio_2 goal: The upper limit of Spo_2 titration range was increased from 88–92% to 88–94%. The goal of 94% was chosen as it still represents an extended conservative range and will possibly accommodate titration needs in patients with ARDS, interstitial lung disease, and occult hypoxemia with skin tone variation. Data for self-reported race and ethnicity along with arterial saturation (Sao_2), arterial oxygen tension (Pao_2), and Spo_2 will be collected. We decided maintain a conservative approach to Fio_2 and tighten the lower limit from Fio_2 greater than or equal to 0.5 to Fio_2 greater than or equal to 0.4. Alerts will be initiated even earlier, now within 45 minutes of endotracheal intubation (**Appendix Fig. 3**, http://links.lww.com/CCX/A999).
2) Decreasing e-alert frequency and increasing fidelity: Alert frequency will be changed from every 30–45 minutes to prevent alert fatigue. More importantly, data generated every minute will be used, and alerts will be sent based on the cumulative values within 45 minutes. For example, alert only if 80% values within 45 minutes are above target range.
3) Reduction in alert fatigue: No more than four alerts will be generated within 6 hours per patient. Alerts will be terminated when care is changed to a comfort care status and during patient transport.
4) Prevention of Fio_2 surges: Directions in the protocol for nursing staff to avoid preemptive Fio_2 surges during events such as turns, suctioning, central venous catheter placement, and other procedures, except for bedside bronchoscopy.
5) Stakeholder engagement and education to improve compliance to protocol: Respiratory therapist oversight committee was involved as a stake holder in the development of these new targets. A biweekly refresher newsletter was sent throughout the duration of the trial.

What Our Definitive Clinical Trial of Automated Oxygen Titration May Contribute to literature

Clinical equipoise persists regarding optimal oxygenation levels in critically ill patients, and studying oxygenation targets remains a research priority for the critical care community (65). We believe our definitive trial will not only be valuable in adding critical information about optimal oxygenation goals but also progressively refine feedback to improve algorithms for automated oxygen titration during a period where maximal effect can be produced. After optimal testing, such algorithms could be used in closed-loop autotitrating ventilators to improve the precision of closely monitored variables and reduce the workload in clinical practice without increasing risks to patient safety. Needed urgently targeted precise oxygenation are biomarkers reflecting hyperoxic injury. We hope to coenroll patients in this trial to study lipidomic biomarkers indicative of oxidative stress. Finally, our study cohort will contribute to data on racial bias and variation in pulse oximetry.

CONCLUSIONS

In summary, our time-sensitive titration strategy resulted a significant reduction of hyperoxemia duration. Those with maximum titration early on during MV demonstrated earlier ventilator liberation and shorter ICU stay. To clarify if rapid implementation of an automated oxygen titration strategy in the ICU leads to improved patient outcomes, such as less severe ventilator-associated lung damage or more rapid weaning from MV, a definitive randomized control trial (Clinicaltrials.gov NCT04481581) is underway.

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