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Clinical paper

Lower versus higher oxygenation targets in hypoxaemic ICU patients after cardiac arrest

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Abstract

Aim: To investigate the effects of lower versus higher oxygenation targets in adult intensive care unit (ICU) patients with hypoxaemic respiratory failure after cardiac arrest.

Methods: Subgroup analysis of the international Handling Oxygenation Targets in the ICU (HOT-ICU) trial which randomised 2928 adults with acute hypoxaemia to targets of arterial oxygenation of 8 kPa or 12 kPa in the ICU for up to 90 days. Here, we report all outcomes up to one year in the subgroup of patients enrolled after cardiac arrest.

Results: The HOT-ICU trial included 335 patients after cardiac arrest: 149 in the lower-oxygenation group and 186 in the higher-oxygenation group. At 90 days, 96/147 patients (65.3%) in the lower-oxygenation group and 111/185 patients (60.0%) in the higher-oxygenation group had died (adjusted relative risk (RR) 1.09, 95% confidence interval (CI) 0.92–1.28, $p = 0.32$); similar results were found at one year (adjusted RR 1.05, 95% CI 0.90–1.21, $p = 0.53$). Serious adverse events (SAEs) in the ICU occurred in 23% of patients in the lower-oxygenation group and 38% in the higher-oxygenation group (adjusted RR 0.61, 95% CI 0.43–0.86, $p = 0.005$); the difference was mainly due to more new episodes of shock in the higher-oxygenation group. No statistically significant differences were observed in other secondary outcomes.

Conclusion: A lower oxygenation target in adult ICU patients with hypoxaemic respiratory failure after cardiac arrest did not result in lower mortality, but fewer SAEs occurred in this group compared to the higher-oxygenation group. All analyses are exploratory only, large-scale trials are needed for confirmation.

Clinical Trial Registry: Clinicaltrials.gov number NCT03174002 (registered May 30, 2017); EudraCT 2017-000632-34 (registered February 14, 2017).

Keywords: Oxygen Inhalation Therapy, Intensive care units, Randomized Controlled Trial, Post-Cardiac Arrest Syndrome, Mortality, Quality of life

Introduction

Oxygen therapy is essential in the immediate care of patients resuscitated from cardiac arrest.[1,2] The period following return of spontaneous circulation (ROSC) is characterised by the post-cardiac arrest syndrome, a unique pathophysiological condition where systemic ischaemia–reperfusion injury occurs.[3] Although it is important to maintain sufficient oxygen delivery to avoid tissue hypoxia, hyperoxaemia may be harmful by exacerbating the production of oxygen free radicals, subsequently worsening reperfusion injury.[4,5] In the past decade, several randomised clinical trials (RCTs) have investigated two or more differentiated oxygenation targets in patients resuscitated from cardiac arrest and admitted to the intensive care unit (ICU) in selected,[6,7] or in heterogenous ICU populations.[8–10] However, results from these trials are equivocal, and the optimum oxygenation target in post-cardiac arrest patients remains a matter of debate.[11,12] Nevertheless, the latest guidelines on post-resuscitation care, co-issued by the European Resuscitation Council and the European Society of Intensive Care Medicine, recommend avoiding both hypoxaemia and hyperoxaemia by maintaining an SpO_2 between 94 and 98%.[1]

The Handling Oxygenation Targets in the ICU (HOT-ICU) trial is the largest published trial exploring the benefits and harms of a lower versus a higher oxygenation target in ICU patients with acute hypox-

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aemic respiratory failure, enrolling a total of 2928 patients.[13] The trial's hypothesis was that an arterial partial pressure of oxygen (PaO_2) of 8 kPa would reduce 90-day all-cause mortality as compared with a PaO_2 of 12 kPa. Results for the entire cohort demonstrated no between-group differences in neither the primary outcome nor in any secondary outcomes.[13,14]

Here we report the analysis of a prespecified subgroup to investigate the benefits or harms of a lower versus a higher oxygenation target during ICU admission in patients resuscitated from cardiac arrest and included in the HOT-ICU trial.[15,16]

Methods

Trial design

This is a subgroup analysis of patients randomised in the HOT-ICU trial and resuscitated from cardiac arrest before randomisation. The HOT-ICU trial was an investigator initiated, international, parallel-group, randomised, pragmatic clinical trial investigating the benefits and harms of a lower versus a higher oxygenation target in patients acutely admitted to the ICU with hypoxaemic respiratory failure.[13] Post-cardiac arrest patients were a planned subgroup of the HOT-ICU trial, specified prior to randomisation of the last patient.[15] The protocol, statistical analysis plan, and primary analyses of the trial have been published elsewhere.[13–16] This report was prepared in agreement with the Consolidated Standards of Reporting Trials (CONSORT) (checklist is presented in the Electronic Supplementary Material (ESM)).[17] The trial was approved by local and national authorities as required (ESM).

Patients

Inclusion criteria in the HOT-ICU trial were: age $\geq$18 years; acutely admitted to an ICU; receiving oxygen supplementation in a closed system (invasive mechanical ventilation, non-invasive mechanical ventilation, or mask/helmet continuous positive airway pressure) at a fraction of inspired oxygen (FiO_2) $\geq$0.50 or receiving $\geq$10 litres of oxygen in an open oxygen supplementation system; having an expected requirement for oxygen supplementation in the ICU for $\geq$24 hours; and having a functioning arterial cannula for arterial blood gas (ABG) sampling. In the current subgroup analysis, only patients resuscitated from cardiac arrest before randomisation were included. Patients were screened for inclusion within 12 hours of ICU admission. Cardiac arrest was defined as cardiac arrest of any type with initiated cardiopulmonary resuscitation (CPR) leading to or happening during the index ICU admission. Additional details are presented in the ESM.

