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Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit
The Oxygen-ICU Randomized Clinical Trial

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Supplemental content

IMPORTANCE Despite suggestions of potential harm from unnecessary oxygen therapy, critically ill patients spend substantial periods in a hyperoxemic state. A strategy of controlled arterial oxygenation is thus rational but has not been validated in clinical practice.

OBJECTIVE To assess whether a conservative protocol for oxygen supplementation could improve outcomes in patients admitted to intensive care units (ICUs).

DESIGN, SETTING, AND PATIENTS Oxygen-ICU was a single-center, open-label, randomized clinical trial conducted from March 2010 to October 2012 that included all adults admitted with an expected length of stay of 72 hours or longer to the medical-surgical ICU of Modena University Hospital, Italy. The originally planned sample size was 660 patients, but the study was stopped early due to difficulties in enrollment after inclusion of 480 patients.

INTERVENTIONS Patients were randomly assigned to receive oxygen therapy to maintain Pao_2 between 70 and 100 mm Hg or arterial oxyhemoglobin saturation (Spo_2) between 94% and 98% (conservative group) or, according to standard ICU practice, to allow Pao_2 values up to 150 mm Hg or Spo_2 values between 97% and 100% (conventional control group).

MAIN OUTCOMES AND MEASURES The primary outcome was ICU mortality. Secondary outcomes included occurrence of new organ failure and infection 48 hours or more after ICU admission.

RESULTS A total of 434 patients (median age, 64 years; 188 [43.3%] women) received conventional (n = 218) or conservative (n = 216) oxygen therapy and were included in the modified intent-to-treat analysis. Daily time-weighted Pao_2 averages during the ICU stay were significantly higher ($P < .001$) in the conventional group (median Pao_2, 102 mm Hg [IQR, 88-116]) vs the conservative group (median Pao_2, 87 mm Hg [IQR, 79-97]). Mortality was lower in the conservative oxygen therapy group. The conservative group had fewer episodes of shock, liver failure, and bacteremia.

	Oxygen Therapy, No. (%)			
	Conservative (n = 216)	Conventional (n = 218)	Absolute Risk Reduction (95% CI)	*P* Value
Primary outcome				
ICU mortality	25 (11.6)	44 (20.2)	0.086 (0.017-0.150)	.01
Secondary outcomes				
Shock	8 (3.7)	23 (10.6)	0.068 (0.020-0.120)	.006
Liver failure	4 (1.9)	14 (6.4)	0.046 (0.008-0.088)	.02
Bacteremia	11 (5.1)	22 (10.1)	0.050 (0.000-0.090)	.049

CONCLUSIONS AND RELEVANCE Among critically ill patients with an ICU length of stay of 72 hours or longer, a conservative protocol for oxygen therapy vs conventional therapy resulted in lower ICU mortality. These preliminary findings were based on unplanned early termination of the trial, and a larger multicenter trial is needed to evaluate the potential benefit of this approach.

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Acute hypoxemia frequently occurs in hospitalized patients and is generally counteracted by supplementation of oxygen in inspired gas. Although this strategy is consistently endorsed by guidelines for the management of critically ill patients, explicit target values for Pao_2 or arterial oxyhemoglobin saturations (Sao_2) are not provided.[1-3]

A lack of attentive oxygen management may expose patients unnecessarily to hyperoxia, leading to potential iatrogenic harm. In humans, direct lung toxicity is perhaps the best-known harmful consequence of hyperoxia with interstitial fibrosis, atelectasis, and tracheobronchitis.[4,5] Systemically, hyperoxia induces peripheral vasoconstriction[6] and, in animal models, increases production of reactive oxygen species.[7] The PROXI trial (Perioperative Oxygen Fraction-Effect on Surgical Site Infection and Pulmonary Complications After Abdominal Surgery) reported an association between perioperative administration of a high fraction of inspired oxygen (Fio_2) and an increase in long-term mortality.[8] Similarly, the recent AVOID trial (Air Versus Oxygen in Myocardial Infarction) showed that in patients with ST-segment elevation myocardial infarction but without hypoxia, supplemental oxygen therapy may increase early myocardial injury and is associated with larger myocardial infarct size at 6 months.[9] Clinical uncertainty still surrounds the safety and benefit of hyperoxia after cerebral ischemia, out-of-hospital cardiac arrest, and cardiac surgery.[10-12]

Despite these numerous suggestions of potential harm from hyperoxia, both treatment guidelines and standard clinician behavior promote prompt, uncontrolled administration of high-flow, high-concentration oxygen therapy to sick patients, with supranormal values of Pao_2 being frequently achieved.[13] Recent observational studies highlight that intensive care unit (ICU) patients are often managed with an excess of Fio_2 and are hyperoxemic for substantial periods.[14,15]

Although a controlled arterial oxygenation strategy appears rational,[3] it has to be validated in clinical practice in terms of safety, efficacy, and applicability. The aim of our randomized clinical study was to determine whether the application of a strict conservative protocol for oxygen supplementation to maintain Pao_2 within physiologic limits could improve outcomes in critically ill ICU patients.

Key Points

Question Among critically ill patients, is a conservative oxygenation strategy aimed to maintain arterial saturation within physiologic limits more beneficial than a conventional strategy?

Findings In this randomized clinical trial that included 480 patients with an expected intensive care unit length of stay of 72 hours or longer, a conservative protocol for oxygen supplementation was associated with an absolute risk reduction for intensive care unit mortality of 8.6% compared with that for patients treated with conventional therapy. However, the trial was terminated early because of difficulty with patient enrollment.

Meaning Among critically ill intensive care unit patients with a length of stay of 72 hours or longer, a conservative protocol for oxygen therapy may be beneficial; however, because the trial was terminated early, these findings must be considered preliminary.

Methods

Study Design and Patients

Oxygen-ICU was a single-center, open-label, 2-parallel-group, randomized clinical trial performed in the medical-surgical ICU of Modena University Hospital. The protocol (available in Supplement 1) and consent forms had been previously approved by the hospital ethics committee. Written informed consent or deferred consent was obtained from each patient or his/her legal surrogate.

From March 1, 2010, through October 30, 2012, all patients aged 18 years or older and admitted to the ICU with an expected length of stay of 72 hours or longer were considered for inclusion. Exclusion criteria included age younger than 18 years, pregnancy, ICU readmission, a decision to withhold life-sustaining treatment, immunosuppression or neutropenia, and enrollment in another study. Because of a different protocol for oxygen supplementation, patients with acute decompensation of chronic obstructive pulmonary disease and acute respiratory distress syndrome with a Pao_2:Fio_2 ratio less than 150 were also excluded.

Randomization and Study Treatment

On admission, enrolled patients were randomized by a computerized random-number generator in a 1:1 ratio into control (conventional) and protocol (conservative) groups. The randomization sequence was concealed from the researchers by use of sequentially numbered, closed, opaque envelopes that were opened after patient study inclusion. In the control group, oxygen therapy was administered according to standard ICU practice, in which each patient received an Fio_2 of at least 0.4, allowing Pao_2 values up to 150 mm Hg and an Spo_2 between 97% and 100%. If the Spo_2 decreased below 95% to 97%, the Fio_2 was increased to reach the target value of Spo_2. In the protocol group, oxygen therapy was administered at the lowest possible Fio_2 to maintain the Pao_2 between 70 and 100 mm Hg or Spo_2 values between 94% and 98%. Alterations in Fio_2 were completed according to a nurse order set. In particular, the Fio_2 was gradually reduced or oxygen supplementation discontinued whenever the Pao_2 or Spo_2 exceeded 100 mm Hg or 98%, respectively. Consistent with our standard ICU practice, control patients received an Fio_2 of 1.0 during intubation, airway suction, or hospital transfer. In protocol patients, supplemental oxygen was administered only if Spo_2 decreased below 94%. Decisions about noninvasive ventilation, intubation or extubation, and ventilator settings were dictated by common clinical criteria. In both groups, arterial blood gas analyses and other laboratory tests were conducted and radiology and microbiological samples were taken according to clinical need. At least 1 arterial blood gas sample was collected per day for each patient.

