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An Extracorporeal Artificial Placenta Supports Extremely Premature Lambs for One Week

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Abstract

Purpose—The treatment of extreme prematurity remains an unsolved problem. We developed an artificial placenta (AP) based on extracorporeal life support (ECLS) that simulates the intrauterine environment and provides gas exchange without mechanical ventilation (MV), and compared it to the current standard of neonatal care.

Methods—Extremely premature lambs (110–120d; term=145d) were used. AP lambs (n=9) were cannulated (jugular drainage, umbilical vein reinfusion) for ECLS. Control lambs (n=7) were intubated, ventilated, given surfactant, and transitioned to high-frequency oscillatory ventilation. All lambs received parenteral nutrition, antibiotics, and steroids. Hemodynamics, blood gases, hemoglobin, and circuit flows were measured.

Results—Four premature lambs survived for 1 week on the AP; one survived 6 days. Adequate oxygenation and ventilation were provided by the AP. The MV lambs survived 2–8 hours. Each of these lambs experienced a transient improvement with surfactant, but developed progressive hypercapnea and hypoxia despite high airway pressures and HFOV.

Conclusions—Extremely premature lambs were supported for 1 week with the AP with hemodynamic stability and adequate gas exchange; mechanically ventilated lambs succumbed within 8 hours. Further studies will assess control of fetal circulation and organ maturation on the AP.

Keywords

Extracorporeal life support (ECLS); prematurity; Extracorporeal Membrane Oxygenation (ECMO); lung development; artificial placenta

Introduction

There are approximately 500,000 premature births in the United States each year [1]. Many of these babies recover with conventional management, but the mortality and morbidity of extremely low gestational age newborns (ELGANs) defined as < 28 weeks estimated gestational age (EGA), is extremely high, with less than 50% surviving without disability [2, 3]. An artificial placenta based on extracorporeal life support (ECLS) was proposed over 50 years ago for the treatment of prematurity-related respiratory failure and was investigated in

animal models [4-6]. As the treatment of prematurity improved with the advent of prenatal maternal steroids, exogenous surfactant and advanced modes of ventilation [7, 8], interest in an artificial placenta waned.

As outcomes for the most premature infants have remained disappointing, interest has returned to the development of an artificial placenta [9-11]. Research in our laboratory initially involved a pumpless arteriovenous system and a pump-driven venoarterial system [12]. Our current model involves pump-driven venovenous ECLS; we previously reported its use to support near-term fetal lambs for 70 hours after initial failure of conventional mechanical ventilation [13]. The purpose of this study was to examine the AP's efficacy a) in providing prolonged support up to one week, b) in supporting extremely premature lambs that more closely model the human ELGAN, and c) as compared to the current standard of care in neonatal intensive care units. Our hypothesis is that the artificial placenta is superior to mechanical ventilation in an extremely premature lamb model and can maintain prolonged gas exchange and hemodynamic stability.

Methods

Based on our preliminary experiments in fetal lambs from 90 to 140 days gestation, and reports in the literature [14], we established comparisons between levels of prematurity in humans and lambs based on histologic lung development and physiologic lung function (Table 1). The 115-120-day lamb fetus simulates the lung developmental status of a 23-24-week human fetus.

Table 2 summarizes the methods used in the AP and MV arms of the study. In all experiments, pregnant ewes were delivered at 115-120d EGA. The ewe was placed under general anesthesia. Under sterile conditions, a monitoring line was placed in the ewe's carotid artery and an infusion line in the ewe's jugular vein. A laparotomy was used to expose the uterus. A small hysterotomy allowed subcutaneous injection of atropine 10 mcg/kg and buprenorphine 0.01 mg/kg into the fetus. The lamb was then partially delivered with intact native-placental support. An incision was made in the right neck to expose the carotid artery and jugular vein. A small catheter was placed in the left carotid artery for hemodynamic monitoring and sampling. The jugular venous drainage and umbilical venous reinfusion cannulae (8 or 10Fr) were placed in the AP sheep and partial ECLS support was initiated. Lambs from both groups then had a small catheter for medication and fluid administration placed in the second umbilical vein. An endotracheal tube (ETT) was placed in all lambs.

