Hyperoxia and Hypocapnia During Pediatric Extracorporeal Membrane Oxygenation: Associations With Complications, Mortality, and Functional Status Among Survivors*

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Objectives: To determine the frequency of hyperoxia and hypocapnia during pediatric extracorporeal membrane oxygenation and their relationships to complications, mortality, and functional status among survivors.

Design: Secondary analysis of data collected prospectively by the Collaborative Pediatric Critical Care Research Network.

Setting: Eight Collaborative Pediatric Critical Care Research Network–affiliated hospitals.

Patients: Age less than 19 years and treated with extracorporeal membrane oxygenation.

Interventions: Hyperoxia was defined as highest Pao_2 greater than 200 Torr (27 kPa) and hypocapnia as lowest $Paco_2$ less than 30 Torr (3.9 kPa) during the first 48 hours of extracorporeal membrane oxygenation. Functional status at hospital discharge was evaluated among survivors using the Functional Status Scale.

Measurements and Main Results: Of 484 patients, 420 (86.7%) had venoarterial extracorporeal membrane oxygenation and 64 (13.2%) venovenous; 69 (14.2%) had extracorporeal membrane oxygenation initiated during cardiopulmonary resuscitation. Hyperoxia occurred in 331 (68.4%) and hypocapnia in 98 (20.2%). Hyperoxic patients had higher mortality than patients without hyperoxia (167 [50.5%] vs 48 [31.4%]; $p < 0.001$), but

no difference in functional status among survivors. Hypocapnic patients were more likely to have a neurologic event (49 [50.0%] vs 143 (37.0%]; $p = 0.021$) or hepatic dysfunction (49 [50.0%] vs 121 [31.3%]; $p < 0.001$) than patients without hypocapnia, but no difference in mortality or functional status among survivors. On multivariable analysis, factors independently associated with increased mortality included highest Pa_{O_2} and highest blood lactate concentration in the first 48 hours of extracorporeal membrane oxygenation, congenital diaphragmatic hernia, and being a preterm neonate. Factors independently associated with lower mortality included meconium aspiration syndrome.

Conclusions: Hyperoxia is common during pediatric extracorporeal membrane oxygenation and associated with mortality. Hypocapnia appears to occur less often and although associated with complications, an association with mortality was not observed. (*Pediatr Crit Care Med* 2018; 19:245–253)

Key Words: child; extracorporeal membrane oxygenation; hyperoxia; hypocapnia; neonate

Hyperoxia has been associated with adverse outcomes from several conditions complicated by reperfusion injury such as cardiac arrest (1–3), traumatic brain injury (4, 5), and neonatal asphyxia (6). The influx of oxygen during reperfusion of ischemic tissue leads to production of reactive oxygen species (ROS) by altered mitochondria and enzymes (7, 8). Hyperoxia during reperfusion may increase production of ROS, exacerbating their pathologic effects. ROS cause peroxidation of lipids, denaturation of proteins, and damage to DNA. The damage produced to these macromolecules can cause abnormal gene expression and impaired cellular functioning. In addition, ROS activate neutrophils and platelets leading to an exaggerated inflammatory and thrombotic cascade.

Hypocapnia has also been associated with adverse outcomes after cardiac arrest (9–12), traumatic brain injury (13, 14), stroke (15), and neonatal asphyxia (6, 16). Hypocapnia may contribute to neurologic injury by causing cerebral vasoconstriction, decreased cerebral blood flow, and increased cerebral ischemia (17). Some have found mild hypercapnia to be neuroprotective (11). In addition to increasing cerebral perfusion, mild hypercapnia may have anticonvulsant, antiinflammatory, and antioxidant effects.

Investigators have begun to explore the potential impact of Pa_{O_2} and Pa_{CO_2} on patient outcomes after extracorporeal circulation including extracorporeal membrane oxygenation (ECMO) and cardiopulmonary bypass (7, 8, 18–21). Extracorporeal circulation exposes the patient's blood to an artificial circuit, which elicits a systemic inflammatory response, and alters the redox equilibrium by increasing production of ROS (7, 8). Hyperoxia may intensify the oxidative stress elicited by the circuit; however, the extent to which hyperoxia during extracorporeal circulation is associated with adverse patient outcomes is not well characterized. Similarly, little clinical data exist on the association between Pa_{CO_2} during extracorporeal circulation and patient outcomes. We hypothesize that both hyperoxia and hypocapnia during pediatric ECMO will be associated with worse patient outcomes. Our objective is to determine the frequency of hyperoxia and hypocapnia during pediatric ECMO and the relationships between these blood gas derangements and complications, mortality, and functional status among survivors.

