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High cumulative oxygen levels are associated with improved survival of children treated with mild therapeutic hypothermia after cardiac arrest☆,☆☆

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ABSTRACT

Aim: The aim of this study was to analyze the relationship between the partial pressure of arterial oxygen (PaO_2) and in-hospital (IH) mortality in children after cardiac arrest (CA) using the conventional cutoff analysis, which was compared with the cumulative analysis, a new method in PaO_2 analysis. Additionally, we analyzed this relationship for children with and without mild therapeutic hypothermia (MTH; 32–34 °C).

Methods: This observational cohort study included all children (aged >28 days) with CA and return of spontaneous circulation (ROSC) between 2002 and 2011.

The first research question was the association between PaO_2 and IH mortality after ROSC. This was analyzed for three hyperoxia cutoff values, and for three time intervals using the cumulative PaO_2 determined with the area under the curve (AUC). For the second research question, these analyses were repeated for children with and without MTH.

Results: Of the 200 patients included (median age 2.6 years), 84 (42%) survived to hospital discharge. Fifty-eight children (29%) were treated with MTH.

With the cutoff analysis and the AUC analysis we found no relationship between PaO_2 and IH mortality. However, analysis of the MTH-group showed a lower IH mortality in children with high cumulative PaO_2 levels on two of the three time intervals. Multivariable analysis showed significantly higher odds of survival (0.643 (95% confidence interval (CI) 0.424–0.976), 0.554 (95%CI 0.335–0.916)).

Conclusions: Cumulative PaO_2 analysis showed that the IH mortality is significantly lower in MTH-treated children with high PaO_2 levels. The effects of cumulative PaO_2 on the outcome need to be studied further, and this will help us to achieve individualized goal-directed therapy.

1. Introduction

Cardiac arrest (CA) in children is uncommon and associated with high mortality (50–90%).[1–6] Oxygen therapy has always been important in the treatment of CA. However, there is increasing evidence for the adverse effects of oxygen. Oxidative stress and reperfusion promote free radical-generated injury contributing to neurologic injury and cardiac dysfunction, and they seem to be associated with increased mortality after CA.[7,8] Furthermore, a meta-analysis of animal studies by Pilcher et al. showed that treatment with 100% oxygen after resuscitation resulted in significantly worse neurological deficit scores than oxygen administered at lower concentrations.[9]

Observational studies in humans examined the influence of arterial oxygen (PaO_2) on in-hospital (IH) mortality. They used

Abbreviations: APLS, advanced pediatric life support; AUC, area under the curve; BLS, basic life support; CA, cardiac arrest; CI, confidence interval; OH, out-of-hospital; IH, in-hospital; MTH, mild therapeutic hypothermia; NICU, neonatal intensive care unit; OR, odds ratio; PaO_2, partial pressure of arterial oxygen; ICU, intensive care unit; ROSC, return of spontaneous circulation; SIRS, systemic inflammatory response syndrome.

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different time intervals after return of spontaneous circulation (ROSC) and different definitions of hyperoxia, or included only patients treated with mild therapeutic hypothermia (MTH), which resulted in contradictory conclusions.[10–16] Most studies used an arbitrary cutoff value to describe the influence of PaO_2 on the IH mortality. Only two studies used an alternative method. Janz et al. used PaO_2 as a continuous value and Ferguson et al. modeled the first PaO_2 within the first hour after ROSC in a non-linear matter.[11,13]

In contrast with previous studies, we hypothesized that not a single value above a previously set cutoff, but rather the cumulative PaO_2 during the first 24 h after ROSC (especially the first 6 h) is associated with worse survival of children with CA. Our first research question was the association between PaO_2 and the IH mortality, analyzed with the commonly used cutoff method and compared with a cumulative method. In addition, although the evidence for the protective effects of MTH is debatable, we hypothesized that MTH is protective against the effects of hyperoxia, as it is the only post-resuscitation intervention, introduced in our hospital in 2007, in accordance with international guidelines.

2. Methods

This observational cross-sectional cohort study was performed at the intensive care unit (ICU) of the Erasmus MC – Sophia Children's Hospital, a tertiary-care university hospital. Our hospital provides health care to children in the southwest of The Netherlands (total population of approximately 4.2 million people), and this population is a representative sample of the Dutch population.

2.1. Patient selection

This study concerned all patients aged >28 days and <18 years with documented CA between January 2002 and December 2011, and admitted to the ICU of the Erasmus MC – Sophia Children's Hospital. CA was defined as absent pulse rate or the need for cardiac compressions. Treatment of children with CA in our hospital has been in line with the European Resuscitation Council guidelines for pediatric life support.[17]

The inclusion criteria were as follows: (1) all children resuscitated in-hospital (e.g. emergency department, ward, or ICU) and out-of-hospital, and consecutively admitted to our ICU, and (2) children resuscitated in a regional hospital or other university hospital, and after ROSC consecutively admitted to our ICU. Neonatal resuscitations, children with cyanotic congenital heart disease, and children without an arterial line were excluded. In addition, only data of the first CA episode were included when a child had multiple arrests.