Randomisation and intervention

Randomisation was performed via a computer-generated allocation sequence with permuted blocks of varying sizes, stratified according to the presence or absence of chronic obstructive pulmonary disease (COPD), presence or absence of active haematological malignancy, and trial site. Patients were randomised 1:1 to a PaO_2 of either 8 kPa or 12 kPa and were to adhere to the allocated target during ICU admission for up 90 days, including any ICU re-admissions. Additional details are available elsewhere.[16] We registered the highest and lowest PaO_2 in pre-defined 12-hour intervals with concomitant values of arterial oxygen saturation (SaO_2) and FiO_2.

Outcomes

The primary outcome was all-cause mortality 90 days after randomisation. Secondary outcomes at 90 days were: days alive without life-support (being respiratory support, circulatory support, or renal replacement therapy (RRT)); days alive and out of hospital; and proportion of patients with one or more serious adverse events (SAEs) in the ICU (defined as new episodes of either shock, cardiac ischaemia, intestinal ischaemia, or cerebral ischaemia). Secondary one-year outcomes were: all-cause mortality, and health-related quality-of-life (HRQoL) measured by EuroQol visual analogue scale score (EQ-VAS), and EuroQol five dimensions five level questionnaire (EQ-5D-5L).[18,19] Additional details are available in the ESM.

Statistical analysis

We performed all analyses in the intention-to-treat cohort being all randomised patients who were resuscitated from cardiac arrest before randomisation except those for whom data was unavailable due to negative or unobtainable consent according to national regulations. Both mortality outcomes, and proportion of patients with one or more SAEs in the ICU were evaluated using a generalised linear model with a binomial error distribution and a log-link to produce a risk ratio (RR), and an identity link to produce a risk difference (RD). We adjusted for the stratification variables COPD and active haematological malignancy; adjustment for trial site was not possible. Additional analyses of both mortality outcomes were conducted using a logistic regression model adjusted for all stratification variables together with important prognostic baseline risk factors being age, active metastatic cancer, type of ICU admission (medical, elective surgical or emergency surgical) and the Sequential Organ Failure Assessment score (SOFA).[20] Mortality analyses were supplemented by Kaplan-Meier plots, and Cox-proportional hazard models adjusted for all stratification variables. Days alive without life-support and days alive and out of hospital were evaluated using the van Elteren test adjusting for trial site only. Regarding HRQoL outcomes as measured by the EQ-VAS and EQ-5D-5L, we primarily report the results for patients alive at one-year follow-up in accordance with our primary analysis of long-term outcomes.[14] A Wilcoxon Rank-Sum test was used in these analyses. Analyses in the entire intention-to-treat population were also conducted, assigning the worst possible scores for EQ-VAS (i.e. zero) and EQ-5D-5L dimensions (i.e. five) to non-survivors, assuming death as the worst possible health state in terms of self-rated scores.[15] Here, a van Elteren test adjusting for trial site only was used.

We assessed the heterogeneity of the intervention effects on all outcomes testing the entire HOT-ICU cohort for the interaction between target allocation and having been resuscitated from cardiac arrest or not at baseline. Dichotomous outcomes were tested using a generalised linear model with a binomial error distribution and a log-link, whereas continuous outcomes were assessed using a generalised linear model with Gaussian distribution and an identity-link, regardless of whether normality assumptions were met or not.

Categorical variables are presented as numbers and percentages, and continuous variables as means and standard deviations, or medians and inter-quartile ranges (IQR), as appropriate. In the adjustment for the stratification variable site, the sites with fewest randomisations were pooled as necessary to obtain convergence in the models. All results are presented with 95% confidence intervals (CIs), and a P-value below 5% was considered statistically significant. No adjustment for multiplicity was performed. Although P-

values were dichotomised for statistical significance at a 5% threshold, all analyses should be considered exploratory. All analyses were conducted using STATA statistical software, release 17 (Stata Nordic).

Results

Patient characteristics

Recruitment in the HOT-ICU trial was conducted from June 20, 2017, to August 3, 2020. Of the 2928 patients included, 335 were resuscitated from cardiac arrest before randomisation and eligible for the current subgroup analysis: 149 patients were randomised to the lower oxygenation target and 186 patients to the higher oxygenation target. Three patients were lost to follow-up at 90 days due to withdrawal of consent yielding a follow-up rate of 99.1% for the primary outcome. Among patients alive after one year post-randomisation, 86/105 (81.9%) participated in HRQoL interviews (Fig. 1). Study groups were similar at baseline, except for a larger proportion of men, and patients with acute respiratory distress syndrome in the lower-oxygenation group (Table 1).

When compared to the remaining HOT-ICU cohort, this subgroup was more rapidly admitted to the ICU, had higher proportions of heart disease, and was more often in long-term dialysis. Around three times as many patients in this subgroup as compared to the remaining cohort had myocardial infarction at randomisation, almost all were invasively mechanically ventilated, a larger proportion received infusion of inotropes or vasopressors, and the baseline SOFA score was higher (Table S1).

