

Relationship Between Arterial Partial Oxygen Pressure After Resuscitation From Cardiac Arrest and Mortality in Children

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Background—Observational studies in adults have shown a worse outcome associated with hyperoxia after resuscitation from cardiac arrest. Extrapolating from adult data, current pediatric resuscitation guidelines recommend avoiding hyperoxia. We investigated the relationship between arterial partial oxygen pressure and survival in patients admitted to the pediatric intensive care unit (PICU) after cardiac arrest.

Methods and Results—We conducted a retrospective cohort study using the Pediatric Intensive Care Audit Network (PICANet) database between 2003 and 2010 (n=122 521). Patients aged <16 years with documented cardiac arrest preceding PICU admission and arterial blood gas analysis taken within 1 hour of PICU admission were included. The primary outcome measure was death within the PICU. The relationship between postarrest oxygen status and outcome was modeled with logistic regression, with nonlinearities explored via multivariable fractional polynomials. Covariates included age, sex, ethnicity, congenital heart disease, out-of-hospital arrest, year, Pediatric Index of Mortality-2 (PIM2) mortality risk, and organ supportive therapies. Of 1875 patients, 735 (39%) died in PICU. Based on the first arterial gas, 207 patients (11%) had hyperoxia ($\text{PaO}_2 \geq 300$ mm Hg) and 448 (24%) had hypoxia ($\text{PaO}_2 < 60$ mm Hg). We found a significant nonlinear relationship between PaO_2 and PICU mortality. After covariate adjustment, risk of death increased sharply with increasing hypoxia (odds ratio, 1.92; 95% confidence interval, 1.80–2.21 at PaO_2 of 23 mm Hg). There was also an association with increasing hyperoxia, although not as dramatic as that for hypoxia (odds ratio, 1.25; 95% confidence interval, 1.17–1.37 at 600 mm Hg). We observed an increasing mortality risk with advancing age, which was more pronounced in the presence of congenital heart disease.

Conclusions—Both severe hypoxia and, to a lesser extent, hyperoxia are associated with an increased risk of death after PICU admission after cardiac arrest. (*Circulation*. 2012;126:335–342.)

Key Words: cardiac arrest ■ cardiopulmonary resuscitation ■ heart arrest ■ oxygen ■ pediatrics

Survival to hospital discharge after in-hospital and out-of-hospital cardiac arrest in children remains low.^{1–3} Even with achievement of return of circulation, many children die in subsequent days, with death usually attributed to neurological injury or cardiovascular dysfunction.¹ Recent research has focused on therapeutic strategies to attenuate the post-cardiac arrest syndrome that accompanies postischemic reperfusion.⁴ Evidence from animal models indicates postischemic hyperoxia promotes free radical-generated injury⁵ and that oxidative stress contributes to both neurological injury⁶ and cardiac dysfunction.⁷ In addition, hyperoxia has also been shown to decrease cardiac output⁸ and reduce regional oxygen delivery to both cerebral and coronary vascular beds.^{9,10}

Clinical Perspective on p 342

The observational studies in adults that have investigated postresuscitation hyperoxia have reported conflicting find-

ings.^{11,12} In a multicenter retrospective study of 6326 adults admitted to an intensive care unit (ICU) after nontraumatic cardiac arrest, the Emergency Medicine Shock Research Network (EMShockNet) investigators found that exposure to arterial hyperoxia after resuscitation, based on the first arterial blood gas after ICU admission, carried an independent risk of in-hospital death. In secondary analysis of this data set, a dose-dependent relationship in the association between supranormal oxygen tension and relative risk of in-hospital mortality was observed.¹³ Bellomo et al¹² repeated the study using a larger data set of 12 108 patients from the Australian and New Zealand Adult Patient Database. Using the lowest recorded arterial PaO_2 during the first 24 hours of ICU admission but otherwise similar methodology as the EMShockNet investigators, they also found increased mortality in both the isolated hypoxemia and hyperoxia groups compared with normoxia; however, the relationship between

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hyperoxia and mortality was weak and no longer achieved statistical significance after adjustment for illness severity.¹²

Clinical data in the pediatric population are lacking. On the basis of laboratory and adult clinical data, recent pediatric resuscitation guidelines recommend avoiding hyperoxia by reducing the fraction of inspired oxygen (FiO_2) to the minimum concentration needed to achieve arterial oxygen saturations of 94% to 98% after return of circulation.^{14,15} We undertook this retrospective cohort study to investigate the relationship between PaO_2 and ICU survival in patients admitted to pediatric intensive care after cardiac arrest. Specifically, we sought to determine whether early hyperoxia or hypoxia after return of circulation in children aged <16 years was significantly associated with ICU death after adjustment for mortality risk. In contrast to the adult studies, we modeled oxygen status as a continuous, nonlinear variable. Our secondary aim was to investigate whether the presence of congenital heart disease (a factor associated with abnormal baseline oxygen saturations and hence PaO_2) influenced this relationship.