Hypothermia was introduced as treatment after CA in children with post-resuscitation coma in 2007. Hypothermia was started as soon as possible following ROSC. Hypothermia was achieved by administering a bolus of cold fluids and applying external cooling using a mattress with Blanketrol® III (Cincinnati Sub-Zero Products, Inc., Sharonville, OH, USA). The target temperature is 32–34 °C for 24 h following ROSC, after which they were rewarmed passively at a rate of 0.5 °C per 2 h. The target temperature must have been reached for MTH to be effective. Children in whom the target temperature range was not reached were classified as "without MTH".

2.2. Data collection

All CA data were retrospectively collected. CA data were derived from ambulance registration forms, clinical medical records, electronic medical records, Patient Data Management System (PDMS), and CA registration forms. The starting point of the time interval of collected data ($T = 0$) was defined as the actual time of ROSC or, if unknown, the time of ICU admission.

The following data were collected: (1) basic patient characteristics (e.g., gender, age, and medical history), (2) CA characteristics (e.g., type of resuscitation (basic life support (BLS)/advanced pediatric life support (APLS)), etiology of arrest, first monitored rhythm, bystander cardiopulmonary resuscitation (CPR), and location), and (3) outcome (IH mortality).

For all children, laboratory values (arterial pH, lactate, and PaO_2) and data regarding MTH (time period before MTH reached, lowest temperature if >34 °C) were retrospectively collected. The laboratory values of all children were automatically recalculated to the value at 37 °C, as this is a standard procedure in our hospital.[18]

2.3. Statistical analysis

The primary outcome measure was IH mortality. The first research question was the association between PaO_2 and IH mortality. The second question was the influence of MTH on this association.

In the first analysis of the first research question, we explored the association between PaO_2 and IH mortality for different cutoff values of hyperoxia (>200, >250 and >300 mmHg) as proposed in the literature.[13–16] Logistic regression analysis was applied to explore the influence of hyperoxia on IH mortality with the highest PaO_2 over the first 24 h. In the multivariable analysis, we calculated an adjusted odds ratio (OR) for pre-selected variables: age, gender, type of resuscitation (BLS/APLS), location, rhythm, lowest pH and highest lactate.

In the second analysis of the first research question, the "area under the curve" (AUC) of PaO_2 was calculated for each patient to determine the influence of the cumulative PaO_2 on IH mortality. The trapezoidal method was used. A minimum of four PaO_2 measurements and an overall time interval of at least 12 h were required to include the arterial measurements and their corresponding time points in the analysis. This resulted in a cumulative PaO_2 over the 0–6 h, 6–24 h, and 0–24 h interval after ROSC. The AUC was corrected for the time in which the PaO_2 was measured, as not all patients had a 24 h time period in which PaO_2 was measured. This resulted in a cumulative PaO_2 per hour, which was converted into the cumulative PaO_2 by multiplying with 6, 18, or 24, respectively.

In univariable logistic regression analyses, the assumption that the AUC of PaO_2 had a linear effect on the logit of IH mortality was tested using the Box–Tidwell test (i.e., an interaction term between the covariate and its natural logarithm was added to the model). If any significant interaction between the covariate and its natural logarithm was present, the linearity assumption was violated. Univariable and multivariable logistic regression analysis (with the same preselected variables as in the cutoff analysis) was applied to evaluate the relationship between cumulative PaO_2 and IH mortality over the three time intervals after ROSC. In advance of the regression analysis, the original AUC variables were rescaled by dividing by 100 to obtain more distinctive results out of the logistic regression analysis.

The same analyses were performed regarding the influence of MTH on the association between PaO_2 and IH mortality.

Univariable comparison of the distribution of patient characteristics and clinical data between survivors and non-survivors was performed by independent sample *t*-tests for normally distributed data, and Mann–Whitney *U* tests for non-normally distributed data. Normality was examined with the Kolmogorov–Smirnov test. Fisher's exact test was used for comparison of dichotomous data. Statistical significance was considered with two-tailed *p*-value of ≤ 0.05.

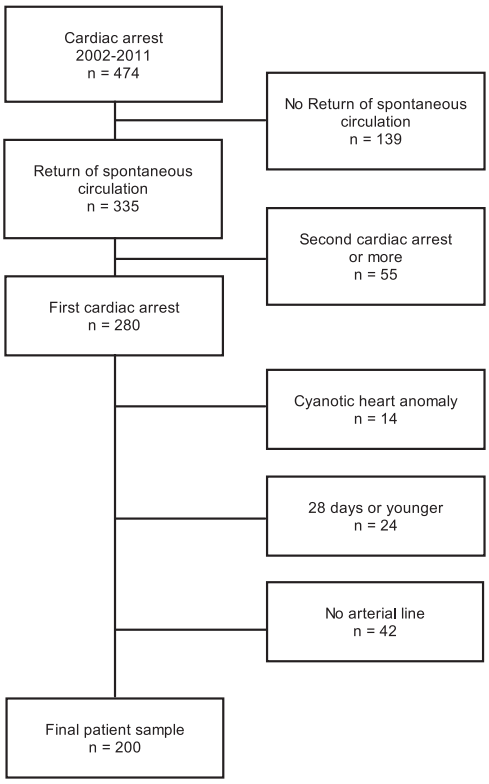

Fig. 1. Overview of the patient inclusion.

All analyses were performed with SPSS 21.0 for Windows (SPSS, Inc., Chicago, IL, USA) or GraphPad Prism 5.00 for Windows (GraphPad Software, Inc.).

