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Extracorporeal Membrane Oxygenation in Single Ventricle Lesions Palliated Via the Hybrid Approach

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Abstract

Background: Describing outcomes for children with hypoplastic left heart syndrome (HLHS) undergoing hybrid palliation (pulmonary artery band and stent placement in the patent ductus arteriosus) requiring extracorporeal membrane oxygenation (ECMO) support for cardiorespiratory failure. **Methods:** We reviewed the Extracorporeal Life Support Organization database for all patients with a diagnosis of an HLHS undergoing hybrid stage 1 palliation supported with ECMO and those patients with hybrid palliation supported with ECMO after comprehensive stage 2 palliation. Patients were identified using a combination of *International Classification of Diseases, Ninth Revision* and registry diagnosis and procedure codes. We report survival to hospital discharge and ECMO complications. **Results:** We identified 44 patients with HLHS requiring ECMO following stage 1 hybrid approach. Median age at cannulation was 13.5 days. Only 16% survived to hospital discharge. In all, 20 (50%) patients had a cardiac arrest prior to going onto ECMO and for 3 (19%) patients, ECMO was initiated during cardiopulmonary resuscitation. **Conclusions:** Overall survival for ECMO support in patients with HLHS palliated via the hybrid approach is very poor (16%) and is worse than 31% survival reported for ECMO after conventional stage 1 palliation. The reasons for these poor outcomes require further investigation.

Keywords
ECMO, HLHS, hybrid palliation, stage 1 Norwood

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Introduction

Extracorporeal membrane oxygenation (ECMO) is increasingly being used to temporarily support patients with single ventricle congenital heart disease.[1] A recent analysis of the Extracorporeal Life Support Organization (ELSO) data registry reported a survival rate of 31% for children supported with ECMO following stage 1 palliation in children with hypoplastic left heart syndrome (HLHS).[2] Children with HLHS require staged palliation to help separate systemic and pulmonary circulation. Traditional staged palliation of HLHS consists of three steps: the first, Norwood operation undertaken in the newborn period, followed by the bidirectional Glenn operation at four to six months of age, and the Fontan operation usually two to four years of age. The most common approach for stage 1 palliation for HLHS is the Norwood procedure.[3] The physiological status of the patient following the Norwood operation is often tenuous and associated with 25% mortality.[4] Recently, a new hybrid palliative procedure that included bilateral pulmonary artery (PA) band placement and a ductal stent has been used for initial palliation for patients thought to be at higher risk of mortality with the traditional Norwood operation.[5,6] Survival following the hybrid approach is now reported between 80% and 97%.[6-8] Furthermore, the hybrid procedure is also used for other single ventricle lesions than HLHS, such as unbalanced atrioventricular septal defects,[9] borderline left ventricle lesions,[10] and interrupted aortic arch.[11]

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Abbreviations and Acronyms

CNS	central nervous system
CPT	Common Procedural Terminology coding
CPR	cardio pulmonary resuscitation
ECMO	extracorporeal membrane oxygenation
ECPR	extracorporeal cardio pulmonary resuscitation
ELSO	Extracorporeal Life Support Organization
HLHS	hypoplastic left heart syndrome
ICD-9	*International Classification of Diseases, Ninth Revision*
PA	pulmonary artery
PAB	pulmonary artery banding

Potential advantages of hybrid palliation include the avoidance of morbidity of cardiopulmonary bypass for the procedure, thereby improving clinical outcomes.[12] However, there are potential disadvantages of the hybrid procedure, including the unrepaired hypoplastic aortic arch, which carries the risk of malperfusion of the aortic arch with obstruction of the ductus (retrograde coarctation) resulting in both systemic and coronary ischemia, restriction of an intra-atrial communication requiring reintervention, mechanical distortion of the branch PAs, and significantly complicated second-stage palliation.[9,12]

Because the aortic arch remains unrepaired in hybrid palliation, providing adequate ECMO flow through an unrepaired aortic arch could be technically challenging. We hypothesized that ECMO outcome for patients with HLHS palliated using the hybrid approach might be poor. The purpose of this present study is to describe the use and outcome of ECMO in infants with HLHS palliated via the hybrid approach for single-ventricle congenital heart disease using multicenter data reported to the ELSO data registry.