Methods

The study used data from the Pediatric Intensive Care Audit Network (PICANet) national database. PICANet is coordinated by the Universities of Leeds and Leicester and collects pediatric ICU (PICU) admission data that include demographics, diagnosis, admission physiology, and individual patient outcome. PICANet was established in 2001 and now records details of all admissions to 33 PICUs within the United Kingdom and Ireland ($n=122\,521$ admissions 2003–2010). Rigorous data quality assurance processes are undertaken by the PICANet team to ensure the data set is of high quality.¹⁶ Efforts include training days to familiarize data entry staff with data definitions, internal logical consistency and range checks at the point of data entry, and monthly unit validation visits by a member of the PICANet team to ensure data are transcribed accurately from the medical notes.¹⁶ Anonymized data were provided with the approval of the PICANet Clinical Advisory Group and Steering Group, with the endorsement of the Pediatric Intensive Care Society. Collection of personally identifiable data has been approved by the Patient Information Advisory Group and ethical approval granted by the Trent Medical Research Ethics Committee.

Patients aged <16 years with an admission diagnosis of cardiac arrest or who had documented cardiac arrest preceding PICU admission (defined as absent pulse or requirement for external cardiac compressions) between 2003 and 2010 were included. We excluded patients without documented arterial blood gas analysis within the time period from the first face-to-face contact with a PICU doctor to 1 hour after admission to the unit and excluded neonates admitted to PICU after resuscitation in the delivery room.

Data Collection

We recorded the following variables: Demographics, cause of cardiac arrest, location of the arrest (in hospital or out of hospital), interhospital transfer to PICU, diagnoses associated with PICU admission (including congenital heart disease), Pediatric Index of Mortality-2 (PIM2) score,¹⁷ interventions during PICU stay (eg, vasoactive drug use), and status at PICU discharge (alive or dead). PIM2 is a mortality risk score calculated via logistic regression from variables that include (1) circumstances of PICU admission (elective/unplanned, recovery from surgical procedure, after cardiopulmonary bypass), (2) 9 key high-risk and 5 low-risk diagnoses, (3) mechanical ventilation within 1 hour of PICU admission, and (4) first measured value of 4 physiological variables (systolic blood pressure, pupillary reaction, base excess in arterial or capillary blood, and ratio of FiO_2 to PaO_2) if taken within 1 hour of PICU admission.¹⁷

Statistical Analyses

The primary outcome measure was death within the PICU. We initially classified oxygen status (based on PaO_2 from the first arterial blood gas obtained within 1 hour of PICU or retrieval team contact) into 3 groups using the same definition as the adult studies.^{11,12} Hypoxia was defined as $\text{PaO}_2 < 60$ mm Hg and hyperoxia as $\text{PaO}_2 \geq 300$ mm Hg.^{11,12} PIM2 was used to estimate mortality risk.¹⁷ Using a similar approach to Bellomo et al,¹² we calculated an adjusted PIM2 index of mortality (PIM2_noO_2), by expressing the score in logit form and then removing the oxygen component.

The relationship between oxygen status after arrest and PICU death was modeled with logistic regression with Stata version 12 (StataCorp). Important covariates were identified a priori on the basis of known relationship to outcome and likely confounding with the variable of interest, oxygen status.¹⁸ These included year of admission, age, sex, Asian ethnicity,¹⁹ presence of congenital heart disease, location of arrest (out of hospital versus in hospital),²⁰ interhospital transfer to PICU, PIM2_noO_2 , and PICU use of mechanical ventilation, vasoactive intravenous drugs, extracorporeal membrane oxygenation, and renal replacement therapy. In contrast to the adult studies, we allowed for oxygen status (and other continuous variables) to be modeled in a nonlinear manner using multivariable fractional polynomials (Stata mfp precommand).²¹ This avoided the loss of valuable information from categorizing a continuous variable²² and provided a means to quantify potentially differential effects at extremes of oxygen status (for example, risk may rise more rapidly at extremes of hypoxia compared with hyperoxia). Extreme values for PaO_2 were truncated at 23 and 600 mm Hg to minimize excessive leverage from outliers.¹⁸

Collinearity was screened for by use of variance inflation factors and the conditioning indices of variance decomposition proportions (coldiag2 ado file, courtesy of Joseph Harkness). FiO_2 was thus not included in the model because of unacceptable collinearity with both oxygen status and mechanical ventilation; in addition, this variable conceivably lies on a continuum with oxygen and death (ie, high oxygen levels are only possible if a high FiO_2 is administered).

