Hyperoxia Is Associated With Poor Outcomes in Pediatric Cardiac Patients Supported on Venoarterial Extracorporeal Membrane Oxygenation*

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Objectives: Patients who require venoarterial extracorporeal membrane oxygenation because of cardiac failure frequently have supranormal blood oxygen tensions (hyperoxia). Recent studies have suggested worse outcomes in patients with hyperoxia after resuscitation from cardiac or respiratory arrests, presumably because of oxidative stress. There are limited data regarding the effect of hyperoxia on outcomes in pediatric patients on venoarterial extracorporeal membrane oxygenation.

Design: Retrospective chart review.

Setting: Pediatric cardiothoracic ICU.

Patients: Cardiac surgery patients less than 1 year old requiring venoarterial extracorporeal membrane oxygenation in the postoperative period from 2007 to 2013.

Measurements and Main Results: In 93 infants (median time on extracorporeal membrane oxygenation, 5 d), mortality at 30 days post surgery (primary outcome) was 38%. Using a receiver operating characteristic curve, a mean Pao_2 of 193 mm Hg in the first 48 hours of extracorporeal membrane oxygenation was determined to have good discriminatory ability with regard to 30-day mortality. Univariate analysis identified a mean Pao_2 greater than 193 mm Hg ($p = 0.001$), longer cardiopulmonary bypass times ($p = 0.09$), longer duration of extracorporeal membrane oxygenation ($p < 0.0001$), and higher extracorporeal membrane oxygenation pump flows ($p = 0.052$) as possible risk factors for 30-day mortality. In multivariable analysis controlling for the variables listed above, a mean Pao_2 greater than 193 mm Hg remained an independent risk factor for mortality ($p = 0.03$). In addition, a mean Pao_2 greater than 193 mm Hg was associated with the need for renal dialysis ($p = 0.02$) but not with neurologic injury ($p = 0.41$) during the hospitalization.

Conclusions: In infants with congenital heart disease who are placed on venoarterial extracorporeal membrane oxygenation postoperatively, hyperoxia (defined as a mean $Pao_2 > 193$ mm Hg in the first 48 hr of extracorporeal membrane oxygenation) was an independent risk factor for 30-day mortality after surgery. Future studies are needed to delineate the causative or associative role of hyperoxia with outcomes, especially in children with baseline cyanosis who may be more susceptible to the effects of oxidative stress. (*Pediatr Crit Care Med* 2016; 17:350–358)

Key Words: extracorporeal membrane oxygenation; heart defects, congenital; hyperoxia; thoracic surgery

The use of mechanical circulatory support after congenital heart surgery in the form of extracorporeal membrane oxygenation (ECMO) is estimated to occur after 3–5% of all surgeries, and the overall mortality for patients is approximately 40–65% (1–3). Common indications for the use of ECMO postoperatively include failure to wean from cardiopulmonary bypass due to myocardial dysfunction, low cardiac output state, cardiac or respiratory arrest, pulmonary hypertension, or shunt occlusion. Postoperative patients are most often supported with venoarterial ECMO (VA-ECMO) where deoxygenated blood is removed from the venous side of the circulation and oxygenated via the oxygenator resulting in highly oxygenated blood (Pao_2, > 400 mm Hg) returned directly to the arterial side of the circulation. The myocardium (via the coronary arteries) and other organs such as the brain, lungs, kidneys, and gastrointestinal tract are, thus, exposed to these high levels of oxygen (hyperoxia).

Potential negative effects of hyperoxia include the generation of reactive oxygen species that leads to increased oxidative stress and cellular damage as well as activation of neutrophils and platelets leading to an exaggerated inflammatory and

*See also p. 371.

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thrombotic cascade (4). The effect of hyperoxia has been extensively studied in other clinical situations such as after resuscitation from cardiac arrest (5–10) or perinatal asphyxia (11, 12) and after myocardial infarctions (13). Furthermore, in cyanotic pediatric patients with congenital heart disease, decreasing the amount of oxygen in the cardiopulmonary bypass circuit to match the patient's preoperative Pao_2 has been shown to lead less end-organ damage, inflammation, and oxidative stress compared with exposing the patients to Pao_2 values between 150 and 200 mm Hg (14, 15).

