ECMO in Neonates with Congenital Diaphragmatic Hernia: The Experience of a Portuguese ECMO Referral Center

ECMO em Recém-nascidos com Hérnia Diafragmática Congénita: A Experiência de um Centro de Referência de ECMO em Portugal

ARTIGO ORIGINAL

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ABSTRACT

Introduction: The use of extracorporeal membrane oxygenation (ECMO) is considered by many authors as one of the most important technological advances in the care of newborns with congenital diaphragmatic hernia. The main objective of this study was to report the experience of a Portuguese ECMO center in the treatment of congenital diaphragmatic hernia.

Material and Methods: Descriptive retrospective study of newborns with congenital diaphragmatic hernia requiring ECMO support in a Pediatric Intensive Care Unit from January 2012 to December 2019. Data collection using the *Extracorporeal Life Support Organization* registration and unit data base.

Results: Fourteen newborns were included, all with left congenital diaphragmatic hernia, in a total of 15 venoarterial ECMO cycles. The median gestational age was 38 weeks and the median birth weight was 2.950 kg. Surgical repair was performed before entry into ECMO in six, during in seven and after in one newborn. The average age at placement was 3.3 days and the median cycle duration was 16 days. Prior to ECMO, all newborns had severe hypoxemia and acidosis despite optimized ventilatory support, with nitric oxide and inotropic therapy. After 24 hours on ECMO, there was correction of acidosis, improvement of oxygenation and hemodynamic stability. All cycles presented mechanical complications, the most frequent being the presence of clots in the circuit. The most frequent physiological complications were hemorrhagic and embolic (three newborns suffered an ischemic stroke during the cycle). Five newborns (35.7%) died, all associated with complications (two strokes, two massive bleedings and one accidental decannulation). Chronic lung disease, poor weight gain and psychomotor developmental delay were the most frequent long-term morbidities.

Discussion: Despite technological advances in respiratory care and improved safety of the ECMO technique, the management of these newborns is complex and there are still several open questions, including the appropriate selection of patients, the best approach and time for surgical correction, and the treatment of pulmonary hypertension in the presence of persistent fetal shunts.

Conclusion: Survival rate was higher than reported in 2017 *Extracorporeal Life Support Organization* report (64% *versus* 50%). Mechanical and hemorrhagic complications were very frequent.

Keywords: Extracorporeal Membrane Oxygenation; Hernias, Diaphragmatic, Congenital; Infant, Newborn; Portugal

RESUMO

Introdução: A utilização de oxigenação por membrana extracorporal (ECMO) é considerada por muitos autores como um dos mais importantes avanços tecnológicos nos cuidados de recém-nascidos com hérnia diafragmática congénita. O principal objetivo deste estudo foi reportar a experiência de um centro de oxigenação por membrana extracorporal português no tratamento de hérnia diafragmática congénita.

Material e Métodos: Estudo retrospetivo descritivo dos recém-nascidos com hérnia diafragmática congénita com necessidade de suporte de ECMO, numa unidade de Cuidados Intensivos Pediátricos de janeiro de 2012 a dezembro de 2019. Colheita de dados com recurso ao registo da *Extracorporeal Life Support Organization* e registo da unidade.

Resultados: Incluídos 14 recém-nascidos, todos com hérnia diafragmática congénita esquerda, num total de 15 ciclos de ECMO veno-arterial. Mediana de idade gestacional de 38 semanas e de peso ao nascer de 2,950 kg. A correção cirúrgica foi realizada antes da entrada em ECMO em seis, durante em sete e após ciclo em um caso. A mediana de idade de colocação foi de 3,3 dias e a média de duração do ciclo foi de 16 dias. Previamente à ECMO, todos os recém-nascidos apresentavam hipoxemia e acidose grave apesar de suporte ventilatório otimizado, com terapêutica com oxido nítrico e inotrópicos. Após 24 horas em ECMO, verificou-se correção de acidose, melhoria de oxigenação e estado hemodinâmico. Todos os ciclos apresentaram complicações mecânicas, sendo a mais frequente a presença de coágulos no circuito. As complicações fisiológicas mais frequentes foram as hemorrágicas e embólicas (três recém-nascidos sofreram acidente vascular cerebral isquémico durante o ciclo). Cinco crianças (35,7%) morreram, estando todos os casos associados a complicações (duas com acidente vascular cerebral, duas com hemorragia maciça e uma descanulação acidental). A doença pulmonar crónica, má progressão ponderal e atraso do desenvolvimento psicomotor foram as morbilidades a longo prazo mais frequentes.