If adverse events occurred, the physician in charge could withdraw the patient from the study. All other treatment decisions were left to the discretion of the attending physician.

Data Collection

An electronic case report form was used to collect data. At study inclusion, this included demographic data, type of patient (medical or surgical), comorbidities, severity of illness as measured by the Simplified Acute Physiology Score-II,[16] documented infections, and respiratory, cardiovascular, renal, and liver failure, defined as a Sequential Organ Failure Assessment (SOFA) score of 3 or more for the corresponding organ.[17-19]

The time-weighted average Fio_2 and Pao_2 were recorded daily until patient death or ICU discharge, as were the use of mechanical ventilation, vasoactive drugs, and renal replacement therapy; urine output; plasma creatinine and bilirubin concentrations; and any evidence of new infection. The daily Fio_2 and Pao_2 time-weighted averages were calculated as the mean value of 2 consecutive measurements multiplied by the time (hours) between the measurements and divided by 24 hours. If only 1 value was available within a 24-hour period, the Pao_2 time-weighted average was equal to that value. Patients with less than 1 arterial blood gas analysis per day were excluded from analysis (see below).

Study Outcomes

The primary outcome was ICU mortality. Secondary outcomes included new-onset respiratory, cardiovascular, liver, and renal failure (defined as a SOFA score ≥3 for the corresponding organ) occurring 48 hours or more after ICU admission[17-19]; need for reoperation in surgical patients; and bloodstream, respiratory, and surgical site infections (defined according to Centers for Disease Control and Prevention definitions[20]). Only microbiologically documented bloodstream and respiratory tract infections were considered. Hospital mortality and ventilation-free hours during the ICU stay were also included as secondary outcomes that were not prespecified.

Statistical Analysis

On the basis of previous data from our institution that showed an ICU mortality of 23% in patients staying longer than 3 days, the originally planned sample size included 660 patients during a 2-year period to detect an absolute difference in mortality of 6% between the protocol and control groups (2-sided α=.05; power, 80%). We decided to stop the study after 32 months (480 patients), as suggested by our statistical reviewer and by the ethics committee after an interim analysis not defined a priori. In May 2012, a violent earthquake (magnitude 5.9) seriously damaged Modena University Hospital, with temporary evacuation of our ICU and 20% to 25% reduction of hospital beds (until the end of 2013). This led to a very low inclusion rate (3-4 patients/mo). At that time, we estimated that for study completion the enrollment should have been prolonged for a further 18-20 months. Completing this period of enrollment would have been difficult, leaving the study at high risk for bias related to possible changes in the standard oxygen therapy management by nurse staff influenced by the previous study period. Therefore, patient recruitment was stopped on October 30, 2012, and we performed an unplanned interim analysis that confirmed the results observed in the planned interim analysis, with a significant difference in the primary outcome between the 2 groups of treatment. Although the rules for stopping the study early were not prespecified in the study protocol, the difficulties to patient inclusion led us to terminate the study early, with our decision supported by a statistical reviewer and delegates of the local ethics committee.

A modified intent-to-treat population, consisting of all randomized patients with an ICU length of stay of 72 hours or longer and for whom at least 1 arterial blood gas analysis had been performed per day, was the primary population for analysis. However, the primary and secondary outcomes were also evaluated in the intent-to-treat population, which included all randomized patients, excluding those who withdrew consent. Baseline and outcome variables were compared with Mann-Whitney *U* and χ^2 tests. The effect of conservative oxygen therapy on the time to death was assessed using Kaplan-Meier analysis and the log-rank test. Patients discharged alive from the hospital were considered to have survived. In a post hoc analysis, we assessed the primary outcome in patients subgrouped by patient characteristics at study enrollment and their ICU length of stay. The relationship between oxygen exposure and ICU mortality was evaluated according to the quartile distribution of the median value of the daily ICU time-weighted Pao_2 values. Any association between Pao_2 quartiles and ICU mortality, occurrence of new organ failure and infection, and ventilation-free hours during the ICU stay were assessed by χ^2 and Cochrane-Armitage tests for trend.

Data are presented as mean (standard deviation) or as median with interquartile ranges (IQRs), unless otherwise indicated. The primary end point was confirmatory tested at a 2-sided significance level of α = .05. All other given *P* values are exploratory. SPSS version 20 was used for statistical analysis.

Results

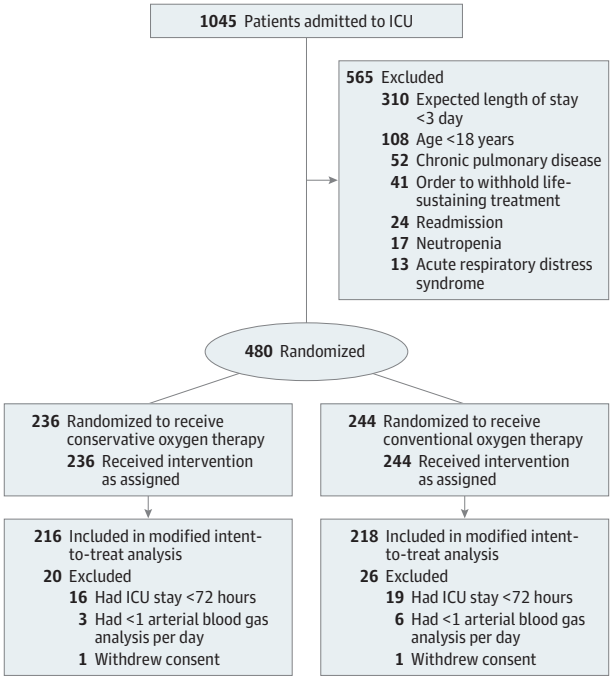
Patients

From March 1, 2010, to October 30, 2012, a total of 480 patients with an expected ICU stay of 72 hours or longer were randomized to conventional (n = 244) or conservative (n = 236) oxygen therapy groups. Forty-six patients were excluded because of withdrawal of consent (n = 2), lack of data during their ICU stay (n = 9), or ICU stay less than 72 hours (n = 35). Therefore, the modified intent-to-treat population included 218 in the conventional group and 216 patients in the conservative group (**Figure 1**). The median age, type of admission, preexisting disease, and clinical characteristics at baseline were similar between the 2 study groups (**Table 1**).

Oxygen Control

In the modified intent-to-treat population, the daily time-weighted Fio_2 and Pao_2 averages during ICU stay were higher in the conventional group (median Fio_2, 0.39 [IQR, 0.35-0.42]; median Pao_2, 102 mm Hg [IQR, 88-116]) than in patients managed conservatively (median Fio_2, 0.36 [IQR, 0.30-0.40]; median Pao_2, 87 mm Hg [IQR, 79-97]; $P < .001$) (eFigure 1 in Supplement 2). The number of arterial blood gas analyses

Figure 1. Patient Flow Diagram of the Oxygen-ICU Trial



ICU indicates intensive care unit.

