ORIGINAL ARTICLE

Oxygen Targets in Comatose Survivors of Cardiac Arrest

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ABSTRACT

BACKGROUND

The appropriate oxygenation target for mechanical ventilation in comatose survivors of out-of-hospital cardiac arrest is unknown.

METHODS

In this randomized trial with a 2-by-2 factorial design, we randomly assigned comatose adults with out-of-hospital cardiac arrest in a 1:1 ratio to either a restrictive oxygen target of a partial pressure of arterial oxygen (PaO_2) of 9 to 10 kPa (68 to 75 mm Hg) or a liberal oxygen target of a PaO_2 of 13 to 14 kPa (98 to 105 mm Hg); patients were also assigned to one of two blood-pressure targets (reported separately). The primary outcome was a composite of death from any cause or hospital discharge with severe disability or coma (Cerebral Performance Category [CPC] of 3 or 4; categories range from 1 to 5, with higher values indicating more severe disability), whichever occurred first within 90 days after randomization. Secondary outcomes were neuron-specific enolase levels at 48 hours, death from any cause, the score on the Montreal Cognitive Assessment (ranging from 0 to 30, with higher scores indicating better cognitive ability), the score on the modified Rankin scale (ranging from 0 to 6, with higher scores indicating greater disability), and the CPC at 90 days.

RESULTS

A total of 789 patients underwent randomization. A primary-outcome event occurred in 126 of 394 patients (32.0%) in the restrictive-target group and in 134 of 395 patients (33.9%) in the liberal-target group (hazard ratio, 0.95; 95% confidence interval, 0.75 to 1.21; P=0.69). At 90 days, death had occurred in 113 patients (28.7%) in the restrictive-target group and in 123 (31.1%) in the liberal-target group. On the CPC, the median category was 1 in the two groups; on the modified Rankin scale, the median score was 2 in the restrictive-target group and 1 in the liberal-target group; and on the Montreal Cognitive Assessment, the median score was 27 in the two groups. At 48 hours, the median neuron-specific enolase level was 17 μg per liter in the restrictive-target group and 18 μg per liter in the liberal-target group. The incidence of adverse events was similar in the two groups.

CONCLUSIONS

Targeting of a restrictive or liberal oxygenation strategy in comatose patients after resuscitation for cardiac arrest resulted in a similar incidence of death or severe disability or coma. (Funded by the Novo Nordisk Foundation; BOX ClinicalTrials.gov number, NCT03141099.)

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Hypoxic–ischemic brain injury is the leading cause of death in patients who have been resuscitated after cardiac arrest.[1] During resuscitation, the brain is exposed to hypoxia, and when spontaneous circulation is reestablished, reperfusion may cause further injury.[2] Patients who remain comatose after cardiac arrest require mechanical ventilation with the administration of supplemental oxygen. Although liberal oxygenation has been associated with an increased risk of ischemic encephalopathy and death in observational studies[3,4] and animal models of cardiac arrest suggest that hyperoxia worsens brain damage,[5] more restrictive oxygen therapy may increase the risk of tissue hypoxia.

A number of small randomized studies have compared different oxygen strategies after cardiac arrest with varying end points, but these studies have not been powered to assess survival or neurologic outcome.[6-10] In critically ill patients being treated in the intensive care unit (ICU), two recent randomized trials comparing higher and lower oxygenation targets did not show improved survival or a reduction of ventilator days in either group.[11,12] However, in ICU-ROX (Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen Therapy), a subgroup analysis suggested a better outcome with conservative oxygen treatment in patients with ischemic encephalopathy.[11]

Thus, equipoise exists regarding the benefits of different oxygenation targets in patients who remain comatose after out-of-hospital cardiac arrest. In the Blood Pressure and Oxygenation Targets in Postresuscitation Care (BOX) trial, we evaluated whether a restrictive or a liberal oxygen target was superior with respect to a composite outcome of death from any cause or discharge from the hospital in a poor neurologic state among comatose patients with out-of-hospital cardiac arrest.

Methods

Trial Design and Oversight

The BOX trial was an investigator-initiated, open-label, randomized trial with a 2-by-2 factorial design in which comatose patients with out-of-hospital cardiac arrest were assigned to a restrictive or a liberal oxygen target and to one of two target blood pressures. The portion of the trial regarding the oxygenation strategy is reported here.

Patients were enrolled at two tertiary cardiac arrest centers in Denmark. Danish legislation permits immediate inclusion of patients who are unable to provide consent in nonpharmaceutical trials and mandates that consent should be obtained at the first given opportunity after inclusion in the trial. Consent for inclusion of comatose patients was obtained from a legal representative, as well as a medical doctor with expertise in the clinical area but with no relation to the trial. Proxy consent was obtained by a medical doctor at the first given opportunity. Informed consent from the patient was obtained if the patient regained consciousness.

