Pediatric Pulmonology 51:557–559 (2016)

Editorial

The Artificial Placenta: Is Clinical Translation Next?

George B. Mychaliska, MD*

Despite significant advances in the treatment of prematurity including antenatal steroids, advanced mechanical ventilation strategies, and exogenous surfactant, the mortality and morbidity remain high for these vulnerable infants. In particular, the mortality and morbidity of extremely low gestational age newborns (ELGANs) defined as <28 weeks estimated gestational age (EGA), is extremely high.[1] A radical paradigm shift in the treatment of extreme prematurity would be to re-create the intra-uterine environment using an extracorporeal artificial placenta (AP).

In this issue, Metelo-Coimbra and Roncon-Albuquerque[2] review recent advances in the field and assess barriers to clinical translation. From the outset, it should be acknowledged that although there is a large number of premature births worldwide (defined as <37 weeks EGA), outcomes have substantially improved for infants >28 weeks EGA. Apart from some specific congenital anomalies like congenital diaphragmatic hernia, the AP is intended for the treatment of ELGANS who experience the most complications of prematurity and whose outcome remains poor.

The authors focus on lung immaturity and provide substantial evidence of the iatrogenic effects of mechanical ventilation on both lung injury and the deleterious cardiovascular effects.[2] It is worth noting that although ELGANS are predisposed to interventricular hemorrhage (IVH) given their immature germinal matrix, mechanical ventilation has been implicated in the pathogenesis of IVH by increasing intrathoracic and intracranial pressure with every breath.[3] The ELGANs who are never subjected to positive airway pressure have fewer complications of prematurity. An appreciation of the deleterious effects of mechanical ventilation and high oxygen concentrations on premature lungs has led to a dramatic shift toward less invasive ventilator strategies for premature infants. Although this strategy appears promising for some patients,[4] there is still a subset of ELGANS that cannot maintain adequate gas exchange with the most invasive ventilator strategies.

Although the pulmonary system is critical to initial survival and long-term pulmonary morbidity is high among survivors, there are other significant complications of ELGANs that warrant consideration. Predictable and unsolved complications associated with prematurity include neurologic injury (IVH, white matter injury), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and sepsis. Our current inability to prevent these complications relates both to organ immaturity and conventional treatment strategies such as positive pressure ventilation, that have historically been developed for full term infants. To potentially solve these problems, the AP must not only recreate the fetal milieu and provide life-sustaining functions such as adequate gas exchange and fetal hemodynamic stability, but it should also protect against organ trauma and allow the normal developmental pathways to occur.

An AP may appear far beyond the reach of modern science, but the idea of creating a life support system to maintain growing fetuses in a womb-like environment with extracorporeal support was first investigated 60 years

Section of Pediatric Surgery, Department of Surgery, Fetal Diagnosis and Treatment Center, University of Michigan Medical School, C.S. Mott Children's Hospital,, 1540 E. Medical Center Drive, SPC 4211, Ann Arbor, Michigan 48109.

Conflict of Interest: None.

Funding source: NIH, Number 1R01HD073475-01A1.

*Correspondence to: George B. Mychaliska, MD, Section of Pediatric Surgery, Department of Surgery, Fetal Diagnosis and Treatment Center, University of Michigan Medical School, C.S. Mott Children's Hospital, 1540 E. Medical Center Drive, SPC 4211, Ann Arbor, MI 48109.
E-mail: mychalis@med.umich.edu

Received 20 February 2016; Accepted 6 March 2016.

DOI 10.1002/ppul.23412
Published online 19 April 2016 in Wiley Online Library (wileyonlinelibrary.com).

ago! Metelo-Coimbra and Roncon-Albuquerque provide a succinct review of AP terminology and history of milestones.[2] Since fetuses normally develop with extracorporeal support, it should perhaps not surprise us that researchers were drawn to this concept shortly after the successful introduction of cardio-pulmonary bypass. For historians of science, it is noteworthy that researchers were on the right path, but got derailed many times due to the state of biomedical technology and insufficient knowledge of the physiology of premature infants. In my view, the history of the development of the AP is marked by many experimental failures with episodic successes. Despite incremental success, many research groups abandoned this work as progress was being made with antenatal steroids, exogenous surfactant, advanced mechanical ventilation strategies, and ECMO for term and near-term infants.

An appreciation of the unsolved problems of extreme prematurity coupled with recent advances detailed by the authors[2] has led to a resurgence of work on the AP. The fetal lamb is the best model, and the lamb gestational age which corresponds to ELGAN lungs is 118 days gestation (term = 145 days). Although the AP is promising and has the potential to radically change the treatment of prematurity, several obstacles remain. As the authors point out,[2] the first issue is the most effective ECLS configuration. A simple pumpless AV-ECLS circuit utilizing the umbilical vessels is appealing, but our experience demonstrated only short-term survival and declining cardiac function.[5] Despite cannulation of the umbilical arteries to the sheep aorta (to obviate vessel spasm) and adding a pump, matching extracorporeal flow to systemic flow is very difficult (the native placenta does this automatically). In addition, given the tortuosity, size, and spasm associated with human umbilical arteries, we transitioned to a pump-driven VV-ECLS model with inflow via the umbilical vein and outflow via the jugular vein. This approach provides 7 days of support with excellent gas exchange and hemodynamic stability.[6] With current technology, we believe this strategy is clinically translatable to extremely premature infants.