Given the concern that hyperoxia may be harmful to patients while on ECMO and the lack of data within this area, we aimed to examine the potential effect of hyperoxia on infants who were placed onto VA-ECMO after cardiac surgery.

MATERIALS AND METHODS

A retrospective chart review of all infants was performed (< 1 yr old) who were placed onto VA-ECMO after surgery for congenital heart disease from July 1, 2007, to June 30, 2013, at the University of Michigan. After study approval from the Institutional Review Board, the internal ECMO registry was reviewed and patients who met the inclusion criteria were identified. Patients who were on ECMO preoperatively, patients who were placed on ECMO greater than 30 days postoperatively, and patients who were supported on ECMO less than 24 hours were excluded from the analysis. Electronic charts and the internal congenital heart surgery database were reviewed, and demographic and clinical data were collected. Surgical procedures were stratified based on complexity per the Society of Thoracic Surgeons and the European Association for Cardio-Thoracic Surgery (STAT) Mortality Categories (16). If available, the first arterial blood gas prior to cannulation for ECMO was collected (if a patient was cannulated in the operating room, then the blood gas prior to surgery was included). In addition, all arterial blood gases in the first 48 hours after cannulation for ECMO were also collected. If individual patients were placed on ECMO multiple times in their life or hospitalization, only data from the first ECMO cannulation were collected.

The primary outcome was 30-day mortality after the initial surgery. Secondary outcomes included ICU length of stay, hospital length of stay, in-hospital mortality, need for dialysis, and neurologic injury during the hospitalization (defined as seizure, stroke, or intracranial hemorrhage). If available, transthoracic echocardiograms performed within the first 48 hours of cannulation on to ECMO were reviewed by an independent physician specialized in echocardiography (S.T.O.) to evaluate the amount of ventricular dysfunction.

With regard to ECMO support, from July 2007 to June 2010, silicone oxygenators from Medtronic (Minneapolis, MN) were used. Starting in July 2010, the ECMO circuits used Quadrox oxygenators from Maquet (Wayne, NJ). From July 2007 to March 2010, ECMO flows were provided by roller pumps. Starting in April 2010, ECMO flow was provided by centrifugal pumps. Ventilator settings were placed at "rest settings" to avoid barotrauma with an Fio_2 of 21%. In patients with systemic to pulmonary artery shunts, it is standard practice to leave the shunt patent in most cases unless there are significant issues with an elevated ratio of pulmonary to systemic blood flow.

Descriptive statistics are reported as frequency with percentage for categorical variables and median with interquartile range (IQR) for continuous variables. The maximum, median, and mean Pao_2 values in the first 48 hours on ECMO were calculated for each patient. Using receiver operating characteristic (ROC) curves, the area under the curves (AUCs) of each of three Pao_2 metrics were compared to determine the most predictive metric of Pao_2 for the primary outcome. The optimal cutoff of the selected metric of Pao_2 in the first 48 hours was then determined as the best combination of sensitivity and specificity for significant discrimination of the primary outcome from the ROC curve. To ascertain the predictive ability of the optimal cutoff, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the overall cohort and for subgroups of neonates and patients who underwent a Norwood procedure with systemic to pulmonary artery shunt placement. Patient and clinical characteristics were compared between patients based on the primary outcome, using chi-square test or Fisher exact test, as appropriate, for the categorical variables and Wilcoxon signed rank test for continuous variables. Variables associated with 30-day mortality in the univariate analysis ($p < 0.1$) were included in the multivariable model to evaluate independent associations of possible risk factors with 30-day mortality. Unadjusted and adjusted odds ratios and their 95% CIs were estimated using logistic regression. Finally, similar univariate comparisons between patients with mean Pao_2 values in the first 48 hours above and below the optimal cutoff were made in patient and clinical characteristics and the secondary outcomes. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). p value less than 0.05 was considered statistically significant.

