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Conservative versus liberal oxygenation targets for mechanically ventilated patients – a pilot multicenter randomized controlled trial

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At a Glance Commentary

Scientific Knowledge on the Subject: Recommendations and practices related to oxygenation targets for mechanically ventilated patients are based on weak evidence. Conventional practice follows a liberal approach to oxygen therapy, often resulting in hyperoxia that may adversely affect outcomes. However, evidence from randomized trials is lacking.

What This Study Adds to the Field: A conservative oxygenation strategy is a feasible alternative to the usual liberal oxygenation strategy employed in mechanically ventilated patients. No harmful effects were observed with the use of a conservative approach to oxygen therapy. It can significantly reduce exposure to hyperoxia compared to standard care. Larger randomized trials of this intervention appear justified.

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This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

Abstract

Rationale: There are no randomized controlled trials (RCTs) comparing different oxygenation targets for Intensive Care Unit (ICU) patients.

Objectives: To determine whether a conservative oxygenation strategy is a feasible alternative to a liberal oxygenation strategy among ICU patients requiring invasive mechanical ventilation (IMV).

Methods: At four multidisciplinary ICUs, 103 adult patients deemed likely to require IMV for ≥24 hours were randomly allocated to either a conservative oxygenation strategy with target SpO_2 of 88-92% (n=52) or a liberal oxygenation strategy with target SpO_2 of ≥96% (n=51).

Measurements and Main Results: The mean area-under-curve and 95% confidence interval (CI) for SpO_2 [93.4% (92.9-93.9%) versus 97% (96.5-97.5%)], SaO_2 [93.5% (93.1-94%) versus 96.8% (96.3-97.3%)], PaO_2 [70 (68-73) mmHg versus 92 (89-96) mmHg] and FiO_2 [0.26 (0.25-0.28) versus 0.36 (0.34-0.39)] in the conservative versus liberal oxygenation arm were significantly different ($p<0.0001$ for all). There were no significant between-group differences in any measures of new organ dysfunction, or ICU or 90-day mortality. The percentage time spent with SpO_2 <88% in conservative versus liberal arm was 1% versus 0.3% ($p=0.03$), and percentage time spent with SpO_2 >98% in conservative versus liberal arm was 4% versus 22% ($p<0.001$). The adjusted hazard ratio for 90-day mortality in the conservative arm was 0.77 (95%CI: 0.40-1.50; $p=0.44$) overall and 0.49 (95%CI: 0.20-1.17; $p=0.10$) in the pre-specified subgroup of patients with a baseline PaO_2/FiO_2 <300.

Conclusions: Our study supports the feasibility of a conservative oxygenation strategy in patients receiving IMV. Larger RCTs of this intervention appear justified.

Trial registration: Australian New Zealand Clinical Trials Registry ACTRN12613000505707

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Introduction

Each year 2 to 3 million ICU patients receive invasive mechanical ventilation (MV) (1, 2) at an estimated annual cost of $15-27 billion in high-income nations alone (1, 3) and with a high associated mortality (1, 4) and morbidity (5). Nearly all ICU patients who receive MV also receive supplemental oxygen therapy. Despite the universal use of oxygen therapy, no randomized controlled trials (RCTs) have investigated the effects of different oxygenation targets during MV (6).

In the absence of RCTs, the recommended oxygenation targets for mechanically ventilated ICU patients are largely based on normal physiological values. For example, in healthy adults at sea level, the usual ranges for CO-oximeter measured arterial oxygen saturation (SaO_2) and arterial oxygen tension (PaO_2) are approximately 95-97% and 88-100 mmHg respectively (7). Moreover, in healthy humans during sleep, the nadir for pulse oximeter measured oxygen saturation (SpO_2) is approximately 90% (8). Accordingly, for acutely ill patients, recommendations vary from near-normal SpO_2 targets of 94-98% (9) to values ≥90% (10). In addition, SpO_2 targets of 88-95% are often accepted in patients with acute respiratory distress syndrome (ARDS) (11-13).

Despite the above recommendations, conventional practice of oxygen therapy is often more liberal and results in hyperoxia (14-20) or in the delivering of supplemental oxygen during non-hypoxemic conditions, without any evidence of benefit (21). For example, the lower limits of the 95% confidence intervals (CI) for daily time-weighted mean SpO_2 were greater than 96%, with the mean concentrations of inspired oxygen (FiO_2) ranging from 0.35 to 0.44, on each of the first seven MV days observed during standard practice at two Australian ICUs (14, 15). This liberal approach may relate to the perception that, outside of very high levels of FiO_2, oxygen therapy is safe. This

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perception of safety, however, is now being challenged by the increasing recognition of the potential harm of excessive FiO_2 (16), hyperoxemia and tissue hyperoxia (6, 21-25). While a liberal use of oxygen may provide a margin of safety against hypoxia (26), a more conservative approach might reduce potentially harmful exposure to excessive FiO_2, hyperoxemia and tissue hyperoxia. However, the relative merits and risks of these two approaches to oxygen therapy in terms of patient centered end-points remain undefined, suggesting the need for RCTs. On the other hand, RCTs focusing on patient-centered outcomes can only be ethically justified if pilot RCTs demonstrate a separation in treatment and protocol compliance (feasibility) and a degree of safety associated with a conservative oxygen therapy approach.

Accordingly, we performed a pilot multicenter, multinational RCT to test the hypothesis that conservative oxygen therapy is feasible, and to obtain preliminary data on the safety of such an approach, with the aim of using such pilot data to inform the design of potential subsequent larger clinical trials.

Methods

This prospective randomized parallel-group trial was conducted at four university-affiliated, multidisciplinary ICUs in Australia, New Zealand and France. The study was prospectively registered (ACTRN12613000505707). The Human Research Ethics Committee at each site approved the study (approval number 12/07/18/4.03, 12/STH/2/AM01 and 121491A-31). Informed consent was obtained from the patient where possible, or from a legal surrogate. This study was monitored by an independent data and safety monitoring board. Additional details of the methods are provided in an online data supplement.

ICU patients, aged ≥18 years, were eligible if they had been receiving invasive MV for <24 hours and their treating clinician expected MV to continue for at least next 24 hours. Exclusion criteria included known pregnancy, imminent risk of death, or if the treating clinician lacked equipoise for the patient to be enrolled in this trial.

Randomization was done in a masked fashion, using opaque sealed envelopes, with a unique computer-generated, permuted block randomization method with random block sizes. Following treatment allocation, the bedside nurse titrated the FiO_2 within a range of 0.21 to 0.80 to achieve the assigned targets of 88-92% SpO_2 for the conservative oxygenation group or ≥96% SpO_2 for the liberal oxygenation group. The study intervention was continued for the entire duration of MV. PEEP levels were determined by the treating clinicians in accordance with usual clinical care. The treating ICU physician could alter oxygenation targets at any time if deemed necessary according to the patient's clinical status. Data on oxygenation parameters and ventilator settings were recorded 4-hourly from day 0 to day 7.

Primary endpoints were the mean area-under-curve (AUC) for SpO_2, SaO_2, PaO_2 and FiO_2 on days 0-7. Secondary endpoints were change from baseline (Δ) SOFA score, Δ PaO_2/FiO_2, new-onset ARDS (27), Δ creatinine, incidence of hemodynamic instability (i.e., cardiac arrest or addition of ≥2 new vasopressor/inotrope agents), vasopressor-free days, arrhythmia-free days, and ventilator-free days until day 28, ICU mortality and 90-day mortality.

Statistics

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Analysis plan and outline of data presentation were pre-specified and reported on the trial registration page (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=364185). Analysis was conducted on an intention-to-treat basis. Based on our previous observational studies (14, 15), we estimated that a sample size of 100 would provide >350 MV days of exposure to both oxygenation strategies. We deemed this sufficient to assess feasibility in this pilot phase. Categorical variables were compared using chi-square tests or Fisher's exact tests, and reported as n (%). Continuous normally distributed variables were compared using Student's t-test and reported as means (standard deviation [SD]), whilst non-normally distributed data were compared using Wilcoxon rank sum test and reported as medians (interquartile range [IQR]). The area-under-curve (AUC), a summary index of longitudinal data, was assessed as an integrated expression of mean oxygenation levels achieved over the active treatment period, and was determined using mixed linear modeling fitting main effects for group and time. Pre-planned subgroup analysis was performed on patients with baseline PaO_2/FiO_2 <300. Survival analysis was presented as Kaplan-Meier curves. Multivariate time-to-event analysis using Cox regression models, adjusted for baseline variables (SOFA score, APACHE III score, COPD and ARDS), was performed with results reported as hazard ratios (95% CI). A two-sided P-value of <0.05 was considered statistically significant.

Results

Patients

We screened 357 patients and enrolled 104 patients between June 2013 and October 2014. Of these, 53 patients were assigned to the conservative oxygenation group and 51 patients to the liberal oxygenation group (Fig. 1 and online supplement). One patient in

the conservative arm withdrew consent, and was excluded. The remaining 103 patients were followed up to day 90. Demographic and clinical characteristics at baseline were similar in the two groups (Table 1). Most patients had a medical diagnosis and the mean duration of MV prior to randomization was 13 (±7) hours.

Process of care

During the study period, ventilator parameters (tidal volume, minute ventilation, PEEP, and peak airway pressure) and the net fluid balance did not differ between the two groups (Table E1). The percentage time-points spent on any mandatory mode of ventilation during the first week of MV in the conservative and liberal arm were 34% and 46% respectively. The odds ratio, adjusted for repeated measures, for the use of mandatory mode of MV within the first week in the conservative arm, as compared to liberal arm, was 0.36 (95% CI: 0.12-1.04; p=0.06). Arterial blood gases were performed more often in the conservative versus liberal arm during the first week of MV (Table E1). There were no significant between-group differences with regards to mean hemoglobin level or the number of units of red cells transfusion during the first week of MV (Table E1).

Feasibility outcomes

Participants spent the majority of time within the intended target range in both groups (Fig. 2A). The mean AUC and 95% CI for SpO_2, SaO_2, PaO_2 and FiO_2 were significantly lower in the conservative group compared to liberal group (Table 2). Overall, participants spent a median of 6% [IQR 0-25%] time off target, but more time was spent off target in the conservative arm than in the liberal arm (14% vs. 3%, p <0.001). Daily mean SpO_2, PaO_2 and FiO_2 for the groups were well separated on all

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seven days of MV (Fig. 2B-D). Participants in the conservative group spent more time at a FiO_2 of 0.21 than those in the liberal group (Fig. 3).

Safety outcomes

There were no significant differences between the groups in regards to any of the measures of organ dysfunction (Δ SOFA score, Δ PaO_2/FiO_2, new-onset ARDS, Δ creatinine, hemodynamic instability, vasopressor-free days, arrhythmia-free days, or ventilator-free days), or ICU or 90-day mortality (Table 2). Vasopressor dose requirement was lower in the liberal arm, but the vasopressor duration and hospital length of stay were similar in both groups (Table 2). The data on percentage time-points per patient spent at different SpO_2 or PaO_2 thresholds are comprehensively presented in Table 3 and the online supplement (Fig. E1-8). The median number of time-points that were spent at different SpO_2, SaO_2, PaO_2 or FiO_2 thresholds, and the lowest and the highest values for oxygenation parameters in each group during the study period are also described in the online supplement (Table E2). 1% of SpO_2 time-points in the conservative arm versus 0.3% of SpO_2 time-points in the liberal arm were spent at SpO_2 <88% (p=0.03). Using the hyperoxia threshold of SpO_2 >98% (9, 28) while FiO_2 >0.21, 4% of SpO_2 values in conservative arm versus 22% of SpO_2 readings in liberal arm were in hyperoxic range (p<0.001). Survival analysis curves for the treatment groups were similar (Fig. 4A). The adjusted hazard ratio for death by day 90 in the conservative arm, as compared to liberal arm, was 0.77 (95%CI: 0.40-1.50; p=0.44).