A critical care protocol for ventilating the MV control lambs was designed with the assistance of a neonatologist who also provided clinical oversight during the experiments. In the MV group, the ETT was used for conventional ventilation. Conventional ventilator settings were started in pressure-control mode with a fraction of inspired oxygen of 100%, positive end-expiratory pressure (PEEP) of 5 cmH₂O, pressure control of 8cmH₂O and respiratory rate of 50 breaths per minute. After a baseline blood gas was collected, intratracheal surfactant (Infasurf, ONY, Buffalo, NY) was administered. Surfactant was administered according to the human administration protocol (two 3mL doses, each given

with a different side of the animal downward, every twelve hours for up to three doses with avoidance of suctioning 30 min after administration). Conventional ventilator settings were adjusted upward as needed based on the blood gas. Once oxygenation and ventilation failed (partial pressure of oxygen [paO_2] below 50mmHg despite a PEEP above 12cmH₂O and partial pressure of carbon dioxide [paCO_2] above 60 mmHg despite tidal volumes above 12cc/kg), we switched the lambs to high-frequency oscillatory ventilation (HFOV) starting at the same mean airway pressure as was previously delivered on the conventional ventilator (figure 1). Frequency was started at 10 Hz, power was started at 45%. Repeated arterial blood gases were used to guide HFOV settings.

The AP circuit included a Capiiox Baby-RX™ polypropylene membrane oxygenator (Terumo, Ann Arbor, MI) and a rotary pump with a collapsible chamber to prevent high negative pressure or pump blowouts (MC3, Ann Arbor, MI) (figures 2 and 3). These were connected with 1/4" inner-diameter silicone tubing for a total circuit volume of approximately 200cc. The circuit was initially primed with saline, then primed with blood drawn from the ewe's arterial line. Wire-wound cannulas (8 or 10Fr) were used for access. A warmer (integrated into the gas exchanger) was used to maintain fetal temperature at 38-39 °C. Animals on the AP received a continuous infusion of prostaglandin E₁ (alprostadil, Pfizer, New York, NY) at 0.1-0.2mcg/kg body weight. Total parenteral nutrition was started the night of delivery. The sweep gas was a compound of oxygen, carbon dioxide, and room air. The composition and flow rates of each component of the sweep gas were titrated in response to paO_2 , paCO_2 and oxygen saturation on hourly blood gases. We targeted a circuit flow of 75-100 cc/min/kg and a paO_2 of 35-50 mmHg. The ETT was opened once a day to top it off with amniotic fluid (to maintain a continuous fluid level without pressurizing it). Oral chlorhexidine was administered around the ETT (1mL daily) to reduce the bacterial burden in the oral cavity and lungs.

Postoperative monitoring for all animals included continuous measurement of heart rate, blood pressure, temperature, and circuit flow. Arterial blood gases were used to evaluate gas exchange, hemoglobin level and electrolyte levels on an hourly basis (or more frequently if needed). Maintenance fluid (dextrose-containing 0.2% saline at 4mL/kg) was administered. All animals were given piperacillin-tazobactam (100 mg piperacillin/kg) empirically. Activated clotting time was maintained between 200 and 300 sec by additional doses of heparin as needed. Vasopressors were used in cases of hypotension refractory to fluid boluses: norepinephrine 0.01-0.2 mcg/kg/min to counteract the inflammatory effects of the blood's contact with circuit tubing, and dopamine 1-5 mcg/kg/min for hypotension thought to be related to insufficient cardiac output. Vasopressors were required in all AP sheep by 12 hours; in the five sheep who survived over 5 days they were weaned by 48 hours.. All MV lambs required vasopressors within 2 hours of birth. Boluses of diazepam 0.1 mg/kg were given for agitation as needed. These were needed no more than 5 times per day in AP animals. Transthoracic echocardiography was performed twice daily. Necropsy was performed immediately after demise of the animal, or at seven days. Postmortem evaluation included blood cultures, assessment of the ductus arteriosus (DA), and investigation of the chest and abdomen. Tissue samples were preserved in formalin.