RESULTS

A total of 93 patients were included in the study. Patient characteristics are presented in **Table 1**. The median age at the time of surgery was 7 days, and 75% were neonates. Eighty-five percent of the patients had STAT scores of 4 or 5, and most (88%) had preoperative cyanotic heart disease. Forty-five percent of patients were cannulated on to ECMO in the operating room, and 66% of patients were placed on to ECMO less than 24 hours after surgery. The median length of time on ECMO was 5 days. The most common indication for ECMO was failure to wean from cardiopulmonary bypass in the operating room (47%), and the majority of patients (86%) were cannulated via the chest. Ten patients had the sweep gas intentionally blended to achieve lower arterial oxygen tensions during the study period. The median of the lowest Fio_2 of the sweep gas in the first 48 hours in these patients was 40% (IQR, 32.5–40). There was 38% mortality at 30 days after surgery and 49% in-hospital mortality. The median ICU length of stay was 22 days (IQR, 16–44). Thirty-eight percent of patients required renal

TABLE 1. Patient and Clinical Characteristics Stratified by Mortality at 30 Days After Surgery

Characteristics	All ($n = 93$)	Mortality at 30 d After Surgery		p
		Yes ($n = 35$)	No ($n = 58$)	
Male sex	54 (58.1)	21 (60.0)	33 (56.9)	0.77
Caucasian race	56 (60.2)	22 (62.9)	34 (58.6)	0.28
Premature (gestational age < 37 wk)	13 (14.0)	5 (14.3)	8 (13.8)	1.00
Genetic syndrome(s)	7 (7.5)	1 (2.9)	6 (10.3)	0.25
Neurologic injury during hospitalization	9 (9.7)	3 (8.6)	6 (10.3)	1.00
Age at surgery, d	7 (5–20)	9 (5–35)	6.5 (4–14)	0.14
Neonate (< 30 d)	70 (75.3)	24 (68.6)	46 (79.3)	0.24
Weight at surgery, kg	3.3 (2.9–3.8)	3.5 (2.9–4.0)	3.3 (2.9–3.7)	0.74
Preoperative cyanosis	82 (88.2)	32 (91.4)	50 (86.2)	0.53
Society of thoracic surgeons–European association for cardiothoracic surgery congenital heart surgery database category				
1–3	14 (15.1)	5 (14.3)	9 (15.5)	0.87
4 or 5	79 (84.9)	30 (85.7)	49 (84.5)	
Norwood procedure	35 (37.6)	13 (37.1)	22 (37.9)	0.94
Cardiopulmonary bypass time, min	156 (101–216)	172 (101–263)	138 (88–197)	0.09
Aortic cross-clamp time, min	45.5 (33.5–83.5)	47 (33–97)	45 (34–79)	0.71
Circulatory arrest time, min ($n = 55$)	38 (31–45)	38.5 (30.5–46)	37 (31–45)	0.94
Sweep gas blended	10 (10.8)	2 (5.7)	8 (13.8)	0.31
Duration on ECMO, d	5.3 (3.0–7.0)	7.4 (3.7–11.2)	4.2 (2.9–5.9)	0.001
≥ 7	24 (24.5)	18 (51.4)	6 (10.3)	< 0.0001
< 7	74 (75.5)	17 (48.6)	52 (89.7)	
Indication for cannulation				
Low cardiac output/poor perfusion	16 (17.2)	7 (20.0)	9 (15.5)	Not applicable
Failure to wean from cardiopulmonary bypass	44 (47.3)	18 (51.4)	26 (44.8)	
Pulmonary hypertension	2 (2.2)	0 (0.0)	2 (3.4)	
Combined cardiac and respiratory failure	26 (28.0)	9 (25.7)	17 (29.3)	
Respiratory failure/hypoxia (not pulmonary hypertension)	2 (2.2)	0 (0.0)	2 (3.4)	
Shunt occlusion	3 (3.2)	1 (2.9)	2 (3.4)	
Cannulation during extracorporeal cardiopulmonary resuscitation	28 (30.1)	10 (28.6)	18 (31.0)	0.8
Location of cannulation				
Operating room	42 (45.2)	17 (48.6)	25 (43.1)	0.61
ICU	51 (54.8)	18 (51.4)	33 (56.9)	
Cannulation site				
Chest	80 (86.0)	30 (85.7)	50 (86.2)	1.00
Neck	13 (14.0)	5 (14.3)	8 (13.8)	

