ORIGINAL ARTICLE

Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome

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ABSTRACT

BACKGROUND

In patients with acute respiratory distress syndrome (ARDS), the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network recommends a target partial pressure of arterial oxygen (Pao_2) between 55 and 80 mm Hg. Prospective validation of this range in patients with ARDS is lacking. We hypothesized that targeting the lower limit of this range would improve outcomes in patients with ARDS.

METHODS

In this multicenter, randomized trial, we assigned patients with ARDS to receive either conservative oxygen therapy (target Pao_2, 55 to 70 mm Hg; oxygen saturation as measured by pulse oximetry [Spo_2], 88 to 92%) or liberal oxygen therapy (target Pao_2, 90 to 105 mm Hg; Spo_2, ≥96%) for 7 days. The same mechanical-ventilation strategies were used in both groups. The primary outcome was death from any cause at 28 days.

RESULTS

After the enrollment of 205 patients, the trial was prematurely stopped by the data and safety monitoring board because of safety concerns and a low likelihood of a significant difference between the two groups in the primary outcome. Four patients who did not meet the eligibility criteria were excluded. At day 28, a total of 34 of 99 patients (34.3%) in the conservative-oxygen group and 27 of 102 patients (26.5%) in the liberal-oxygen group had died (difference, 7.8 percentage points; 95% confidence interval [CI], −4.8 to 20.6). At day 90, 44.4% of the patients in the conservative-oxygen group and 30.4% of the patients in the liberal-oxygen group had died (difference, 14.0 percentage points; 95% CI, 0.7 to 27.2). Five mesenteric ischemic events occurred in the conservative-oxygen group.

CONCLUSIONS

Among patients with ARDS, early exposure to a conservative-oxygenation strategy with a Pao_2 between 55 and 70 mm Hg did not increase survival at 28 days. (Funded by the French Ministry of Health; LOCO$_2$ ClinicalTrials.gov number, NCT02713451.)

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Acute respiratory distress syndrome (ARDS) is a common problem in patients who are admitted to the intensive care unit (ICU).[1] In most patients with ARDS, high levels of inspired oxygen are warranted in order to maintain adequate oxygenation.[2,3] In the LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) study, patients underwent ventilation on day 1 with a median fraction of inspired oxygen (F_{IO_2}) of 0.6 (interquartile range, 0.45 to 0.85) and a median oxygen saturation as measured by pulse oximetry (S_{PO_2}) of 96% (interquartile range, 93 to 98). Overall mortality at 28 days remained high, at 30 to 40%, depending on the severity of respiratory failure.[4]

Goals for arterial oxygenation do not rely on robust interventional experimental data. A conservative-oxygenation strategy was tested in a before–after study involving more than 15,000 patients in the ICU; this study showed the feasibility of this strategy, with an overall reduction of the median partial pressure of arterial oxygen (P_{AO_2}) from 87 mm Hg (interquartile range, 74 to 107) to 76 mm Hg (67 to 89). The strategy was deemed by the investigators to be safe with respect to mortality in the ICU and the hospital.[5] To provide additional data, we conducted the $LOCO_2$ (Liberal Oxygenation versus Conservative Oxygenation in Acute Respiratory Distress Syndrome) trial, a prospective, multicenter, randomized, open-label trial involving patients with ARDS, to determine whether conservative oxygenation, as compared with the usual liberal-oxygen strategy, would reduce mortality at 28 days among patients who received these therapies early in the course of ARDS.

Methods

Trial Oversight

The investigator-initiated $LOCO_2$ trial was conducted in 13 ICUs in France from June 2016 through September 2018. The trial, which was designed and overseen by a steering committee, was funded by a grant from the French Ministry of Health, with additional oversight by the University Hospital of Besançon. The funder had no influence on the trial design, the collection or analysis of the data, or the writing of the manuscript; no commercial support was provided for this trial.

