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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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 PaO2 between 70 and 100 mm Hg or arterial oxyhemoglobin saturation (SpO2) between 94% and 98% (conservative group) or, according to standard ICU practice, to allow PaO2 values up to 150 mm Hg or SpO2 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 PaO2 averages during the ICU stay were significantly higher (P < .001) in the conventional group (median PaO2, 102 mm Hg [IQR, 88-116]) vs the conservative group (median PaO2, 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.

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<tr>
<th>Oxygen Therapy, No. (%)</th>
<th>Absolute Risk Reduction (95% CI)</th>
<th>P Value</th>
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<tr>
<td></td>
<td>Conservative (n = 216)</td>
<td>Conventional (n = 218)</td>
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<tr>
<td>Primary outcome</td>
<td>25 (11.6)</td>
<td>44 (20.2)</td>
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<td>ICU mortality</td>
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<td>Shock</td>
<td>8 (3.7)</td>
<td>23 (10.6)</td>
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<td>Liver failure</td>
<td>4 (1.9)</td>
<td>14 (6.4)</td>
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<tr>
<td>Bacteremia</td>
<td>11 (5.1)</td>
<td>22 (10.1)</td>
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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 PaO₂ or arterial oxyhemoglobin saturations (SaO₂) 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 vasoconstriction⁶ 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 (FiO₂) 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 PaO₂ being frequently achieved.¹³ Recent observational studies highlight that intensive care unit (ICU) patients are often managed with an excess of FiO₂ and are hyperoxic for substantial periods.¹⁴⁻¹⁵

Although a controlled arterial oxygenation strategy appears rational,¹⁶ 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 PaO₂ within physiologic limits could improve outcomes in critically ill ICU patients.

**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 PaO₂/FiO₂ 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 FiO₂ of at least 0.4, allowing PaO₂ values up to 150 mm Hg and an SpO₂ between 97% and 100%. If the SpO₂ decreased below 95% to 97%, the FiO₂ was increased to reach the target value of SpO₂.

In the protocol group, oxygen therapy was administered at the lowest possible FiO₂ to maintain the PaO₂ between 70 and 100 mm Hg or SpO₂ values between 94% and 98%. Alterations in FiO₂ were completed according to a nurse order set. In particular, the FiO₂ was gradually reduced or oxygen supplementation discontinued whenever the PaO₂ or SpO₂ exceeded 100 mm Hg or 98%, respectively. Consistent with our standard ICU practice, control patients received an FiO₂ of 1.0 during intubation, airway suction, or hospital transfer. In protocol patients, supplemental oxygen was administered only if SpO₂ 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.

**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.
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 FiO2 and PaO2 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 FiO2 and PaO2 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 PaO2 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 admission17-19, need for reoperation in surgical patients; and bloodstream, respiratory, and surgical site infections (defined according to Centers for Disease Control and Prevention definitions20). 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 560 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-treatment 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-treatment population, which included all randomized patients, excluding those who withdrew consent. Baseline and outcome variables were compared with Mann-Whitney U and χ² 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 PaO2 values. Any association between PaO2 quartiles and ICU mortality, occurrence of new organ failure and infection, and ventilation-free hours during the ICU stay were assessed by χ² 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-treatment population, the daily time-weighted FiO2 and PaO2 averages during ICU stay were higher in the conventional group (median FiO2, 0.39 [IQR, 0.35-0.42]; median PaO2, 102 mm Hg [IQR, 88-116]) than in patients managed conservatively (median FiO2, 0.36 [IQR, 0.30-0.40]; median PaO2, 87 mm Hg [IQR, 79-97]; P < .001) (eFigure 1 in Supplement 2). The number of arterial blood gas analyses...
with a PaO₂ 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 PaO₂ value less than 100 mm Hg was significantly higher in the conservative group compared with the conventional 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, 0.086 [95% CI, 0.017-0.150]; relative risk, 0.35 [95% CI, 0.16-0.75]; P = .01). 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).