(*Continued*)

TABLE 1. (*Continued*). Patient and Clinical Characteristics Stratified by Mortality at 30 Days After Surgery

Characteristics	All ($n = 93$)	Mortality at 30 d After Surgery: Yes ($n = 35$)	Mortality at 30 d After Surgery: No ($n = 58$)	p
Additional ECMO cannulation	11 (11.8)	1 (2.9)	10 (17.2)	0.048
Pump flows in the first 48 hr, cc/kg				
Minimum	82.7 (66.1–100)	85.0 (66.7–117)	82.6 (65.2–93.1)	0.17
≥ 120	12 (12.9)	8 (22.9)	4 (6.9)	0.052
< 120	80 (86.0)	27 (77.1)	53 (91.4)	
Mean Pao_2 (during first 48 hr), mm Hg				
> 193	73 (78.5)	34 (97.1)	39 (67.2)	0.001
< 193	20 (21.5)	1 (2.9)	19 (32.8)	

ECMO = extracorporeal membrane oxygenation.

dialysis, and 42% had evidence of neurologic injury (stroke, seizures, or intracranial hemorrhage).

Arterial blood gases prior to cannulation for ECMO were available in 83 patients. The median pH was 7.35 (IQR, 7.19–7.39), Pao_2 was 40.0 mm Hg (IQR, 32.8–62.2), and lactate was 3.5 mmol/L (IQR, 1.3–13.0).

The median number of arterial blood gas measurements in the first 48 hours of ECMO was 15 (range, 4–28) across the entire cohort. Using ROC curves, the mean Pao_2 in the first 48 hours was the most predictive metric for mortality 30 days after surgery (AUC, 0.65; 95% CI, 0.54–0.76) compared with other Pao_2 metrics (AUC, 0.58 and 0.61 in maximum and median Pao_2, respectively). A mean Pao_2 of 193 mm Hg in the first 48 hours showed a good discrimination between the outcomes, with a sensitivity of 97%, specificity of 33%, PPV of 47%, and NPV of 95%. Seventy-three patients (78%) in the cohort had a mean Pao_2 greater than 193 mm Hg in the first 48 hours of ECMO.

The mean Pao_2 in the first 48 hours also demonstrated good discriminatory abilities in the subgroups: AUC, 0.72 (95% CI, 0.60–0.84) in neonates and 0.71 (95% CI, 0.54–0.89) in patients who underwent a Norwood procedure with a systemic to pulmonary artery shunt. In neonates, a mean Pao_2 of 193 mm Hg had a sensitivity of 100%, a specificity of 37%, and an NPV of 100%, whereas in patients who underwent a Norwood procedure, the cutoff had a sensitivity of 100%, a specificity of 50%, and an NPV of 100%. The distribution of the mean Pao_2 in the first 48 hours with regard to the primary outcome is shown in **Figure 1** for the overall cohort and the subgroups.

In univariate analysis, factors significantly associated with mortality 30 days after surgery included longer duration on ECMO ($p < 0.0001$) and a mean Pao_2 in the first 48 hours of greater than 193 mm Hg ($p = 0.001$) (Table 1). With exclusion of the patients who had the sweep gas blended, a mean Pao_2 greater than 193 mm Hg was still significantly associated with increased 30-day mortality ($p = 0.001$). Longer cardiopulmonary bypass times and higher minimum ECMO pump flows in the first 48 hours trended toward a significant association with 30-day mortality ($p = 0.09$ and 0.052, respectively).