Two potentially important interactions were considered a priori and tested during the model fitting process; both included congenital heart disease: Heart disease by oxygen status and heart disease by age. The former interaction was considered to accommodate the fact that a proportion of congenital heart disease patients have a degree of hypoxia as their “normal” status, because of anatomic shunts, and the second to allow for the possibility that age may have a differential effect on mortality risk in this group compared with children without congenital heart disease. Inclusion of interactions in the final model was based on joint likelihood ratio tests with the χ^2 distribution (with appropriate degrees of freedom).¹⁸ Influential observations were screened via plots of δ -model χ^2 versus probability and dfit β versus probability. Overall model fit was assessed via the C statistic and Hosmer-Lemeshow goodness-of-fit test.

The model-fitting procedure outlined above used complete case data only. We also quantified the impact of missing arterial blood gases (present in 832 cases, or 31% of the total sample) by refitting the final model after multiple imputation. Absence of arterial blood gases affected 2 variables: PIM2_noO_2 (because of missing base excess) and PaO_2 . Both were imputed using (1) all variables within the main model, (2) the 18 supplementary diagnostic subcategories shown in Table 1, and (3) 2 physiological variables (presence of fixed pupils and systolic blood pressure). Imputation was via predictive mean matching (to account for nonnormality of missing variables and to keep the PaO_2 within the truncated boundaries of 23 and 600 mm Hg), whereby 20 imputations were performed and then pooled into a final single set of results by use of Rubin’s combination rules.²³

Results

There were 2721 patients from 33 PICUs who met the inclusion criteria. Of these, 31% were excluded: 832 (31%) had no arterial blood gas measured up to 1 hour after PICU admission, 13 (0.5%) were admitted after resuscitation at

Table 1. Cause of Cardiac Arrest

Cause of Arrest	All Patients With Arterial Gas (n=1875)	Normoxia (n=1220)	Hypoxia (n=448)	Hyperoxia (n=207)	No Arterial Gas (n=832)
Anaphylaxis	6 (0.3)	3 (0.2)	1 (0.2)	2 (1)	3 (0.4)
Cardiovascular					
Arrhythmia (non-CHD)	56 (3)	36 (3)	7 (2)	13 (6)	19 (2)
Cardiomyopathy/myocarditis	95 (5)	68 (6)	18 (4)	9 (4)	33 (4)
Congenital heart disease	227 (12)	89 (7)	130 (29)	8 (4)	96 (12)
Hypovolemic shock	15 (1)	9 (1)	3 (1)	3 (1)	10 (1)
Pulmonary hypertension of newborn	24 (1)	8 (1)	15 (3)	1 (0.5)	2 (0.2)
Septic shock	161 (9)	107 (9)	42 (9)	12 (6)	40 (5)
Other cardiovascular	42 (2)	26 (2)	8 (2)	8 (4)	17 (2)
Drug overdose/ingestion	12 (1)	9 (1)	2 (0.4)	1 (0.5)	1 (0.1)
Electrolyte imbalance	35 (2)	25 (2)	5 (1)	5 (2)	14 (2)
Neurological (excludes trauma)	132 (7)	102 (8)	14 (3)	16 (8)	67 (8)
Respiratory					
Airway obstruction	54 (3)	40 (3)	6 (1)	8 (4)	60 (7)
Asthma	46 (2)	36 (3)	1 (0.2)	9 (4)	12 (1)
Bronchiolitis	45 (2)	40 (3)	4 (1)	1 (0.5)	36 (4)
Drowning/asphyxia	80 (4)	64 (5)	8 (2)	8 (4)	13 (2)
Other respiratory failure	198 (11)	129 (11)	53 (12)	16 (8)	101 (12)
Trauma	103 (5)	76 (6)	8 (2)	19 (9)	19 (2)
Unknown at admission or not stated	544 (29)	353 (29)	123 (27)	68 (33)	289 (35)

CHD indicates congenital heart disease.

birth, and 1 patient had missing outcome data. Baseline characteristics are given in Tables 1 and 2 and include the characteristics of the patients who were excluded without having undergone arterial blood gas analysis. Compared with the group with measured PaO_2 , patients in the excluded no-gas group were younger (median age 6 versus 11 months) and had a lower proportion of out-of-hospital arrests (31% versus 45%) and mechanical ventilation on PICU admission (72% versus 97%). The PICU mortality rate was 29% in the no-gas group.

Of 1875 patients undergoing arterial blood gas analysis, 448 (24%) were hypoxic, 207 (11%) were hyperoxic, and 1220 (65%) were normoxic. Hyperoxia was more common among patients without congenital heart disease, and hypoxia was more common among those with congenital heart disease (Figure 1). There were 839 patients (45%) admitted after out-of-hospital cardiac arrest. More than half of all patients (62%) were transported to the PICU from other hospitals. Of these, 94% were transported by a specialist retrieval team. Almost all (97%) patients were mechanically ventilated at admission to PICU.

