Pumpless Extracorporeal Support of the Preterm Infant: Bridging Fetal and Postnatal Physiology

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Education Gaps

There are limitations to current extracorporeal membrane oxygenation technology, particularly for use in very preterm neonates.

Abstract

Preterm birth is a major cause of neonatal mortality and childhood morbidity and remains an unsolved clinical challenge despite advances in neonatal care. The preterm infant needs to be supported in an extracorporeal system physiologically analogous to the sterile fluid intrauterine environment. This would support ongoing growth and organ maturation with the potential to substantially improve survival and reduce morbidity. A physiologic system would require the ability to achieve gas exchange via the umbilical circulation, with the fetal heart acting as the pump that drives circuit flow. Previous efforts at developing such a system have borrowed from conventional extracorporeal membrane oxygenation technology, with the application of external pump-driven circuits to support fetal perfusion. These have demonstrated proof in principle of extracorporeal maintenance of fetal survival but have failed to achieve physiologic homeostasis or the long-term stability required for clinical application. Our laboratory has developed a system for extracorporeal support of the preterm infant, which we call EXtracorporeal Transitional Environment for Neonatal Development (EXTEND). Using this system, we have now achieved stable support of fetal lambs that are developmentally equivalent to the 22- to 24-week gestational age human infant for up to 4 weeks with stable hemodynamics, growth, and development. The achievement of long-term physiologic extracorporeal support of the extremely preterm infant has the potential to fundamentally change the management and clinical outcomes of this population.

Objectives After completing this article, readers should be able to:

1. Describe the limitations of gas ventilation for normal lung development.

AUTHOR DISCLOSURE Drs Partridge, Davey, Hornick, and Flake have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

BPD	bronchopulmonary dysplasia
ECMO	extracorporeal membrane oxygenation
EXTEND	EXtracorporeal Transitional Environment for Neonatal Development

2. Outline (in general terms) the history of extracorporeal support systems for the preterm infant.
3. Describe the rationale for pumpless arteriovenous oxygenator circuits.
4. Discuss the advantages of a sterile fluid environment for normal neonatal development.

THE PROBLEM OF PREMATURITY

Preterm birth is the leading cause of neonatal mortality and childhood morbidity, and management of extreme prematurity remains an unsolved clinical challenge. In 2011, 6% of all live births in the United States were extremely preterm (<28 weeks' gestation), (1) with preterm birth accounting for one-third of all infant deaths (2) and with major associated morbidity present in 80% of all children born between 22 and 28 weeks' gestation. (3) Advances in neonatal intensive care have achieved improved outcomes and pushed the limitations of viability to 22 to 23 weeks' gestation, correlating with the transition from the canalicular to saccular stages of lung development and the acquisition of anatomic capability for gas exchange.

Immaturity of the developing pulmonary parenchyma remains a limiting factor in the achievement of adequate respiratory function to support survival. Although lifesaving, the institution of gas-based ventilatory support frequently results in bronchopulmonary dysplasia (BPD), an arrest in lung development secondary to premature transition from liquid to gas ventilation. BPD is observed at high rates in preterm infants and represents the most common cause of chronic lung disease in survivors of extreme prematurity. (4) The development of an extrauterine system to support ongoing fetal growth and development without the perturbations induced by gas ventilation and postnatal intensive care would improve survival and reduce long-term morbidity in infants with extreme prematurity.

THE "ARTIFICIAL PLACENTA"

Initial interest in the development of an artificial placenta arose following the development of cardiopulmonary bypass support and was borne out in a series of short experiments in the 1960s. In these experiments, fetal lambs were cannulated via the umbilical vessels and perfused with first-generation bubble membrane oxygenators, with perfusion supported for 40 minutes to 2 days. (5)(6) While the animals were supported over these brief incubation periods, most experiments were terminated as a result of death of the animal secondary to uncontrolled infections, complications of the oxygenator, and gradual decline in cardiac function. The development of extracorporeal membrane oxygenation (ECMO) allowed for innovation in the support of gas exchange in preterm infants. (7) This led to renewed interest in the development of an artificial placenta, with a series of experiments using pump-supported circuits and umbilical cannulation.

