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Oxygen targets and 6-month outcome after out of hospital cardiac arrest: a pre-planned sub-analysis of the targeted hypothermia versus targeted normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial

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Abstract

Background: Optimal oxygen targets in patients resuscitated after cardiac arrest are uncertain. The primary aim of this study was to describe the values of partial pressure of oxygen values (PaO_2) and the episodes of hypoxemia and hyperoxemia occurring within the first 72 h of mechanical ventilation in out of hospital cardiac arrest (OHCA) patients. The secondary aim was to evaluate the association of PaO_2 with patients' outcome.

Methods: Preplanned secondary analysis of the targeted hypothermia versus targeted normothermia after OHCA (TTM2) trial. Arterial blood gases values were collected from randomization every 4 h for the first 32 h, and then, every 8 h until day 3. Hypoxemia was defined as $PaO_2 < 60$ mmHg and severe hyperoxemia as $PaO_2 > 300$ mmHg. Mortality and poor neurological outcome (defined according to modified Rankin scale) were collected at 6 months.

Results: 1418 patients were included in the analysis. The mean age was 64 ± 14 years, and 292 patients (20.6%) were female. 24.9% of patients had at least one episode of hypoxemia, and 7.6% of patients had at least one episode of severe hyperoxemia. Both hypoxemia and hyperoxemia were independently associated with 6-month mortality, but not with poor neurological outcome. The best cutoff point associated with 6-month mortality for hypoxemia was 69 mmHg (Risk Ratio, RR = 1.009, 95% CI 0.93–1.09), and for hyperoxemia was 195 mmHg (RR = 1.006, 95% CI

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0.95–1.06). The time exposure, i.e., the area under the curve (PaO_2-AUC), for hyperoxemia was significantly associated with mortality ($p = 0.003$).

Conclusions: In OHCA patients, both hypoxemia and hyperoxemia are associated with 6-months mortality, with an effect mediated by the timing exposure to high values of oxygen. Precise titration of oxygen levels should be considered in this group of patients.

Trial registration: clinicaltrials.gov NCT02908308, Registered September 20, 2016.

Keywords: Cardiac arrest, Hypoxemia, Hyperoxemia, Mortality, Neurological outcome

Background

Cardiac arrest is a major cause of mortality and morbidity, and over the last years [1, 2], attention has risen toward the levels of oxygenation to achieve as an essential determinant of secondary brain injury and worsened outcomes [3]. Mechanical ventilation is commonly required to avoid hypoxemia [4], which is a well-known cause of anoxic brain injury promoting secondary brain and reperfusion-related damage [5, 6]. Recent literature has also focused on the role of hyperoxemia in critically ill patients [7–10]. Supplemental oxygen can correct hypoxemia, thereby supporting cell function, metabolism, and limiting organ dysfunction. However, it might have detrimental effects on patients' outcomes through different pathophysiological mechanisms, such as the production of reactive oxygen species and free radicals yielding secondary damage due to reperfusion injury [11–17]. Studies exploring the role of hypo- and hyperoxemia after cardiac arrest are not conclusive. They present several heterogeneities in terms of study design, sample size and outcome definition, as well as inconsistent results, especially when compared to the preclinical cardiac arrest models [8, 18–21].

We therefore performed a secondary analysis of the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial that included Out-of-Hospital Cardiac Arrest (OHCA) patients. The aim was to assess the oxygen targets, the incidence of episodes of hypoxemia and hyperoxemia in the first 72 h of mechanical ventilation, and their association with patients' 6-months outcome (mortality and neurological status).

Methods

This was a pre-planned secondary analysis of the TTM2 trial, which was an international, multicenter randomized controlled trial comparing the effects of normothermia (temperature ≤ 37.5 °C), versus hypothermia (target 33 °C until 28 h after randomization, and then rewarming to 37 °C) [22, 23]. This sub-analysis was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [24] (Additional file 1: Table S1). Ethical approval was obtained in the coordinating center and in each participating center as well as informed consent according to local regulations. This sub-study was conducted in accordance with the principles of the Declaration of Helsinki, and the Medical Research Involving Human Subjects Act (WMO) and was approved on the 23rd of February 2017 by the TTM2 steering committee (https://ttm2trial.org/substudy-proposals). The protocol of the analysis was published [22]. No further ethical approval was necessary for the development of this study.

Objectives and definitions

The primary aim was to describe the arterial partial pressure of oxygen (PaO_2) values observed in OHCA patients in the first 72 h of mechanical ventilation and the occurrence of episodes of hypo/hyperoxemia. As previous studies have considered arterial oxygen thresholds of < 60 mmHg and > 300 mmHg when evaluating associations between oxygen exposure and outcome [7, 8, 18, 25], we pre-specified that we would initially evaluate the same thresholds, and then, we aimed to calculate the "best" threshold of hypo/hyperoxemia associated with poor outcome. For primary analysis, three patients' groups according to conventional thresholds were defined: (1) hypoxemia with one or more episodes of PaO_2 levels < 60 mmHg; (2) normoxemia (including mild-moderate hyperoxemia, with PaO_2 levels between 60 and 300 mmHg; and (3) severe hyperoxemia with one or more PaO_2 levels > 300 mmHg. The secondary objectives were to assess: (1) the association between hypo/hyperoxemia during the first 72 h of mechanical ventilation with mortality and neurological outcome at 6-months; (2) the best threshold of hypo/hyperoxemia associated with mortality and poor neurological outcome; (3) the cumulative effect of the "dose" (oxygen exposure over time, PaO_2-Area Under the Curve, AUC) of hypo/hyperoxemia on mortality and poor neurological outcome at 6-months; 4) the effect of PaO_2 on outcome according to randomization in the normothermia versus hypothermia group.