The trial was approved by the regional ethics committee of the Capital Region of Denmark, and a data-handling agreement was approved by the relevant authority. The trial was designed and overseen by the steering committee (whose members are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org). Data were gathered by all the authors and were analyzed by the second and last authors; the latter wrote the first draft of the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol (available at NEJM.org).

An independent data and safety monitoring committee oversaw the trial and reviewed the two planned interim analyses after 200 and 400 patients had completed the 90-day follow-up. Trial data were reviewed at the sites by external monitors in accordance with Good Clinical Practice guidelines. The trial protocol was published before the enrollment of the last patient.[13]

Patients

Comatose adult patients who had been admitted to the hospital after resuscitated cardiac arrest and who had a sustained return of spontaneous circulation were eligible for enrollment. A complete list of all inclusion and exclusion criteria is provided in the Supplementary Appendix.

Treatment Protocol

All the patients underwent temperature control at 36°C with sedation and mechanical ventilation for at least 24 hours.[14] The target for the core body temperature was achieved with the use of commercially available surface cooling (CritiCool, Belmont Medical Technologies) or intravenous cooling (Thermogard XP and Cool Line Catheter,

Zoll). After the maintenance period at 36°C, the core temperature was gradually raised to normothermia, and sedation was weaned.

RANDOMIZATION

The patients underwent randomization as soon as possible after hospital admission, usually in the ICU. Randomization was performed by means of a Web-based system using random permuted-block sizes of 2, 4, or 6 that were stratified according to site. The target oxygenation interventions were initiated immediately after randomization and maintained until extubation.

Patients were assigned to receive a partial pressure of arterial oxygen (PaO_2) of 9 to 10 kPa (68 to 75 mm Hg) in the restrictive-target group or 13 to 14 kPa (98 to 105 mm Hg) in the liberal-target group. Serial blood-gas measurements were performed at prespecified time points within 120 hours (5 days) after randomization or until removal of the arterial catheter. The initial fraction of inspired oxygen (FIO_2) was to be set at 0.3 in the restrictive-target group and at 0.6 in the liberal-target group. The FIO_2 was adjusted to the assigned target but was increased if peripheral arterial blood saturation fell below 93% on peripheral pulse oximetry. Ventilator settings, including positive end-expiratory pressure, were set at the discretion of the treating physician.

OUTCOMES

The primary outcome was a composite of death from any cause or discharge from the hospital with severe disability or coma, whichever occurred first within 90 days after randomization. Severe disability or coma was defined as a Cerebral Performance Category (CPC) of 3 or 4 (categories range from 1 [no symptoms] to 5 [death or brain death]). For patients who were discharged with a CPC of 3 or 4, events were recorded at the time of discharge.

A secondary outcome was the plasma neuron-specific enolase level at 48 hours, which was measured by electrochemiluminescence and by a COBAS analyzer system (Roche Diagnostics). (This enzyme is a biochemical marker of neurologic damage, for which higher levels are associated with more extensive brain injury.[15]) Additional secondary outcomes were death from any cause, along with 90-day scores on the Montreal Cognitive Assessment, the modified Rankin scale, and the CPC,[16,17] as determined by trained research personnel. Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating more severe disability. The Montreal Cognitive Assessment tests different types of cognitive abilities and assigns a score between 0 and 30, with a score of 26 or higher considered to indicate normal function. Because of pandemic restrictions during the trial period, these assessments were performed by means of telephone interview or review of hospital charts in some patients, which excluded the performance of the Montreal Cognitive Assessment in these patients.

Adverse events that were assessed included bleeding, infection, arrhythmia, electrolyte derangement, metabolic derangement, acute kidney injury with renal-replacement therapy, and seziures.[13]

STATISTICAL ANALYSIS

We determined that the enrollment of 732 patients would provide 80% power (and enrollment of 846 patients would provide 90% power) to detect an absolute between-group difference of 10 percentage points for the primary composite outcome, assuming a mortality of 28% at a two-sided alpha level of 0.05. (Previous data from our department had indicated a 6-month mortality of 33% in this patient population.[18]) Therefore, we aimed for the randomization of 800 patients (400 to the restrictive-target group and 400 to the liberal-target group), with at least 90 days of follow-up after the last patient had been enrolled. In determining the sample size for enrollment, we assumed no interaction with the parallel blood-pressure intervention.

We performed Cox proportional-hazards analysis with adjustment for trial site to calculate the hazard ratio and 95% confidence interval for the primary composite outcome in the oxygenation intervention. The assumption of proportional hazards was fulfilled. Event-free survival was calculated in a Kaplan–Meier plot with a maximum follow-up of 90 days.

We performed prespecified subgroup analyses of the primary outcome (with tests of interaction) with respect to sex, median age, history of chronic obstructive pulmonary disease at the time of cardiac arrest, shockable primary rhythm, return of spontaneous circulation above the median, and ST-segment elevation acute myocardial infarction.[13] No imputations for missing data were performed. Analyses of outcomes

were performed in the intention-to-treat population.