METHODS

Design and Setting

The study was a secondary analysis of data collected for the Bleeding and Thrombosis during ECMO (BATE) study (22), which aimed to describe the frequency of bleeding and thrombosis in neonatal and pediatric ECMO patients. In the BATE study, prospective observational data were collected at eight children's hospitals affiliated with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network between December 2012 and September 2014. The Institutional Review Boards for each hospital and the Data Coordinating Center at the University of Utah approved the study with waiver of parental permission.

Study Subjects

All patients less than 19 years old treated with ECMO in a neonatal, pediatric, or cardiac ICU were included in the BATE study ($n = 514$). Only the initial ECMO course was included for patients who required multiple courses of ECMO. Three patients had no arterial blood gases collected in the first 48 hours of ECMO and were excluded from this secondary analysis. In addition, 27 patients with hypoxia (i.e., highest $Pa_{O_2} < 60$ Torr [8 kPa] in the first 48 hr of ECMO) were excluded (see Statistical Analysis, below).

Data Collection

Trained research coordinators collected all data daily via direct observation, discussion with bedside clinicians, and review of medical records. Data included demographics; body weight; history of prematurity; acute and chronic diagnoses; occurrence of an operative procedure or cardiopulmonary bypass in the 24 hours prior to ECMO initiation; indications for ECMO; mode of ECMO; Vasoactive Inotrope Score (VIS) (23, 24) and oxygenation index (OI) (25) at the time of ECMO initiation; body temperature, arterial blood gases (pH, Pa_{O_2}, Pa_{CO_2}), and lactate concentration closest and prior to ECMO initiation (baseline); arterial blood gases, lactate concentration, and ECMO blood flow rate recorded closest to 7 AM on each ECMO day; and clinical site.

Demographics included age at ECMO initiation, sex, race, and ethnicity. Prematurity was less than 37 weeks gestational age at birth and collected for neonates only. Indications for ECMO were categorized as respiratory, cardiac, or extracorporeal cardiopulmonary resuscitation (ECPR). Mode of ECMO was categorized as venoarterial or venovenous. Venovenous ECMO that was converted to venoarterial was categorized as venoarterial ECMO. VIS (23, 24) was calculated from the

hourly dose of dopamine, dobutamine, epinephrine, milrinone, vasopressin, and norepinephrine administered at the time of ECMO initiation. Higher VIS scores indicate greater vasoactive and inotropic support. OI (25) was calculated from the mean airway pressure (MAP), F_{IO_2}, and Pa_{O_2} at the time of ECMO initiation as MAP × F_{IO_2} × 100/Pa_{O_2}. Higher OI scores indicate greater intensity of ventilatory support to maintain oxygenation. Hyperoxia was defined as highest Pa_{O_2} greater than 200 Torr (27 kPa) and hypocapnia as lowest Pa_{CO_2} less than 30 Torr (3.9 kPa) during the first 48 hours of ECMO (7, 26, 27). The first 48 hours of ECMO was selected in order to reflect the most vulnerable period for ischemia reperfusion injury (1, 3, 12, 18). Blood flow rate was the average blood flow rate in mL/kg/min over the first 48 hours of ECMO.

Outcome Measures

The primary outcome was in-hospital mortality. Other outcomes included complications during ECMO; duration of ECMO, and ICU and hospital stay; and functional status at hospital discharge among survivors. Complications included bleeding events, thrombotic events, neurologic events, hepatic dysfunction, and renal failure. Bleeding events were defined as blood loss requiring a transfusion or intracranial hemorrhage. Thrombotic events included intracranial infarction, limb ischemia, pulmonary embolus, intracardiac thrombus, aortopulmonary shunt thrombus, other sites of thrombosis, and circuit thrombosis requiring replacement of a circuit component. Neurologic events included seizures (clinical or electrographic), intracranial hemorrhage or infarction, and brain death. Hepatic dysfunction was defined as an international normalized ratio greater than two. Renal failure was defined as a creatinine concentration greater than 2 mg/dL (> 176.8 µmol/L) or use of renal replacement therapy. Functional status at hospital discharge was evaluated among survivors using the Functional Status Scale (FSS) (28). The FSS assesses function in six domains: mental, sensory, communication, motor, feeding, and respiratory. Total FSS scores range from 6 to 30 and are categorized as 6–7 (good), 8–9 (mildly abnormal), 10–15 (moderately abnormal), 16–21 (severely abnormal), and greater than 21 (very severely abnormal).

