Venovenous ECMO for Congenital Diaphragmatic Hernia: Role of Ductal Patency and Lung Recruitment

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We report a case of antenatally diagnosed left-sided congenital diaphragmatic hernia, managed on venovenous extracorporeal membrane oxygenation with an hemodynamic and ventilation strategy aimed at preventing left and right ventricular dysfunction. Keeping the ductus arteriosus open with prostaglandin infusion and optimizing lung recruitment were effective in achieving hemodynamic stabilization and an ideal systemic oxygen delivery. The patient was discharged from the hospital and had normal development at 1 year of age. The combination of ductal patency and lung recruitment has not been previously reported as a strategy to stabilize congenital diaphragmatic hernia patients undergoing venovenous extracorporeal membrane oxygenation. We believe that this approach may deserve further evaluation in prospective studies.

Mortality for congenital diaphragmatic hernia (CDH) can be as high as 30% to 40%,[1] with no survival advantages conferred by maximized medical therapy.[2,3] The use of extracorporeal membrane oxygenation (ECMO) in CDH is highly controversial because irreversible lung disease is one of the major contraindications to ECMO. Patients requiring ECMO may present with extreme lung hypoplasia, often not amenable to any treatment.[4,5] Nevertheless, ECMO is commonly offered to CDH patients, despite the fact that the survival rate (51%) is the worst among neonatal ECMO indications.[6] We describe a case of left-sided CDH on venovenous ECMO (VV-ECMO), where a combined hemodynamic and ventilation strategy, based on prostaglandin (PGE) administration and lung recruitment (LR), proved effective in optimizing hemodynamics and oxygenation.

PATIENT

A 38 weeks' gestational age (GA) male, weighing 2.43 kg, was diagnosed prenatally with left-sided CDH. Observed to expected lung-to-head ratio at 20 weeks' GA was 44%, and liver herniation has been confirmed by fetal MRI at 26 weeks of GA.[7] Immediately after birth, at the referral center, he required high-frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO), and nasogastric sildenafil administration for refractory pulmonary hypertension (PH). Cardiac echo showed suprasystemic pulmonary pressures (60 mm Hg) estimated by tricuspid regurgitation (TR), dilation of the right ventricle (RV), continuous right-to-left shunt through the ductus arteriosus (DA), D-shaped left ventricle (LV) with restrictive physiology confirmed by a left-to-right shunt through the foramen ovale. Cardiovascular support was provided with continuous infusion of dopamine, dobutamine,

abstract

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Drs Moscatelli and Pezzato designed the case report, drafted the initial manuscript, and revised the manuscript; Dr Lista critically revised and reviewed the manuscript; Drs Petrucci and Buratti carried out the initial analysis of the case, reviewed the literature, and revised the manuscript; Dr Castagnola designed the data collection, performed the statistical analysis, and revised the manuscript; Dr Tuo coordinated and conceptualized the initial manuscript and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2016-1034

Accepted for publication Jul 14, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Moscatelli A, Pezzato S, Lista G, et al. Venovenous ECMO for Congenital Diaphragmatic Hernia: Role of Ductal Patency and Lung Recruitment. *Pediatrics.* 2016;138(5):e20161034

and PGE1 to maintain patent the DA, thus unloading the RV and preventing a low cardiac output state (LCOS).

