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The artificial placenta: Continued lung development during extracorporeal support in a preterm lamb model

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ABSTRACT

Purpose: An artificial placenta (AP) utilizing extracorporeal life support (ECLS) could avoid the harm of mechanical ventilation (MV) while allowing the lungs to develop.
Methods: AP lambs (n = 5) were delivered at 118 days gestational age (GA; term = 145 days) and placed on venovenous ECLS (VV-ECLS) with jugular drainage and umbilical vein reinfusion. Lungs remained fluid-filled. After 10 days, lambs were ventilated. MV control lambs were delivered at 118 ("early MV"; n = 5) or 128 days ("late MV"; n = 5), and ventilated. Compliance and oxygenation index (OI) were calculated. After sacrifice, lungs were procured and H&E-stained slides scored for lung injury. Slides were also immunostained for PDGFR-α and α-actin; alveolar development was quantified by the area fraction of alveolar septal tips staining double-positive for both markers.
Results: Compliance of AP lambs was 2.79 ± 0.81 C_{dyn} compared to 0.83 ± 0.19 and 3.04 ± 0.99 for early and late MV, respectively. OI in AP lambs was lower than early MV lambs (6.20 ± 2.10 vs. 36.8 ± 16.8) and lung injury lower as well (1.8 ± 1.6 vs. 6.0 ± 1.2). Double-positive area fractions were higher in AP lambs (0.012 ± 0.003) than early (0.003 ± 0.0005) and late (0.004 ± 0.002) MV controls.
Conclusions: Lung development continues and lungs are protected from injury during AP support relative to mechanical ventilation.
Level of evidence: n/a (basic/translational science).

One in ten infants born in the United States each year is premature [1]. About 5% of these are deemed extremely low gestational age newborns (ELGANs), defined as neonates born at ≤28 weeks' estimated gestational age (EGA) [2]. Morbidity and mortality are unacceptably high in this population, with survival well below 50% for infants born before 24 weeks. Morbidities in these patients arise from the immaturity of multiple organ systems, perhaps most notably the lungs [3–6]. Fetal lungs transition from the canalicular to saccular phase of development at approximately 22–24 weeks' EGA; this currently marks the cusp of viability for preterm infants [7]. The current standard of care for respiratory support of these ELGANs is mechanical ventilation. However, this technology is often inadequate, or even harmful to the neonate, leading to pulmonary injury and arrested lung development [8–10].

A solution to this problem is the development of an artificial placenta (AP). This technology consists of four components: 1) extracorporeal life support (ECLS), 2) maintenance of fluid-filled lungs, 3) avoidance of mechanical ventilation, and 4) preservation of fetal circulation. Given that pulmonary morbidity decreases with increasing gestational age [3], the goal of the AP is to allow premature lungs to grow and develop to the point where they can provide adequate gas exchange to support the neonate, with or without the safe assistance of mechanical ventilation. Prior experimentation in our laboratory has shown that the AP can support otherwise moribund premature lambs for over seven days [11]. We more recently have sought to determine if lung development continues during AP support, and if so, if this continued

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development allows for transition from AP support to mechanical ventilatory support. We hypothesized that, in an ovine model of prematurity, AP support would allow for continued lung development, and that as a result, safe transition to mechanical ventilation is possible.

1. Methods

The sheep in this experiment were treated in compliance with the *Guide for Care and Use of Laboratory Animals* (US National Institutes of Health publication No. 85-23, National Academy Press, Washington D.C., revised 1996) and all methods were approved by the University of Michigan Institutional Animal Care and Use Committee (protocol 00007211).

Premature lambs were placed in three experimental groups, all with n = 5: AP, early MV, and late MV. Of note, the AP lambs in this study represent a cohort within a larger group of experimental animals (n = 12) in whom the goal was to transition from mechanical ventilation following AP support. The other animals within this group were not transitioned to mechanical ventilation following support and were used for alternative experiments, the results of which are not reported in the present study.