Pre-specified subgroup analyses

The subgroup analysis for patients with a baseline PaO_2/FiO_2 <300 is presented in Table E3. The separation in mean FiO_2 exposure between the two arms was wider in this subgroup. However, outcomes including survival (Fig. 4B) were similar. In this

subgroup, the adjusted hazard ratio for death by day 90 in the conservative arm was 0.49 (95% CI: 0.20-1.17; p=0.10).

One patient in the conservative arm was treated according to liberal oxygenation protocol in error. However, results were unchanged in per-protocol analysis (Table E4). To probe further for any signal of major harm associated with oxygenation parameters, survivors and non-survivors were compared in a post hoc analysis (Table 3, E2 and E5), but no significant differences were evident.

Discussion

Key findings

In this pilot multicenter randomized clinical trial, we assessed the feasibility of a conservative oxygenation strategy (target SpO_2 88-92%) compared with a liberal oxygenation strategy (target SpO_2 ≥96%) during invasive MV for adult ICU patients. The study protocol was implemented well. We identified clear separation in the mean SpO_2, SaO_2, PaO_2, and FiO_2 values between the two groups, confirming treatment feasibility. The conservative oxygenation arm had a significantly lower incidence of hyperoxemia but a higher incidence of hypoxemia. There were no significant between-group differences in the secondary endpoints of new organ dysfunction or mortality, and the use of a conservative SpO_2 target was not associated with harm. In the pre-specified subgroup of patients with impaired gas exchange, the between-group separation in mean FiO_2 exposure was wider, but outcomes were similar.

Relationship to previous studies

AJRCCM Articles in Press. Published on 03-September-2015 as 10.1164/rccm.201505-1019OC

In recent years, several observational studies from varied critical care settings have reported liberal use of supplemental oxygen in standard practice (14-18). In this regard, the oxygenation levels achieved in the liberal arm of our study were similar to those previously reported in conventional practice by other observational studies (14, 15, 18). However, the percentage time spent with hyperoxia in the liberal arm was lower than previously reported (15, 17). Only a single-center prospective before-and-after feasibility study has compared a conservative oxygenation target to conventional practice (28). Our results are consistent with this study in demonstrating protocol compliance, feasibility and lack of any major adverse events with a conservative oxygenation strategy. In the aggregate, our study and the previous before-and-after study have now exposed 106 patients to a total of more than 800 MV days of conservative oxygenation strategy. In the before-and-after study, a conservative oxygenation strategy was associated with lower incidence of new organ dysfunction (28). In contrast, we did not find any significant between-group differences in any of the measures of new organ dysfunction. In our study, vasopressor dose requirement was lower in the liberal oxygenation arm although there was no between-group difference in duration of vasopressor therapy or vasopressor-free days. One explanation of this finding might be related to the vasoconstrictor effect of higher oxygenation levels as previously reported for different vascular beds (29-33).

In conservative oxygenation group, we noticed a trend to lower use of mandatory MV mode, which might indicate earlier attempts to wean patients in response to lower FiO_2 requirement. However, it did not result in any difference in the duration of MV or ventilator-free days. In our study, the percentage time spent with hypoxemia was higher in the conservative arm, and the percentage time spent with hyperoxia was higher in the liberal arm. These findings are not unexpected, as the likelihood of finding SpO_2 values

<88% will be high with a target SpO_2 range of 88-92% when compared to a target SpO_2 range of ≥96%. Likewise, the lack of an upper limit alarm for SpO_2, as is often the case in conventional practice, could have led to more exposure to hyperoxia in the liberal arm. Future studies might consider a closed loop feedback system (34, 35) to titrate FiO_2 more closely to the intended SpO_2 target range. Although there is no defined threshold for permissive hypoxemia (36), the SpO_2 range of 88-92% in the conservative oxygenation arm of our study might be considered an approximate approach of permissive hypoxemia. Indirect evidence suggests that permissive hypoxemia might improve outcomes in some patient groups by reducing the potential dose-dependent adverse effects of the traditional liberal oxygen therapy (22, 23). In our study, the point estimate for 90-day mortality was lower with conservative oxygenation strategy. This is consistent with recent meta-analyses that reported an association between hyperoxia and mortality in some patient subgroups (6, 25).

Implication of the study findings

Our study findings support the feasibility of delivering conservative oxygen therapy in patients on invasive MV. Assigned SpO_2 targets in this study were achieved by titrating FiO_2. The lack of a significant difference in PEEP levels observed between the treatment groups provides reassurance that this approach is feasible and does not result in a major imbalance of a co-intervention. Exposure to hyperoxia was significantly reduced with the conservative approach to oxygen therapy. However, exposure to hypoxemia was also marginally higher. These data, and the data from a previous before-and-after study (28), justify continued and prudent investigation of conservative oxygen therapy. Given the unexpected harm evident from a strategy of lower oxygen targets (SpO_2 85-89%) in recent RCTs among preterm infants (37-39), safety considerations are paramount. Our preliminary data provide low-level evidence in support of the safety

AJRCCM Articles in Press. Published on 03-September-2015 as 10.1164/rccm.201505-1019OC

of a conservative oxygen approach (SpO_2 88-92%) in adult ICU patients requiring mechanical ventilation. However, due to our small sample size, these data should be regarded as exploratory.

Existing data support the hypothesis that conservative oxygen therapy could potentially reduce the risk of pulmonary oxygen toxicity compared to a liberal approach (40-42). Our pilot data may also inform the design of the potential subsequent larger clinical trials (43). In our study the observed standard deviation (SD) of ventilator-free days (VFDs) (44) is ≈0.7 of the mean in both the conservative and liberal oxygen groups. Thus, using the VFDs observed in the liberal (standard care) arm as baseline [i.e., 16.4 days (SD 11.3)] and assuming the SD is the same proportion of mean in the experimental group, a sample size of 800 participants will provide 90% power to detect a minimum clinically important difference of 2.6 VFDs (45), using a two tailed hypothesis at an alpha of 0.05.

Strengths and limitations

The major strength of this study is its multicenter multinational randomized controlled design. Although two other studies evaluating different oxygenation strategies in the ICU have been completed recently [NCT01319643 (OXYGEN-ICU), NCT01722422 (HYPER-2S)], our study is the first multicenter trial to be reported. Our study endpoints were objective, and *a priori* specified criteria were used to assess secondary outcomes. Protocol adherence was good, separation clear and detailed longitudinal data available. Despite SpO_2 targets of 88-92%, the percentage time spent with SpO_2 <88% in the conservative arm was low. Additionally, despite SpO_2 targets of ≥96% in the liberal arm, the percentage time spent with SpO_2 >98% was less than in previous observational studies. Our study design was pragmatic and allowed clinicians the freedom to choose a

particular oxygenation target if deemed clinically indicated. We studied a broad group of ICU patients to which supplemental oxygen is administered in routine practice. Our study, however, has some limitations. First, the intervention was not blinded. We tried to minimize ascertainment bias by collating data on oxygenation levels measured with two independent methods (pulse oximetry measured SpO_2 and CO-oximeter measured SaO_2 and PaO_2). Furthermore, data analysis and data presentation were performed according to a pre-specified analysis plan. Second, our study was not adequately powered to test superiority of different oxygenation strategies or to demonstrate safety of the conservative oxygenation strategy. Therefore, the lack of any significant between-group difference in the safety endpoints may represent a type II error. We regard the observed point estimates of effect for all secondary outcomes as hypothesis-generating and our findings do not provide definitive data in relation to safety or the efficacy of either treatment strategy. Further, the differences in secondary outcomes observed in this feasibility study may be attributable to imbalances in baseline variables that were either measured or unmeasured. Third, we did not assess some of the other potentially important endpoints such as neurocognitive outcomes (46, 47) and incidence of delirium. Fourth, as treating clinicians were free to alter oxygenation targets, it could have led to some instances where the decision to alter oxygenation targets might have been influenced more by inherent bias rather than scientific evidence. However, the percentage of time-points spent off target in the study was modest. Fifth, 69 out of 357 screened patients were excluded because of lack of equipoise. Although we did not collect specific reasons for lack of equipoise, this may reflect clinical conditions where the most appropriate approach to oxygen management is well established such as exacerbation of COPD. Sixth, we did not measure any biomarker in this study and this could be a subject of further investigations. Seventh, we did not measure plateau pressure and therefore cannot comment on driving pressure, which has recently been

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suggested as a predictor of outcome in patients with ARDS (48). Lastly, the mean SpO_2 levels that were achieved in the conservative arm were higher than the intended target range. This was primarily due to the limit of FiO_2 titration, since it was not possible to titrate FiO_2 below 0.21.

Conclusions

In conclusion, our study demonstrates that a conservative oxygenation strategy is a feasible alternative to the usual liberal oxygenation strategy, while being effective in reducing exposure to hyperoxia. These data justify continued and prudent investigation of conservative oxygen therapy.

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References

1. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM. The epidemiology of mechanical ventilation use in the United States. *Crit Care Med* 2010; 38: 1947-1953.

2. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. *Lancet* 2010; 376: 1339-1346.

3. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. *Crit Care Med* 2005; 33: 1266-1271.

4. Metnitz PG, Metnitz B, Moreno RP, Bauer P, Del Sorbo L, Hoermann C, de Carvalho SA, Ranieri VM, Investigators S. Epidemiology of mechanical ventilation: analysis of the SAPS 3 database. *Intensive Care Med* 2009; 35: 816-825.

5. Kahn JM, Benson NM, Appleby D, Carson SS, Iwashyna TJ. Long-term acute care hospital utilization after critical illness. *Jama* 2010; 303: 2253-2259.

6. Damiani E, Adrario E, Girardis M, Romano R, Pelaia P, Singer M, Donati A. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. *Crit Care* 2014; 18: 711.

7. Crapo RO, Jensen RL, Hegewald M, Tashkin DP. Arterial blood gas reference values for sea level and an altitude of 1,400 meters. *Am J Respir Crit Care Med* 1999; 160: 1525-1531.

8. Gries RE, Brooks LJ. Normal oxyhemoglobin saturation during sleep. How low does it go? *Chest* 1996; 110: 1489-1492.

9. O'Driscoll BR, Howard LS, Davison AG, British Thoracic S. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; 63 Suppl 6: vi1-68.

10. Slutsky AS. Consensus conference on mechanical ventilation--January 28-30, 1993 at Northbrook, Illinois, USA. Part I. European Society of Intensive Care Medicine, the ACCP and the SCCM. *Intensive Care Med* 1994; 20: 64-79.

11. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342: 1301-1308.

12. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE, Lung Open Ventilation Study I. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *Jama* 2008; 299: 637-645.

13. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L, Expiratory Pressure Study G. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *Jama* 2008; 299: 646-655.

14. Panwar R, Capellier G, Schmutz N, Davies A, Cooper DJ, Bailey M, Baguley D, Pilcher V, Bellomo R. Current oxygenation practice in ventilated patients-an observational cohort study. *Anaesthesia and intensive care* 2013; 41: 505-514.

15. Suzuki S, Eastwood GM, Peck L, Glassford NJ, Bellomo R. Current oxygen management in mechanically ventilated patients: a prospective observational cohort study. *J Crit Care* 2013; 28: 647-654.

16. Rachmale S, Li G, Wilson G, Malinchoc M, Gajic O. Practice of excessive F(IO(2)) and effect on pulmonary outcomes in mechanically ventilated patients with acute lung injury. *Respiratory care* 2012; 57: 1887-1893.