3. Results

3.1. Patient and CA characteristics

Between January 2002 and December 2011, a total of 474 CA events were documented. ROSC was achieved in 335 events (70%). An overview of the patient inclusion is given in Fig. 1. The basic patient characteristics are presented in Table 1.

MTH was initiated in 63 (32%) children, 58 (92%) of whom reached the target temperature in a median time of 6.7 h (range: 0.8–21.3) for survivors and 6.3 h (range: 0.4–25.5) for non-survivors after ROSC.

Eventually, 116 of the 200 children (58%) died within a median of 2 days (range: 0–135; 40 died within the first 24 h) after ROSC. The major cause of death was withdrawal of life-sustaining treatment (poor physical and/or (neuro)psychological outcome based on repeated neurological examination, brain imaging, and electroencephalography) ($n = 52$, 45%), followed by brain death based on the criteria of whole-brain death ($n = 31$, 27%), cardiorespiratory failure/multiple-organ failure ($n = 31$, 27%), and underlying disease ($n = 2$, 2%).

3.2. PaO_2 cutoff analysis

All 200 patients were included in the cutoff analysis. No significant difference between survivors and non-survivors was found (Table 1).

The influence of the highest measured PaO_2 on the overall mortality is presented in Table 2.

Table 3 displays the influence of PaO_2 on IH mortality for patients with and without MTH. The univariable analysis of maximum PaO_2 values >250 mmHg showed a significantly lower survival rate of children without MTH treatment, which was no longer present in the multivariable analysis.

3.3. Cumulative PaO_2 analysis

Forty-eight children (24%) were excluded from the AUC calculation (less than four measurements and/or time interval <12 h) (Table 1).

The results of the Box–Tidwell tests showed no significant non-linear effects of the AUC of PaO_2 on the logit of IH mortality.

Univariable and multivariable regression analyses showed no significant relationship between the cumulative AUC of PaO_2 and IH mortality (Table 2).

Multivariable regression analysis, evaluating the relationship between cumulative PaO_2 and IH mortality for patients with and without MTH, showed an overall significant difference (OR 0.916, 95% CI 0.843–0.995; $p = 0.038$) toward a lower risk of mortality over the 0–24 h interval in patients with MTH. This was also found on the 6–24 h interval (OR 0.882, 95% CI 0.792–0.981; $p = 0.021$) in patients with MTH (Fig. 2).

3.3.1. Clinical relevance

As shown by five examples (Fig. 3), both methods led to substantially different results. As to the cumulative PaO_2 in patients with MTH, the *mean* AUC of survivors with MTH was 502.7 points higher over the 0–24 h interval, and 469.9 points higher over the 6–24 h interval, than that of non-survivors. As the AUC was rescaled before being entered in the regression analysis, the mean difference had to be rescaled by dividing by 100. Ultimately, this resulted in a clinically relevant difference in OR of 0.643 (95% CI 0.424–0.976) and 0.554 (95% CI 0.335–0.916). The odds of survival are significantly increased in children with higher cumulative PaO_2 levels over the 6–24 h and 0–24 h interval.

4. Discussion

The innovative aspect of this study is that it uses a novel and simple method to analyze cumulative PaO_2. We found that patients with MTH and higher cumulative PaO_2 had a lower mortality rate. With the cumulative PaO_2 measurement, we could not reproduce the relationship between higher PaO_2 and IH mortality in children after CA as found in various cutoff studies. It is important to note that, due to the retrospective nature, small sample size, and heterogeneous population, we did not determine causation in this study, this study is hypothesis generating.

4.1. Patient and CA characteristics

The patient sample was heterogeneous in terms of location and etiologies, among other things, which was also the case in other studies.[10,11,13,15] Half of the CAs were out-of-hospital CAs, the proportion of which was within the range reported in other studies (from 43% to 58%).[12,13,16] In our population, out-of-hospital CA was also more common (70%) in patients with MTH.

Only 32% underwent MTH after CA, because MTH was newly introduced in our clinical protocol in 2007 and it was only used in children with post-resuscitative coma after CPR. Similar to other studies our median time to reach the MTH target temperature was >6 h, most probably due to unfamiliarity with the new protocol and failure of the technique.[19,20] The exact timing to start hypothermia after ROSC is controversial, as well as the duration and temperature.[21–23] There could be a therapeutic window in which hypothermia should be applied.[21,23] Furthermore, controlling the effects of systemic inflammatory response syndrome (SIRS) with continued normothermia could be important.[22]

Table 1
Patient characteristics and cardiac arrest characteristics.