The statistical analysis plan (available with the protocol) included a sensitivity analysis in which missing scores on the Montreal Cognitive Assessment and scores for deceased patients were assigned the lowest observed score (a score of 15).[13] In addition, an analysis of test results in patients who had completed the test was performed. Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for the remaining outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of a hypothesis test.

A two-sided P value of less than 0.05 was considered to indicate statistical significance. The two-sided alpha level for the analysis of the primary outcome was 0.047 after correction for the two planned interim analyses. All statistical analyses were performed with the use of SAS Enterprise software, version 7.15 (SAS Institute).

RESULTS

PATIENTS

From March 2017 through December 2021, a total of 802 patients were enrolled in the trial. Consent was declined in 12 patients and 1 patient underwent randomization twice, so 789 patients were included in the intention-to-treat population (394 in the restrictive-target group and 395 in the liberal-target group) (Fig. S1 in the Supplementary Appendix). Four patients died before the intervention had been initiated. Two patients were transferred to hospitals outside Denmark with a loss of follow-up, and data for these patients were censored on days 12 and 13.

The characteristics of the patients in the oxygen-target groups were well balanced at baseline (Table 1 and Tables S2 and S3). The median interval from cardiac arrest to randomization was 146 minutes (interquartile range, 113 to 187). The patients' temperatures at the time of randomization and during the initial 30 hours are summarized in Table S4.

OXYGEN INTERVENTION

On arrival in the ICU, the patients in the two groups had similar values of PaO_2 and FIO_2. Separation of oxygenation levels between the two target groups was seen within 2 to 4 hours and remained thereafter through the first 48 hours (Fig. 1A and 1B). Details regarding the FIO_2, the PaO_2-to-FIO_2 ratio, and positive end-expiratory pressure are shown in Figure 1C and Figures S2 and S3. The median duration of mechanical ventilation was 57 hours (interquartile range, 39 to 110) in the restrictive-target group and 61 hours (interquartile range, 40 to 111) in the liberal-target group.

OUTCOMES

At 90 days, a primary-outcome event (death or hospital discharge with severe disability or coma) had occurred in 126 of 394 patients (32.0%) in the restrictive-target group and in 134 of 395 patients (33.9%) in the liberal-target group (adjusted hazard ratio, 0.95; 95% confidence interval, 0.75 to 1.21; P=0.69) (Table 2 and Fig. 2). The results appeared to be consistent across prespecified subgroups (Fig. 3), and there was no interaction with the blood-pressure intervention.

Within 90 days, death had occurred in 113 of 394 patients (28.7%) in the restrictive-target group and in 123 of 395 patients (31.1%) in the liberal-target group (Fig. S5). The 90-day results on the CPC, modified Rankin scale, and Montreal Cognitive Assessment, as well as the plasma neuron-specific enolase level at 48 hours, are summarized in Table 2. Results on the CPC, modified Rankin scale, and Montreal Cognitive Assessment for patients with missing scores and for deceased patients are summarized in Figures S6, S7, and S8.

ADVERSE EVENTS

Prespecified adverse events are reported in Table 2. The most frequent adverse events were infection, bleeding, and seizures. There were no significant between-group differences in any prespecified adverse events.

DISCUSSION

In this randomized trial, we compared a restrictive oxygenation target of 9 to 10 kPa (68 to 75 mm Hg) with a liberal oxygenation target of 13 to 14 kPa (98 to 105 mm Hg) in comatose patients who had been resuscitated after out-of-hospital cardiac arrest. We found no significant difference between liberal and restrictive oxygen-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Restrictive Oxygen Target (N=394)	Liberal Oxygen Target (N=395)
Age — yr		
Mean	62±13	63±14
Range	20–89	18–90
Male sex — no. (%)	325 (82.5)	312 (79.0)
Medical history — no./total no. (%)		
Hypertension	179/394 (45.4)	183/393 (46.6)
Diabetes	53/394 (13.5)	57/395 (14.4)
Myocardial infarction	89/393 (22.6)	83/394 (21.1)
Atrial fibrillation	56/391 (14.3)	71/394 (18.0)
Heart failure	58/393 (14.8)	79/394 (20.1)
Chronic obstructive pulmonary disease	29/392 (7.4)	34/394 (8.6)
Stroke	32/393 (8.1)	27/395 (6.8)
Chronic kidney disease	19/393 (4.8)	20/395 (5.1)
Renal-replacement therapy	1/393 (0.3)	3/395 (0.8)
Out-of-hospital cardiac arrest		
Features — no./total no. (%)		
Shockable rhythm	334/393 (85.0)	333/394 (84.5)
Pulseless electrical activity	15/393 (3.8)	20/394 (5.1)
Witnessed asystole	15/393 (3.8)	15/394 (3.8)
Witnessed arrest	333/394 (84.5)	339/394 (86.0)
Bystander cardiopulmonary resuscitation	346/388 (89.2)	333/388 (85.8)
First defibrillation by automated external defibrillator	79/386 (20.5)	103/390 (26.4)
Time until return of spontaneous circulation — min†	21±13	21±14
Findings and procedures at hospital arrival‡		
pH	7.21±0.12	7.21±0.13
Lactate — mmol/liter	5.8±3.7	5.9±4.0
Partial pressure of arterial oxygen — kPa	16.1±8.5	17.1±8.8
Immediate coronary angiography — no. (%)	363 (92.1)	359 (90.9)
Percutaneous coronary intervention — no. (%)	159 (40.4)	177 (44.8)