On postnatal day 4, our ECMO team was deployed for retrieval because of indication to ECMO (oxygenation index: 64). The infant was transported by ambulance on high-frequency percussive ventilation (HFPV) and iNO, sedated, and paralyzed. Dobutamine and dopamine were switched to epinephrine and milrinone to have a more effective inotropic support, avoid the dopamine-related increase of pulmonary vascular resistance (PVR), and take advantage of the pulmonary vasodilatory and LV lusitropic effect of milrinone.[3,8] On day 3 after admission, he was stable on HFOV (mean airway pressure 16 cmH_2O, amplitude 34 cmH_2O, frequency 9 Hz, inspiratory time, 33%, fraction of inspired oxygen [Fio_2] 0.5), pulse oxygen saturation [Spo_2] 94%, partial pressure of carbon dioxide (arterial; $Paco_2$) 38 mm Hg, iNO 10 ppm, nasogastric sildenafil (0.8 mg/kg 4 times daily), and continuous infusion of epinephrine (0.05 mcg/kg/min), milrinone (0.4 mcg/kg/min), and PGE1 (0.025 mcg/kg/min); DA shunt was mainly left-to-right with no TR and good hemodynamic stability (average mean arterial pressure 60–65 mm Hg). Meeting clinical criteria for surgery eligibility, CDH repair was not delayed further because the prominent mediastinal shift with compression of the lungs and LV were considered possible contributors to cardiorespiratory impairment. ECMO was taken into consideration as eventual rescue strategy after surgery. Reduction in the abdomen of the herniated viscera, which included a portion of the left lobe of the liver, stomach, small bowel, and spleen was difficult, given the discrepancy with the available space. Because of an almost complete absence of diaphragmatic rims, the large defect was closed with an abdominal wall muscular flap. The infant presented a relapse of severe PH 66 hours after surgery (oxygenation index: 61), requiring ECMO. Bicaval double-lumen cannulation (Avalon Elite 13 Fr) was carried out percutaneously under real-time transthoracic echo control.[9] The patient was assisted on VV-ECMO for 23 days with Levitronics Pedivas pump (Thoratec Corporation, Pleasanton, CA), and Lilliput 2 ECMO oxygenator (Sorin, Mirandola, Modena, Italy). Sweep gases (Fio_2 0.8–1.0) were set in a 1:1 ratio to the blood flow and then adjusted according to the $Paco_2$ (ratio up to 2.5:1), with a target blood flow of 280 mL/min. The activated clotting time was maintained between 180 and 200 seconds. ECMO proved effective in providing adequate oxygenation and CO_2 removal (Table 1). After ECMO initiation, mechanical ventilation on HFOV was set to minimize ventilator induced lung injury while ensuring adequate LR (right diaphragm at the eighth posterior rib): mean airway pressure 10 cmH_2O, amplitude 24 cmH_2O, frequency 10 Hz, inspiratory time 33%, Fio_2 0.3. Nevertheless, the infant experienced episodes of lung derecruitment, characterized by worsening of PH with continuous right-to-left ductal shunt and RV dilation; ductal patency prevented a LCOS to occur. Optimization of LR included HFPV (peak inspiratory pressure, 32 cmH_2O, positive end-expiratory pressure 12 cmH_2O, mean airway pressure 10 cmH_2O; inspiratory/expiratory time 1.2/1; convective rate 30/min, percussive rate 620/min, high frequency inspiratory/expiratory time 1/1, Fio_2 0.3) preceded by surfactant bronchoalveolar lavage (20 mg/mL solution with normal saline, administered in 3-mL aliquots, total volume 12 mL), and administration (100 mg/Kg; Curosurf, Chiesi). A pigtail chest drain was also inserted percutaneously to relieve lung compression and mediastinal shift. Pleural effusion evacuation was intermittent and carefully balanced to avoid hyperinflation of the hypoplastic lung and limit ventilator induced lung injury. This strategy was effective in optimizing PVR, with reversal of ductal shunt and recovery of RV dysfunction (Fig 1). One such episode was concomitant with an attempt to taper down PGE1 infusion to contain tissue edema, with unwanted reduction of the DA diameter. In this case, acute RV dysfunction and dilation with TR and LCOS were not responsive to LR alone, requiring an increase in the PGE1 dose to widen the DA. HFPV was then chosen as resting ventilation, to ensure LR until ECMO weaning. On PICU day 19, endothelin 1 receptor inhibition (bosentan, 1 mg/kg twice daily) was added. The patient was weaned from ECMO on pressure assist-control ventilation (peak inspiratory pressure 16 cmH_2O, positive end-expiratory pressure

