Artificial placenta - Lung assist devices for term and preterm newborns with respiratory failure

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ABSTRACT

Respiratory insufficiency is a major cause of neonatal mortality and long-term morbidity, especially in very low birth weight infants. Today, non-invasive and mechanical ventilation are commonly accepted procedures to provide respiratory support to newborns, but they can reach their limit of efficacy. To overcome this technological plateau and further reduce mortality rates, the technology of an “artificial placenta”, which is a pumpless lung assist device connected to the umbilical vessels, would serve to expand the therapeutic spectrum when mechanical ventilation becomes inadequate to treat neonates with severe respiratory insufficiency.

The first attempts to create such an artificial placenta took place more than 60 years ago. However, there has been a recent renaissance of this concept, including developments of its major components like the oxygenator, vascular access via umbilical vessels, flow control, as well as methods to achieve hemocompatibility in extracorporeal circuits. This paper gives a review of past and current development, animal experiments and human case studies of artificial placenta technology.

KEY WORDS: Respiratory support, Blood oxygenation, Gas exchange, Extracorporeal membrane oxygenation, Umbilical catheter

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INTRODUCTION

The first attempts to develop an artificial placenta as a lung assist device were made in the mid-20th century in search of an effective technique to provide respiratory support for newborns (1). The artificial placenta was designed to mimic partial fetal circulation and placental gas exchange while directly connected to the umbilical vessels. These efforts were abandoned in the late 20th century with the successful developments of mechanical ventilation, surfactant replacement therapy, and nasal continuous positive airway pressure (CPAP), which led to a significant decrease in neonatal mortality. In comparison to these respiratory therapies, the principle of the artificial placenta appeared too complex for the technology available at that time to make it safe for clinical use (2).

Considerable effort has been made to develop more advanced respiratory treatments using mechanical ventilation, such as high frequency oscillation ventilation (HFO). Despite technological advancements, these technologies seem to have reached their pinnacle of clinical potential. Mechanical ventilation has been associated with increased risk of lung
Lung assist devices for newborns

damage and a significant proportion of newborn fatalities in neonatal intensive care units (NICUs) have been attributed to respiratory insufficiency (3). New advancements in ventilator technology that would overcome this technological plateau and reduce the fatalities do not seem likely over the next decade.

An alternative approach is to provide extra-pulmonary and thus ventilator-free gas exchange of the blood through the use of extracorporeal membrane oxygenation (ECMO). This approach provides a system similar to the lungs and could potentially alleviate many of the disadvantages of mechanical ventilation. However, current ECMO systems are invasive, requiring vascular cut down, full body anticoagulation, and cardiovascular assistance with pumps. These systems are limited to infants >2.0 kg in body weight and cannot be used for premature babies (4). In light of these limitations, recent publications (5-7) have highlighted the potential of artificial placenta lung assist devices as an innovative technology in the treatment of neonatal respiratory distress.

The concept of the artificial placenta as a postnatal lung assist device for newborns

In utero, the developing fetus is connected to the placenta, which serves as the interface between maternal and fetal circulations and provides fetal nutrient uptake, metabolite elimination, and gas exchange via the mother’s blood. On the fetal side, the placenta is connected in parallel to the systemic circulation of the fetus; blood from the descending aorta is channeled through the umbilical arteries to the placenta and back to the body and central venous system via the umbilical vein. Fetal blood flow through the placenta ranges from 90 to 180 mL/kg per min, depending on gestational age of the fetus, which represents about 20% to 30% of total cardiac output (8, 9).

After birth, the newborn is disconnected from the placental supply and the function of its organs must immediately adapt to the extra-uterine environment. In preterm and term infants that develop severe postnatal respiratory insufficiency, it would be desirable to re-connect these newborns to a placenta and allow partial fetal circulation to facilitate extracorporeal gas exchange. Although this cannot be done with the natural placenta, it may be worthwhile to construct a device in its place (Fig. 1). This artificial placenta could partially take over gas exchange function until the infant recovers from the initial cause of the lung failure during the early postnatal period. This device could be applied to the newborn in conjunction with other forms of respiratory support. The additional extracorporeal gas exchange would improve survival rates of preterm and term newborns with respiratory failure when mechanical ventilation is insufficient. Further, the artificial placenta could decrease the occurrence of chronic lung disease by reducing the amount of mechanical ventilation. This later application would especially benefit early preterm infants.

Such an artificial placenta would be defined by the following characteristics (Fig. 2).

1. It is a lung assist device for newborns with respiratory failure which is connected to the umbilical vessels,
similar to the natural placenta, and would be in parallel with systemic circulation. Using this natural vascular access is beneficial for ease of use and also avoids complications associated with surgical access to large vessels.

2. This device would be pumpless, and be driven by the arterio-venous pressure difference alone. Parallel to re-establishing a partial fetal circulation through the artificial placenta, the lungs will simultaneously be perfused and ventilated, which is different from the in utero situation. The artificial placenta will significantly contribute to gas exchange of the newborn, however, since residual lung function is still available it is not supposed to provide total body needs (5, 7, 10). Consequently, less blood flow is needed to circulate the extracorporeal device, thereby reducing the risk of cardiac high-output failure.

3. In addition, such a miniature lung assist device would benefit from having a priming volume of below 10 mL/kg body weight. This layout would allow the device to be primed with normal saline: as the normal blood volume of a newborn is 95 to 100 mL/kg body weight, the concentration of hemoglobin would not drop by more than 11%. This is also comparable to the commonly used approach to give saline fluid boluses of 10 to 20 mL/kg body weight to infants with hypotension (11, 12).

4. All inner surfaces being in contact with blood will be hemocompatible, requiring no systemic anticoagulation. Furthermore, the artificial placenta would not contribute to other placental functions like nutrient and metabolic products exchange.