Inclusion and exclusion criteria

Inclusion criteria of the TTM2 trial were patients 18 years of age or older admitted to the hospital after OHCA of non-traumatic or unknown cause with a return of spontaneous circulation (ROSC) requiring ICU admission and mechanical ventilation. Exclusion criteria were the following: unwitnessed OHCA with an initial rhythm of asystole, an interval from ROSC to screening over 180 min, temperature on admission < 30 °C, obvious or suspected pregnancy, intracranial bleeding at admission [22, 23]. For this sub-analysis, we further excluded patients who had no available data on PaO_2 in the first 24 h from hospital admission.

Data management and collection

Details on the study procedure and patients' clinical management have been previously described [22, 23]. Ventilatory management was performed according to local practice. Patients' data were collected at hospital admission, during the intensive care unit (ICU)-stay, at ICU-discharge, at hospital-discharge, and at 6-month follow-up [22, 23]. Data collected included patients' demographic characteristics, pre-cardiac arrest comorbidities (including Charlson comorbidity index [26]), location, timing, type and management of cardiac arrest, clinical presentation (presence of shock, ST-elevation myocardial infarction—STEMI), data on ventilator settings/parameters (tidal volume—V_T, positive end-expiratory pressure—PEEP, respiratory rate—RR, fraction of inspired oxygen—FiO_2, plateau pressure—Pplat, peak pressure—Ppeak, compliance of respiratory system—Crs), and arterial blood gases (ABG) values (pHa, PaO_2, partial pressure of carbon dioxide—$PaCO_2$, base excess) and clinical outcomes. Ventilatory settings and ABG values were collected from randomization every 4 h for the first 32 h, and then, every 8 h until day 3 (72 h).

Clinical outcome measures

Clinical outcome measures were mortality and patients' neurological outcome at 6-month follow-up, the latter evaluated through the Modified Rankin Scale (mRS). The mRS score for neurologic disability is a 7 categories scoring system, ranging from no symptoms (score 0) to patient's death (score 6), where poor neurological outcome is defined as a score ranging from 4 to 6. Follow-up data were obtained by study participants through telephone interview, postal questionnaire, or a face-to-face visit. Responses were obtained from patients or from a next of kin in cases of impaired cognitive capacity, which could prevent patient interview.

Statistical analysis

At baseline, data on patient characteristics, ventilator settings, and ABG were presented as means ± standard deviation, or medians [interquartile range (IQR)] for continuous variables, or as percentages for the categorical ones. The comparisons of means, medians, and frequencies among the three categories for PaO_2 were carried out using one-way ANOVA, Kruskal–Wallis' test, and chi-square test, respectively. When building a regression model, the process of variable selection comprised an initial model with: (1) patients' clinical characteristics (age, sex, body mass index—BMI, height, Charlson comorbidity index, state of shock at admission, and STEMI diagnosis on admission); (2) onsite-related cardiopulmonary resuscitation (CPR) related variables (ROSC time, bystander CPR, OHCA physical location, initial cardiac rhythm, witnessed OHCA); (3) treatment variables from the original trial (randomization arm and tympanic temperature at admission); and (4) ABG values and (5) ventilatory settings parameters. From this initial set of covariates, a more parsimonious model was developed by backward elimination using a multivariable fractional polynomial (FP) procedure [27]. The linearity assumption of continuous variables was tested, and the variable transformed with the appropriate FP when the assumption was not met. Risk estimates from the Cox regression and logistic regression models were expressed as hazard ratios (HRs) and Odds ratios (ORs) with 95% confidence intervals (95% CI), respectively. If PaO_2/PaO_2-AUC (as continuous) were modeled with a FP, their association with the endpoint was instead depicted through a graph where the HR/OR on the y-scale is plotted against the continuum of the marker.

The independent association between baseline PaO_2 (or PaO_2 groups-PaO_2_class) with 6-months mortality was evaluated with Cox regression analysis. As a sensitivity analysis, the area under the receiving operator curve (ROC) curve of all PaO_2 values (PaO_2-AUC) was calculated for each patient and tested in a Cox regression for mortality, which was built considering the repeated measures of PaO_2 as a single time point representing the numerical integration of PaO_2 values and the time between measurements. Therefore, PaO_2-AUC represents a sequential (cumulative) integration over time of all PaO_2 preceding values obtained during the first 72 h since ICU admission. Because we were interested exploring the prognostic value of PaO_2-AUC on hypoxemia and hyperoxemia, an interaction with PaO_2_class was included in the Cox regression model.

A 2-sided p value of < 0.05 was the threshold used for significance in all analyses. Stata 16.1 was used for data

clean-up, preparation, and statistical analysis. Further details on statistical methods are presented in the Additional file 1.

Results

Characteristics of the patients in the whole population

From a total of 1861 patients included in the TTM2 trial, 443 patients were excluded due to missing values in PaO_2 in the first 24 h, leaving a sample of 1418 patients (Table 1, Additional file 1: Tables S2, S3). The median age was 65 [IQR = 55–74] years, and 292 (20.6%) were female. At 6-month follow-up, 696 (49.1%) patients were dead, and 740 (55.9%) had poor neurological outcome. Additional file 1: Table S2 and S3 present patients' clinical characteristics, outcome measures, and ventilator settings, respectively, and according to the different classes of PaO_2.