Congenital heart disease was more common in the hypoxia group (30% versus 9% in normoxia and 5% in hyperoxia groups). Cardiac arrest was of cardiovascular causes in 620 patients (33%) and of respiratory causes in 423 (23%; Table 1). Trauma was an uncommon cause of cardiac arrest (5%). The cause of the cardiac arrest was unknown at PICU admission or not stated in 29% of cases.

The median length of PICU stay was 2 days (interquartile range 1–4) in nonsurvivors and 6 days (interquartile range 3–10) in survivors. Interventions within the PICU are summarized in Table 3. Nearly two thirds of patients received vasoactive medication by continuous intravenous infusion, and 69 patients (4%) were supported with extracorporeal membrane oxygenation. Renal support was used in 147 children (8%). Continuous veno-venous hemofiltration, hemodialysis, and peritoneal dialysis were used in 5%, 1%, and 3% of patients, respectively.

Overall, 735 (39%) of 1875 children died before PICU discharge. The unadjusted death rate was slightly higher in the hyperoxic group (44%) and lower for hypoxic patients (37%). The multivariable association between PaO_2 and mortality was both nonlinear (the optimal transformation expressed PaO_2 to the powers -2 and -1) and significant ($P=0.01$ and 0.04 , respectively; Table 4). However, there was no interaction between PaO_2 and congenital heart disease (model $\chi^2=6.68$, 4 *df*, $P=0.15$), and thus, this was excluded from the final model. Both congenital heart disease and age were associated with mortality, as was their interaction (model $\chi^2=16.44$, 4 *df*, $P=0.002$).

The complexity of the relationship between PaO_2 , age, and congenital heart disease is shown in Figure 2. This demonstrates several important findings. First, mortality risk was lowest at a PaO_2 of ≈ 60 to 75 mm Hg. Second, mortality risk increased with both hypoxia and hyperoxia, although more steeply for the former. Compared with the optimal PaO_2 (60–75 mm Hg), the odds ratios for the extremes of hypoxia

Table 2. Baseline Characteristics of the Study Population

Patient Characteristics	All Patients With Arterial Gas (n=1875)	Normoxia (n=1220)	Hypoxia (n=448)	Hyperoxia (n=207)	No Arterial Gas (n=832)
Median age, mo (IQR)	11 (2–61)	15 (3–77)	4 (1–19)	17 (3–70)	6 (2–33)
Male, n (%)	1086 (58)	718 (59)	249 (56)	119 (57)	453 (54)
Race/ethnicity, n (%)					
White	1072 (57)	695 (57)	265 (59)	112 (54)	470 (56)
Asian	213 (11)	143 (12)	49 (11)	21 (10)	97 (12)
Black	93 (5)	54 (4)	25 (6)	14 (7)	54 (6)
Other/not stated	497 (27)	328 (27)	109 (24)	60 (29)	211 (25)
Out-of-hospital arrest, n (%)	839 (45)	578 (47)	142 (32)	119 (57)	262 (31)
Retrieval to PICU, n (%)	1165 (62)	794 (65)	233 (52)	138 (67)	355 (43)
Comorbidities, n (%)					
Congenital heart disease	253 (13)	108 (9)	135 (30)	10 (5)	121 (15)
Hypoplastic left heart syndrome	48 (3)	6 (0.5)	41 (9)	1 (0.5)	15 (2)
Leukemia/lymphoma*	13 (0.7)	9 (0.7)	3 (0.7)	1 (0.5)	10 (1)
Neurodegenerative disorder	39 (2)	25 (2)	8 (2)	6 (3)	19 (2)
Severe combined immunodeficiency	10 (0.5)	6 (0.5)	3 (0.7)	1 (0.5)	8 (1)
Severe developmental delay	92 (5)	63 (5)	21 (5)	8 (4)	77 (9)
Markers of severity					
Median PIM2 risk of death (IQR), %	40 (25–69)	37 (24–65)	48 (30–75)	44 (25–75)	16 (6–31)
Median PIM2 risk of death (no oxygen)† (IQR), %	34 (22–63)	33 (22–61)	38 (22–64)	42 (24–74)	
Vital signs on admission to PICU					
Systolic BP, mm Hg, median (IQR)	90 (70–110)	92 (75–110)	79 (60–98)	95 (75–113)	90 (71–105)
Base deficit, mmol/L, median (IQR)	6.8 (2–13.4)	6.7 (2–12.3)	6.3 (0.6–14.9)	9 (3–15.8)	
Pupils fixed and dilated, n (%)	279 (15)	187 (15)	48 (11)	44 (21)	63 (8)
Mechanical ventilation at PICU admission, n (%)	1816 (97)	1185 (97)	427 (95)	204 (99)	597 (72)

IQR indicates interquartile range; PICU, pediatric intensive care unit; PIM2, Pediatric Index of Mortality-2; and BP, blood pressure.