The trial protocol and the statistical analysis plan, available with the full text of this article at NEJM.org, were approved for all centers by the ethics committee of Besançon-Est II (Comité de Protection des Personnes Est II) according to French law. The trial was monitored by an independent data and safety monitoring board that planned to meet at the beginning of the trial and after the enrollment of 50 patients, 200 patients, and then every 200 patients or at the sponsor's request. The data and safety monitoring board was informed of all serious adverse events, and data were provided by the safety monitoring team. The steering committee vouches for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Patients

Patients were eligible for enrollment if they had undergone intubation and had been receiving mechanical ventilation for less than 12 hours for ARDS (defined according to the Berlin definition),[1] with a ratio of P_{AO_2} to F_{IO_2} (P_{AO_2}:F_{IO_2}) of 300 mm Hg or less, at a positive end-expiratory pressure (PEEP) of 5 cm of water or more, less than 7 days between a known clinical insult (i.e., lung damage) and new or worsening respiratory symptoms, and if they had bilateral opacities on chest imaging and respiratory failure that was not fully explained by heart failure or fluid overload. The main exclusion criteria were the use of long-term oxygen therapy or noninvasive ventilation at home and cardiac arrest, traumatic brain injury, or cranial hypertension as the reason for hospitalization in the ICU. Further details are available in Section 2a in the Supplementary Appendix, available at NEJM.org.

If patients were unable to provide written informed consent, information was given to their next of kin and patients were included with the use of emergency consent procedures. A definitive post hoc consent was obtained from all the patients. This procedure was accepted by the ethics committee because of the short time window between intubation and inclusion.

Trial Procedures

Randomization was stratified according to center, age (<45 years, 45 to 65 years, or >65 years), and severity of respiratory failure evaluated according to the P_{AO_2}:F_{IO_2} (≤150 mm Hg or >150 mm Hg), with a PEEP of 5 cm of water and a F_{IO_2}

of 60 to 100%. Computer randomization was performed in blocks of four. This was an open-label trial because of the impossibility of masking treatment assignments with the use of Spo_2 and Pao_2 monitoring in the ICU.

Patients were assigned to either the liberal-oxygen group (Pao_2 target between 90 and 105 mm Hg) or the conservative-oxygen group (Pao_2 target between 55 and 70 mm Hg) over the first 7 days of invasive mechanical ventilation or until extubation, if the latter was performed earlier. During the 6-hour interval between the two measurements of levels of arterial blood gases, the Spo_2 was maintained at a level of at least 96% in the liberal-oxygen group and between 88 and 92% in the conservative-oxygen group. If the Pao_2 was not within the predefined range according to the levels of arterial blood gases, the Fio_2 was modified by 0.05 (absolute value) if the difference from the assigned target was less than 5 mm Hg and by 0.10 if the difference was greater. When the level of arterial blood gases was measured, the pulse oximetry was compared with the arterial oxygen saturation (Sao_2) to adapt Spo_2 monitoring. During the 6-hour interval between the two measurements of levels of arterial blood gases, the Fio_2 was modified by 0.05 (absolute value) every 5 minutes until the desired Spo_2 target was reached.

In the case of an intervention such as fibroscopy or patient transport for imaging or to the operating room, oxygenation was managed at the discretion of the clinician. We recommended following the protocol as far as possible and returning to the protocol as soon as possible. No transient elevation in the Fio_2 was systematically performed during tracheal suctioning.

VENTILATION AND WEANING PROTOCOL

The volume assist–control mode of ventilation was recommended, with a tidal volume of 6 ml per kilogram of predicted body weight (Section 2b in the Supplementary Appendix). The PEEP was adjusted according to the Pao_2:Fio_2. If the Pao_2:Fio_2 was between 200 and 300 mm Hg, the PEEP was set to between 5 and 10 cm of water. If the Pao_2:Fio_2 was less than 200 mm Hg, the PEEP was set at the maximal value to reach a plateau pressure of 28 to 30 cm of water after setting a tidal volume at 6 ml per kilogram of predicted body weight. The PEEP was adjusted to between 5 and 10 cm of water if the Pao_2:FiO_2 remained at 200 mm Hg or higher for 12 hours.[6]

Neuromuscular blocking agents were recommended for 48 hours in patients with a Pao_2:Fio_2 of less than 150 mm Hg.[7] Prone positioning was recommended in patients with a Pao_2:Fio_2 of less than 150 mm Hg.[8]

TRIAL OUTCOMES

The primary outcome was death from any cause at 28 days after randomization among the patients, including those for whom care was limited or withdrawn. Secondary outcomes were death in the ICU and at day 90; the Sequential Organ Failure Assessment score (which ranges from 0 to 20, with higher scores indicating more severe organ failure) calculated without the respiratory component at days 0, 3, and 7 (Section 2c in the Supplementary Appendix); ventilator-associated pneumonia during the first 28 days; and septicemia during the first 28 days.

