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Pumpless arteriovenous extracorporeal membrane oxygenation: A novel mode of respiratory support in a lamb model of congenital diaphragmatic hernia

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ABSTRACT

Background: Extracorporeal membrane oxygenation (ECMO) is commonly required in neonates with congenital diaphragmatic hernia (CDH) complicated by pulmonary hypertension (PH). ECMO carries significant risk, and is contraindicated in the setting of extreme prematurity or intracranial hemorrhage. Pumpless arteriovenous ECMO (P-ECMO) may represent an alternative for respiratory support. The present study summarizes our initial experience with P-ECMO in a lamb model of CDH.

Study design: Surgical creation of CDH was performed at 65–75 days' gestation. At term (135–145 days), lambs were delivered into the P-ECMO circuit. Three animals were maintained on a low-heparin infusion protocol (target ACT 160–180) and three animals were maintained with no systemic heparinization.

Results: Animals were supported by the circuit for 380.7 +/− 145.6 h (range, 102–504 h). Circuit flow rates ranged from 97 to 208 ml/kg/min, with adequacy of organ perfusion demonstrated by stable serum lactate levels (3.0 +/− 1.7) and pH (7.4 +/− 0.3). Necropsy demonstrated no evidence of thrombogenic complications.

Conclusion: Pumpless extracorporeal membrane oxygenation achieved support of CDH model lambs for up to three weeks. This therapy has the potential to bridge neonates with decompensated respiratory failure to CDH repair with no requirement for systemic anticoagulation, and may be applicable to patients currently precluded from conventional ECMO support.

Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly affecting 1 in every 2500–4000 live births. Despite advances in surgical technique and neonatal care, mortality and morbidity remain high [1], with pulmonary hypoplasia and persistent pulmonary hypertension (PH) representing the most significant factors determining survival [2,3]. Severe PH represents the most frequent indication for the initiation of salvage therapy with extracorporeal membrane oxygenation (ECMO). Rates of ECMO usage in CDH range as high as 60% in the literature [4,5], with mortality rates ranging from 25% to 50% in patients requiring ECMO support [4,6].

While often life-saving, conventional ECMO is associated with significant morbidity and mortality. Thromboembolic and hemorrhagic complications are the most common sources of injury in patients supported on ECMO, with neonatal patients disproportionately affected compared to their adult counterparts owing to the relative immaturity of clotting and regulatory factors and platelet function in newborns [7]. Anticoagulation is necessitated during ECMO support owing to the large thrombogenic surface area of conventional circuits. Mechanical insults are also imposed on blood cells during pump-driven perfusion, which may cause hemolysis and further potentiate clotting.

Conventional venoarterial ECMO relies on passive venous outflow to deliver blood to an oxygenator, with return of oxygenated blood via a roller or centrifugal pump. This allows for adequate gas exchange but provides continuous flow to the left-sided circulation, which can increase afterload and impose cardiac strain [8]. An appealing alternative for the delivery of extracorporeal oxygenation may be provided by a simplified pumpless circuit design with minimal priming volumes and surface area, taking advantage of the native cardiac output and endogenous arteriovenous pressure gradient to drive flow. Initial experimental efforts include a canine model, with cannulation of the femoral artery and vein achieving favorable gas exchange profiles over a 24-h period of support [9], and a perinatal lamb model with cannulation of the umbilical vessels which reported no impairment of myocardial performance at rates of perfusion up to 30% of total systemic flow [10]. A number of further experimental animal and clinical models have since been

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reported, consistently demonstrating promising results [11–13]. The smaller size and reduced surface area of such circuits, as well as technological advances in antithrombogenic surfacing for perfusion devices, have made possible the design of a fully coated circuit which may substantially reduce the risk of clotting and hemorrhagic complications [14].

Here we describe the design and preclinical implementation of a pumpless ECMO circuit (P-ECMO) with minimal priming volume and surface area, antithrombogenic coating of all surfaces, and pumpless arteriovenous configuration achieving innate regulation of blood flow and systemic pressures by the heart itself. We have achieved complete physiologic support of surgically created CDH lambs for up to three weeks of P-ECMO support, with stable hemodynamics and no requirement for systemic anticoagulation.

1. Methods

Animals were treated according to approved protocols by the Institutional Animal Care and Use Committee of the Children's Hospital of Philadelphia.