Table 1. Characteristics of the Patients at Study Inclusion by Oxygen Therapy Group

	Oxygen Therapy Group, No. (%)	
	Conservative (n = 216)	Conventional (n = 218)
Sex, female	95 (44.0)	93 (42.7)
Age, median (IQR), y	63 (51-74)	65 (52-76)
Type of ICU admission		
Medical	77 (35.7)	86 (39.5)
Surgical	139 (64.3)	132 (60.7)
Preexisting condition		
Chronic obstructive pulmonary disease	7 (3.2)	11 (5.0)
Chronic renal failure	13 (6.0)	13 (6.0)
Chronic liver disease	28 (12.9)	31 (14.2)
Cancer	72 (33.3)	70 (31.1)
Respiratory failure	121 (56.0)	129 (59.2)
Mechanical ventilation	143 (66.2)	148 (67.9)
Shock	68 (31.4)	72 (33.0)
Septic	46 (21.3)	47 (21.6)
Hypovolemic or hemorrhagic	7 (3.2)	9 (4.1)
Cardiogenic	12 (5.6)	8 (3.7)
Mixed	3 (1.4)	8 (3.7)
Liver failure	40 (18.5)	45 (20.6)
Renal failure	32 (14.8)	35 (16.1)
Documented infections[a]	81 (37.5)	88 (40.4)
SAPS II, median (IQR) score[a]	37 (26-49)	39 (28-55)

Abbreviations: ICU, intensive care unit; IQR, interquartile range; SAPS, Simplified Acute Physiology Score.

[a] Documented infections: only microbiologically documented bloodstream and respiratory tract infections were considered. SAPS II is calculated from a point score of 12 routinely measured physiologic and biochemical variables within the first 24 hours of ICU admission. The range is 0 to 163 points, with more extreme values scoring more points.

with a PaO_2 value less than 70 mm Hg per patient during the ICU stay was similar (conventional: median, 1 [IQR, 0-2]; conservative: median, 1 [IQR, 0-2]), whereas the number of analyses with a PaO_2 value less than 100 mm Hg was significantly higher in the conventional group compared with the conservative group (median [IQR], 4 [2-7] vs 1 [0-3]); $P < .001$).

Outcome Data

In the modified intent-to-treat population, 25 patients in the conservative group (11.6%) died during their ICU stay compared with 44 who died in the conventional group (20.2%) (absolute risk reduction, 0.086 [95% CI, 0.017-0.150]; relative risk, 0.57 [95% CI, 0.37-0.90]; $P = .01$). Hospital mortality, not a prespecified outcome, was also lower in the conservative oxygen strategy group (24.2% vs 33.9%; absolute risk reduction, 0.099 [95% CI, 0.013-0.182]; relative risk, 0.71 [95% CI, 0.52-0.96]; $P = .03$) (**Table 2** and **Figure 2**).

No significant difference was observed between the 2 study groups with respect to the occurrence of new respiratory or renal failure, although the number of patients with a new shock episode (absolute risk reduction, 0.068 [95% CI, 0.020-0.120]; relative risk, 0.35 [95% CI, 0.16-0.75]; $P = .006$) and liver failure (absolute risk reduction, 0.046 [95% CI, 0.008-0.088]; relative risk, 0.29 [95% CI, 0.10-0.82]; $P = .02$) during their ICU stay was lower in the conservative group. Although the occurrence of new infections was similar between groups, the conservative oxygen strategy was associated with a lower risk for bloodstream infection (absolute risk reduction, 0.05 [95% CI, 0.00-0.09]; risk reduction, 0.50 [95% CI, 0.25-0.998; $P = .049$) and more hours free from mechanical ventilation (median difference 24 hours; $P = .02$) (Table 2).

The analysis of the intent-to-treat population, which included 478 patients, yielded results similar to those of the modified intent-to-treat analysis with respect to primary outcome, hospital mortality, and secondary outcomes (eTable 2; eFigure 4 in Supplement 2).

In the subgroup post hoc analysis, the conservative oxygen strategy reduced the risk for ICU mortality in patients with respiratory failure (absolute risk reduction, 0.05 [95% CI, 0.00-0.09]; relative risk, 0.67 [95% CI, 0.46-0.96]) who received mechanical ventilation at study enrollment (relative risk, 0.69; 95% CI, 0.49-0.98) or who had a length of stay less than the overall median (relative risk, 0.46; 95% CI, 0.21-0.98) (eTable 1 in Supplement 2).

Discussion

In this single-center randomized clinical trial in a medical-surgical population of adult critically ill patients, oxygen supplementation titrated to a more conservative oxygen

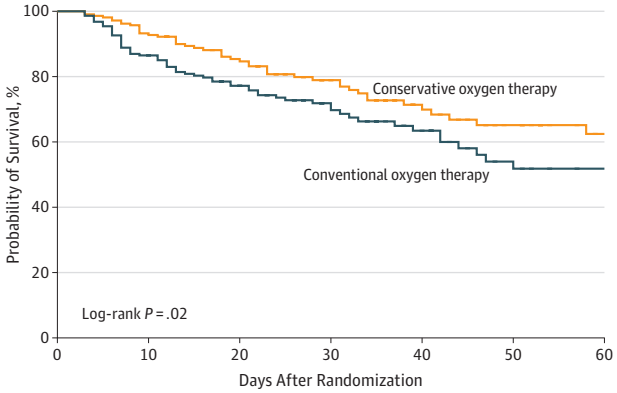
Table 2. Primary and Secondary Outcomes

	Oxygen Therapy, No. (%)			
	Conservative (n = 216)	Conventional (n = 218)	Absolute Risk Difference (95% CI)	*P* Value
Primary outcome				
ICU mortality	25 (11.6)	44 (20.2)	0.086 (0.017 to 0.150)	.01
Secondary outcomes				
Hospital mortality	52 (24.2)	74 (33.9)	0.099 (0.013 to 0.182)	.03
New organ failure during ICU stay	41 (19.0)	56 (25.7)	0.067 (−0.012 to 0.145)	.09
Respiratory failure	14 (6.5)	14 (6.4)	−0.126 (−0.189 to −0.064)	.98
Shock	8 (3.7)	23 (10.6)	0.068 (0.020 to 0.120)	.006
Liver failure	4 (1.9)	14 (6.4)	0.046 (0.008 to 0.088)	.02
Renal failure	26 (12.0)	21 (9.6)	−0.024 (−0.084 to 0.035)	.42
New infections during ICU stay	39 (18.1)	50 (22.9)	0.049 (−0.027 to 0.124)	.21
Respiratory	30 (13.9)	37 (17.0)	0.031 (−0.038 to 0.099)	.37
Bacteremia	11 (5.1)	22 (10.1)	0.050 (0.000 to 0.090)	.049
Surgical site[a]	10 (7.2)	12 (9.1)	0.019 (−0.048 to 0.088)	.68
Surgical revision[a]	18 (12.9)	16 (12.1)	−0.008 (−0.088 to 0.073)	.84
Mechanical ventilation–free hours, median (IQR)	72 (35 to 110)	48 (24 to 96)	24 (0 to 46)	.02
ICU length of stay, median (IQR), d	6 (4 to 10)	6 (4 to 11)	0 (0 to 2)	.33
Hospital length of stay, median (IQR), d	21 (13 to 38)	21 (12 to 34)	0 (−5 to 1)	.21

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

[a] Only in surgical patients (139 in the conservative group and 132 in the conventional group).