PaO_2 distribution and the occurrence of episodes of hypo/hyperoxemia

At admission, the median PaO_2 value in the overall population was 108 mmHg [IQR = 83–163]. Seventy-nine patients (5.6%) presented a $PaO_2 < 60$ mmHg (median $PaO_2 = 51$ mmHg [IQR = 39.7–56.2]); 100 (7.1%) patients a $PaO_2 > 300$ mmHg (median $PaO_2 = 363$ mmHg [IQR = 330–433]); and 1239 (87.4%) patients had a PaO_2 between 60 and 300 mmHg (median $PaO_2 = 108$ mmHg [IQR = 85.5–148.5]). PaO_2 trajectories over the 72 h study period are shown in Additional file 1: Figure S1. Over the study period, 24.9% of patients had at least one episode of $PaO_2 < 60$ mmHg and 7.6% of patients had at least one episode of $PaO_2 > 300$ mmHg, Fig. 1. In most cases, patients had 1 or 2 episodes over the first 72 h, whereas more than 2 episodes were less frequent. The incidence rates (number of episodes per

Table 1 Baseline patients' characteristics, comorbidities, pre-hospital settings/interventions of the overall population and stratified according to oxygen values

	Overall (*n* = 1418, 100.0%)	$PaO_2 < 60$ mmHg (*n* = 79, 5.6%)	PaO_2 60–300 mmHg (*n* = 1239, 87.4%)	$PaO_2 > 300$ mmHg (*n* = 100, 7.1%)	*p* value
Baseline patient characteristics					
Age, years, median (IQR)	65 (55; 74)	66 (57; 75)	65 (55; 74)	66 (56; 74)	0.415
Gender, female, *n* (%)	292 (20.6)	13 (16.5)	250 (20.2)	29 (29.0)	0.071
Height, cm, median (IQR)	175 (170; 180)	176 (170; 180)	175 (170; 180)	170 (165; 179)	0.005
Weight, kg, median (IQR)	80 (73; 90)	85 (80; 93)	80 (73; 91)	80 (70; 88)	0.001
BMI, kg/m^2, median (IQR)	26.3 (24.1; 29.7)	27.4 (25.0; 30.6)	26.3 (24.1; 29.7)	26.1 (23.3; 28.4)	0.021
Chronic comorbidities					
Hypertension, yes, *n* (%)	504 (35.5)	25 (31.6)	449 (36.2)	30 (30.0)	0.115
Diabetes mellitus, yes, *n* (%)	266 (18.8)	15 (19.0)	234 (18.9)	17 (17.0)	0.896
Myocardial infarction, yes, *n* (%)	230 (16.2)	14 (17.7)	201 (16.2)	15 (15.0)	0.244
Percutaneous coronary intervention, yes, *n* (%)	210 (14.8)	14 (17.7)	181 (14.6)	15 (15.0)	0.130
Coronary artery bypass graft, yes, *n* (%)	112 (7.9)	7 (8.9)	98 (7.9)	7 (7.0)	0.219
Heart failure, yes, *n* (%)	145 (10.2)	9 (11.4)	127 (10.3)	9 (9.0)	0.206
Charlson comorbidity index, points, median (IQR)	4.0 (2.0; 5.0)	4.0 (3.0; 6.0)	4.0 (2.0; 5.0)	4.0 (2.3; 5.8)	0.517
Pre-hospital setting/interventions					
Location of cardiac arrest, *n* (%)					
Home	741 (52.3)	42 (53.2)	638 (51.5)	61 (61.0)	
Public place	509 (35.9)	27 (34.2)	452 (36.5)	30 (30.0)	
Other	168 (11.8)	10 (12.7)	149 (12.0)	9 (9.0)	0.474
Witnessed cardiac arrest, yes, *n* (%)	1295 (91.3)	71 (89.9)	1131 (91.3)	93 (93.0)	0.753
Bystander performed CPR, yes, *n* (%)	1148 (81.0)	63 (79.7)	1007 (81.3)	78 (78.0)	0.696
Type of rhythm, *n* (%)					
Not shockable	390 (27.5)	24 (30.4)	331 (26.7)	35 (35.0)	
Shockable	1028 (72.5)	55 (69.6)	908 (73.3)	65 (65.0)	0.558
Time of ROSC, minutes, median (IQR)	25 (17; 39)	25 (19; 39)	25 (17; 39)	25(18.3; 35.8)	0.558
TTM randomization treatment, *n* (%)					
Normothermia	712 (50.2)	46 (58.2)	615 (49.6)	51 (51.0)	0.330
Hypothermia	706 (49.8)	33 (41.8)	624 (50.4)	49 (49.0)	

Data are reported as median (interquartile range, IQR) and number (percentage, %). Legend: *n* = number of patients, BMI, body mass index, IBW, ideal body weight, ROSC, return of spontaneous circulation, CPR, cardio-pulmonary resuscitation, TTM, target temperature management