The aim of this review is to survey the development of life support systems that form partial fetal circulation for newborn infants under respiratory distress. The content of this paper is organized based on the critical components that constitute the gas exchange system such as oxygenators, vascular access catheters, flow control components, and surface treatments for hemocompatibility. Various technologies and materials used in their development are highlighted and their performance compared. Subsequently, animal studies that have been performed using the concept of an artificial placenta as a lung assist device are reviewed. Finally, human case reports that present the use of an artificial placenta for gas exchange are discussed. The review covers the relevant time frame from 1948 to 2012.

SEARCH STRATEGY AND SELECTION CRITERIA

MEDLINE (via Ovid), PubMed, and ISI Web of Knowledge were systematically searched for the application of an artificial placenta in in vivo studies published from March 1948 to October 2012 using different combinations of the following search terms: “artificial placenta”, “extracorporeal circulation”, “extracorporeal membrane oxygenation”, “oxygenator”, and “umbilical vessels”. The search was restricted to the neonatal period. Only studies in which an oxygenator was connected to the umbilical vessels for respiratory support were eligible for inclusion. Studies were excluded if arterio-venous bypass was achieved all or partly through access to other central vessels. Additionally MEDLINE (via Ovid), PubMed, and ISI Web of Knowledge were searched for studies about technological features of the concept of an artificial placenta as well as studies presenting clinical and pathophysiological data using search terms of descriptive and related topics. The references of the retrieved articles were screened for further relevant papers. Publications citing the retrieved articles were also identified using ISI Web of Knowledge. We excluded publications not written in English.

RESULTS

The systematic search generated 344 hits from MEDLINE (via OVID), PubMed, and ISI Web of Knowledge, of which 20 articles met our inclusion criteria for in vivo studies. Seventeen animal studies using lamb, goat, and piglet models have so far been published and three human case reports on human fetuses or terminally ill newborns have been identified. No clinical studies, randomized controlled trials, or meta-analyses were found.

OXYGENATOR

Review of concept

Oxygenators such as ECMO are typically used to assist or replace lung function in clinical applications. In this method, venous blood is oxygenated by the device and returned to the systemic circulation. However, current commercially available oxygenators for ECMO have been designed only
Lung assist devices for newborns

for infants (weight ≥2.0 kg) or adults (4, 13). These oxygenators are connected by surgery to the central vessels, have large filling volumes and usually require pumps to circulate blood (4, 13).

In comparison, the artificial placenta lung assist device for newborns would be connected by simply introducing catheters into the umbilical vessels, which is currently an established practice for parenteral nutrition, drug delivery, and monitoring of critically ill infants in the NICU. The oxygenator should be modular in design to enable customization over a wide range of preterm and term infant body weight (400 to 4000 g), provide adequate gas exchange, and yet have low filling volumes. Furthermore, the oxygenator would be used for bypassing the systemic circulation via the umbilical artery descending from the aorta to the umbilical vein leading into the ductus venosus. This design will allow the oxygenator to oxygenate hypoxic arterial blood when lung gas exchange is insufficient.

Published evidence

There are two configurations by which gas exchange is commonly achieved in an oxygenator:

1. Direct contact: In this configuration flowing blood is in direct contact with ambient air. Bubble and film oxygenators operate in this configuration. In the past, bubble oxygenators have been used in cardiac surgery to facilitate gas exchange by bubbling air through a column of blood (14). Film oxygenators provide gas exchange by direct contact between a thin film of blood and the surrounding air or gas. Although bubble and film oxygenators are effective, gas exchange is less controlled. Furthermore, direct contact of air with blood leads to denaturation of plasma proteins, activation of the coagulation system, and impairment of erythrocytes (14-16). Risk of infection from these oxygenators is high (17).

2. Indirect contact: In this configuration, the flowing blood is indirectly exposed to air through a gas-permeable membrane, which is similar in principle to the operation of the human lung. Oxygenators under this category are composed of homogenous or microporous membranes in either a hollow fiber or flat sheet design. Hollow fiber oxygenators are composed of a packed bundle of fibers, whereupon blood can flow either through or around the fiber while gas is on the other side of the membrane. These oxygenators can be applied extracorporeally or intravascularly. They are made of either plasma-tight (polymethylpentene) fibers for long-term use (up to one month) or highly porous fibers that are not “plasma-tight” (polypropylene) for short-term use (several hours). Hollow fiber oxygenators are available for newborns, however their priming volumes are approximately 40 mL (18), which is considered undesirable for extremely low birth weight infants (<1,000 g) with a total body blood volume less than 90 mL (19). Large priming volumes are not desirable because it would necessitate blood transfusions and could lead to associated complications.

Flat sheet oxygenators consist of membranes, which are flat, folded or coiled, across which gas exchange occurs (14-16). More recently, miniature or “microfluidic” oxygenators of flat sheet design have been developed for cell culture applications to maintain dissolved oxygen concentrations in culture media. These oxygenators are designed for blood flow through an array of micro-channels which mimics capillary circulation. Gas exchange occurs across a thin membrane commonly made of polydimethylsiloxane (PDMS) (20).

Oxygenators used as artificial placenta (Tab. I): In the mid-20th century, the first oxygenators used in artificial placenta studies were film oxygenators with a rotating disc design (21-24). Such rotating disc oxygenators facilitated gas transfer and blood flow through the extracorporeal circuit. The devices were composed of a series of discs on which thin layers of blood were exposed to surrounding gas. As blood flows through these series of discs due to the rotational movement of the device it is exposed to the gas which increases the oxygen saturation of the blood. On average, 50 discs could provide an oxygenation performance level of 2 l/min. This design was also flexible in that additional discs could be added to increase the oxygenation ability of the device. It was estimated that a device with 120 discs may have an oxygenation level of 5 l/min (25).