*Leukemia or lymphoma after completion of first induction chemotherapy.

†PIM2 risk of death with oxygenation component removed from PIM2 score.

(23 mm Hg) and hyperoxia (600 mm Hg) were 1.92 (95% confidence interval [CI], 1.80–2.11) and 1.25 (95% CI, 1.17 to 1.37), respectively. Third, ICU mortality risk increased with age during early childhood and then plateaued; this

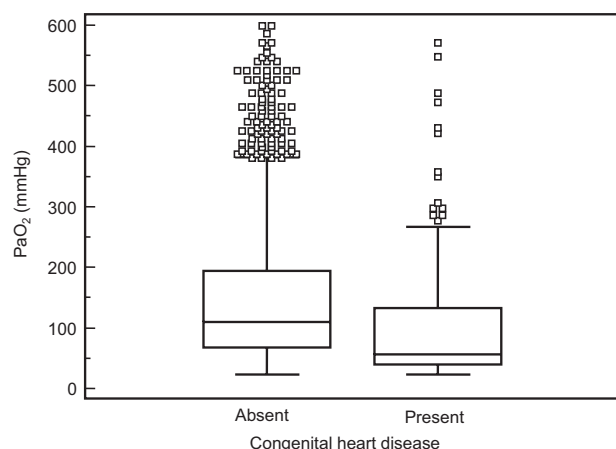


Figure 1. Distribution of P_{aO_2} according to the presence of congenital heart disease.

effect was more pronounced among patients with congenital heart disease (Figure 2). For example, the odds ratio for death after cardiac arrest for a 5-year-old compared with a 1-month-old infant was 2.13 (95% CI, 1.85 to 2.47) among the group without congenital heart disease; this rose to 9.86 (95% CI, 8.53 to 11.40) for the same age comparison in the congenital heart disease group.

Finally, 3 other findings were apparent. First, out-of-hospital arrests were nearly twice as likely to result in PICU death (odds ratio, 1.97; $P<0.0001$). Second, patients undergoing interhospital transfer (typically, this was because of transfer from the presenting district hospital to the tertiary PICU) were at increased risk of death (odds ratio, 1.40; $P=0.008$). Finally, there was a trend toward a 5% year-on-year reduction in adjusted mortality risk (odds ratio, 0.95; $P=0.08$).

The model was not appreciably altered after multiple imputation. Of note, the odds ratios for P_{aO_2} were similar, changing from 1.17 to 1.11 (–5.5%), and from 0.66 to 0.74 (an increase of 11.5%), respectively. In addition, both imputed odds ratios retained statistical significance: 1.11 (95% CI, 1.01–1.22; $P=0.036$) and 0.74 (95% CI, 0.55–0.99;

Table 3. Interventions During PICU Stay

Interventions in PICU, n (%)	All Patients With Arterial Gas (n=1875)	Normoxia (n=1220)	Hypoxia (n=448)	Hyperoxia (n=207)	No Arterial Gas (n=832)
ECMO	69 (4)	36 (3)	24 (5)	9 (4)	17 (2)
Renal support*	147 (8)	93 (8)	38 (8)	16 (8)	37 (4)
Vasoactive intravenous infusion†	1158 (62)	724 (59)	310 (69)	124 (60)	349 (42)
Ventricular assist device	8 (0.4)	3 (0.2)	2 (0.4)	3 (1.4)	5 (0.6)

PICU indicates pediatric intensive care unit; ECMO, extracorporeal membrane oxygenation.

*Includes peritoneal dialysis, continuous veno-venous hemofiltration, and hemodialysis.

†Includes continuous intravenous infusion of inotrope, vasopressor, vasodilator, or prostaglandin.

$P=0.04$), respectively. The imputed odds ratios for the remaining variables exhibited similarly modest changes, ranging from minus 12.9% to plus 13.1%.

Discussion

This is the first study to date to investigate the relationship between P_{aO_2} and mortality in children after return of spontaneous circulation after cardiac arrest. We have demonstrated that severe hypoxia and, to a lesser extent, hyperoxia, after return of circulation are associated with an increased probability of death in children admitted to PICU. We have also shown an association between survival to PICU discharge after pediatric cardiac arrest and age, in that infants and younger children are more likely to survive than older children.

