# Hyperoxia After Pediatric Cardiac Arrest: Association with Survival and Neurological Outcomes

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## Abstract

Hyperoxia After Pediatric Cardiac Arrest: Association with Survival and Neurological Outcomes

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Objective: To evaluate the association between hyperoxia in the first 24 hours after in-hospital pediatric

cardiac arrest and mortality and poor neurological outcome.

Design: Retrospective cohort study.

Setting: Tertiary care freestanding children's hospital.

Patients: Patients younger than 18 years of age with in-hospital cardiac arrest between December 2012 and December 2019, who achieved return of circulation (ROC) for longer than 20 minutes, survived at least 24 hours after cardiac arrest, and had documented PaO2 or SpO2 during the first 24 hours after ROC.

Interventions: None.

Main Results: There were 187 patients who met eligibility criteria, of whom 48% had hyperoxia (PaO2 > 200 mmHg) during the first 24 hours after cardiac arrest. In-hospital mortality in this

cohort of patients was 41%, with similar mortality between oxygenation groups (hyperoxia 45% vs no hyperoxia 38%). We did not observe an association between hyperoxia and in-hospital mortality or poor neurological outcome after adjusting for confounders (odds ratio 1.2, 95% confidence interval 0.5-2.8). On sensitivity analysis using two additional cutoffs of PaO2 (>150 mmHg and > 300 mmHg), there was also no association with in-hospital mortality or poor neurological outcome after adjusting for confounders. Similarly, on multivariable logistic regression using SpO2 > 99% as the exposure, there was no difference in the frequency of death or poor neurological outcome at hospital discharge.

Conclusions: In this cohort of patients, hyperoxia after pediatric cardiac arrest was common and was not associated with worse in-hospital outcomes.

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**Introduction**

In-hospital cardiac arrest (IHCA) in children is associated with both a high risk of death during that hospitalization and, among survivors, a high incidence of neurologic complications(1, 2). Efforts to improve outcomes have largely focused on rapid detection of prearrest conditions and providing high-quality cardiopulmonary resuscitation (CPR). Recent resuscitation research has highlighted the importance of preventing the post-cardiac arrest syndrome (PCAS) to improve outcomes after arrest(3). PCAS is characterized by persistent neurological and myocardial dysfunction mediated by ischemia-reperfusion injury. During reperfusion following return of circulation, blood carries reactive oxygen species to ischemic tissues that are deplete of antioxidants, forming free radicals and leading to oxidative stress and free radical-mediated cell injury(4–7).

In animal models, hyperoxia worsens neuronal damage through free radical production(8). In addition, hyperoxia causes an increase in coronary vascular resistance and subsequent reduction in coronary blood flow and myocardial oxygen consumption(9). However, studies in adults and children have not observed a consistent association between hyperoxia and mortality after cardiac arrest(10–17). Despite limited data, current pediatric resuscitation guidelines recommend avoiding hyperoxia, targeting a saturation of oxygen (SpO2) between 94% and 99% after cardiac arrest(2).

The objective of this study was to evaluate the association between the presence of hyperoxia in the first 24 hours after cardiac arrest and in-hospital mortality in children. We also examined the occurrence of poor neurological outcomes in relation to hyperoxia following cardiac arrest, which has been studied only once before in children(16).

## Methods

*Study Design and Participants*

This is a retrospective cohort study of patients at a tertiary free-standing pediatric hospital. Patients were identified for inclusion using an institutional code blue database. We included patients younger than 18 years of age with in-hospital cardiac arrest (receiving at least one minute of chest compressions) between December 2012 and December 2019, who achieved return of circulation (ROC) for longer than 20 minutes, survived at least 24 hours after cardiac arrest, and had documented PaO2 or SpO2 during the first 24 hours after ROC. Patients were excluded if they had missing data on survival to hospital discharge and/or PCPC scores. For patients with more than one cardiac arrest during the study period, only the first arrest event was included in the analysis (**Figure 1)**. This study was approved by the Institutional Review Board of Seattle Children's Hospital in Seattle, Washington (STUDY00001932).