	Survivors (n = 84)			Non-survivors (n = 116)			p-Value[d]
	n[a]			n[a]			
Age (months)[b]	84	20.4	(1.0–211.9)	116	37.6	(1.0–262.6)	0.069
Male gender[c]	84	49	(58%)	116	61	(53%)	0.472
Advanced pediatric life support (APLS)[c]	84	64	(76%)	116	107	(92%)	0.002
Out-of-hospital arrest[c]	84	37	(44%)	116	61	(53%)	0.254
Bystander CPR[c]	79	74	(88%)	112	93	(80%)	0.044
Initial rhythm non-shockable[c]	77	64	(76%)	107	99	(85%)	0.060
Etiology	84			116			
-Cardiac[c]		27	(32%)		33	(39%)	0.640
-Arrhythmia[c]	27	8	(30%)	33	3	(9%)	
-Cardiomyopathy[c]	27	8	(30%)	33	8	(24%)	
-Hypovolemic shock[c]	27	1	(4%)	33	5	(15%)	
-Obstructive shock[c]	27	2	(7%)	33	2	(6%)	
-Septic shock[c]	27	6	(22%)	33	14	(42%)	
-Other[c]	27	2	(7%)	33	1	(3%)	
-Respiratory[c]		49	(58%)		46	(40%)	0.010
-Aspiration[c]	49	1	(2%)	46	6	(13%)	
-Bronchomalacia/spasm[c]	49	4	(8%)	46	1	(2%)	
-Congenital[c]	49	3	(6%)	46	3	(7%)	
-Drowning[c]	49	19	(39%)	46	12	(26%)	
-Hanging[c]	49	2	(4%)	46	2	(4%)	
-Insufficiency/infection[c]	49	8	(16%)	46	11	(24%)	
-Obstruction other[c]	49	9	(18%)	46	3	(7%)	
-Pulmonary hypertension[c]	49	2	(4%)	46	1	(2%)	
-Other[c]	49	1	(2%)	46	7	(15%)	
-Neurologic[c]		2	(2%)		26	(22%)	<0.001
-Herniation[c]	2	0	(0%)	26	3	(12%)	
-Vascular accident[c]	2	0	(0%)	26	3	(12%)	
-Trauma[c]	2	0	(0%)	26	18	(69%)	
-Other[c]	2	2	(100%)	26	2	(8%)	
-ALTE/SIDS[c]		3	(4%)		6	(5%)	0.737
-Other/unkown[c]		3	(4%)		5	(4%)	1.000
Pre-existing condition[c,e]	83	36	(43%)	114	44	(38%)	0.558
-Cardiac[c]		20	(56%)		23	(52%)	0.824
-Respiratory[c]		13	(36%)		16	(36%)	1.000
-Neurologic[c]		2	(6%)		3	(7%)	1.000
-Other/unkown[c]		1	(3%)		2	(5%)	1.000
Mild therapeutic hypothermia[c,f]	84	26	(31%)	116	37	(31%)	1.000
- 32–34 °C reached[c]	26	22	(85%)	37	36	(97%)	0.150
Lowest pH[b]	84	7.18	(6.47–7.53)	116	7.04	(6.36–7.46)	<0.001
Highest lactate[b]	83	4.5	(1.1–24.0)	112	12.1	(0.9–25.0)	<0.001
Lowest PaO_2[b]	84	66.0	(18.8–171.8)	116	54.8	(12.8–240.0)	0.154
Highest PaO_2[b]	84	229.9	(32.3–624.8)	116	273.4	(27.0–628.6)	0.394
Min. PaO_2 < 60 mmHg[c]	84	31	(37%)	116	61	(53%)	0.032
Max. PaO_2 > 200 mmHg[c]	84	51	(61%)	116	76	(66%)	0.551
Max. PaO_2 > 250 mmHg[c]	84	37	(44%)	116	65	(56%)	0.115
Max. PaO_2 > 300 mmHg[c]	84	31	(37%)	116	52	(45%)	0.309
AUC 0–24 h mmHg[b]	69	2966.9	(1271.6–5785.5)	83	3157.2	(565.9–5405.5)	0.585
-mmHg/h	69	123.6	(53.0–241.1)	83	131.5	(23.6–225.2)	
AUC 0–6 h mmHg[b]	64	854.0	(297.8–2066.9)	78	870.7	(166.7–2290.2)	0.925
-mmHg/h	64	142.3	(49.6–344.5)	78	145.1	(27.8–381.7)	
AUC 6–24 h mmHg[b]	68	2063.0	(930.3–4645.2)	81	2199.6	(424.4–3911.5)	0.424
-mmHg/h	68	114.6	(51.7–258.1)	81	122.2	(23.6–217.3)	

Abbreviations: ALTE = apparent life threatening event, AUC = area under the curve, max. = maximum, n = number, PaO_2 = partial pressure of arterial oxygen, SIDS = sudden infant death syndrome.

[a] Number of subjects in whom the variable was obtained.
[b] Median (range).
[c] Number of subjects (%).
[d] p-Value: independent sample t-test for continuous data or Mann–Whitney U test dependent on normality; Fisher's exact test for dichotomous data.
[e] Children with a pre-existing medical history that was the cause of CA, classified by the etiology of the CA.
[f] Children in whom mild therapeutic hypothermia was initiated (n = 63).

4.2. Method of PaO_2 analysis

Most studies on hyperoxia and CA used a single cutoff value to describe PaO_2 over different time periods after ROSC.[10,12,14–16] Such cutoff analyses may be limited, however, in their ability to approximate the complex oxygen physiology as fluctuations of PaO_2 are common. Using AUC as a measure of cumulative exposure to oxygen, patients with MTH and high cumulative PaO_2 levels had a lower mortality rate, which was not found in the cutoff analyses. In addition, we did not find any harmful effects of the high cumulative arterial oxygen levels whatsoever. This supports our hypothesis that the method of analysis is important in the approximation of oxygen physiology. A dichotomous cutoff value cannot account for the amount of oxygen and duration, an inherent problem of summarizing a continuous variable with an important time course as a dichotomous variable.