Figure 2. Probability of Survival From Study Inclusion (Day 0) Through Day 60 for Patients in the Conservative and Conventional Oxygen Strategy Groups



No. at risk

Conservative oxygen therapy	216	201	188	181	173	170	169
Conventional oxygen therapy	218	189	172	163	158	152	152

Patients discharged alive from the hospital were considered to have survived, and their median follow-up was 22 days for the conservative group (interquartile range, 13-37) and 24 days for the conventional group (interquartile range, 15-35).

saturation target (94%-98%) was associated with improved outcomes compared with conventional oxygen administration in which oxygen partial pressures were significantly higher. An absolute reduction of 8.6% was observed in the conservative oxygen group. To our knowledge, this is the first randomized clinical trial to evaluate the effect of a conservative oxygen therapy on mortality compared with a standard, more liberal approach in a medical-surgical population of adult critically ill patients. Furthermore, as previously observed,[15] our data revealed a U-shaped relationship between time-weighted Pao_2 values and mortality, with the highest mortality observed in patients exposed to an overall average time-weighted Pao_2 of 107 mm Hg or higher during their ICU stay.

Several observational studies demonstrated an association between arterial hyperoxia and increased mortality in different subsets of critically ill patients.[21] In accordance with our data, a recent prospective before-after study in mechanically ventilated patients showed that a conservative oxygen supplementation strategy was feasible, safe, and associated with a trend toward less nonrespiratory organ dysfunction and greater reduction of lactate levels.[22] Oxygen administration in the conservative group of this study was titrated to obtain Spo_2 values of 90% to 92%, lower than those used in our study (94%-98%), whereas the Spo_2 targets in the conventional group were similar.

In our trial, conservative oxygen administration was associated with new infections, mostly bacteremia, and fewer new episodes of shock. These findings may be explained by the possible detrimental effects of hyperoxia on the innate immune system. In vitro, exposure to short-term high levels

of normobaric hyperoxia (Fio_2 ≥80%) attenuates cytokine production by human leukocytes[23] and induces structural changes within alveolar macrophages, with a significant impairment of their antimicrobial activity and a marked reduction in the production of inflammatory cytokines in response to stimulation.[24,25] In an animal model of pneumonia, dissemination of infection within the lung and spleen, as well as mortality rates, increased significantly in mice exposed to normobaric hyperoxia compared with infected mice maintained in room air.[26] Similarly, in a cecal ligation and puncture model, rats subjected to higher inspired oxygen concentrations showed greater increases in reactive oxygen species production, serum IL-6 and IL-10 levels, and infected biological samples, suggesting a possible influence of hyperoxia on the inflammatory response and mechanisms of bacterial clearance.[27] In the above-cited models, the animals were exposed for a short time to considerably higher inspired oxygen levels than those used in our study. Human studies on the effects of hyperoxia on the immune system are scarce. In patients undergoing thyroid surgery, the postoperative levels of C-reactive protein, IL-6, and IL-1b were lower because of use of perioperative supplemental 80% Fio_2 rather than 30% Fio_2.[28] On the other hand, Kiers et al[29] recently observed that a short period of hyperoxia (3.5 hours; Fio_2 100%) does not influence whole blood cytokine production, neutrophil phagocytosis, or reactive oxygen species generation during an experimental murine and human endotoxemia.

Hyperoxia-induced pulmonary toxicity leads to histopathologic changes similar to those observed in acute respiratory distress syndrome and ventilator-induced lung injury.[30,31] However, in the present study, the occurrence of new respiratory failures did not differ between the 2 groups. The high percentage of patients with respiratory failure at study inclusion (58%) may have hampered the sensitivity of our study to this outcome. Nevertheless, patients assigned to the conservative group did show an increase in mechanical ventilation–free hours in comparison with those assigned to the conventional group, for whom excessive oxygen supplementation may have exacerbated the preexisting lung injury or hindered recovery. In addition, the post hoc analysis showed that the conservative strategy seemed to provide a significant reduction of ICU mortality risk in patients with respiratory failure who received mechanical ventilation at baseline (eTable 1 in Supplement 2). Our data do not allow further speculation on this hypothesis, which should be explored with appropriate study.

Several limitations must be acknowledged. This was a single-center open-label study, albeit of reasonable size, conducted in the ICU of a university hospital and stopped early for low inclusion rate because of difficulties with access to eligible patients. The unplanned early termination of the trial may have exaggerated the effect size. By assuming the same mortality observed, the estimation of study results had the trial continued to accrue patients until the planned size (330 patients per group) resulted in 95% CIs from 2% to 14%. Because the planned difference for futility of 6% was not entirely ruled out by these CIs, confirmation of effect and generalizability need to be tested by larger clinical trials. To avoid incomplete and uncertain data on the occurrence of new organ dysfunctions and infections during ICU stay, we used a modified intention-to-treat population for primary analysis, excluding patients with length of stay less than 72 hours and less than 1 arterial blood gas analysis per day. Nevertheless, the analysis of primary and secondary outcomes in the intention-to-treat population (478 patients) confirmed data observed in the modified intent-to-treat population (see eTable 2 and eFigure 4 in Supplement 2). The sample size did not allow a detailed analysis of the effects of hyperoxia in different population subsets; the modified intent-to-treat population included only 31 patients (6.9%) with cerebral stroke or traumatic brain injury and 19 (4.4%) with acute myocardial infarction. In addition, despite randomization, patients in the conventionally treated group tended toward higher illness severity at baseline. The Simplified Acute Physiology Score II and the percentage of patients who received mechanical ventilation, had shock, had documented infection, and had respiratory, liver, or renal failure were slightly larger in this group. This imbalance may have been responsible, at least in part, for the differences observed in ICU mortality. The use of daily time-weighted Pao_2 may be only an approximation of the true exposure to hyperoxia in patients for whom only 1 to 2 blood gas analyses were performed daily. As advised by our ethics committee, we did not perform more frequent Pao_2 assessments to avoid possible confounding introduced by changes in the standard of care rather than by different oxygen exposures. In addition, the incidence of new infection may have been underestimated because only those ascertained by microbiological samples were considered.

Conclusions

Among critically ill patients with an ICU length of stay of 72 hours or longer, a conservative protocol for oxygen therapy compared with conventional therapy resulted in a lower ICU mortality. However, these preliminary findings were based on unplanned early termination of the trial, and a larger multicenter trial is needed to evaluate the potential benefit of such conservative oxygen therapy in critically ill patients.

ARTICLE INFORMATION

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MAINTAINING A STRICT CONDITION OF NORMOXIA IN INTENSIVE CARE UNIT: RANDOMIZED CONTROLLED TRIAL

BACKGROUND

Oxygen therapy is commonly used in numerous pathological conditions and is essential in the treatment of patients with absolute or relative hypoxia. However, exposure to inhalation of oxygen-rich mixtures (hyperoxic) is recognized as a potential cause of organ damage as well as lung injury (1-4). In vitro and in vivo recent studies on animals and humans identify the mechanisms in which hyperoxia alters the normal cell physiology promoting: the formation of oxygen free radicals, activation of apoptotic pathways, the expression of pro and anti-inflammatory that lead to cell death, and altering the innate immunity by exposing to a higher risk for the development of infections (5-8).