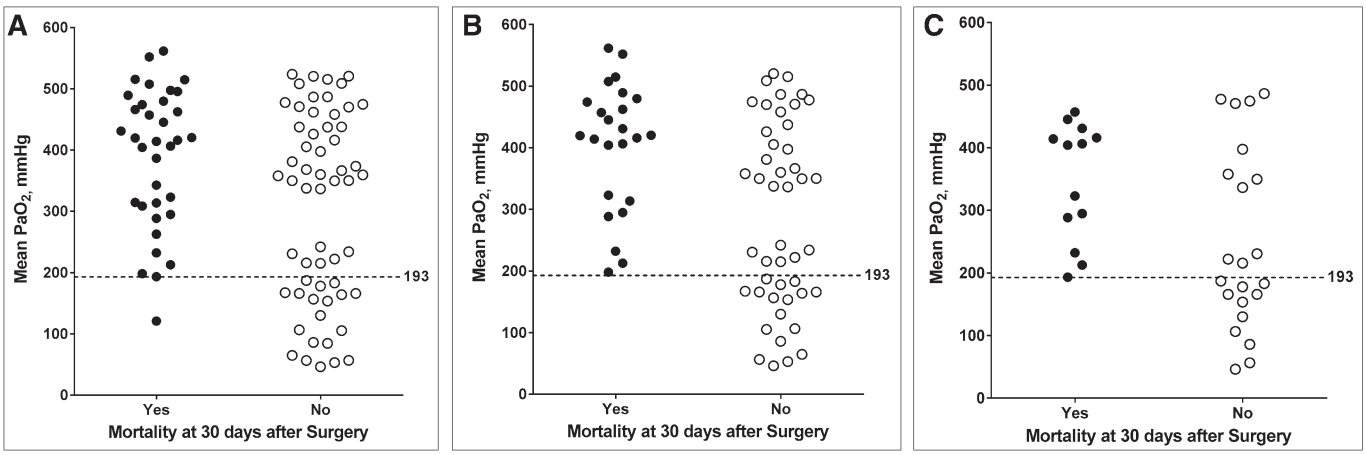

Figure 1. Distribution of mean Pao_2 in the first 48 hr of extracorporeal membrane oxygenation with regard to 30-d mortality in infants (age < 1 yr) (**A**), neonates (age < 30 d) (**B**), and neonates who underwent a Norwood procedure with a systemic to pulmonary artery shunt (**C**).

In multivariable analysis, a mean Pao_2 in the first 48 hours greater than 193 mm Hg and longer duration on ECMO remained independently associated with 30-day mortality (**Table 2**).

The entire patient cohort was stratified by a mean Pao_2 of 193 mm Hg in the first 48 hours, and patient and clinical characteristics were compared (**Table 3**). Factors significantly associated with a mean Pao_2 in the first 48 hours greater than 193 mm Hg included longer cardiopulmonary bypass ($p = 0.02$) and aortic cross-clamp times ($p = 0.01$), longer duration on ECMO ($p < 0.0001$), and higher ECMO pump flows. Ventricular function (normal or mildly depressed vs moderately or severely depressed) on an echocardiogram within 48 hours of cannulation was not associated with mean Pao_2 values ($p = 0.19$).

In terms of end-organ disease, the prevalence of renal dialysis ($p = 0.02$) but not neurologic injury ($p = 0.41$) was significantly higher in the patients with a mean Pao_2 greater than 193 mm Hg (Table 3).

DISCUSSION

In infants with congenital heart disease who are placed on VA-ECMO in the postoperative setting, hyperoxia (defined in this study as a mean $Pao_2 > 193$ mm Hg in the first 48 hr of ECMO) was an independent risk factor for 30-day mortality. To our knowledge, this is the first study to investigate the potential effects of hyperoxia on patients supported on ECMO. In this study, we aimed to choose a narrow subset of patients given the vast heterogeneity of clinical and surgical characteristics of patients who are placed on ECMO and therefore the multiple confounders that could contribute to outcomes. The patients in this cohort are all infants who had cardiac surgery requiring cardiopulmonary bypass for repair of congenital heart lesions. We excluded patients without congenital heart disease or those that were placed onto ECMO outside of the postoperative setting to limit confounders given that cardiopulmonary bypass in infants is known to cause a significant systemic inflammatory response (17).

Overall, the majority of the patients in the cohort were neonates, and approximately a third of the patients underwent a Norwood arch reconstruction with a systemic to pulmonary artery shunt. These factors in addition to the fact that the majority of patients had a STAT mortality score of 4 or 5 indicate that the cohort, as expected, is a high-risk patient group. Longer duration on ECMO was found to be a risk factor for mortality after congenital heart surgery, which is similar to previously published data (18, 19).