Oxygenation parameters and ICU treatment

The daily patient-means of PaO_2, SaO_2, and FiO_2 for the first 30 days are presented in Fig. 2. Data on oxygenation parameters for the entire 90-day intervention period are presented in Figs. S1-S3. An average of 6–7 ABGs were conducted daily per patient in both groups as shown in Table S2, where details on the number of

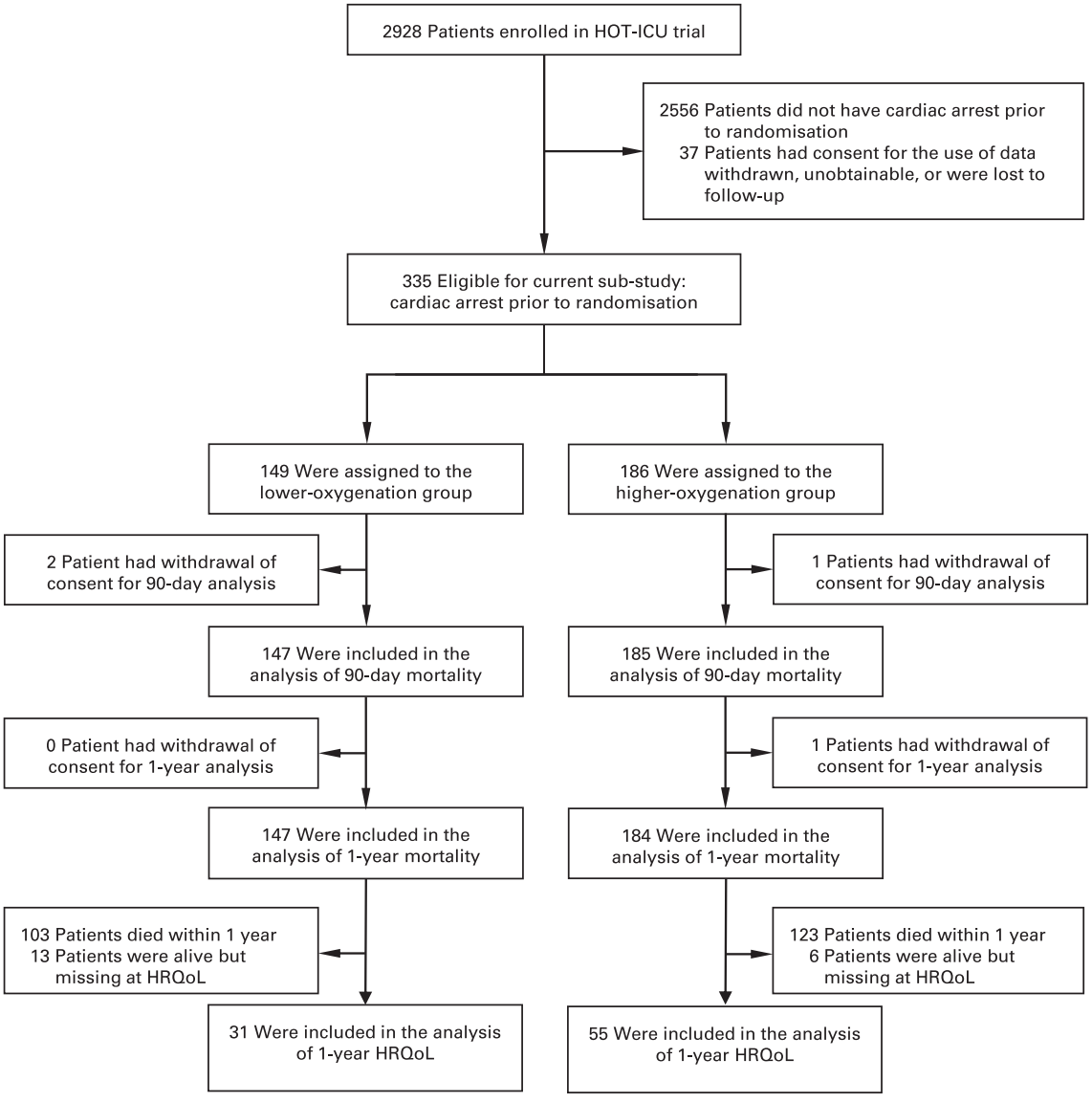


Fig. 1 – Patient flow. HOT-ICU denotes Handling Oxygenation Targets in the Intensive Care Unit; HRQoL health-related quality of life.

