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Original Articles

Extracorporeal fetal support: A new animal model with preservation of the placenta

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ABSTRACT

Background: Previous models of support for premature sheep fetuses have consisted of cesarean delivery followed by catheterization of umbilical or central vessels and support with extracorporeal membrane oxygenation (ECMO). The limitations of these models have been insufficient blood flow, significant fetal edema, and hemorrhage related to anticoagulation.
Methods: We performed a gravid hysterectomy on 13 ewes between 135 and 145 days gestational age. The uterine vessels were cannulated bilaterally and circulatory support was provided via ECMO. Successful transition was defined as maintenance of fetal heart rate for 30 minutes after establishing full extracorporeal support. Circuit flow was titrated to maintain mixed venous oxygen saturation (SvO_2) of 70–75%.
Results: Seven experiments were successfully transitioned to ECMO, with an average survival time of 2 hours 9 minutes. The longest recorded time from cannulation to death was 6 hours 14 minutes. By delivering a circuit flow of up to 2120 ml/min, all but one of the transitioned uteri were maintained within the desired SvO_2 range.
Conclusion: We report a novel animal model of fetal ECMO support that preserves the placenta, mitigates the effects of heparin, and allows for increased circuit flow compared to prior techniques. This approach may provide insight into a technique for future studies of fetal physiology.
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One in ten live births in the United States is premature (defined as <37 weeks of gestational age) [1]. These preterm infants face considerable challenges to survive mostly related to organ immaturity. For example, respiratory distress syndrome (RDS) and anemia of prematurity occur very frequently in infants of less than 30 weeks gestation because the adequate production of surfactant and erythropoietin occurs later during pregnancy [2]. Since it is difficult to decrease the preterm birth rate, neonatologists have made tremendous efforts to improve the survival of these patients.

Another approach to help preterm infants and the health conditions they face is through an ex-utero fetal support system. Attempts of ex-utero fetal support have been described since the 1950s [3]. These research models are based on maintaining a delivered fetus in an environment that mimics the protective intrauterine setting in addition to providing an extracorporeal life support system, the oxygenation and support that originally came from the mother's placenta.

Ethical considerations have shaped and dictated the development of animal models of ex-utero fetal support. Sheep in particular, have been established as the most feasible model owing to its availability and key similarities with humans, including low number of fetuses per pregnancy, fetal size, and vessel anatomy [4]. These models of fetal support are based on using extracorporeal membrane oxygenation (ECMO) to substitute the function of the immature pulmonary system. This is done by establishing intravascular access to the fetus (using the umbilical vessels or internal jugular and carotid) and keeping the fetus in a saline tank to avoid exposure to an air environment. An important parameter of success of such models is the length of survival of the fetus after premature birth. In 1969, Zapol

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et al. published a 55 hour ex-utero survival on a sheep fetus and the longest time reported is three weeks by Kuwabara and Unno in the early 1990s [5,6]. By using ECMO, these models attempt to provide some of the support that the fetus would otherwise have in the uterus, and therefore the term “artificial placenta” is used to define them.

Previous models of artificial placenta have identified common limitations intrinsic to the use of an ECMO circuit such as limited blood flow owing to vessel caliber, significant fetal edema and hemorrhage owing to heparin associated coagulopathy [7,8]. We have developed a new animal model that aims to overcome these limitations by preserving the placenta and using the uterine vessels for cannulation.

1. Methods

We obtained approval from the Johns Hopkins Institutional Animal Care and Use Committee (protocol SH08M268). Experiments were performed in thirteen pregnant Dorset sheep. A gravid hysterectomy was done at 130–140 days of gestational age (average gestation is around 145 days) to have a mature fetus that could potentially tolerate the physiologic disturbance related to ECMO. The sheep was placed in supine position and anesthetized using isoflurane and ketamine. After obtaining a preoperative ultrasound to evaluate the fetal heart rate, a midline incision was performed and the pregnant uterus was exposed allowing for dissection of the uterine arteries and veins bilaterally to prepare for cannulation and provision of full ECMO support (defined as all uterine vessel flow supplied by the ECMO circuit). Two different methods were used for vessel cannulation:

1) *Cannulation before hysterectomy*: The uterine vein was cannulated on the right side followed immediately by the cannulation of the right uterine artery. After this, unilateral ECMO support was started on the right side of the uterus and the left uterine vasculature was accessed in the same fashion. The uterus was placed on bilateral ECMO support and a stapled transcervical hysterectomy was performed for complete separation from the ewe.
2) *Hysterectomy before cannulation*: The uterine vessels were dissected bilaterally. A stapled transcervical hysterectomy was done and the four uterine vessels were ligated and transected. The uterus was immediately transferred to a side table where the vessels were cannulated as quickly as possible by one surgeon on each side. After cannulation the uterus was placed in ECMO support to return blood flow to the uterus.