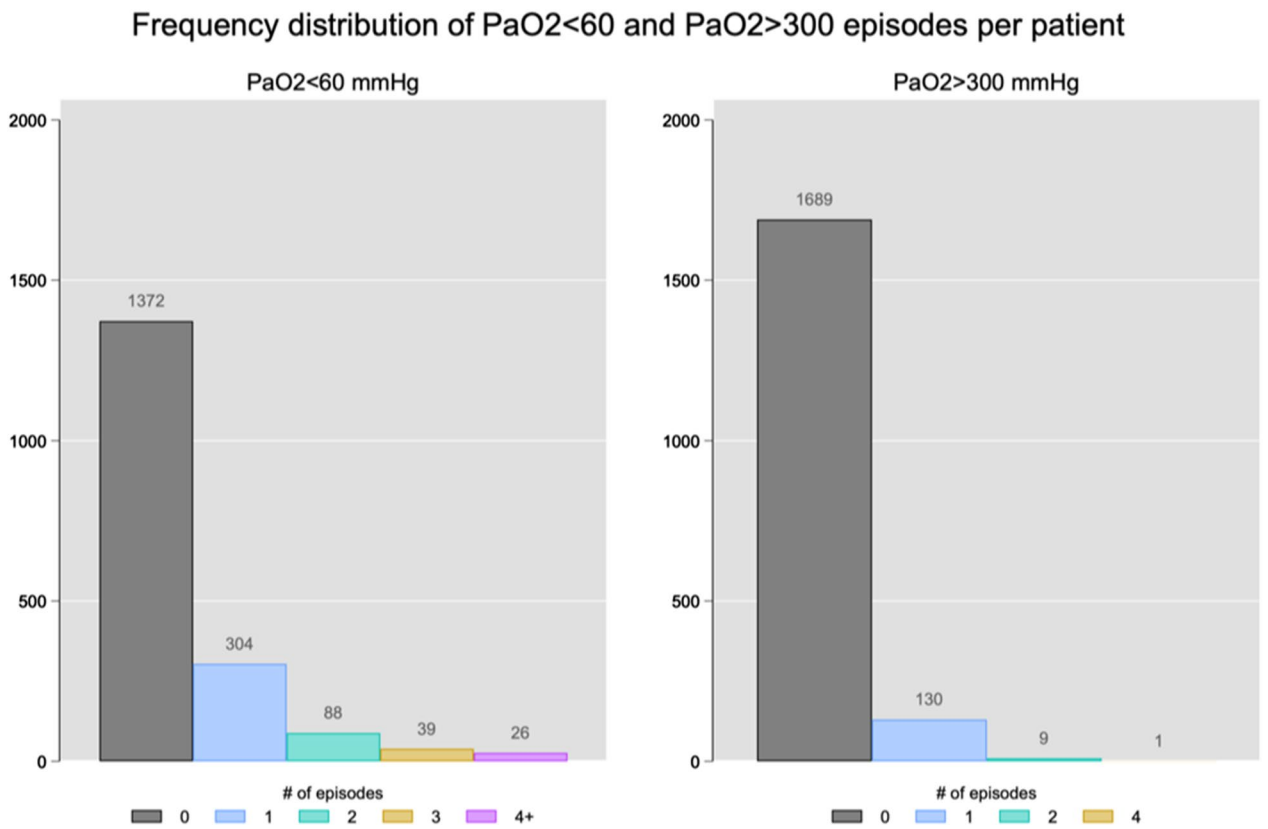

Fig. 1 Frequency distribution of arterial partial pressure of oxygen (PaO_2) classes (conventional thresholds). Number of hypoxemia (PaO_2 < 60 mmHg) or severe hyperoxemia (PaO_2 > 300 mmHg) episodes per patient during the first 72 h after intensive care unit admission. This figure was based on all patients included in the cohort, with a percent distribution as follow: Episodes of Hypoxemia = 0 (*n* = 1372 (75.01%), 1 (*n* = 304 (16.62%), 2 (*n* = 88 (4.81%), 3 (*n* = 39 (2.13%), 4 + (*n* = 26 (1.42%). Episodes of Hyperoxemia = 0 (*n* = 1689 (92.35%), 1 (*n* = 130 (7.11%), 2 (*n* = 9 (0.49%), 4 (*n* = 1 (0.05%)

person in the 72 h follow-up) for PaO_2 < 60 mmHg and PaO_2 > 300 mmHg were 0.42 (95% CI 0.39–0.45) and 0.08 (95% CI 0.07–0.10), respectively.

The association between hypo- and hyperoxemia with 6-months mortality

Figure 2 presents the adjusted PaO_2 trajectories according to survival status. PaO_2 values decreased significantly until the 40th hour and then, leveled-off afterward both in survivors and non-survivors. The differences between the two trajectories according to survival status were statistically significant up to the first 32 h of measurement (omnibus *p* value = 0.007). Higher PaO_2 values were associated with better survival. The Kaplan–Meier curve (Additional file 1: Figure S2) suggested a trend toward better survival in the normoxemia group, compared to both the hypoxemia and severe hyperoxemia groups, although not statistically significant. At multivariable Cox regression, PaO_2 followed a U-shape risk profile, demonstrating that both hypo- and hyperoxemia were independently associated with higher mortality rates (omnibus *p* value = 0.0006; Fig. 3).

Definition of the "best" threshold of hypoxemia and hyperoxemia associated with 6-months mortality

Figure 4 shows the "best" threshold of hypoxemia and hyperoxemia for the prediction of 6-month mortality in our cohort. The best cut-off point for hypoxemia was a PaO_2 of 69 mmHg (Risk Ratio = 1.009, 95% CI 0.93–1.09) and for hyperoxemia was a PaO_2 of 195 mmHg (Risk Ratio = 1.006, 95% CI 0.95–1.06). The characteristics of the patients according to the best thresholds calculated are shown in Additional file 1: Table S4–S6. At admission, 165 patients (11.6%) presented with hypoxemia (median value 60 mmHg [IQR = 51.7–65.2]), 263 (18.5%) with hyperoxemia (273 mmHg [IQR = 231.7–342.7]), and 990 patients (69.8%) with normoxemia (105 mmHg [IQR = 87–133]). Over the study period, 55.9% of patients had at least one episode of hypoxemia and 21.7% had at least one episode of hyperoxemia, and in most cases