Additional secondary outcomes were cardiovascular complications, defined as new-onset arrhythmia or a cardiac ischemic event and the use of vasopressors (recorded every morning) over the first 7 days. In addition, respiratory weaning success was determined at days 28 and 90, and neurologic status was measured according to the daily Richmond Agitation and Sedation Scale (scores range from 4 [combative] to −5 [unresponsive], with a score of 0 indicating that the patient is alert and calm). Other secondary outcomes were seizures, new cerebral stroke on imaging, administration of neuroleptics, and delirium.

STATISTICAL ANALYSIS

We performed a power calculation with the published results of two available prospective trials on oxygen targets in ICU populations.[9,10] The estimated percentage difference was derived from the odds ratio of 0.62 in the reduction in the risk of death observed with a conservative-oxygenation strategy in the CLOSE (Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients) trial[9] and the OXYGEN-ICU (Effect of Conservative versus Conventional Oxygen Therapy on Mortality among Patients in an Intensive Care Unit) trial.[10] We determined that the inclusion of 850 patients would provide a power of 90% to show an absolute between-group difference of 9 percentage

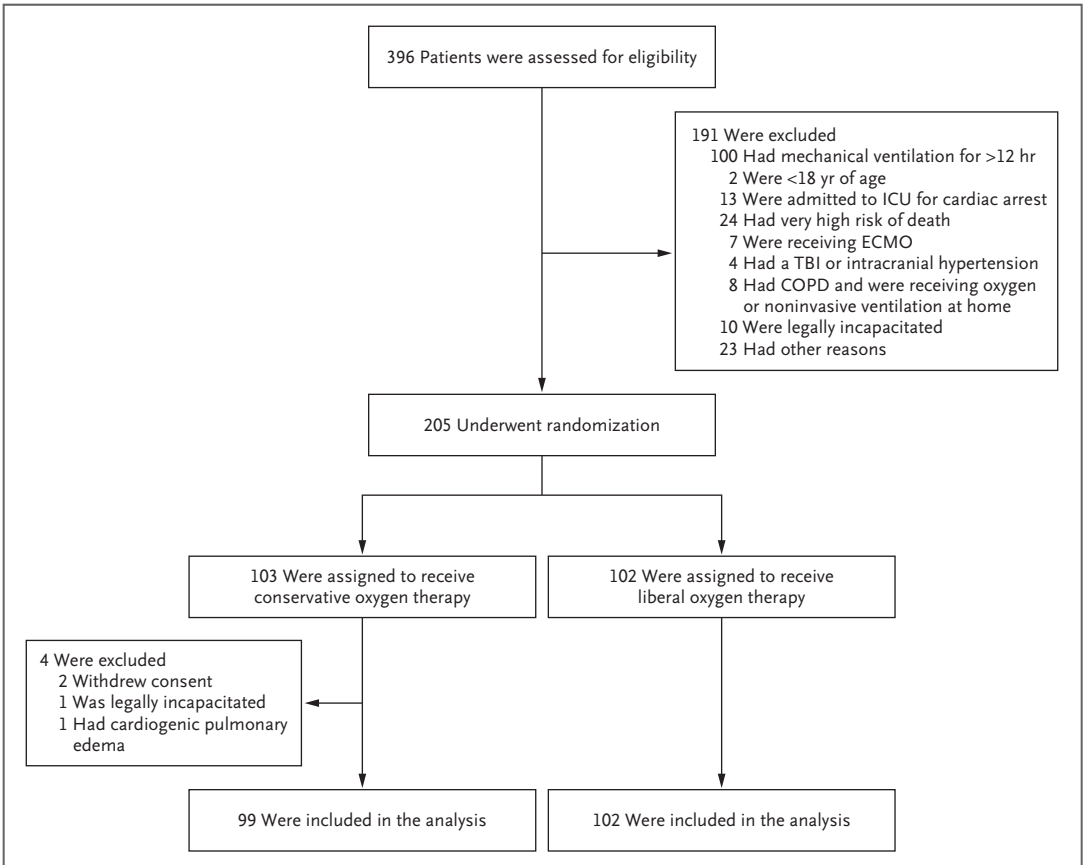

Figure 1. Screening, Randomization, and Analysis.