There has been a considerable amount of interest recently in the potential effects of hyperoxia during and after periods of tissue ischemia. The introduction of high amounts of oxygen to previously ischemic tissues leads to the generation of reactive oxygen species and activation of inflammatory pathways via cytokines (20). Reactive oxygen species lead to lipid peroxidation and protein changes, which cause cell injury via direct damage or apoptosis (21). The effect may be even more pronounced in pediatric patients as neonates, and infants are known to have immature antioxidant defenses and thus may be more susceptible to the reactive oxygen species (22). In addition, the reactive oxygen species can activate neutrophils and platelets leading to an exaggerated inflammatory and thrombotic response (4), which could theoretically increase the risk of complications on ECMO.

A review of the current literature indicates that across a wide variety of clinical scenarios and situations, the effect of hyperoxia is unclear. After resuscitation from cardiac arrests, hyperoxia in adults has been associated with increased risk of mortality (9, 23). On the other hand, supplemental oxygen therapy after myocardial infarctions was not shown to have

TABLE 2. Factors Associated With Mortality 30 Days After Surgery

	Unadjusted			Adjusted		
Characteristics	**OR**	**95% CI**	***p*[a]**	**AOR**	**95% CI**	***p*[b]**
Cardiopulmonary bypass time	1.004	1.00–1.01	0.08	1.00	0.994–1.01	0.88
Duration on extracorporeal membrane oxygenation, d						
≥ 7	9.18	3.29–28.9	< 0.0001	5.3	1.61–17.4	0.01
< 7	Ref			Ref		
Minimum pump flows in the first 48 hr, cc/kg						
≥ 120	3.86	0.94–19.2	0.052	2.11	0.47–9.38	0.33
< 120	Ref			Ref		
Mean Pao_2 during first 48 hr, mm Hg						
> 193	16.6	3.17–305	0.001	9.79	1.18–81.0	0.03
< 193	Ref			Ref		

OR = odds ratio (unadjusted), AOR = adjusted odds ratio, Ref = reference category.

[a]*p* value from univariate logistic regression.

[b]*p* value from multivariable logistic regression.

TABLE 3. Patient Characteristics and Secondary Outcomes by Mean Pao_2 in the First 48 Hours

Characteristics	Mean Pao_2 in the First 48 hr		*p*
	> 193 mm Hg (*n* = 73)	< 193 mm Hg (*n* = 20)	
Age at surgery, d	8 (5–31)	5.5 (3–8)	0.09
Neonate (< 30 d)	53 (72.6)	17 (85.0)	0.38
Weight at surgery, kg	3.3 (2.9–3.8)	3.4 (3.2–3.7)	0.65
Preoperative cyanosis	64 (87.7)	18 (90.0)	1.00
Society of thoracic surgeons–European association for cardiothoracic surgery congenital heart surgery database category			
1–3	13 (17.8)	1 (5.0)	0.29
4 or 5	60 (82.2)	19 (95.0)	
Norwood procedure	24 (32.9)	11 (55.0)	0.07
Cardiopulmonary bypass time, min	159 (107–236)	128 (81–179)	0.02
Aortic cross-clamp time, min	49.5 (35–99.5)	38 (16–46.5)	0.01
Circulatory arrest time, min (*n* = 55)	38 (28–45)	38 (34–45)	0.84
Sweep gas blended	3 (4.1)	7 (35.0)	0.001
Duration on ECMO, d	6.1 (3.8–9.1)	2.9 (2.3–3.6)	< 0.0001
≥ 7	24 (32.9)	0 (0.0)	0.003
< 7	49 (67.1)	20 (100.0)	
Indication for cannulation			
Low cardiac output/poor perfusion	14 (19.2)	2 (10.0)	Not applicable
Failure to wean from cardiopulmonary bypass	37 (50.7)	7 (35.0)	
Pulmonary hypertension	1 (1.4)	1 (5.0)	
Combined cardiac and respiratory failure	20 (27.4)	6 (30.0)	
Respiratory failure/hypoxia (not pulmonary hypertension)	0 (0.0)	2 (10.0)	
Shunt occlusion	1 (1.4)	2 (10.0)	
Cannulation during extracorporeal cardiopulmonary resuscitation	21 (28.8)	7 (35.0)	0.59
Location of cannulation			
Operating room	36 (49.3)	6 (30.0)	0.12
ICU	37 (50.7)	14 (70.0)	
Cannulation site			
Chest	63 (86.3)	17 (85.0)	1.00
Neck	10 (13.7)	3 (15.0)	
Additional ECMO cannulation	8 (11.0)	3 (15.0)	0.7
Pump flows in the first 48 hr, cc/kg			
Minimum	86.6 (71.7–103)	64.8 (56.2–82.6)	0.003
≥ 120	11 (15.1)	1 (5.0)	0.45
< 120	61 (83.6)	19 (95.0)	