* Plus–minus values are means ±SD.
† Data regarding the time until the return of spontaneous circulation were missing for 9 patients in the restrictive-target group and for 9 in the liberal-target group.
‡ Data that were obtained soon after hospital arrival were missing regarding the pH in 43 patients (23 in the restrictive-target group and 20 in the liberal-target group), the serum lactate level in 23 patients (13 and 10, respectively), and the partial pressure of arterial oxygen in 38 patients (22 and 16, respectively).

ation targets in the composite outcome of death or survival with a poor neurologic outcome. The results were consistent in all prespecified subgroups.

Two recent randomized, multicenter trials involving critically ill patients have investigated the potential benefit of restrictive as compared with liberal oxygen therapy.[11,12] In the Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial, investigators assigned 2888 patients with acute respiratory failure to a restrictive target (PaO_2 of 8 kPa [60 mm Hg]) or a usual target (PaO_2 of 12 kPa [90 mm Hg]).[12] The restrictive-oxygenation target did not result in lower mortality at 90 days. In ICU-ROX, which involved 965 patients requiring mechanical ven-

tilation,[11] the target oxygenation strategy had no effect on the primary outcome of ventilator-free days. A post hoc analysis involving 166 patients with ischemic encephalopathy suggested a possible benefit of conservative oxygen therapy,[11] a finding that was not robust after adjustment for baseline covariates.[19]

