Association of Extracorporeal Membrane Oxygenation Support Adequacy and Residual Lesions With Outcomes in Neonates Supported After Cardiac Surgery*

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Objectives: There is a paucity of data regarding the impact of extracorporeal membrane oxygenation support, adequacy of surgical repair, and timing of intervention for residual structural lesions in neonates cannulated to extracorporeal membrane oxygenation after cardiac surgery. Our goal was to determine how these factors were associated with survival.

Design: Retrospective study.

Setting: Cardiovascular ICU.

Subjects: Neonates (≤ 28 d old) with congenital heart disease cannulated to extracorporeal membrane oxygenation after cardiac surgery during 2006–2013.

Interventions: None.

Measurements and Main Results: Eighty-four neonates were cannulated to venoarterial extracorporeal membrane oxygenation after cardiac surgery. Survival to discharge was 50%. There was no difference in survival based on surgical complexity and those with single or biventricular congenital heart disease. Prematurity (≤ 36 wk gestation; odds ratio, 2.33; $p = 0.01$), preextracorporeal membrane oxygenation pH less than or equal to 7.17 (odds ratio, 2.01; $p = 0.04$), need for inotrope support during extracorporeal membrane oxygenation (odds ratio, 3.99; $p = 0.03$), and extracorporeal membrane oxygenation duration greater than 168 hours (odds ratio, 2.04; $p = 0.04$) were all associated with increased mortality. Although preextracorporeal membrane oxygenation lactate was not significantly different between survivors and nonsurvivors, unresolved lactic acidosis greater than or equal to 72 hours after cannulation (odds ratio, 2.77; $p = 0.002$) was associated with increased mortality. Finally, many patients ($n = 70$; 83%) were noted to have residual lesions after cardiac surgery, and time to diagnosis or correction of residual lesions was significantly shorter in survivors (1 vs 2 d; $p = 0.02$).

Conclusions: Our data suggest that clearance of lactate is an important therapeutic target for patients cannulated to extracorporeal membrane oxygenation. In addition, timely identification of residual lesions and expedient interventions on those lesions may improve survival. (*Pediatr Crit Care Med* 2016; 17:1045–1054)

Key Words: cardiac surgery; extracorporeal membrane oxygenation; lactate; neonates; pediatrics

*See also p. 1093.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/pccmjournal).

Dr. Nathan disclosed he is supported by a K23 grant and Co-Chair of project supported by the Pediatric Heart Network for work not related to this publication. Dr. Kulik received funding from malpractice insurance company and from meeting organizers. Dr. Thiagarajan received financial support for serving as a member of an Events Adjudication Committee for Bristol Myers Squibb. His institution received funding from Bristol Myers Squibb. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/PCC.0000000000000943

Repairs of complex congenital heart defects are increasingly undertaken in the neonatal period. Improvements in diagnosis, surgical technique, and postoperative care have contributed to the successful conduct of these operations and postoperative survival. Still, some neonates returning from the operating room are critically ill with refractory hypoxemia or a profound low cardiac output state (LCOS). Although many respond to medical management with mechanical ventilation and inotrope support, venoarterial extracorporeal membrane oxygenation (ECMO) has become an increasingly important in those failing these therapies. For these neonates, ECMO can be lifesaving. According to the January 2016 Extracorporeal Life Support Organization International Summary, 6,269 neonates have been supported with ECMO for cardiac indications with a

survival rate of roughly 41%. The majority of those patients were cannulated postcardiac surgery (1). Despite familiarity with the use of ECMO in the postoperative period to support neonates undergoing cardiac surgery, post-ECMO mortality remains high.

Prior studies following postcardiotomy ECMO in children have shown that younger age, lower body weight, single ventricle congenital heart disease, indication for ECMO support, duration of ECMO support, multiple cannulations, bleeding, and acute kidney injury were all associated with mortality (2–13). Few studies, however, have examined the impact of adequate ECMO support, adequacy of surgical repair, and timing of intervention for residual structural lesions on survival. Therefore, we studied a cohort of neonates cannulated to ECMO after cardiac surgery at our institution to evaluate factors associated with in-hospital mortality. We also evaluated the influence of adequacy of ECMO support, residual structural lesions, and timing of intervention for residual lesions on mortality in our cohort.

METHODS

Neonates (age, ≤ 28 d) supported with ECMO after repair of congenital heart disease at Boston Children's Hospital during calendar years 2006 through 2013 were included in the study. Neonates cannulated to ECMO prior to a surgical procedure were excluded even if they were supported with ECMO in the postoperative period. Data were obtained from electronic health records and an ECMO database maintained by the ECMO program. Boston Children's Hospital Committee on Clinical Investigation approved the review of patient medical records and granted a waiver for informed consent.