17. de Graaff AE, Dongelmans DA, Binnekade JM, de Jonge E. Clinicians' response to hyperoxia in ventilated patients in a Dutch ICU depends on the level of FiO2. *Intensive Care Med* 2011; 37: 46-51.

18. de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PH, Bosman RJ, de Waal RA, Wesselink R, de Keizer NF. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008; 12: R156.

19. Parke RL, Eastwood GM, McGuinness SP, George Institute for Global H, Australian, New Zealand Intensive Care Society Clinical Trials G. Oxygen therapy in non-intubated adult intensive care patients: a point prevalence study. *Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine* 2013; 15: 287-293.

20. Ihle JF, Bernard S, Bailey MJ, Pilcher DV, Smith K, Scheinkestel CD. Hyperoxia in the intensive care unit and outcome after out-of-hospital ventricular fibrillation cardiac arrest. *Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine* 2013; 15: 186-190.

21. Iscoe S, Beasley R, Fisher JA. Supplementary oxygen for nonhypoxemic patients: O2 much of a good thing? *Crit Care* 2011; 15: 305.

AJRCCM Articles in Press. Published on 03-September-2015 as 10.1164/rccm.201505-1019OC

22. Capellier G, Panwar R. Is it time for permissive hypoxaemia in the intensive care unit? *Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine* 2011; 13: 139-141.

23. Martin DS, Grocott MP. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. *Crit Care Med* 2013; 41: 423-432.

24. Budinger GR, Mutlu GM. Balancing the risks and benefits of oxygen therapy in critically III adults. *Chest* 2013; 143: 1151-1162.

25. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association Between Arterial Hyperoxia and Outcome in Subsets of Critical Illness: A Systematic Review, Metaanalysis, and Meta-Regression of Cohort Studies. *Crit Care Med* 2015.

26. Panwar R, Young P, Capellier G. Conservative oxygen therapy in mechanically ventilated patients. *Crit Care Med* 2014; 42: e630-631.

27. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *Jama* 2012; 307: 2526-2533.

28. Suzuki S, Eastwood GM, Glassford NJ, Peck L, Young H, Garcia-Alvarez M, Schneider AG, Bellomo R. Conservative oxygen therapy in mechanically ventilated patients: a pilot before-and-after trial. *Crit Care Med* 2014; 42: 1414-1422.

29. Gao Z, Spilk S, Momen A, Muller MD, Leuenberger UA, Sinoway LI. Vitamin C prevents hyperoxia-mediated coronary vasoconstriction and impairment of myocardial function in healthy subjects. *European journal of applied physiology* 2012; 112: 483-492.

30. Dallinger S, Dorner GT, Wenzel R, Graselli U, Findl O, Eichler HG, Wolzt M, Schmetterer L. Endothelin-1 contributes to hyperoxia-induced vasoconstriction in the human retina. *Investigative ophthalmology & visual science* 2000; 41: 864-869.

31. Kawamura J, Meyer JS, Terayama Y, Weathers S. Cerebral hyperemia during spontaneous cluster headaches with excessive cerebral vasoconstriction to hyperoxia. *Headache* 1991; 31: 222-227.

32. Moulder PV, Lancaster JR, Harrison RW, Michel SL, Snyder M, Thompson RG. Pulmonary arterial hyperoxia producing increased pulmonary vascular resistance. *The Journal of thoracic and cardiovascular surgery* 1960; 40: 588-601.

33. McNulty PH, Robertson BJ, Tulli MA, Hess J, Harach LA, Scott S, Sinoway LI. Effect of hyperoxia and vitamin C on coronary blood flow in patients with ischemic heart disease. *Journal of applied physiology* 2007; 102: 2040-2045.

34. Tehrani FT, Bazar AR. A feedback controller for supplemental oxygen treatment of newborn infants: a simulation study. *Medical engineering & physics* 1994; 16: 329-333.

35. Iobbi MG, Simonds AK, Dickinson RJ. Oximetry feedback flow control simulation for oxygen therapy. *Journal of clinical monitoring and computing* 2007; 21: 115-123.

36. Gilbert-Kawai ET, Mitchell K, Martin D, Carlisle J, Grocott MP. Permissive hypoxaemia versus normoxaemia for mechanically ventilated critically ill patients. *Cochrane Database Syst Rev* 2014; 5: CD009931.

37. Schmidt B, Whyte RK, Asztalos EV, Moddemann D, Poets C, Rabi Y, Solimano A, Roberts RS, Canadian Oxygen Trial G. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. *Jama* 2013; 309: 2111-2120.

38. Group BIUKC, Group BIAC, Group BINZC, Stenson BJ, Tarnow-Mordi WO, Darlow BA, Simes J, Juszczak E, Askie L, Battin M, Bowler U, Broadbent R, Cairns P, Davis PG, Deshpande S, Donoghoe M, Doyle L, Fleck BW, Ghadge A, Hague W, Halliday HL, Hewson M, King A, Kirby A, Marlow N, Meyer M, Morley C, Simmer K, Tin W, Wardle SP, Brocklehurst P. Oxygen saturation and outcomes in preterm infants. *N Engl J Med* 2013; 368: 2094-2104.

39. Network SSGotEKSNNR, Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, Yoder BA, Faix RG, Das A, Poole WK, Schibler K, Newman NS, Ambalavanan N, Frantz ID, 3rd, Piazza AJ, Sanchez PJ, Morris BH, Laroia N, Phelps DL, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O'Shea TM, Bell EF, Ehrenkranz RA, Watterberg KL, Higgins RD. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010; 362: 1959-1969.

40. Freeman BA, Crapo JD. Hyperoxia increases oxygen radical production in rat lungs and lung mitochondria. *The Journal of biological chemistry* 1981; 256: 10986-10992.

41. Phillips M, Cataneo RN, Greenberg J, Grodman R, Gunawardena R, Naidu A. Effect of oxygen on breath markers of oxidative stress. *The European respiratory journal* 2003; 21: 48-51.

42. Carpagnano GE, Kharitonov SA, Foschino-Barbaro MP, Resta O, Gramiccioni E, Barnes PJ. Supplementary oxygen in healthy subjects and those with COPD increases oxidative stress and airway inflammation. *Thorax* 2004; 59: 1016-1019.

43. Chow S SJ, Wang H, editor. Sample Size Calculations in Clinical Research. Chapman and Hall/CRC; 2007.

AJRCCM Articles in Press. Published on 03-September-2015 as 10.1164/rccm.201505-1019OC

44. Schoenfeld DA, Bernard GR, Network A. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med* 2002; 30: 1772-1777.

45. McAuley DF, Laffey JG, O'Kane CM, Perkins GD, Mullan B, Trinder TJ, Johnston P, Hopkins PA, Johnston AJ, McDowell C, McNally C, Investigators H-, Irish Critical Care Trials G. Simvastatin in the acute respiratory distress syndrome. *N Engl J Med* 2014; 371: 1695-1703.

46. Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, Localio AR, Demissie E, Hopkins RO, Angus DC. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med* 2012; 185: 1307-1315.

47. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF, Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2005; 171: 340-347.

48. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, Richard JC, Carvalho CR, Brower RG. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; 372: 747-755.

Fig. 1: **Patient flow diagram**

Fig. 2: Pooled frequency histogram of the percentage time spent at each SpO_2 level (A) and treatment separation (B, C, D) in both arms

Fig. 3: **SpO_2 time-points per patient spent at a FiO_2 of 0.21 in both arms**

Fig. 4: **Survival curve overall (A) and for the subgroup with baseline PaO_2/FiO_2 ratio <300 (B) in relation to day 90 mortality.**

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Table 1: **Baseline characteristics of the patients**

Characteristics	Conservative oxygenation arm (n=52)	Liberal oxygenation arm (n=51)	P value
Age, mean (SD), y	62.4 (14.9)	62.4 (17.4)	1.00
Male gender, n (%)	32 (62%)	33 (65%)	0.74
BMI, mean (SD), kg/m^2	27.6 (10.3)	27.6 (10.1)	0.98
Diagnosis type			
Trauma, n (%)	3 (6%)	2 (4%)	1.00
Medical, n (%)	39 (75%)	41 (80%)	0.51
Surgical, n (%)	10 (19%)	8 (16%)	0.64
APACHE III, median [IQR]	79.5 [61-92.5]	70 [50-84]	0.06
SOFA score, mean (SD)	7.9 (2.9)	7.4 (3.1)	0.44
Active smoker, n (%)	10 (19%)	14 (27%)	0.32
COPD, n (%)	11 (21%)	5 (10%)	0.11
Ischemic heart disease, n (%)	6 (12%)	5 (10%)	0.78
Pre-randomization MV period, mean (SD), h	13.6 (7.2)	13.2 (7.4)	0.78
SpO_2, mean (SD), %	95 (3)	96 (3)	0.17
SaO_2, mean (SD), %	95.5 (3)	96 (2.7)	0.37
PaO_2, median [IQR], mmHg	81 [68-109]	82 [75-104]	0.54
Hemoglobin, mean (SD), g/l	110 (23)	115 (23)	0.3
$PaCO_2$, mean (SD), mmHg	38 (7)	39 (6)	0.35
pH, mean (SD)	7.36 (0.07)	7.37 (0.07)	0.6
Lactate, median [IQR], mmol/l	1.99 [1.4-2.9]	1.65 [1.2-2.6]	0.24
FiO_2, mean (SD), %	0.44 (0.2)	0.44 (0.18)	0.93
PEEP, mean (SD), cmH_2O	8.2 (3)	7.3 (3)	0.14
V_T*, mean (SD), ml/kg PBW†	8 (1.8)	8 (1.9)	0.95
PaO_2/FiO_2, mean (SD)	248 (112)	247 (113)	0.96
ARDS, n (%)	17 (33%)	10 (20%)	0.13
Peak airway pressure, mean (SD), cmH_2O	22 (6)	21 (5)	0.71
Minute ventilation, mean (SD), liter	9.2 (2.3)	9.1 (2.6)	0.8

Abbreviations: SD: standard deviation; IQR: interquartile range; BMI: body mass index; APACHE III: Acute Physiology and Chronic Health Evaluation score III is the sum of three components at the time of randomization: an acute physiology score (0 to 252), chronic health evaluation score (0 to 23), and age score (0 to 24), with total score ranging from 0 to 299, where higher score indicate more severe disease; SOFA: Sequential Organ Failure Assessment score includes sub-scores ranging from 0-4 for each of five organ system (circulation, lungs, liver, kidneys and coagulation), with score ranging from 0-20, and higher scores indicating more severe organ failure; COPD: Chronic Obstructive Pulmonary Disease; PEEP: Positive End-expiratory Pressure; * V_T: Tidal Volume; † PBW: Predicted Body Weight; ARDS: acute respiratory distress syndrome as defined according to the Berlin definition