*Variables*

The exposure was hyperoxia during the first 24 hours after cardiac arrest, using four different definitions: a single arterial partial pressure of oxygen (PaO2) above 150, 200, or 300 mmHg in the first 24 hours after cardiac arrest, and time spent with saturation of oxygen (SpO2) > 99% in the first 24 hours after cardiac arrest. The 24-hour period after ROSC was chosen based on risk of systemic ischemia-reperfusion injury and its use in previous studies(4). As no formal definition of hyperoxia exists, PaO2 cutoffs were chosen based on results of prior adult and pediatric studies(10–18). The single highest PaO2 value in 24 hours was chosen given that our unit does not have a protocol for drawing blood gases at specified time intervals. A SpO2 cutoff of 99% was selected based on pediatric resuscitation guidelines that recommend maintaining SpO2 below 99% after cardiac arrest(2). Time spent with SpO2 > 99% during the first 24 hours after ROC was divided into quartiles of minutes for analysis.

The study outcomes were in-hospital mortality and a composite endpoint of death or poor neurological outcome at hospital discharge, defined as a Pediatric Cerebral Performance Category (PCPC) of 3 or more, or an increase between hospital admission and hospital discharge for those with an abnormal pre-arrest PCPC score. A PCPC score of 1 is normal, 2 is mild disability, 3 is moderate disability, 4 is severe disability, 5 is coma, and 6 is brain death(19).

The covariates included demographic characteristics (age, sex, race, ethnicity), presence of comorbidities (congenital heart disease, prematurity), severity of illness (PRISM III score)(20), cardiac arrest characteristics (location inside vs outside the ICU, extracorporeal cardiopulmonary resuscitation (ECPR), duration of chest compressions, shockable rhythm), and use of organ-support therapies during the first 24 hours after cardiac arrest (extracorporeal life support (ECLS), continuous renal replacement therapy (CRRT), mechanical ventilation). In addition, variables associated with poor neurological outcome, including fever (temperature > 38C), hypoventilation (partial pressure of carbon dioxide ($PaCO_2$) > 50mmHg), hypoglycemia (glucose < 100 mg/dL), and hypotension (mean arterial pressure (MAP) below 50th percentile for age) (21), during the first 24 hours following the arrest were included. These cutoffs were chosen based on our institutional post-cardiac arrest guidelines.

*Statistical Analysis*

We used median and interquartile range (IQR) for continuous variables and frequencies and proportions for categorical variables to describe each oxygenation group. We performed univariable analysis and multivariable logistic regression to evaluate the association between hyperoxia and in-hospital mortality and poor neurological outcome, using $PaO_2$ > 200 and time with $SpO_2$ > 99% as the definitions of hyperoxia. We then performed sensitivity analysis using additional cutoffs ($PaO_2$ > 150 and $PaO_2$ > 300). All variables that led to a change in the odds

ratio of at least 10% were included in the logistic regression models. Because the results were similar after removing several patients in the age group not represented in the 'no hyperoxia' group (older than 24 months of age) from the 'hyperoxia' group, all patients were retained in the analysis. Statistical analysis was performed with R Statistical Software Version 4.0.4.

**Results**

There were 187 patients who met eligibility criteria (Figure 1), of whom 48% had hyperoxia (PaO2 > 200) during the first 24 hours after cardiac arrest. The median age was 6 months (IQR 1-36) and 45% of patients were girls. Compared with patients without hyperoxia in the first 24 hours after arrest, patients in the hyperoxia group were older, had a higher median PRISM III score, longer duration of chest compressions, presence of a shockable rhythm, and use of ECPR. The use of ECLS and CRRT during the first 24 hours after arrest was also more frequent in the hyperoxia group **(Table 1)**.

In-hospital mortality in this cohort of patients was 41%, with similar mortality between oxygenation groups (hyperoxia 45% vs no hyperoxia 38%). We failed to find an association between hyperoxia (PaO2 > 200 mmHg) and in-hospital mortality on univariable analysis, or on multivariable analysis after adjusting for duration of chest compressions and use of ECLS in the first 24 hours after arrest **(Table 2).** Poor neurological outcome at hospital discharge was similar between oxygenation groups (hyperoxia 22% vs no hyperoxia 20%). There was no association between hyperoxia (PaO2 > 200mmHg) and the combined outcome of death or poor neurological outcome on multivariable analysis after adjusting for duration of chest compressions and use of ECLS in the first 24 hours after arrest **(Table 3).** On sensitivity analysis, using two alternative cutoffs of PaO2 (>150 mmHg and > 300 mmHg), we found no association with in-hospital mortality or poor neurological outcome after adjusting for confounders **(Table 4).** Finally, the

findings did not change after eliminating 67 patients from the 'no hyperoxia' group and 35 patients from the 'hyperoxia' group who also experienced hypoxia (PaO2 < 60 mmHg) in the first 24 hours after arrest.