We chose to use different time periods in the AUC analysis, as both direct cell injury after an ischemic event and delayed cell death known as reperfusion injury have an important influence on the outcome. Therefore, it is difficult to compare our results with other

Table 2
Univariable and multivariable logistic regression analyses of all children with survival as dependent variable.

Variable	Crude			Adjusted[a]		
	OR (95% CI)		*p*-Value	OR (95% CI)		*p*-Value
Max. PaO_2 > 200 mmHg	1.230	(0.687)–(2.198)	0.813	0.810	(0.413)–(1.590)	0.541
Max. PaO_2 > 250 mmHg	1.618	(0.920)–(2.849)	0.095	1.107	(0.581)–(2.114)	0.756
Max. PaO_2 > 300 mmHg	1.389	(0.782)–(2.469)	0.262	0.905	(0.465)–(1.761)	0.770
AUC 0–24 h mmHg[b]	0.998	(0.966)–(1.030)	0.894	0.984	(0.949)–(1.021)	0.403
AUC 0–6 h mmHg[b]	0.998	(0.924)–(1.078)	0.957	0.971	(0.892)–(1.057)	0.497
AUC 6–24 h mmHg[b]	0.997	(0.955)–(1.042)	0.903	0.980	(0.933)–(1.031)	0.447

Abbreviations: AUC = area under the curve, max. = maximum, OR = odds ratio, PaO_2 = partial pressure of arterial oxygen.
[a] Adjusted for: age, gender, location of arrest, rhythm, basic life support/advanced pediatric life support, lowest pH, and highest lactate.
[b] Value was rescaled by dividing by 100 in advance of the regression analysis.

studies, but these different methods extend our knowledge of these concepts.

The cumulative PaO_2 can be legitimately measured with the trapezoidal AUC method.[24] This method is commonly used in pharmacokinetic research to measure the total drug exposure, and it has also been used in other medical fields, for instance in metabolic research and pulmonary research.

4.3. Cumulative PaO_2 and outcome

The analysis of patients without MTH showed no significant relationship between PaO_2 and IH mortality, regardless of the method used. This is similar to findings of Bellomo et al., who found no significant difference after Cox proportional-hazards modeling in a large retrospective cohort of 12,108 patients.[10]

In multivariable analysis, clinically relevant differences in OR were found. There are various explanations for our findings. One important new theory is that of a therapeutic window for oxygen. As suggested by Martin et al., precise control of arterial oxygenation may avoid harmful effects associated with unnecessary extremes of arterial oxygenation.[25] Based on physiological principles, they constructed a scheme with an optimal therapeutic oxygenation range. This optimal range will probably be dependent on factors such as age, clinical setting, underlying disease, and other comorbidities. In our retrospective cohort, the cumulative oxygen levels in survivors with MTH were higher than in the non-survivors with MTH. This suggests that MTH might shift the optimal therapeutic range wherein high cumulative oxygen levels could be favorable compared to lower cumulative oxygen levels.

An alternative explanation is the possibility of impairments in microcirculatory function. As shown by van Genderen et al. and Buijs et al., macrocirculatory parameters cannot estimate microcirculatory function and MTH causes abnormalities in microcirculation and peripheral tissue perfusion.[26,27] Buijs et al. found that the microcirculation was impaired during MTH and more severely impaired at the start of MTH in non-survivors. Despite

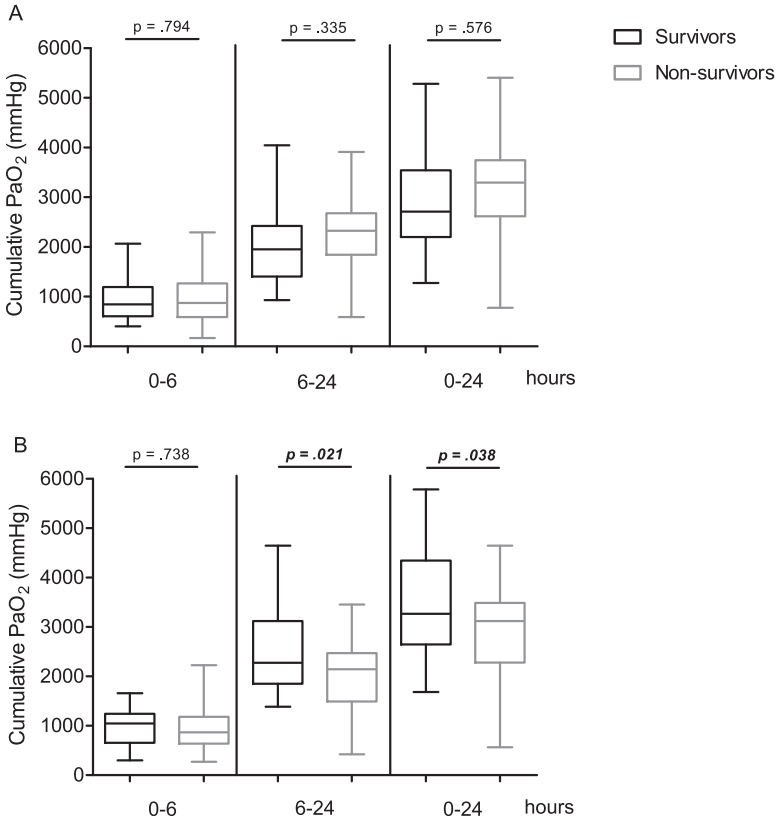

Fig. 2. Cumulative PaO_2 of all children with and without MTH treatment. (A) Cumulative PaO_2 in children without hypothermia. (B) Cumulative PaO_2 in children with hypothermia. Each boxplot shows a minimum, 25th percentile, median, 75th percentile, and maximum value. The *p*-values of the multivariable regression analysis are shown.