The benefit of restrictive oxygen therapy has

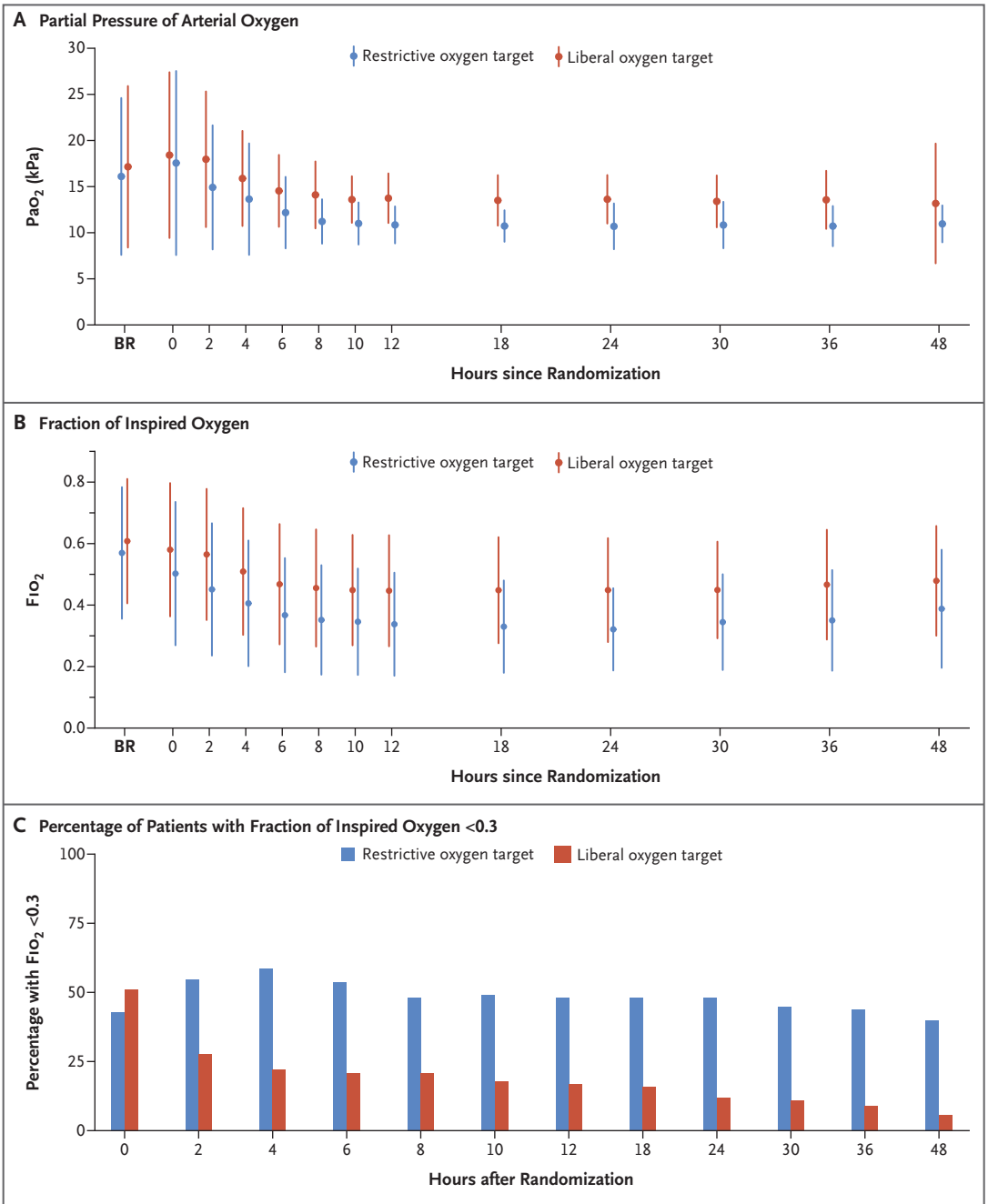


Figure 1. Oxygenation during the First 48 Hours.

Shown are data during the first 48 hours after admission to the intensive care unit for the partial pressure of arterial oxygen (PaO_2) (Panel A), the fraction of inspired oxygen (FIO_2) (Panel B), and the percentage of patients with an FIO_2 of less than 0.3 (Panel C), according to the oxygenation group. The vertical lines in Panels A and B represent the standard deviation. BR denotes before randomization.

Table 2. Primary and Secondary Outcomes and Adverse Events.*

Variable	Restrictive Oxygen Target (N=394)	Liberal Oxygen Target (N=395)	Treatment Effect (95% CI)†	P Value
Primary outcome				
Death from any cause or CPC 3 or 4 at discharge — no. (%)‡	126 (32.0)	134 (33.9)	0.95 (0.75–1.21)	0.69
Secondary outcomes				
Death from any cause at 90 days — no. (%)	113 (28.6)	123 (31.1)	0.93 (0.72–1.20)	
Acute kidney injury with renal-replacement therapy — no. (%)	34 (8.6)	47 (11.9)	0.85 (0.69–1.03)	
Median CPC at 90 days (IQR)‡	1 (1–5)	1 (1–5)		
Median score on modified Rankin scale at 90 days (IQR)§	2 (0–6)	1 (0–6)		
Median score on Montreal Cognitive Assessment at 90 days (IQR)¶	27 (24–29)	27 (24–28)		
Median neuron-specific enolase at 48 hr (IQR) — μg/liter‖	17 (11–36)	18 (11–34)		
Adverse events — no. (%)				
Infection**	103 (26.1)	109 (27.6)	0.96 (0.82–1.13)	0.65
Arrhythmia††	57 (14.5)	52 (13.2)	1.06 (0.86–1.30)	0.60
Bleeding				
Any	82 (20.8)	92 (23.3)	0.93 (0.79–1.10)	0.40
Uncontrolled bleeding‡‡	17 (4.3)	21 (5.3)	0.90 (0.67–1.21)	0.62
Acute kidney injury with renal-replacement therapy	34 (8.6)	47 (11.9)	0.85 (0.69–1.03)	0.13
Electrolyte disorder§§	32 (8.1)	25 (6.3)	1.15 (0.85–1.56)	0.33
Metabolic disorder¶¶	34 (8.6)	28 (7.1)	1.12 (0.84–1.48)	0.42
Seizure‖‖	81 (20.6)	83 (21.0)	0.99 (0.83–1.17)	0.14

* IQR denotes interquartile range.

† Hazard ratios are shown for primary and secondary outcomes and relative risks for adverse events. Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary outcomes, results are reported as point estimates and 95% confidence intervals (CI). The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of a hypothesis test.

‡ The Cerebral Performance Category (CPC) ranges from 1 (no symptoms) to 5 (death or brain death). For the secondary analysis among patients who were alive at 90 days, results were available for 777 patients (387 in the restrictive-target group and 390 in the liberal-target group).

§ Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating more severe disability. At 90 days, scores were available for 774 patients (385 in the restrictive-target group and 389 in the liberal-target group).

¶ Scores on the Montreal Cognitive Assessment range from 0 to 30, with a score of 26 or higher considered to indicate normal function. At 90 days, scores were available for 359 patients (179 in the restrictive-target group and 180 in the liberal-target group).

‖ Reference values for neuron-specific enolase range from 0 to 16.3 μg per liter. Levels at 48 hours were available for 625 patients (313 in the restrictive-target group and 312 in the liberal-target group).