The median time spent in hyperoxia with SpO2 > 99% during the first 24 hours was 4.8 hours (IQR 0.3 – 12 hours). On multivariable logistic regression using SpO2 > 99% as the exposure, we found no difference in the frequency of death or poor neurological outcome at hospital discharge after adjusting for duration of chest compressions, PRISM III category and use of ECLS and CRRT during the first 24 hours after ROC. The lowest quartile of time was used as the reference category, and there was no association found with increasing time spent in hyperoxia **(Table 5).**

## Discussion

In this cohort of patients, we found that hyperoxia after cardiac arrest was common and not associated to any appreciable extent with in-hospital mortality and poor neurological outcome. These results are similar to those obtained in previous observational pediatric studies evaluating hyperoxia after cardiac arrest **(Table 6)**(13–17). One study in children did find a higher likelihood of death with increasing hyperoxia when PaO2 was modeled as a continuous variable, with a reported increase in odds ratio for mortality of 1.12 per 100mmHg increase in PaO2(13). Similar to our study, the prevalence of hyperoxia in these studies was as high as 63%, suggesting that normoxia after cardiac arrest often is not achieved despite recommendations in pediatric resuscitation guidelines.

It is plausible that in children oxidative stress could be harmful in the post-arrest setting, given the findings of studies in adults after cardiac arrest(10–12), neonates(22), critically ill children(18, 23–25), and children exposed to ECLS(26) and cardiac bypass(27). However, the

collective results of the present and prior studies suggest that if a deleterious impact of hyperoxia following a cardia arrest is present, it is small in magnitude. This suggests that the effects of hyperoxia may differ across specific populations of patients. For instance, in adults, in whom the etiology of cardiac arrest is more often acute coronary syndrome, hyperoxia may lead to worse outcomes due to coronary vasoconstriction and reduction in coronary blood flow(9). It is also possible that the uncertainty around this association may be related to the lack of an existing definition for pathologic hyperoxia, given that different PaO2 cutoffs and timing are used across these studies. Preclinical data suggest that hyperoxia during the early post-arrest period may be more detrimental compared to a later period when antioxidant reserves have recovered, and it is possible that existing studies have not uniformly captured this critical stage of exposure to hyperoxia(28). In addition, this timeline may vary from patient to patient based on the severity of post-cardiac arrest syndrome and their clinical trajectory(4).

Our study found that hyperoxia after cardiac arrest was more common in patients with higher severity of illness, longer duration of chest compressions, presence of a shockable rhythm, and use of ECPR. These findings may suggest higher clinician concern and hesitation to wean oxygen therapies due to perceived risk of worse outcomes or concerns about the harmful effects of hypoxemia after cardiac arrest. To address this potential concern, we controlled for these variables in the multivariable models, and continued to observe no appreciable association between hyperoxia and mortality or impaired neurological function. It is also possible that following cardiac arrest, more seriously ill patients received more respiratory support, and that this influenced both their ability to achieve hyperoxia and their outcomes after arrest. However, we did not have information available on the characteristics of the respiratory support received by each hyperoxia

group. Given the frequency of respiratory etiology of cardiac arrests in the pediatric population, future studies should include this data element in their analysis.