The harmful effect of hypoxia after cerebral injury has been widely reported,^{24,25} and in adults, hypoxemic patients after cardiac arrest have particularly poor outcomes.^{11,12} We found a sharp rise in odds of death with increasing hypoxemia, which was more pronounced than that shown by 2 adult studies: Odds ratios of 1.92 (present study) versus 1.3¹¹ and 1.4.¹² However, direct comparison is difficult because of likely differences in the study populations: (1) In the adult studies, hypoxia was defined as either $P_{aO_2} < 60$ mm Hg or a P/F ratio < 300 mm Hg, which results in a higher proportion of hypoxic patients (74% and 63% versus 24% in the present study); (2) we have no information about the distribution of individual P_{aO_2} values within the hypoxia groups; and (3) the present study estimated hypoxia as a quantitative rather than a qualitative variable. A somewhat surprising finding was that the P_{aO_2} risk profile in the present study was not influenced by congenital heart disease (interaction effect, $P=0.15$). However, this may have been caused by limitations in the database, because we were unable to reliably differentiate cyanotic from acyanotic congenital heart disease patients.

Although it is important to avoid severe hypoxia, the present data lend support to the hypothesis that exposure to hyperoxia after cardiac arrest is detrimental. We found hyperoxia to be independently associated with increased risk of ICU mortality after adjustment for a broad range of covariates. The magnitude of the effect of hyperoxia on mortality in the present study is similar to that reported recently by Bellomo et al in adults.¹² They found an odds ratio of 1.2 (95% CI 1.0–1.5) for hospital mortality in patients with hyperoxia versus normoxia in a multiple regression

model that incorporated illness severity; however, the significance of this relationship did change depending on the type of analysis performed.¹² In agreement with Kilgannon and colleagues,¹³ we found that the association between hyperoxia and mortality risk was not limited to extreme oxygen tension values, and similarly, we observed no single threshold for harm from hyperoxia. However, the association between degree of hyperoxia and mortality in the present study was not as pronounced as that for adults. We demonstrated an increase in the odds ratio for mortality of ≈ 1.12 (because of the nonlinear relationship; Figure 2) per 100-mm Hg increase in P_{aO_2} , compared with 1.24 in the study by Kilgannon et al.¹³ This is not surprising given the different spectrum of confounders between the adult and pediatric populations.

The present findings are also consistent with laboratory data demonstrating the deleterious effects of exposure to 100% oxygen after resuscitation from cardiac arrest.^{5,6} We chose to use only the first arterial blood gas taken within 1 hour of contact with the PICU or retrieval team to investigate the effect of hyperoxia early after reperfusion. Laboratory data^{5,6} and a preliminary clinical study²⁶ support the concept of harm from supranormal oxygen tension in the first hour after return of circulation. It is unknown whether more prolonged exposure to hyperoxia would increase the risk of death further. In our model, the optimal P_{aO_2} after cardiac arrest was 60 to 75 mm Hg. The results of the present study lend further support to the postulated target arterial oxygen saturations of 94% to 96% in future clinical trials of controlled titration of F_{iO_2} after return of circulation after cardiac arrest.¹³

Children may be more at risk of hyperoxia than adults because of exposure to high F_{iO_2} administration during transport. In the present study, more than half of the children admitted to the PICU after resuscitation were transported from an outside hospital, and almost all ($>98\%$) were mechanically ventilated. Many portable transport ventilators are unable to deliver F_{iO_2} below 0.5,²⁷ and additionally, the use of hand ventilation with a flow-inflating anesthesia bag with 100% oxygen further risks exposure to hyperoxia. This may explain in part the increased risk with interhospital transfer seen in the present study (odds ratio 1.4).

Age was an important risk factor for death in the present study cohort. Infants and young children admitted to the PICU after cardiac arrest were much more likely to survive to ICU discharge than older children after adjustment for factors

Table 4. Multiple Logistic Regression Model With Death in PICU as the Dependent Variable

Variable	Odds Ratio (95% CI)	P
Blood oxygen		
PaO_2^{-2}	1.17 (1.04–1.32)	0.01
PaO_2^{-1}	0.66 (0.44–0.99)	0.04
Demographics		
Male	0.86 (0.69–1.08)	0.20
Ethnicity (Asian)	1.05 (0.74–1.49)	0.88
Out-of-hospital arrest	1.97 (1.56–2.49)	<0.0001
Interhospital transfer to PICU	1.40 (1.09–1.80)	0.008
Age ¹	6.40 (2.84–14.45)	<0.0001
Age ²	0.40 (0.25–0.65)	<0.0001
Congenital heart disease	3.44 (1.55–7.66)	0.002
CHD×age ¹	384 (11–13549)	0.001
CHD×age ²	0.005 (0.0002–0.11)	0.001
Year	0.95 (0.90–1.01)	0.08
Disease severity		
PIM2_noO ₂ logit ³	313 (117–836)	<0.0001
PIM2_noO ₂ logit ³ ×ln(PIM2_noO ₂ logit)	1.1×10^{-5} (9×10^{-8} –0.001)	<0.0001
Vasoactive medication	1.70 (1.31–2.21)	<0.0001
Mechanical ventilation	1.12 (0.72–1.75)	0.60
Renal replacement therapy	1.27 (0.84–1.91)	0.26
Extracorporeal membrane oxygenation	1.29 (0.72–2.30)	0.40

PICU indicates pediatric intensive care unit; CI, confidence interval; PaO_2 , arterial oxygen partial pressure; and CHD, congenital heart disease.