Table 2: **Primary and secondary outcomes**

Characteristics	Conservative oxygenation arm (n=52)	Liberal oxygenation arm (n=51)	P value
SpO_2 for day 0-7, mean AUC* (95% CI), %	93.4 (92.9 -93.9)	97 (96.5 -97.5)	<0.001
SaO_2 for day 0-7, mean AUC* (95% CI), %	93.5 (93.1 -94)	96.8 (96.3 -97.3)	<0.001
FiO_2 for day 0-7, mean AUC* (95% CI)	0.26 (0.25 -0.28)	0.36 (0.34 -0.39)	<0.001
PaO_2 for day 0-7, mean AUC* (95% CI), mmHg	70 (68 -73)	92 (89 -96)	<0.001
Percentage time spent 'off target'†, median [IQR], %	14 [4-36]	3 [0-10]	<0.001
Incidence of new-onset ARDS‡, n (%)	11 (32%)	11 (28%)	0.65
Δ§ PaO_2/FiO_2, mean (SD)	50 (97)	21 (102)	0.15
Δ§ Worst PaO_2/FiO_2, mean (SD)	−50 (115)	−66 (114)	0.46
Number of significant episodes of arterial desaturation per patient ‖, median [IQR]	1 [0 -5]	0 [0 -0]	<0.001
MV-free days** until day 28, mean (SD)	14.7 (10.3)	16.4 (11.3)	0.42
Pneumothorax-free days** until day 28, median [IQR]	28 [16 -28]	28 [20 -28]	0.96
Incidence of hemodynamic instability††, n (%)	9 (17%)	12 (24%)	0.43
Vasopressor-free** days until day 28, median [IQR]	25.3 [6.7 -27.3]	25.8 [14.6 -27]	0.71
Arrhythmia-free** days until day 28, median [IQR]	28 [16 -28]	28 [20 -28]	0.78
Vasopressor dose‡‡ during first week, median [IQR], µg/kg/min	0.08 [0.04 -0.16]	0.04 [0.02 -0.09]	0.009
Hours on vasopressors, median [IQR]	49 [11 -101]	35 [14 -73]	0.52
Δ§ Serum creatinine, mean AUC* (95% CI), µmol/l	−5 (−34 -25)	3 (−31 -37)	0.74
RRT-free** days until day 28, median [IQR]	28 [9 -28]	28 [11 -28]	0.81
Serum lactate, mean AUC* (95% CI), mmol/ l	1.9 (1.6 -2.1)	1.7 (1.4 -1.9)	0.23
Δ§ SOFA score, mean AUC* (95% CI)	−1.4 (−2.2 -−0.6)	−1.9 (−2.7 -−1.1)	0.41
ICU length of stay, median [IQR]	9 [5 -13]	7 [4 -12]	0.19
Hospital length of stay, median [IQR], days	20 [10 -25]	16 [7 -30]	0.80
ICU mortality rate, n (%)	13 (25%)	12 (24%)	0.86
90-day mortality rate, n (%)	21 (40%)	19 (37%)	0.74

Abbreviations: *AUC: Area under the curve- a summary measure of longitudinal data- was determined using mixed linear modeling fitting main effects for group and time; CI: Confidence Interval; IQR: interquartile range; SD: standard deviation; ARDS: Acute Respiratory Distress Syndrome; ‖ Significant hypoxemic episodes were those

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episodes recorded by the bedside nurses when SpO_2 <86% lasted >5 minutes; RRT: Renal Replacement Therapy; MV: Mechanical Ventilation; †Derived as percentage of total time-points when SpO_2 was not within the alarm limits assigned to each arm and there was further room for FiO_2 titration (i.e. $0.21 < FiO_2 < 0.80$). § Δ or 'Delta' refers to the change in variable value during day 0-7 as compared to its baseline value. ††Hemodynamic instability was defined as 'cardiac arrest' or 'addition of two or more new vasopressor/inotrope agents in a day'. **Event-free days were defined as those days when a patient was alive and free of that event. ‡New-onset ARDS was defined as subsequent occurrence of ARDS in those patients who did not have ARDS on day 0, and where ARDS was defined according to the Berlin definition. SOFA: Sequential Organ Failure Assessment score includes sub-scores ranging from 0-4 for each of the five organ system (circulation, lungs, liver, kidneys and coagulation), with score ranging from 0-20, and higher scores indicating more severe organ failure. ‡‡ Sum-total of noradrenaline and adrenaline dose;

Table 3: **A post hoc analysis of the percentage time spent at following SpO_2 or PaO_2 levels**

% Time-points* spent at following levels	Conservative group	Liberal group	P value	Survivors	Non-survivors	P value
SpO_2 <88%, while at FiO_2 <1, % (n/N)	1% (16/1526)	0.3% (3/1184)	0.026	0.9% (14/1599)	0.5% (5/1111)	0.22
PaO_2 <55 mmHg, while at FiO_2 <1, % (n/N)	7% (72/1006)	1% (7/764)	<0.001	5% (56/1074)	3% (23/696)	0.27
SpO_2 >98%, while at FiO_2 >0.21, % (n/N)	4% (41/933)	22% (246/1138)	<0.001	14% (191/1334)	13% (96/737)	0.61
PaO_2 >120 mmHg, while at FiO_2 >0.21, % (n/N)	3% (22/641)	13% (92/734)	<0.001	9% (79/889)	7% (35/486)	0.88

* These were punctual prospective pre-decided four-hourly time-points.

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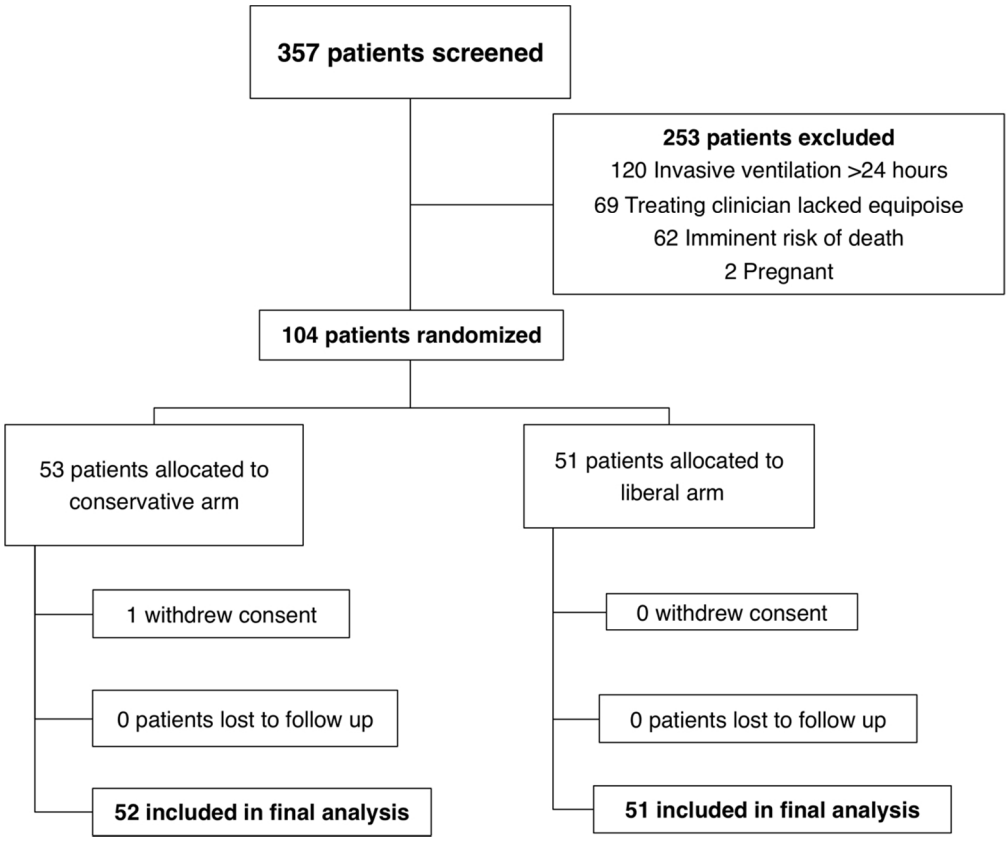

Figure 1. Patient flow diagram
110x92mm (300 x 300 DPI)

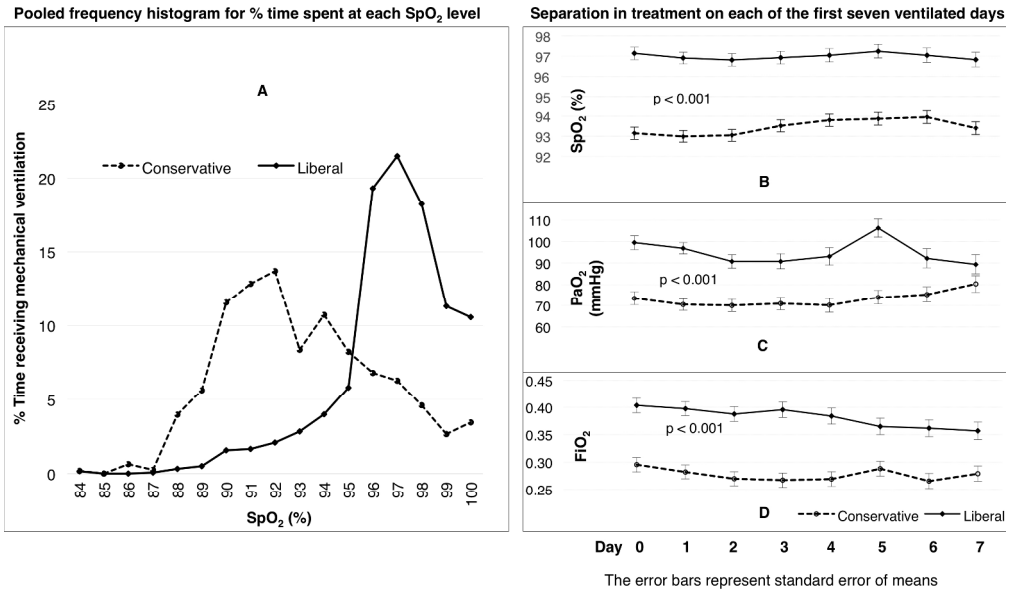

Figure 2. Pooled frequency histogram of the percentage time spent at each SpO2 level (A) and treatment separation (B, C, D) in both arms
253x147mm (300 x 300 DPI)

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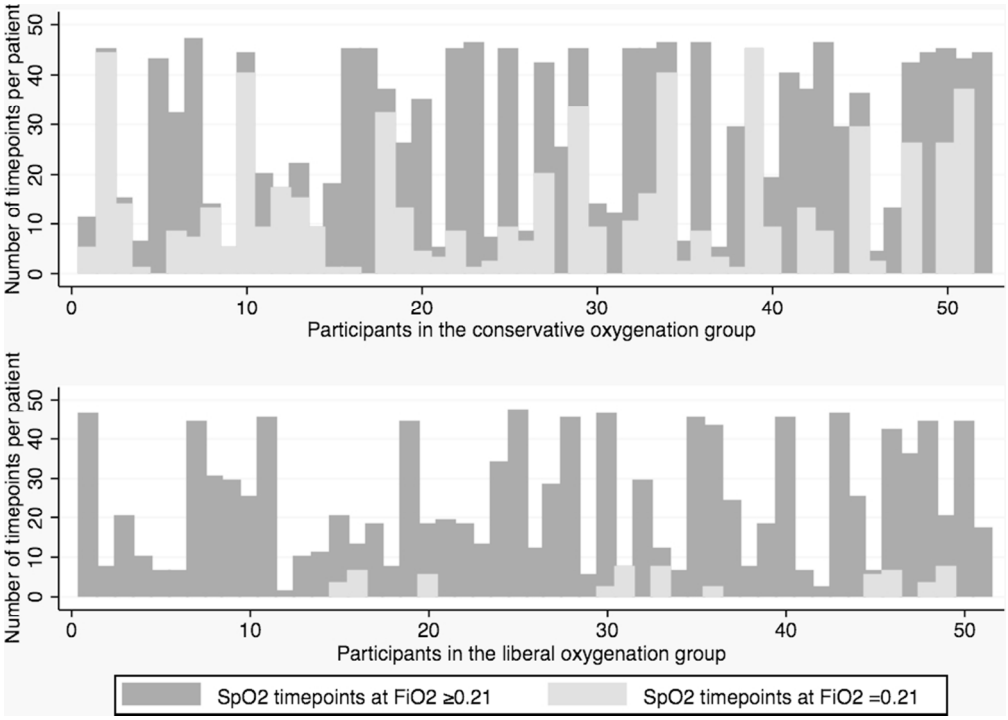