Patient demographics, patient status, pre-ECMO support, measures of ECMO support, and complications of ECMO were collected. Demographic factors included gestational age, weight, gender, age at cannulation, genetic syndromes, and nongenetic comorbidities. Congenital heart disease type was separated into single and biventricular physiology. Surgical complexity was categorized using the Risk Adjustment for Congenital Heart Surgery (RACHS)-1 method (14). Residual lesions present after repair or palliation of congenital heart disease were characterized by using the Technical Performance Score (TPS). First validated by Nathan et al (15), TPS scoring uses postoperative echocardiography to assess the adequacy of repair following congenital heart surgery; with class 1 is considered "optimal" (no residua), class 2 "adequate" (minor residua), and class 3 "inadequate" (major residua or predischarge reintervention for major residua). A small subset of patients ($n = 8$) were noted to have multiple ECMO runs during the index hospital admission. Only information for the first ECMO run was used for analysis.

ECMO indications were divided into failure to wean from cardiopulmonary bypass (CPB), cardiac arrest, LCOS, and hypoxemia. Pre-ECMO laboratory data, ventilation, and hemodynamic support prior to ECMO cannulation were collected. The pre-ECMO hemodynamic and lactate values collected represented the worst values in the previous 6 hours prior to cannulation. The Vasoactive Inotrope Score (VIS) was used to quantify pre-ECMO vasoactive support and was calculated at the time of cannulation (16). Information on ECMO support included cannulation location (procedural suite or ICU), type of cannulation (open chest or neck cannulation), use of left atrial decompression, ECMO flow, and ECMO duration. Transfusion data and need for operative chest washout procedures were also recorded. We defined adequacy of ECMO support as time to achieve a serum lactate level of less than or equal to 2 mmol/L after onset of ECMO. We collected information of all cardiac catheterization (both hemodynamic and interventional) and surgical procedures during the entire duration of hospitalization including those performed during or after ECMO support. Surgical procedures were defined as those requiring patient transfer to the operating room and did not include bedside intervention for management of bleeding or cardiac tamponade. We defined time to intervention as time from ECMO deployment to first procedure.

Complication data including neurologic (intracerebral hemorrhage, cerebral infarction, and seizures), mechanical (circuit clots, oxygenator failure, and cannula-related issues), and bleeding were also collected. Renal failure, defined as a creatinine greater than or equal to 1.5 or use of renal replacement therapy, and hepatic failure, defined as aspartate alanine transferase value of greater than or equal to 950 IU/L or total bilirubin of greater than 15 mg/dL were recorded. Our primary outcome was survival to discharge to home or another institution. We also collected 1-year survival for neonates surviving to hospital discharge.

STATISTICAL ANALYSIS

We compared demographic, pre-ECMO support, and ECMO-related variables between survivors and nonsurvivors. Continuous data are shown as median with interquartile range (25–75th percentile of distribution) and numbers and percentage for categoric data. Continuous variables were compared using the Mann-Whitney test. Categoric variables were compared be using the chi-square test, and the Fisher exact test was used when expected counts were less than 5 in more than 20% of the cells. We compared time to lactate clearance after institution of ECMO between survivors and nonsurvivors using Kaplan-Meier analysis

We evaluated factors associated with mortality (time to death after ECMO initiation) using a Cox proportional hazards model. The primary predictor tested in the multivariable model was time to achieve serum lactate to less than 2 mmol/L after institution of ECMO. We categorized patients based on time to achieve lactate less than 2 mmol/L into two groups, one containing patients achieving serum lactate less than 2 mmol/L in less than or equal to 72 hours from ECMO start and those whose lactate levels were greater than or equal to 2 mmol/L after 72 hours of ECMO. The 72-hour cut off was based on the median time to lactate less than 2 mmol/L among nonsurvivors. Eight patients (seven nonsurvivors and one survivor) did not achieve lactate levels less than 2 mmol/L during ECMO support or prior to death. To prevent loss of information, patients who did not achieve a serum lactate less than 2 mmol/L during ECMO or prior to death were assigned to the latter group. Variables

with p value less than 0.05 from the univariate analysis were considered as candidates for the multivariable model. Because of small sample size and outcomes, we only included those variables retaining statistical significance when tested with the primary predictor in a Cox regression model. Candidate variables tested in the final model included unresolved lactic acidosis, gestational age less than 36 weeks, failure to wean CPB, pre-ECMO blood gas pH, need for inotropes on ECMO, platelet transfusion during ECMO, and liver dysfunction. Variable inclusion and exclusion in the multivariable Cox regression model was set to an adjusted p value of less than or equal to 0.05. Proportional hazard assumption for the Cox model was tested using a log minus log plot. A p value of less than or equal to 0.05 was considered statistically significant.