Patients and Methods

Data for purposes of this analysis were obtained from the ECMO registry of the ELSO. Data are reported to this registry by 230 US and international centers.[1] The registry contains demographics, *International Classification of Diseases*, *Ninth Revision* (*ICD-9*) diagnosis codes, procedural information (using Common Procedural Terminology coding [CPT]), pre-ECMO status, ECMO indication, ECMO support details, complications, and outcomes.

Selection of Study Patients

The registry does not use a specific code to identify patients undergoing the hybrid procedure nor is there a CPT. Therefore, we included all patients who reported to the ELSO registry with a primary admission diagnosis of HLHS (*ICD-9*, code 746.7; or ELSO registry code 1700-1800) and a CPT code for PA banding (PAB; 33690). The review board of the Leiden University Medical Center waived the need for approval to conduct this research based on the anonymous nature of ELSO data.

Definitions

Duration of mechanical ventilation before ECMO included duration of ventilation from tracheal intubation to initiation of ECMO and covered pre- and postoperative periods. Pre-ECMO arrest was defined as a cardiac arrest at any time prior to initiation of ECMO and did not include extracorporeal cardiopulmonary resuscitation (ECPR), which was defined as ECMO cannulation with cardiopulmonary resuscitation (CPR). Complications were categorized using complication codes created by ELSO.[13] Central cannulation was defined as use of the right atrium and/or the aorta.

The specifics of the ductal stent (eg, timing of placement, size, and position) were not collected by ELSO and were not available for analysis. Survival was defined as survival to hospital discharge to home or to another institution.

Statistical Analysis

All data were compared between survivors and nonsurvivors using descriptive statistics. The Kolmogorov-Smirnov test was used to test normal distribution. Continuous data were compared using the Mann-Whitney *U* test and the chi-square test was used for categorical data. When the expected frequencies were <5, the Fisher exact test was used. All data are presented as mean with confidence intervals when normally distributed. Data not normally distributed are presented as the median with interquartile ranges (25th-75th percentile). The data were analyzed using SPSS, version 20.0 (SPSS, Chicago, Illinois).

Results

Extracorporeal Membrane Oxygenation for Hybrid Stage-1 Palliation

Between January 2002 and December 2011, 44 patients undergoing the hybrid operation needed ECMO support and could be identified from the ECMO database based on our extraction criteria. Median age at cannulation was 13.5 days (interquartile range, 3.3-32.8), with a median weight of 3.2 kg (interquartile range, 2.7-3.6). All were supported with venoarterial ECMO. In all, 20 (50%) patients had had a cardiac arrest prior to ECMO use and 3 (18.8%) had ECPR. Indications were low-cardiac output in 33 (91%) of 44 and miscellaneous indications in 10 (22.7%) of 44. Respiratory failure was not reported as an indication for ECMO in any patient. We have not further analyzed indications as they are not mutually exclusive and we might bias results.

In all, 16 (36%) patients were peripherally cannulated through the neck vessels (right internal jugular vein and right common carotid artery) and 27 (62%) patients were centrally cannulated (right atrium and aorta or PA), and for 1 (2%) patient cannula information was missing from the database.

A total of 22 (50%) patients were weaned from ECMO and 7 (16%) survived to hospital discharge. The most common complications were the need for inotropes during

Table 1. Demographic and pre-ECMO Data in Survivors Versus Nonsurvivors.