Statistical Analysis

The relationship of hyperoxia and hypocapnia to pre-ECMO patient characteristics and outcomes was assessed with Fisher exact test for nominal variables and the Wilcoxon rank-sum test for ordinal variables. Prior to developing logistic regression models of in-hospital mortality, the relationship of highest Pa_{O_2} and lowest Pa_{CO_2} in the first 48 hours of ECMO to mortality was explored using bar charts (**Figs. 1** and **2**). Pa_{CO_2} did not appear to have a strong relationship with mortality, but there was some tendency toward higher mortality with both low and high Pa_{CO_2} and lower mortality with moderate Pa_{CO_2}. Therefore, Pa_{CO_2} could not be included as an interval predictor. Instead, a nominal variable was created with three levels, Pa_{CO_2} less than 30 Torr (3.9 kPa), 30–50 Torr (3.9–6.6 kPa), and greater than 50 Torr (> 6.6 kPa). Pa_{O_2} was found to have a strong linear relationship with mortality, with higher Pa_{O_2} predicting a higher risk of mortality. The only exception to this was the 27 hypoxic patients (Pa_{O_2} < 60 Torr [< 8 kPa]) who also had a high mortality rate. Rather than discretize Pa_{O_2} into a few levels, the 27 hypoxic patients were excluded from the analyses. This allowed Pa_{O_2} to be included as an interval variable, so that the model could take full advantage of the strong linear relationship.

Mortality was modeled with univariable logistic regression in order to identify potential predictors. Variables associated with mortality in univariable models ($p < 0.20$) were considered potential predictors if data were missing for less than 10% of the cohort. The branch-and-bound algorithm of Furnival and Wilson (29) was used to identify the subset of potential predictors that generate the multivariable logistic regression model with the best penalized fit in terms of the Bayesian Information Criterion (BIC). Only models that included the primary variables of interest, Pa_{O_2} and Pa_{CO_2}, were considered. In this way, the primary predictors were forced into the multivariable models.

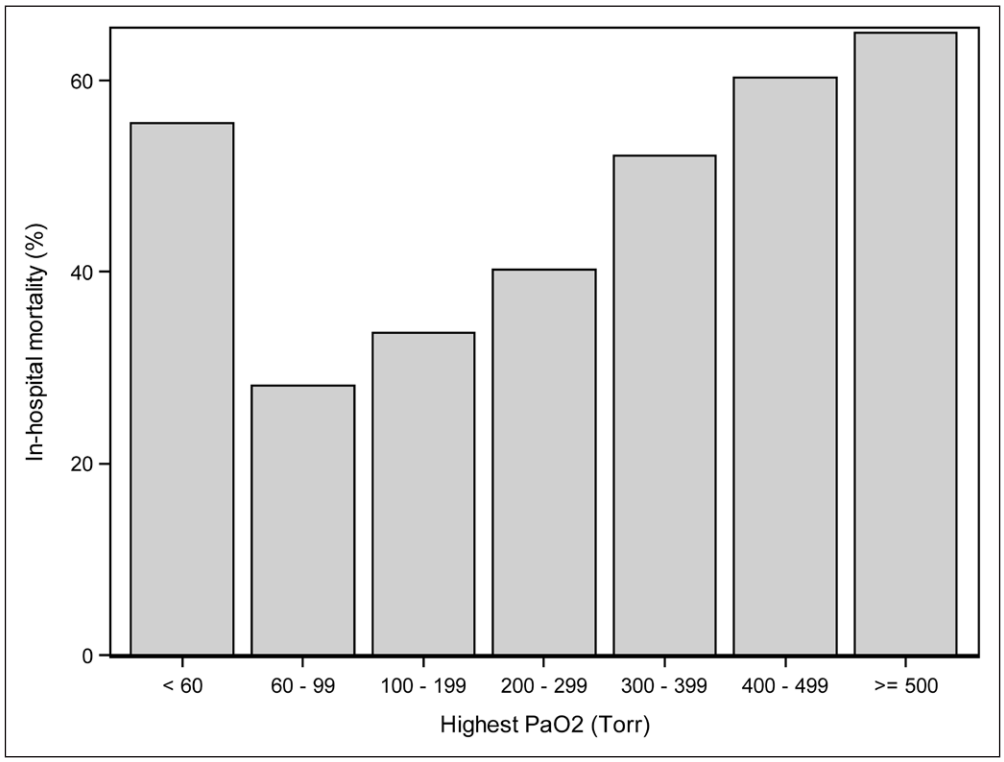

Figure 1. In-hospital mortality by the highest Pa_{O_2} in the first 48 hr of extracorporeal membrane oxygenation.