Results

In the AP group, four animals survived to the goal of seven days (figure 4). One lamb fell just short of this mark, succumbing on day six. Four lambs suffered complications earlier; one died of pericardial tamponade, one died after a cannula fractured and fatal bleeding followed, and two died of arrhythmias without clear causes of death found on necropsy. Gas exchange was steady throughout each experiment (figure 5). Circuit flow averaged 87.4 ± 17.9 cc/min/kg of body weight. Mean arterial pressure was supported above 30 mmHg with vasopressors, but after day 3 vasopressors were no longer required. On necropsy, all sheep had a functionally closed DA (although permanent obliteration of the lumen had not yet occurred), concordant with echocardiograms. Each of the lambs had ascites. Lungs were collapsed and fully atelectatic. Blood cultures in these lambs were negative.

Lambs who underwent mechanical ventilation initially had dramatic improvements in oxygenation after administration of intratracheal surfactant; partial pressures of oxygen reached 300mmHg in some lambs a half hour after administration (figure 6). However this improvement was short-lived; all lambs went on to have refractory hypoxia. The lambs all had persistently low oxygen levels and rising CO₂ levels despite eventually receiving HFOV with 100% oxygen, airway pressures of 40 cm H₂O, and maximal power settings. The mean survival on MV for 7 extremely premature lambs was 3.8 ± 2.5 h. The DA remained open in these lambs. To validate our mechanical ventilation protocol, we tested it in 2 near-term lambs (128-130d EGA). These two lambs remained stable on mechanical ventilation without requiring HFOV. These experiments were continued for two days and then stopped. On necropsy their lungs were well-inflated, their DA was closed, and they had no evidence of intraabdominal hemorrhage, pneumothorax or other deleterious changes. Unlike the AP lambs, they required frequent diazepam 0.1 mg/kg.

Discussion

This is the first study to test the efficacy of an artificial placenta in an extremely premature lamb model compared to the current standard of neonatal critical care. We supported four extremely premature lambs for one week on the AP; one more survived 6 days. These lambs had stable hemodynamics and gas exchange, while lambs treated under the MV protocol were unstable and survived for less than 4 hours on average.

This work builds on previous efforts in our laboratory. Initial efforts used pumpless arteriovenous (AV)- ECLS as an artificial placenta, but were abandoned when resistance climbed and heart failure developed in a few hours [15]. Subsequent efforts focused on pump-driven AV- ECLS, but umbilical artery spasm thwarted adequate drainage. Despite cannulation of the aorta via the umbilical artery, we could not solve the problem of persistent hypotension. We transitioned to a model of venovenous (VV) ECLS with jugular drainage and umbilical reinfusion and supported lambs for up to 92 hours [13, 16]. We found that this model of an AP provided adequate perfusion to the brain despite the ligation of one carotid artery for monitoring line placement [17]. The next logical step toward eventual clinical application was to test the VV-ECLS AP in extremely premature lambs for a longer duration.

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Prolonged extracorporeal support of large animals has been described previously; studies have described goat fetuses supported on an artificial placenta for a remarkable 534 hours using AV-ECLS [18, 19]. These studies demonstrated the feasibility of prolonged AV extracorporeal support, while our series represents the first long-term support of extremely premature fetal lambs with VV- ECLS that was also compared to a group treated with mechanical ventilation only.