Figure 3. SpO2 time-points per patient spent at a FiO2 of 0.21 in both arms
84x59mm (300 x 300 DPI)

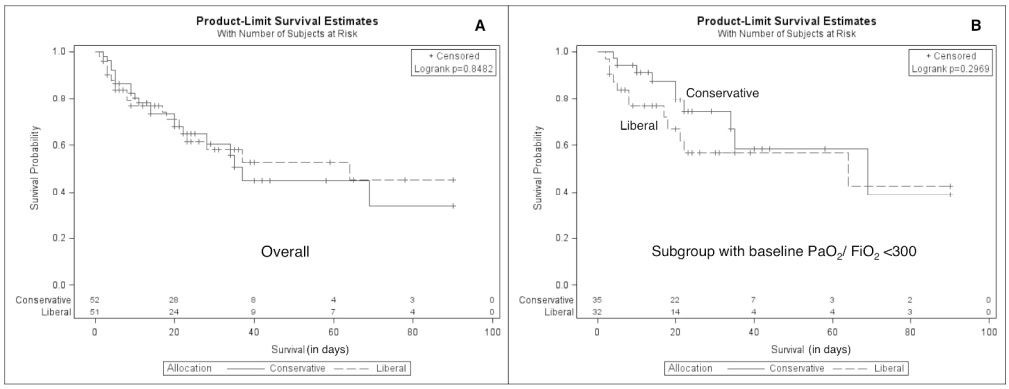

Figure 4. Survival curve overall (A) and for the subgroup with baseline PaO2/FiO2 ratio <300 (B) in relation to day 90 mortality
253x96mm (300 x 300 DPI)

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Online supplement

Conservative versus liberal oxygenation targets for mechanically ventilated patients – a pilot multicenter randomized controlled trial

Rakshit Panwar; Miranda Hardie; Rinaldo Bellomo; Loïc Barrot; Glenn M Eastwood; Paul J Young; Gilles Capellier; Peter WJ Harrigan; Michael Bailey; CLOSE study investigators and the ANZICS Clinical Trials Group.

Methods

Eligibility criteria

ICU patients, aged ≥18 years, were eligible if they had been receiving invasive MV for <24 hours and their treating clinician expected MV to continue for at least next 24 hours. The reason for the inclusion criterion of 'invasive MV for <24 hours' was to ensure that patients who would be assigned to the conservative oxygen group did not get exposed to standard liberal oxygen therapy for prolonged periods prior to randomization.

Exclusion criteria included known pregnancy, imminent risk of death, or if the treating clinician lacked equipoise for the patient to be enrolled in this trial. The exclusion criterion of 'lack of equipoise' included those clinical situations where the most appropriate approach (conservative versus liberal) to oxygen therapy is well established. For example, in hypercapnic patients with chronic respiratory failure or exacerbation of chronic obstructive pulmonary disease (COPD), there is level I evidence supporting a conservative approach to oxygen therapy (1) and in patients with carbon monoxide poisoning or necrotizing fasciitis a liberal approach is preferred. However, among patients who had COPD listed as one of the prior co-morbid conditions, the treating

clinicians could allow enrolment of those patients who were admitted for reasons unrelated to COPD.

Randomization

Enrolled patients were randomly allocated using opaque sealed envelopes to either liberal oxygenation arm or conservative oxygenation arm. Using a web-based computer program, a third party generated a randomization list for each site. The randomization method was via permuted block randomization with variable block sizes. Randomization number and the allocated arm were typewritten in a lighter font on a colored A4 page, which was then folded and inserted in a sequentially numbered opaque envelope for each patient. It was impossible to decipher the allocated arm by holding the envelope against a bright light. All envelopes were sealed and securely stored in a locked cabinet. Envelopes were opened just prior to initiation of trial intervention. Patients were unaware of their assigned group but blinding of treating clinicians was not considered feasible.

Intervention

The oxygenation goal in this study was based on pulse oximeter measured arterial blood oxygen saturation (SpO_2). The protocol did not require CO-oximeter measured arterial oxygen saturation (SaO_2) from arterial blood gases. However, SaO_2 could be used instead as per routine practice in the participating centers, particularly in situations where the peripheral perfusion was poor or SpO_2 readings were unreliable. PEEP was applied at the discretion of the treating clinician. Clinicians were advised to adjust PEEP as they deem fit and what they would normally do in their routine practice regardless of assigned SpO_2 targets. In both groups, the bedside nurse then titrated FiO_2

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within a range of 0.21 to 0.80 to achieve the assigned SpO_2. Assigned SpO_2 targets applied to the participants' entire duration of MV in ICU.

For the *conservative* oxygen therapy group, when FiO_2 requirement was <0.50 an SpO_2 of 90-92% was recommended, and when FiO_2 requirement was ≥0.50 an SpO_2 of 88-90% was recommended. The acceptable lower limit of PaO_2 was left to the discretion to the treating clinician. We did not specify a lower limit for acceptable PaO_2, as the overall contribution of PaO_2 in determining blood oxygen content or tissue oxygen delivery is considered to be very modest (2). The lower-limit monitor alarm for SpO_2 was set at 87% and the higher-limit alarm for SpO_2 was set at 93%.

For the *liberal* oxygen therapy group, the SpO_2 target was set at ≥96%. If FiO_2 of 0.60 or more was required to achieve SpO_2 of at least 96%, then SpO_2 target could be adjusted by the clinicians if they felt it was their usual practice to do so. The lower-limit monitor alarm for SpO_2 was set at 95%. No upper alarm limit was set.

We chose to protocolize the standard care arm of our study to minimize the risk of "contamination" due to a carry-over effect that might otherwise occur when clinicians were simultaneously treating patients assigned to a conservative oxygen approach.

Standard practices in both groups

The treating intensive care physician could alter oxygenation targets at any time if deemed necessary. Temporary measures to improve oxygenation for planned procedures involving upper airways such as tracheostomy or bronchoscopy or transport for radiological investigations followed standard practices at each site. Such temporary adjustments in oxygenation parameters were limited to the shortest duration possible. Patients who were re-intubated continued in the same study arm. Participating sites were requested to adhere to best practice guidelines, regardless of group allocation, in relation to other potentially confounding co-interventions such as adjustment of tidal

volume, positive end-expiratory pressure (PEEP), fluid management, blood transfusion, muscle relaxation, sedation interruption, ventilator weaning, nutrition, use of steroids, early mobilization and physiotherapy.

Data collection

Trained investigators or research coordinators at each site collected data in a standardized format. Baseline data were obtained on demographics, severity scores (3, 4), history of ischemic heart disease, chronic obstructive pulmonary disease (COPD), current smoker, admission diagnosis, presence of ARDS (5), current oxygenation parameters and ventilator settings at the time of randomization. Data on oxygenation parameters and ventilator settings, including use of mandatory mode of ventilation, were recorded 4-hourly from day 0 to day 7 and then 12-hourly from day 8 to day 28. Data on the use of vasopressor, renal replacement therapy (RRT), new arrhythmias, new pneumothorax, and incidence of significant episodes of arterial blood desaturation (SpO_2 <86% for >5 minutes) were collected daily for the first 28 days. Patients were followed up until day 90 after randomization, or death.

Outcomes

Primary endpoints were mean area-under-curve (AUC) for SpO_2, SaO_2, PaO_2 and FiO_2 on days 0-7, and percentage time-points spent off target (i.e., beyond the assigned alarm limits) in both arms. Secondary endpoints were measures of organ dysfunction such as ventilator-free days, RRT-free days, and arrhythmia-free days until day 28, incidence of hemodynamic instability (i.e., cardiac arrest or addition of two or more new vasopressor/inotrope agents), incidence of new-onset ARDS (5), serum lactate, change from baseline (Δ) SOFA score, Δ PaO_2/FiO_2, Δ serum creatinine, ICU and 90-day mortality.

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Statistical analysis

The analysis plan and outline of data presentation was pre-specified on the trial registration page (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=364185). Analysis was conducted on an intention-to-treat basis. Based on previous observational studies (6, 7) we estimated that a sample size of 100 would provide at least 350 MV days of exposure to both oxygenation strategies. We deemed this sufficient for this pilot phase to assess feasibility and any major signal of harm. All data were initially assessed for normality and log-transformed where appropriate. Continuous normally distributed variables were compared using Student's t-tests and reported as means (standard deviation (SD)), whilst non-normally distributed data were compared using Wilcoxon rank sum tests and reported as medians (interquartile range (IQR)). Categorical data were compared using chi-square tests for equal proportions or Fisher's exact tests where numbers were small and reported as n (%). Normally distributed longitudinal data were compared between groups using mixed linear modeling fitting main effects for group and time and an interaction between group and time to determine if the relationship between group and outcome changed significantly over time. Results were reported as least square means thus facilitating a measure of area under the curve (AUC). Binomial outcomes were longitudinally compared between groups using generalized linear mixed modeling with results reported as odds ratios (95% CI). Survival analysis was performed using log-rank tests and presented as Kaplan Meier curves. Multivariable survival analysis was conducted using Cox proportional hazards regression adjusted for a-priori defined baseline variables (SOFA score, APACHE III score, COPD and ARDS) with results reported as hazard ratios (95% CI). Pre-planned subgroup analysis was performed on patients with baseline PaO_2/FiO_2 <300. All analysis was conducted using

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and a two-sided p-value of <0.05 was considered to be statistically significant.

Post hoc analyses

Post hoc analyses were performed to assess incidence of hypoxemia and hyperoxemia in both groups during the study period. We assessed incidence of hypoxemia and hyperoxemia among survivors and non-survivors to assess any associated signal of harm. All these data are presented as tables and figures in the online supplement.

Comments

120 out of 357 patients screened could not be enrolled as they had been on invasive MV for >24 hours at the time of screening. This was probably related to the research processes in place at the participating sites. These patients were not screened within 24 hours of MV because research staff was not always available within this timeframe. 69 out of 357 patients screened could not be enrolled as the treating clinician lacked equipoise with regards to SpO_2 targets. These were the conditions where either the lower or conservative SpO_2 target was considered beneficial or a part of standard care such as, COPD exacerbation or hypercapnic chronic respiratory failure or severely impaired gas exchange needing FiO_2 ≥0.80 at the time of screening. The exclusion could also relate to those conditions where a higher SpO_2 target was considered beneficial or a part of standard care such as carbon monoxide poisoning.

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References

1. Austin MA, Wills KE, Blizzard L, Walters EH, Wood-Baker R. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. *Bmj* 2010; 341: c5462.

2. Grocott MP, Martin DS, Levett DZ, McMorrow R, Windsor J, Montgomery HE, Caudwell Xtreme Everest Research G. Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med* 2009; 360: 140-149.

3. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; 100: 1619-1636.

4. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998; 26: 1793-1800.

5. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *Jama* 2012; 307: 2526-2533.

6. Panwar R, Capellier G, Schmutz N, Davies A, Cooper DJ, Bailey M, Baguley D, Pilcher V, Bellomo R. Current oxygenation practice in ventilated patients-an observational cohort study. *Anaesthesia and intensive care* 2013; 41: 505-514.

7. Suzuki S, Eastwood GM, Peck L, Glassford NJ, Bellomo R. Current oxygen management in mechanically ventilated patients: a prospective observational cohort study. *J Crit Care* 2013; 28: 647-654.