RESULTS

Study Population

A total of 84 (8.8%) neonates among 948 neonates undergoing cardiac surgical procedure during the time period underwent 93 runs of ECMO support after cardiac surgery during the study period. Median gestational age was 38 weeks, age at cannulation was 5.5 days, and birth weight was 3 kg. 14 patients (17%) in the cohort were premature with a gestational age of less than or equal to 36 weeks. Chromosomal anomalies were present in eight patients (10%) (DiGeorge syndrome, 4; trisomy 21, 2; and other, 2); noncardiac structural anomalies were seen in nine neonates (11%) (congenital diaphragmatic hernia, lung hypoplasia, and airway anomalies, 6; CNS, 2; and skeletal, 1). Forty-one patients (49%) were categorized as having a single ventricle. Higher complexity procedures (RACHS-1, 5 or 6) were performed in 36 (34%), and only five procedures (6%) were performed without CPB.

The most common ECMO indication was cardiac arrest (n = 39; 46%), followed by failure to wean from CPB (n = 21; 25%), LCOS (n = 18; 21%), and hypoxemia (n = 6; 7%). The majority of patients (n = 82; 98%) were cannulated for ECMO using the right atrium and aorta. Among the 77 patients in whom a TPS could be assigned, 60 (71%) were assigned to the class 3 (inadequate repair) category. Median duration of ECMO support was 105 hours. Overall, 42 (50%) survived to hospital discharge. Three patients received cardiac transplantation prior to hospital discharge, with two bridged on ECMO, and one transplanted after weaning off ECMO. Only the patient transplanted after successful ECMO weaning survived to hospital discharge.

Demographic and Pre-ECMO Support in Survivors and Nonsurvivors

Differences in demographic variables and pre-ECMO support are shown in **Tables 1** and **2**. Neonates of higher birth weight and gestational age more than 36 weeks had improved survival. In addition, nonsurvivors had increased prevalence of genetic syndromes. Interestingly, there were no differences between survivors and nonsurvivors with regard to single- versus two- ventricle lesions, surgical complexity, TPS, or CPB support times. However, there were a higher number of class 3 TPS among nonsurvivors. Severity of illness prior to ECMO as indicated by mean blood pressure, serum lactate levels, VIS, use of inhaled nitric oxide, renal function, and liver function were also not significantly different between survivors and nonsurvivors. Survivors, however, did have a significantly higher pre-ECMO pH than nonsurvivors.

ECMO Support and Complications

Differences in ECMO support and complications between survivors and nonsurvivors are shown in **Table 3**. Although not statistically significant, more nonsurvivors were cannulated in the catheterization laboratory or operating room. Survivors and nonsurvivors did not differ by route of cannulation, use of left atrium decompression, and ventilatory support during ECMO.

Serum lactate levels in the first 24–48 hours after ECMO was significantly lower in survivors compared to nonsurvivors (Table 3). In addition, the time to lactate clearance (to achieve serum lactate levels of < 2 mmol/L) was faster in the survivors compared to nonsurvivors (Table 3 and **Fig. 1**) and fewer nonsurvivors achieved serum lactate less than 2 mmol/L within 72 hours compared to nonsurvivors. Furthermore, fewer survivors required inotropic support during ECMO compared to nonsurvivors (28 vs 39; p = 0.004) (Table 3).

Blood product usage including packed red cells and platelet transfusion was higher in nonsurvivors compared to survivors (Table 3). Nonsurvivors had a higher incidence of cannulation and surgical site bleeding and required more chest exploration procedures compared to nonsurvivors. Other complications occurring while on ECMO, including mechanical, neurologic, renal, and liver failure were all increased in nonsurvivors.

ECMO Duration and Survival

Median ECMO duration was significantly shorter in survivors (4 vs 11 d; p = 0.001). For the entire cohort, there were no survivors after being on ECMO longer than 10 days, and none of the single ventricle patients survived after being on ECMO for greater than 5 days (**Fig. 2**).

Multivariable Model of Factors Associated With Mortality

A multivariable model was developed to explore factors associated with mortality (**Table 4**). Candidate variables for multivariable analysis included gestational age (categorized as < 36 and ≥ 36 wk), ECMO for failure to wean CPB, pre-ECMO arterial blood pH (categorized as pH < 7.17 and ≥ 7.17), need for inotropes during ECMO, volume of platelet transfusion during ECMO (categorized as < 723 mL vs ≥ 723 mL), and ECMO duration (categorized as < 168 and ≥ 168 hr). After analysis, gestational age 36 weeks old or younger, pre-ECMO blood pH less than or equal to 7.17, need for inotrope support on ECMO, and ECMO duration of greater than 168 hours were associated with a significantly higher hazard ratio (HR) of mortality prior to hospital discharge. In addition, patients with unresolved lactic acidosis beyond 72 hours after start of ECMO had increased mortality (HR, 2.77 [1.36–5.06]; p = 0.002). All patients with genetic abnormalities died prior to hospital discharge.