** Categories of infection included severe sepsis, septic shock, pneumonia, and other.

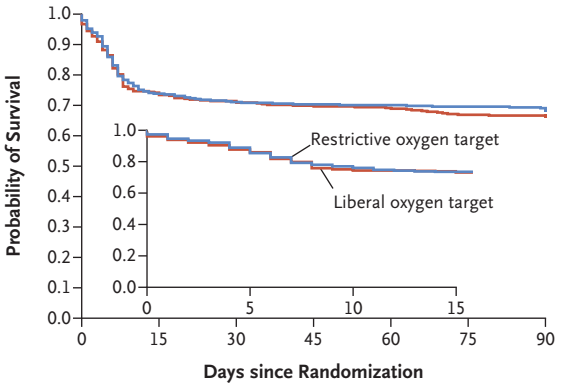
†† Arrhythmia was defined as ventricular fibrillation, ventricular tachycardia, tachycardia of more than 130 beats per minute, bradycardia of less than 40 beats per minute, atrial flutter, atrial fibrillation, need for pacing, or circulatory collapse mandating cardiopulmonary resuscitation.

‡‡ Uncontrolled bleeding was defined as hemorrhage that results in the administration of more than 1 unit of blood per 10 kg of body weight per hour or that leads to death, symptomatic bleeding in critical organs (e.g., intracranial, intraspinal, intraocular, intraarticular, or pericardial), and other bleeding (e.g., retroperitoneal, muscular, solid-organ, thoracic with a hemoglobin value of <50 g per liter and requiring >2 units of transfused blood).

§§ An electrolyte disorder was defined as hypokalemia (<3.0 mmol per liter), hypophosphatemia (<0.7 mmol per liter), or hypomagnesemia (<0.7 mmol per liter).

¶¶ A metabolic disorder was defined as sustained hyperglycemia (>10 mmol of glucose per liter for >4 hours) or hypoglycemia (<3.0 mmol per liter on one measure).

‖‖ Seizures included tonic–clonic, myoclonic, and electrographic status epilepticus.



No. at Risk

Restrictive target	394	290	279	276	275	273	271
Liberal target	395	292	281	275	272	263	262

Figure 2. Kaplan–Meier Estimates of Survival.

Shown is the probability of survival without disability or coma at 90 days after randomization (the primary composite outcome) in the two oxygenation groups. Disability or coma was defined as a Cerebral Performance Category of 3 or 4. Data are for the 789 patients who were included in the intention-to-treat population. The inset shows the same data truncated at 15 days after randomization.

also been suggested in a meta-analysis, although the heterogeneity of the oxygen interventions was considerable and data from the HOT-ICU trial were not available.[20] The potential pathophysiological link between brain injury and oxygenation seems to occur in the early period after cardiac arrest and to be driven by reperfusion injury with mitochondrial dysfunction and tissue inflammation.[21,22] Experimental studies have suggested that this process may be exacerbated by hyperoxemia.[5]

In our current trial, the patient population included those at high risk for hypoxic–ischemic encephalopathy. In the trial, we saw a substantial separation of PaO_2 values starting at 2 hours after ICU admission, a separation that was maintained beyond 48 hours. Despite this result, we found no significant between-group difference in the primary outcome.

Our trial has several limitations. We enrolled patients with cardiac arrest that had a presumed cardiac cause. However, even though the incidence of primary-outcome events was similar to those reported at our centers, it was relatively low and reflected a population with a high prevalence of acute coronary syndrome. Thus, our results may not be applicable to patients with other causes of cardiac arrest. A strength of the trial is that the PaO_2 was measured directly multiple times at predefined time points, which allowed for maintenance of oxygen targets rather than reliance on less reliable methods.[23] Although a clear separation of PaO_2 values occurred early, the restrictive-target group still had a PaO_2 at the upper limit of the oxygenation target. The PaO_2-to-FIO_2 ratio was considerably higher in our trial than that in the HOT-ICU trial,[12] which suggests that hypoxic respiratory failure was infrequent in our trial. Thus, in some patients, the spontaneous PaO_2 value may have exceeded the restrictive oxygenation target of 9 to 10 kPa (68 to 75 mm Hg), even without additional oxygen supplementation during mechanical ventilation. Thus, we cannot rule out the possibility that the population was "too healthy" for benefit. On arrival in the ICU, the PaO_2 was higher than 15 kPa (113 mm Hg) in most patients, so the intervention was not evident until 2 hours after randomization. Observational studies have indicated the negative effects of hyperoxygenation at higher PaO_2 values than the target in our trial. We targeted oxygen levels that we deemed to be clinically acceptable but that did not result in hyperoxygenation. Thus, whether earlier, more aggressive, or even prehospital intervention would have changed the result is speculative.