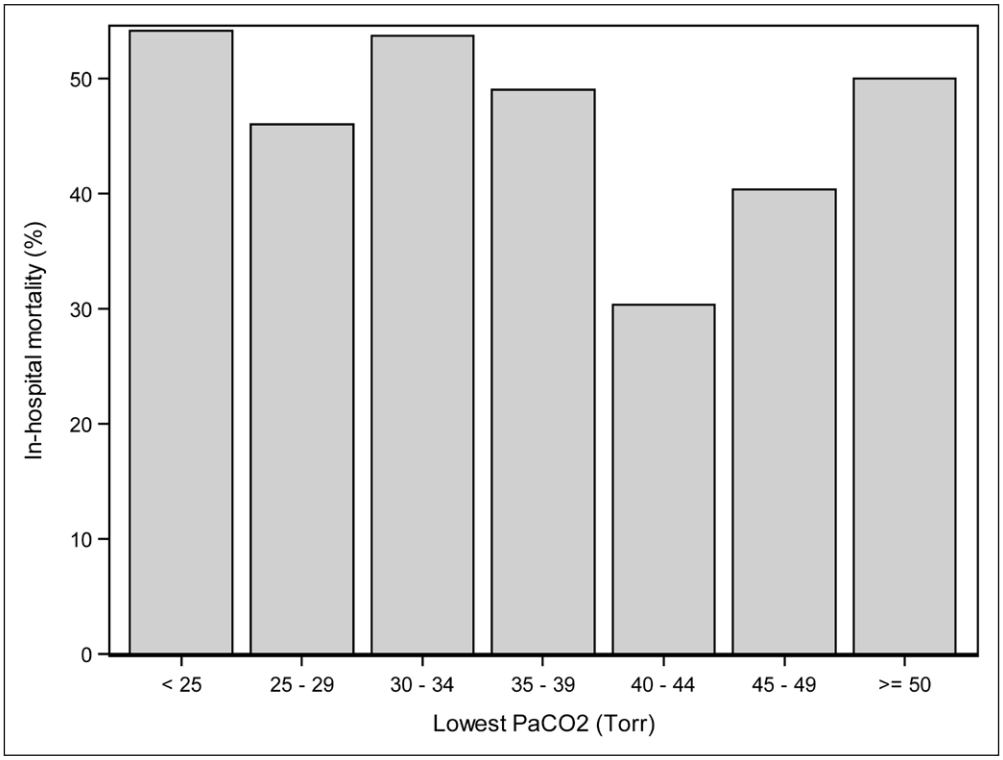

Figure 2. In-hospital mortality by the lowest $Paco_2$ in the first 48 hr of extracorporeal membrane oxygenation.

In addition to the subset of predictors achieving the best penalized fit, one additional model was within two points of this BIC. These two models are regarded as statistically equivalent in terms of penalized fit. Since both models achieved equivalent penalize fit, the authors selected the model with the most clinically relevant predictors as the final multivariable model. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Of 484 patients included in the study, 48 (9.9%) were preterm neonates, 209 (43.2%) full-term neonates, and 227 (46.9%) infants, children, and adolescents (**Table 1**). Two hundred eighty (57.9%) were male, and 239 (49.4%) were White. Three hundred thirty-one (68.4%) had hyperoxia and 98 (20.2%) had hypocapnia during the first 48 hours of ECMO. Median highest Pao_2 was 261 Torr (interquartile range [IQR], 155–364) (35 kPa [IQR, 20–48]), and median lowest $Paco_2$ was 37 Torr (IQR, 31–43) (4.9 kPa [IQR, 4.1–5.7]) during the first 48 hours of ECMO. Two hundred fifteen patients (44.4%) died.

Hyperoxia

Patients with hyperoxia were more likely to have a cardiac indication for ECMO, receive venoarterial ECMO, have an acute diagnosis of cardiovascular disease (acquired, congenital, or arrhythmia), have an acute diagnosis of immune dysfunction, and receive cardiopulmonary bypass and/or an operative procedure in the 24 hours prior to ECMO than patients without hyperoxia (Table 1). Patients with hyperoxia were less likely to have meconium aspiration syndrome or persistent pulmonary hypertension of the newborn than patients without hyperoxia. Baseline OI was lower, and pH was higher in patients with hyperoxia compared with those without hyperoxia. Average ECMO blood flow rate in the first 48 hours of ECMO was higher in patients with hyperoxia than those without hyperoxia (106 [88–127] mL/kg/min vs 101 [80–118] mL/kg/min; $p = 0.039$). Hyperoxia was also associated with clinical site.

Patients with hyperoxia had higher mortality than patients without hyperoxia and shorter durations of ECMO and ICU stay (**Table 2**). The shorter durations were not related to early death on ECMO for hyperoxic patients (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/A594). Among survivors, functional status at hospital discharge did not differ between those with and without hyperoxia.

Hypocapnia

Patients with hypocapnia were more likely to be neonates, receive ECPR, and have an acute diagnosis of cardiovascular disease (congenital or arrhythmia) (Table 1). Patients with hypocapnia were less likely to be White or have an acute diagnosis of pneumonia or bronchiolitis than those without hypocapnia. Body weight and baseline OI were lower, and baseline pH was higher in patients with hypocapnia compared with those without hypocapnia. Hypocapnia was also associated with clinical site.

Patients with hypocapnia were more likely to have a neurologic event and hepatic dysfunction than patients without hypocapnia (Table 2). Patients with hypocapnia had shorter duration of ECMO. Mortality did not differ between patients with and without hypocapnia, nor did functional status at hospital discharge among survivors.