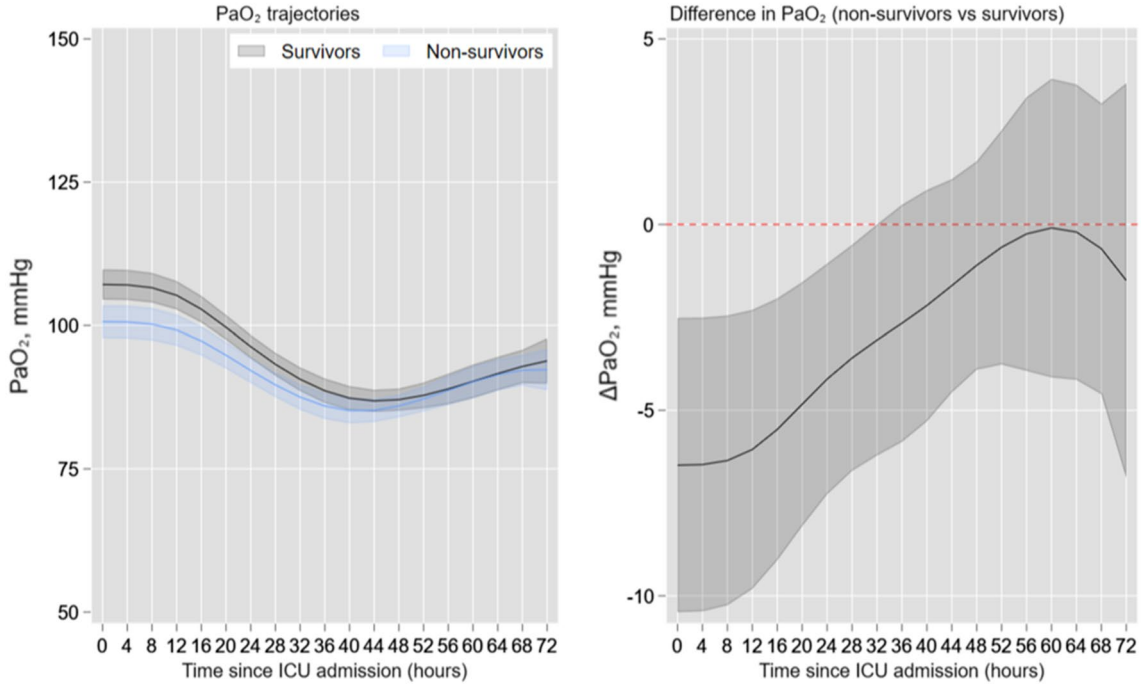

Fig. 2 Adjusted hourly trajectories of partial pressure of oxygen according to 6-month survival status. Left panel shows the predicted partial pressure of oxygen (PaO_2) trajectories according to survival status. Right panel shows the PaO_2 differences between survivors and non-survivors at each time point. For this analysis, mixed regression model included a random intercept on patients ID and a random coefficient on the time variable (time elapsed between measurements). These predicted trajectories were adjusted for TTM2 randomization arms, age (year), gender, Charlson comorbidity index, state of shock at admission, return to spontaneous circulation-ROSC- time, initial cardiac rhythm (shockable vs non-shockable), witnesses of cardiac arrest, respiratory rate (breath/min), plateau pressure (cmH_2O),positive end expiratory pressure (cmH_2O), arterial partial pressure of carbon dioxide, $PaCO_2$ (mmHg), pH, Base excess (mEq/L), and fraction of inspired O_2 (%). Right panel confirmed that the differences between these two trajectories (survivors/non-survivors) are statistically significant up to the first 32 h of measurement (omnibus p value = 0.0074). ICU, Intensive Care Unit

patients experienced only 1 or 2 episodes of hypoxemia and/or hyperoxemia over the first 72 h of mechanical ventilation. The incidence (number episodes per person in the 72 h follow-up) for hypoxemia and hyperoxemia considering the best thresholds was 1.34 (95% CI 1.29–1.40) and 0.26 (95% CI 0.24–0.29), respectively (Fig. 5).

Dose of oxygen and interaction between oxygen values and TTM2-arms.

Additional file 1: Figure S3 shows the hypoxemia and hyperoxemia mortality risk difference considering the exposure over time or "dose" of oxygen defined as PaO_2-AUC. PaO_2-AUC for hyperoxemia showed to be associated with higher mortality risk as compared to normoxemia (interaction p value = 0.0039).

Additional file 1: Figure S4 shows the interaction between PaO_2 and TTM2-arms (hypothermia versus normothermia). No difference was observed on the effect of PaO_2 on mortality between the TTM2-randomization groups (interaction p value = 0.997). HRs of hypoxemia and hyperoxemia on mortality for the hypothermia group were 1.07 (95% CI 0.58–1.98; $p = 0.82$), and 1.38 (95% CI 0.82–2.32; $p = 0.22$), respectively.

The association between hypo- and hyperoxemia with neurological outcome

No differences were observed in the trajectories of PaO_2 values in the first 72 h according to poor and good neurological status (omnibus value $p = 0.35$). Also, the distribution of the mRS score was not different among PaO_2 classes (Additional file 1: Figure S5, $p = 0.55$). At multivariate analysis, no significative association with poor neurological outcome (mRS = 4–6) was observed (omnibus value, $p = 0.63$), even considering separately mRS 4 and 5 (Additional file 1: Figure S6). Accordingly, we were not able to find a best cut-off point for neurological outcome (Additional file 1: Figure S7).