As mentioned previously, the AP strategy will require long-term support (2–4 weeks in humans) and demonstration that organs are maturing and protected from trauma. This corresponds to 10–14 days in the 118 day lamb model. As such, an in-depth study of lung development, long-term support, and weaning to a ventilator and air breathing will be required. A crucial aspect of lung development will be the airway strategy during AP support. In our early work, the fetal lambs were submerged in a warmed "amniotic bath" effectively recreating the intrauterine environment.[5,7] While appealing in some regards, there are infection and patient access issues with this approach. More recently, we have been intubating the fetal lambs, filling them with amniotic fluid or Perflubron and either capping the endotracheal tube or maintaining 5–8 cm H_2O pressure. It is possible to harness the power of mechanotransduction with this approach and possibly accelerate lung growth.[8,9]

Apart from lung development which is crucial during AP support, other vulnerable premature organs need to be examined. Brain perfusion, function, and development are critical to understand. Although the sheep is not a good model for IVH, brain physiology and evidence of white matter injury can be assessed. With a high incidence of NEC in premature infants, optimal nutrition and perfusion of the gastrointestinal system warrants investigation. Long term survivors of the AP should be examined for evidence of retinopathy of prematurity. Lastly, renal and hepatic function should be addressed.

As a general rule, extracorporeal support is reserved for infants $\geq$ 34 weeks EGA due to a higher rate of IVH in extremely premature infants. The authors point out the feasibility of "preemie ECMO" in infants from 29 to 33 weeks,[2] but ELGANs would have prohibitively high rates of IVH. As such, a critical barrier to clinical application will be the development of non-thrombogenic surfaces that will obviate the need for anti-coagulation.[10,11] Lastly, clinical application will require a clinical prognostication tool to select premature infants at the highest risk for mortality on the first day of life.[12]

Given recent advances and ongoing work, we believe that the AP will be used in ELGANs in the next 5 years.

REFERENCES

1. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 2010;126:443–456.
2. Metelo-Coimbra C, Roncon-Albuquerque R, Jr. Artificial placenta: recent advances and potential clinical applications. Pediatr Pulmonol. doi: 10.1002/ppul.23401.
3. Aly H, Hammad TA, Essers J, Wung JT. Is mechanical ventilation associated with intraventricular hemorrhage in preterm infants? Brain Dev 2012;34:201–205.
4. Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ 2013;347:f5980.
5. Reoma J, Rojas A, Kim A, Khouri J, Boothman E, Brown K, Grotberg J, Cook K, Bartlett R, Hirschl R, et al. Development of an artificial placenta I: pumpless arterio-venous extracorporeal life support in a neonatal sheep model. J Pediatr Surg 2009;44:53–59.
6. Bryner B, Gray B, Perkins E, Davis R, Hoffman H, Barks J, Owens G, Bocks M, Rojas-Pena A, Hirschl R, et al. An extracorporeal artificial placenta supports extremely premature lambs for 1 week. J Pediatr Surg 2015;50:44–49.
7. Gray BW, El-Sabbagh A, Rojas-Pena A, Kim AC, Gadepali S, Koch KL, Capizzani TR, Bartlett RH, Mychaliska GB. Development of an artificial placenta IV: 24 hour venovenous extracorporeal life support in premature lambs. ASAIO J 2012;58:148–154.
8. Mychaliska G, Bryner B, Dechert R, Kreutzman J, Becker M, Hirschl R. Safety and efficacy of perflubron-induced lung growth in neonates with congenital diaphragmatic hernia: results of a prospective randomized trial. J Pediatr Surg 2015;50:1083–1087.

9. Shue EH, Miniati D, Lee H. Advances in prenatal diagnosis and treatment of congenital diaphragmatic hernia. Clin Perinatol 2012;39:289–300.
10. Major TC, Brant DO, Burney CP, Amoako KA, Annich GM, Meyerhoff ME, Handa H, Bartlett RH. The hemocompatibility of a nitric oxide generating polymer that catalyzes S-nitrosothiol decomposition in an extracorporeal circulation model. Biomaterials 2011;32:5957–5969.
11. Major TC, Brant DO, Reynolds MM, Bartlett RH, Meyerhoff ME, Handa H, Annich GM. The attenuation of platelet and monocyte activation in a rabbit model of extracorporeal circulation by a nitric oxide releasing polymer. Biomaterials 2010;31:2736–2745.
12. Reid S, Bajuk B, Lui K, Sullivan EA. Comparing CRIB-II and SNAPPE-II as mortality predictors for very preterm infants. J Paediatr Child Health 2015;51:524–528.