General Data Subgroup HLHS Cardiac Addendum	Total (n = 44)	Nonsurvivors (n = 37)	Survivors (n = 7)	*P*
Age, days	13.5 (3.3-32.8)	13 (3.5-33.5)	19 (2-34)	.83
Duration ECMO median, days	178 (80-286)	183 (100-294)	124 (61-193)	.30
Weight, kg	3.2 (2.74-3.59)	3.2 (2.8-3.5)	4.4 (2.9-5.75)	.85
Pre-ECLS arrest	20 (45.5%)	15 (40.5%)	5 (71.4%)	.13
ECPR	3 (18.8%)	0	3 (37.5%)	.2
Fio_2 (SD)	57.5 (34)	60 (34.5)	45.6 (34.5)	.41
Peak Insp pressure, cm H_2O	25.3 (5.5)	25.5 (5.9)	24.6 (3.6)	.76
PEEP, cm H_2O	5.4 (1.4)	5.5 (1.5)	4.8 (0.5)	.33
Rate, /min	27 (7.5)	27 (7.7)	26 (6.9)	.87
MAP, cm H_2O	11.5 (3.6)	11.7 (3.7)	10.8 (3.8)	.65
pH	7.18 (0.15)	7.16 (0.16)	7.23 (0.12)	.32
Pco_2, mm Hg	52 (22.6)	53.9 (24.5)	44.6 (10.0)	.33
Po_2, mm Hg	44.2 (42.9)	35.9 (17.6)	78.7 (87.1)	.24
HCO_3^-	19.8 (5.8)	20.1 (5.9)	18.7 (5.2)	.57
Sao_2 (%)	61.1 (25.5)	57.5 (26.5)	75.4 (14.6)	.09
Syst BP, mm Hg	54 (21)	54 (22)	58 (20)	.71
Diast BP, mmHg	31 (14)	32 (15)	26 (8)	.43
Mean BP, mm Hg	40 (18)	40 (18)	37 (4)	.82
Chest cannulation	27	21	6	.17

Abbreviations: BP, blood pressure; diast, diastolic; ECMO, extracorporeal membrane oxygenation; ECLS, extracorporeal cardiopulmonary support; ECPR, extracorporeal cardio pulmonary resuscitation; HLHS, hypoplastic left heart syndrome; Insp, inspiratory; PEEP, positive end expiratory pressure; SD, standard deviation; syst, systolic; MAP, mean airway pressure.

Table 2. Complication Data in Survivors Versus Nonsurvivors.

Complications	Total (n = 44)	Dead (n = 37)	Alive (n = 7)	*P* (Chi-square)
Clot in ECMO circuit	15 (34.1%)	14 (37.8%)	1 (14.3%)	.39
Bleeding: anywhere	17 (38.6%)	15 (40.5%)	2 (28.6%)	.69
Hemolysis	10 (22.7%)	9 (24.3%)	1 (14.3%)	1.00
Diffuse intravascular coagulation	6 (13.6%)	6 (16.2%)	0	.57
CNS hemorrhage	12 (27.3%)	12 (32.4%)	0	.16
CNS: any complication	15 (34.1%)	15 (40.5%)	0	.08
Renal failure	24 (54.5%)	21 (56.8%)	3 (42.9%)	.68
Inotropes on ECLS	28 (63.6%)	23 (62.2%)	5 (71.4%)	1.00
Myocardial stun	5 (11.4%)	5 (13.5%)	0	.57
Arrhythmia	5 (11.4%)	4 (10.8%)	1 (14.3%)	1.00
Infection (culture proven)	7 (15.9%)	7 (18.9%)	0	.58
Metabolic: pH < 7.20	8 (18.2%)	8 (21.6%)	0	.32

Abbreviations: CNS: central nervous system; ECMO, extracorporeal membrane oxygenation; ECLS, extracorporeal cardiopulmonary support.