The first three experiments were done with cannulation before hysterectomy but successful support was only established in one case. Hysterectomy before cannulation was attempted as a second method to allow easier manipulation of the large uterus but after failing to transfer three uteri to full support we went back to the first technique.

After bilateral ECMO support was established, the uterus was transferred to a warm saline tank. Fetal heart rate and mixed venous oxygen content (SvO_2) of circuit blood were continuously recorded and laboratory values such as hemoglobin, electrolytes, blood gas, activated clotting time (ACT) and glucose were serially checked from samples obtained from the ECMO circuit. Abnormalities in laboratory values were treated following common clinical conduct. Blood gases were obtained from the venous and arterial sides of the circuit to assess oxygen consumption and function of the oxygenator. Continuous fetal heart monitoring (FHM) was obtained and the endpoint for the experiment was fetal demise defined as asystole. A cardiographic probe, similar to the one used for fetal heart rate monitoring in obstetrics was used. If the fetal heart rate could not be registered with the probe, asystole was confirmed with ultrasound imaging. We arbitrarily defined a successful transition when we were able to maintain a fetal heart rate 30 minutes after establishing full ECMO support.

1.1. Tank

A 150 liter fish tank was used, prefilled with normal saline and heated to 38.5 °C to mimic the sheep's core temperature. Two grams of ampicillin were dispersed in the tank. pH was kept at physiologic values using drops of sodium carbonate and sulfuric acid mixed with water. After transfer, the uterus was partially submerged in the tank and held in using a net (Fig. 1). The tank's temperature was maintained at 38.5 °C with a submersible heater.

1.2. ECMO

The veno-arterial (VA) ECMO circuit consisted of a 4.5 m^2 surface area silicone membrane (Medtronic, Minneapolis, MN), a BIOtherm™ heat exchanger (Medtronic), and a gravity filled R-38 bladder/compliance chamber (Medtronic) incorporated into the circuit with a Stockert–Shiley rollerhead pump (Sorin, Milan, Italy). The sweep gas was powered by an air and oxygen blender system (Model 3600; Sechrist Corp, Anaheim, CA). The circuit was primed with sheep's whole blood obtained from different donor ewes, 25% human albumin, sodium bicarbonate, heparin and calcium chloride totaling 750 ml. After hysterectomy, the ewe was euthanized and whole blood was used to keep the ECMO circuit flow which was monitored by the rollerhead. ECMO flow was regulated to keep a SvO_2 of 70–75% and crystalloid fluids were used when whole blood supply ran out. Electrolytes, glucose and heparin were administered as needed.

The cannulas varied in size, a 21fr venous cannula was the most commonly used for venous access and a 12fr to 14fr for the arterial cannula. These were inserted at a depth of 4–10 cm.

2. Results

We performed 13 fetal support experiments, 11 twin and two singleton pregnancies. Eleven of the 13 experiments had at least one live fetus that survived the first minutes after cannulation of the uterine vessels. Only in seven experiments did we have a successful ECMO transition in which the fetus survived for more than 30 minutes on full ECMO support. The average survival time for the fetuses that had a successful transition was 2 hours and 9 minutes. Uterine vessel cannulation prior to hysterectomy was associated with a better outcome (Table 1).

Blood samples obtained from the ECMO circuit yielded variable values throughout the experiments. Most of the experiments sustained persistent metabolic acidosis, and hemoglobin was typically very low (range 2.0–8.3 g/dL). These problems were difficult to treat since we

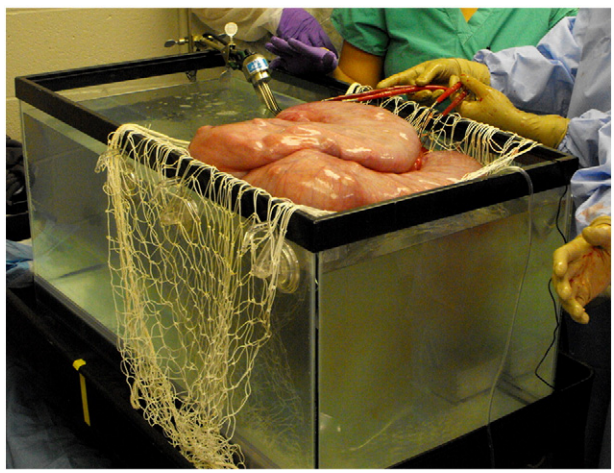

Fig. 1. ECMO-supported bicornuate sheep gravid uterus in saline tank.

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