COPD denotes chronic obstructive pulmonary disease, ECMO extracorporeal membrane oxygenation, ICU intensive care unit, and TBI traumatic brain injury.

points in the primary outcome, assuming a death rate of 30% at day 28 in the liberal-oxygen group, a one-sided test, and a significance level of 0.05.

A total of 833 days after the enrollment of the first patient, when 205 patients had been enrolled, the data and safety monitoring board decided to stop the trial because of the potential increased risk of serious adverse events and futility. Follow-up by the research team was completed for 149 patients and external auditing of the data by independent reviewers was completed for 56 patients at that time. Contrary to the initial plan to perform an interim analysis after 425 patients had been enrolled, no interim analysis was conducted because the trial was stopped prematurely, and two-sided tests were performed in the final statistical analysis.

Categorical variables are reported as numbers and percentages, and quantitative variables as means and standard deviations or medians and interquartile ranges. Results in the two groups and the differences between the two groups with respect to the primary and secondary outcomes are presented with 95% confidence intervals that have not been adjusted for multiple comparisons. For explanatory purposes, multilevel linear or logistic models were designed to investigate the relationship between the treatment groups and repeated measurements of biologic, physiological, and ventilation variables. A two-level hierarchical structure (patients and measurements [longitudinal approach]) was considered for analysis. This allowed us to estimate a time-adjusted difference or time-adjusted odds ratio between the two groups on repeated measurements. A complementary analysis regarding mor-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Conservative Oxygen (N=99)	Liberal Oxygen (N=102)
Age — yr	63.0±15.5	63.5±14.5
Male sex — no. (%)	65 (65.7)	64 (62.7)
BMI†	27.9±7.2	27.9±6.6
Tidal volume — ml/kg of predicted body weight‡	6.0±0.3	6.2±0.5
Minute ventilation — liters/min	9.4±2.1	9.6±2.1
PEEP — cm of water	6.2±2.7	6.4±3.5
Plateau pressure — cm of water	19.8±5.1	20.8±4.8
Respiratory-system compliance — ml/cm of water	31.1±11.86	28.6±8.99
Pao_2:FIo_2 — mm Hg§	116.8±47.4	120.1±53.6
Pao_2 — mm Hg	90.3±38.8	92.3±44.8
FIo_2 (%)	80.3±18.4	80.1±19.2
Use of catecholamines — no. (%)	70 (70.7)	73 (71.6)
Arterial pH	7.31±0.11	7.31±0.1
Lactate level — mmol/liter	2.2±1.4	2.6±2.2
Hemoglobin level — g/liter	113±25	118±24
SAPS III¶	66.9±13.7	67.9±14.4
SOFA score‖	9.3±3.68	8.9±3.6
Main cause of ARDS		
Pulmonary	78 (78.8)	74 (72.5)
Extrapulmonary	21 (21.2)	28 (27.5)

* Plus–minus values are means ±SD. ARDS denotes acute respiratory distress syndrome, FIO_2 fraction of inspired oxygen, and PEEP positive end-expiratory pressure.
† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
‡ P=0.02 between the two groups.
§ The partial pressure of arterial oxygen (Pao_2) was measured in millimeters of mercury.
¶ The Simplified Acute Physiology Score (SAPS) III ranges from 0 to 217, with higher scores indicating a higher risk of death. It is calculated from 20 variables at admission of the patient.
‖ Aggregated Sequential Organ Failure Assessment (SOFA) scores range from 0 to 20, with higher scores indicating more severe organ failure. Subscores range from 0 to 4 for each of five components (circulation, liver, kidneys, and neurologic function, and coagulation).

tality was conducted at 28 days, 90 days, and in the ICU with the use of a Cox model. Both models were adjusted for age, Pao_2:FIo_2, and Simplified Acute Physiology Score (SAPS) III.