A level or a duration of hyperoxia considered harmful is not determined for the onset of cellular insult as there are no clinical trials on humans that evaluate the appropriate percentage of oxygen considered safe to maintain an adequate tissue oxygen availability. In patients suffering from acute respiratory distress syndrome (ARDS) a number of volumetric and pressure parameters in the ventilation have been studied (9), leading however to the recommendation to use the smallest fraction of inspired oxygen for the maintenance of normoxia (10). Conflicting data have been published on the role of hyperoxia in the onset of postoperative nausea and vomiting, the normalization of oxidative metabolism in patients with brain trauma or stroke, in preconditioning of the ischemia-reperfusion injury in cardiac surgery and the onset of the infection site surgery (SSI) (11-18). The use of oxygen in intensive care unit (ICU) is quite variable and, despite being spread some concern about its possible toxicity, the administration is not regulated, as was demonstrated by a recent Canadian survey in ICUs (19). The toxicity of hyperoxia in patients undergoing mechanical ventilation was the subject of a retrospective study of a recent Dutch study, in which inspiratory fractions of oxygen and high PaO2 values were associated with a higher mortality in ICU (20). However, no prospective clinical trials have evaluated the degree of oxygenation to maintain or the effects of hyperoxia in critically ill patients admitted to ICU (ventilated and not). The frequency of the effects of hyperoxia at the clinical level, although it has been studied in vitro and in healthy volunteers, is therefore not known.

A recent publication describes in detail the mechanisms in which hyperoxia exerts its harmful effects and concludes that the amount of oxygen to be administered should be as low as possible with the aim of preserving tissue oxygenation and calls for a clinical study in order to examine a "hypoxia permissive" or a conservative approach to the administration of oxygen to limit the adverse effects (21).

Following the example of a recent trial (22), the purpose of this study is to assess whether, in critically ill patients, the maintenance of a state of normoxia determine better outcomes in terms of mortality, incidence of organ failure and outbreaks of infections compared to the state of hyper-oxygenation obtained through the conventional oxygen strategy.

MAIN OBJECTIVES

The primary objective of the study is to evaluate if the maintenance of a 'strict' state of normoxia in critical patients, avoiding hyperoxic and hypoxic phases, can result in a reduction of mortality in ICU. Mortality will be assessed for both groups as the number of deaths from any cause that will occur during the ICU stay.

SECONDARY OBJECTIVES

The secondary objectives of the study is to evaluate if the maintenance of a 'strict' state of normoxia in critical patients, avoiding hyperoxic and hypoxic phases, determines:

- a reduction in the onset of organ failure (respiratory, cardiovascular, renal and hepatic) in intensive care

- a reduction in the occurrence of infections in ICU (lung, blood) or in hospital (surgical site). Only microbiologically documented bloodstream and respiratory tract infections were considered.

TYPE, PHASE, SIZE OF THE STUDY

The oxygen is a drug widely used in current clinical practice for decades, so it is a Phase IV to evaluate the safety and efficacy of the therapeutic use of this medical gas. The study is single-blind because, after the explanation of the protocol for the informed consent, the patient will not be informed about the doses of oxygen administered and criteria of administration applied, thus ignoring the group of enrolment. Assuming a two-sided alpha level of <0.05 and a power of 80%, we calculated that 330 patients are needed per arm to detect an absolute mortality reduction of 8.0% (relative risk reduction of 40%) compared to 20% mortality observed in patients hospitalized in intensive care for at least three days in 2007.

OPERATING PROTOCOL

Inclusion Criteria

Criteria for Inclusion in the study contemplate enrolment of all patients admitted in the surgical ICU (TIPO) of the Policlinico of Modena in the study period from 01/12/2009 to 30/11/2011 for which an ICU length of stay (LOS) of at least 3 days was estimated, after obtaining informed consent from the patient or after informing family members if the person concerned is unable to provide it (patients in metabolic coma, post-anoxic coma, traumatic coma or coma induced pharmacologically).

Exclusion Criteria

- patients aged under 18 years,
- patients discharged from the ICU and then re-entered during the study period
- patients enrolled in other prospective studies
- patients with life expectancy of less than 24 hours.

Randomization and group management

On admission, eligible patients will be randomly assigned (by the use of a computerized random number generator in a 1:1 ratio) to a group of liberal conventional oxygen (A) or a group of conservative experimental oxygen (B).

Within the group A patients will receive a fraction of inspired oxygen (FiO2) aiming to maintain a peripheral oxygen saturation (SpO2) above 97%, accepting an upper limit of partial pressure of arterial oxygen (PaO2) of 150 mmHg and a lower limit of 60 mmHg. The blood gas analysis (BGA) control will be taken according to clinical indication. Similarly the decision to Non Invasive Ventilation or intubation and mechanical ventilation will be dictated by common clinical criteria. Consistent with our standard ICU practice, control patients received an FiO_2 of 1.0 during endotracheal intubation, airway suction or hospital transfer.

Patients in Group B will receive a FiO2 established to maintain SpO2 between 94 and 98%, or possibly a PaO2 above 70 mmHg and still less than 100 mmHg. BGA controls will be performed as clinically indicated. It will be given a supplementation of oxygen only if the SpO2 falls below 94%, while the pre-oxygenation at 100% will not be performed during transport or in anticipation of diagnostic and therapeutic manoeuvres, as above. The clinical criteria will dictate the need: to obtain artificially airway control and to guide the choice about the mode of ventilatory support.

Culture test will be performed on patients as clinically indicated during ICU stay and wards transfer. ICU criteria for diagnosis of infections will adhere to agreed definitions in the reference document drawn up in May 2009 by the Regional Health Agency (23). It will be considered positive for respiratory infections evidence of microbial organisms with more than 1000000 colony forming units (CFU) per millilitre in the case of tracheal aspirates and 10000 CFU/ml in the case of bronchial alveolar lavage. The positive for bacteremia and/or infections related to vascular catheter will be evaluated by blood cultures from peripheral

blood and central venous catheter site if at least in site from 48 hours. The evaluation for surgical site infections will be performed in accordance with standards to date by the CDC in 2009 (24).

Data to be collected in the Case Report Form (CRF)

At the entrance to the ward will be recorded on a special case report form (CRF) (see appendix 1) demographic information (gender, age) and those related to the disease that resulted in the ICU admission, and co-morbidities, history of cancer or kidney failure who determined the severity of the clinical picture, also quantified by the Simplified Acute Physiology Score II (SAPS II) scoring. Data collection will be completed with the acquisition of information about ICU admission regarding the input mode of admission (emergency or programmed), the type of ICU admission (medical, elective surgery, emergency surgery), type of specialized surgery which underwent the study patients, the disease developed during ICU stay, ICU new onset organ failure, type of practice used and duration of their application.

The CRF also provides for the collection of values of PaO2 and FiO2 for each patient at least once a day, where we will get the PaO2/FiO2 ratio required for the definition of respiratory failure. It will also annotated during ICU stay: the duration of ventilatory support in hours, the use of vasoactive amines, the increase of creatinine (> 2.5 mg/dL) and bilirubin (> 4 mg/dl) and use Renal replacement therapy (haemodialysis, continuous veno-venous hemofiltration) subsequent to the first 24 hours of ICU stay, the occurrence of respiratory infections, blood and surgical site developed after 48 hours after ICU admission, ICU LOS and hospital LOS. The primary outcome will be assessed on the basis of all-cause mortality in the ICU. In view of the fact that patients are exposed to the protocol of oxygen only during the ICU stay, and not in the next period of hospitalization in ordinary wards of the hospital (during which the use of oxygen remains quite liberal and at the discretion of the clinical department) or even less at home, it was decided not to extend the monitoring of the survival period after the ICU stay.

