Artificial Placenta: Recent Advances and Potential Clinical Applications

Catarina Metelo-Coimbra, MD,1 and Roberto Roncon-Albuquerque, Jr., MD, PhD1,2*

Summary. Lung immaturity remains a major cause of morbidity and mortality in extremely premature infants. Positive-pressure mechanical ventilation, the method of choice for respiratory support in premature infants, frequently promotes by itself lung injury and a negative impact in the circulatory function. Extracorporeal lung support has been proposed for more than 50 years as a potential alternative to mechanical ventilation in the treatment of severe respiratory failure of extremely premature infants. Recent advances in this field included the development of miniaturized centrifugal pumps and polymethylpentene oxygenators, as well as the successful use of pump-assisted veno-venous extracorporeal gas exchange systems in experimental artificial placenta models. This review, which includes studies published from 1958 to 2015, presents an update on the artificial placenta concept and its potential clinical applications. Special focus will be devoted to the milestones achieved so far and to the limitations that must be overcome before its clinical application. Notwithstanding, the artificial placenta stands as a promising alternative to mechanical ventilation in extremely premature infants. Pediatr Pulmonol. 2016;51:643–649.

Key words: Artificial placenta; bronchopulmonary dysplasia; extracorporeal membrane oxygenation; extremely premature infant; respiratory distress syndrome.

INTRODUCTION

According to the World Health Organization, 15 million premature infants are born every year, with almost 1 million deaths directly attributed to prematurity.1 Although all premature infants are at risk for complications, extremely premature (EPT) infants, born at or before 28 weeks of gestation, suffer the greatest morbidity and mortality.1 Respiratory distress syndrome and bronchopulmonary dysplasia remain a major cause of morbidity and mortality in EPT infants.2 This relates with pulmonary immaturity, given that EPT infants are born during the canalicular period of lung development, characterized by capillarization and pulmonary acini morphogenesis, with insufficient surfactant production.3

Positive-pressure mechanical ventilation with high oxygen concentrations remains the method of choice to provide lung support in preterm infants with severe respiratory failure.4 However, mechanical ventilation in preterm infants promotes, by itself, lung injury that negatively impacts survival. The known direct mechanisms of ventilator-induced lung injury are barotrauma, volutrauma, and atelectrauma.5 These mechanisms promote biotrauma with capillary endothelium, alveolar epithelium, and basal membrane damage, which results in fluid, protein and blood extravasation into the airways,

1Department of Physiology and Cardiothoracic Surgery, Faculty of Medicine of Porto, Porto, Portugal.

2Department of Emergency and Intensive Care Medicine, Hospital de S. João, Porto, Portugal.

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Correspondence to: Roberto Roncon-Albuquerque, Jr., MD, PhD, Department of Physiology and Cardiothoracic Surgery, Faculty of Medicine of Porto and, Department of Emergency and Intensive Care Medicine, Hospital de S. João, Al. Prof. Hernani Monteiro, Porto 4200-319, Portugal. E-mail: rra_jr@yahoo.com

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alveoli, and pulmonary interstitium, with consequent surfactant inhibition and activation of local and systemic inflammatory responses. Mechanical ventilation also adversely affects the circulatory function of preterm infants, reducing pulmonary blood flow and left ventricular output. In fact, positive-pressure mechanical ventilation decreases the alveolar/capillary transmural pressure gradient, causing compression of the intra-alveolar capillaries, which increases pulmonary vascular resistance, therefore decreasing pulmonary blood flow. Further increases in airway pressure and pulmonary vascular resistance may sustain pulmonary arterial pressures above systemic arterial pressures, potentiating continued right-to-left shunt through the ductus arteriosus. The effect of positive-pressure ventilation is not limited to the pulmonary vasculature, with direct compressive effects observed on the newborn heart, resulting in reduced cardiac performance and ventricular output. This could be particularly relevant in the immature myocardium of the preterm heart that presents low contractility with an inability to cope with increasing afterload in the days after birth.