In the 1970s, membrane oxygenator devices became more widely used due to their effective gas exchange properties. Zapol et al (26), Bui et al (27), and Awad et al (28) used coiled membrane oxygenators with priming volumes of 60 to 70 mL and gas exchange surfaces between 0.4 m² and 0.8 m². Microporous (polypropylene) hollow fiber oxygenators with priming volumes between 90 mL and 100 mL and membrane surfaces of 0.3 m² to 0.5 m² were also widely used in the late twentieth century (5, 28, 29), although...
TABLE I - OVERVIEW OF ARTIFICIAL PLACENTA ANIMAL EXPERIMENTS

<table>
<thead>
<tr>
<th>Model</th>
<th>Weight [g]</th>
<th>Submersion</th>
<th>Year</th>
<th>Oxygenator (surface area)</th>
<th>Pump</th>
<th>Priming Volume [mL]</th>
<th>Catheter (diameter, length)</th>
<th>Flow Measurement</th>
<th>Flow Rate Oxygen Exchange (in vivo)</th>
<th>Oxygen</th>
<th>Anticoagulation</th>
<th>Duration [hours]</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piglet</td>
<td>152-335</td>
<td>Yes</td>
<td>1962</td>
<td>Rotating disc film (2.5 m$^2$)</td>
<td>Yes</td>
<td>200-250</td>
<td>Artery (1.3 mm, 3.2 cm), Vein (1.8-2.4 mm, 1.9 cm)</td>
<td>Photo-electric drop counter</td>
<td>5-20 mL/min</td>
<td>1.0-4.0 mL/kg/min</td>
<td>Heparin</td>
<td>7 (21)</td>
<td></td>
</tr>
<tr>
<td>1,100-1,700</td>
<td>No</td>
<td>2011</td>
<td>Microfluidic oxygenator</td>
<td>No</td>
<td>8</td>
<td>Artery (1.2 mm, 11 cm), Vein (1.7 mm, 8 cm)</td>
<td>Transonic flowmeter</td>
<td>4 mL/min</td>
<td>0.2-0.5 mL/kg/min</td>
<td>Heparin</td>
<td>4 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamb</td>
<td>600-4,000</td>
<td>Yes</td>
<td>1963</td>
<td>Rotating disc film, Membrane (N/A)</td>
<td>Yes</td>
<td>1,400-1,500</td>
<td>N/A</td>
<td>Electromagnetic flowmeter</td>
<td>13-60 mL/kg/min</td>
<td>N/A</td>
<td>Heparin</td>
<td>0.6 (24)</td>
<td></td>
</tr>
<tr>
<td>2,600-5,000</td>
<td>No</td>
<td>1964</td>
<td>Rotating disc film (N/A)</td>
<td>Yes</td>
<td>N/A</td>
<td>Artery (3-4 mm, N/A), Vein (3-4 mm, N/A)</td>
<td>Derived from pumps</td>
<td>60-180 mL/kg/min</td>
<td>N/A</td>
<td>Heparin</td>
<td>1 (39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,000-5,100</td>
<td>Yes</td>
<td>1965</td>
<td>Rotating disc film, Membrane (N/A)</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
<td>Electromagnetic flowmeter</td>
<td>13-100 mL/kg/min</td>
<td>N/A</td>
<td>Heparin</td>
<td>0.3-3 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>730-2,180</td>
<td>Yes</td>
<td>1968</td>
<td>Rotating disc film (N/A)</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
<td>Electromagnetic flowmeter</td>
<td>43-150 mL/kg/min</td>
<td>N/A</td>
<td>Heparin</td>
<td>24 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,050</td>
<td>Yes</td>
<td>1969</td>
<td>Silicone coiled (0.4 m$^2$)</td>
<td>Yes</td>
<td>240</td>
<td>Artery (2.6 mm, N/A), Vein (3.8 mm, N/A)</td>
<td>N/A</td>
<td>70-150 mL/kg/min</td>
<td>6.0 ± 0.5 mL/kg/min</td>
<td>Heparin</td>
<td>4-55 (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,500-3,500</td>
<td>No</td>
<td>1979</td>
<td>Microchannel (0.6 m$^2$)</td>
<td>Yes</td>
<td>80 + 150-220 (tubing)</td>
<td>Artery (2.7 mm, N/A), Vein (2.7 mm, N/A)</td>
<td>N/A</td>
<td>100-150 mL/kg/min</td>
<td>1.4-4.5 mL/min</td>
<td>Heparin</td>
<td>N/A (34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,500-3,500</td>
<td>No</td>
<td>1984</td>
<td>Membrane (0.4 m$^2$)</td>
<td>Yes</td>
<td>116</td>
<td>Artery (4.8 mm, N/A), Vein (4.8 mm, N/A)</td>
<td>Electromagnetic flowmeter</td>
<td>70 mL/kg/min</td>
<td>N/A (CO$_2$: 9-14 mL/kg/min)</td>
<td>Prostacyclin and Heparin</td>
<td>6 (37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,200-4,500</td>
<td>No</td>
<td>1992</td>
<td>Coiled membrane (0.8 m$^2$)</td>
<td>Yes</td>
<td>N/A</td>
<td>Artery (2 mm, N/A), Vein (3.3 mm, N/A)</td>
<td>Derived from roller pump</td>
<td>40-140 mL/kg/min</td>
<td>N/A</td>
<td>Heparin</td>
<td>48 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,200-5,400</td>
<td>No</td>
<td>1995</td>
<td>Coiled silicone membrane, polypropylene hollow fiber (0.4 m$^2$)</td>
<td>No</td>
<td>60</td>
<td>Artery (1.7-2.7 mm, 15 or 38 cm), Vein (1.7-2.7 mm, 15 or 38 cm)</td>
<td>Electromagnetic flowmeter</td>
<td>0-100 mL/min</td>
<td>N/A (CO$_2$: 13-35 mL/min)</td>
<td>Heparin</td>
<td>4-6 (28)</td>
<td></td>
<td></td>
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</tbody>
</table>