Our study has multiple strengths, including the use of multiple definitions of hyperoxia and an evaluation of poor neurological outcome. Notably, the use of SpO2 has not been used in previous pediatric studies despite its widespread use in clinical practice and recommendations targeting an SpO2 < 99% in the post-arrest period. The analysis of time spent with SpO2 > 99% also allows for a more comprehensive approach to exposure to hyperoxia that may be missed with the use of isolated measurements. The limitations of our study include those associated with the use of retrospective data, such as missingness, misclassification bias, and residual confounding. Defining clinically meaningful hyperoxia is challenging, and we may have underestimated or overestimated the exposure despite the use of multiple measurements of oxygenation. The variability in timing of blood gas collection presents challenges in measuring hyperoxia and could have prevented the identification of critical periods of hyperoxia exposure within the 24-hour period following arrest. We hoped to overcome this last point by using time spent in hyperoxia in addition to isolated PaO2 measurements.

## Conclusion

In this retrospective cohort of patients at a single institution, hyperoxia after pediatric cardiac arrest was not associated with poor outcomes. Pediatric resuscitation guidelines continue to emphasize the importance of avoiding hyperoxia after cardiac arrest based on preclinical data and adult studies. The fact that hyperoxia in children after cardiac arrest has not clearly been shown to be harmful suggests a need for larger studies, including the use of different definitions and timing of hyperoxia. Understanding the effect of hyperoxia in children after cardiac arrest would

help guide clinicians weigh the risks and benefits of frequent lab monitoring and prioritize competing elements of the post-arrest care bundle in improving outcomes after cardiac arrest.

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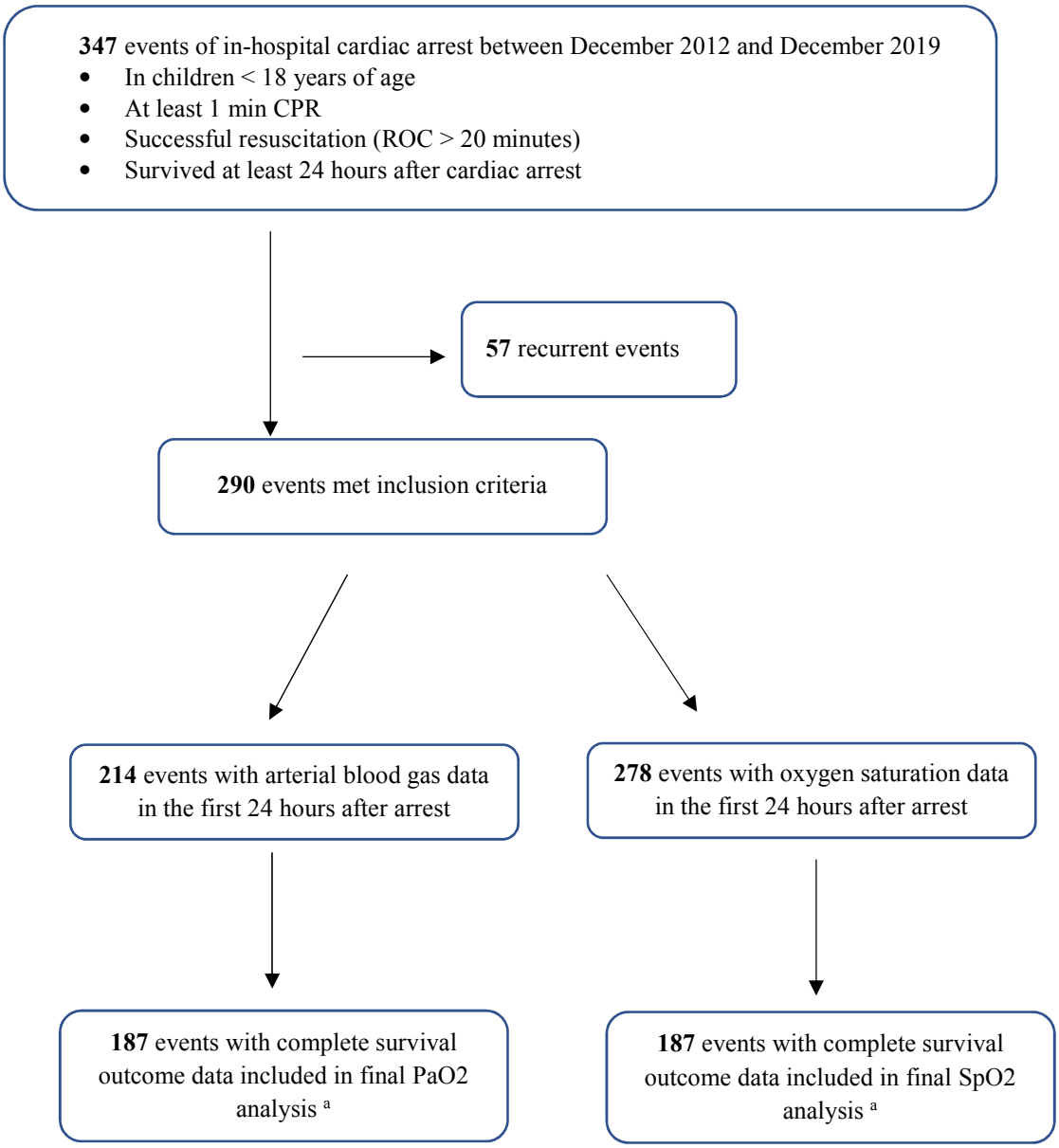