Mortality

Patient factors associated with in-hospital mortality on univariable analyses ($p < 0.2$ and less than 10% missing data) included the highest Pao_2 and lactate and lowest pH in the first 48 hours of ECMO, mode of ECMO, cardiovascular disease (congenital), pneumonia or bronchiolitis, meconium aspiration syndrome, congenital diaphragmatic hernia, persistent pulmonary hypertension of the newborn, renal failure, neurologic condition, congenital anomaly or chromosomal defect, cardiopulmonary bypass and/or operative procedures in the

TABLE 1. Description of Preextracorporeal Membrane Oxygenation Characteristics by Hyperoxia and Hypocapnia

Characteristics	Hyperoxia (Pao_2 > 200 mm Hg)			Hypocapnia ($Paco_2$ < 30 mm Hg)		
	No (*n* = 153)	Yes (*n* = 331)	*p*	No (*n* = 386)	Yes (*n* = 98)	*p*
Age, *n* (%)			0.052[a]			0.003[a]
Preterm neonate	16 (10.5)	32 (9.7)		33 (8.5)	15 (15.3)	
Full-term neonate	78 (51.0)	131 (39.6)		155 (40.2)	54 (55.1)	
Infant	27 (17.6)	82 (24.8)		95 (24.6)	14 (14.3)	
Child	17 (11.1)	60 (18.1)		65 (16.8)	12 (12.2)	
Adolescent	15 (9.8)	26 (7.9)		38 (9.8)	3 (3.1)	
Weight (kg), median (IQR)	3.5 (3.0–5.9)	3.9 (3.0–8.8)	0.268[b]	3.9 (3.0–9.9)	3.2 (2.8–4.0)	< 0.001[b]
Male, *n* (%)	93 (60.8)	187 (56.5)	0.428[a]	230 (59.6)	50 (51.0)	0.137[a]
Race, *n* (%)			0.564[a]			0.004[a]
Unknown/not reported	50 (32.7)	82 (24.8)		101 (26.2)	31 (31.6)	
Black or African American	22 (14.4)	66 (19.9)		69 (17.9)	19 (19.4)	
White	74 (48.4)	165 (49.8)		202 (52.3)	37 (37.8)	
Other	7 (4.6)	18 (5.4)		14 (3.6)	11 (11.2)	
Hispanic or Latino, *n* (%)	23 (15.0)	61 (18.4)	0.308[a]	68 (17.6)	16 (16.3)	0.520[a]
Primary ECMO indication, *n* (%)			< 0.001[a]			< 0.001[a]
Respiratory	99 (64.7)	116 (35.0)		182 (47.2)	33 (33.7)	
Cardiac	38 (24.8)	162 (48.9)		161 (41.7)	39 (39.8)	
Extracorporeal cardiopulmonary resuscitation	16 (10.5)	53 (16.0)		43 (11.1)	26 (26.5)	
Mode of ECMO, *n* (%)			< 0.001[a]			0.131[a]
Venoarterial	115 (75.2)	305 (92.1)		330 (85.5)	90 (91.8)	
Venovenous	38 (24.8)	26 (7.9)		56 (14.5)	8 (8.2)	
Clinical site, *n* (%)			0.017[a]			< 0.001[a]
A	29 (19.0)	35 (10.6)		49 (12.7)	15 (15.3)	
B	36 (23.5)	63 (19.0)		77 (19.9)	22 (22.4)	
C	10 (6.5)	25 (7.6)		14 (3.6)	21 (21.4)	
D	17 (11.1)	44 (13.3)		50 (13.0)	11 (11.2)	
E	19 (12.4)	36 (10.9)		50 (13.0)	5 (5.1)	
F	17 (11.1)	46 (13.9)		54 (14.0)	9 (9.2)	
G	2 (1.3)	26 (7.9)		19 (4.9)	9 (9.2)	
H	23 (15.0)	56 (16.9)		73 (18.9)	6 (6.1)	

(*Continued*)

TABLE 1. (*Continued*). Description of Preextracorporeal Membrane Oxygenation Characteristics by Hyperoxia and Hypocapnia