Discussão: Apesar dos avanços tecnológicos nos cuidados respiratórios e melhoria da segurança da técnica ECMO, o manuseamento destes recém-nascidos é complexo e existem ainda várias questões em aberto, incluindo a selecção apropriada dos doentes,

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a melhor abordagem e tempo de correcção cirúrgica, e o tratamento da hipertensão pulmonar na presença de shunts fetais persistentes.

Conclusão: A taxa de sobrevivência foi superior à reportada no relatório da *Extracorporeal Life Support Organization* de 2017 (64% *vs* 50%). As complicações mecânicas e hemorrágicas foram muito prevalentes.

Palavras-chave: Hérnias Diafragmáticas Congénitas; Oxigenação por Membrana Extracorporal; Portugal; Recém-Nascido

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is associated with significant morbidity and mortality in the neonatal population, with an incidence of 1 to 3 per 10,000 live births in Europe (data from the EUROCAT Registry of Congenital Anomalies).[1,2] It consists of a defect of the diaphragm that allows herniation of abdominal organs into the thorax, compromising the normal development of the ipsilateral and contralateral lung.

Mortality and morbidity in infants with CDH are mainly related to the combination of pulmonary hypoplasia and pulmonary hypertension, associated with severe respiratory failure within the first hours after birth. Due to pulmonary hypoplasia, there is an impairment of the generation of new vessels (vasculogenesis) and their progressive branching (angiogenesis), with inadequate perfusion of the lung and inability to accommodate the right ventricular output (with right-left shunt). Abnormal pulmonary vascularisation, hypoxaemia, acidosis and ventilator-associated lung injury lead to an increasing risk of developing persistent pulmonary hypertension of the newborn (PPHN), with poorer outcome in premature neonates, with chromosomal anomalies or other malformations. CDH may also be associated with different degrees of hypoplasia and left ventricular dysfunction, usually transient and with recovery after seven to 10 days of life.[3-4]

The postnatal survival rate in tertiary centres has slowly improved due to changes in treatment protocols, with current rates ranging between 70% and 92%.[5,6] Early surgical management of critically ill neonates has been replaced by stabilisation with intensive preoperative support, aimed to prevent lung injury, followed by surgical repair. Significant advances in perinatal care in recent decades have led to improved care of these patients, including the adoption of minimal ventilation parameters and permissive hypercapnia, the availability of inhaled nitric oxide (NO), high frequency oscillatory ventilation (HFOV) and extracorporeal membrane oxygenation (ECMO).[4-6]

The benefits of ECMO in the improvement of survival of severely ill patients with CDH have been described by different studies, specifically its role as rescue therapy and peri-operative stabilisation.[7,8] However, it is worth mentioning that ECMO is associated with significant complications related to the technique itself, which may cause significant morbidity and mortality among survivors.[3]

Only four cases have been described so far in Portugal.[9,10] This study was mainly aimed at the description of the experience of a Portuguese ECMO centre in the treatment of CDH, including ECMO criteria, complications, short and long-term mortality and morbidity.

MATERIAL AND METHODS

This was a descriptive retrospective study of all neonates (age ≤ 28 days) with CDH and requiring ECMO for cardiorespiratory support, admitted to the Paediatric Intensive Care Unit (PICU) (a reference centre for ECMO at the *Centro Hospitalar Universitário Lisboa Norte*) throughout an 8-year period (January 2012 to December 2019).

Data were collected according to the unit's registry and the ELSO (Extracorporeal Life Support Organization) registry, an international organisation for the record of patients who underwent ECMO. The following data were included: demographic characteristics; pre- and neonatal medical history; underlying congenital anomalies; ventilation and pre-ECMO therapies; surgical correction time; pre- and on ECMO haemodynamic and blood gas analysis (BGA); ECMO cycle characteristics; complications, ECMO-related morbidity and mortality.