ECMO (63.6%), renal failure (54.5%), bleeding (38.6%), clot in ECMO circuit (34.1%), and neurological (34.1%). There were no statistically significant differences in demographic, pre-ECMO, or complication data between survivors and nonsurvivors while on ECMO (Tables 1 and 2). Peripheral oxygen saturation was lower before initiating ECMO in nonsurvivors (57.5%; standard deviation [SD] 26.5) compared to survivors (75.4%; SD 14.6) and approached statistical significance ($P = .09$).

Comment

In 44 patients who were supported with ECMO after hybrid palliation, the overall survival to discharge was only 16%. This survival rate is clearly much lower than the recently reported survival rate of 31% for all neonates with HLHS supported with ECMO in the postoperative period after undergoing the conventional stage-1 palliation operation.[2]

The reasons for these poor outcomes are unclear from our data but they show that providing rescue ECMO in these patients may be challenging.

We identified 20 (50%) patients who had had a cardiac arrest prior to ECMO use, which is higher than the 32% reported by Sherwin et al.[2] Need for CPR prior to ECMO may be one reason for poor survival in the hybrid patients. Unfortunately, the ELSO database does not give information about the timing of the cardiac arrest in relation to the moment of going on to ECMO and therefore a causative relation cannot be ascertained. Three (18.8%) patients who underwent hybrid ECMO were receiving CPR while going onto ECMO (ECPR),

which is similar to the 14% in the group, reported by Sherwin et al.[2] Cardiac arrest or ECPR could not be statistically identified as risk factors for mortality in our group because of the low number of survivors. There were, however, more pre-ECMO cardiac arrests among the nonsurvivors (15 of 20 = 75%) compared to the survivors (5 of 20 = 25%). The only data available from the ELSO database concerning severity of illness prior to ECMO were arterial blood gas analysis and inotropic support, neither were associated with mortality. We have no data available whether ductal stents caused retrograde aortic arch obstruction as a possible cause for cardiac arrest prior to ECMO support.

The only risk factor for mortality that approached statistical significance was a lower peripheral oxygen saturation at the time of ECMO initiation of 57% (SD 26.5) in nonsurvivors compared to 75% (SD 14.6) in the survivors ($P = .07$). Hypoxemia in patients with single ventricle supported with ECMO has been previously shown to have a favorable outcome (81% survival) when compared to hypotension or low-cardiac output (29% survival) because hypoxemia was often due to an obstructed systemic to pulmonary shunt, which can relatively easily be addressed.[14] Other causes for hypoxemia in Norwood patients include poor cardiac output, aortic valve regurgitation, or PA thrombosis which can also be present in hybrid patients. Another cause of hypoxemia in hybrid patients might be due to a restriction of pulmonary blood flow from tight PA band. The reason for hypoxia cannot be as easily addressed in our study as these details were not collected by the ELSO registry. Therefore, poor survival in hybrid patients who need ECMO support needs to be further investigated. Interestingly, hypoxemia was not reported in these patients as an indication for initiating ECMO. We have no data available whether PA bands required tightening during ECMO support.

Low-cardiac output as an indication for ECMO in this study was 83% and is slightly higher than the 69% reported by Sherwin et al[2] and may be due to higher incidence of low-cardiac output and higher pulmonary to systemic blood flow in hybrid patients compared to traditional Norwood patients as shown by Li et al.[15] Low-cardiac output as an indication for ECMO has been shown to be a marker of poor outcome in patients with single ventricle supported with ECMO.[14]

An unrestrictive PAB can also contribute to ventricular volume overload and subsequent ventricular failure[8] and usually presents with high peripheral oxygen saturation. However, we found increased mortality in those with lower oxygen saturation suggesting that either other mechanisms such as lung disease or advanced cardiac failure resulting in poor outcome was present in our group. Unfortunately, pre-ECMO severity of cardiorespiratory dysfunction could not be addressed using the ELSO registry data. It is also very interesting to note that there is a considerable mortality following recovery of cardiovascular dysfunction and successful weaning off ECMO (50% survival to decannulation) with only 16% surviving to discharge. This high mortality despite successful ECMO weaning (15 of 22 = 32%) is comparable to 28% mortality following weaning after traditional stage 1 and requires further investigation.[2]