Analyses were performed in the intention-to-treat population, defined as all patients who underwent randomization except those who did not provide consent, those for whom the family declined inclusion, and those who did not meet the inclusion criteria as defined in the protocol. All analyses were performed with the use of SAS software, version 9.3 (SAS Institute), and MLwiN software, version 3.02 (Centre for Multilevel Modeling, University of Bristol, United Kingdom).

RESULTS

TRIAL POPULATION

The results presented here are based on the final data set completed 6 months after enrollment was discontinued. Overall, 103 patients were randomly assigned to the conservative-oxygen group and 102 to the liberal-oxygen group. Four patients were excluded after randomization because they did not meet eligibility criteria or they withdrew consent (Fig. 1). Baseline characteristics of the patients did not differ significantly between the two groups (Table 1 and Table S1 in the Supplementary Appendix). There was no sig-

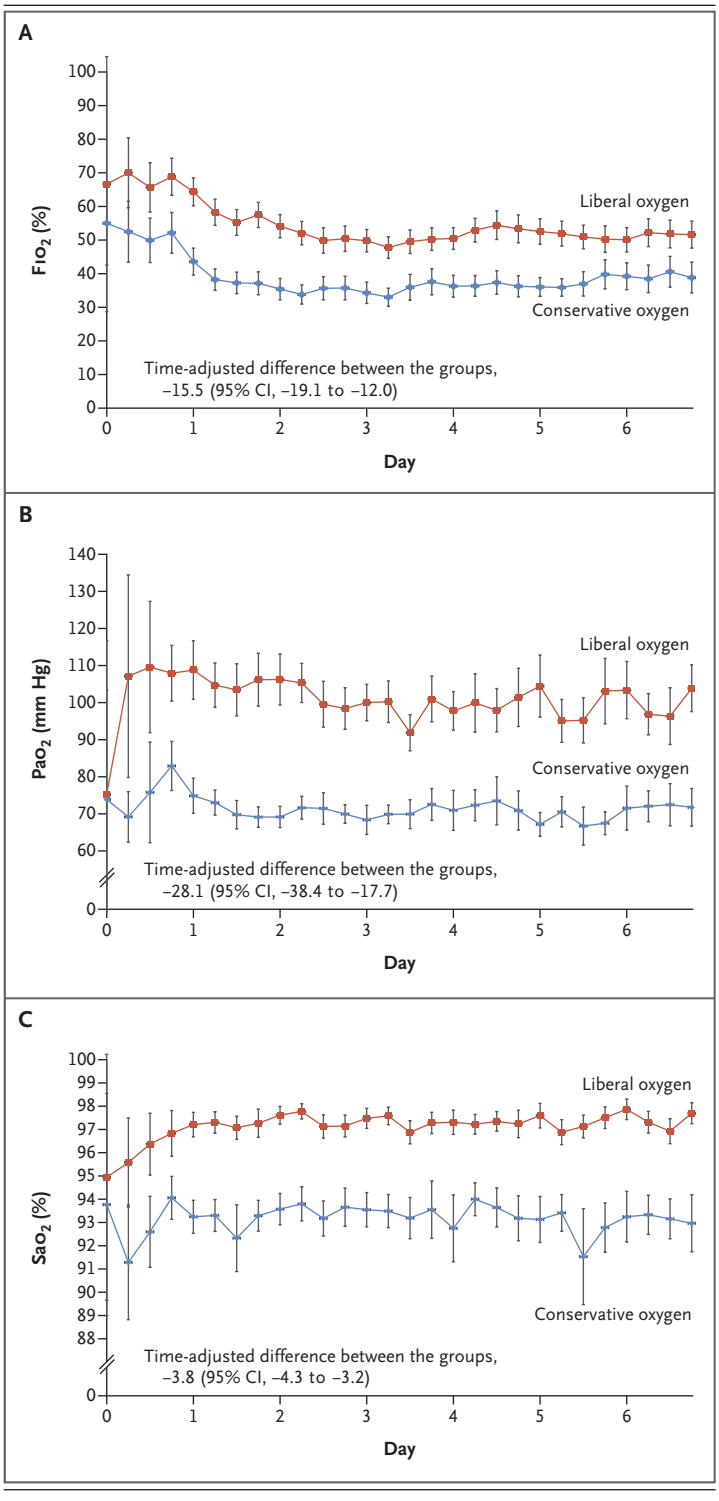

Figure 2. Oxygen Exposure.