TABLE 1 Paired *t* Test Comparing Pre- and Post-ECMO Variables

	4 Hours Pre-ECMO	4 Hours Post-ECMO	Further Observations
	Mean (Range)	Mean (Range)	Mean (Range)
pH	7.26 (7.20–7.28)	7.43* (7.40–7.41)	7.40 (7.32–7.48)
$Paco_2$ (mm Hg)	75.1 (65.8–90.3)	43.9* (40.9–47.0)	38.4 (32.0–46.4)
Pao_2 (mm Hg)	27.8 (20.6–39.7)	77.5* (60.5–102.0)	52.1 (38.8–70.8)
Spo_2 (%)	54.5 (45–65)	99.3* (98–100)	88.7 (78–97)
Lactates mg/dL	45.0 (35–58)	20.3* (18–22)	10.0 (4–12)

Data from the 4 hours before and after ECMO initiation. ECMO was effective in increasing pH, Spo_2, and partial pressure of carbon dioxide (arterial; Pao_2) and in lowering $Paco_2$ and lactates ($P < .01$). This was true throughout the whole ECMO run (further observations: hourly SpO_2, and values from any other determination of the blood gas analysis beyond 4 hours of ECMO).

* $P < .01$.

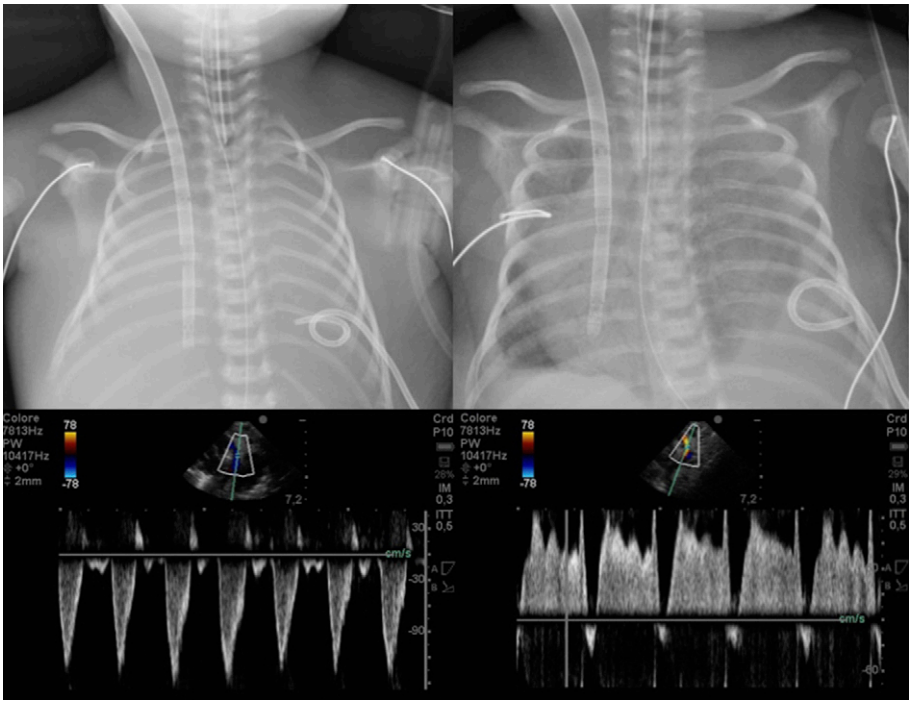

FIGURE 1
Effect of lung recruitment on pulmonary vascular resistances as assessed by ductal shunt. Lung recruitment caused an evident fall of pulmonary vascular resistance, with a switch from pulmonary hypertension to growing pattern of flow.

5 cmH_2O; inspiratory time 0.38–0.40 sec; spontaneous respiratory rate 35–50/min; Fio_2 0.4), and iNO (10 ppm), under continuous infusion of milrinone and PGE1, and sildenafil and bosentan treatment. Extubation to nasal continuous positive airway pressure followed iNO weaning and was performed on PICU day 34. DA closed spontaneously a few days after discontinuation of milrinone and PGE1. The patient was discharged from the hospital at 65 days of life without oxygen support. At 1 year of age, he has normal neurologic development, assessed by 12 months Bayley-III scale (composite scores: cognitive 95, language 94, motor 97, socioemotional 90, general adaptive 95), and no echocardiographic signs of PH without therapy.