Age is represented in months in the model.

CHD×age represents the product of 2 independent variables: CHD (present=1, absent=0) and age.

PIM2_noO₂ logit represents PIM2 logit with oxygenation component removed. ln(PIM2_noO₂ logit) represents the natural logarithm of this logit.

Powers for PaO_2 , age, CHD×age, and PIM2_noO₂ logit represent optimal powers chosen by multivariable fractional polynomial algorithm. Odds ratios for congenital heart disease and age should not be interpreted in isolation because of the interaction effect.

Model C statistic=0.81; Hosmer-Lemeshow goodness-of-fit $\chi^2=8.29$; $P=0.41$.

associated with worse outcome, including PIM2 mortality risk and out-of-hospital cardiac arrest. This is in agreement with recent studies of pediatric in-hospital cardiac arrest.^{2,28} In contrast, worse outcome has been reported in infants after out-of-hospital cardiac arrest.^{3,29} However, most out-of-hospital cardiac arrests in infants occur at home and are not witnessed, and as a result, return of circulation is less likely to be attained.²⁹ The present cohort included only patients who survived to PICU admission after cardiac arrest. In patients with return of circulation for >20 minutes after out-of-hospital cardiac arrest, Moler et al³⁰ found survivor and nonsurvivor groups to be similar with respect to age. It has been hypothesized that improved outcome in younger children relates to the increased compliance of the chest wall, which results in more effective cerebral and coronary perfusion during cardiopulmonary resuscitation.³¹

The present data also demonstrate an interaction between congenital heart disease and age, in that the incremental

increase in risk with advancing age was more pronounced in the setting of congenital heart disease. We hypothesize that the poorer relative survival in older children with congenital heart disease may be caused by differences in anatomic subtype, with older children manifesting a higher proportion of chronic heart failure as a result of long-term palliated conditions (eg, the “failing Fontan” operation in the setting of a single ventricle).

There was a trend toward survival benefit with time, with an adjusted 5% year-on-year decrease in mortality (odds ratio, 0.95; $P=0.08$). This is consistent with improvements in standardized mortality seen among the entire PICU population over this time period.¹⁶

Study Strengths and Limitations

This study has several strengths. Data from >1850 children admitted to 33 centers throughout the United Kingdom and Ireland were included in the analysis. PICANet data were collected prospectively, and mortality risk was estimated with PIM2, which has been validated with United Kingdom PICU data.¹⁷ Analysis with logistic regression with multivariable fractional polynomials allowed demonstration of the nonlinear relationship between PaO_2 and outcome and avoided the use of arbitrary cutoffs to define hypoxia and hyperoxia exposure.

There are a number of limitations. The observational study design can only address associations, and no causal inferences can be made. The association between hyperoxia and mortality may be confounded by deliberate administration of high FiO_2 in patients with ongoing physiological instability after resuscitation, who likely have the highest mortality risk, and the greater likelihood of obtaining blood gases in hyperoxic patients with ongoing physiological instability. The possibility of such selection bias is supported by the higher PIM2 risk of death scores in the hyperoxia group than in the normoxia group and the much lower PIM2 risk of death scores in the group with no arterial gas. Only clinical trials can address whether the association between hyperoxia and mortality is a causal relationship. The study is potentially prone to selection bias because of the exclusion of one third of the children who did not have arterial blood gas measurement within the first hour of PICU admission; however, it is reassuring that the multiple-imputation analysis produced similar odds ratios for PaO_2 . The PICANet database is primarily an audit database of PICU care. As such, the primary end point was survival to PICU discharge rather than survival to hospital discharge, as based on the Utstein criteria.³² However, mortality after resuscitation from cardiac arrest peaks rapidly, particularly after out-of-hospital cardiac arrest,¹ and the majority of deaths will occur within the PICU. Neurological outcome was not measured in the present study. We were unable to adjust for additional confounding variables with a known association with mortality (for example, blood glucose and postarrest pH) that were not collected as part of the PICANet data set. Although postarrest pH and PaCO_2 were not recorded, the metabolic component of pH (base excess) was used in the calculation of the PIM2 score. We acknowledge that mortality risk varies between congenital heart disease lesions and that unmeasured differences in