Fig. E1: Time-points per patient spent with SpO_2 <88% while at FiO_2 <1 in both groups

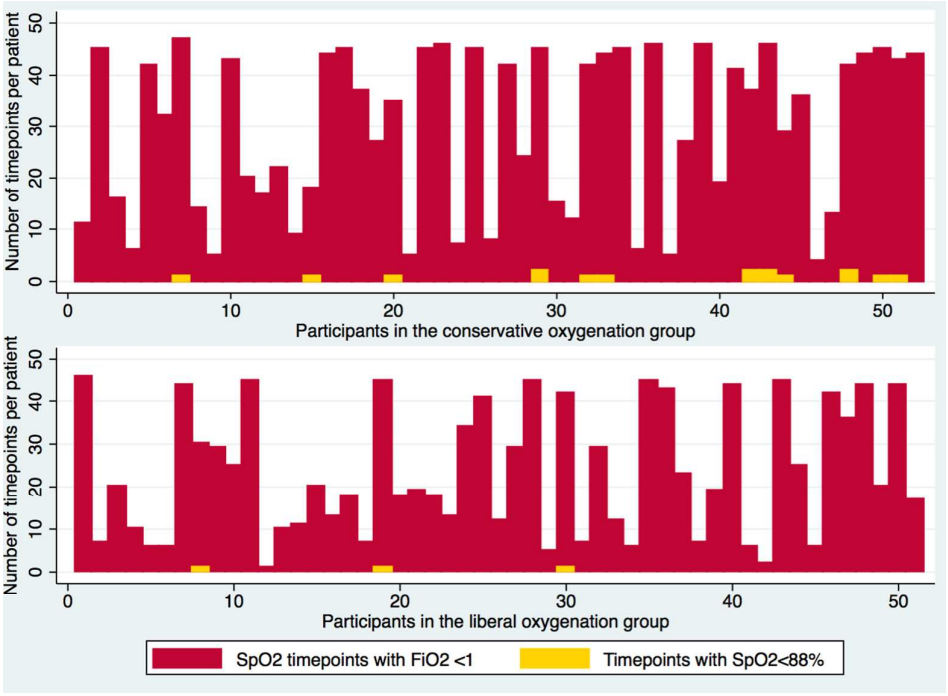
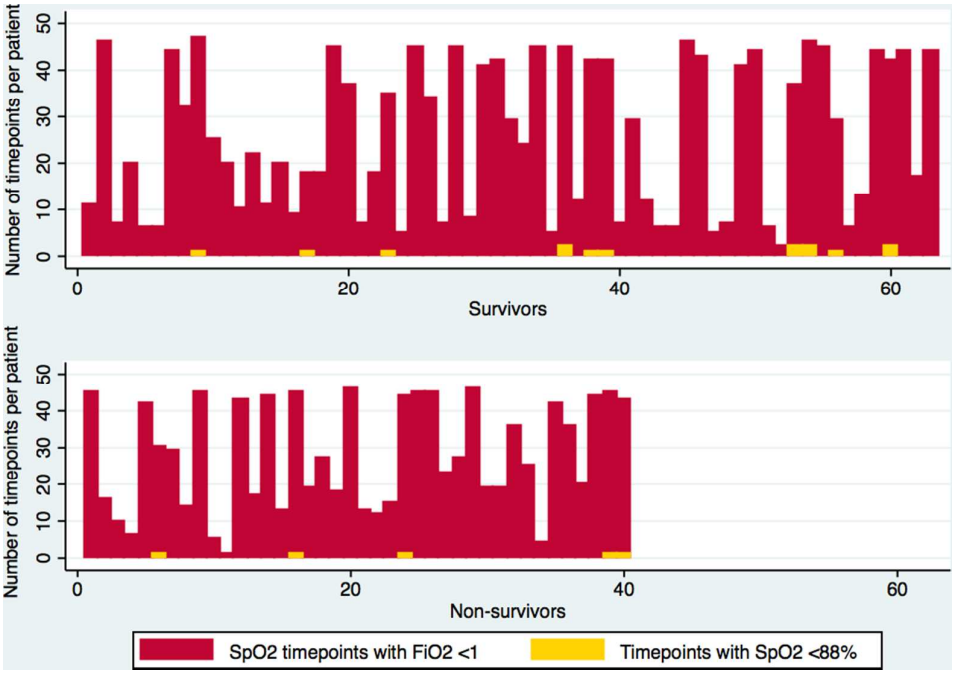


Fig. E2: Time-points per patient spent with SpO_2 <88% while at FiO_2 <1 among survivors and non-survivors



AJRCCM Articles in Press. Published on 03-September-2015 as 10.1164/rccm.201505-1019OC

Fig. E3: Time-points per patient spent with PaO_2 <55 mmHg while at FiO_2 <1 in both groups

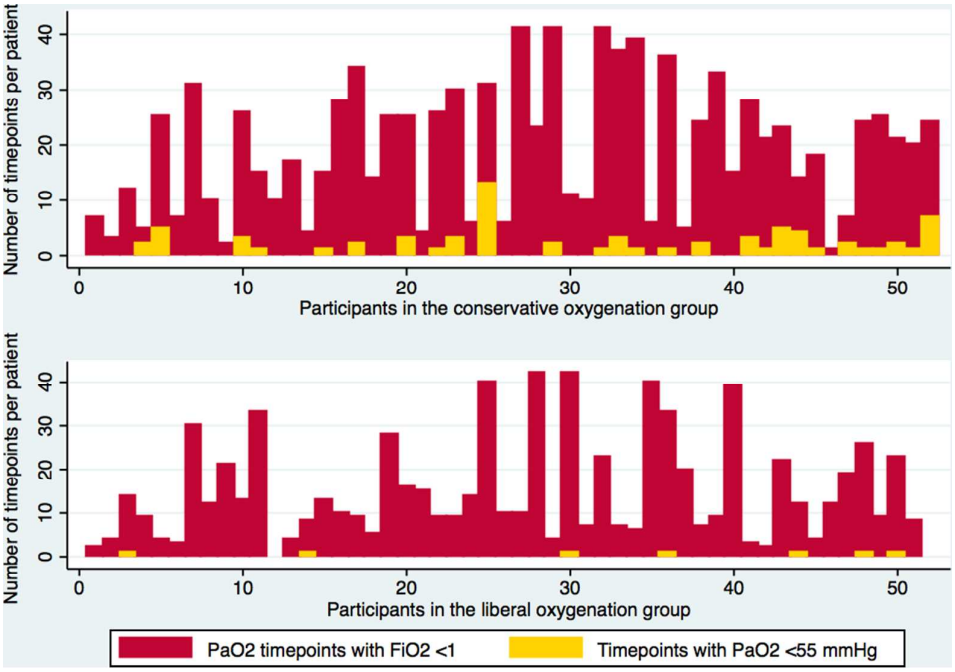


Fig. E4: Time-points per patient spent with PaO_2 <55 mmHg while at FiO_2 <1 among survivors and non-survivors

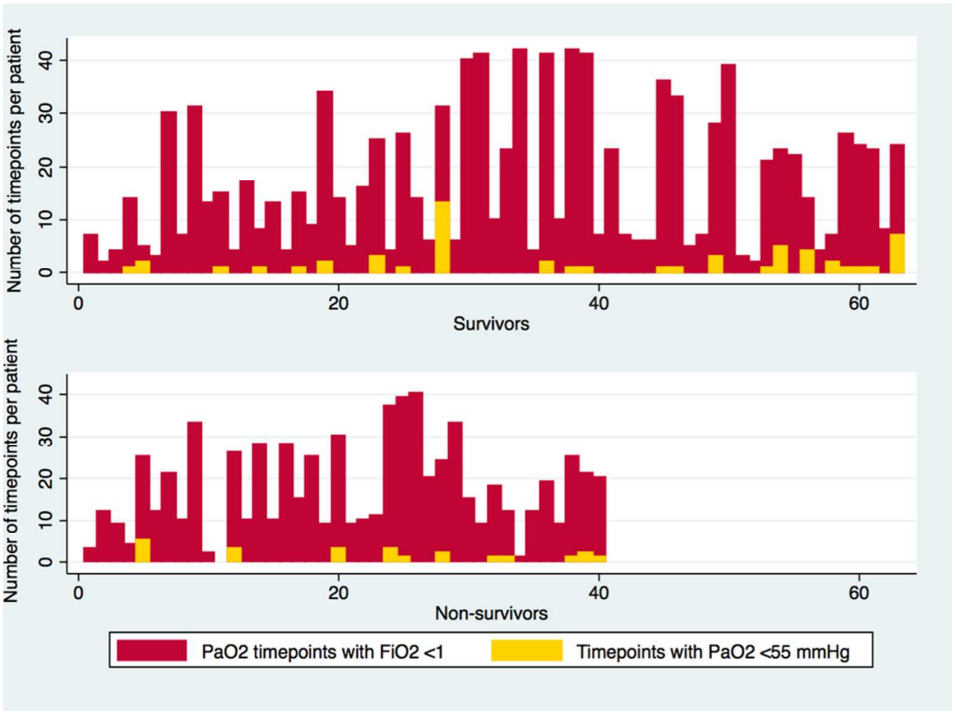


Fig. E5: Time-points per patient spent with SpO_2 >98% while at FiO_2 >0.21 in both groups

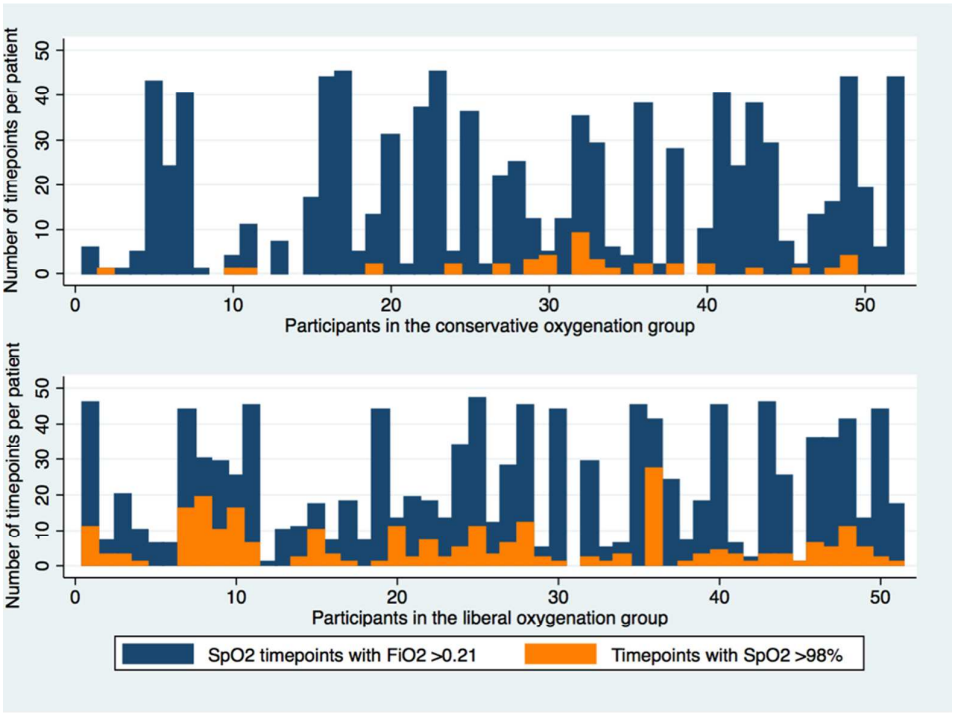


Fig. E6: Time-points per patient spent with SpO_2 >98% while at FiO_2 >0.21 among survivors and non-survivors