Differences in the mean fraction of inspired oxygen (F_{IO_2}) (Panel A), partial pressure of arterial oxygen (Pa_{O_2}) (Panel B), and arterial oxygen saturation (Sa_{O_2}) (Panel C) over the first 7 days of mechanical ventilation are shown. Between-group differences were significant for the three variables. Blood gas analysis was performed every 6 hours. I bars represent confidence intervals.

nificant difference in the severity of ARDS between the two groups at randomization (Table S2) or in the methods used to diagnose ARDS (Table S3). A total of 75.8% of the patients in the conservative-oxygen group and 76.5% of those in the liberal-oxygen group had a Pa_{O_2}:F_{IO_2} of 150 mm Hg or less.

OXYGEN EXPOSURE

During the 7 protocol-specified days, the mean Pa_{O_2}, Sa_{O_2}, and F_{IO_2} were significantly lower in the conservative-oxygen group than in the liberal-oxygen group (time-adjusted difference) (Fig. 2). In the arterial blood gases sampled every 6 hours in 58 patients in the conservative-oxygen group, a median of 2 (interquartile range, 1 to 3) arterial blood gas samples had a Pa_{O_2} (range, 33.0 to 54.8 mm Hg) that was less than the threshold of 55.0 mm Hg; in 97 patients, a median of 6 samples (interquartile range, 3 to 10) had a Pa_{O_2} (range, 70.1 to 269.0 mm Hg) that was greater than the threshold of 70.0 mm Hg. In the liberal-oxygen group, all the patients except 4 had arterial blood gases with a Pa_{O_2} (range, 40.8 to 89.9 mm Hg) that was less than the threshold of 90.0 mm Hg with a median of 8 samples (interquartile range, 5 to 11), and 98 patients had arterial blood gases with a Pa_{O_2} (range, 105.8 to 366.0 mm Hg) that was greater than the threshold of 105.0 mm Hg with a median of 7 samples (interquartile range, 4 to 10).

VENTILATORY PROTOCOL AND PATIENT TREATMENT

In accordance with the protocol, the initial ventilation strategy was the same for all the patients. However, differences emerged over the trial period. During the 7 protocol-specified days, there was less use of prone positioning and the PEEP level was slightly lower in the conservative-oxygen group than in the liberal-oxygen group, whereas more patients were breathing with the volume assist–control mode of ventilation in the liberal-oxygen group (see Sections 3 and 4 in the Supplementary Appendix).

FOLLOW-UP AND OUTCOMES

At day 28, mortality was not significantly different between the two groups (34 of 99 patients

Table 2. Outcomes.