DISCUSSION

The rationale behind the application of ECMO to CDH is that some newborns may decompensate for reversible causes, and ECMO can allow time for recovery.[10,11] The challenge is to identify those who might benefit from ECMO, namely, patients who have shown potential for adequate lung function. Some authors have advocated the use of physiologic parameters for this purpose: ability to maintain preductal oxygen saturation >80% at any moment in the initial treatment, lowest pre-ECMO $Paco_2$ <70 mm Hg.[4,12–14]

Evidence from the recent literature seems to contradict this practice; in non premature CDH patients, without associated lethal anomalies, combined physiologic parameters failed to predict mortality: survival reached 50% even in patients with the most severe predicted outcomes. If these data are confirmed, it is ethical to offer ECMO to any CDH patient regardless of the severity in the first hours of life.[15] VV-ECMO has many advantages compared with venoarterial ECMO (VA-ECMO) in CDH: no ligation of the carotid artery, pulsatile flow and perfusion of well-oxygenated blood to the pulmonary circulation (pulmonary vasodilation) and coronary arteries (prevention of myocardial stun), no increase in LV afterload, and entrapment of emboli from the ECMO circuit in the pulmonary vascular bed.[16] On the contrary, it does not provide direct hemodynamic support, with possible RV and LV failure.[17] Current evidence supports the use of VV-ECMO in CDH because this modality is comparable to VA-ECMO in terms of mortality and has a lower incidence of neurologic complications.[16–18] Nevertheless, CDH is often characterized by hemodynamic instability, leading to frequent use of the VA configuration in these patients. A conversion from VV to VA is required in up to 18% of the runs started on VV, with an increase in the odds of mortality[17]

when this occurs. We speculate that our circulatory approach might confer more effectiveness to the VV configuration, reducing the need for VA conversion. As already proposed in non-ECMO CDH patients, keeping the DA open with PGE could help in obtaining an optimal hemodynamic stabilization.[19] In fact, the right-to-left shunt through the DA unloads the RV, preventing its failure, and reduces the pulmonary venous return to the left atrium (LA), avoiding the increase of LA pressures secondary to the transitory LV hypoplasia and compression associated with left-sided herniation and RV dilation. This eliminates a possible retrograde component of PH due to LA hypertension. Furthermore, on VV-ECMO, right-to-left ductal shunt of highly oxygenated blood ensures an adequate cardiac output despite severe PH crises, allowing optimal tissue oxygenation.[3,19,20] This is clearly shown in our patient by the variation of partial pressure of oxygen (arterial), Spo_2, and serum lactates with ECMO (Table 1). The best ventilation strategy on ECMO is extremely controversial; most centers target lung rest not focusing on LR.[21,22] Given that the pulmonary circulation is not bypassed on VV-ECMO, LR plays a critical role in minimizing PVR (Fig 1), with additional beneficial effects to ductal patency on RV and LV function.[23,24] In our patient, optimization of lung volume on VV-ECMO with surfactant and HFPV had dramatic effects on reduction of PVR.[25–27]

Although our experience is limited to 1 case, we believe that this approach to hemodynamic stabilization and PVR modulation, which has not been described before in VV-ECMO, is founded on strong pathophysiological principles and could confer improved effectiveness and success of VV-ECMO. Further evaluation of this strategy by prospective studies is warranted.

ABBREVIATIONS

CDH: congenital diaphragmatic hernia
DA: ductus arteriosus
ECMO: extracorporeal membrane oxygenation
Fio_2: fraction of inspired oxygen
GA: gestational age
HFOV: high-frequency oscillatory ventilation
HFPV: high-frequency percussive ventilation
iNO: inhaled nitric oxide
LA: left atrium
LCOS: low cardiac output state
LR: lung recruitment
LV: left ventricle
$Paco_2$: partial pressure of carbon dioxide, arterial
PGE: prostaglandin
PH: pulmonary hypertension
PVR: pulmonary vascular resistance
RV: right ventricle
Spo_2: pulse oxygen saturation
TR: tricuspid regurgitation
VA-ECOM: venoarterial ECMO
VV-ECMO: venovenous ECMO

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DOI: 10.1542/peds.2016-1034

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