Table 3
Univariable and multivariable logistic regression analyses of all children with and without mild therapeutic hypothermia treatment with survival as dependent variable.

Variable	Survivors		Non-survivors		*p*-Value[d]	Crude		Adjusted[e]	
	n[a]		*n*[a]			OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
No hypothermia[g]									
Max. PaO_2 > 200 mmHg[b]	62	37 (60%)	80	52 (65%)	0.600	1.255 (0.633)–(2.488)	0.516	0.899 (0.394)–(2.053)	0.801
Max. PaO_2 > 250 mmHg[b]	62	23 (37%)	80	45 (56%)	0.028	2.179 (1.106)–(4.310)	0.024	1.912 (0.866)–(4.237)	0.109
Max. PaO_2 > 300 mmHg[b]	62	19 (31%)	80	35 (44%)	0.120	1.761 (0.876)–(3.534)	0.112	1.166 (0.518)–(2.625)	0.711
AUC 0–24 h mmHg[c,f]	47	2712.2 (1271.6–5283.4)	48	3295.0 (778.2–5405.5)	0.100	1.025 (0.983)–(1.067)	0.245	1.014 (0.964)–(1.067)	0.576
-mmHg/h[c]	47	113.0 (53.0–220.1)	48	137.3 (32.4–225.2)					
AUC 0–6 h mmHg[c,f]	45	844.6 (399.0–2066.9)	45	874.0 (166.7–2290.2)	0.812	1.006 (0.913)–(1.107)	0.909	0.985 (0.881)–(1.101)	0.794
-mmHg/h[c]	45	140.8 (66.5–344.5)	45	145.7 (27.8–381.7)					
AUC 6–24 h mmHg[c,f]	47	1954.8 (930.3–4045.5)	46	2326.7 (586.8–3911.5)	0.031	1.047 (0.986)–(1.111)	0.131	1.037 (0.963)–(1.116)	0.335
-mmHg/h[c]	47	108.6 (51.7–224.8)	46	129.3 (32.6–217.3)					
Hypothermia[h]									
Max. PaO_2 > 200 mmHg[b]	22	14 (64%)	36	24 (67%)	1.00	1.143 (0.376)–(3.472)	0.814	0.435 (0.076)–(2.488)	0.349
Max. PaO_2 > 250 mmHg[b]	22	14 (64%)	36	20 (56%)	0.593	0.714 (0.240)–(2.123)	0.545	0.218 (0.034)–(1.399)	0.108
Max. PaO_2 > 300 mmHg[b]	22	12 (55%)	36	17 (47%)	0.787	0.746 (0.257)–(2.160)	0.589	0.398 (0.087)–(1.818)	0.235
AUC 0 – 24 h mmHg[c,f]	22	3264.8 (1682.5–5785.5)	35	3119.9 (565.9–4643.3)	0.159	0.945 (0.890)–(1.004)	0.069	0.916 (0.843)–(0.995)	0.038
-mmHg/h[c]	22	136.0 (70.1–241.1)	35	130.0 (23.6–193.5)					
AUC 0–6 h mmHg[c,f]	19	1046.3 (297.8–1661.4)	33	867.5 (268.1–2221.8)	0.549	0.980 (0.861)–(1.117)	0.769	0.975 (0.839)–(1.133)	0.738
-mmHg/h[c]	19	174.4 (49.6–276.9)	33	144.6 (44.7–370.3)					
AUC 6–24 h mmHg[c,f]	21	2278.1 (1384.3–4645.2)	35	2144.0 (424.4–3452.9)	0.110	0.923 (0.854)–(0.997)	0.041	0.882 (0.792)–(0.981)	0.021
-mmHg/h[c]	21	126.6 (76.9–258.1)	35	119.1 (23.6–191.8)					

Abbreviations: AUC = area under the curve, max. = maximum, *n* = number, OR = odds ratio, PaO_2 = partial pressure of arterial oxygen.

[a] Number of subjects in whom the variable was obtained.

[b] Number of subjects (%).

[c] Median (range).

[d] *p*-Value: independent sample *t*-test for continuous data or Mann–Whitney *U* test dependent on normality; Fisher's exact test for dichotomous data.

[e] Adjusted for: age, gender, location of arrest, rhythm, basic life support/advanced pediatric life support, lowest pH, and highest lactate.

[f] Value was rescaled by dividing by 100 in advance of the regression analysis.

[g] Children without mild therapeutic hypothermia treatment or where the target temperature of 32–34 °C was not reached.