In light of these limitations, extracorporeal lung support has been proposed more than 50 years ago as a potential alternative to mechanical ventilation in the treatment of severe respiratory failure of EPT infants. Its main benefits reside in the fact that, by bypassing the lungs completely, the AP avoids potential barotrauma resulting from mechanical ventilation. However, by then, artificial organ technology was still in its infancy and the understanding of EPT pathophysiology was very limited. More recently, important developments in extracorporeal lung assist technology were observed, fostering a renewed interest in artificial placenta (AP) research.

In this review, an update on the AP concept and its potential applications is presented. Special focus will be devoted to the milestones achieved so far and to the major limitations that must be overcome before its clinical application.

METHODS

Eligible studies were identified by an electronic search of PubMed and Scopus, involving studies published from 1958 to 2015. The sensitive search strategy combined the following keywords: artificial placenta; bronchopulmonary dysplasia; extracorporeal lung assist; extracorporeal membrane oxygenation; extremely premature infants; polymethylpentene oxygenator; and respiratory distress syndrome. All articles and cross-referenced studies from retrieved articles were screened for pertinent information and reviewed by both Authors.

Inclusion criteria consisted in experimental and systematic review articles, published as original studies, with available abstract. Publications not written in English or not related to the neonatal period were excluded.

ARTIFICIAL PLACENTA: THE CONCEPT

The terminology describing extracorporeal life support (ECLS) in premature infants is divided in three categories, established according to the gestational age: (i) neonatal ECMO: for infants of at least 34 weeks of gestation (moderate to late preterm newborns); this technique is successfully used in clinical practice for more than 30 years; (ii) preemie ECMO: for premature infants between 29 and 33 weeks of gestation (very preterm newborns); although technically feasible, reduced survival and increased rates of intra-ventricular hemorrhage have been reported; and (iii) artificial placenta: for EPT infants, born before 28 weeks; the AP currently remains under experimental research.

Therefore, the AP concept consists in extracorporeal membrane gas exchange (blood oxygenation and extracorporeal CO₂ removal) for EPT infants with immature pulmonary system and severe respiratory failure, as a bridge to the development of native lung function. The AP does not include provision of other placental functions such as nutrient or metabolic product exchange.

AP models are generally defined by the following characteristics: (i) extracorporeal lung support with preservation of fetal circulation: either the umbilical artery (pumpless arteriovenous ECLS, A-V-ECLS) or a central vein (pump-assisted venovenous ECLS, VV-ECLS) are used for blood outflow from the patient to the extracorporeal circuit; the umbilical vein is always used for inflow to the patient from the extracorporeal circuit (Fig. 1); (ii) low partial pressure of oxygen, given that oxygen-binding capacity of fetal hemoglobin and hematocrit are increased; (iii) absence of positive-pressure mechanical ventilation; (iv) simulated fetal breathing with fluid-filled lungs; (v) biocompatibility of the extracorporeal circuit inner surfaces in direct contact with blood; high levels of systemic anticoagulation associate with an unacceptable risk of intracranial hemorrhage in EPT infants.

Pump-assisted VV-ECLS systems presents several advantages when compared to pumpless AV-ECLS: (i) arterial vessel cannulation is not required; cannulation of umbilical arteries in EPT infants is technically challenging and frequently complicates with vessel spasm; (ii) an external blood reservoir is not required given that the EPT infant’s own venous system is used as blood reservoir; (iii) it operates in parallel with systemic circulation, therefore not increasing afterload of the fetal heart; differently, pumpless AV-ECLS operates in series with systemic circulation, increasing the fetal heart workload that can complicate with high-output heart failure.
Membrane lung permeability to O₂ and CO₂ is a critical factor influencing AP performance. Silicone rubber membranes were initially used, composed of a permeable non-porous polymeric material with loosely packed polymeric chains. Another type of oxygenator is the hollow-fiber membrane, which has woven capillary tubes composed of microporous polypropylene. Despite higher gas permeability, polypropylene membranes are less frequently used given the high plasma leakage risk with increased extracorporeal circuit blood pressures. Moreover, silicone rubber membranes present higher biocompatibility when compared with polypropylene fibers for long-term ECLS.