Some technical issues related to the conduct of ECMO may theoretically help explain poor outcomes for hybrid stage 1 palliation patients supported with ECMO such as the challenges faced while cannulating patients with aortic arch obstruction for ECMO. The aortic arch has to be perfused through the ductal stent and thus positioning the arterial cannula to provide adequate systemic perfusion may be challenging. Furthermore, the retrograde perfusion of the coronary arteries may be inadequate, resulting in poor myocardial recovery. Finally, because the aortic cannula is placed in the base of the PA, the tip may be placed close to the pulmonary end of the ductus which can create significant run off of flow to the pulmonary circulation if the PA bands are not perfectly tightened. This pulmonary runoff would need to be compensated for by using higher ECMO flows to achieve adequate systemic circulation or by other means of restricting pulmonary blood flow, such as increasing positive end-expiratory pressure or even tightening both PA bands. In conventional Norwood patients supported with ECMO, pulmonary overcirculation is compensated by using higher flows, and need for restricting pulmonary blood flow by clipping the Blalock–Taussig shunt has been shown to decrease ECMO survival.[16,17] In our study, however, mortality was not influenced by cannulation site, $P = .17$ (see Table 1); this could be due to small sample size and needs to be further investigated. Duration of ECMO support in the hybrid patients tended to be longer in nonsurvivors (183 [100-294]) compared to survivors (124 hours [61-193]) but was not statistically different. Overall, it was longer than reported for all patients with single ventricle supported with ECMO, as previously reported.[2]

In this study, there were no significant differences in complications between survivors and nonsurvivors (Table 2). Compared to the ELSO database[18] and the specific report in single ventricle ECMO, we did identify more renal insufficiency (54.5%), central nervous system (CNS) hemorrhage (27.3%), and hemolysis (22.7%).[2] Whether this higher complication rate was due to the longer duration of ECMO support and whether it attributed to mortality remain speculative. None of the survivors had a CNS complication, a myocardial stunning, or a culture-proven infection but the numbers are too small to make any statistical comments. Other common complications were the need for inotropes during ECMO (63.6%) and bleeding (38.6%) comparable to previous reports and as reported by the ELSO.[18]

A major limitation of this study is that important variables such as pre-ECMO severity of illness, timing of ECMO in relation to the hybrid procedure, and other variables that may influence outcome such as HLHS subtype, operation, and physiology at the time of ECMO cannulation, and anticoagulation strategies were not collected by the ELSO database and therefore not available for analysis. Also, the ELSO definition of survival includes both survival to hospital discharge and survival to transfer to another institution. Therefore, we may have underestimated mortality. Other limitations are that it is retrospective in nature,

that we are reliant on different centers for entering the data to the database correctly, and most importantly that there is no specific diagnosis code (CPT or ELSO) for the hybrid procedure and therefore we may have either missed other hybrid patients or included patients with HLHS managed with PAB and prolonged prostaglandin infusion making our mortality estimate inadequate. For future reference and research, it is therefore essential that a specific hybrid procedure code or ductal stenting will be appointed. Furthermore, we have no data regarding long-term neurological outcome and future research and follow-up will need to address this essential topic in both hybrid and traditional Norwood patients requiring ECMO.

Conclusions

Patients with HLHS, palliated via the hybrid approach needing ECMO support following stage-1 palliation, have a very low survival rate of 16%. No predictors of mortality could be identified. Further research is needed to improve our understanding of factors associated with mortality in this high-risk population. Creating unique codes for identifying patients supported with ECMO after undergoing hybrid palliation accurately can help improve data capture and better estimate outcomes in this population

Authors' Note

The authors had full control of the design of the study, methods used, outcome parameters, analysis of data, and production of the written report. These data were presented at the first Euro-ELSO conference, May 2012, Rome, Italy.

Declaration of Conflicting Interests

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