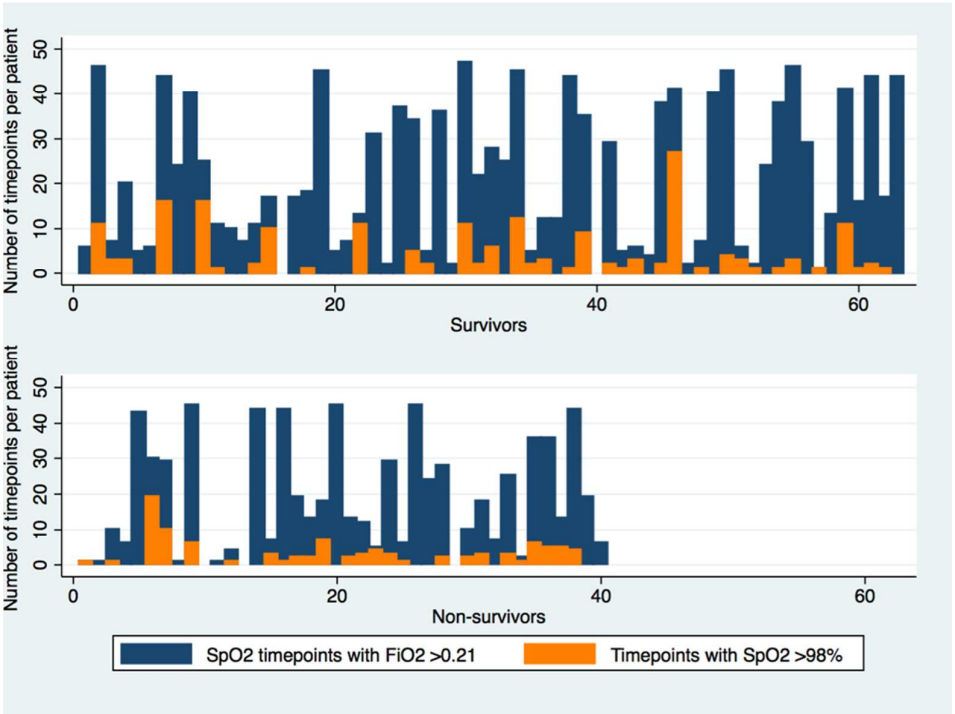


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Fig. E7: Time-points per patient spent with PaO_2 >120 mmHg while at FiO_2 >0.21 in both groups

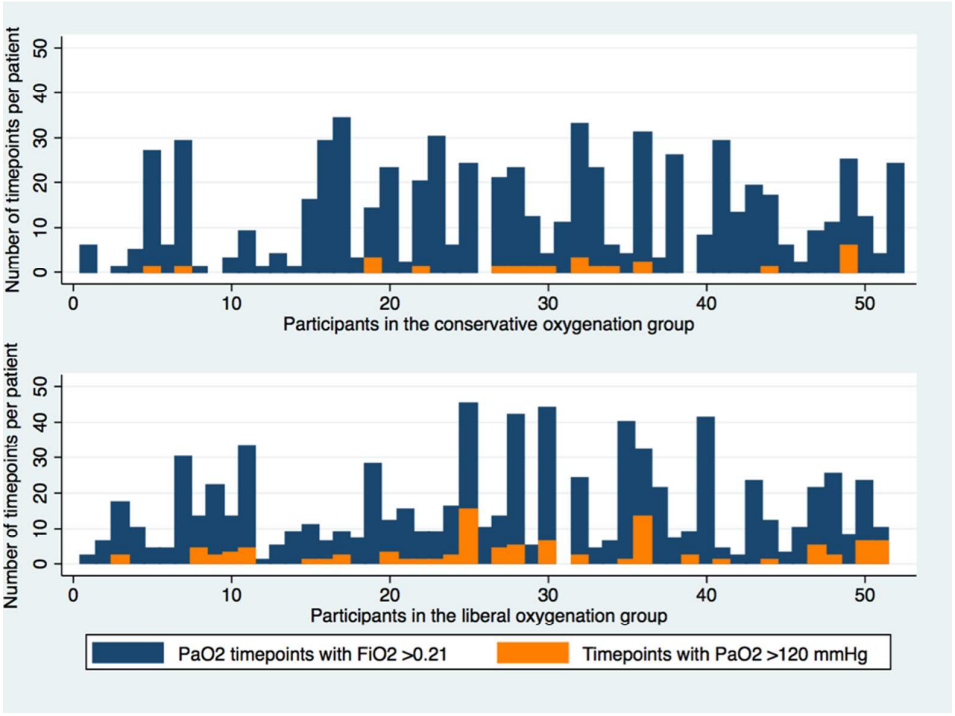

Fig. E8: Time-points per patient spent with PaO_2 >120 mmHg while at FiO_2 >0.21 among survivors and non-survivors

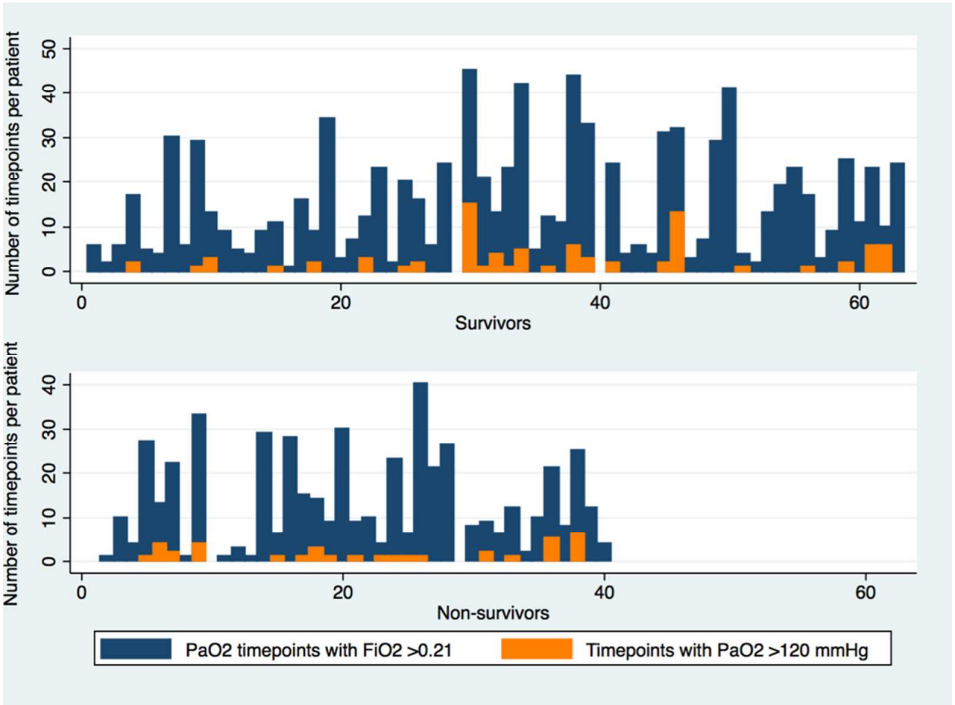

Fig. E9: SpO_2 time-points per patient spent at a FiO_2 >0.50 in both arms

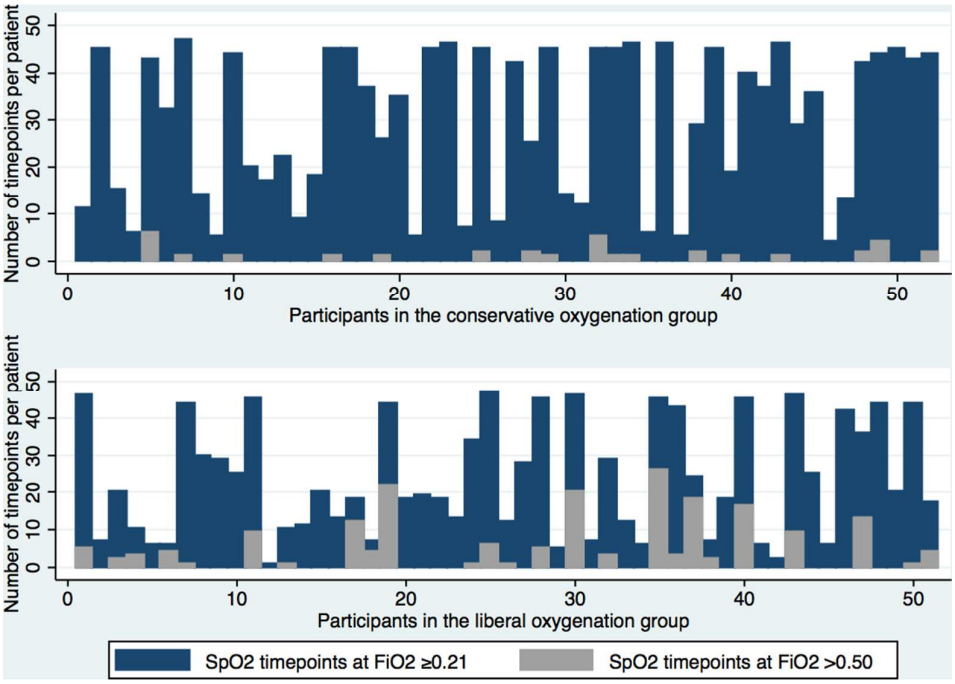

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Table E1: Other characteristics of the study treatment period

Characteristics	Conservative oxygenation arm	Liberal oxygenation arm	P value
V_T*, mean (95% CI), ml/kg PBW†	7.9 (7.5 -8.4)	7.9 (7.5 -8.3)	0.96
Minute Ventilation, mean (95% CI), ml/kg PBW/minute	155 (144 -166)	142 (132 -153)	0.10
PEEP, mean (95% CI), cmH_20	6.8 (6.2 -7.4)	7.5 (6.9 -8.2)	0.07
Peak Airway Pressure, mean (95% CI), cmH_2O	19 (18 -21)	21 (19 -22)	0.19
Hours on MV‡, median [IQR]	138 [60-251]	90 [49-206]	0.13
Number of ABGs in first week, median [IQR]	23 [12 -36]	14 [9 -26]	0.04
Hemoglobin levels during first week**, mean AUC§ (95% CI), g/l	99 (93-105)	98 (92-104)	0.89
Number of units of red-cell transfusion, median [IQR] ††	0 [0-1]	0 [0-0]	0.12
Net fluid balance for first week, mean (95% CI), ml/ kg PBW†	10.8 (8.6 -13.5)	8.8 (7 -11.2)	0.22

Abbreviations: * V_T: Tidal Volume; † PBW: Predicted Body Weight; CI: Confidence Interval; ABG: Arterial Blood Gas; SD: standard deviation; IQR: inter-quartile range; ‡ MV: mechanical ventilation; PEEP: Positive End-expiratory Pressure; § AUC: Area-under-the-curve; ** Data available for 82 patients. †† Mean number of the units of red cells transfusion during the first week were 0.56 (conservative) versus 0.57 (liberal).