Polymethylpentene (PMP) oxygenators have been used in clinical practice for a decade. PMP fibers have an asymmetric pore structure with a very thin dense outer skin that allows gas transfer while suppressing the direct contact of blood and gas across micropores. These features enhance durability and greatly reduce plasma leakage. Moreover, PMP oxygenators present more efficient priming, reduced hemodynamic resistance and better preservation of coagulation proteins.

EARLY MILESTONES

Following the development and implementation of the heart–lung machine, it was soon recognized that this concept could be similarly applied to the treatment of severe respiratory failure of the premature infant. In 1958, Westin et al. prolonged the life of preivable human fetuses by cannulating the umbilical vessels and circulating the fetal blood through a rotating oxygenator. When injecting regular doses of glucose solution, the fetal heart continued to beat for a period up to 12 hr. The fetuses were maintained in a warm artificial amniotic fluid bath.

Callaghan et al. were the first to develop the AP concept in animal experiments, back in 1961. A pump-assisted VV-ECLS circuit with a rotating disc oxygenator was used in eight sheep. Blood outflow from the animal to the extracorporeal circuit was performed via both femoral and jugular veins, while inflow to the animal from the extracorporeal circuit was made either through the right atrium or the right ventricle. In 1962, a period of up to 2.5 hr survival of mongrel dogs using this procedure was reported.

These achievements have been overcome by Lawn and McCance, who conceived a pumpless AV-ECLS circuit with a dialyzer that was tested in preivable pig fetuses. Blood drained from the umbilical arteries circulated through the oxygenator and then through cellophane tubing immersed in a suitable rinse. Blood returned to the umbilical vein without requiring external pump assistance. A similar perfusion apparatus was constructed in 1964 by Alexander et al., but the dialyzer was excluded. It was concluded from their experiments that a perfusion system with constant volume would be necessary, due to changes in venous pressure.

Meanwhile, SenGupta et al. described a portable, self-contained and self-powered AP consisting of a flexible, inert silicone elastomer membrane oxygenator and a pump. Their first experiment had 11 out of 16 survivors during up to 5 hr of connection to the AP. Two years later, there were 16 survivors out of 20 dogs, and most perfusions took more than 2 hr. Though satisfactory oxygenation was obtained, the short period of survival was considered unsafe.

Significant progress was achieved in 1969 by Zapol et al., when a premature lamb fetus was totally sustained by extracorporeal perfusion using a silicone-membrane
blood oxygenator. The animal received parenteral nutritional support and remained metabolically stable for up to 55 hr. A study with 10 lamb fetuses using angiocardiographic techniques was presented the following year. Zapol et al. also described the modulation of ductus arteriosus and pulmonary blood flow by blood oxygen tension in their AP model. 

Efforts on the development of an AP were almost entirely abandoned by 1979, when a completely different approach to treat severe respiratory failure in premature infants was implemented: positive-pressure mechanical ventilation. This led to a dramatic improvement of premature infants survival, although many problems remained. Compared with positive-pressure mechanical ventilation, the AP was at that time too complex and unsafe for clinical use leading to a gap of research in the next decade.

In 1987, Kuwabara et al. developed a novel AP system. They compared two types of circuits, with and without a blood reservoir, using goat fetuses. In the first group, the duration of incubation was increased to 165 hr, in contrast to the 8 hr achieved by the control group. The oxygenator was made of silicone, and blood was drained from the umbilical arteries and returned to the umbilical vein. This was the first report on animal experiments of prostaglandin E1. This last experiment suggested that the administration of prostaglandin E1 improved lung function and protected from meconium aspiration. 