TABLE 1. Demographics of Neonates Surviving Extracorporeal Membrane Oxygenation Course After Cardiac Surgery Versus Those Not Surviving

Variable	Survivors ($n = 42$)	Nonsurvivors ($n = 42$)	p
Age at ECMO cannulation (d)	6 (4–13)	5 (3–11)	0.25
Weight (kg)	3.1 (2.8–3.6)	2.9 (2.3–3.1)	0.009
Weight ≤ 2.5 kg, *n* (%)	8 (19)	19 (45)	0.01
Female gender, *n* (%)	21 (50)	16 (38)	0.27
Gestational age (wk)	38.5 (37–39)	38 (36–38)	0.007
Prematurity (≤ 36 wk), *n* (%)	5 (12)	14 (33)	0.02
Genetic syndrome	0	8 (19%)	0.005[a]
Nongenetic comorbidities	2	7 (17%)	0.16[a]
Congenital heart disease type, *n* (%)			
Single ventricle	22 (52)	19 (45)	0.51
Two ventricle	20 (48)	23 (55)	
Surgical complexity, *n* (%)			
RACHS 1–3	8 (19)	6 (14)	0.8[a]
RACHS 4–6	30 (71)	33 (79)	
Not eligible	4 (10)	3 (7)	
Technical Performance Score			
Class 1: optimal	5	2	0.36[a]
Class 2: adequate	8	4	
Class 3: inadequate	26	32	
Not assigned	3	4	
Cardiopulmonary bypass time (min)	142 (83–177)	158 (108–261)	0.08
Multiple ECMO runs, *n* (%)	1 (2)	9 (21)	0.007[a]

ECMO = extracorporeal membrane oxygenation, RACHS = Risk Adjustment in Congenital Heart Surgery categories.
[a]Fisher exact test.

Surgical- and Catheter-Based Intervention in the Study Cohort

In our cohort, the majority of patients underwent cardiac catheterization or surgical procedures for investigation or management of residual lesions during or after ECMO support ($n = 65$; 77%) (**Table 5**). Of these, 55 neonates (65%) underwent a procedure during ECMO (cardiac catheterization, 31; surgery, 4; and both, 20), and 30 neonates (36%) underwent post-ECMO procedures (cardiac catheterization, 16; surgery, 4; and both, 10). For the entire cohort, there was no difference in survival among patients undergoing a procedure after ECMO deployment compared to those not undergoing a procedure (53% vs 49%; $p = 0.8$). Similarly, among patients with significant residual lesions (TPS categories, 2 and 3), there was no difference in survival between patients undergoing a procedure and those not undergoing a procedure after ECMO deployment (50% vs 50%; $p = 1$). However, in patients with significant residual lesions, interventions occurred sooner in the ECMO course in survivors compared to nonsurvivors (median, 1 vs 2 d; $p = 0.02$). Further information can be found in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/PCC/A309).

Long-Term survival

Among the 42 patients surviving to hospital discharge, eight (32%) died during a median follow-up duration of 2.5 years (range, 0–8). There were more deaths after discharge in patients with single ventricle anatomy (7/22; 19%) compared with those with two-ventricle anatomy (1/20; 5%, Fisher exact $p = 0.05$).

DISCUSSION

In this study, we describe a cohort of 84 neonates cannulated to ECMO after cardiac surgery for congenital heart disease. Most patients had complex cardiac operations and many were noted to have residual structural cardiac lesions after repair. Consistent with other studies, increased mortality in our neonatal cohort was associated with prematurity, pre-ECMO blood pH, need for

TABLE 2. Patient Status and Support Before Extracorporeal Membrane Oxygenation Cannulation