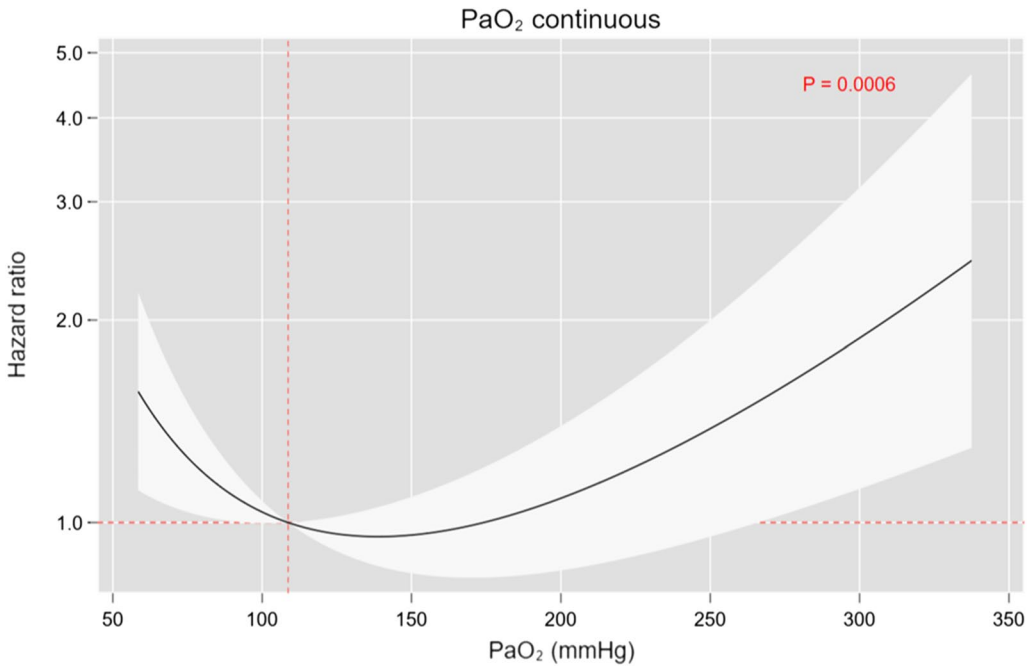

Fig. 3 Arterial partial pressure of oxygen (PaO_2) mortality risk profile. In this Cox regression, PaO_2 was modeled with a fractional polynomial (FP) of second degree FP [0–1], and included the following covariates: TTM2 randomization group, tympanic temperature at admission, age (years), gender, Charlson comorbidity index, cardiac arrest witnessed, time to return to spontaneous circulation, ROSC (min), bystander performed cardiopulmonary resuscitation, CPR, shockable rhythm, cardiac arrest location (home, public place, other), shock diagnosis on admission, ST-Elevated myocardial infarction (STEMI) diagnosis on admission, respiratory rate (breath/min), positive end-expiratory pressure, arterial partial pressure of carbon dioxide ($PaCO_2$) (mmHg), pHa, and Base excess (mEq/L), Driving pressure (cmH_20), and mechanical power (J/min). Along the PaO_2 continuum, values before and after its median (108.7 mmHg and used as reference—see vertical line in red) were statistically associated with mortality if the 95% confidence interval (CI) did not cover the y-line of 1 (horizontal line in red)

Discussion

In a large cohort of OHCA patients included in an international multicenter randomized clinical trial, we found that: (1) hypoxemia and severe hyperoxemia events are uncommon after OHCA, considering the conventional thresholds suggested in the literature; (2) the "best" cut-off values of oxygen associated with the risk for mortality were a PaO_2 below 69 mmHg and above 195 mmHg; with the use of these cut-offs, the incidence of episodes of hypoxemia and hyperoxemia markedly increased; (3) hypoxemia and hyperoxemia are independently associated with 6-months mortality but not with neurological outcome; the time-exposure (or "dose") of hyperoxemia was associated with 6-months mortality; and 4) these results were consistent across the group of randomization (normothermia or hypothermia).

To the best of our knowledge, this is the largest prospective study exploring the targets of oxygen as well as the association of hypoxemia and hyperoxemia with outcome in a homogeneous population of OHCA patients. We believe that our results are relevant and confirm not only the important effects of hypoxemia but also of hyperoxemia on 6-months mortality. In addition, we identified new thresholds of PaO_2 which are at risk for poor outcome.

Several studies highlighted the importance of maintaining appropriate ventilation targets and levels of PaO_2 in OHCA patients [27]. Post-cardiac arrest syndrome includes a number of pathophysiological mechanisms such as brain edema, reperfusion injury and oxidative stress, which can lead to neuronal damage and brain injury [28]. Hypoxemia caused by cardiac arrest yields to an alteration of cerebral metabolism, neuronal cell injury and death [7, 29].

The occurrence of hypoxemia and hyperoxemia is variable in the literature, with overall incidence of about 19% for hypoxemia [7] and between 3 and 60% for hyperoxemia [7, 25, 30]. Considering the conventional thresholds, the incidences of episodes of hypoxemia and severe hyperoxemia in our study were compatible with previous literature. The use of new "best" thresholds for oxygenation compared to traditional ones led to a marked increase in the number of patients exposed to at least one episode of hypoxemia or hyperoxemia.

The PaO_2 threshold responsible for the onset of hypoxic neuronal damage is not completely defined, and

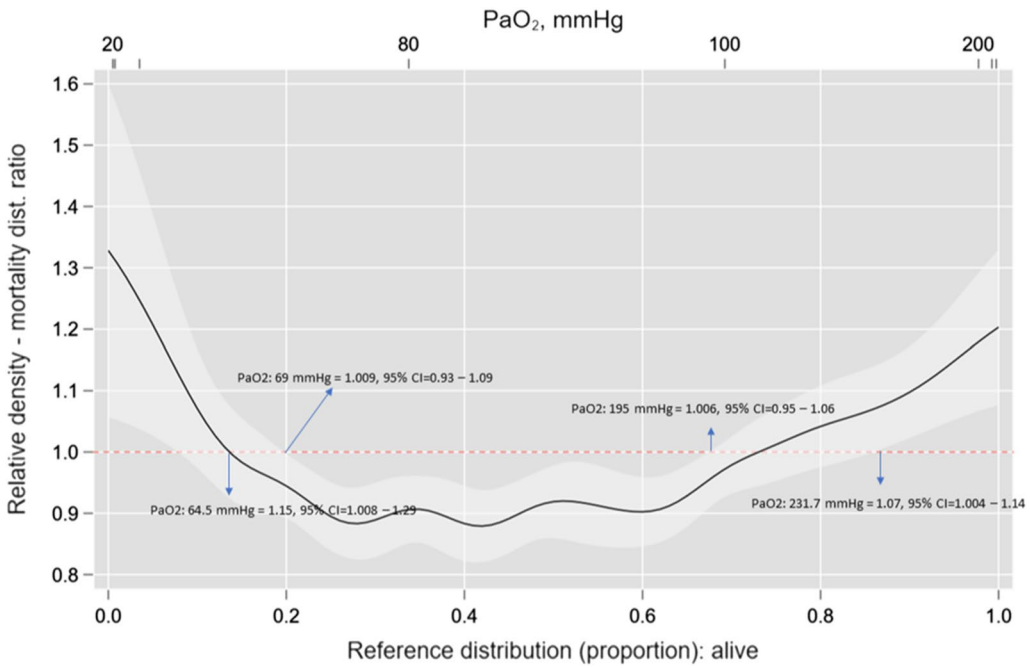

Fig. 4 Relative distribution analysis for the definition of the best cut-off of arterial partial pressure of oxygen (PaO_2) associated with mortality. Best cutoff point along the continuum of the marker that separated survivors versus non-survivors at the end of the follow-up. In this analysis, the quantile (or proportion) distribution of the marker survivors (plotted on the *x*-axis plus the corresponding marker values at the top) is plotted against the proportion ratio of the marker distribution for non-survivors

it is generally considered at 60 mmHg [31–34]. This value could underestimate the risk of hypoxemia in the OHCA population as the "best" lower threshold associated with increased mortality was found at PaO_2 of 69 mmHg.