(*Continued*)

TABLE 3. (*Continued*). Patient Characteristics and Secondary Outcomes by Mean Pao_2 in the First 48 Hours

Characteristics	Mean Pao_2 in the First 48 hr		*p*
	> 193 mm Hg (*n* = 73)	< 193 mm Hg (*n* = 20)	
Need for renal dialysis	32 (43.8)	3 (15.0)	0.02
Neurologic injury during hospitalization	29 (39.7)	10 (50.0)	0.41
Seizure	21 (28.8)	2 (10.0)	0.14
Stroke	9 (12.3)	4 (20.0)	0.47
Intracranial hemorrhage	12 (16.4)	6 (30.0)	0.21
ICU length of stay, d	21 (14–42)	28.5 (20–52)	0.08
Hospital length of stay, d	28 (18–63)	48 (31–64)	0.09
In-hospital mortality	41 (56.2)	5 (25.0)	0.01

ECMO = extracorporeal membrane oxygenation.

any clinically apparent effect (13). In pediatric patients, the data are mixed as hyperoxia has been shown to be both associated (6, 8) and not associated with increased risk of mortality (5, 7) after cardiac arrests. In neonates with asphyxia, hyperoxia was associated with increased mortality and risk of brain injury (11, 12). Finally, in children undergoing cardiac surgery to repair congenital heart lesions (which often necessitates a period of tissue hypoxia during cardioplegic arrest of the heart or during deep hypothermic circulatory arrest), patients on cardiopulmonary bypass who were exposed to hyperoxia had increased evidence of end-organ damage, oxidative stress, and inflammation (14, 15).

There are also limited data to suggest that hyperoxia may be beneficial in certain situations. In animal models, hyperoxia after cardiac arrest was associated with improved myocardial function (24) and also shown to be neuroprotective in cerebral ischemia (25). Early data in human subjects showed that selective perfusion of coronary arteries with a hyperoxemic solution resulted in improved left ventricular function (26); however, subsequent studies have failed to show any significant effect (27).

As a result of the data suggesting the negative effects of hyperoxia, there has been considerable interest in modifying oxygen exposure to patients. Current resuscitation guidelines in pediatrics and adults recommend titration of supplemental oxygen after a cardiac arrest (28, 29). In patients supported on VA-ECMO, clinicians can titrate (or blend) the oxygen content of the sweep gas of the oxygenator to achieve more "physiologic" Pao_2 levels. However, the practice is not universal. Our group conducted an informal survey of other pediatric cardiac ICUs and found that two-thirds of units are titrating to goal Pao_2 levels, whereas the other third maintain elevated Pao_2 levels. In our study, only a minority (11%) of patients had the sweep gas blended (likely at supervising physician discretion) at the end of the time period of the chart review. With both inclusion and exclusion of this group of patients, a mean Pao_2 greater than 193 mm Hg was associated with increased 30-day mortality.