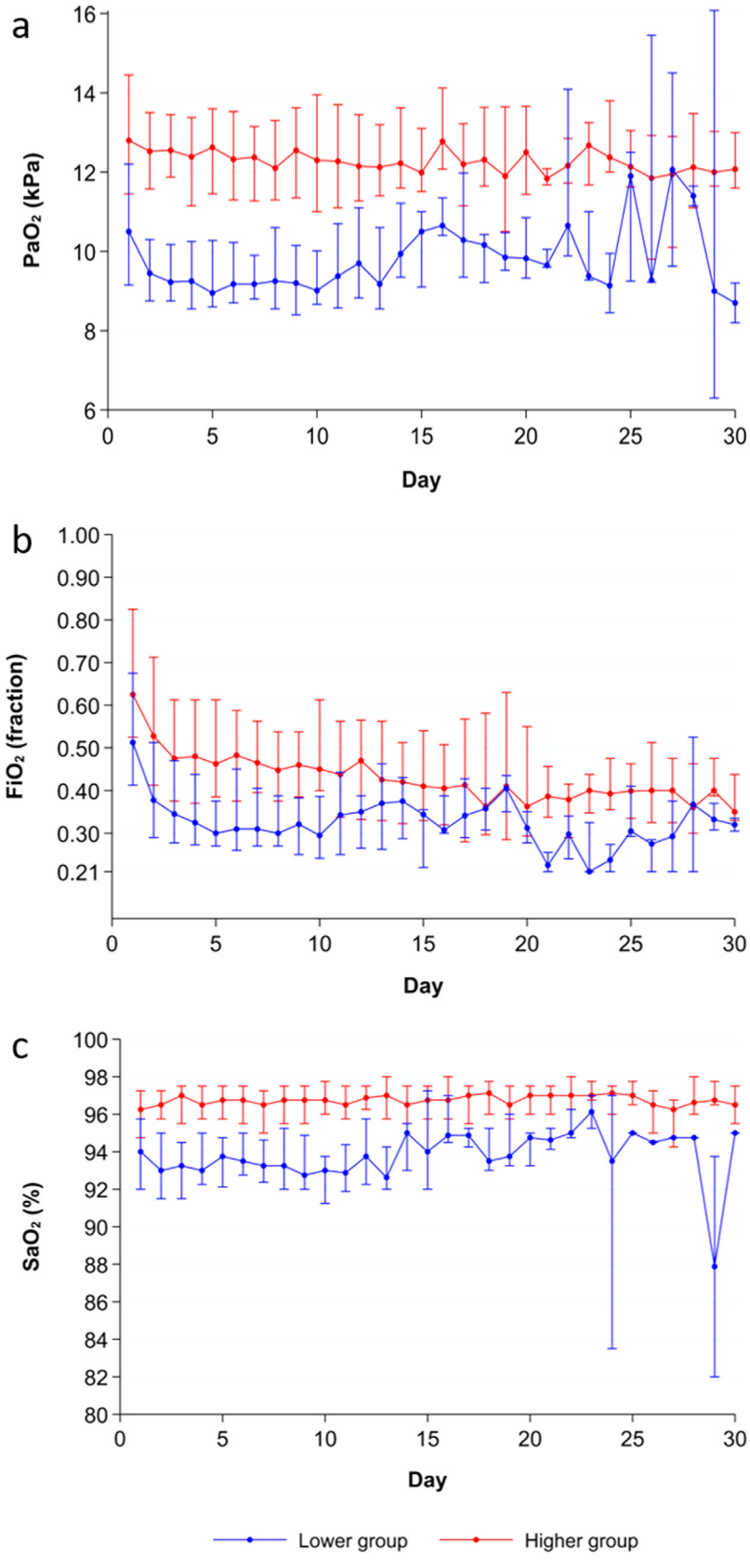
Table 1 – Baseline characteristics of patients resuscitated from cardiac arrest.

Variable	Lower-oxygenation group (N = 149)	Higher-oxygenation group (N = 186)
Age, median (IQR)	70 (62–76)	71 (64–78)
Male sex, n (%)	92 (61.7)	138 (74.2)
Median interval between hospital admission and randomisation, days (IQR)	1 (0–4)	1 (0–2)
Median time from ICU admission to randomisation, hours (IQR)	4 (2–6)	3 (2–6)
Co-existing illness, n (%)		
Ischaemic heart disease	30 (20.1)	45 (24.2)
Chronic heart failure	18 (12.1)	35 (18.8)
Active metastatic cancer	3 (2.0)	5 (2.7)
Long-term dialysis	4 (2.7)	10 (5.4)
COPD	19 (12.8)	37 (19.9)
Active haematological malignancy	9 (6.0)	6 (3.2)
Type of admission		
Medical	138 (92.6)	156 (83.9)
Elective surgery	0 (0.0)	2 (1.1)
Emergency surgery	11 (7.4)	28 (15.1)
Acute illness, n (%)		
Pneumonia	49 (32.9)	61 (32.8)
Multiple trauma	0 (0.0)	1 (0.5)
Haemorrhagic or ischaemic stroke	5 (3.4)	4 (2.2)
Traumatic brain injury	2 (1.3)	1 (0.5)
Myocardial infarction	18 (12.1)	34 (18.3)
Intestinal ischaemia	2 (1.3)	3 (1.6)
Active haematological malignancy	9 (6.0)	6 (3.2)
ARDS	20 (13.4)	12 (6.5)
Invasive mechanical ventilation		
Patients, n (%)	142 (95.3)	175 (94.1)
Median tidal volume, ml (IQR)	491 (402–554)	500 (430–579)
Median end-expiratory pressure, cmH_2O (IQR)	8 (6–10)	8 (6–10)
Median peak pressure, cmH_2O (IQR)	26 (21–31)	26 (21–29)
Non-invasive ventilation or CPAP		
Patients, n (%)	1 (0.7)	3 (1.6)
Median end-expiratory pressure, cmH_2O (IQR)	5 (5–5)	10 (7–16)
Open system, n (%)	6 (4.0)	8 (4.3)
Median PaO_2, kPa (IQR)	11.0 (9.2–14.3)	11.3 (9.1–13.8)
Median SaO_2, % (IQR)[a]	95 (92–98)	95 (91–97)
Median FiO_2, fraction (IQR)	0.70 (0.60–0.90)	0.70 (0.60–0.90)
Median PaO_2:FiO_2 ratio, kPa (IQR)	17.2 (12.1–22.5)	16.6 (11.9–21.8)
Median lactate concentration, mM (IQR)	3.3 (1.9–6.4)	3.2 (1.7–5.6)
Use of vasopressors, n (%)	11 (7.4)	11 (5.9)
Median SOFA score (IQR)	11 (10–12)	11 (9–12)