Table E2: **Other post hoc analyses related to hypoxemia and hyperoxemia**

Variables	Conservative oxygenation arm (n=52)	Liberal oxygenation arm (n=51)	P value	Survivors (n=63)	Non-survivors (n=40)	P value
Lowest SpO_2 value, median [IQR], %	88 [88-91]	94 [92-96]	<0.001	92 [88-95]	90 [88-94]	0.49
Highest SpO_2 value, median [IQR], %	98 [96-100]	100 [99-100]	<0.001	100 [97-100]	99 [98-100]	0.65
Lowest SaO_2 value, median [IQR], %	89 [86-91]	94 [92-96]	<0.001	92 [88-94]	92 [89-94]	0.98
Highest SaO_2 value, median [IQR], %	98 [96-99]	99 [98-100]	0.01	98 [97-99]	99 [97-99]	0.28
Lowest PaO_2 value, median [IQR], mmHg	54 [50-60]	67 [60-77]	<0.001	59 [52-71]	61 [53-71]	0.61
Highest PaO_2 value, median [IQR], mmHg	100 [87-131]	126 [107-155]	0.001	109 [93-142]	120 [100-142]	0.29
Lowest FiO_2 value, median [IQR]	0.21 [0.21-0.21]	0.30 [0.25-0.35]	<0.001	0.21 [0.21-0.30]	0.21 [0.21-0.30]	0.85
Highest FiO_2 value, median [IQR]	0.40 [0.31-0.60]	0.50 [0.40-0.75]	0.045	0.50 [0.35-0.65]	0.48 [0.35-0.78]	0.82
Number of time-points spent with SpO_2 <88% while at FiO_2 <1, per patient, median [IQR]	0 [0-0] (Mean*=0.31)	0 [0-0] (Mean*=0.06)	0.01	0 [0-0]	0 [0-0]	0.56
Highest number of time-points spent with SpO_2 <88% while at FiO_2 <1	2	1	-	2	1	-
Incidence of any exposure to SpO_2 <88% while at FiO_2 <1, n (%)	12 (23%)	3 (6%)	0.01	10 (16%)	5 (13%)	0.78
Number of time-points spent with SaO_2 <88% while at FiO_2 <1, per patient, median [IQR]	0 [0-1] (Mean*=0.60)	0 [0-0] (Mean*=0.02)	<0.001	0 [0-0]	0 [0-0]	0.82
Highest number of time-points spent with SaO_2 <88% while at FiO_2 <1	5	1	-	5	4	-

AJRCCM Articles in Press. Published on 03-September-2015 as 10.1164/rccm.201505-1019OC

Incidence of any exposure to SaO_2 <88% while at FiO_2 <1, n (%)	16 (31%)	1 (2%)	<0.001	10 (16%)	7 (18%)	0.82
Number of time-points spent with PaO_2 <55 mmHg while at FiO_2 <1, per patient, median [IQR]	1 [0-2]	0 [0-0]	<0.001	0 [0-1]	0 [0-1]	0.40
Highest number of time-points spent with PaO_2 <55 mmHg while at FiO_2 <1	13	1	-	13	5	-
Incidence of any exposure to PaO_2 <55 mmHg while at FiO_2 <1, n (%)	27 (52%)	7 (14%)	<0.001	23 (37%)	11 (28%)	0.34
Number of time-points spent with SpO_2 >98% while at FiO_2 >0.21, per patient, median [IQR]	0 [0-1]	3 [1-6]	<0.001	1 [0-3]	1 [0-4]	0.78
Highest number of time-points spent with SpO_2 >98% while at FiO_2 >0.21	9	27	-	27	19	-
Incidence of any exposure to SpO_2 >98% while at FiO_2 >0.21, n (%)	17 (33%)	43 (84%)	<0.001	36 (57%)	24 (60%)	0.77
Number of time-points spent with PaO_2 >120 mmHg while at FiO_2 >0.21, per patient, median [IQR]	0 [0-1]	1 [0-2]	<0.001	0 [0-2]	0 [0-1]	0.87
Highest number of time-points spent with PaO_2 >120 mmHg while at FiO_2 >0.21	6	15	-	15	6	-
Incidence of any exposure to PaO_2 >120 mmHg while at FiO_2 >0.21, n (%)	14 (27%)	28 (55%)	0.003	24 (38%)	18 (45%)	0.49

*Means are reported here for increased interpretability, as the differences are significant whereas the medians are uninformative.

Table E3: Outcomes for the pre-specified subgroup of patients with baseline PaO_2/FiO_2 <300

Characteristics	Conservative oxygenation arm (n= 35)	Liberal oxygenation arm (n= 32)	P value
SpO_2 for day 0-7, mean (95% CI), %	92.6 (91.9 -93.4)	96.6 (96.1 -97.1)	<0.001
PaO_2 for day 0-7, mean (95% CI), mmHg	69 (67 -72)	92 (87 -98)	<0.001
FiO_2 for day 0-7, mean (95% CI)	0.29 (0.27 -0.31)	0.42 (0.39 -0.45)	<0.001
Incidence of new-onset ARDS‡, n (%)	7 (37%)	9 (41%)	0.79
Δ§ PaO_2/FiO_2, mean (SD)	62 (53)	57 (59)	0.70
MV-free** days until day 28, mean (SD)	16.4 (9.9)	15.8 (11.4)	0.83
Incidence of hemodynamic instability††, n (%)	6 (17%)	7 (22%)	0.62
Vasopressor-free** days until day 28, median [IQR]	25.8 [15.6 -27.4]	24.8 [10.6 -26.9]	0.38
Arrhythmia-free** days until day 28, median [IQR]	28 [27 -28]	27.5 [15 -28]	0.048
Δ§ Serum creatinine, mean (95% CI), µmol/l	−4 (−39 -32)	−5 (−47 -37)	0.96
RRT-free** days until day 28, mean (SD)	28 [21 -28]	28 [7 -28]	0.26
Δ§ SOFA score, mean (95% CI)	−2.4 (−3.2 -−1.5)	−2 (−2.9 -−1.1)	0.61
ICU length of stay, median [IQR], d	9 [6 -19]	8 [4 -13]	0.23
Hospital length of stay, median [IQR], d	21 [13 -34]	21 [7 -30]	0.55
ICU mortality rate, n (%)	6 (17%)	9 (28%)	0.28
90-day mortality rate, n (%)	10 (29%)	12 (38%)	0.44

Abbreviations: RRT: Renal Replacement Therapy; MV: Mechanical Ventilation. § Δ or 'Delta' refers to the change in variable value during day 0-7 as compared to its baseline value. ††Hemodynamic instability was defined as 'cardiac arrest' or 'addition of two or more new vasopressor/inotrope agents' on a given day. **Event-free days were defined as those days when a patient was alive and free of that event. ‡New-onset ARDS was defined as subsequent occurrence of ARDS in those patients who did not have ARDS on day 0, and where ARDS was defined according to the Berlin definition. SOFA: Sequential Organ Failure Assessment score includes sub-scores ranging from 0-4 for each of the five organ systems (circulation, lungs, liver, kidneys and coagulation), with score ranging from 0-20, and higher scores indicating more severe organ failure.

AJRCCM Articles in Press. Published on 03-September-2015 as 10.1164/rccm.201505-1019OC

Table E4: Outcomes according to per protocol analysis

Characteristics	Conservative oxygenation arm (n=51)	Liberal oxygenation arm (n=52)	P value
SpO_2 for day 0-7, mean (SD), %	93 (2)	97 (1)	<0.001
PaO_2 for day 0-7, mean (SD), mmHg	72 (10)	95 (15)	<0.001
FiO_2 for day 0-7, mean (SD)	0.28 (0.06)	0.39 (0.1)	<0.001
Incidence of new-onset ARDS‡, n (%)	10 (30%)	12 (29%)	0.92
Δ§ PaO_2/FiO_2, mean (SD)	49 (98)	22 (101)	0.17
MV-free** days until day 28, mean (SD)	14.8 (10.4)	16.2 (11.2)	0.5
Incidence of hemodynamic instability††, n (%)	8 (16%)	13 (25%)	0.24
Vasopressor-free** days until day 28, median [IQR]	25.3 [6.9-27.4]	25.6 [14.3-27]	0.87
Arrhythmia-free** days until day 28, median [IQR]	28 [13.9-28]	28 [20-28]	0.64
RRT-free** days until day 28, median [IQR]	28 [21-28]	28 [7-28]	0.26
ICU mortality rate, n (%)	12 (24%)	13 (25%)	0.86
90-day mortality rate, n (%)	20 (39%)	20 (38%)	0.94

Abbreviations: RRT: Renal Replacement Therapy; MV: Mechanical Ventilation. § Δ or 'Delta' refers to the change in variable value during day 0-7 as compared to its baseline value. ††Hemodynamic instability was defined as 'cardiac arrest' or 'addition of two or more new vasopressor/inotrope agents' on a given day. **Event-free days were defined as those days when a patient was alive and free of that event. ‡New-onset ARDS was defined as subsequent occurrence of ARDS in those patients who did not have ARDS on day 0, and where ARDS was defined according to the Berlin definition.

Table E5: **Post hoc analysis of survivors *versus* non-survivors at day 90**

Characteristics	Survivors (n=63)	Non-survivors (n=40)	P value
Age, mean (SD), y	58 (17)	70 (12)	<0.001
APACHE III, mean (SD)	69 (25)	83 (24)	0.005
SpO_2 for day 0-7, mean (95% CI), %	95.1 (94.4-95.8)	95.3 (94.6-96)	0.63
PaO_2 for day 0-7, mean (95% CI), mmHg	83 (78-87)	85 (80-90)	0.55
FiO_2 for day 0-7, mean (95% CI)	0.34 (0.32-0.36)	0.33 (0.29-0.37)	0.6
Hours on MV‡, median [IQR]	94 [44-239]	120 [66-248]	0.28
Number of significant episodes of arterial desaturation ‖, median [IQR]	0 [0-2]	0 [0-1.5]	0.77
Vasopressor dose during first week, median [IQR], µg/kg/min	0.05 [0.02-0.12]	0.07 [0.02-0.13]	0.57
Hours on vasopressors, median [IQR]	30 [13-63]	49 [9-149]	0.13
ICU length of stay, median [IQR], days	7.8 [4.3 -12.4]	8.1 [3.7 -14.3]	0.87
Hospital length of stay, median [IQR], days	21 [11-35]	15.5 [6-24]	0.06

Abbreviations: SD: standard deviation; IQR: interquartile range; BMI: body mass index; APACHE III: Acute Physiology and Chronic Health Evaluation score III is the sum of three components at the time of randomization: an acute physiology score (0 to 252), chronic health evaluation score (0 to 23), and age score (0 to 24), with total score ranging from 0 to 299, where higher score indicate more severe disease; ‡ MV: mechanical ventilation; ‖ Significant hypoxemic episodes were those episodes recorded by the bedside nurses when SpO_2 <86% lasted >5 minutes;

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Table E6: Post hoc analysis of patients exposed to FiO_2 >0.50*

Characteristics	Conservative oxygenation arm (n=17)	Liberal oxygenation arm (n=25)	P value
Baseline SOFA (non-GCS), median [IQR]	9 [7-10]	8 [5-10]	0.37
APACHE III at randomization, median [IQR]	79 [60-84]	67 [50-80]	0.14
Lactate (in mmol/l) at randomization, mean (SD)	2.6 (1.7)	2.1 (1.2)	0.37
SpO_2 for day 0-7, mean (SD), %	93 (2)	96 (2)	<0.001
PaO_2 for day 0-7, mean (SD), mmHg	73 (11)	94 (17)	<0.001
FiO_2 for day 0-7, mean (SD)	0.32 (0.06)	0.47 (0.07)	<0.001
Incidence of new-onset ARDS, n (%)	6 (55%)	6 (35%)	0.44
Δ PaO_2/FiO_2, mean (SD)	61 (127)	28 (88)	0.32
MV-free days until day 28, median [IQR]	11.4 [0-17.9]	19 [5.7-25]	0.08
Incidence of hemodynamic instability, n (%)	4 (24%)	6 (24%)	1.00
Vasopressor-free days until day 28, median [IQR]	15.6 [2.1-25]	25.4 [18.4-26.5]	0.04
RRT-free days until day 28, median [IQR]	17 [4.8-28]	28 [19-28]	0.09
ICU mortality rate, n (%)	7 (41%)	5 (20%)	0.17
90-day mortality rate, n (%)	9 (53%)	7 (28%)	0.12

* Because the subgroup of patients who received an FiO_2 >0.50 is not defined by a baseline characteristic, any comparison between treatment groups based on this post-randomization subgroup is subject to bias and might be potentially misleading.