A series of these experiments performed from the late 1980s to early 2000s, primarily in Japan, produced intriguing advances in the duration of extracorporeal support of the extrauterine goat fetus, though results remained limited by technical and physiological challenges. (8)(9)(10)(11)(12)(13) These studies were highly innovative and overcame a number of limitations identified by previous investigators. Specifically, the introduction of a passively filled reservoir in the circuit to avoid afterload-induced heart failure and hemodialysis to improve fluid and electrolyte balance resulted in experiments of up to 236 hours. Iatrogenic complications, such as hemorrhagic and thromboembolic events, as well as sepsis secondary to contamination of the fluid incubation system, were reported in a number of these studies. However, animals not affected by iatrogenic complications ultimately succumbed to cardiac failure with the development of progressive circulatory depression, arrhythmias, hydrops fetalis, and eventual demise on the circuit. These studies culminated in a study that added continuous paralysis to the system, with survival of 2 preterm goats for 494 and 543 hours, respectively. However, these goats could not be given mechanical ventilation and succumbed to respiratory insufficiency.

The continued demonstration of circulatory overload in pump-supported fetal ECMO suggests an unacceptable preload or afterload imbalance imposed by these circuits, resulting in eventual cardiac failure. The large priming volume of the circuit is substantially higher than the excess of the innate placental reserve, resulting in an increased volume of distribution. In addition, the large surface area of such circuits results in a requirement of high levels

of systemic anticoagulation. This can be associated with significant morbidity and mortality as a result of thromboembolic and hemorrhagic complications. Mechanical insults are also imposed on blood cells during pump-driven perfusion, which may cause hemolysis and further potentiate clotting. Neonates supported with ECMO are disproportionately affected compared to their adult counterparts because of the relative immaturity of clotting factors, regulatory factors, and platelet function in newborns. (14) For these reasons, only infants of more than 34 weeks' gestation or over 2 kg in weight are currently eligible for ECMO. (15)

A pumpless circuit may offer advantages over current ECMO technology, including reduced priming and distribution volumes, shorter exposure of blood to thrombogenic surfaces, and the potential for innate regulation of blood flow and pressure by the fetal heart itself that is analogous to perfusion of the umbilical-placental unit. However, previous attempts to design a pumpless system for fetal or neonatal perfusion have yielded discouraging results. (16)(17)(18)(19)(20) Awad et al (16) described the use of a pumpless circuit in a series of lambs with surgically created congenital diaphragmatic hernias, with perfusion for up to 6 hours, but circuit flow rates and oxygenation levels were inadequate to sustain ongoing support.

Reoma et al (19) reported their experience with a pumpless extracorporeal circuit using a hollow-fiber oxygenator (MC3, Ann Arbor, MI) and umbilical cannulation in 4 near-term lambs (gestational age, 140 days). Animals were supported for up to 4 hours in this system but declining circuit flows and oxygenation resulted in early death and foreshortened experiments. This group's unsuccessful experience with pumpless support, a fluid environment, and use of the umbilical veins prompted them to develop a less physiologic approach for support of the premature fetus. This system is essentially a venovenous ECMO circuit with drainage from the jugular vein and return of blood via the umbilical vein. The group reports support of extremely preterm lambs in relatively stable physiologic condition for up to 1 week (21)(22)(23) with mean (± standard deviation) circuit flows of 87.4±17.9 mL/kg per minute. They also report the requirement for vasopressors for the first 3 days, need for sedation throughout the experiment, and findings of closure of the ductus venosus on necropsy, with the development of ascites and pleural effusions. In addition, 5 of 9 lambs died prior to 1 week as a result of catheter-related complications or arrhythmia.

Miura et al (17) reported their experience with a pumpless extracorporeal circuit in lambs at a gestational age of 130±1.6 days, with cannulation of a single umbilical artery and the umbilical vein. The 5 animals studied survived for an average of 18.2±3.2 hours but developed a progressive lactic acidosis, resulting in cardiac failure and death. Administration of pressors to increase cardiac contractility and inotropes to induce peripheral vasodilation did not achieve long-term survival in this system.

Miura et al (18) reported survival of lamb fetuses on a pumpless parallelized circuit using both umbilical arteries for up to a predetermined limit of 60 hours. In this report, the animals remained relatively hemodynamically stable. However, external flow regulators were required to reduce blood flow though the circuit to reverse lactic acidosis, and evidence of white matter brain injury was observed on histology. Finally, Schoberer et al reported the development of a miniaturized low-volume oxygenator studied over a 6-hour period of support. (20) However, all animals developed progressive hypotension and metabolic acidosis, with 3 of the 7 experimental animals ultimately requiring catecholamines over the course of the experiments.