**Figure 1. Patient selection**

[a] Outcome data from the VPS registry missing for all patients in the neonatal ICU, patients in the cardiac ICU after May 2018, and some patients in the pediatric ICU missed on initial data collection

Abbreviations: CPR = Cardiopulmonary resuscitation, ROC = Return of circulation, PaO2 = Arterial partial pressure of oxygen, SpO2 = Saturation of oxygen, VPS = Virtual Pediatric Systems, ICU = Intensive care unit

**Table 1. Patient demographics and clinical characteristics by oxygenation status**

| | Hyperoxia[a] n = 89 n (%) | No hyperoxia n = 98 n (%) |
|---|---|---|
| **Demographics** | | |
| Age, median (IQR) months | 8 (1-64) | 5 (0-24) |
| Female | 38 (43) | 46 (47) |
| Race | | |
| *White* | 46 (52) | 46 (47) |
| *AI/AN* | 9 (10) | 3 (3) |
| *Black* | 9 (10) | 9 (9) |
| *Asian* | 6 (7) | 5 (5) |
| *NH/PI* | 1 (1) | 4 (4) |
| *Other* | 11 (12) | 20 (20) |
| Hispanic | 16 (18) | 24 (24) |
| **Comorbidities and Illness Severity** | | |
| Prematurity | 10 (14) | 8 (12) |
| Congenital Heart Disease | 21 (24) | 25 (26) |
| PRISM III score, median (IQR) | 11 (5-24) | 5 (3-13) |
| ICU Length of stay, median (IQR) days | 19 (7-37) | 22 (8-47) |
| **Cardiac Arrest Details** | | |
| Location of event | | |
| *ICU* | 75 (84) | 84 (86) |
| *Outside of the ICU* | 14 (16) | 14 (14) |
| Duration of compressions | | |
| *< 20 min* | 73 (82) | 93 (95) |
| *> 20 min* | 16 (18) | 5 (5) |
| Presence of Shockable Rhythm | 14 (16) | 9 (9) |
| ECPR | 27 (30) | 10 (11) |
| **Organ Supportive Therapies During ICU Stay** (after code) | | |
| Mechanical ventilation | 39 (44) | 36 (37) |
| ECLS | 31 (35) | 10 (10) |
| CRRT | 12 (13) | 6 (6) |
| **Post-arrest care** [b] | | |
| Hypoventilation [c] | 73 (82) | 74 (76) |
| Fever [d] | 23 (26) | 21 (22) |
| Hypoglycemia [e] | 55 (62) | 58 (59) |
| Hypotension, median (IQR) [f] | 77 (65-91) | 100 (84-100) |

[a] Defined as PaO2 > 200 mmHg
[b] During the first 24 hours after ROC as defined by post-arrest care guidelines at our institution
[c] At least one value of PCO2 > 50 mmHg in the first 24 hours after ROC
[d] At least one temperature > 38C in the first 24 hours after ROC
[e] At least one glucose < 80 mg/dL in the first 24 hours after ROC
[f] Percentage of MAP values below the 50th percentile for age