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Despite incorporating other key elements of neonatal critical care (surfactant, HFOV, vasopressors and steroids), the MV protocol could not support extremely premature lambs for longer than 8 hours, with an average of under 4 hours. After an initial spike in oxygenation as a result of surfactant administration, lambs experienced progressive hypoxia and eventually arrested. We did not redose surfactant since we wished to follow the standard of human neonatal care and administer it every twelve hours. Our model of prematurity corresponds to ELGANs at 24-26 weeks EGA; at this point in human fetal development the lungs are in the canalicular stage [20]. Other investigators have been unable to ventilate lambs for longer than four hours at this gestational age [21, 22]. We were able to successfully support two near-term lambs with our MV protocol, from which we conclude that the 7 extremely premature lambs that died after several hours of MV did so because of insufficient lung development, not a deficit in our protocol.

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Intracranial hemorrhage (ICH), a particularly devastating complication of prematurity, represents the main obstacle to the use of ECLS in premature babies. The anticoagulation necessary for circuit function has unacceptable risks in premature babies who are predisposed to intracranial hemorrhage. In these lambs, we saw no evidence of intracranial hemorrhage, although lambs have not been considered a solid model of intracranial hemorrhage because the germinal matrix matures much earlier than in humans [23]. However, sheep are a good model for assessment of white matter injury, which we are pursuing with examination of postmortem magnetic resonance imaging (MRI) and targeted neuropathologic analysis [24, 25]. We speculate that the iatrogenic element of ICH may be mitigated by the artificial placenta. Hemodynamic instability, fluid shifts, and high intrathoracic pressure from mechanical ventilation have been implicated in the development of ICH, all of which are stabilized with the AP [26, 27]. Our long-term goal is to coat circuits with novel nonthrombogenic surfaces under investigation in our lab to reduce or eliminate heparin use, lowering the risk of ICH further [28, 29].

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The extremely premature lambs in our model are physically larger than premature human neonates at the same stage of pulmonary development (lambs weighed 3-3.5 kg). Cannulation was certainly easier in these lambs than it would be in equally premature humans, but we believe that small cannulas can be successfully inserted into the jugular and umbilical veins of ELGANs and provide adequate flow. We believe VV-ECLS is an effective platform for an AP, since unlike VA-ECLS it avoids the use of the tortuous and narrow umbilical artery which is prone to spasm. VV-ECLS also allows for preservation of the patient's carotid artery and only requires a small cutdown in the neck to access the jugular vein.

Maintaining patency of the ductus arteriosus critical to preserving fetal circulation on AP support. The DA functionally closed in all lambs on the AP despite our efforts to maintain its patency. We administered prostaglandin E₁ as a continuous infusion, but absorption of prostaglandins by the plastic tubing in the circuit may have reduced its effect [30]. Closure of the DA may also stem from a paO₂ higher than the fetal norm since we targeted a paO₂ from 35-50 mmHg [31]. The reasons for this higher target included a) a desire to compensate for the higher oxygen affinity of the maternal hemoglobin infused into the lamb with the circuit prime, b) our experience that lactate levels rise in animals on the AP whose paO₂ is consistently below 35mmHg, and c) a desire to maintain greater fetal oxygen reserve in case of fluctuations in circuit flow or abrupt problems with the AP circuit. We are pursuing assessment of fetal hemoglobin dilution using tonometry to guide paO₂ targets. Another factor leading to closure of the DA may be exogenous steroids, which we empirically gave to the lambs in this study in response to hypotension over the first 36-48 hours of perfusion; we suspect this was due to a systemic inflammatory response from blood contacting the foreign material of the AP circuit and decreased cortisol in premature animals.