Preterm delivery was defined as any birth before or up to 37 completed weeks of gestation and term delivery was defined as between 37 and 40 weeks and six days. Anatomical and chromosomal abnormalities were assessed.

Mechanical ventilation was classified as high-frequency oscillatory ventilation (HFOV) or conventional mechanical ventilation. Other pre-ECMO variables were obtained, including the presence of culture-proven infections, mechanical ventilation (median peak inspiratory pressure, positive end-expiratory pressure and mean airway pressure, type and duration of ventilation) and arterial blood gas (pH, PaCO2, PaO2 and SaO2) parameters. Oxygenation index, defined as [mean airway pressure × inspired oxygen fraction (FiO2) × 100 / PaO2] was obtained from the ELSO registry.

The mode of ECMO was classified as veno-arterial (VA) or veno-venous (VV). The number of ECMO cycles has also been obtained.

The complications occurring on ECMO were classified as mechanical or physiological according to the ELSO registry. Mechanical complications included: oxygenator membrane failure; pump failure; circuit breakage; cannula problems (malposition, clot obstruction); gas embolism. Physiological complications included bleeding (into the surgical territory, cannula insertion site, haemopericardium, retroperitoneum, central nervous system (CNS), gastrointestinal and pulmonary); acute kidney injury, defined as serum creatinine > 1.5 mg/dL and/or the need for renal replacement therapy (dialysis or continuous veno-venous haemodiafiltration); CNS injury, including seizures (clinical and/or electrographic evidence), imaging evidence of ischaemic or haemorrhagic brain injury; hydroelectrolytic and metabolic imbalances; cardiac complications, including hypertension, arrhythmia, ischaemia, cardiac tamponade and the use of

inotropic / vasopressor agents; in addition, all other complications, including infections, pneumothorax, haemolysis and pressure ulcers were assessed, in addition to morbidity and mortality.

Long-term follow-up data analysis was carried out, considering all the neonates aged at least one year after the end of the ECMO cycle. Cerebral palsy, blindness, deafness, profound comprehension disorders and epilepsy were considered as major sequelae. The presence and degree of chronic lung disease were defined according to the 2001 NICHD (National Institute of Child Health and Human Development) consensus criteria for bronchopulmonary dysplasia. The presence of psychomotor developmental delay was diagnosed by a paediatrician. Poor weight gain was defined as weight below the 3rd percentile or crossing more than two percentiles in the 2006 World Health Organization growth curves (currently in use in Portugal).

A descriptive statistical analysis using Microsoft Excel© software has been obtained. The primary outcome was pre-discharge death. The study was carried out in accordance

Table 1 – Characteristics of our group of patients with CHD on ECMO

Total number of patients, n	14
Total number of cycles of ECMO, n	15
Male gender, n (%)	10 (71.4)
Antenatal diagnosis, n (%)	13 (92.9)
Left sided CHD, n (%)	14 (100)
Congenital anomalies, n (%)	0
Antenatal approach (endotracheal balloon), n (%)	2 (14.2)
Preterm delivery, n (%)	3 (21.4)
Gestational age, median (range)	38 (35; 40)
Birth weight, gr, median (range)	2,950 (2,255; 4,680)
Type of delivery, n (%)	
Eutocic	4 (28.6)
Dystocic	1 (7.1)
Elective/emergency C-section	4 (28.6)/ 5 (35.7)
Apgar score 1 min/ 5 min, median (P25 - P75)	7 (5 - 9)/ 8 (8 - 9)
Pre-ECMO characteristics	
Pre-ECMO ventilation duration, h, median (range)	79 (16; 473)
< 8 h, n (%)	1 (7.1)
8 h – 48 h, n (%)	6 (42.9)
> 48 h, n (%)	7 (50)
Pre-ECMO therapy, n (%)	
Inotropic/vasopressor perfusion	14 (100)
Inhaled nitric oxide	14 (100)
Other vasodilators	2 (14.3)
Surfactant	4 (28.6)
Bicarbonate perfusion	8 (57.1)
Pre-ECMO cardiac arrest, n (%)	1 (7.1)
Pre-ECMO culture-proven infection, n (%)	2 (14.3)
Surgery, n (%)	
Pre-ECMO	6 (42.9)
Intra ECMO	7 (50)
Post-ECMO	1 (7.1)
Surgical technique, n (%)	
Laparotomy	14 (100)
Prosthetic surgery	7 (50)
ECMO characteristics	
Age at ECMO, days, median (range)	3.3 (0; 20)
VA ECMO mode, n (%)	15 (100)
Transport on ECMO from another centre, n (%)	4 (28.6)
ECMO duration, h, mean ± SD	384 ± 196
< 7 days, n (%)	2 (13.3)
7 - 15 days, n (%)	6 (40)
> 15 days, n (%)	7 (46.7)
ECMO discontinuation, n (%)	4 (28.6)
Due to patient's death or limitation of care	2 (14.3)
Due to technical complications	2 (14.3)
Mortality, n (%)	5 (35.7)
During ECMO	4 (28.6)
Days between ECMO placement and death, median (range)	14 (3; 27)