Characteristics	Hyperoxia (Pao_2 > 200 mm Hg)			Hypocapnia ($Paco_2$ < 30 mm Hg)		
	No (*n* = 153)	Yes (*n* = 331)	*p*	No (*n* = 386)	Yes (*n* = 98)	*p*
Acute diagnoses, *n* (%)						
Airway abnormality	5 (3.3)	6 (1.8)	0.336[a]	9 (2.3)	2 (2.0)	1.000[a]
Immune dysfunction	4 (2.6)	28 (8.5)	0.017[a]	27 (7.0)	5 (5.1)	0.651[a]
Cardiac arrest	13 (8.5)	34 (10.3)	0.622[a]	39 (10.1)	8 (8.2)	0.703[a]
Cardiovascular disease (acquired)	7 (4.6)	56 (16.9)	< 0.001[a]	55 (14.2)	8 (8.2)	0.131[a]
Cardiovascular disease (arrhythmia)	1 (0.7)	17 (5.1)	0.017[a]	9 (2.3)	9 (9.2)	0.004[a]
Cardiovascular disease (congenital)	46 (30.1)	141 (42.6)	0.009[a]	137 (35.5)	50 (51.0)	0.005[a]
Hypoxic/anoxic injury	3 (2.0)	14 (4.2)	0.290[a]	14 (3.6)	3 (3.1)	1.000[a]
Gastrointestinal disorder	5 (3.3)	14 (4.2)	0.802[a]	14 (3.6)	5 (5.1)	0.559[a]
Pertussis or sepsis	31 (20.3)	50 (15.1)	0.190[a]	62 (16.1)	19 (19.4)	0.450[a]
Pneumonia or bronchiolitis	9 (5.9)	11 (3.3)	0.220[a]	20 (5.2)	0 (0.0)	0.019[a]
Shock (nonseptic)	3 (2.0)	11 (3.3)	0.564[a]	12 (3.1)	2 (2.0)	0.745[a]
Respiratory distress/failure	53 (34.6)	103 (31.1)	0.465[a]	132 (34.2)	24 (24.5)	0.070[a]
Meconium aspiration syndrome	24 (15.7)	18 (5.4)	< 0.001[a]	35 (9.1)	7 (7.1)	0.689[a]
Congenital diaphragmatic hernia	17 (11.1)	38 (11.5)	1.000[a]	43 (11.1)	12 (12.2)	0.724[a]
Persistent pulmonary hypertension of the newborn	38 (24.8)	45 (13.6)	0.003[a]	67 (17.4)	16 (16.3)	0.882[a]
Renal failure	4 (2.6)	8 (2.4)	1.000[a]	11 (2.8)	1 (1.0)	0.474[a]
Neurologic condition	5 (3.3)	10 (3.0)	1.000[a]	9 (2.3)	6 (6.1)	0.093[a]
Chronic diagnoses, *n* (%)						
Immune dysfunction	1 (0.7)	12 (3.6)	0.072[a]	13 (3.4)	0 (0.0)	0.081[a]
Congenital anomaly or chromosomal defect	34 (22.2)	77 (23.3)	0.907[a]	86 (22.3)	25 (25.5)	0.503[a]
Neurologic condition	4 (2.6)	20 (6.0)	0.120[a]	23 (6.0)	1 (1.0)	0.063[a]
Cardiovascular disease (congenital)	30 (19.6)	60 (18.1)	0.707[a]	74 (19.2)	16 (16.3)	0.564[a]
Chronic lung disease	7 (4.6)	9 (2.7)	0.286[a]	16 (4.1)	0 (0.0)	0.051[a]
Cardiopulmonary bypass in the 24 hr prior, *n* (%)	26 (17.0)	117 (35.3)	< 0.001[a]	107 (27.7)	36 (36.7)	0.084[a]
Operative procedure in the 24 hr prior, *n* (%)	35 (22.9)	136 (41.1)	< 0.001[a]	130 (33.7)	41 (41.8)	0.155[a]
Vasoactive Inotropic Score, *n* (%)			0.111[a]			0.661[a]
None	38 (24.8)	111 (33.5)		116 (30.1)	33 (33.7)	
Low	48 (31.4)	102 (30.8)		123 (31.9)	27 (27.6)	
High	67 (43.8)	118 (35.6)		147 (38.1)	38 (38.8)	
Oxygenation index, median (IQR)	35.3 (24.0–53.7)	19.8 (7.8–41.3)	< 0.001[b]	29.2 (12.4–51.3)	16.0 (7.5–36.4)	0.005[b]
Lactate (mmol/L), median (IQR)	3.1 (1.6–7.4)	4.4 (1.8–9.1)	0.052[b]	3.9 (1.8–8.0)	4.5 (1.7–8.8)	0.717[b]
pH, median (IQR)	7.25 (7.14–7.33)	7.29 (7.14–7.38)	0.032[b]	7.27 (7.14–7.37)	7.32 (7.19–7.38)	0.048[b]
Temperature (Celsius), median (IQR)	36.7 (36.0–37.1)	36.6 (36.0–37.1)	0.797[b]	36.7 (36.0–37.1)	36.7 (36.2–37.1)	0.684[b]

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range.

[a]*p* value is based on Fisher exact test.

[b]*p* value is based on the Wilcoxon rank-sum test.