Variable	Survivors (*n* = 42)	Nonsurvivors (*n* = 42)	*p*
ECMO indication, *n* (%)			
Failure to separate from cardiopulmonary bypass	6 (14)	15 (36)	0.01[a]
Cardiac arrest	19 (45)	20 (47)	
Low cardiac output state	11 (26)	7 (17)	
Hypoxemia	6 (14)	0	
Pre-ECMO ventilatory support, *n* (%)			
Hand ventilation	6 (17)	5 (19)	0.49
Conventional	29 (83)	29 (77)	
High-frequency oscillatory ventilation	0	1 (2)	
Mean airway pressure (cm H_2O)[b]	9 (8–10)	10 (8–12)	0.21
Pre-ECMO inhaled nitric oxide use, *n* (%)	7 (17)	6 (14)	0.76
Pre-ECMO blood pH	7.29 (7.19–7.35)	7.25 (7.12–7.32)	0.04
Blood pH ≤ 7.17[b], *n* (%)	5 (14)	15 (36)	0.02
Vasoactive Inotrope Score	17.5 (4.4–25)	10.5 (4.5–30.5)	0.91
Pre-ECMO mean blood pressure[b]	32 (28–42)	31 (27–38)	0.47
Pre-ECMO lactate (mmol/L)[b]	9.3 (6.1–15.8)	11.8 (8.2–17.6)	0.13
Pre-ECMO hematology			
Hematocrit (%)	38 (35–46)	38 (34–44)	0.33
WBC (c/mm^3)[b]	12.6 (8–18)	10 (8–13.8)	0.26
Platelets (c/mm^3)[b]	261 (139–405)	169 (105–238)	0.17
Pre-ECMO renal function			
Blood urea nitrogen (mg/dL)[b]	14 (7–18)	10 (6–21)	0.64
Serum creatinine (mg/dL)[b]	0.6 (0.4–0.7)	0.6 (0.4–0.7)	0.95
Pre-ECMO liver function			
Serum aspartate transferase (IU/L)[b]	46 (28–89)	50 (34–136)	0.30
Serum alanine transferase (IU/L)[b]	12 (8–15)	17 (9–50)	0.10
Bilirubin (mg/dL)[b]	5.3 (3.1–7.6)	4.5 (2.5–7.1)	0.49

ECMO = extracorporeal membrane oxygenation.

[a]Fisher exact test.

[b]Missing data: mean blood pressure, *n* = 11; preextracorporeal membrane oxygenation (pre-ECMO) pH, *n* = 4; pre-ECMO lactate, *n* = 4; pre-ECMO WBC, *n* = 1; pre-ECMO platelets, *n* = 1; pre-ECMO blood urea nitrogen, *n* = 1; pre-ECMO serum creatinine, *n* = 1; pre-ECMO serum aspartate transferase, *n* = 22; pre-ECMO serum alanine transferase, *n* = 22; pre-ECMO bilirubin, *n* = 11; pre-ECMO ventilatory support, *n* = 23; pre-ECMO mean airway pressure, *n* = 27.

inotrope support during ECMO, longer duration ECMO, and multiple ECMO runs (4, 7, 17).

One of the most prominent findings in our study was the relationship between lactate clearance and survival. In the multivariable analysis, we found that the presence of unresolved lactic acidosis at greater than or equal to 72 hours of cannulation was associated with increased mortality. Pre-ECMO lactate values were similar between those who survived and those who did not. However, neonates with maximum postcannulation lactate levels greater than 7 mmol/L and those who had delayed lactate clearance were more likely to die. It is well known that increased lactate levels are a marker of inadequate tissue oxygenation, and adult studies have shown that lactate clearance may be an important predictor of survival in postcardiotomy ECMO patients (18, 19). There is less data on lactate clearance in neonates undergoing ECMO after cardiac

TABLE 3. Differences in Extracorporeal Membrane Oxygenation Support and Complications Amongst Survivors and Nonsurvivors

Variable	Survivors (*n* = 42)	Nonsurvivors (*n* = 42)	*p*
Cannulation location			0.053
Procedural suite	8	16	
Cardiac ICU	34	26	
Open chest cannulation, *n* (%)	41 (98)	41 (98)	1
Left atrial decompression, *n* (%)	2 (5)	2 (2)	1
ECMO flow (mL/kg/min)			
4 hr	410 (300–500)	390 (308–485)	0.72
24 hr	425 (350–505)	495 (290–500)	0.28
Ventilatory support on ECMO			
Type[a], *n* (%)			0.5
Conventional[a]	35	39 (95)	
High-frequency oscillatory ventilation[a]	0	2 (5)	
Mean airway pressure on ECMO[a]	8 (7–9)	8 (7–9)	0.91
Fio_2	0.3 (0.3–0.4)	0.4 (0.2–0.4)	0.92
Inhaled nitric oxide use on ECMO, *n* (%)	5 (12)	6 (14)	0.75
Blood gas during ECMO			
pH	7.46 (7.43–7.49)	7.47 (7.43–7.50)	0.64
$Paco_2$ (mm Hg)	44 (40–48)	49 (44–54)	0.004
Pao_2 (mm Hg)	135 (79–185)	174 (118–202)	0.09
Standardized Hco_3 (mmol/L)	32 (30–35)	32 (27–33)	0.3
$Pco_2 \geq 51$, *n* (%)	28 (67)	36 (86)	0.04
Inotropes on ECMO, *n* (%)	28 (67)	39 (93)	0.003
Post-ECMO lactate (mmol/L)	3.4 (2.6–4.8)	4.9 (3.2–9.6)	0.004
Lactate > 7 mmol/L, *n* (%)	3 (7.1)	18 (43)	< 0.001
Time to lactate clearance (hr)[a]	46 (30,75)	74 (42–115)	0.009
Lactate cleared ≤ 72 hr[a], *n* (%)	30 (71)	16 (38)	0.002
Post-ECMO hematology			
Hematocrit (%)	38 (37–41)	40 (36–41)	0.52
WBC (c/mm^3)	5.4 (3.7–7.4)	3.7 (2.7–5.5)	0.01
Platelets (c/mm^3)	147 (102–181)	142 (113–169)	0.84
PRBCs during ECMO (mL)	874 (350–1038)	1828 (608–2690)	0.001
PRBC > 2 L, *n* (%)	4 (10)	17 (41)	0.001
Platelet transfusion (mL)[a]	260 (96–372)	662 (213–939)	< 0.001
Platelet transfusion > 725 mL, *n* (%)	3 (7)	17 (41)	< 0.001
Chest washout procedures, *n* (%)	14 (33)	27 (64)	0.005