PUMPLESS EXTRACORPOREAL SUPPORT OF THE NEWBORN

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 may increase afterload and impose undue cardiac strain on the developing fetal heart. (24) Pumpless circuits have been applied with preliminary success in the experimental clinical setting in neonates as well as older children, supporting the ongoing development of this mode of extracorporeal oxygenation. The first application of a pumpless, centrally placed paracorporeal oxygenator in a neonate was reported in 2013 following a diagnosis of alveolar capillary dysplasia on the second day after birth. (25) The infant was initially supported with conventional ECMO, but in anticipation of the requirement for lung transplantation and long waiting times associated with neonatal recipients, support was converted to an extracorporeal oxygenator with a cannulation strategy using inflow from the pulmonary artery and return to the left atrium. Anticoagulation was delivered to conventional ECMO target levels (activated clotting time, 180–220 seconds), and the patient was successfully supported for 54 days before the onset of bilateral intracranial hemorrhages resulting in withdrawal of support.

A subsequent study of this pulmonary artery–to–left atrium cannulation strategy in the neonatal and pediatric population was reported by Hoganson and colleagues, (26) with 1 neonate and 3 children successfully maintained

for 44±29 days, exceeding the average wait times for lung transplantation. Although intrathoracic cannulation represents an invasive and potentially morbid intervention, this approach achieved adequate oxygenation to permit extubation and mobilization, representing a significant advance over the limitations imposed by conventional ECMO therapy. However, it is likely possible to support infants on a pumpless circuit via the standard arteriovenous ECMO cannulation. Preliminary work in our laboratory in the lamb model supports the ability of the small pumpless circuit, described later in this article, to support late gestational lambs with surgically created congenital diaphragmatic hernia, without the need for anticoagulation, for up to 3 weeks.

PUMPLESS EXTRACORPOREAL SUPPORT OF THE PRETERM INFANT/FETUS

Based on the promising experiences of pumpless support of neonates and the refinements in hollow fiber membrane oxygenator development, we conceptualized the design of an artificial placenta incorporating a simplified low-resistance arteriovenous pumpless circuit with minimal priming volumes and surface area, with flow driven by the native cardiac output and endogenous arteriovenous pressure gradient. Circuit design included an oxygenator with near-zero measured resistance and a priming volume of 81 mL (Maquet Quadrox-ID Pediatric Oxygenator, Maquet Cardiopulmonary AG, Rastatt, Germany), with short segments of tubing to deliver blood from the arterial circulation to the oxygenator with return to the venous circulation. All blood contacting surfaces incorporated an antithrombogenic agent to reduce clotting risk and reduce requirements for systemic anticoagulation. (27)

Initial experiments used a carotid artery/jugular vein cannulation strategy in near-term lambs (120–140 days; full-term, 145 days) to avoid umbilical spasm. After exposure by maternal hysterotomy, the vessels were cannulated, with connection of the cannulas to the circuit tubing to establish extracorporeal flow before transferring the fetus into a fluid-filled incubator. From our earliest pilot experiments, animals supported with EXtracorporeal Transitional Environment for Neonatal Development (EXTEND) have demonstrated remarkable hemodynamic stability without evidence of progressive acidosis or circulatory failure.

Sepsis secondary to contamination of the incubator fluid was observed at high rates in our early studies, precluding experiments in excess of more than 1 to 2 weeks. Our early models for fluid-filled incubation relied on recirculation and filtration of synthetic amniotic fluid, which resulted in high rates of bacterial growth within the experimental apparatus. A key component of our success was the development of the "Biobag," a closed fluid environment incorporating continuous exchange of synthetic amniotic fluid rather than recirculation (Figure). This design allows complete continuous turnover of the fluid from 4 to 10 incubator volumes per day, analogous to fluid exchange in utero. (28) Since institution of the Biobag, we have not observed any clinically significant infections in our lambs despite maintenance on EXTEND for up to 4 weeks.

The canalicular stage of lung development occurs between 22 and 24 weeks' gestation in the human infant, (29) corresponding to 100 to 115 days gestation in the lamb. (30) Our initial pilot studies in 110-day gestation lambs using the carotid artery and jugular vein for vascular access demonstrated diminishing circuit flows and progressive edema analogous to the results of previously published attempts at pumpless perfusion. Analysis of the hemodynamics in these lambs confirmed reduced perfusion pressure of the circuit as a result of the high-flow, high-pressure venous return via the superior vena cava. This was in contrast to the normal low-pressure venous return via the umbilical vein and ductus venosus with baffling of oxygenated blood across the foramen ovale to the left atrium.