SD: standard deviation; CHD: congenital diaphragmatic hernia; ECMO: extracorporeal membrane oxygenation; VA: veno-arterial

with the regulations established by the Clinical Research Committee and Ethics Committee of the institution where the study took place. As an observational study involving data confidentiality and privacy, using data from an international platform approved by the Board of Directors of the hospital, the submission for approval by the committees was not considered necessary by the authors.

RESULTS

Sample

A total of 14 neonates with CDH in need of cardiopulmonary support on ECMO were admitted throughout the eight-year study period (15 cycles in total). The characteristics of our group of patients are shown in Table 1.

Different times of surgical repair of CDH were found (seven patients underwent surgery during the ECMO cycle, six before ECMO and one after the ECMO cycle). Laparotomy was used in all cases, with a prosthetic repair in half of the cases.

A 3.3-day median age at the time of cannulation has been found. All neonates had reached maximum therapeutic optimisation before the initiation of ECMO: they presented with hypoxaemia (median oxygenation index 81.8) and severe acidosis despite ventilatory and cardiovascular support, with conventional mechanical ventilation/HFOV with aggressive ventilatory parameters and under 100% inspired oxygen fraction, nitric oxide and inotropic therapy (Tables 1 and 2). One of the patients on ECMO had suffered a previous cardiac arrest, with recovery after a short period of cardiopulmonary resuscitation.

VA ECMO was used in all patients, with drainage through the cannulation of the right internal jugular vein with 8F to 12F Bio-Medicus® cannulae and return through the cannulation of the right primitive carotid artery with 8F to 10F cannulae. The cannulation was performed by surgical technique with debridement and exposure of the vessels.

Mean ± SD of ECMO duration was 384 ± 196 hours (16 days ± 8.2 days), four patients presented with the need for discontinuation of ECMO: two due to technical complications (one with accidental decannulation and one due to pump failure); the other two patients on ECMO have died or discontinuation was decided due to poor outcome, namely due to severe neurological lesions.

Clinical progression of patients on ECMO

The clinical progression of patients on ECMO, represented by the haemodynamic assessment and BGA pre and at 24 hours on ECMO (Table 2), has clearly improved: reduced ventilation parameters to minimum rest ventilator settings, showing a significant improvement in oxygenation; correction of severe acidosis and significantly improved haemodynamic status, with median values of mean blood