Our trial was also limited by the number of patients who could be evaluated in person at 90 days, which was lower than expected. The trial follow-up was challenged by pandemic restrictions that did not permit outpatient visits for extended periods in 2020 and 2021. Although this restriction had no effect on the primary outcome, it did affect the completeness of Montreal Cognitive Assessment scores at 90 days. Blood samples in the biobank were available for 86% of the patients who were alive at 48 hours, a proportion that was lower than expected. This result was at least partly explained by the logistic challenges of sampling for the biobank at one site (Odense University Hospital) at the beginning of the trial. However, it appears that blood samples were missing at random. Although the estimated effect of the sample-size estimation may have been overly optimistic, the risk of a type II error seems to be low in light of the consistency of the find-

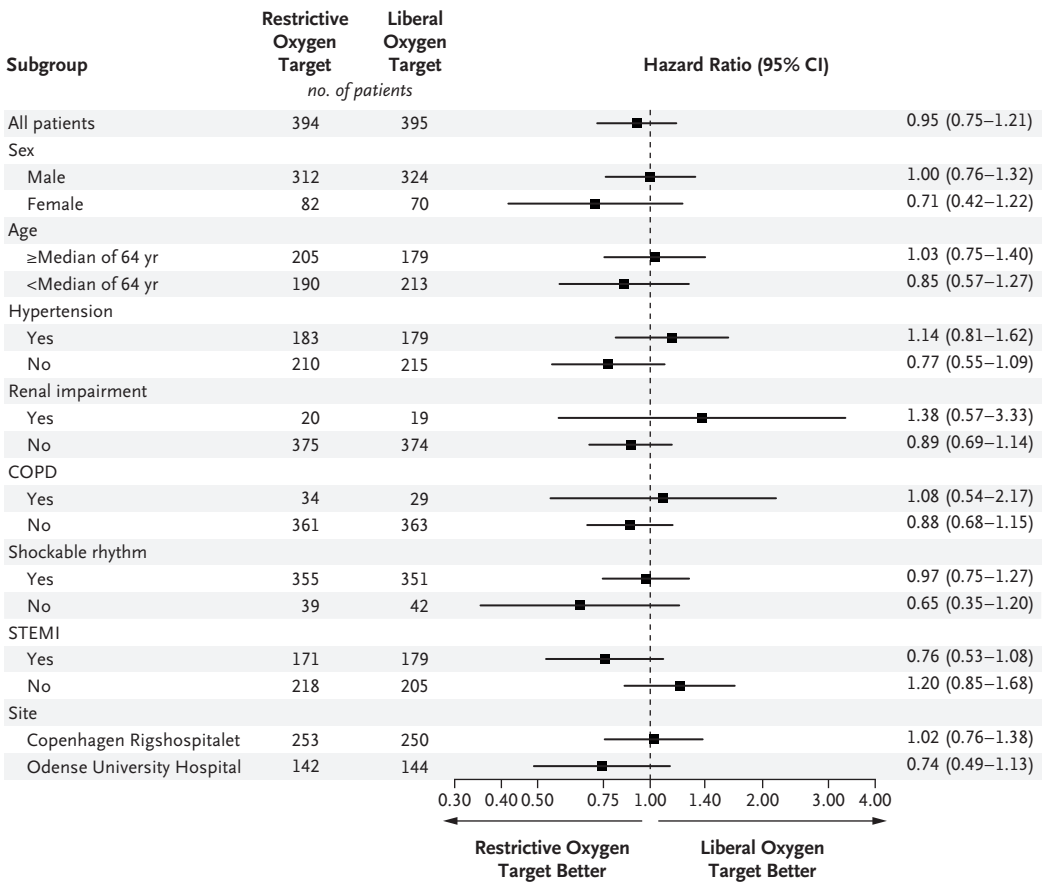


Figure 3. Subgroup Analysis of the Primary Outcome.

Shown are the results of the prespecified subgroup analysis of the primary outcome (death from any cause or discharge from the hospital with disability or coma [Cerebral Performance Category 3 or 4]). The forest plot shows the hazard ratios with 95% confidence intervals (horizontal bars). COPD denotes chronic obstructive pulmonary disease, and STEMI ST-segment elevation acute myocardial infarction.

ings. Finally, the open-label nature of the trial may have biased choices regarding continued life-sustaining therapies, despite the use of a predefined algorithm for making such choices.[24,25]

In comatose patients who had been resuscitated after out-of-hospital cardiac arrest, we found no difference between a restrictive oxygenation target and a liberal oxygenation target with respect to the incidence of death or severe disability or coma at 90 days.

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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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REFERENCES

1. Sandroni C, Cronberg T, Sekhon M. Brain injury after cardiac arrest: pathophysiology, treatment, and prognosis. Intensive Care Med 2021;47:1393-414.