Statistical analysis

The assessment of the primary endpoint will be made in the intention-to-treat manner. It intends to make an interim analysis at 12 months (30/11/2010) and then the final analysis at the end of the enrolment period (30/11/2011). Mortality will be assessed for both groups as the number of deaths from any cause that will occur during the ICU stay. The onset of organ failure will be evaluated as a number of new organ failure occurring during hospitalization in ICU. The differences within the groups will be conducted through $\chi 2$ test.

Data ownership and publication

Considering that the aim of the study proposed is to improve the knowledge of the oxygen, the effects of oxygen therapy in critically ill patients and the risk-benefit ratio resulting from the administration of oxygen to patients admitted to intensive care, and that the patients will have freely joined in the belief that the results will be useful for the improvement of care for the diseases from which they are suffering, the investigator agrees on the need to ensure wider publication and dissemination of data in a consistent and responsible way.

Therefore, the promoter of the trial, even under Circ. Min. Health No. 6 of 09.02.02, is obliged to make public the results of the study within 12 months of its completion.

The investigator has the right to present the methods and results of the study at symposia and conferences, and to publish the methods and results of the study and other documents related to the study in scientific journals, theses, dissertations or other publications or presentations.

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ICU PROTOCOL and NURSE ORDER SET

1) ICU ADMISSION

- Complete Inclusion and exclusion criteria check list
- Attribution patient to group A (conventional) or B (restrictive) according to sequential table (table hanging on the closet of the ICU)
- Collect informed consent and place it in the pan on the counter dedicated.
- Write on therapy form (voice O2 therapy): A (conventional); B (restrictive)

2) TREATMENT

Group A - Conventional

- FiO2 established to maintain SaO2 (SpO2) 97-100%
- EGA as clinically indicated
- Upper limit accepted PaO2: 150 mmHg
- Suctioning, bronchoscopy, transport, other manoeuvres: pre-oxygenation and 100% O2 during manoeuvres or as clinically indicated
- Possible intubation or NIV according clinical criteria

Group B – Restrictive

- FiO2 established to maintain SpO2 between 94-98% or PaO 2 less than 100 mmHg and, where possible, higher-than 70 mmHg
- increase FiO2 to SpO2 <94%; reduce FiO2 to SpO2> 98%-
- Suctioning, bronchoscopy, transport, other manoeuvres: no pre-oxygenation and 100% O2 during manoeuvres. Intervene with supplemental O2 if SpO2 <94% as clinically indicated
- Possible intubation or NIV according with clinical criteria

Oxygen-ICU

CASE REPORT FORM

Name and Surname	Nosological Code	Group and number of randomization	ICU admission date	Reason for ICU admission

Gender	Age	SAPS II	Type of ICU admission	Medical History
			☐ medical ☐ elective surgery ☐ emergency surgery	☐ cancer ☐ cardiac disease ☐ Other ……

Date/hour	PaO2	FiO2	MV	Amines	urea/creat	CVVH/dialysis	Bilirubine

242

Respiratory infections in ICU	Bloodstream infections in ICU	Surgical site infections	
		In ICU	In ward
date	date	date	date
date	date	date	date
date	date	date	date

243

Date of ICU discharge	Alive/Dead	Date of hospital discharge	Alive/Dead

244

245

NOTES

246

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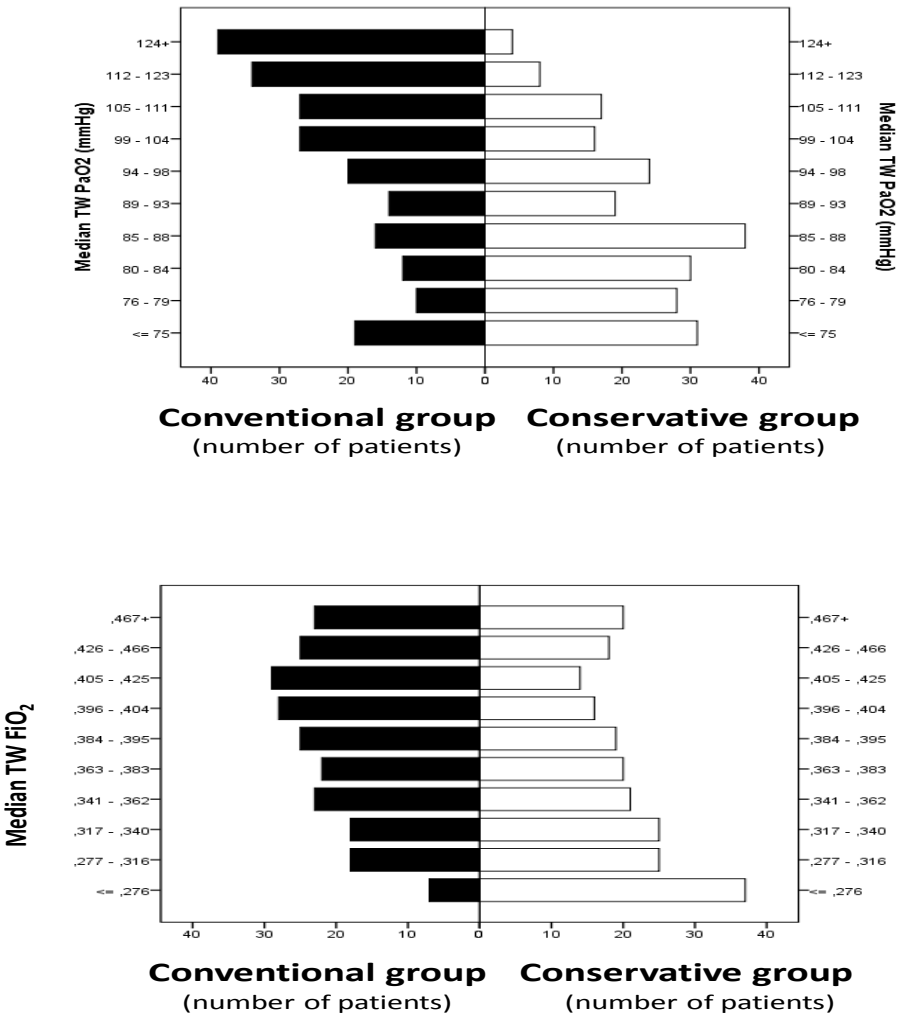
Supplementary Online Content

Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the Oxygen-ICU randomized clinical trial. *JAMA*. doi:10.1001/jama.2016.11993