There were no significant differences between groups in any baseline characteristic except proportion of men ($p = 0.01$) and patients with ARDS ($p = 0.03$). A chi-squared test for categorical data and a Wilcoxon rank-sum test for continuous data were used. IQR denotes interquartile range, ICU intensive care unit, COPD chronic obstructive pulmonary disease, ARDS acute respiratory distress syndrome, CPAP continuous positive airway pressure, PaO_2 arterial partial pressure of oxygen, SaO_2 arterial oxygen saturation, FiO_2 fraction of inspired oxygen, SOFA score sequential organ failure assessment score. SOFA scores range from 0 to 24, with higher scores indicating more severe organ failure.[20]

[a] Data for arterial oxygen saturation (SaO_2) were not available for 13 patients in the lower-oxygenation group and for 12 patients in the higher-oxygenation group because this parameter was not available in blood gas analyses at one site.

Fig. 2 – Values of the daily patient-means of PaO_2, FiO_2, and SaO_2 stratified by treatment allocation. Displayed as median values of arterial partial pressure of oxygen (PaO_2) (a), fraction of inspired oxygen (FiO_2) (b), and arterial oxygen saturation (SaO_2) (c) until 30 days after randomisation. Bars represent inter-quartile ranges. Daily patient-means were calculated from the 12-hours highest and lowest PaO_2 with concomitant FiO_2 and SaO_2. Data for arterial oxygen saturation (SaO_2) were not available for 13 patients in the lower-oxygenation group and for 12 patients in the higher-oxygenation group because this parameter was not available in blood gas analyses at one site. Details on number of patients providing data for each parameter are provided in Table S2. Additional data on oxygenation parameters are presented in Figs. S1-S3.


a
PaO2 (kPa)
16
14
12
10
8
6
0
5
10
15
20
25
30
Day
b
FiO2 (fraction)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.21
0
5
10
15
20
25
30
Day
c
SaO2 (%)
100
98
96
94
92
90
88
86
84
82
80
0
5
10
15
20
25
30
Day
Lower group
Higher group

patients providing data on oxygenation by days are available. Median PaO_2 in the ICU through-out the 90-day intervention period in the lower-oxygenation group was 9.8 kPa (IQR 9.1–10.8 kPa) versus 12.7 kPa (IQR 11.7–13.2 kPa) in the higher-oxygenation group; median FiO_2 in the lower-oxygenation group was 0.39 (IQR 0.33–0.51) versus 0.53 (IQR 0.44–0.67) in the higher-oxygenation group; median SaO_2 in the lower-oxygenation group was 93% (IQR 91–95%), versus 96% (IQR 95–97%) in the higher-oxygenation group. We found no differences in the use of invasive mechanical ventilation or ventilator settings, inhaled vasodilators, prone positioning, extracorporal membrane oxygenation, vasopressors or inotropes, red blood cell transfusions, or RRT (Table S3).

Outcomes

At 90 days post-randomisation, 96 of 147 patients (65.3%) in the lower-oxygenation group and 111 of 185 patients (60.0%) in the higher-oxygenation group had died: adjusted RR 1.09 (95% CI 0.92–1.28), $p = 0.32$. At one year, 103 of 147 patients (70.1%) in the lower-oxygenation group and 123 of 184 patients (66.9%) in the higher-oxygenation group had died: adjusted RR 1.05 (95% CI 0.90–1.21), $p = 0.53$ (Table 2). Mortality results were similar in the secondary analyses adjusted for stratification variables and important prognostic baseline risk factors (Table 2). Kaplan-Meier survival plots are presented in Fig. 3. SAEs occurred in 22.8% in the lower-oxygenation group and in 38.2% in the higher-oxygenation group: adjusted RR 0.61 (95% CI 0.43–0.86, $p = 0.005$) (Table 2). The remaining secondary 90-day outcomes are presented in Table 2. In survivors at one-year follow-up the median EQ-VAS was 75 (IQR 60 to 80) in the lower-oxygenation group versus 70 (IQR 50 to 85) in the higher-oxygenation group ($p = 0.65$) (Table 2). A higher frequency of moderate pain was reported in the lower-oxygenation group (Fig. 4 and Table S4). The analyses of HRQoL in the intention-to-treat population are reported in Tables 2 and S5.

When tested in the entire HOT-ICU cohort, a significant interaction between target allocation and being resuscitated from cardiac arrest was found for the SAE outcome ($p = 0.006$) whereas no significant interaction was found for the remaining outcomes (Table S6).

Table 2 – Outcomes.

Variable	Lower-oxygenation group (N = 149)	Higher-oxygenation group (N = 186)	Adjusted RR (95% CI)[a]	Adjusted RD (95% CI)[a]	Adjusted OR (95% CI)[b]	P-value
90-day all-cause mortality, n (%)[c]	96 (65.3)	111 (60.0)	1.09 (0.92–1.28)	5.6 (-4.9–16.0)	1.26 (0.77–1.99)	0.32[e]
1-year all-cause mortality, n (%)[d]	103 (70.1)	123 (66.9)	1.05 (0.90–1.21)	3.4 (-6.7–13.5)	1.19 (0.71–1.99)	0.53[e]
Median number of days alive without life-support at 90 days (IQR)[f]	0 (0 to 81)	9 (0 to 81)				0.18[g]
Median number of days alive and out of hospital at 90 days (IQR)	0 (0 to 56)	0 (0 to 55)				0.20[g]
Number of patients with one or more SAEs in the ICU, n (%)	34 (22.8)	71 (38.2)	0.61 (0.43–0.86)	−14.9 (-24.5–5.2)		0.005[e]
New episode of shock	30 (20.1)	67 (36.0)				
New myocardial infarction	2 (1.3)	2 (1.1)				
New ischaemic stroke	0 (0.0)	0 (0.0)				
New intestinal ischaemia	5 (3.4)	3 (1.6)				
Median EQ-VAS (IQR)						
Intention-to-treat population	0 (0–0)	0 (0–40)				0.11[h]
Survivors[i]	75 (60–80)	70 (50–85)				0.65[j]