(*Continued*)

TABLE 3. (*Continued*). Differences in Extracorporeal Membrane Oxygenation Support and Complications Amongst Survivors and Nonsurvivors

Variable	Survivors ($n = 42$)	Nonsurvivors ($n = 42$)	p
ECMO duration (d)	11 (4–17)	4 (2–5)	< 0.001
ECMO duration > 168 hr, *n* (%)	3 (7)	18 (43)	< 0.001
CNS complication, *n* (%)	7 (17)	14 (33)	0.08
Intracerebral hemorrhage	6 (14)	5 (12)	
Stroke	1 (2)	1 (2)	
Mechanical complications, *n* (%)	16 (38)	25 (59)	0.05
Circuit clots	2 (5)	11 (26)	
Oxygenator failure	0	2 (5)	
Cannula related	1 (2)	3 (7)	
Cannulation/surgical site bleeding, *n* (%)	14 (33)	22 (52)	0.08
Renal failure, *n* (%)	0	16 (38)	< 0.001
Liver failure, *n* (%)	3 (7)	13 (31)	0.005

ECMO = extracorporeal membrane oxygenation, PRBC = packed red blood cell.

[a]Denotes missing data: left atrial decompression, 0–1; ECMO flow at 24 hr, 4; ventilatory support on ECMO type, 8; high-frequency oscillatory ventilation, 8; mean airway pressure, 6; time to lactate clearance, 8; platelet transfusion, 1.

surgery but there are studies that show elevated lactate, both after cardiac surgery and while on ECMO, are associated with increased mortality. Specifically, Charpie et al (20) published that rate of rise of lactate greater than 0.75 mmol/L per hour was associated with poor outcomes in neonates after cardiac surgery. In addition Kumar et al (21) and Polimenakos et al (22) reported that elevated lactate at 24 hours postcannulation was associated with increased mortality in neonates on cardiac ECMO. The increase in mortality associated with elevated lactate in our study population likely represents a tissue oxygen deficit from inadequate oxygen delivery.

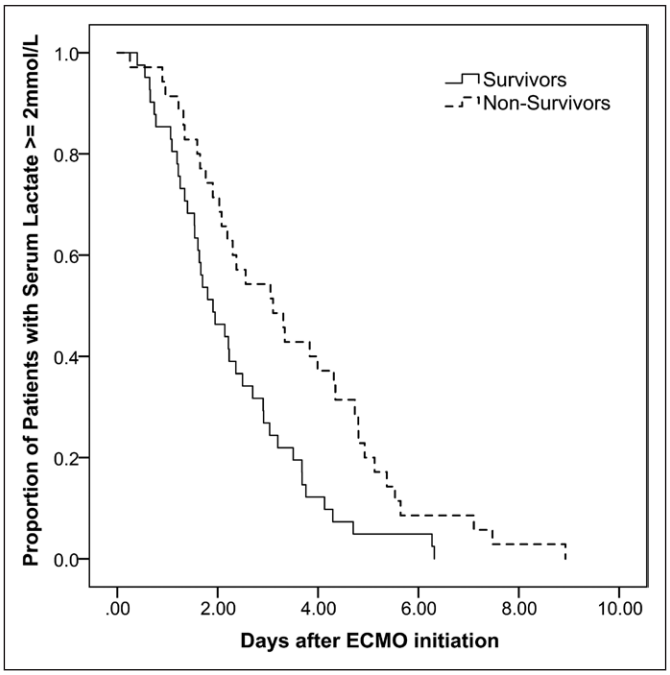

Figure 1. Time to achieve serum lactate less than 2 mmol/L in survivors and nonsurvivors ($p = 0.007$). ECMO = extracorporeal membrane oxygenation.