1.1. CDH creation

Time-dated pregnant ewes were operated on at gestational ages of 65 to 75 days (term = 145 days). CDH defects were created as originally described [15]. Briefly, ewes were anesthetized with 15 mg/kg of intramuscular ketamine, with maintenance of general anesthesia with 2%–4% inhaled isoflurane in O_2. Intraoperative hemodynamic monitoring included pulse oximetry, with a constant infusion of isotonic saline administered via a central venous line placed in the right jugular vein to maintain maternal fluid balance. A lower midline laparotomy was created to expose the uterus, with a small hysterotomy performed using electrocautery to achieve externalization and exposure of the torso and lower limbs of the fetal lamb (Fig. 1A). A posterolateral left thoracotomy was created in the 9th intercostal space, with the lung retracted superiorly and the posterior–lateral diaphragm incised widely. The stomach was then gently pulled up into the chest (Fig. 1B). The thoracotomy was closed in one layer, followed by closure of the hysterotomy with a running locked monofilament suture. The amniotic fluid was restored with warm Lactated Ringers solution and Penicillin G (10e6 U) was administered into the amniotic fluid prior to

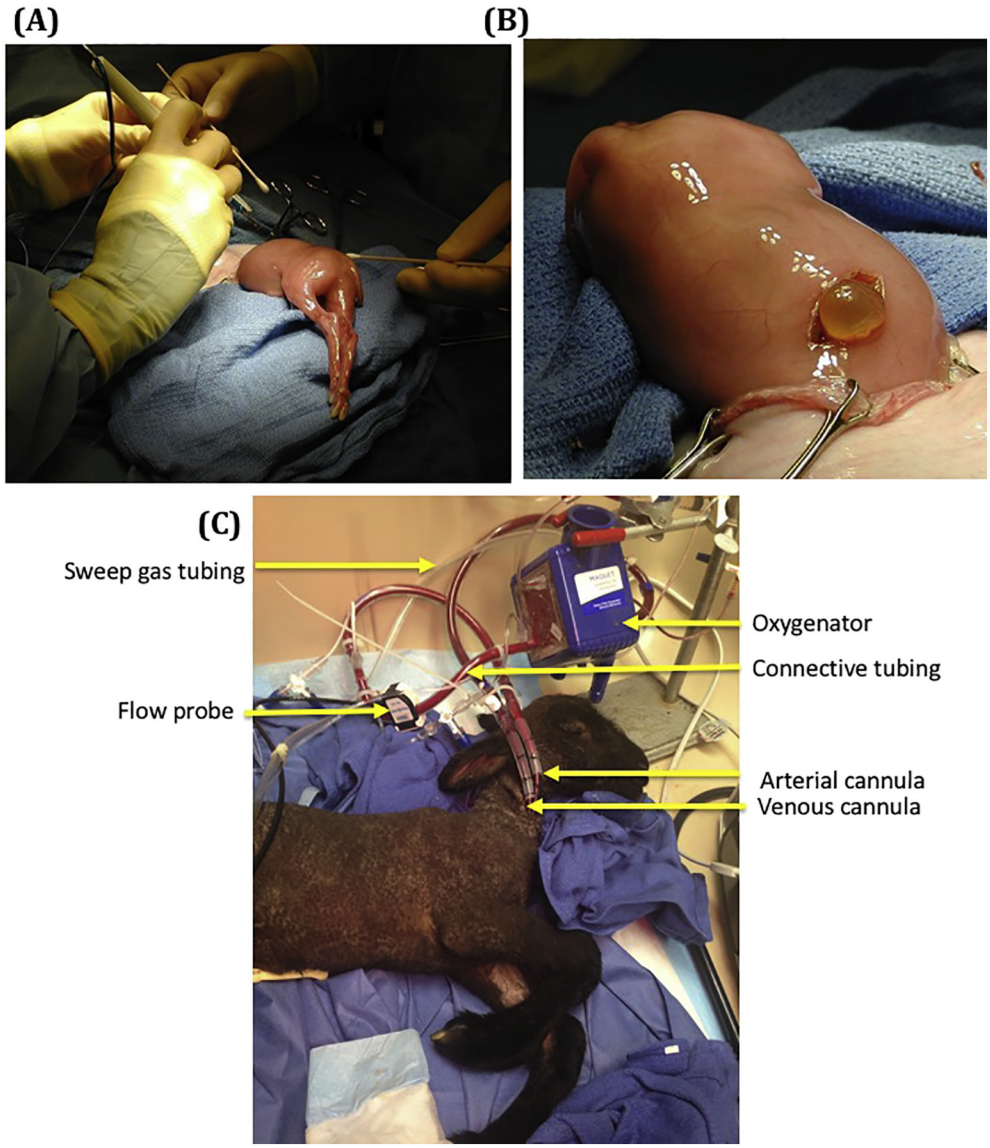

Fig. 1. Experimental design. **(A)** Creation of the lamb CDH model by exteriorization of the fetal thorax and hindlimbs and **(B)** herniation of the abdominal viscera through the diaphragmatic defect; **(C)** CDH lambs are delivered at term onto the P-ECMO circuit.

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