2. Schneider A, Böttiger BW, Popp E. Cerebral resuscitation after cardiocirculatory arrest. Anesth Analg 2009;108:971-9.

3. Kilgannon JH, Jones AE, Parrillo JE, et al. Relationship between supranormal oxygen tension and outcome after resuscitation from cardiac arrest. Circulation 2011;123:2717-22.

4. Roberts BW, Kilgannon JH, Hunter BR, et al. Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability: prospective multicenter protocol-directed cohort study. Circulation 2018;137:2114-24.

5. Pilcher J, Weatherall M, Shirtcliffe P, Bellomo R, Young P, Beasley R. The effect of hyperoxia following cardiac arrest — a systematic review and meta-analysis of animal trials. Resuscitation 2012;83:417-22.

6. Bray JE, Hein C, Smith K, et al. Oxygen titration after resuscitation from out-of-hospital cardiac arrest: a multi-centre, randomised controlled pilot study (the EXACT pilot trial). Resuscitation 2018;128:211-5.

7. Jakkula P, Reinikainen M, Hästbacka J, et al. Targeting two different levels of both arterial carbon dioxide and arterial oxygen after cardiac arrest and resuscitation: a randomised pilot trial. Intensive Care Med 2018;44:2112-21.

8. Kuisma M, Boyd J, Voipio V, Alaspää A, Roine RO, Rosenberg P. Comparison of 30 and the 100% inspired oxygen concentrations during early post-resuscitation period: a randomised controlled pilot study. Resuscitation 2006;69:199-206.

9. Thomas M, Voss S, Benger J, Kirby K, Nolan JP. Cluster randomised comparison of the effectiveness of 100% oxygen versus titrated oxygen in patients with a sustained return of spontaneous circulation following out of hospital cardiac arrest: a feasibility study. PROXY: post ROSC OXYgenation study. BMC Emerg Med 2019;19:16.

10. Young P, Bailey M, Bellomo R, et al. HyperOxic Therapy OR NormOxic Therapy after out-of-hospital cardiac arrest (HOT OR NOT): a randomised controlled feasibility trial. Resuscitation 2014;85:1686-91.

11. Mackle D, Bellomo R, Bailey M, et al. Conservative oxygen therapy during mechanical ventilation in the ICU. N Engl J Med 2020;382:989-98.

12. Schjørring OL, Klitgaard TL, Perner A, et al. Lower or higher oxygenation targets for acute hypoxemic respiratory failure. N Engl J Med 2021;384:1301-11.

13. Kjaergaard J, Schmidt H, Møller JE, Hassager C. The "blood pressure and oxygenation targets in post resuscitation care, a randomized clinical trial": design and statistical analysis plan. Trials 2022;23:177.

14. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. N Engl J Med 2021;384:2283-94.

15. Stammet P, Collignon O, Hassager C, et al. Neuron-specific enolase as a predictor of death or poor neurological outcome after out-of-hospital cardiac arrest and targeted temperature management at 33°C and 36°C. J Am Coll Cardiol 2015;65:2104-14.

16. Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in adults: an advisory statement from the International Liaison Committee on Resuscitation. Circulation 2018;137(22):e783-e801.

17. van Gils P, van Heugten C, Hofmeijer J, Keijzer H, Nutma S, Duits A. The Montreal Cognitive Assessment is a valid cognitive screening tool for cardiac arrest survivors. Resuscitation 2022;172:130-6.

18. Wiberg S, Hassager C, Schmidt H, et al. Neuroprotective effects of the glucagon-like peptide-1 analog exenatide after out-of-hospital cardiac arrest: a randomized controlled trial. Circulation 2016;134:2115-24.

19. Young P, Mackle D, Bellomo R, et al. Conservative oxygen therapy for mechanically ventilated adults with suspected hypoxic ischaemic encephalopathy. Intensive Care Med 2020;46:2411-22.

20. Young PJ, Bailey M, Bellomo R, et al. Conservative or liberal oxygen therapy in adults after cardiac arrest: an individual-level patient data meta-analysis of randomised controlled trials. Resuscitation 2020;157:15-22.

21. Bro-Jeppesen J, Johansson PI, Kjaergaard J, et al. Level of systemic inflammation and endothelial injury is associated with cardiovascular dysfunction and vasopressor support in post-cardiac arrest patients. Resuscitation 2017;121:179-86.

22. Wiberg S, Stride N, Bro-Jeppesen J, et al. Mitochondrial dysfunction in adults after out-of-hospital cardiac arrest. Eur Heart J Acute Cardiovasc Care 2020;9:Suppl:S138-S144.

23. Ebmeier SJ, Barker M, Bacon M, et al. A two centre observational study of simultaneous pulse oximetry and arterial oxygen saturation recordings in intensive care unit patients. Anaesth Intensive Care 2018;46:297-303.

24. Nolan JP, Sandroni C, Böttiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. Intensive Care Med 2021;47:369-421.

25. Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Intensive Care Med 2014;40:1816-31.