RR denotes relative risk, RD risk difference and is presented in percentages points; OR odds ratio; CI confidence interval; SAE serious adverse event; ICU intensive care unit; EQ-VAS EuroQol visual analogue scale. EQ-VAS score ranges from 0 to 100, with higher scores indicating better health status.[18,19] Non-survivors at one-year were assigned the lowest possible EQ-VAS score of 0.

[a] Generalised linear model for the RR or the RD with a log-link or an identity-link, respectively, and binomial error distribution with adjustment for the presence or absence of chronic obstructive pulmonary disease (COPD), and of active haematological malignancy. Adjustment for trial site at randomisation was not possible.

[b] Logistic regression model with adjustments for COPD, active haematological malignancy, and trial site at randomisation together with important prognostic baseline risk factors being age, active metastatic cancer, type of ICU admission (medical, elective surgical or emergency surgical) and the Sequential Organ Failure Assessment score.[20] The 10 sites with fewest randomisations were pooled to obtain convergence in the models.

[c] 2 missing patients in the lower-oxygenation group and 1 missing patient in the higher-oxygenation group.

[d] 2 missing patients in the lower-oxygenation group and 2 missing patients in the higher-oxygenation group.

[e] P-value of the adjusted relative risk.

[f] Life support defined as the use of invasive mechanical ventilation, non-invasive ventilation, continuous positive airway pressure (non-intermittently), vasopressor or inotropic infusion, or any type of renal replacement therapy.

[g] van Elteren test, adjusted for trial site at randomisation. The 12 sites with fewest randomisations were pooled to obtain convergence in the model.

[h] van Elteren test, adjusted for trial site at randomisation. The 7 sites with fewest randomisations were pooled to obtain convergence in the model.

[i] 31 patients in the lower-oxygenation group and 55 patients in the higher-oxygenation group responded to the health-related quality of life (HRQoL) questionnaire. 13 patients were alive but missing at the HRQoL questionnaire in the lower-oxygenation group and 6 in the higher-oxygenation group. 1 patient in the higher-oxygenation group had unobtainable answer for EQ-VAS.

[j] Wilcoxon Rank-Sum test.

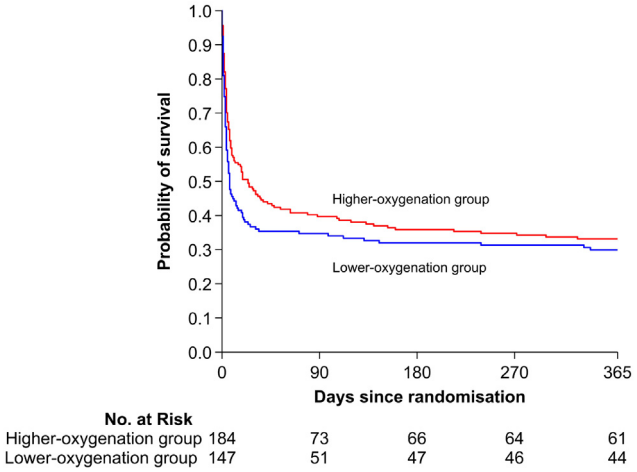


Fig. 3 – Kaplan-Meier plots for survival, administratively censored at 365 days. Hazard ratios from Cox proportional-hazards models adjusted for the presence or absence of chronic obstructive pulmonary disease, presence or absence of active haematological malignancy, and trial site: 90-day all-cause mortality: 1.29 (95% CI 0.98–1.71); 1-year all-cause mortality: 1.24 (95% CI 0.95–1.61).

Discussion

In this subgroup analysis of the HOT-ICU trial,[13] including patients resuscitated from cardiac arrest and admitted to the ICU with hypoxaemic respiratory failure, a lower oxygenation target (PaO_2 = 8 kPa) did not improve survival at 90 days nor one year, as compared with a higher oxygenation target (PaO_2 = 12 kPa). It appeared that fewer patients in the lower-oxygenation group had one or more SAEs in the ICU within 90 days than those in the higher-oxygenation group. No statistically significant differences were detected in other secondary outcomes, except for the pain component of EQ-5D-5L questionnaire among survivors.

We included all patients resuscitated from cardiac arrest prior to randomisation in the HOT-ICU trial, being 335 patients, equivalent to 11% of the entire cohort. Almost all patients were invasively mechanically ventilated at baseline, suggestive of an initial comatose status as the result of cardiac arrest. The overall mortality in the present subgroup was remarkably higher than in the main trial cohort; 62% versus 42% at 90 days, and 67% versus 48% at one year.[13,14] A shorter time interval between hospital admission and randomisation, higher SOFA score, and a larger proportion needing vasopressors and/or inotropes at baseline reflect increased disease severity in this subpopulation in comparison with the remaining cohort. The point estimates of the mortality outcomes are suggestive of a potential benefit of the higher oxygenation target. However, the wide CIs do not preclude important clinical benefit of the lower oxygenation strat-