TO BE CONTINUED
<table>
<thead>
<tr>
<th>Model</th>
<th>Weight [g]</th>
<th>Submersion</th>
<th>Year</th>
<th>Oxygenator (surface area)</th>
<th>Pump Priming Volume [mL]</th>
<th>Catheter (diameter, length)</th>
<th>Flow Measurement</th>
<th>Flow Rate Oxygen Exchange (in vivo)</th>
<th>Anticoagulation</th>
<th>Duration [hours]</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3,560-6,450</td>
<td>No</td>
<td>2009</td>
<td>Hollow fiber (N/A)</td>
<td>No 100</td>
<td>Artery (3.3-4.7 mm, N/A)</td>
<td>Transonic flow probe</td>
<td>176-382 mL/min</td>
<td>3.4-5.9 mL/kg/min</td>
<td>Heparin 4</td>
<td>(5)</td>
</tr>
<tr>
<td></td>
<td>1,950-3,800</td>
<td>No</td>
<td>2011</td>
<td>Polypropylene hollow fiber (0.09m²)</td>
<td>No 19 (12)</td>
<td>Artery (2.1 mm, 6-8 cm)</td>
<td>Transonic flow probe</td>
<td>3 mL/kg/min</td>
<td>N/A</td>
<td>Heparin 3</td>
<td>(6)</td>
</tr>
<tr>
<td>Goat</td>
<td>1,750-4,800</td>
<td>Yes</td>
<td>1989</td>
<td>Silicone hollow fiber (0.3-0.5mm²)</td>
<td>Yes 160</td>
<td>Artery (2.7-3.3 mm, N/A)</td>
<td>Electromagnetic flowmeter</td>
<td>93 ± 14 mL/kg/min</td>
<td>6.6 mL/kg/min</td>
<td>Heparin 147 ± 61</td>
<td>(33)</td>
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<tr>
<td></td>
<td>1,600-2,400</td>
<td>Yes</td>
<td>1993</td>
<td>Silicone hollow fiber (0.5 m²)</td>
<td>Yes 230</td>
<td>Artery (3.3 mm, N/A)</td>
<td>Electromagnetic flowmeter</td>
<td>80-180 mL/kg/min</td>
<td>5-10 mL/kg/min</td>
<td>Heparin 494-542</td>
<td>(32)</td>
</tr>
<tr>
<td></td>
<td>2,000±100</td>
<td>Yes</td>
<td>1998</td>
<td>Polyolefin hollow fiber (0.4m²)</td>
<td>Yes 95</td>
<td>Artery (3-3.3 mm, 25 cm)</td>
<td>Electromagnetic flowmeter</td>
<td>150-200 mL/kg/min</td>
<td>N/A</td>
<td>Heparin 87-237</td>
<td>(30)</td>
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<td></td>
<td>2,000±100</td>
<td>Yes</td>
<td>1998</td>
<td>Polyolefin hollow fiber (0.4m²)</td>
<td>Yes 95</td>
<td>Artery (3 mm, 25 cm)</td>
<td>Electromagnetic flowmeter</td>
<td>113-193 mL/kg/min</td>
<td>4.4-5.3 mL/kg/min</td>
<td>Heparin 87-237</td>
<td>(31)</td>
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<tr>
<td></td>
<td>820-2,329</td>
<td>Yes</td>
<td>2002</td>
<td>Hollow fiber (0.3 m²)</td>
<td>Yes 200</td>
<td>Artery (3.3mm, 15cm)</td>
<td>Electromagnetic flowmeter</td>
<td>65-220 mL/kg/min</td>
<td>3.9-7.0 mL/kg/min</td>
<td>Heparin 34</td>
<td>(29)</td>
</tr>
</tbody>
</table>

N/A, not available; Ref, reference; "beyond umbilicus, $ priming volume only given for oxygenator without tubing etc.
non-microporous (silicone or polyolefin) hollow fiber devices became more common over the last decade (30-33). However, the most recent study conducted by Arens et al employed miniature hollow fiber oxygenators with polypropylene membranes and a priming volume of 19 mL for pumpless perfusion (6). Evidence of a micro-channel oxygenator was also found in a study by Griffith et al (34), who used an oxygenator with high gas exchange properties and a priming volume of 80 mL/unit for perfusion of neonatal lambs.

In the context of gas exchange properties, low priming volume, and design flexibility, our review shows that there has been significant improvement in the development of oxygenators for neonatal applications. Recent studies have introduced and tested oxygenators with priming volumes less than 20 mL, some as low as 4 mL (6, 7). Gas exchange for these devices has reached performance levels between 0.2 and 0.5 mL O₂/kg per min (7). Furthermore, design flexibility has also been described with the construction of a bundle oxygenator made of single functional units (7). We believe these improvements have advanced the current status of artificial placenta development. However, further work is needed to improve gas exchange in neonatal devices to support the infant’s respiratory needs in a pumpless lung assist device that is connected to the umbilical vessels (5, 7, 10). Further testing with animal models is necessary to ensure consistent gas transfer rates.

VASCULAR ACCESS

Review of concept

An ideal artificial placenta should be pumpless and only the heart should drive the blood through the extracorporeal circuit. It is also desirable to connect the device to the vascular system through a natural access such as the umbilical artery and vein. This approach avoids the complications associated with surgical implantation of vascular access. Although the intra-abdominal umbilical vessels begin to constrict after the newborn is disconnected from the natural placenta, it is still possible to catheterize the umbilical vessels to obtain catheter access for application of the artificial placenta. In this configuration, the blood will flow from the aorta through the umbilical artery into the oxygenator device. It will then return through the umbilical vein leading to the ductus venosus and inferior vena cava. Since this design is pumpless and essentially driven by the heart, the diameter of the bore access that can be achieved by cannulation of the umbilical artery and vein is of critical importance. According to the Hagen-Poiseuille law, resistance to flow in a tube under laminar flow conditions is inversely related to the fourth power of the diameter. Thus, a large bore diameter of the vascular access is required for low pressure drop across the catheter and to maintain an appropriate extracorporeal blood flow under conditions where the heart is pumping.