Although recommendations suggest to give the maximum feasible inspired oxygen during CPR [8, 18, 35] to avoid hypoxemia [36, 37], recent evidence suggests a possible harmful effect also of hyperoxemia after OHCA [38]. A systematic review reported higher mortality in hyperoxemic compared to normoxemic patients with cardiac arrest and extracorporeal life support, but not in other groups of patients [39]. Another recent meta-analysis of observational studies [40] showed that severe hyperoxemia ($PaO_2 > 300$ mmHg) was associated with worse outcome, especially if hyperoxemia occurred during the first 36 h after cardiac arrest. However, high heterogeneity was found among the studies included in the meta-analysis, regarding the threshold of oxygen adopted, patient selection, the use of TTM, outcome measurement, methods of analyzing blood gas and often lack a pre-defined sampling protocol [20, 21, 41]. Many studies just considered PaO_2 values in the very early phases from ROSC [42], did not evaluate the duration of hyperoxemia (the dose), had limited sample sizes, or had retrospective designs or prospective design with a post hoc analysis [7, 8, 18, 43]. In the present preplanned study, both hypoxemia and hyperoxemia as well as the dose (AUC) of hyperoxemia over time were associated with mortality. This implies that the pathophysiological effect of hyperoxemia importantly depends not only on the intensity, but also on the duration of the exposure to high oxygen values. Also, the best upper threshold of PaO_2 associated with the risk for mortality was above 195 mmHg. This point is of critical importance and makes our results unique, potentially explaining why in previous studies using the conventional threshold of 300 mmHg a non-consistent association with outcome was found [41, 44–46]. We hypothesize that the risk for hyperoxemia might have been underestimated considering the traditional thresholds, and that in the post-ROSC phase clinicians should pay attention in the titration of oxygen to lower levels than thought before.

Different oxygen targets have been proposed by trials on oxygen [47–49], and the recent BOX trial [49], which compared 2 targets of PaO_2 68–75 mmHg vs 98–105 mmHg, showed similar incidence of death or severe disability or coma among groups, suggesting that question remains especially about the higher target of oxygen to be applied in this population, which requires further investigation.