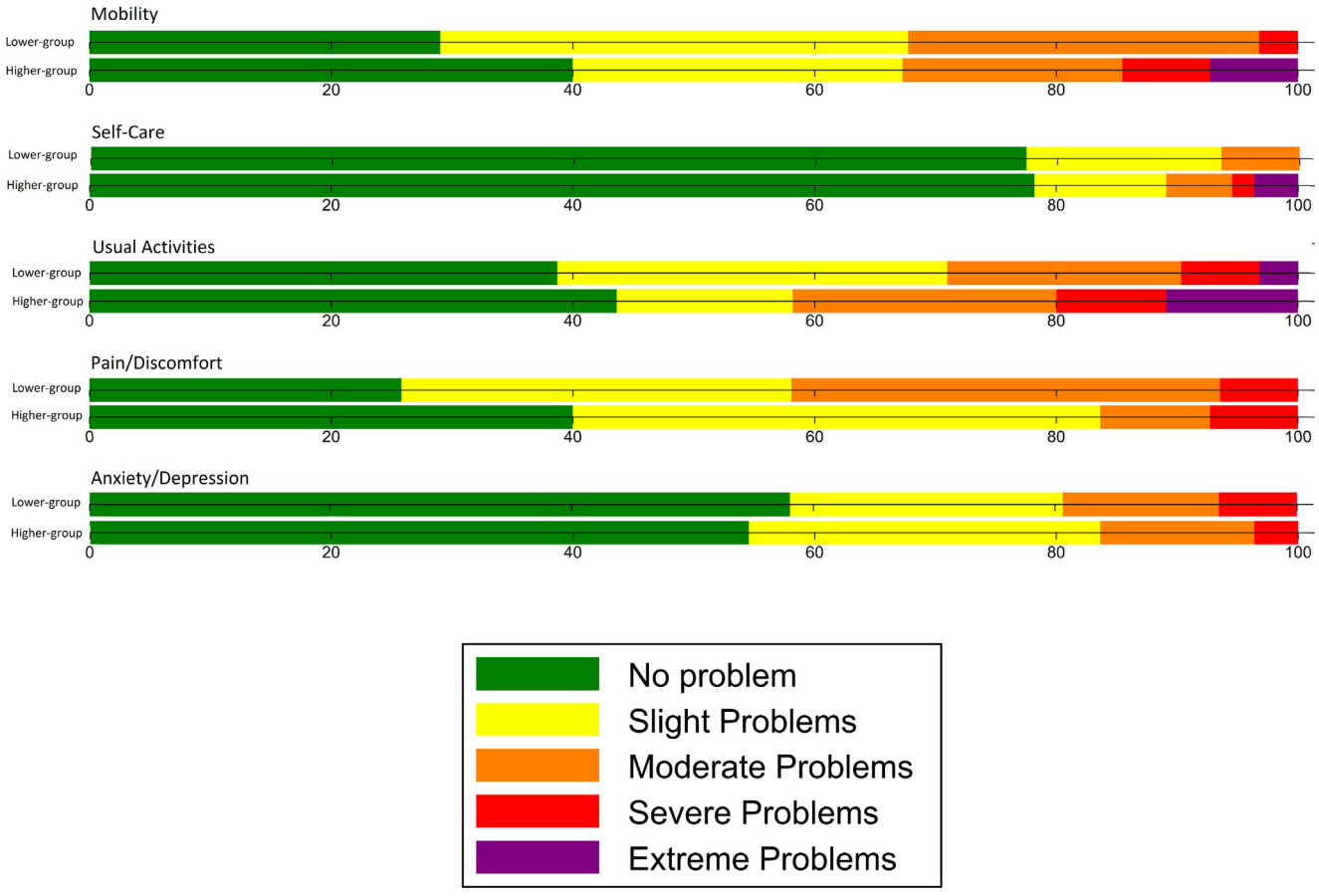


Fig. 4 – Distribution of EQ-5D-5L scores among one-year survivors. EQ-5D-5L denotes EuroQol five dimensions five-level questionnaire.[18,19] Values are from the responding survivors (N = 31 in the lower oxygenation group; N = 55 in the higher oxygenation group). The corresponding numeric data are presented in Table S5.

egy, which underscores the need for larger trials to inform clinical practice. Conversely, we found a significant difference in the proportion of patients with one or more SAEs, estimating a risk reduction between 14% and up to 57% favouring the lower-oxygenation group, supported by a significant interaction test on this outcome for patients resuscitated from cardiac arrest versus the remaining trial cohort. This effect was predominantly driven by a marked reduction in new episodes of shock during ICU admission. The discrepancy in point estimates between SAE and mortality outcomes might be explained by the definition of shock in the HOT-ICU trial being a plasma lactate above 2 mmol/L and the use of continuous vasopressor or inotropic treatment, which may not represent disease severity or impact mortality significantly. Interestingly however, the finding matches a recent meta-analysis which found a lower incidence of SAEs in the general ICU population when using lower oxygenation strategies.[21] Nevertheless, the result should be interpreted with caution due to the explorative nature of the current analyses. The HRQoL scores in survivors at one-year follow-up indicated a slightly better status in comparison with main HOT-ICU trial cohort,[14] but still reduced compared to the general Danish population.[22] The domains of EQ-5D-5L questionnaire were well-balanced between the groups except for pain, where a higher frequency of moderate problems was observed in the lower-oxygenation group. This finding is possibly of spurious nature, given the small population, and absence of multiple imputation analysis accounting for missing patients.