Published evidence

In utero, the diameters of the umbilical vessels allow enough blood to bypass the systemic circulation (90-180 mL/kg per min) through the placenta for complete gas exchange required for the fetal body (8). Dependent on gestational age (24-40 weeks), the umbilical vein diameter ranges between 6.0 mm and 8.7 mm (9), while the umbilical artery diameter ranges from 3.4 mm to 4.2 mm (Tab. II) (35). Umbilical vein length measured from the abdominal wall to the inferior vena cava is 5 cm to 7 cm (36). Umbilical artery length measured from the abdominal wall to the internal iliac arteries is 9 cm to 12 cm (36).

Vascular access has been established in the past through the umbilical vessels using large-bore catheters and pumps. Goat newborns were cannulated using catheters with a diameter of 2.7-3.3 mm for the umbilical artery and 3.3-4 mm for the umbilical vein (29-33). Neonatal lambs were cannulated with 2-3.3 mm for arterial catheters and 3.3-4.7 mm for umbilical vein catheters (5, 24–26, 35). In these experiments, the length of the umbilical artery catheters was approximately 38 cm, while the umbilical vein catheters were 15 cm long (28). The study by Lawn et al chose a piglet model, using 1.3 mm, 3.2 cm long umbilical artery catheters and 2.3 mm, 1.9 cm long umbilical vein catheters (21). As well, in one human case report, term newborns were cannulated with 1.7 mm umbilical artery catheters and 2.7 mm umbilical venous catheters (38). Although vascular access was established, many of these extracorporeal support systems required the use of roller pumps and centrifugal pumps to maintain adequate blood flow for gas exchange (22-24, 39). Because of the high resistance and low performance of the artificial placenta, few attempts were made to implement
Lung assist devices for newborns

Development of long-term support that is pumpless would minimize mechanical stress on blood components. In 1965, Callaghan et al attempted pumpless support, but was unsuccessful as it resulted in poor perfusion rates with poor performance of gas exchange and high mortality (23). A study in 2009 described an attempt to create a pumpless extracorporeal system using low resistance hollow fiber oxygenators (5). Perfusion lasted only 4 hours in the neonatal lamb model, and the authors of the study concluded that a lower resistance circuit was crucial for long-term support (5). Similarly in 2011, Arens et al were able to provide pumpless support to premature lambs for a 3-hour test period using miniature hollow fiber oxygenators (6).

Although recent proof-of-principle studies have been done for pumpless extracorporeal circuits, more tests are needed to establish a long-term pumpless extracorporeal support in small animal models (5, 6). Alternative evidence suggesting feasibility of a pumpless lung assist device can be seen in extracorporeal circuits. For example, juvenile piglets were successfully perfused in 2009 with a cardiopulmonary bypass circuit between the carotid artery and jugular vein (40). This success has clearly demonstrated the potential for developing a pumpless lung assist device in the clinical application of an artificial placenta.

### TABLE II - DIAMETER AND CROSS-SECTIONAL AREA OF UMBILICAL VESSELS BY GESTATIONAL AGE

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Umbilical vein diameter (mm)</th>
<th>Umbilical vein cross-sectional area (mm²)</th>
<th>Umbilical artery diameter (mm)</th>
<th>Umbilical artery cross-sectional area (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>6.0 ± 3.7</td>
<td>28.0 ± 11.0</td>
<td>3.4 ± 1.2</td>
<td>8.9 ± 4.0</td>
</tr>
<tr>
<td>26</td>
<td>6.9 ± 3.9</td>
<td>37.4 ± 12.0</td>
<td>3.7 ± 1.3</td>
<td>10.7 ± 4.1</td>
</tr>
<tr>
<td>28</td>
<td>7.6 ± 4.1</td>
<td>45.1 ± 13.0</td>
<td>3.9 ± 1.4</td>
<td>12.1 ± 4.1</td>
</tr>
<tr>
<td>30</td>
<td>8.1 ± 4.2</td>
<td>51.1 ± 14.0</td>
<td>4.1 ± 1.4</td>
<td>13.1 ± 4.1</td>
</tr>
<tr>
<td>32</td>
<td>8.4 ± 4.4</td>
<td>55.4 ± 15.1</td>
<td>4.2 ± 1.4</td>
<td>13.7 ± 4.2</td>
</tr>
<tr>
<td>34</td>
<td>8.6 ± 4.5</td>
<td>58.0 ± 16.1</td>
<td>4.2 ± 1.5</td>
<td>13.9 ± 4.2</td>
</tr>
<tr>
<td>36</td>
<td>8.7 ± 4.7</td>
<td>58.9 ± 17.1</td>
<td>4.2 ± 1.6</td>
<td>13.8 ± 4.2</td>
</tr>
<tr>
<td>38</td>
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<td>4.1 ± 1.6</td>
<td>13.2 ± 4.2</td>
</tr>
<tr>
<td>40</td>
<td>8.4 ± 4.9</td>
<td>55.6 ± 19.1</td>
<td>4.0 ± 1.7</td>
<td>12.3 ± 4.3</td>
</tr>
</tbody>
</table>

Equation for mean cross-sectional area of umbilical vein: \( y = -217.801 + 15.355x - 0.213x^2; \text{SD} = -1.27 + 0.51x; \) where \( x \) is gestational age. Equation for mean cross-sectional area of umbilical artery is: \( y = -42.309 + 3.286x - 0.048x^2; \text{SD} = 3.520 + 0.019x; \) where \( x \) is gestational age (35). Diameter of the umbilical vessels was derived from cross sectional area \( (D = 2\sqrt{y/\pi}) \).

FLOW CONTROL

Review of concept

It is known that the establishment of a partial fetal circulation bears the risk of high cardiac output failure. Thus, a functional artificial placenta requires an instrument capable of monitoring blood flow in a pumpless device and a method to easily adjust blood flow.