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 infections (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

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...
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 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, our data revealed a U-shaped relationship between time-weighted PaO2 values and mortality, with the highest mortality observed in patients exposed to an overall average time-weighted PaO2 of 107 mmHg 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. 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. Oxygen administration in the conservative group of this study was titrated to obtain SpO2 values of 90% to 92%, lower than those used in our study (94%-98%), whereas the SpO2 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

Table 2. Primary and Secondary Outcomes

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<tr>
<th>Oxygen Therapy, No. (%)</th>
<th>Absolute Risk Difference (95% CI)</th>
<th>P Value</th>
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<tr>
<td>Primary outcome</td>
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<tr>
<td>ICU mortality</td>
<td>Conservative (n = 216)</td>
<td>0.086 (0.017 to 0.150)</td>
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<td></td>
<td>Conventional (n = 218)</td>
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<td>Secondary outcomes</td>
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<tr>
<td>Hospital mortality</td>
<td>Conservative (n = 216)</td>
<td>0.099 (0.013 to 0.182)</td>
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<td>Conventional (n = 218)</td>
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<td>New organ failure during ICU stay</td>
<td>Conservative (n = 216)</td>
<td>0.067 (-0.012 to 0.145)</td>
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<td>Conventional (n = 218)</td>
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<td>Respiratory failure</td>
<td>Conservative (n = 216)</td>
<td>-0.126 (-0.189 to -0.064)</td>
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<td>Conventional (n = 218)</td>
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<td>Shock</td>
<td>Conservative (n = 216)</td>
<td>0.068 (0.020 to 0.120)</td>
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<td>Conventional (n = 218)</td>
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<td>Liver failure</td>
<td>Conservative (n = 216)</td>
<td>0.046 (0.008 to 0.088)</td>
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<td>Conventional (n = 218)</td>
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<td>Renal failure</td>
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<td>-0.024 (-0.084 to 0.035)</td>
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<td>Conventional (n = 218)</td>
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<td>New infections during ICU stay</td>
<td>Conservative (n = 216)</td>
<td>0.049 (-0.027 to 0.124)</td>
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<td>Conventional (n = 218)</td>
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<tr>
<td>Respiratory failure</td>
<td>Conservative (n = 216)</td>
<td>0.031 (-0.038 to 0.099)</td>
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<td>Bacteremia</td>
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<td>0.050 (0.000 to 0.090)</td>
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<td>Surgical sitea</td>
<td>Conservative (n = 216)</td>
<td>0.019 (-0.048 to 0.088)</td>
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<td>Conventional (n = 218)</td>
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<td>Surgical revisiona</td>
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<td>-0.008 (-0.088 to 0.073)</td>
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<td>Conventional (n = 218)</td>
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<td>Mechanical ventilation–free hours, median (IQR)</td>
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<td></td>
<td>Conventional (n = 218)</td>
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<td>ICU length of stay, median (IQR), d</td>
<td>Conservative (n = 216)</td>
<td>6 (4 to 11)</td>
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<td></td>
<td>Conventional (n = 218)</td>
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<td>Hospital length of stay, median (IQR), d</td>
<td>Conservative (n = 216)</td>
<td>21 (13 to 34)</td>
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<td>Conventional (n = 218)</td>
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Abbreviations: ICU, intensive care unit; IQR, interquartile range.

* Only in surgical patients (139 in the conservative group and 132 in the conventional group).
of normobaric hyperoxia (FiO₂ ≥80%) attenuates cytokine production by human leukocytes 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. 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. 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. 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-1β were lower because of use of perioperative supplemental 80% FiO₂ rather than 30% FiO₂. On the other hand, Kiers et al recently observed that a short period of hyperoxia (3.5 hours; FiO₂ 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. 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 PaO₂ 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 PaO₂ 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.
Conservative vs Conventional Oxygen and ICU Mortality

Preliminary Communication Research

Authors.

Administrative, technical, or material support: Donati, Rinaldi.

Statistical analysis: Antonelli, Singer.

Critical revision of the manuscript for important contributions: Martani, Mariani, and Buoncristiano.

Acquisition, analysis, or interpretation of data: Buoncristiano, Marudi, and Morelli.

No additional contributions: Marudi, Morelli, Singer.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Singer reported serving as the data monitoring chair for a phase 2 study sponsored by InflaRx, on the antibiotic advisory board for Bayer, and on sepsis advisory boards for Bioteck and Merck. No other disclosures were reported.

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REFERENCES