Variable	Conservative Oxygen (N = 99)		Liberal Oxygen (N = 102)	
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Death				
At day 28	34/99	34.3 (25.0–43.7)	27/102	26.5 (17.9–35.0)
In the ICU	36/99	36.4 (26.9–45.8)	27/102	26.5 (17.9–35.0)
At day 90	44/99	44.4 (34.7–54.2)	31/102	30.4 (21.5–39.3)
Mesenteric ischemia	5/99	5.1 (1.7–11.4)	0/102	
Cardiac adverse events				
Arrhythmia	23/99	23.2 (14.9–31.6)	16/102	15.7 (8.6–22.7)
New-onset atrial fibrillation	21/99	21.2 (13.2–29.3)	13/102	12.7 (6.3–19.2)
Events leading to treatment	23/99	23.2 (14.9–31.6)	14/102	13.7 (7.0–20.4)
Patients receiving catecholamines*				
Day 1	80/97	82.5 (74.9–90.0)	85/100	85.0 (78.0–92.0)
Day 3	48/88	54.6 (44.1–64.9)	57/94	60.6 (44.1–64.9)
Day 6	32/73	43.8 (32.5–55.2)	32/83	38.6 (28.1–49.0)
Patients receiving mechanical ventilation†				
Day 28	10/62	16.1 (7.0–25.3)	11/73	15.1 (6.9–23.3)
Day 90	2/53	3.8 (0.4–13.6)	2/69	2.9 (0.3–10.5)
Infectious adverse events				
Ventilator-associated pneumonia	17/99	17.2 (9.7–24.6)	22/102	21.6 (13.6–29.6)
Septicemia	11/99	11.1 (4.9–17.3)	19/102	18.6 (11.1–26.2)
Neurologic adverse events				
Seizure	2/99	2.0 (0–7.1)	0/102	0 (0–3.6)
Stroke	4/99	4.0 (1.1–10.0)	1/102	1.0 (0–5.3)
Delirium	11/99	11.1 (4.9–17.3)	11/102	10.8 (4.8–16.8)

* The mean number of days of catecholamine use was 8.0 (95% confidence interval [CI], 5.5 to 10.5) in the conservative-oxygen group and 7.2 (95% CI, 5.9 to 8.4) in the liberal-oxygen group.

† Mechanical ventilation includes invasive and noninvasive techniques or high-flow oxygen through a nasal cannula during the first 28 days. The mean number of days of mechanical ventilation was 14.0 (95% CI, 10.0 to 18.0) in the conservative-oxygen group and 14.5 (95% CI, 11.8 to 17.1) in the liberal-oxygen group.

[34.3%] in the conservative-oxygen group and 27 of 102 patients [26.5%] in the liberal-oxygen group; difference, 7.8 percentage points; 95% confidence interval [CI], −4.8 to 20.6). At day 90, mortality was significantly higher in the conservative-oxygen group than in the liberal-oxygen group (44 of 99 patients [44.4%] and 31 of 102 patients [30.4%], respectively; difference, 14.0 percentage points; 95% CI, 0.7 to 27.2) (Table 2). A comparison of the two survival curves showed a significant difference with a lower probability of survival in the conservative-oxygen group after adjustment for age, Pao_2:Fio_2, and SAPS III (adjusted hazard ratio, 1.62; 95% CI, 1.02 to 2.56) (Fig. 3 and Section 3 in the Supplementary Appendix).

Five mesenteric ischemic events occurred in the conservative-oxygen group and none occurred in the liberal-oxygen group (Table S4). Patients in the conservative-oxygen group had a higher heart rate than those in the liberal-oxygen group (Fig. S5). Other outcomes were not significantly different between the two groups (Table 2 and Table S5).

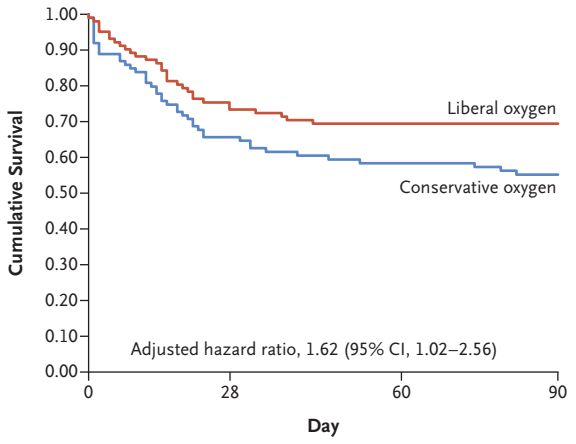

Figure 3. Kaplan–Meier Survival Curves over the First 90 Days.
Data regarding survival were censored at 90 days. Mortality was adjusted for age, ratio of Pao_2 to Fio_2, and Simplified Acute Physiology Score III.

DISCUSSION

In this prospective randomized trial involving patients with a very common form of ARDS, slightly more than 40% of whom had a Pao_2:Fio_2 lower than 100 mm Hg, a conservative-oxygenation strategy during the first 7 days of mechanical ventilation did not reduce mortality at 28 days as expected.[11,12] There was also a worrisome but not established signal of increased mortality at 90 days and mesenteric ischemia. At the time of the last meeting of the data and safety monitoring board, the trial was stopped prematurely after the enrollment of 205 patients because of this risk.