Published evidence

Two non-invasive techniques for flow measurement have been used in the artificial placenta. These are electromagnetic and ultrasonic flowmeters. In the case of electromagnetic flowmeters, flow is determined by measuring the induced voltage as the blood flows through a magnetic field. This method is dependent on fluid velocity, magnetic field strength, and vessel or tubing dimensions (41). As such, it may be difficult to obtain stable readings because these parameters are difficult to control or maintain in clinical settings. In ultrasonic flowmeters, flow is determined by the transit time for sound waves to travel between two transducers and a reflector. An ultrasonic wave is emitted from one transducer through the vessel, reflected from a fixed “acoustic reflector”, and then received by the other transducer. The difference
of downstream (sound direction from transducer 1 to 2) and upstream (from transducer 2 to 1) time yields flow rate. Flow measurement is not affected by blood composition and reports flow volume rather than velocity (42).

The choice of flow monitors has shifted over the period of artificial placenta development. One of the earliest artificial placenta experiments in 1962 employed a photo-electric drop counter as a flow monitor (21). Over the years, researchers shifted towards electromagnetic flowmeters (22, 23, 28-30, 32). Today, ultrasonic flowmeters are preferred for flow monitoring. In a recent study conducted by Reoma et al, investigators placed ultrasonic probes in various blood vessels for flow measurement, including the aorta and carotid arteries (5). Compared to electromagnetic flowmeters, ultrasonic devices yielded more reliable measurements of blood flow (41, 42).

Numerous methods for flow control have been used over the years; however, there have been few in vitro or in vivo studies testing the effectiveness of such methods. Several studies have incorporated occlusive pumps and tube occluders within the circuit. Eccentric clamps, wide-screw clips on the inflow and elevation of the oxygenator relative to the newborn were also used (23, 39).

As the development of the artificial placenta progresses, it may be necessary to determine more effective methods for flow control to ensure sufficient gas transfer through the oxygenator. Ease of use, cost-effectiveness, and non-invasiveness must be considered in the design requirements for both flow measurement and flow control systems.

HEMOCOMPATIBILITY

Review of concept

The artificial placenta is developed to support newborns with severe respiratory insufficiency for several days until there has been a significant improvement in lung function. As a result, all components of the artificial placenta including the oxygenator, tubing, and catheters would be made compatible with blood for safe, long-term perfusion in the newborn (i.e., not causing significant protein adsorption, platelet adhesion/activation, damage to blood proteins and cells, and/or other adverse cell and protein responses).

Published evidence

We have identified five coating materials that have been reported in the literature to prevent blood clotting in oxygenators: heparin, nitric oxide, mixed endothelial cells, silicone, and hydrophilic polymers. Immobilized surface heparin promotes anticoagulation via antithrombin binding and also inhibits immune responses by interfering with the activation of the classical and alternate complement pathways (43). Membrane oxygenators coated with heparin were shown to exhibit reduced leukocyte adhesion, fibrinogen adsorption, and platelet binding (44). Nitric oxide is known to inhibit platelet activation and inflammatory reactions. Recently it was shown that exogenous nitric oxide infusion enhances the effect of a heparin-coated bypass circuit on the biocompatibility of an extracorporeal circuit (45).

Another strategy using silicone coatings showed slightly decreased complement activation in hollow fiber oxygenators when compared to untreated devices (46). However, silicone coats were less effective at reducing clotting and platelet activation (46).

Currently, endothelial cell layers are being investigated as an efficient way to enhance biocompatibility in oxygenator devices. Results from a study by Polk et al suggest that by imitating vascular endothelium ex vivo, platelet activation and protein deposition in microporous hollow fiber oxygenators is significantly reduced (47). Furthermore, the coating of the device with an endothelial cell layer did not impair gas exchange in the in vitro model.

Hydrophilic polymers like polyethylene glycol (PEG) have also been used for extracorporeal devices. When grafted onto materials such as PDMS, the hydrophilic property of polyethylene glycol prevents surface interactions with blood proteins and cells (platelets in particular), thus minimizing inflammatory and clotting responses (48). In a study comparing untreated and hydrophilic polymer-coated (poly-2-methoxyethyl acrylate, PMEA) membrane oxygenators, hydrophilic polymer-type coatings effectively reduced platelet activation and inflammatory cytokine levels in the blood when compared to untreated membranes (48).

In our review, we found that systemic anticoagulation with heparin was more commonly used to achieve biocompatibility. In both of their experiments, Callaghan et al continuously infused up to 3 mg heparin per kg of body weight into the circuit to support sheep fetuses for over 6 hours (23, 24). Others administered doses to attain a
steady concentration of heparin within the circuit (34)
or used heparinized blood to prime the ECMO system
(5, 21, 28, 29, 32). However, in many experiments, investi-
gators observed a consistent decline in blood flow, which
indicated clotting within the oxygenator or inadequate
anticoagulation.
In one study, infusion of prostacyclin PGI₂ at 600 ng/kg
per min was used as an alternative to systemic hepariniza-
tion (37). Infusion of prostacyclin has been shown to be
a slightly more effective strategy for anticoagulation than
systemic heparinization in arterio-venous extracorporeal
circuits (49).
In summary, we consider systemic anticoagulation such as
using heparin or prostacyclin in preterm infants to be highly
unfavorable as it might increase the risk of germinal matrix
hemorrhage (50). It is necessary to develop and test alter-
natives to systemic heparinization, such as extracorporeal
device coatings with heparin, mixed endothelial cells, sili-
cone, or hydrophilic polymers. Furthermore, the artificial
placenta is a complex system of catheters, oxygenator, and
tubing. The use of one material rather than multiple mate-
rials to produce these components will make it easier to
achieve a uniform level of biocompatibility throughout the
extracorporeal system.