In 1993, continuing this work, Unno et al. tried a new protocol to study the influence of body movement on goat fetuses’ survival. It was demonstrated that AV-ECLS with umbilical blood access could support premature goat fetuses for up to 3 weeks. The following studies focused on fetal hemodynamics, such as fetal ductal blood velocity through Doppler echocardiography and the effect of prostaglandin E1. This last experiment suggested that the administration of prostaglandin E1 prevented the constriction of ductus arteriosus, a phenomenon that was found to disturb fetal circulation to the AP. This research group also compared four different methods to control blood flow in an AV-ECLS circuit, concluding that the control of extracorporeal circulation flow by altering the circuit resistance was one of the main contributing factors to the success of long-term incubation.

In 1998, Sakata et al. reported the successful use of a centrifugal pump, which allowed higher extracorporeal flow rates. This group used polyolefin hollow fiber membrane oxygenators, which contributed to low circuit resistance. In the same year, Yasufuku et al. refined the AP concept by performing upper tracheal ligation, which maintained lung expansion and protected from meconium aspiration.

**RECENT MILESTONES**

In 2012 Gray et al., from the University of Michigan ECLS Laboratory, hypothesized that a pump-assisted VV-ECLS circuit would preserve systemic fetal circulation while providing adequate extracorporeal gas exchange. The right jugular vein was cannulated for outflow from the animal to the extracorporeal circuit, whereas an umbilical vein was used for blood inflow to the animal from the extracorporeal circuit. Blood cavitation was reduced, since blood was passively drained from the right atrium. A miniaturized polypropylene hollow fiber oxygenator was used. The experiment was successful, being the first report of a 24 hr survival of five Lamb fetuses using a pump-assisted VV-ECLS circuit. Continuing this work, seven lambs were incubated on a dry heated waterbed and maintained on VV-ECLS for up to 70 hr. This AP model was able to provide hemodynamic stability and efficient extracorporeal gas exchange, with preservation of cerebral perfusion for an extended period of time. No signs of gross or microscopic intra-ventricular hemorrhage were found despite systemic anticoagulation with heparin.

In 2015, Bryner et al. compared a pump-assisted VV-ECLS system with positive-pressure mechanical ventilation in EPT lamb fetuses. Four lambs were successfully supported for 1 week using a polypropylene oxygenator and a rotary pump. Differently, lambs treated with positive-pressure mechanical ventilation survived on average less than 4 hr, despite the use of exogenous surfactant and steroids. No evidence of intracranial hemorrhage was observed. The main issues faced by researchers were directly related to cannulation, with one case of pericardial tamponade and arrhythmias.

Besides the improvements in extracorporeal circuit configuration, important advances were achieved in oxygenator technology. Arens et al. developed a miniaturized oxygenator to be used in AP models. This research group catheterized lambs through two umbilical arteries and two umbilical veins, and the fetuses were kept in a warming bed. Their oxygenator, NeonatOx, was placed as close as possible to the lambs, allowing short tubing and low circuit resistance. Furthermore, the oxygenator was miniaturized to a priming volume of only 20 ml. This reduced device surface area, decreasing thrombogenesis and inflammation. NeonatOx allowed successful extracorporeal gas exchange for 6 hr in six out of seven animals. One limitation related to the durability of umbilical vascular accesses, since artificial amniotic medium submersion was not performed.

Meanwhile, Canadian investigators designed a micro-fluidic oxygenator with efficient gas exchange. Four different gas permeable membranes were tested using human blood. The porous polydimethylsiloxane
membrane had the highest gas exchange rate. Recently, further improvements were performed to this oxygenator, with the novel device being modifiable according to the EPT infants’ body weight. This microfluidic oxygenator was tested in piglets during 4 hr.

FUTURE DIRECTIONS

Although much progress has been made in the AP field and despite the different models studied so far (Tables 1 and 2), several limitations still preclude its clinical application.

Regarding the extracorporeal circuit itself, pump-assisted VV-ECLS models have shown many advantages over pumpless AV-ECLS circuits. Although its simplicity is appealing, the use of pumpless AV-ECLS in EPT infants seems technically impracticable due to the small size and tortuosity of the umbilical arteries, as well as to the need of prolonged extracorporeal lung support and hemodynamic stability.