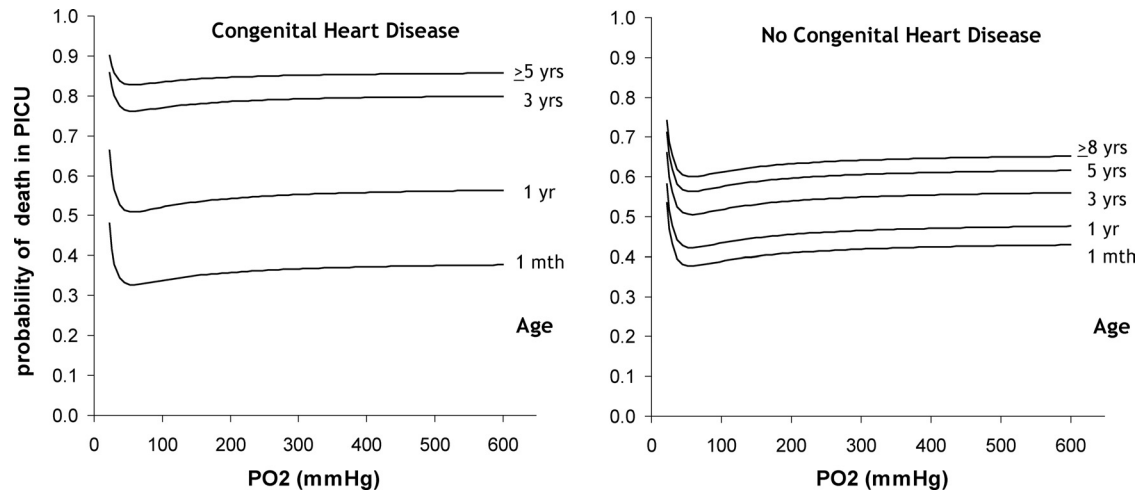


Figure 2. Relationship between PaO_2 , congenital heart disease, age, and probability of death in the pediatric intensive care unit (PICU) after admission after cardiac arrest. The graphs are constructed to show estimated risk of death for a patient in 2010 with the following attributes: Median Pediatric Index of Mortality-2 (PIM2) risk with oxygenation component removed, female sex, non-Asian ethnicity, out-of-hospital arrest, no interhospital transfer, and receiving mechanical ventilation, inotropes, and renal replacement therapy.

patients with acyanotic disease have the potential to act as confounders in the interpretation of association between PaO_2 and outcome in this subgroup.

The PICANet database does not allow us to identify whether therapeutic hypothermia was used. A survey of United Kingdom pediatric intensivists in 2008 demonstrated wide variation in the use of therapeutic hypothermia, with 52% of respondents “never” or “rarely” using this therapy.³³ In those who did use the therapy, there was wide variation in duration, depth of cooling, and speed of rewarming, with 90% of units lacking a protocol.³³ In view of the variation in practice, therapeutic hypothermia is thus unlikely to be a major confounder. Of note, we included a year effect in the model that may be influenced by therapeutic hypothermia if it became more widely used over time.

Finally, the classification into oxygenation groups was based on the first arterial blood gas, and the duration of exposure to hypoxia or hyperoxia in the study population is unknown. Although we sought to investigate the effect of hyperoxia and hypoxia early after return of circulation, we acknowledge that only 27% of patients had in-hospital cardiac arrest within the same hospital as the PICU and that the first arterial blood gas within 1 hour of PICU or retrieval team contact in those patients who had out-of-hospital cardiac arrest or were retrieved was likely to be >1 hour after cardiac arrest.

Conclusions

In this large multicenter study of children admitted to the PICU after cardiac arrest, we have demonstrated an independent association between both hypoxia, and to a lesser extent, hyperoxia and the risk of death after adjustment for illness severity. We have also demonstrated that survival is age dependent and that this relationship is altered in the setting of congenital heart disease. Further clinical study is needed to determine whether avoidance of hyperoxia and hypoxia after resuscitation will result in better long-term neurological outcome.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Postresuscitation care is an important component that affects outcome after cardiac arrest. Adult studies have suggested a relationship between exposure to hyperoxia and survival in this setting. We undertook a national retrospective cohort study that involved 1875 patients from all pediatric intensive care units in the United Kingdom and Ireland to investigate the relationship between arterial partial oxygen pressure (PaO₂) after resuscitation from cardiac arrest and mortality. We found exposure to supranormal oxygen tension was common, with 33% of patients having PaO₂ >150 mm Hg on the first blood gas. We demonstrated a significant association between early postarrest hyperoxia and increased mortality after admission to the pediatric intensive care unit. A stronger association was also seen between the degree of hypoxia and mortality. Our data lend support for intervention studies to assess the safety and efficacy of using the lowest inspired oxygen concentration that maintains arterial oxyhemoglobin saturation of 94% to 96% in the postresuscitation period.

Relationship Between Arterial Partial Oxygen Pressure After Resuscitation From Cardiac Arrest and Mortality in Children

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