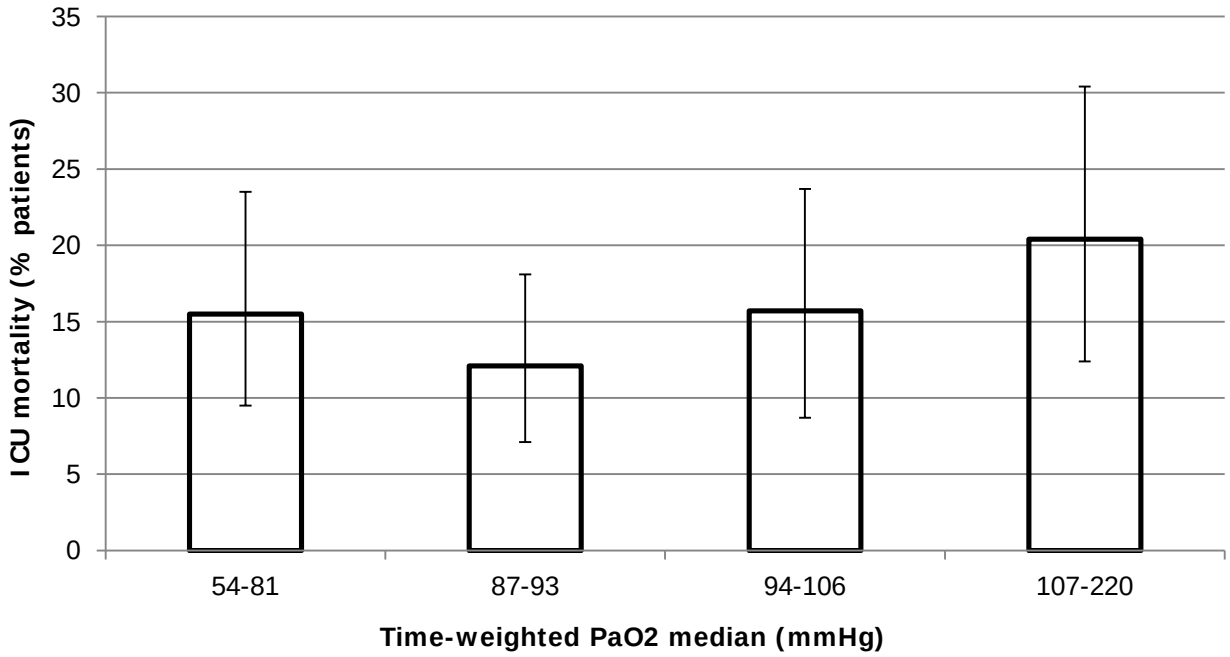
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1: Distribution of median daily time-weighted PaO_2 (TWPaO2, upper panel) and FiO_2 (TWFiO2, lower panel) averaged across the patients' ICU stay in conventional (218 patients, black bars) and conservative group (216 patients, white bars).



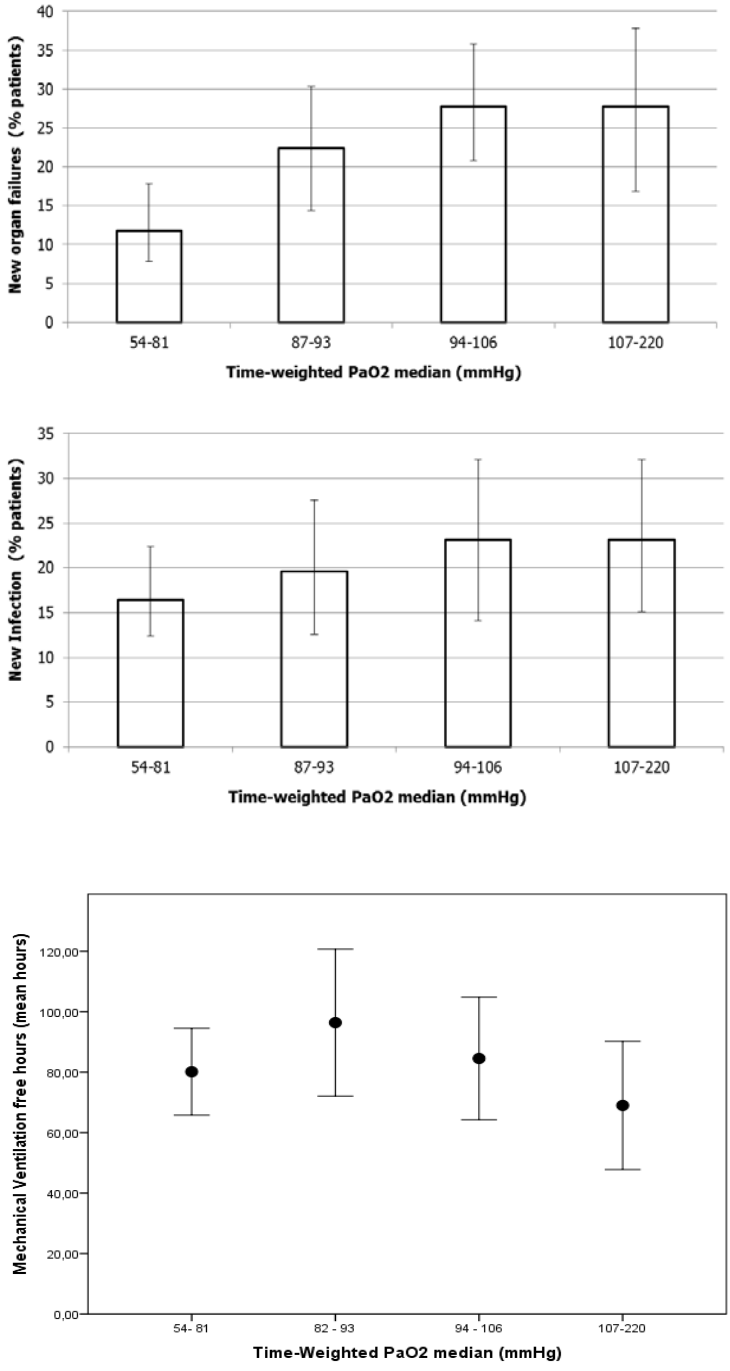
The median TWPaO2 and TWFiO2 were categorized according to their deciles distribution in the studied populations.

eFigure 2: Intensive care mortality (ICU mortality) by quartile distribution of the median daily time-weighted PaO_2 averages across the patients' ICU stay. X-axis categories: quartile range for the daily time-weighted median PaO_2.



Error bars indicate 95%CI. P>0,05 by Cochrane-Armitage test for trend. Number of patients for each quartile: <= 81 mmHg, n 110; 87 mmHg, n= 108; 100 mmHg, n =108; 108+ mmHg, n= 108. Median values for each quartile are 75, 87, 100 and 123 mmHg

eFigure 3: New organ failure (upper panel), new infections (middle panel), mechanical ventilation free-hours (lower panel) according to quartile distribution of median values of the daily time-weighted averages PaO_2 across the patients' ICU stay.