1.1. AP lambs

AP lambs of EGA 118 ± 3 days were delivered via midline laparotomy and transverse hysterotomy. This gestational age was selected as previous experimentation has determined that fetal sheep lung development at this stage is analogous to that of a 24-week human fetus [11]. While the lamb was supported by the native placenta, the right jugular vein was exposed and cannulated with a 10–14Fr drainage cannula (Terumo: Ann Arbor, MI). A 10–12Fr reinfusion cannula was placed in the umbilical vein, and the circuit was completed using ¼" tubing (Tygon: Lima, OH), a roller pump (MC3: Ann Arbor, MI), and oxygenator/heat exchanger (either Capiox Baby Rx, Terumo: Ann Arbor MI, or Medos HiLite, Xenios: Heilbronn, Germany; Fig. 1). The umbilical cord was then divided and venovenous (VV) ECLS was initiated. A 5Fr triple lumen venous line was placed in the second umbilical vein and used for IV fluid and medication administration, and a 5Fr umbilical arterial line (both lines from Covidien-Medtronic: Minneapolis, MN) was placed in the umbilical artery for hemodynamic monitoring and arterial blood gas (ABG) sampling. The lambs were then intubated, and the endotracheal tube (ETT) was either filled with amniotic fluid and capped (n = 1), connected to pressure line primed with Ringer's Lactate (LR) at 4–6 mmHg (n = 3), or filled with perfluorodecalin (Origen: Austin, TX) to a visible meniscus in the ETT (n = 1), as these strategies would maintain fluid-filled lungs and positive intrapulmonary pressure akin to that seen in the intrauterine environment [12]. ECLS was managed according to goal ABG parameters: pH 7.30–7.45, pCO_2 35–50, pO_2 25–35, and SpO_2 60–75. AP support was continued for 10 days. Lambs were given total parenteral nutrition (TPN), empiric piperacillin–tazobactam, and solumedrol 0.63 mg/kg every 6 h (owing to low baseline cortisol levels in premature lambs). Heparin sulfate was administered by IV infusion, starting at 100 U/h, and titrated to a goal activated clotting time (ACT) of 200–250, checked every 2–3 h. Prostaglandin E_1 (0.2 μg/kg/min) was administered continuously to prevent ductus arteriosus closure. Buprenorphine (0.3 mg) and diazepam (2.5 mg) were given sparingly as needed for pain and/or agitation, and lambs were not paralyzed. Echocardiography was performed daily to assess for patency of the ductus arteriosus.

After 10 days, the lambs' lungs were suctioned of fluid, exogenous surfactant (Survanta, Abbvie, North Chicago, IL) was administered to maximize initial compliance and oxygenation and to represent standard therapy [11], prostaglandin was discontinued, and mechanical ventilation (MV) was initiated using a Maquet Servo-I pediatric ventilator (Maquet Holding B.V. and Co., Rastatt, Germany). Initial ventilator settings included (pressures in cmH_2O): respiratory rate = 60, positive end-expiratory pressure (PEEP) = 5, inspiratory pressure (IP) = 15, and fraction of inspired oxygen (FiO_2) = 40%, and were adjusted based on arterial blood gas values. Concurrent AP support and MV support were continued for at least a 24 h of lung recruitment, during

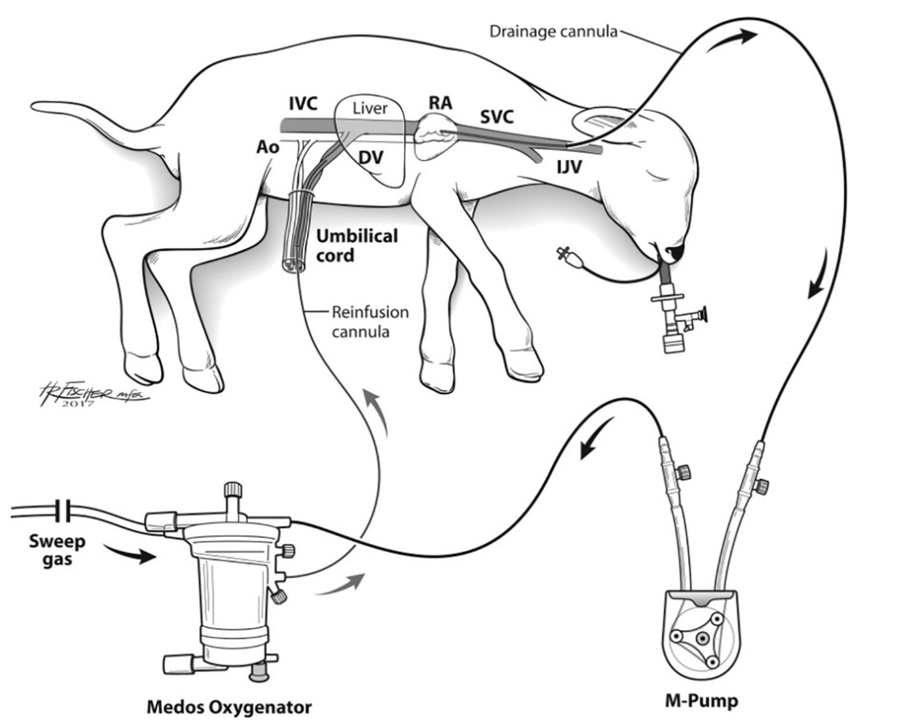

Fig. 1. Schematic of the artificial placenta. Blood is drained from the right jugular vein by a collapsible-tubing roller pump (M-pump, MC3: Ann Arbor, MI) and propelled to an oxygenator/heat exchanger (Medos HiLite, Xenios: Heilbronn, Germany), then returned via an umbilical vein. The second umbilical vein is accessed for IV fluid and medication administration, and an umbilical arterial line is placed for hemodynamic monitoring and blood gas sampling. The lamb is intubated and the lungs remain filled with amniotic fluid by clamping the endotracheal tube. Ao, aorta; DV, Ductus venosus; IJV, internal jugular vein; IVC, inferior vena cava; RA, right atrium; SVC, superior vena cava.