The potential reasons for inadequate oxygen delivery are numerous and may include inadequate ECMO support, bleeding, residual lesions, and the management of residual lesions. With regards to single ventricle patients with Blalock-Tausig shunts higher flows may be required for tissue oxygenation given that some ECMO flow (i.e., cardiac output) will be distributed to the lungs. Thus an oxygen deficit may persist if flows are not increased to match demands. One way of reducing inadequate distribution is reducing shunt flow. Within our cohort of 25 single ventricle patients palliated with a Blalock-Taussig shunt, shunt flow was reduced by decreasing the diameter of the shunt using a surgical clip in 11 patients (44%). Of these, seven (64%) survived to hospital discharge. While previous studies have shown increasing mortality with mechanical reduction of shunt flow in ECMO patients, we believe that shunt reduction may be considered when lactates remain elevated despite maximal ECMO support (23, 24).

Within our cohort, the use of vasoactive and inotropic agents was associated with increased mortality. One explanation may be that patients requiring vasoactive agents are critically ill and not achieving adequate support with ECMO. Thus, additional means of supporting oxygen delivery were utilized. It should be noted, however, that the inotropic and chronotropic effects of vasoactive agents may lead to incomplete myocardial rest and thus delayed myocardial recovery. There is also some evidence that vasopressors, namely epinephrine, may inherently increase lactate through their effect

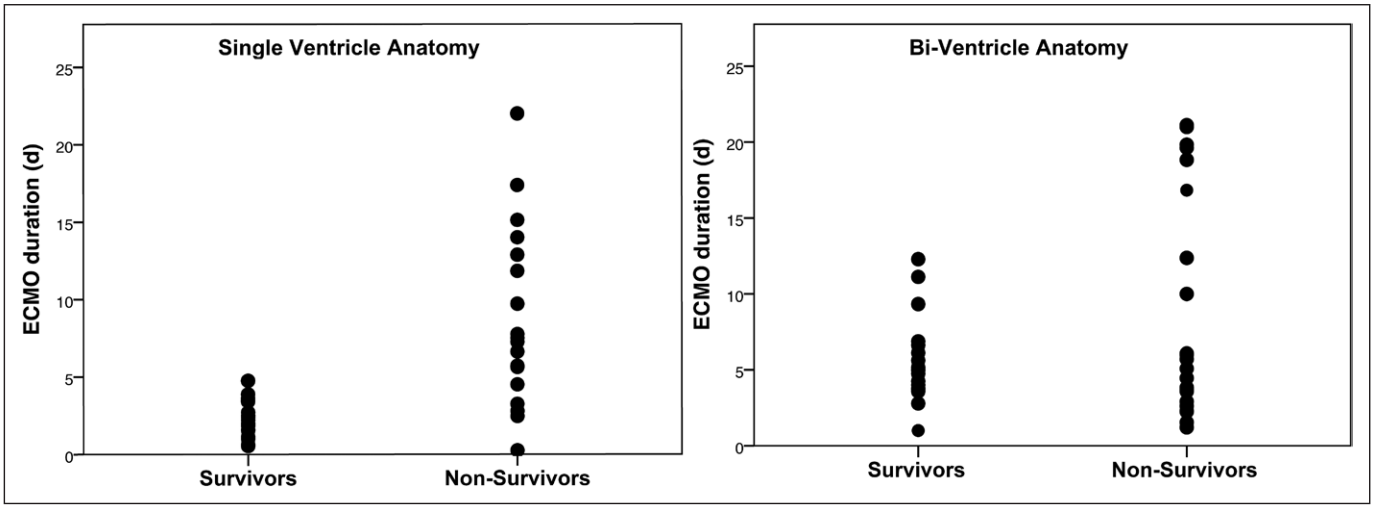

Figure 2. Duration of extracorporeal membrane oxygenation (ECMO) in survivors and nonsurvivors with single- and two-ventricle congenital heart disease.

TABLE 4. Multivariable Model of Factors Associated With Mortality After Neonatal Extracorporeal Membrane Oxygenation

Variable	Hazard Ratio	95% CI	*p*
Unresolved lactate ≥ 72 hr after ECMO[a]	2.77	1.36–5.06	0.002
Gestational age ≤ 36 wk	2.33	1.20–4.52	0.01
Pre-ECMO blood pH ≤ 7.17	2.01	1.03–3.93	0.04
Need for inotrope support on ECMO	3.99	1.18–13.57	0.03
ECMO duration > 168 hr	2.04	1.05–3.99	0.04

ECMO = extracorporeal membrane oxygenation.
[a]Missing = 8 assigned to lactate cleared > 72 hr group.
n = 79; preextracorporeal membrane oxygenation pH had five missing values.

on Na-K-adenosine triphosphatase (25). In addition, vasopressors have also been shown to increase oxygen consumption via their catecholaminergic properties (26). It is unclear if this has deleterious consequences but may serve to perpetuate its use in clinical scenarios. We believe that working to optimize ECMO support, through flow rates, correction of residual lesions, or shunt management, may be more beneficial than the use of vasoactive agents.