There are other factors that can contribute to changes in the arterial oxygen tension in patients supported on VA-ECMO. Rarely, mechanical issues with the oxygenator can lower the Pao_2 values. In addition, oxygen tension of blood ejected from the systemic ventricle and the ratio of mixing of blood from the systemic ventricle and the arterial ECMO cannula can affect the overall arterial (and hence end organ) oxygen tension. Pulmonary venous desaturation from lung disease (common in postoperative patients on ECMO) or mixing at the atrial and/or ventricular levels may cause relatively decreased oxygen tension of the blood ejected from the systemic ventricle in relation to blood returning from the arterial cannula. Most patients in our study were cannulated for ECMO in the postoperative setting due to low cardiac output or failure to wean from cardiopulmonary bypass and therefore likely had some element of ventricular dysfunction. One could hypothesize that a patient with better ventricular function would, therefore, eject more blood that has a relatively lower oxygen tension, thus mixing with the highly oxygenated blood from the aortic cannula and leading to overall decreased oxygen tension. However, in this study, when we analyzed available echocardiograms in the first 48 hours after ECMO cannulation, worse ventricular function was not found to be significantly associated with a higher mean Pao_2.

Another important factor is ECMO pump flow as higher flows would presumably decrease the amount of pulmonary venous return and therefore decrease preload to the systemic ventricle. This could lead to decreased ejection of the "deoxygenated" blood into the aorta. Interestingly, when adjusting for ECMO pump flow and other factors, a mean Pao_2 greater than 193 mm Hg was still associated with increased risk of 30-day mortality, suggesting that the association is not dependent on the requirement for increased ECMO support. In addition, although we observed that higher ECMO pump flows

trended toward a significant association with mortality in the univariate analysis and patients with a higher average Pa_{O_2} had significantly higher pump flows, higher ECMO pumps flows were not an independent risk factor for 30-day mortality in the multivariable analysis. Thus, there is some suggestion from this study that elevated Pa_{O_2} levels may have a causative (due to reactive oxygen species or other mechanisms) effect on clinical outcome versus simply being associative due to improved clinical parameters. Although further studies are required to delineate these phenomena, the results of this study showed that hyperoxia has a very high sensitivity and NPV for mortality. As shown in the results, there were very few patients who did not survive to 30 days after surgery with a mean Pa_{O_2} less than 193 mm Hg.

Secondary outcomes, such as the need for dialysis or neurologic injury, were investigated to evaluate for potential end-organ injury due to hyperoxia. There was no statistical difference in terms of neurologic injury (seizures, intracranial hemorrhage, or strokes). However, only a limited number of patients in the cohort had brain MRI, which is considered to be the standard evaluation of white-matter brain injury. Future studies would be helpful to further evaluate brain matter injury and neurodevelopmental outcomes of patients exposed to hyperoxia while on ECMO.

The data did suggest that there was an increased risk for the need for renal replacement therapy in those patients with a mean Pa_{O_2} greater than 193 mm Hg. Previous studies have also indicated that renal failure is a risk factor for death while on ECMO (18). As discussed above, it is possible that the need for dialysis could be due to the negative effects of hyperoxia with generation of reactive oxygen species leading to worsening renal failure. However, it is also possible that the need for dialysis was simply a marker of a more critically ill patient with worse ventricular function and the need for higher ECMO pump flows although these variables were not seen as independent risk factors.

Limitations of this study include the fact that it was a retrospective chart review performed at a single center and that there may have been other important clinical variables that could not be measured in a retrospective manner. Specifically, data were not available or collected with regard to the total oxygen delivery such as specific ventilator settings and the variation in hemoglobin of each patient. In addition, variation among individual intensivists with regard to clinical practice of patients on ECMO may have contributed to confounding data. Finally, due to the retrospective nature of the data collection, advanced data analysis using longitudinal mixed modeling to further define the relationship between Pa_{O_2} values and outcomes could not be performed.

CONCLUSIONS

In the postoperative period, a mean Pa_{O_2} greater than 193 mm Hg while on ECMO was an independent risk factor for mortality in infants with congenital heart disease. The results of the study indicate that not only are future prospective studies necessary to investigate the effect of hyperoxia while on ECMO but also that a change of practice in management of these patients in many centers may be prudent. In addition, we would propose that hyperoxia on ECMO may be used as a tool for clinicians to prognosticate potential ventricular recovery and the likelihood of survival after ECMO decannulation, which may influence decisions regarding further intervention or institution of long-term mechanical support (i.e., ventricular assist devices).

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