ANIMAL EXPERIMENTS

An overview of artificial placenta lung assist prototypes
that have been tested in previous newborn animal experi-
ments is presented in Table I. These experiments follow
two approaches. The first approach aims to recreate the
intrauterine environment by submerging the newborn in
artificial amniotic fluid immediately after birth. This re-
quires total gas exchange to be performed by the artifi-
cial placenta. All experiments required the use of pumps
to provide an appropriate extracorporeal blood flow to
ensure sufficient gas exchange by the artificial placenta.
The second approach applies the artificial placenta to a
newborn animal that is adapted to the extra-uterine en-
vironment. The application of the artificial placenta using
the second approach, establishes partial fetal circulation
via umbilical vessels and the ductus venous. The artifi-
cial placenta “tops up” the gas exchange rate of the im-
mature or sick lung. The reduced need for gas exchange
with less extracorporeal blood circulation makes smaller
devices in a pumpless setting feasible. This scenario
more closely mimics the clinical situation of newborns
with respiratory failure.

Pump-driven artificial placenta configuration

In 1962, Lawn et al first demonstrated feasibility of the arti-
ficial placenta application by supporting healthy fetuses for
more than 7 hours (21). Then in 1969, 55 hours of perfusion
was achieved (26). Subsequently in 1998, Yasufuku et al
and Sakata et al were able to perfuse goat fetuses for an
average of 138 hours (30, 31). In 2002, Pak et al supported
fetuses using an artificial placenta device for approximate-
ly 24 hours (29).
In other pump-driven experiments, investigators analyzed
survival time of animal models after removal of the artifi-
cial placenta device. In 1963, Callaghan et al submerged
premature lambs in amniotic fluid to simulate intrauterine
conditions. Researchers supported the fetuses for a total
of 40 minutes (24), which later increased to 165 minutes
of support in Callaghan’s subsequent experiment in 1965
(23). After removing the device from the lambs, investiga-
tors simulated birth. Among 10 animals delivered in atmo-
spheric conditions, there were three short-term survivors
(>6 hours) and one long term survivor (>4 months) in the
1965 study. In a similar study design, Alexander et al per-
fused newborn lambs for 60 minutes. Results of the ex-
periment showed a survival time of at least 24 hours after
the lambs were removed from artificial placenta support
(22). The longest duration of artificial placenta support was
achieved by Unno et al in 1993 who applied the device
to premature goat fetuses for 21 days. Subjects survived
more than 1 week after removal of the device (32).

Pumpless artificial placenta configuration

Although advances in perfusion time of pump-driven sys-
tems had been made, long-term perfusion using pump-
less artificial placenta devices remained a challenge. In
1995, an attempt to provide pumpless support us-
ing silicone membrane oxygenators failed due to poor
blood flow. Investigators eventually used hollow fiber
membrane oxygenators that provided lower resistance
to achieve 4 to 6 hour perfusions in the neonatal lamb
model (28). Similarly in 2009, Reoma et al demonstrated
survival for 4 hours on the artificial placenta device. How-
ever, decreases in blood flow and hemodynamic insta-
bility were observed toward the end of the experimental
period and investigators concluded lower resistance in the circuit was needed for long-term pumpless support (5). In 2011, Arens et al successfully applied a pumpless lung assist device to neonatal lambs for 3 hours. All animals remained hemodynamically stable within the testing period with mean arterial pressure >35 mmHg and heart rate >140 bpm (6). Another recent study yielded similar results (7). A microfluidic oxygenator bundle in the form of a lung assist device was applied to a hypoxic piglet model. Under a frequency of inspired oxygen of 12% ($\text{FiO}_2 = 0.12$), peripheral oxygen saturation increased 40% and the piglet was supported on the device for 4 hours. However, obtaining large bore access via the umbilical vessels was difficult to achieve and blood flow through the device was relatively low. Thus, despite the establishment of short-term pumpless support, pumpless perfusions longer than 8 hours in animals have yet to be achieved due to the insufficient blood flow through the devices.

Causes of fatality during experiments

The primary causes of death in past experiments included circulatory failure or cardiac arrest. Cardiopulmonary histology was examined by Bui et al in 1992 when artificial placenta support was compared to mechanical ventilation (27). Right heart dilatation was observed in lamb models after 48 hours of perfusion. Investigators attributed this to high-output failure of the right heart as a result of increased venous return from the artificial placenta device (27). In 1969, one of the eight experiments in Zapol et al’s study underwent cardiac arrest and died. Post-mortem examinations found *Klebsiella* and *Aerobacter* species present in the fetal blood which may have contributed to an increased amount of peritoneal fluid under sepsis (26). In 2002, circulatory failure was the cause of death in eight of twelve study subjects after establishment of artificial placenta support by Pak et al. At autopsy, pleural effusion, ascites, intraperitoneal hemorrhage, intraabdominal petechiae, and subcutaneous edema in the fetuses were found (29). Then in 2009, four of seven lamb models were associated with complications such as hypoxia and cardiac arrest. These complications were thought to be caused by high resistance in the cannulas or cannula-umbilical artery interface leading to vasospasm of the umbilical artery (5).

Other causes of death included blood cloting and unsuccessful cannulation. Death by hypoxia due to coagulation in the extracorporeal blood flow was noted for one of twelve study subjects in 2002. In the same experimental setting in 2002, three of twelve subjects died from catheter malfunctions which were not explained in the report (29).

Since the early 1950s, studies have established the concept of the artificial placenta and demonstrated its feasibility as an application for neonatal respiratory failure in various animal models. Advances in the future on further development of a pumpless extracorporeal support system and improved blood flow through the device by obtaining large bore access via the umbilical vessels will be critical for realization of such a system.

HUMAN STUDIES

Until now, there had been no evidence of successful treatment by an artificial placenta in newborns with severe respiratory failure. However, artificial placenta applications have been studied in terminally ill newborns and pre-viable human fetuses. These case reports are described in Table III.