TABLE 2. Complications and Outcomes by Hyperoxia and Hypocapnia

Complication	Hyperoxia (Pao_2 > 200 Torr) (> 27 kPa)			Hypocapnia ($Paco_2$ < 30 Torr) (< 3.9 kPa)		
	No (*n* = 153)	Yes (*n* = 331)	*p*	No (*n* = 386)	Yes (*n* = 98)	*p*
Duration of extracorporeal membrane oxygenation (d), median (IQR)	5.9 (3.1–10.5)	4.7 (2.5–8.0)	0.009[a]	5.2 (2.8–9.5)	4.2 (2.5–6.8)	0.050[a]
Length of ICU stay (d), median (IQR)	30.5 (15.6–54.0)	25.0 (12.8–48.2)	0.045[a]	27.9 (14.3–51.4)	25.7 (10.0–47.8)	0.391[a]
Length of hospital stay (d), median (IQR)	39.1 (19.7–64.8)	33.2 (13.4–67.5)	0.130[a]	36.3 (17.0–66.4)	31.6 (11.1–69.9)	0.231[a]
Bleeding event[b], *n* (%)	103 (67.3)	240 (72.5)	0.282[c]	271 (70.2)	72 (73.5)	0.619[c]
Thrombotic event[b], *n* (%)	58 (37.9)	125 (37.8)	1.000[c]	149 (38.6)	34 (34.7)	0.560[c]
Neurologic event[b], *n* (%)	53 (34.6)	139 (42.0)	0.135[c]	143 (37.0)	49 (50.0)	0.021[c]
Hepatic organ failure[b], *n* (%)	44 (28.8)	126 (38.1)	0.052[c]	121 (31.3)	49 (50.0)	< 0.001[c]
Renal organ failure[b], *n* (%)	54 (35.3)	117 (35.3)	1.000[c]	135 (35.0)	36 (36.7)	0.813[c]
In-hospital mortality, *n* (%)	48 (31.4)	167 (50.5)	< 0.001[c]	166 (43.0)	49 (50.0)	0.255[c]
Functional status at hospital discharge (among survivors), *n* (%)			0.296[a]			0.295[a]
Good	40 (38.1)	44 (26.8)		72 (32.7)	12 (24.5)	
Mildly abnormal	35 (33.3)	71 (43.3)		86 (39.1)	20 (40.8)	
Moderately abnormal	22 (21.0)	43 (26.2)		52 (23.6)	13 (26.5)	
Severely abnormal	7 (6.7)	6 (3.7)		10 (4.5)	3 (6.1)	
Very severely abnormal	1 (1.0)	0 (0.0)		0 (0.0)	1 (2.0)	

IQR = interquartile range.

[a]*p* value is based on the Wilcoxon rank-sum test.

[b]Complications occurred on at least 1 study day.

[c]Values represent absolute count and percentage based on column totals; *p* value is based on Fisher exact test.

24 hours prior to ECMO, age, indication for ECMO, and average ECMO blood flow rate in the first 48 hours of ECMO (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/PCC/A595). Using multivariable analysis, factors independently associated with increased mortality included highest Pao_2 and highest blood lactate concentration in the first 48 hours of ECMO, congenital diaphragmatic hernia, and being a preterm neonate (**Table 3**; and **Supplemental Table 3**, Supplemental Digital Content 3, http://links.lww.com/PCC/A596). Factors independently associated with lower mortality included meconium aspiration syndrome.

DISCUSSION

Our findings suggest that hyperoxia is common during pediatric ECMO and independently associated with increased in-hospital mortality. The frequency of hyperoxia observed in our study is similar to that reported in a smaller retrospective cohort of infants treated with venoarterial ECMO after congenital heart disease surgery (18). This prior study found that 78% of infants had hyperoxia (Pao_2 > 193 Torr) in the first 48 hours of ECMO. Our finding of higher in-hospital mortality among hyperoxic ECMO patients is also consistent with the prior study's finding of higher 30-day postoperative mortality (18). A recent adult ECMO study also found a relationship between moderate hyperoxia (Pao_2 101–300 Torr) and mortality (30).

The pathophysiology underlying the increase in mortality among ECMO patients with hyperoxia may be related to increased generation of ROS after a period of tissue ischemia (7, 8). During reperfusion, ROS pathologically activate neutrophils and platelets (7). Activated neutrophils display increased adhesion to damaged endothelium causing microvascular blockage and induce the production and release of proinflammatory cytokines. Activated platelets display increased aggregation and potential for thrombosis. Despite these known effects, we did not find a significant association between hyperoxia and thrombosis, bleeding, neurologic events, hepatic dysfunction, or renal failure. The lack of association suggests that direct injury to these organs from hyperoxia is not responsible for the increased mortality or that our global assessments of organ dysfunction are inadequate to detect these cellular and microvascular changes. Another possibility is that hyperoxia during ECMO may be a marker of poor cardiac output making