[h] Children with mild therapeutic hypothermia treatment, where the target temperature of 32–34 °C was reached.

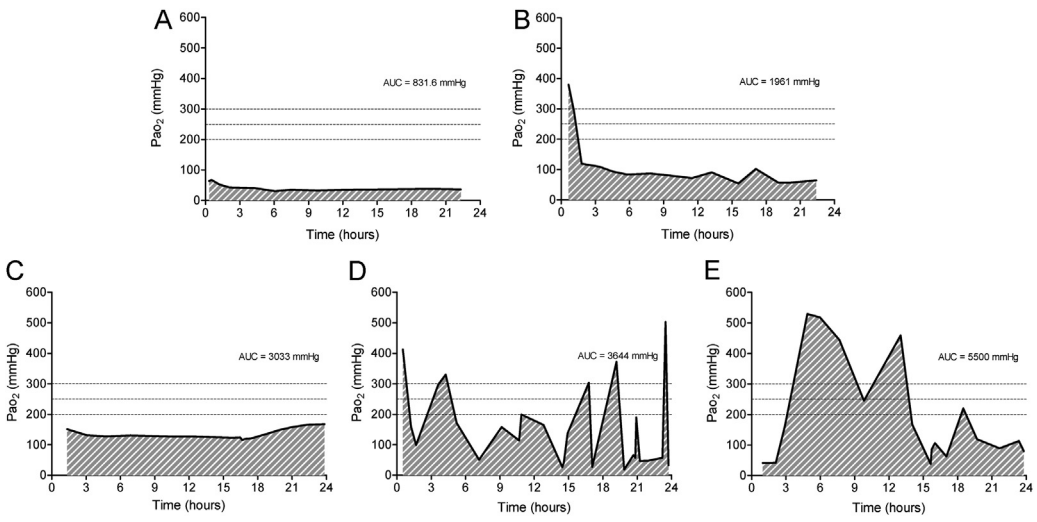

Fig. 3. Observations of PaO_2 for five selected patients in the dataset, cutoff versus area under the curve (AUC). (A) Low AUC value, no PaO_2 above a cutoff value. (B) Low AUC value, PaO_2 above cutoff values. (C) High AUC value, no PaO_2 above a cutoff value. (D) High AUC value, fluctuating PaO_2 above cutoff values. (E) High AUC value, PaO_2 above cutoff values.

impairments in microcirculatory function during MTH, increased amounts of dissolved oxygen could have maintained oxygen supply to the organs in the patients in the present study. Measurement of systemic and cerebral tissue oxygenation by near-infrared spectroscopy, Laser–Doppler spectroscopy, functional imaging, and perhaps even invasive methods, is necessary to study the interacting effects of hyperoxia and hypothermia on the outcome in children after CA.

Another explanation could be the synergistic effect of hypothermia and hyperoxia. It has been demonstrated that hypothermia attenuates oxidative stress after traumatic brain injury (TBI) in children.[28] Hyperoxia has been shown to improve organ function, and to attenuate tissue apoptosis and oxidative stress during early septic shock.[29] Even anti-inflammatory effects of hyperoxia are reported.[30]

Hyperoxia causes vasoconstriction. The mechanisms underlying this vasoconstriction are not well understood, but there are different theories as mentioned by Sjoberg and Singer.[30]

4.4. Limitations

Several limitations of our study should be acknowledged. First, this is an observational, retrospective, single-center cohort study in a heterogeneous population without a control group over a relatively long study interval. Changes in clinical care during this study period will have improved the outcome after CA; however this probably did not change the impact of high oxygen levels on the outcome, as the attention was more focused on preventing hypoxia, rather than avoiding hyperoxia. Only recent international CA guidelines have recommended avoiding an arterial oxygen saturation of 100%.[17]

Another limitation is that the time intervals of PaO_2 measurements were not standardized. We would recommend measuring PaO_2 at least every hour, which permits a more precise measurement of the AUC and thus a better estimation of the influence of PaO_2 on mortality.

A third limitation is the small number of patients in which MTH was applied, as therapeutic hypothermia was introduced halfway through the study period. However, this number of patients was not smaller than that in other studies.[19,31] As our findings stem from a small heterogeneous group of patients, we expect they will most probably be confirmed by larger, homogeneous groups of patients.

A fourth limitation is that some important variables are lacking, such as fluid administration during CPR, and time to ROSC.

Lastly, the information on temperature is limited. We recorded the time in which MTH was reached, but we did not document the course of the temperature during the following 24 h and during rewarming. In addition, we did not document the presence of fever.

5. Conclusions

Aware of the limitations of our study, we would recommend standardized prospective collection of all CA-related data in children in large multicenter networks. Retrospective analysis of a large set of prospective collected data will help us to answer such difficult questions in our very heterogeneous populations. Additionally, we need to study the effects of PaO_2 on physical outcome, neuropsychological outcome and health-related quality of life. Combining this information will help us to achieve goal-directed therapy which can automatically adjust the fraction of inspired oxygen to the individual physical demands of a child. Until individualized therapy can be practiced, we must use oxygen carefully within the therapeutic window and avoid the harmful effects of extreme values of PaO_2.

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Conflict of interest statement

None of the authors has declared a conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2014.12.013.