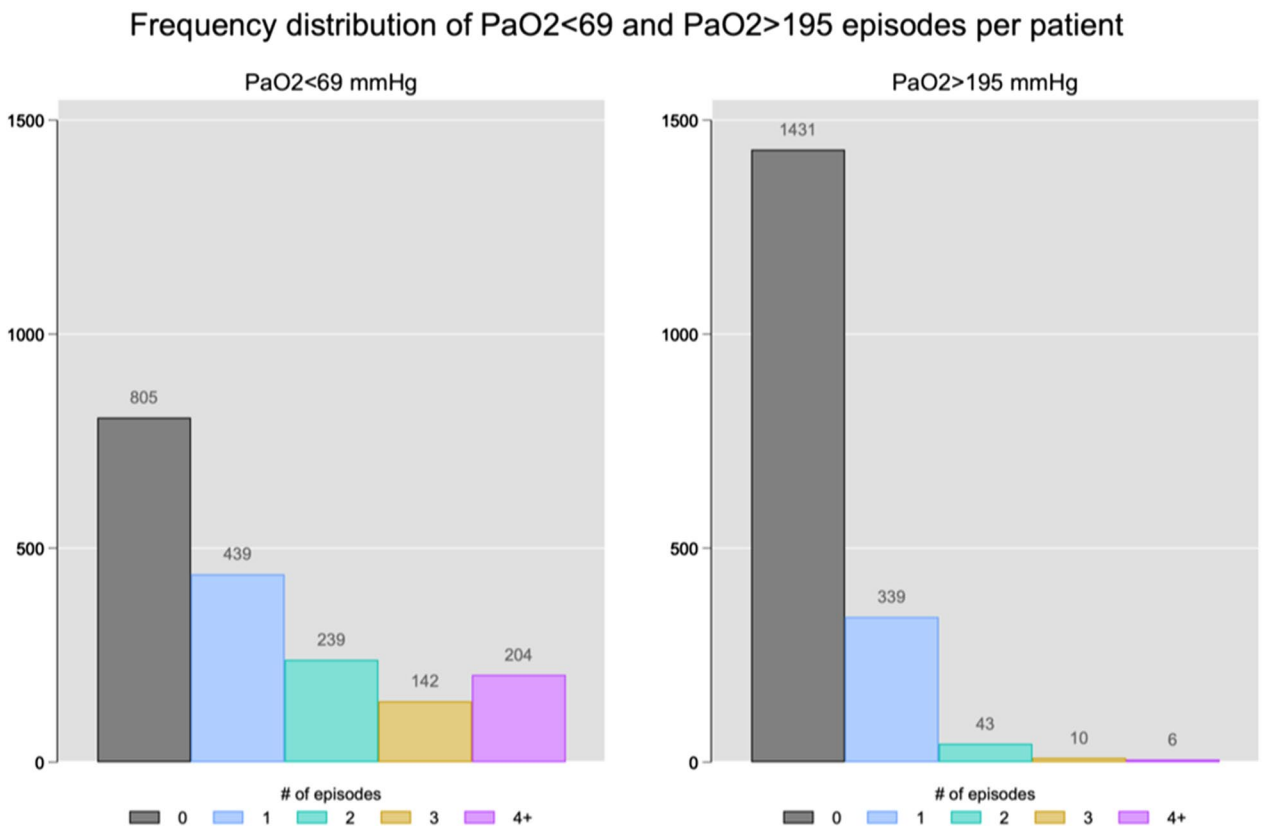

Fig. 5 Frequency distribution of arterial partial pressure of oxygen (PaO_2) classes (according to best threshold). Numbers of hypoxemia/hyperoxemia episodes per patient during the first 72 of mechanical ventilation. This figure was based on all patients included in the cohort, with a percent distribution as follow: Episodes of Hypoxemia = 0 (n = 805 (44.01%), 1 (n = 439 (24.00%), 2 (n = 239 (13.07%), 3 (n = 142 (7.76%), 4 + (n = 204 (11.05%). Episodes of Hyperoxemia = 0 (n = 1431 (76.90%), 1 (n = 339 (18.53%), 2 (n = 43 (2.35%), 3 (n = 10 (0.55%), 4 + (n = 6 (0.33%)

When splitting the patients according to the use of hypothermia and normothermia, no statistically differences were found in outcome between the two groups, thus suggesting that temperature 33 °C does not improve oxygen tolerance and could further explain the lack of protective effect of hypothermia [23]. The fact that hypoxemia and hyperoxemia were not associated with poor neurological outcome (mRS 4 and 5) might be explained by different factors. Firstly, the scale used to evaluate neurological disability does not specifically account for specific cognitive dysfunction; further, neurological outcome may be affected by many different post-acute factors such as systemic complications or secondary brain damage during the ICU stay, in the hospital, or during rehabilitation. In particular, despite we used a robust statistical model which took in consideration several confounding factors, oxygen derangements might be a marker for systemic clinical events that can lead to an increase in mortality, i.e., pneumonia, sepsis, without a definitive effect on neurological outcome.

Limitations

This study has several limitations. Firstly, although this was a preplanned secondary analysis of the TTM2 trial, this is an observational study, and our results should be regarded as hypothesis-generating, and we cannot make any causality statements from our results. A randomized clinical trial will be in fact necessary to confirm our findings, with the aim to explore the effect of oxygen more deeply on neurological outcome and the interaction of oxygen derangements with systemic factors.

Secondly, we hypothesized that oxygen pressure in-between PaO_2 measurement was linear, and we were not able to account for short-term variations of PaO_2. Nevertheless, the present study includes the highest number of available data on PaO_2 measures with serial measurements. Third, although this was a preplanned study, some information is lacking in eCRF, and some data are missing in the database. Finally, the conventional thresholds used in this analysis were adopted according to robust observational studies, but these values present important heterogeneity in the literature [18, 25, 47], with no

definitive conclusions regarding the optimal oxygen targets, especially for the higher threshold of oxygen. The ongoing Mega-ROX trial [48] is exploring two different levels of oxygen mainly based on SpO_2 and a recently published RCT [49], compared 2 targets of PaO_2 with higher target of 98–105 mmHg. Our results can pave the way to the definition of further RCTs and better define the best thresholds of oxygenation to be applied in this population.

Conclusions

In mechanically ventilated patients after out of hospital cardiac arrest, we found novel "best" cutoff values of oxygen associated with the risk for mortality at PaO_2 below 69 mmHg and above 195 mmHg; with the use of these cut-offs, episodes of hypoxemia and hyperoxemia are common in this population. Both hypoxemia and hyperoxemia are associated with higher 6-months mortality, and this may be mediated by the timing exposure to high values of oxygen. More cautious titration of oxygen levels should be considered in this group of patients until stronger evidence is available.

Abbreviations

ABG: Arterial blood gas; AUC: Area under curve; BMI: Body mass index; CI: Confidence interval; CO_2: Carbon dioxide; Crs: Respiratory system compliance; eCRF: Electronic case record form; CPR: Cardiopulmonary resuscitation; FiO_2: Fraction of inspired oxygen; FP: Fractional polynomial; HR: Hazard ratio; ICU: Intensive care unit; IQR: Interquartile range; LOS: Length of stay; mRS: Modified Rankin Scale; OHCA: Out of hospital cardiac arrest; OR: Odds ratio; $PaCO_2$: Arterial partial pressure of CO_2; PaO_2: Arterial partial pressure of oxygen; PEEP: Positive end-expiratory pressure; pHa: Arterial pH; PI: Principal investigator; Ppeak: Peak pressure; Pplat: Plateau pressure; ROSC: Return of spontaneous circulation; RR: Respiratory rate; STEMI: ST elevation myocardial infarction; STROBE: STrengthening the Reporting of OBservational studies in Epidemiology; TTM2: Target temperature management 2 Trial; V_T: Tidal volume.

Supplementary Information

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Additional file 1: Additional statistical analysis of subgroups population and association with outcome.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained in the coordinating center and in each participating centers as well as informed consent according to local regulations. This sub-study was approved on the 23rd of February 2017 by the TTM2 steering committee (https://ttm2trial.org/substudy-proposals). The protocol of the analysis was previously approved by the TTM2 steering committee and then published. No further ethical approval was necessary for the development of this study.

Consent for publication

Not applicable.

Competing interests

Dr. Saxena is receiving consulting fees from Bard Medical; Dr. Young is receiving lecture fees from Bard Medical; Dr. Taccone is receiving grant support from Bard Medical and ZOLL Medical; Dr. Nichol is receiving grant support, paid to University College Dublin, from AM Pharma and grant sup-port, paid to Monash University, from Baxter Healthcare; Dr. Chew is receiving lecture fees from Edwards Lifesciences; Dr. Friberg is receiving fees for academic advising from TEQCool; and Dr. Nielsen is receiving lecture fees from Bard Medical and consulting fees from BrainCool. Dr Badenes is supported by INCLIVA. Dr Robba received fees for lectures from Masimo, and GE. Dr. Battaglini received fees for lectures from Baxter. No other potential conflict of interest relevant to this article was reported.

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