X-axis categories: quartile range for the daily time-weighted median PaO_2. Error bars indicate 95%CI. P>0,05 by Cochrane-Armitage test for trend. Number of patients for each quartile: <= 81 mmHg, n 110; 87 mmHg, n= 108; 100 mmHg, n =108; 108+ mmHg, n= 108. Median values for each quartile are 75, 87, 100 and 123 mmHg

eTable 1. *Post-hoc* analysis of ICU mortality in patients sub-grouped by patient characteristics at study enrolment and their ICU length of stay

	Conservative O2 therapy N = 216	**ConventionalO2 therapy N = 218**	**Absolute risk reduction (95% CI)**	**P value**
SAPS, no. (%)*				
≤ 38	3/117 (2.6)	6/104 (5.8)	3.2 (-2.4 – 9.7)	0.23
>38	22/99 (22.2)	38/114 (33.3)	11-1 (-1.0 – 22.6)	0.072
Type of ICU admission, no. (%)				
medical	18/77 (23.4)	30/86 (34.9)	11.5 (-2.5 – 24.8)	0.086
surgical	7/139 (5.0)	14/132 (10.6)	5.6 (-0.9 – 12.5)	0.086
Respiratory failure at admission, no. (%)	21/121 (17.4)	39/129 (30.2)	12.8 (2.3 – 23.0)	0.017
Mechanical Ventilation at admission, no. (%)	23/143 (16.1)	40/148 (27.0)	10.9 (1.5 – 20.2)	0.023
Shock at admission, no. (%)	20/68 (29.4)	27/72 (37.5)	8.1 (-7.5 – 23.0)	0.31
Liver failure at admission, no. (%)	9/40 (22.5)	15/45 (33.3)	10.8 (-8.4 – 28.6)	0.266
Renal failure at admission, no. (%)	8/32 (25.0)	16/35 (45.7)	20.7 (-2.2 – 40.6)	0.077
Documented infections at admission, no. (%)	22/81 (27.2)	26/88 (29.5)	2.3 (-11.2 – 15.7)	0.73
ICU length of stay, no. (%) *				
≤ 6 days	5/120 (4.2)	15/110 (13.6)	9.4 (2.2– 14.2)	0.011
> 6 days	20/96 (20.8)	29/108 (26.9)	6.1 (-5.8 – 17.4)	0.314

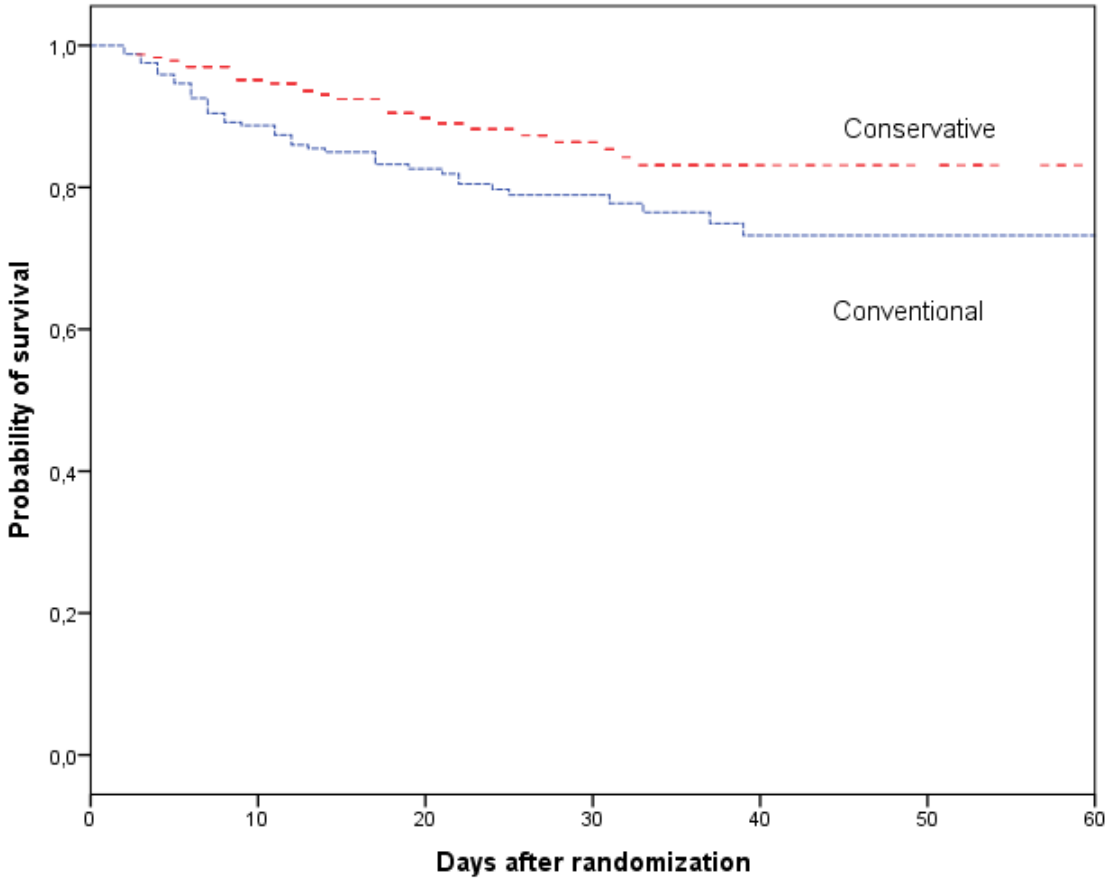
Simplified Acute Physiology Score (SAPS) II ; * Thirty-eight is the overall median value of SAPS II; Six days was the overall median for ICU length of stay

eTable 2- Outcomes for intention to treat population n = 478. The analysis includes all the randomized patients (n =480) but 2 patients with consent withdrawal.

	Conservative O2 therapy N =235	**ConventionalO2 therapy N =243**	**Absolute risk reduction (95% CI)**	**P value**
ICU mortality, no. (%)	27/235 (11,5)	49/243 (20,2)	0.087 (0,021 – 0,152)	0.009
Hospital mortality, no. (%)	58/235 (24,7)	80/243 (32,9)	0.082 (0,000 – 0,161)	0.047
New organ failure during ICU stay, no. (%)§	42/220 (19.1)	58/225 (25.8)	0.067 (-0.011 – 0.144)	0.091
Respiratory failure §	14/220 (6.4)	16/225 (7.1)	0.008 (-0.041 – 0.056)	0.75
Shock	8/220 (3.6)	24/225 (10.7)	0.070 (0.023 – 0.121)	0.004
Liver failure	4/220 (1.8)	15/225 (6.7)	0.049 (0.011 – 0.090)	0.011
Renal failure	27/220 (12.3)	22/225 (9.8)	-0.25 (-0.084 – 0.034)	0.40
New Infections during ICU stay, no. (%)§	40/220 (18.2)	52/225 (23.1)	0.049 (-0.026 – 0.124)	0.20
Respiratory	30/220 (13.6)	37/225 (16.4)	0.028 (-0.039 – 0.095)	0.41
Bacteremia	11/220 (5.0)	22/225 (9.8)	0.048 (-0.002 – 0.099)	0.054
Surgical Site*	11/142 (7.7)	12/136 (8.8)	0.012 (-0.071 – 0.049)	0.71
Surgical revision, no. (%)*	18/142 (12.7)	17/136 (12.5)	-0.002 (-0.076 – 0.074)	0,96
Mechanical ventilation free-hours, median (IQR)	68 (24-96)	48 (24-96)	20 (0 – 32)	0.018
ICU length of stay, days- median (IQR)	5 (3-10)	6 (4-11)	- 1 (-2 – 0)	0.60
Hospital length of stay,, days- median (IQR)	21 (13-37)	21 (12-33)	0 (-4 – 1)	0.27

Abbreviations: IQR, interquartile range, § only in patients with a ICU stay ≥48 hours (220 in in O_2 conservative group and 225 in O_2 liberal group), * only in surgical patients (142 in O_2 conservative group and 136 in O_2 liberal group).

eFigure 4: Probability of survival from study inclusion through day 60 for intention to treat population n = 478.



Conservative	235	217	201	194	186	183	182
Conventional	243	211	192	183	177	171	166

The analysis includes all the randomized patients (n =480) but 2 patients with consent withdrawal.