Concerning anticoagulation, the development of novel biomaterials will presumably improve surface biocompatibility of the extracorporeal circuit, reducing (or even eliminating) the need for systemic anticoagulation, importantly decreasing intracranial hemorrhage risk. In this regard, research is underway towards the development of non-thrombogenic surface extracorporeal circuit coating.

Artificial placenta miniaturization will also be improved, decreasing extracorporeal surface area and circuit resistance. The use of PMP oxygenators, which present high durability and reduced plasma leakage, is a predictable next step, given its successful use in adult ECMO.

Further studies are required to show that the lung is protected and continues to mature during AP support. This implies that lung development between the stages of birth, AP support and progression to air breathing needs to be demonstrated and documented.

Concerning the brain, studies need to show that there is adequate brain perfusion and that this organ in protected without bleeding or white matter injury during AP support. This is essential given that, regarding neurological complications, the majority of sequelae appear to be related to hypoxemia and hemodynamic instability that occurs before the onset of ECLS.

The impact of the AP in the cardiovascular, gastrointestinal, and renal systems also deserves further investigation. Cardiovascular stability during pump-assisted VV-ECLS in EPT infants also needs to be confirmed.

| Reference | Year | Model | Circuit | Oxygenator | Pump | Submersion | Survival |
|-----------|------|-------|---------|------------|------|------------|----------|
| 25        | 1958 | Human | AV-ECLS | Rotating film | Yes | Yes | 5–12 hr |
| 26        | 1961 | Lamb  | VV-ECLS | Rotating disc | Yes | Yes | 8–19 hr |
| 27        | 1962 | Dog   | VV-ECLS | Rotating disc | Yes | Yes | 2.5 hr |
| 28        | 1962 | Piglet| AV-ECLS | Rotating disc film | Yes | Yes | 8 hr |
| 29        | 1963 | Lamb  | AV-ECLS | Rotating disc film | Yes | Yes | 40 min |
| 30        | 1964 | Lamb  | AV-ECLS | Rotating disc film | Yes | No | 1 hr |
| 31        | 1964 | Dog   | AV-ECLS | Membrane | Yes | — | 2–5 hr |
| 32        | 1965 | Lamb  | AV-ECLS | Rotating disc film | No | Yes | 0.3–3 hr |
| 33        | 1966 | Human | AV-ECLS | Coiled membrane | Yes | — | 1.5–5 hr |
| 34        | 1968 | Lamb  | AV-ECLS | Rotating disc film | Yes | Yes | 24 hr |
| 35        | 1969 | Lamb  | AV-ECLS | Silicone coiled | Yes | Yes | 4–55 hr |
| 36        | 1979 | Lamb  | AV-ECLS | Microchannel membrane | Yes | No | — |
| 37        | 1987 | Goat  | AV-ECLS | Silicone hollow fiber | Yes | Yes | Up to 165 hr |
| 38        | 1989 | Goat  | AV-ECLS | Silicone hollow fiber | Yes | Yes | Up to 236 hr |
| 39        | 1993 | Goat  | AV-ECLS | Silicone hollow fiber | Yes | Yes | Up to 542 hr |
| 40        | 1998 | Goat  | AV-ECLS | Polyolefin hollow fiber | Yes | Yes | Up to 237 hr |

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before establishing this configuration as the preferred AP circuit.

The ability of EPT infants to wean from AP support without major lung sequelae is a central issue that needs further demonstration. This will impact on clinical criteria for AP use, which remain to be established.

CONCLUSION

Lung immaturity still associates with high morbidity and mortality in EPT infants. Extracorporeal lung support has been proposed for more than 50 years as a potential treatment of severe respiratory failure of EPT infants. Recent progresses in extracorporeal circuit biotechnology renewed the interest in experimental and clinical AP research. Notwithstanding the several challenges remaining, the AP remains an attractive potential alternative for EPT infants failing positive-pressure mechanical ventilation. The successful application of the AP into clinical practice would definitely be a milestone in neonatal medicine.

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