Normalization of the arteriovenous pressure gradient on EXTEND was achieved by cannulation of the umbilical vessels, with the development of a technique for umbilical cannulation that maintains a length of native umbilical cord (~5 cm because sheep have a very short umbilical cord) between the cannula tips and the abdominal wall. The use of the umbilical cord takes advantage of its natural resistance to mechanical obstruction, and minimization of cannula length within the vessels avoids issues of kinking, trauma, or erosion. Spasm of the umbilical vessels, a major concern, was avoided with the use of meticulous surgical technique, rapid reinstitution of blood flow, papavarine when needed, and maintenance of low oxygen tension and normal temperature in the circuit blood. With these measures, umbilical vascular spasm has not been limiting; in fact, we have observed autoregulation of circuit blood flow by an increase in umbilical venous resistance. The result has been that we have observed normal or near-normal "placental" blood flow of 150 to 250 mL/kg per minute in our 105- to 115-day lambs (developmentally equivalent to 22–25 weeks' human gestation) for up to 4 weeks, allowing for normal growth, oxygen delivery, and organ maturation. Daily echocardiography confirmed maintenance of the fetal circulation with excellent contractility and function.

We observed significant qualitative growth and development over the course of the experiments, with the

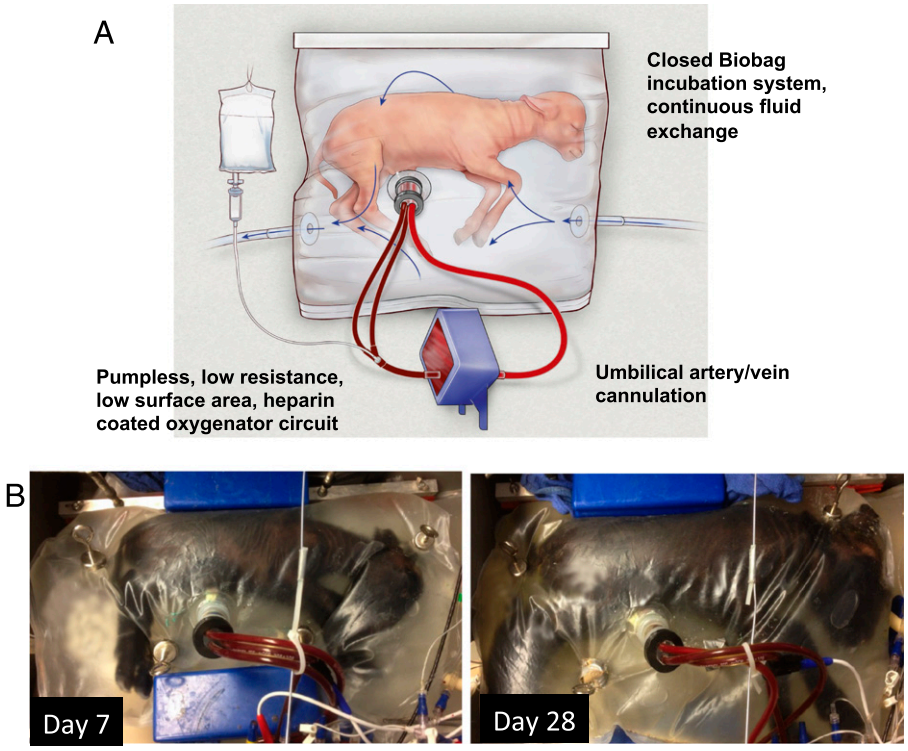

Figure. UA/UV Biobag System Design. A. Circuit and system components. B. Representative lamb supported on day 7 through day 28 demonstrating interval growth.

animals opening their eyes, becoming more active, displaying normal breathing and swallowing movements, and growth of wool over the course of incubation. Tissue histology after 4 weeks of support demonstrated evidence of normal growth and development, with lung morphometric analysis showing progression from the canalicular to saccular stage of development in parallel with age-matched normal control specimens. Animal brains showed normal histology and weight, with no evidence of hemorrhage or infarct on whole sectioning. Most importantly, animals have generally required minimal levels of ventilator support after removal from the circuit and a few animals have made the transition off ventilator support after up to 28 days on EXTEND.

The development of an artificial placenta raises enormous possibilities for clinical innovation in the care of the critically preterm infant, with other possible applications for therapeutic intervention in the setting of intrauterine growth restriction, congenital malformations of major organs, and genetic or biochemical congenital anomalies. Presently, the substantial risk of morbidity and mortality in this patient population represents an unmet need in neonatal medicine and justifies further development and an experimental clinical trial. We envision an approach using a modified ex utero intrapartum treatment ("EXIT") procedure to achieve stable and sterile cannulation, with initial clinical efforts limited to a small number of patients in a center with substantial experience in ECMO and fetal surgery.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the indications, techniques, effects, and risks of extracorporeal membrane oxygenation (ECMO).

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