Table 2 – Comparison pre- *vs.* 24h on ECMO

	Pre-ECMO	24h on ECMO
Type of ventilation, n (%)		
Conventional	1 (6.7)	12 (80)
High-frequency (HFOV)	14 (93.3)	3 (20)
Ventilation parameters, median (P25 - P75)		
PIP, cmH_2O	27 **(n = 1)**	20 (20 - 21) **(n = 12)**
PEEP, cmH_2O	6 **(n = 1)**	5 **(n = 12)**
MAP, cmH_2O	19.5 (18 - 21) **(n = 14)**	11 (10 - 12) **(n = 3)**
Delta P	41 (38 - 45) **(n = 14)**	23 **(n = 3)**
FiO_2, %	100	40
BGA, median (P25 - P75)		
pH	7.05 (6.87 - 7.18)	7.37 (7.34 - 7.385)
$PaCO_2$, mmHg	74 (62.4 - 95.0)	39 (37.2 - 47.0)
PaO_2, mmHg	25.7 (19.0 - 35.0) **(n = 11)**	78 (46.5 - 80.0) **(n = 10)**
SaO_2, %	53 (46.5 - 69.5) **(n = 13)**	98 (46.5 - 80.0)
Oxygenation index	81.8 (54.3 - 100.0) **(n = 11)**	5.9 (5.5 - 10.4) **(n = 10)**
SvO_2, %	41 (34.5 - 53.5) **(n = 4)**	84 (78 - 86)
Haemodynamic parameters, median (P25 - P75)		
Systolic BP, mmHg	42 (39.0 - 54.0)	66 (54.5 - 74.0)
Diastolic BP, mmHg	30 (20.5 - 32.0)	40 (34.0 - 53.0)
Mean BP, mmHg	35 (30.0 - 39.0)	45 (42.5 - 59.0)

Data regarding the 15 cycles, although not all data are available.

CDH: congenital diaphragmatic hernia; ECMO: extracorporeal membrane oxygenation; PIP: peak inspiratory pressure; PEEP: positive end-expiratory pressure; MAP: mean airway pressure; FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of oxygen in arterial blood; SaO_2: arterial oxygen saturation; SvO_2: saturation of venous blood returning to the venae cavae; FiO_2: fraction of inspired oxygen; BGA: blood gas analysis; BP: blood pressure

pressure progressing from 35 to 45 mmHg after 24 hours on ECMO. The ECMO pump output ranged between 0.26 and 0.45 L/min 24 hours after ECMO was started.

Complications related to the use of ECMO

Complications related to the use of ECMO are shown in Table 3. Mechanical complications have been found in all ECMO cycles, mostly related to the presence of clots in the circuit, leading to multiple circuit changes and frequent clot removal. Haemorrhagic complications, culture-proven infections, the development of pneumothorax and chylothorax were mostly found. CNS complications are worth mentioning, namely the presence of ischaemic stroke which was described in three patients, associated to high mortality and morbidity (two of these patients died in this sequence and the other presented with spastic tetraparesis).

Mortality and morbidity

Five patients died, including the four patients requiring ECMO discontinuation. A median time of 14 days (range 3-27) was found between the initiation of ECMO support and patient's death. The patient who required two cycles of ECMO survived.

The five deaths were all related to haemorrhagic or embolic complications: one patient presented with ischaemic stroke after undergoing an emergent Rashkind septostomy for left cavity dilation, secondary to ECMO flow in the aorta; one patient presented with stroke after an episode of sudden circuit interruption, with the need for resuscitation manoeuvres; one patient died from massive brain, lung and gastrointestinal bleeding after surgical correction of CDH during the ECMO cycle; one patient died from massive bleeding through abdominal and chest drain, with the need for discontinuation as anticoagulation was not possible; finally, one patient died from accidental decannulation after arterial cannula replacement.

When comparing survivors with non-survivors (Table 4), even considering the small size of our group of patients, preventing from any statistical treatment, it is clear that mostly preterm neonates and with lower birth weight did not survive.

All nine surviving patients were followed-up by intensive care, development, paediatric surgery and paediatric respiratory teams, for an average of 4.8 years (range 1-8 years). Long-term morbidities mostly included poor weight gain, psychomotor developmental delay and moderate to severe bronchopulmonary dysplasia (Table 5). One patient developed severe and irreversible neurological complications with spastic tetraparesis and epilepsy.