We faced problems with cannulation leading to the demise of one animal, which we have addressed by using new cannulae. Another lamb succumbed to pericardial tamponade, which we have not previously seen in sheep experiments, but have addressed by controlling activated clotting time in a narrower range. Two other lambs died because of arrhythmias, which we attribute to electrolyte abnormalities: in upcoming efforts we will employ a regimen of parenteral nutrition and electrolyte supplementation which will be customized to individual days of life. Despite these challenges, we successfully supported four extremely premature lambs for one week. The next phase of our animal study will prove that the AP can support a fetal lamb from the canalicular stage of lung development to the sacular stage, with weaning to air breathing and healthy long term survival. As part of our investigations into lung development we will incorporate more sophisticated management of the amniotic fluid column in the trachea, including dynamic pressure on the column, and recirculating the amniotic fluid. Several other hurdles remain before the AP can be implemented clinically, including the development of nonthrombogenic surfaces to eliminate heparin, control of the ductus arteriosus, optimization of neurologic perfusion, confirmation of on going development of other organs, and resolving metabolic and nutritional issues. The stability of our VV-ECLS AP provides a reliable platform to answer these questions. Once these obstacles are overcome, the AP has the potential to recreate of the intrauterine environment and ameliorate many of the complications associated with extreme prematurity.

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Figure 1.

Experimental setup for mechanical ventilation arm. In the foreground, an extremely premature lamb lies in a modified waterbed. The lamb is intubated and being supported with a high-frequency oscillatory ventilator since conventional ventilation has failed. Monitoring lines and the ventilator circuit are seen above the lamb's head.

Figure 2.

Experimental setup for Artificial Placenta support. On the right is an extremely premature lamb which has been intubated but is not being ventilated. The drainage cannula and tubing coming from the jugular vein and the reinfusion cannula and tubing entering the umbilical vein are next to the lamb. The oxygenator is below and to the left of the lamb, and the collapsible-tubing rotary pump is at the bottom of the picture. Blood pressure and heart rate are tracked on the monitor.

Figure 3.
Schematic of artificial placenta circuit.

Figure 4.

Survival of extremely premature lambs supported by the artificial placenta (AP) or mechanical ventilation (MV). Four of nine lambs survived one week on the AP. Extremely premature lambs could not be ventilated for more than 8h (mean 3.8 ± 2.5 h).

Figure 5.
Hemodynamics and gas exchange during support of five extremely premature lambs with an artificial placenta.

Figure 6.

Hemodynamics and gas exchange during support of seven premature lambs with mechanical ventilation. The spike in pO₂ between hours 1 and 2 is a result of surfactant administration.

Table 1

Stages of human and sheep lung development.

Lung Development	Canalicular			Saccular	Term
Human	20 wks	22 wks	24 wks	30 wks	40 wks
Sheep	90 days	110 days	118 days	128 days	145 days

Summary of methods used for Artificial Placenta (experimental) and Mechanical Ventilation (control) groups in our experiment

Table 2

	Artificial Placenta arm	Mechanical Ventilation arm
Delivery	Caesarean section via midline laparotomy, with instrumentation under native placental support	
Monitoring line	Carotid arterial line	
Medication line	Umbilical venous line	Jugular venous line
Extracorporeal support	Venovenous (drainage from jugular vein, reinfusion via umbilical vein, collapsible rotary-action pump, variable-composition sweep gas and heat exchanger)	
Management of fetal circulation	Continuous prostaglandin E1 infusion	None
Airway management	Intubation with 3.5-4.5mm ET tube; filled with amniotic fluid to mimic fetal environment	Intubation with 3.5-4.5mm ET tube; used for mechanical ventilation
Exogenous intratracheal surfactant	none	6mL calfactant (Infasurf [®] , ONY, Buffalo, NY) every 12 hours
Mechanical ventilation	none	Pressure-control ventilation; High-frequency oscillatory ventilation (HFOV) for refractory hypoxia
Sedation	Diazepam as needed for agitation	Diazepam as needed for agitation; propofol infusion as necessary
Adjunct therapies	Empiric steroids (methylprednisolone 0.5mg/kg IM every 12 hours); vasopressors as needed for hypotension; transfusions of maternal or placental blood as needed; total parental nutrition	
Data collection	Hemodynamics, blood gases, hemoglobin and electrolyte levels; circuit flow	