In the 1950s, seven fetuses weighing 100 g to 375 g obtained from spontaneous abortions were kept alive for 5 to 12 hours postpartum on artificial placenta support. Fetuses were connected to rotating disk oxygenators with a filling volume of 250 mL (51). The system was prefilled with O-Rh negative blood and systemic anticoagulation was achieved with heparin (5 mg/100 mL). Oxygen exchange within the oxygenator was 7.6 mL O$_2$/kg per min and blood flow rate was 14.2 mL blood/min in a 275 g infant. In a 100 g infant, oxygen exchange was 1.0 mL O$_2$/kg per min with a blood flow rate of 2.7 mL blood/min.

Another study published in 1968 obtained eight healthy fetuses from hysterotomy for therapeutic termination. These fetuses ranged from 300 g to 980 g in weight and were attached to coil membrane oxygenators via the umbilical vessels. Smaller fetuses lasted an average of 90 minutes into perfusion, while the largest subject weighing 980 g survived 5 hours. Investigators attributed the short survival time to inappropriate vessel access which ultimately resulted in poor return blood flow to the extracorporeal circuit via the umbilical arteries. This was followed by decreased oxygen support to the fetus (52).

In 1970, Dorsen et al reported the application of an artificial placenta to five terminal newborns (1.1-4.9 kg) under severe respiratory distress. In this study, coiled silicone oxygenators composed of 80 to 120 tubes with a roller pump was attached to the umbilical vessels of the newborns (38). Adequate oxygenation and carbon dioxide removal
was described, although investigators were concerned with poor blood flow through the oxygenator. All subjects died within 21 hours of extracorporeal lung assist (38). Following the last human experiment in 1970, there was a period of relative inactivity in the development of an artificial placenta (38). This was attributed to the advancements of continuous positive airway pressure (CPAP) and mechanical ventilation in the clinical field, leading to significant decreases in neonatal mortality rates. Since then, researchers have deemed the idea of an artificial placenta to be too risky for clinical use in light of the successes in treating respiratory distress with CPAP or mechanical ventilation (2).

In summary, we have examined features of an artificial placenta including the oxygenator, vascular access, flow control, and hemocompatibility. Although many gas exchange devices exist, none of them meet all of the requirements for newborns. Lung assist technology appears to be more advanced for adults and children than for newborns. One such lung assist device that has been clinically approved for use in adults contains many of the required properties and components of an artificial placenta. Also known as an artificial lung, this surface-coated lung assist device is a femoral arterio-venous bypass system that provides gas exchange support. It has been clinically approved for use up to 1 month. The technology employs a method of simple gas diffusion across a polymethylpentene membrane oxygenator hooked to a circuit in an arterio-venous configuration (53). Blood is drawn through the femoral arteries into the lung assist circuit, saturated with oxygen through the device, and returned to normal circulation through the femoral vein. The device requires no pump; instead, blood flow is facilitated solely by the patient’s arterial blood pressure. The entire circuit is coated with heparin to provide an anti-thrombogenic surface to meet hemocompatibility requirements to minimize blood trauma and clotting (53, 54). Furthermore, this pumpless lung assist device has also been successfully used to treat pediatric patients with ventilatory insufficiency (55). This achievement in adults indicates the potential for promising developments of an artificial placenta for newborns with respiratory insufficiency.

CONCLUSIONS

Since the early 1950s, scientists have studied lamb, goat, and piglet models of the artificial placenta. Few studies on human fetuses and terminally ill newborns have been described so far. Currently, mechanical ventilation is the method of choice to treat newborns with severe respiratory failure but the in-built risk of lung damage affects the quality of survival. Associated impairments may result in a life-long dependency and place considerable strain on social cost and cost of medical follow-up. In addition, there are still a number of infants that die from severe respiratory insufficiency for whom there is no effective treatment. In this review, we have presented all available data on the concept of the artificial placenta. In its current status, there is no artificial placenta device yet ready for application to humans. However, the concept of an artificial placenta

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**TABLE III - OVERVIEW OF HUMAN CASE REPORTS**

<table>
<thead>
<tr>
<th>Year</th>
<th>Weight [g]</th>
<th>Oxygenator (surface area)</th>
<th>Pump</th>
<th>Priming Volume [mL]</th>
<th>Catheter (diameter, length)</th>
<th>Flow Measurement</th>
<th>Flow Rate [mL/min]</th>
<th>Oxygen Exchange [mL/kg/min]</th>
<th>Anticoagulation</th>
<th>Duration [hours]</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1958</td>
<td>200-375</td>
<td>Rotating film (0.4 m²)</td>
<td>Yes</td>
<td>100-250</td>
<td>N/A</td>
<td>Photo-electric drop counter</td>
<td>2.7-14.2</td>
<td>1.0-7.6</td>
<td>Heparin</td>
<td>5-12</td>
<td>(51)</td>
</tr>
<tr>
<td>1968</td>
<td>300-980</td>
<td>Coiled membrane (0.45 m²)</td>
<td>Yes</td>
<td>150-290</td>
<td>N/A</td>
<td>N/A</td>
<td>15-40</td>
<td>N/A</td>
<td>Heparin</td>
<td>1.5-5</td>
<td>(52)</td>
</tr>
<tr>
<td>1970</td>
<td>1,100-4,920</td>
<td>Coiled membrane silicone (N/A)</td>
<td>Yes</td>
<td>N/A</td>
<td>Artery (1.7-2.7 mm, 14 cm), Vein (1.7-2.7 mm, 14 cm)</td>
<td>Derived from pump</td>
<td>24-80</td>
<td>0.5-3.5</td>
<td>Heparin</td>
<td>5-21</td>
<td>(38)</td>
</tr>
</tbody>
</table>
bears an enormous potential to expand the therapeutic spectrum in neonatal intensive care medicine. Although it will not become the first line of treatment for neonatal respiratory distress, the artificial placenta has the potential to rescue infants with end-stage lung failure. Creating the technology of an artificial placenta as a lung assist device would be a milestone in the innovation of neonatal medicine.

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REFERENCES


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Lung assist devices for newborns