Table 3 – ECMO-related complications

Mechanical, n (%)	
Clotting of the circuit	15 (100.0)
Other	10 (66.7)
Pump failure	2 (13.3)
Air in circuit	1 (6.7)
Oxygenator dysfunction	1 (6.7)
Accidental decannulation	1 (6.7)
Physiological, n (%)	
Renal	
Acute kidney injury	1 (6.7)
Renal replacement therapy	1 (6.7)
Haematologic	
Disseminated intravascular coagulation	4 (26.7)
Thrombolysis	1 (6.7)
Haemorrhagic	
Surgical site bleeding	7 (46.7)
Cannulation site bleeding	5 (33.3)
Gastrointestinal	4 (26.7)
Haemothorax	2 (13.3)
Other	2 (13.3)
Pulmonary	1 (6.7)
Cardiac	
Pericardial effusion	1 (6.7)
Cardiopulmonary resuscitation during ECMO	1 (6.7)
Myocardial stunning	1 (6.7)
Metabolic	
Hyperbilirubinaemia	3 (20.0)
CNS	
Ischaemic stroke	3 (20.0)
Haemorrhagic	2 (13.3)
Seizures	1 (6.7)
Others	
Culture-proven infection	5 (33.3)
Pneumothorax (treatment required)	2 (13.3)
Chylothorax	2 (13.3)

ECMO: extracorporeal membrane oxygenation; CNS: central nervous system

DISCUSSION

The use of ECMO in patients with CDH

Neonates with CDH often present with severe cardiorespiratory failure within the immediate postnatal period and the first weeks of life, which is the most common indication for ECMO due to neonatal respiratory failure and corresponding to approximately 28% of all indications for ECMO in the neonatal period.[7] Therefore, antenatal referral to an ECMO centre is crucial, particularly regarding the most severe cases, in order to avoid inter-hospital transport of patients on ECMO, should this technique be necessary.

Although survival rates above 70% are available for infants with CDH, a survival rate of around 50% has been described in patients requiring ECMO, which has remained unchanged over the past few decades. A 64% survival rate has been found in our group of neonates with CDH on ECMO, higher than the 50% rate described in the latest ELSO Registry Report assessing separately patients with CDH (data for 2017 regarding 7,889 cycles of ECMO in patients with CDH).[7] This difficult improvement in survival rate may be explained in part by the selection of patients, since only neonates with the most severe conditions who are not candidates for early surgical repair or with severe pulmonary hypertension will be candidates for ECMO.[6,7,11,12]

The rationale for using ECMO in these neonates regards the fact that pulmonary vascular reactivity and pulmonary hypertension will spontaneously improve within the

Table 4 – Survivors *vs.* non-survivors

	Survivors (n = 9)	**Non-survivors** (n = 5)
Pre-ECMO factors		
Preterm delivery, n	0	3
Gestational age, median (range)	39 (37; 40)	36 (36; 39)
Birth weight, gr, median (range)	3,050 (2,340; 4,680)	2,725 (2,255; 3,200)
Duration of pre-ECMO ventilation, h, median (range)	55.5 (16; 473)	79 (17; 219)
Pre-ECMO cardiac arrest, n	1	0
Pre-ECMO culture-proven infection, n	2	0
Surgery, n		
Pre-ECMO	4	2
During ECMO	4	3
Post-ECMO	1	0
Prosthetic	4	3
Pre-ECMO BGA, median (P25 - P75)		
pH	6.89 (6.82 - 7.05)	7.26 (7.13 - 7.3)
Oxygenation index	85.5 (40.0 - 100.9) **(n = 6)**	80.8 (55.7 - 149.2)
Mean BP, mmHg, median (P25 - P75)	34.5 (28.0 - 38.0)	36 (29.0 - 49.5)
ECMO-related factors		
Age when ECMO was started, days, median (range)	2 (0; 20)	3 (1; 9)
ECMO duration, h, median (range)	363 (75; 737)	356 (53; 524)
ECMO discontinuation, n	0	4

CDH: congenital diaphragmatic hernia; ECMO: extracorporeal membrane oxygenation; BGA: blood gas analysis; BP: blood pressure

first weeks of life and, even though pulmonary hypoplasia remains, the cardiopulmonary support provided by ECMO may be crucial beyond this period.

However, the approach to neonates with CDH on ECMO is a challenging task and there are still several open questions despite significant research, including an appropriate patient selection, the best timing for surgical repair and the treatment of pulmonary hypertension in the presence of persistent foetal shunts. Pulmonary hypertension, respiratory failure or complications such as bleeding or embolism are the leading causes of death on ECMO.