Abbreviations: IQR = interquartile range, AI/AN = American Indian/Alaska Native, NH/PI = Native Hawaiian/Pacific Islander, PaO2 = Partial pressure of arterial oxygen, ICU = Intensive Care Unit, ECPR = Extracorporeal cardiopulmonary resuscitation, ECLS = Extracorporeal life support, CRRT = Continuous renal replacement therapy, PCO2 = Partial pressure of carbon dioxide, MAP = Mean arterial blood pressure

**Table 2. Univariable and multivariable logistic regression analyses for in-hospital mortality as the outcome variable**

| *Variable* | *Died* | *Survived* | *Crude OR (95% CI)* | *Adjusted OR (95% CI)* |
|---|---|---|---|---|
| Hyperoxia [a] | 40 | 49 | 1.4 (0.8, 2.4) | 1.1 (0.6, 2.1) [b] |
| No hyperoxia | 37 | 61 | | |

[a] Defined as at least one value of PaO2 > 200 mmHg in the first 24 hours after cardiac arrest

[b] Adjusted for duration of chest compressions, extracorporeal life support during the first 24 hours following cardiac arrest

**Table 3. Univariable and multivariable logistic regression analyses with death or poor neurological outcome at hospital discharge as the outcome variable**

| *Variable* | *Death or poor neurological outcome* [b] | *Survival with good neurological outcome* | *Crude OR (95% CI)* | *Adjusted OR (95% CI)* |
|---|---|---|---|---|
| Hyperoxia [a] | 46 | 43 | 1.3 (0.7, 2.3) | 1.2 (0.5, 2.8) [c] |
| No hyperoxia | 44 | 54 | | |

[a] Defined as at least one value of PaO2 > 200 mmHg in the first 24 hours after cardiac arrest

[b] Poor neurological outcome defined as PCPC score $\geq$ 3 or increase from baseline

[c] Adjusted for duration of chest compressions, extracorporeal life support during the first 24 hours following cardiac arrest

**Table 4. Sensitivity analysis with different cutoffs of PaO2 and death or poor neurological outcome at hospital discharge as the outcome variable**

| *Variable* | *Death or poor neurological outcome* [a] | *Survival with good neurological outcome* | *Crude OR (95% CI)* | *Adjusted OR (95% CI)* |
|---|---|---|---|---|
| PaO2 > 150mmHg | 60 | 54 | 1.6 (0.9, 2.9) | 1.6 (0.6, 4.3) [b] |
| No PaO2 > 150mmHg | 30 | 43 | | |
| PaO2 > 300mmHg | 24 | 24 | 1.1 (0.6, 2.1) | 1.9 (0.5, 3.4) [c] |
| No PaO2 > 300mmHg | 66 | 73 | | |

[a] Poor neurological outcome defined as PCPC score $\geq$ 3 or increase from baseline

[b] Adjusted for PRISM III score, extracorporeal life support, continuous renal replacement therapy during the first 24 hours following cardiac arrest

[c] Adjusted for PRISM III score, duration of chest compressions, continuous renal replacement therapy during the first 24 hours following cardiac arrest

**Table 5. Multivariable logistic regression model with hyperoxia defined as SpO2 > 99% and death or poor neurological outcome at hospital discharge as the outcome variable**

| *Variable* | *Death or poor neurological outcome* [b] | *Survival with good neurological outcome* | *Adjusted OR (95% CI)* [c] |
|---|---|---|---|
| Time spent with SpO2 > 99% (mins) [a] | | | |
| Quartile 1 | 19 | 28 | Reference |
| Quartile 2 | 31 | 16 | 2.1 (0.6, 7.8) |
| Quartile 3 | 19 | 27 | 0.5 (0.1, 2.1) |
| Quartile 4 | 21 | 26 | 1.5 (0.4, 5.7) |

[a] Minutes spent with SpO2 > 99% in the first 24 hours after cardiac arrest, categorized into quartiles: 0-19 mins, 20-286 mins, 287-720 mins, 721-1428 mins

[b] Poor neurological outcome defined as PCPC score $\geq$ 3 or increase from baseline

[c] Adjusted for duration of chest compressions, PRISM III category, and extracorporeal life support and continuous renal replacement therapy during the first 24 hours following cardiac arrest