References

1. Donoghue AJ, Nadkarni V, Berg RA, et al. Out-of-hospital pediatric cardiac arrest: an epidemiologic review and assessment of current knowledge. Ann Emerg Med 2005;46:512–22.
2. Tibballs J, Kinney S. A prospective study of outcome of in-patient paediatric cardiopulmonary arrest. Resuscitation 2006;71:310–8.
3. Meert KL, Donaldson A, Nadkarni V, et al. Multicenter cohort study of in-hospital pediatric cardiac arrest. Pediatr Crit Care Med 2009;10:544–53.
4. Moler FW, Meert K, Donaldson AE, et al. In-hospital versus out-of-hospital pediatric cardiac arrest: a multicenter cohort study. Crit Care Med 2009;37:2259–67.
5. Topjian AA, Nadkarni VM, Berg RA. Cardiopulmonary resuscitation in children. Curr Opin Crit Care 2009;15:203–8.
6. Moler FW, Donaldson AE, Meert K, et al. Multicenter cohort study of out-of-hospital pediatric cardiac arrest. Crit Care Med 2011;39:141–9.
7. Becker LB. New concepts in reactive oxygen species and cardiovascular reperfusion physiology. Cardiovasc Res 2004;61:461–70.
8. Richards EM, Fiskum G, Rosenthal RE, Hopkins I, McKenna MC. Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism. Stroke 2007;38:1578–84.
9. 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.
10. Bellomo R, Bailey M, Eastwood GM, et al. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. Crit Care 2011;15:R90.
11. Janz DR, Hollenbeck RD, Pollock JS, McPherson JA, Rice TW. Hyperoxia is associated with increased mortality in patients treated with mild therapeutic hypothermia after sudden cardiac arrest. Crit Care Med 2012;40:3135–9.
12. Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest in-hospital mortality. J Am Med Assoc 2010;303:2165–71.
13. Ferguson LP, Durward A, Tibby SM. Relationship between arterial partial oxygen pressure after resuscitation from cardiac arrest and mortality in children. Circulation 2012;126:335–42.
14. Del Castillo J, Lopez-Herce J, Matamoros M, et al. Hyperoxia, hypocapnia and hypercapnia as outcome factors after cardiac arrest in children. Resuscitation 2012;83:1456–61.
15. Bennett KS, Clark AE, Meert KL, et al. Early oxygenation and ventilation measurements after pediatric cardiac arrest: lack of association with outcome. Crit Care Med 2013;41:1534–42.
16. Guerra-Wallace MM, Casey 3rd FL, Bell MJ, Fink EL, Hickey RW. Hyperoxia and hypoxia in children resuscitated from cardiac arrest. Pediatr Crit Care Med 2013;14:e143–8.
17. Biarent D, Bingham R, Eich C, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 6. Paediatric life support. Resuscitation 2010;81:1364–88.
18. Miller RD, Afton-Bird G. Miller anestesia. Madrid: Elsevier; 2005.
19. Fink EL, Clark RS, Kochanek PM, Bell MJ, Watson RS. A tertiary care center's experience with therapeutic hypothermia after pediatric cardiac arrest. Pediatr Crit Care Med 2010;11:66–74.
20. Topjian A, Hutchins L, DiLiberto MA, et al. Induction and maintenance of therapeutic hypothermia after pediatric cardiac arrest: efficacy of a surface cooling protocol. Pediatr Crit Care Med 2011;12:e127–35.
21. Nielsen N, Hovdenes J, Nilsson F, et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. Acta Anaesthesiol Scand 2009;53:926–34.
22. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 °C versus 36 °C after cardiac arrest. N Engl J Med 2013;369:2197–206.
23. Che D, Li L, Kopil CM, Liu Z, Guo W, Neumar RW. Impact of therapeutic hypothermia onset and duration on survival, neurologic function, and neurodegeneration after cardiac arrest. Crit Care Med 2011;39:1423–30.
24. Tai MM. A mathematical model for the determination of total area under glucose tolerance and other metabolic curves. Diabetes Care 1994;17:152–4.
25. Martin DS, Grocott MP. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. Crit Care Med 2013;41:423–32.
26. van Genderen ME, Lima A, Akkerhuis M, Bakker J, van Bommel J. Persistent peripheral and microcirculatory perfusion alterations after out-of-hospital cardiac arrest are associated with poor survival. Crit Care Med 2012;40:2287–94.
27. Buijs EA, Verboom EM, Top AP, et al. Early microcirculatory impairment during therapeutic hypothermia is associated with poor outcome in post-cardiac arrest children: a prospective observational cohort study. Resuscitation 2014;85:397–404.
28. Bayir H, Adelson PD, Wisniewski SR, et al. Therapeutic hypothermia preserves antioxidant defenses after severe traumatic brain injury in infants and children. Crit Care Med 2009;37:689–95.
29. Barth E, Bassi G, Maybauer DM, et al. Effects of ventilation with 100% oxygen during early hyperdynamic porcine fecal peritonitis. Crit Care Med 2008;36:495–503.
30. Sjoberg F, Singer M. The medical use of oxygen: a time for critical reappraisal. J Intern Med 2013;274:505–28.
31. Doherty DR, Parshuram CS, Gaboury I, et al. Hypothermia therapy after pediatric cardiac arrest. Circulation 2009;119:1492–500.