Several studies have identified risk factors associated with an increased mortality of infants with CDH on ECMO, including low birth weight, presence of acidaemia and/or refractory hypoxemia. Contraindications for ECMO include irreversible and pre-existing pathologies that significantly limit the quality of life, such as the presence of severe CNS lesions.[3-5] Neonate weight and the need for systemic anticoagulation are the main technical limitations, even though mostly relative contraindications exist and any case should always be discussed with an ECMO centre.

Table 5 – Long-term follow-up of survivors (n = 8)

Left pulmonary hypoplasia	8
Chronic pulmonary disease	7
Abnormal weight gain	6
Neuropsychomotor developmental delay	3
Cerebral palsy	1
Autism spectrum disorder	1
Hyperactivity and attention deficit disorder	1
Epilepsy	1
Complication-free survival	6

Data regarding only eight of the nine surviving patients, due to insufficient follow-up time of one case

Although there are no uniform criteria for the initiation of ECMO, neonates weighing more than 2 kg and over 34 weeks of gestational age, with no other life-limiting abnormalities are mostly considered for ECMO, after a maximum optimisation of ventilatory and cardiovascular support has been achieved. The 2015 CDH EURO Consortium Consensus recommendations are followed in our unit and are shown in Table 6.

Current recommendations for neonates with CDH are in favour of minimising barotrauma by limiting peak airway pressure and suggest that early initiation of ECMO in neonates in whom this strategy fails may prevent lung injury.[6,7]

Mode of ECMO in patients with CDH

Although most infants with CDH have been managed with veno-arterial (VA) ECMO, some studies have suggested that veno-venous (VV) ECMO could be equally effective.[6,8,13]

Many patients with CDH require ECMO due to the cardiovascular compromise related to right heart overload secondary to severe pulmonary hypertension and, in some cases, relative ventricular hypoplasia with pulmonary ve-

Table 6 – CDH EURO Consensus Consortium – 2015 Update of ECMO criteria[6]

• Inability to maintain preductal saturations > 85% or postductal saturations > 70%;
• Increased $PaCO_2$ and respiratory acidosis with pH < 7.15 despite optimisation of ventilator management;
• Peak inspiratory pressure > 28 cmH_2O or mean airway pressure > 17 cmH_2O is required to achieve saturation > 85%;
• Inadequate oxygen delivery with metabolic acidosis as measured by elevated lactate ≥ 5 mmol/L and pH < 7.15;
• Systemic hypotension, resistant to fluid and inotropic therapy, resulting in urine output < 0.5 mL/kg/h for at least 12-24 h;
• Oxygenation index ≥ 40 present for at least 3 h.

nous hypertension. VA ECMO allows decreasing the volume directed to the right heart, helping its recovery despite the persistent elevation of pulmonary vascular resistance. However, VA ECMO is associated with carotid artery manipulation and ligation, with higher risk of complications, particularly haemorrhagic, which is relevant in these patients who may need surgical treatment on ECMO. Another possible complication associated to VA ECMO is a significant output inducing systemic arterial hypertension and severe left ventricular dysfunction.

VV ECMO is technically challenging in small neonates, even though it allows the preservation of pulmonary blood flow with oxygenated blood, increasing pulmonary vasodilation.

Inconclusive data on the association between the ECMO mode and mortality have been found and several studies have shown equivalent survival outcomes for both techniques. However, a lower risk trend for neurological complications seems to relate to VV ECMO and is considered by several authors to be the preferred method for infants with CDH. However, if this technique fails, conversion from VV to VA ECMO is associated with a 56% increase in mortality.[8,13] All neonates included in our study underwent VA ECMO, mostly due to the presence of severe pulmonary hypertension requiring cardiovascular support, which is only possible with the VA technique. Another factor that influenced the choice of technique in this age group was the fact that there were no double-lumen wired cannulae available in the Portuguese market at the time when the ECMO program was started and currently they have been withdrawn from the market internationally. It is not possible to safely perform VV ECMO in neonates without these cannulae, as the femoral vein is too small in this age group to allow the cannulation and the PVC (polyvinyl chloride plastic) double-lumen cannulae may collapse with the centrifugal pumps that are currently used.