## Table 6. Pediatric studies evaluating hyperoxia and poor outcomes after pediatric cardiac arrest

| *Author, year* | *Sample size, study design, years of data collection* | *Population, exposure, and outcome definitions* | *Confounders adjusted for in analysis* | *Findings* |
|---|---|---|---|---|
| *Ferguson, 2012* | N = 1875<br><br>Retrospective multicenter cohort (33 UK and Ireland PICUs)<br>2003-2010 | Children 1 month -16 years with CA before PICU admission and ABG within 1 hour of admission<br>*Exposure:* PaO2 ≥ 300 mmHg on first ABG<br>*Outcome:* mortality in the PICU | Age, sex, ethnicity, CHD, OHCA, year, PIM2, mortality risk, mechanical ventilation, RRT, ECLS, vasoactives | 11% had PaO2 > 300<br>39% mortality in the PICU<br><br>RR 1.14 (95% CI 0.97, 1.34) [a] |
| *Del Castillo, 2012* | N = 223<br><br>Prospective multicenter cohort<br>2007-2009 | Children 1 month-18 years with IHCA + at least one ABG at ROSC and at 24h<br>*Exposure:* PaO2 ≥ 300 mmHg on first gas after CA<br>*Outcome:* In-hospital mortality | None | 8.5% had PaO2 > 300<br>40% in-hospital mortality<br><br>RR 1.36 (95% CI 0.86, 2.15) [a] |
| *Guerra-Wallace, 2013* | N = 74<br><br>Retrospective single-center cohort<br>2004-2008 | Children who survived for at least 48h after CA<br>*Exclusion*: use of ECLS, CHD<br>*Exposure* PaO2 > 200 or > 300 mmHg in the first 24h after CA<br>*Outcome*: mortality at 6 months | Age, etiology of arrest | 51% had PaO2 > 300<br>70% had PaO2 > 200<br>28% mortality at 6 months<br><br>PaO2 > 300: RR 0.94 (95% CI 0.34, 2.60)<br>PaO2 > 200: RR 0.66 (95% CI 0.21, 2.11) |
| *Bennett, 2013* | N = 195<br><br>Retrospective multicenter cohort (15 hospitals within PECARN)<br>2003-2004 | Children 1 day-18 years who survived for at least 6h after CA<br>*Exclusion*: Patients in the NICU, cyanotic CHD<br>*Exposure:* PaO2 > 200mmHg in the first 6h after CA<br>*Outcome:* survival to hospital discharge with good neurological outcome [b] | Age, arrest location, rhythm, number of epinephrine doses | 54% had PaO2 > 200<br>37% survival to hospital discharge with good neurological outcome<br><br>OR 1.02 (95% CI 0.46, 2.27) |
| *van Zellem, 2014* | N = 200<br><br>Retrospective single-center cohort<br>2002-2011 | Children 28 days to 18 years<br>*Exclusion*: cyanotic CHD<br>*Exposure:* PaO2 >200, >250, >300 mmHg using highest PaO2 in 24h<br>*Outcome:* In-hospital mortality | Age, sex, type of resuscitation (BLS/ PALS), location, rhythm, lowest pH, highest lactate | 63% had PaO2 > 200<br>58% in-hospital mortality<br><br>PaO2 > 200: OR 0.81 (95% CI 0.41, 1.59)<br>PaO2 > 250: OR 1.11 (95% CI 0.58, 2.11)<br>PaO2 > 300: OR 0.91 (95% CI 0.47, 1.76) |

[a] Unadjusted RR calculated using raw data provided in the manuscript
[b] PCPC 1-2 or no change between baseline and discharge

Abbreviations: PICUs = Pediatric Intensive Care Units, CA = cardiac arrest, ABG = arterial blood gas, PaO2 = Partial pressure of arterial oxygen, CHD = congenital heart disease, OHCA = out-of-hospital cardiac arrest, PIM2 = Pediatric Index of Mortality-2, RRT = renal replacement therapy, ECLS = extracorporeal life support, IHCA = in-hospital cardiac arrest, ROSC = return of spontaneous circulation, PECARN = Pediatric Emergency Care Applied Research Network, NICU = neonatal intensive care unit, PCPC = Pediatric Cerebral Performance Category, AUC = area under the curve, BLS = basic life support, PALS = pediatric advanced life support