TABLE 3. Multivariable Model of In-Hospital Mortality

Characteristics	OR (95% CI)	*p*
Highest[a] Pao_2 (10 Torr) (1.3 kPa)	1.03 (1.01–1.04)	< 0.001
Lowest[a] $Paco_2$ (Torr)		0.695
< 30 (< 3.9 kPa)	0.81 (0.47–1.37)	
30–50 (3.9–6.6 kPa)	Reference	
> 50 (> 6.6 kPa)	0.83 (0.34–2.00)	
Highest[a] lactate (mmol/L)	1.13 (1.09–1.17)	< 0.001
Meconium aspiration syndrome	0.09 (0.02–0.42)	0.002
Preterm neonate	2.97 (1.42–6.21)	0.004
Congenital diaphragmatic hernia	2.12 (1.10–4.09)	0.025

OR = odds ratio.

[a]Extremum for each subject is assessed over the 48 hr after extracorporeal membrane oxygenation initiation.

the relative oxygen delivery from the ECMO circuit high. Thus, increased mortality with hyperoxia could be due to myocardial failure with relatively little patient cardiac output to mix with the highly oxygenated circuit flow. Average ECMO blood flow in the first 48 hours of ECMO was somewhat higher in hyperoxic than nonhyperoxic patients; however, ECMO blood flow was not an independent predictor of mortality in our multivariable model.

Hyperoxic patients had a shorter duration of ECMO and ICU stay than nonhyperoxic patients. These findings were not due to early death on ECMO for hyperoxic patients. The shorter durations could be related to the higher number of patients in the hyperoxia group who were placed on venoarterial ECMO for a cardiac indication. Cardiovascular patients in general have shorter ECMO runs than respiratory failure patients (31). Functional status at hospital discharge did not differ among survivors with and without hyperoxia. This finding may be due to a lack of preillness functional status assessment, and thus, our inability to adjust discharge functional status for preexisting disabilities.

Hypocapnia occurred less often in our study than hyperoxia, and although associated with complications, it was not associated with mortality or functional status among survivors. Patients with hypocapnia were more likely to have a neurologic event. Hypocapnia may cause cerebral vasoconstriction, decreased cerebral blood flow, and increased cerebral ischemia (17). ECMO itself alters cerebral autoregulation (32) and cerebral blood flow velocity (33), and the degree of decline in $Paco_2$ at initiation of ECMO has been associated with mortality (34). Patients with hypocapnia were also more likely to develop hepatic dysfunction. The cellular and biochemical derangements that occur during hepatic ischemia-reperfusion injury are diverse and complex (35). Whether the association between hypocapnia and hepatic dysfunction observed in our study represents a unique effect of hypocapnia on the liver or a spurious finding is unknown.

Our findings differ from prior studies demonstrating an association between hypocapnia and mortality after pediatric cardiac arrest and traumatic brain injury (12, 13). In these conditions, hypocapnia is produced by excessive mechanical ventilation rather than by the sweep gas in the ECMO circuit. Increased intrathoracic pressure from mechanical ventilation may decrease venous return and coronary perfusion pressure contributing to higher mortality (17, 36). Co_2 is relatively easy to clear on ECMO, and the "cost" of clearance may be less than for mechanically ventilated patients. Overall, our findings suggest both hyperoxia and hypocapnia be avoided during pediatric ECMO. This may be accomplished by judicious use of oxygen and careful attention to sweep gas flow rate-to-blood flow rate ratio.

Other patient factors independently associated with increased mortality in our study included higher blood lactate concentration in the first 48 hours of ECMO, congenital diaphragmatic hernia, and being a preterm neonate. Meconium aspiration was independently associated with decreased mortality. These findings are consistent with previous reports (31, 37).

Strengths of this study include the multisite design and daily prospective data collection. Limitations include recording only the blood gas values closest to 7 AM rather than all values and the lack of a standardized protocol for ECMO across all sites. Our definitions of hyperoxia and hypocapnia were based on dichotomized values described in other studies (7, 26, 27) and do not account for the degree or duration of hyperoxia or hypocapnia. Thus, exact levels of Pao_2 and $Paco_2$ or the duration of exposure associated with harm cannot be determined. Three patients had no blood gas values collected in the first 48 hours of ECMO; whether clinicians did not obtain blood gases or whether the research coordinators missed recording their values is unknown. Although many variables were evaluated, potential unmeasured confounders exist. Importantly, this is an observational study, and the associations observed do not infer causation. For example, neurologic complications during ECMO are multifactorial and not entirely caused by blood gas derangements.

CONCLUSIONS

Hyperoxia is common during pediatric ECMO and associated with mortality. Hypocapnia occurs less often and is associated with complications but not mortality. Judicious use of oxygen and avoidance of hyperoxia and hypocapnia may be indicated.

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