Relationship to previous trials

Four RCTs have investigated the potential benefits of lower versus higher oxygenation strategies in post-cardiac arrest patients in the ICU setting.[6–10] The Carbon Dioxide, Oxygen and Mean arterial pressure After Cardiac Arrest and REsuscitation (COMACARE) trial (N = 60) and the Blood Pressure and Oxygenation Targets in Post Resuscitation Care (BOX) trial (N = 802) included patients resuscitated from out-of-hospital cardiac arrest of presumed cardiac cause and needing mechanical ventilation.[6,7] Neither trial found statistically significant differences in mortality nor in proportion of patients with favourable neurologic outcome. The reported mortality rates were substantially lower than ours, potentially due to differences in inclusion criteria – i.e., moderate-to-severe hypoxaemia and cardiac arrest of any cause to be included in this subgroup of the HOT-ICU trial. A sub-study of the Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen Therapy (ICU-ROX) trial analysed patients with suspected hypoxic ischaemic encephalopathy, regardless of the location or cause of cardiac arrest (N = 166/1000).[9] Similarly, the recently published Pragmatic Investigation of Optimal Oxygen Targets (PILOT) cluster-crossover trial investigating three ranges of SpO_2 in mechanically ventilated patients admitted to a medical ICU, also included patients resuscitated from cardiac arrest of any cause (N = 334/2541).[10] Both trials suggested a possible benefit of a lower oxygenation target in the post-cardiac arrest subset of patients, and they reported higher mortality rates than the COMACARE and the BOX trial, with the subgroup of the PILOT trial having a similar mortality (69.8%) as our current subgroup. Importantly, a key limitation in comparing all these trials is that they vary vastly in several aspects of their conduct. Patients included in the HOT-ICU trial differ from others given the presence of hypoxaemia which may have affected the disease severity of the subpopulation. Regarding the oxygenation thresholds, the COMACARE trial systematically targeted moderate hyperoxaemia, whereas the ICU-ROX, HOT-ICU, and BOX trials targeted oxygenation levels within the normoxic range. In the higher-oxygenation group of the PILOT trial, moderate hyperoxaemic values were also recorded. Enrolment windows and lengths of intervention periods are also markedly heterogenous among the trials.

Strengths and limitations

A strength of our sub-study is the clear separation in oxygenation parameters for the entire intervention period, corresponding to a between-group difference of almost 3 kPa, which is greater than that observed in the ICU-ROX,[8,9] and similar to the COMACARE and PILOT trials.[6,10] The BOX trial did not report the exact levels of the oxygenation targets, but an overlap between the two groups was noticed in the first 48 hours post-randomisation.[7] In our study, robust division in oxygenation parameters was reached from day one, further strengthening our findings since the early period after cardiac arrest has been advocated as crucial in the potential pathophysiological cascade between high oxygen levels and brain injury.[23,24] Some limitations must be considered. We did not record information of specific relevance to this population, such as cardiac arrest location and timing, bystander response, first monitored rhythm, quality of CPR, and time intervals to response and to ROSC.[25] The lack of registered data which strongly predict outcomes in cardiac arrest is a major limitation since potential between-group imbalances at baseline may have affected our results. Another limitation is that patients in both oxygenation groups presented with higher-than-intended median PaO_2 (i.e., 9.8 versus 8 kPa in the lower-oxygenation group, and 12.7 versus 12 kPa in the higher-oxygenation group) when considering the entire intervention period; the numbers were even higher when compared to the main cohort (9.6 kPa and 12.4 kPa, respectively). These deviations can be caused by several reasons: clinicians´ hesitance to target oxygenation levels lower than those considered safe in the daily practice, especially in the care of post-cardiac arrest patients where the risk of hypoxic-ischaemic encephalopathy is consistent;[3] the fact that we only registered the 12-hour highest and lowest PaO_2 values, thus lending weight to the higher extreme measurements; and that patients may achieve higher PaO_2 values despite FiO_2 of 0.21. Moreover, the present study is markedly underpowered to detect the suggested mortality effects: with 80% power and an alpha of 5%, a total of 2614 patients would be needed to detect the suggested 90-day effect, and 6614 patient patients would be required for the suggested one-year effect. The adjustment for the stratification variable site was not possible in some analyses due to few randomisations at certain sites. Finally, the risk for type I error is large due to several subgroup analyses and no adjustment for multiplicity.

Conclusions

In conclusion, in ICU patients with hypoxaemic respiratory failure after cardiac arrest, a lower oxygenation target did neither result in reduced 90-day or one-year mortality nor in improved one-year HRQoL as compared with a higher oxygenation target. A lower target may have reduced the occurrence of SAEs in the ICU within 90 days. The current findings derive from exploratory analyses, and further large-scale trials are needed to provide sufficiently robust data to inform clinical practice.

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Ethics and Patient Consent

Consent was obtained from patients or legal surrogates according to applicable laws and regulations. Enrolment according to an emergency procedure (i.e., consent from a doctor independent of the trial followed by consent from relatives and/or patients) was allowed at many sites; additional details were presented in the primary report. HYPERLINK "SPS:refid::bib13" 13

CRediT authorship contribution statement

Elena Crescioli: Writing – original draft, Writing – review & editing. **Thomas Lass Klitgaard:** Writing – review & editing. **Anders Perner:** Conceptualization, Writing – review & editing. **Olav Lilleholt Schjørring:** Conceptualization, Writing – review & editing. **Bodil Steen Rasmussen:** Conceptualization, Writing – review & editing, Funding acquisition, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2023.109838.

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