Surgical correction time

The approach regarding the timing of surgical repair during ECMO is very variable between centres: some advocate an early repair (< 72 hours) to allow earlier lung recovery, while others advocate a late repair, including after the ECMO cycle, to minimise bleeding complications. The development of anti-fibrinolytic therapy has made possible a reduction in the bleeding risk during surgical repair on ECMO.

Several studies have suggested a better survival in early ECMO and post-decannulation repair, but studies are inconclusive regarding which is more advantageous. Although there has been some progress in post-decannulation repair in the recent years, this technique is still performed in few centres worldwide.[14-16] Only one patient in our group underwent surgical repair after a cycle of ECMO and, despite a good outcome, it was not possible to draw any conclusions on the influence of timing of surgical repair on the survival rate.

Mortality and morbidity of infants with CDH on ECMO

Increasing mean ECMO cycle times have been found over the past few decades, reaching more than 200 hours per cycle, compared with approximately 150 hours in the 1990s.[7] The mean ECMO cycle length in our sample was 125 hours longer than what was described in the latest 2017 ELSO Registry Report (384 *vs.* 259 hours, data regarding patients with CDH).[7]

Longer ECMO cycles and lower survival rates suggest that ECMO is increasingly used as rescue therapy in critically ill patients and/or those with more comorbidities.[4] The limits of treatment duration on ECMO are not yet established, although data suggest the presence of limited utility beyond four to six weeks: 56% survival rate at discharge upon two weeks of ECMO, 43% upon four weeks, 15% upon five weeks and no survivors beyond 40 days of ECMO.[4,17]

Right sided CDH occurs in about 25% of all the cases and is associated with increasingly severe pulmonary hypoplasia, greater need for pulmonary vasodilator therapy and tracheostomy.[18] No cases of right sided CDH were included in our group of patients.

As described, ECMO is associated with a risk of significant complications and morbidity, related to the technique itself. Mechanical and haemorrhagic complications were very prevalent in our group of patients and were significant contributing factors to poor outcomes. Over time, these complications led to some changes in anticoagulation strategy, including the use of aspirin in the absence of bleeding, dosing and correction of anti-thrombin III levels and the development of techniques to remove clots from cannulae without the need for cannula replacement.

An incidence of chronic lung disease or bronchopulmonary dysplasia ranging from 33 to 52% has been found in CDH survivors. However, studies show that this figure may

increase by about nine times in neonates on ECMO.[17] Moderate to severe chronic lung disease requiring prolonged oxygen therapy was quite prevalent in our group of patients, affecting seven out of eight survivors with significant follow-up time (87%).

The risk of neurological abnormalities is higher in survivors who required ECMO, including sensorineural hearing loss, psychomotor developmental delay and autism spectrum disorder. The use of ECMO is also associated with a 17-fold increased risk of poor weight gain at 12 months of life.[19] All these possible morbidities make the follow-up of these children up to adolescence very important.

Limitations of the study

As a retrospective, unicentric study, based on a small sample, with limited data, as these were obtained from an international database and with limited follow-up time in some of the more recent patients were the major limitations of the study.

CONCLUSION

Despite the technological advances in respiratory care of neonates and improved safety of ECMO, survival rates of neonates with CDH remain low. The use of ECMO allows survival in more severe cases, but is not without risk: in about one third to half of the cases it does not prevent death and is associated with a significant risk of pulmonary and neurological morbidity in survivors. Variations between centres often reflect different criteria in the selection of patients with CDH on ECMO support.

In our study, a higher survival rate in patients with CDH on ECMO has been found, when compared to the average described in international registries. Although the study has important limitations, it provides an insight into the reality of a reference centre in Portugal and is also aimed at raising the awareness among obstetricians, neonatologists and paediatric surgeons on the importance of discussing and making a timely referral of patients with severe CDH to an ECMO reference centre.

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HUMAN AND ANIMAL PROTECTION

The authors declare that this project complied with the regulations that were established by the Ethics and Clinical Research Committee, according to the 2013 Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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