The oxygen exposures, as defined by either the Fio_2 or the Pao_2, were different between the two groups. The difference in Fio_2 between the conservative-oxygen group and the liberal-oxygen group was larger in our trial than in the OXYGEN-ICU trial[10] and the CLOSE trial.[9] In our trial, the oxygen exposure in the liberal-oxygen group was closer to that in the control group of the other trials, whereas the oxygen exposure in our conservative-oxygen group was close to the lower limits recommended in various ARDS trials and guidelines.[13-16]

Our results suggest a clinically relevant excess of mortality in the conservative-oxygen group, with mortality that was 14.0 percentage points higher than that in the liberal-oxygen group at 90 days. Several factors could explain our results. First, in our trial, the respiratory severity evaluated with the use of the Pao_2:Fio_2 was higher than that in the OXYGEN-ICU[10] and CLOSE trials.[9] Second, the trial intervention was administered in the first 12 hours and for the first 7 days, or for the duration of mechanical ventilation if less than 7 days. Although decreasing oxygen exposure (lower Fio_2) might decrease the lung damage at the early phase of the disease,[17] patients were exposed to hypoxemia. Although some clinicians recommend adjustment of the oxygenation target according to the severity of lung disease, the use of a low range of Pao_2 (55 to 70 mm Hg) might have exposed the patients to unsafe Pao_2 levels.[2] Increased mortality with a Pao_2 lower than 67 mm Hg was reported in a retrospective study from the Netherlands.[18] Furthermore, in the OXYGEN-ICU trial, mortality was lowest among patients with a median time-weighted Pao_2 between 87 and 93 mm Hg, and it was increased among those with a median time-weighted Pao_2 between 54 and 81 mm Hg. In the recent ICU-ROX (Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen Therapy)[19] substudy involving patients with sepsis, there was a signal for higher mortality in the group exposed to conservative oxygenation.[20] Third, targeting lower oxygenation might decrease oxygen content and transport.[13] Hemoglobin levels were not different during follow-up between the two groups, and we did not find a difference in arterial lactate levels. The heart rate was higher in the conservative-oxygen group, a finding that has been linked to a high mortality among patients in the ICU.[21] Fourth, the gut is sensitive to low oxygen delivery according to its blood supply characteristics.[22]

The strengths of this trial are its prospective, multicenter design with a clear protocol for ventilation management and oxygenation targets. The two groups were well balanced. However, several limitations warrant attention. First, the investigators were aware of the intervention because the masking of the results of arterial blood gases and the Spo_2 has been problematic. Second, the Pao_2:Fio_2 was used to set the PEEP level (according to the 200 mm Hg threshold) and the weaning process. Unfortunately, the Pao_2:Fio_2

is dependent on the F_{IO_2} at which it is measured, and this factor might have affected weaning in the conservative-oxygen group.[23,24] However, clinicians might have been more inclined to switch from controlled ventilation to a mode allowing unassisted ventilation in the presence of a lower F_{IO_2}. Third, targeting a P_{aO_2} of 55 mm Hg might have exposed patients to unexpected and undetected lower arterial oxygen levels, since it is difficult to maintain a lower-limit P_{aO_2} on a continuous basis. We cannot rule out the possibility that S_{pO_2} values were not precise enough to avoid hypoxemic events between blood gas samples. Fourth, we used a one-sided P value in the sample-size estimation, which was common practice at the time this trial was designed, although it is not currently recommended. Fifth, the trial was prematurely discontinued because of a worrisome safety concern, and the number of patients who were included was lower than planned. Sixth, we did not study the patients' biologic profiles or types, which might have affected their response to such strategies, as reported recently.[25]

In conclusion, among patients with ARDS, early exposure to a conservative-oxygenation strategy with a P_{aO_2} between 55 and 70 mm Hg did not increase survival at 28 days. A worrisome safety signal was observed in the group assigned to a lower oxygen exposure. The meaning of this signal to clinical practice is unclear.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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