Numerous patients in our study had residual lesions. Within the subset of patients with significant lesions, those who received earlier catheterization or cardiac surgery were more likely to survive. This finding was also seen by Agarwal et al (27) who found that earlier detection of residual cardiac lesions, primarily via cardiac catheterization, improved survival in a pediatric postcardiac surgery ECMO population. It is likely that these residual lesions contribute to inadequate cardiac output and increased myocardial oxygen demand and may prolong the use of ECMO. It is well known that prolonged ECMO duration is associated with increased mortality and our data was consistent with prior studies (5–7, 9). No patient within our study group survived after being cannulated greater than 11 days, and no patient with a single ventricle lesion survived more than 5 days. Therefore, it is imperative to investigate early for residual lesions and to act expeditiously upon the finding if feasible. Recently, Callahan et al (28) demonstrated that early diagnostic and interventional catheterization on ECMO was safe. In addition, our data also showed that prudent intervention might be necessary even when successfully weaned off ECMO in order to improve outcomes. Of note, while earlier cannulation to ECMO has been shown in some studies to improve survival, our data showed no difference between cannulation in the procedural suite and cannulation in the cardiac ICU (29, 30)

It is well known that mortality on ECMO is related to the complications inherent to the modality and the illness severity in patients. Our data demonstrate that hepatic failure, neurologic issues, bleeding complications, renal failure, increased blood product use, and mechanical complications were all associated with worse outcomes (2, 3, 7, 10, 13, 21). Notably in our cohort, all patients with renal failure died. Renal failure during ECMO has been shown to be a risk factor for mortality in multiple studies. It is possible that inadequate ECMO support may play a role in renal ischemia and eventually injury emphasizing the need to strive to provide adequate ECMO support so that tissue oxygen delivery is maintained while awaiting cardiac recovery. As shown in previous studies, there was also decreased survival in the premature neonates undergoing

TABLE 5. Cardiac Catheterization and Interventional Procedures in the Study Cohort and in Those With Residual Abnormalities

Variable	Survivors (*n* = 42)	Nonsurvivors (*n* = 42)	*p*
All patients			
Any procedure, *n* (%)	32 (76)	33 (79)	0.8
During ECMO, *n* (%)	24 (57)	31 (74)	0.1
Catheterization	17	14	
Surgery	1	3	
Both	6	14	
After ECMO, *n* (%)	17 (41)	13 (31)	0.4
Catheterization	9	7	
Surgery	3	1	
Both	5	5	
Technical Performance Score 2, 3 categories			
Any procedure, *n* (%)	27 (79)	30 (83)	0.7
During ECMO, *n* (%)	21 (60)	27 (75)	0.2
Catheterization	15	9	
Surgery	1	3	
Both	4	15	
After ECMO, *n* (%)	16 (46)	11 (31)	0.2
Catheterization	8	6	
Surgery	3	1	
Both	5	4	
Days to procedure[a]	1 (0–2)	2 (1–5)	0.02

ECMO = extracorporeal membrane oxygenation.
[a]Median days to procedure, followed by interquartile ranges in parenthesis.

ECMO (4). Given the progression of cardiac surgery and the ability to perform surgery on smaller neonates, further studies should be undertaken to help resolve this issue.

Finally, we found no survivors among patients with genetic abnormalities. It should be noted, however, that Cashen et al (31) demonstrated that patients with trisomy 21 had similar outcomes as those without trisomy 21. Thus patients with genetic abnormalities should not be categorically excluded from ECMO support, but further work is necessary to investigate this important question.

LIMITATIONS

The limitations of this article include those inherent to a retrospective review, including missing data and ascertainment errors. In addition, the population within our study is small and, while there were several significant variables identified, a larger sample size may reveal some important clinical issues missed by our study and may also deemphasize others we found significant. Specific to our lactate analysis, it should be noted that there were eight total patients who died prior to clearing of lactate. These patients were added in with patients who did not clear lactate prior to 72 hours for purposes of analysis. This could contribute to selection bias. We also used TPSs as a way to standardize residual lesions in our patients. While we believe this is an appropriate way to help weigh various postoperative residua, we also realize the score has not been validated in a neonatal ECMO population. In addition, due to the retrospective nature of this analysis, we could not capture indications for intervention procedures, differences in medical decision making, ECMO management or use of multiple ECMO runs. Despite these issues, the strength of this study is its homogenous population and single center experience, which may control for practice variability. Thus, this study provides good input into the neonatal postcardiac surgery ECMO population.

CONCLUSION

In this cohort of 84 neonates cannulated to ECMO after cardiac surgery, we found a survival to discharge of 50%. Presence of

residual lesions and increased time to correction of these residual was associated with poorer outcomes. In addition, persistently elevated lactate, a potential marker of inadequate oxygen delivery, and increased ECMO duration were strong predictors of mortality. Our data suggest that ensuring adequate ECMO support and early intervention on residual lesions early may improve outcomes.

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