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2 July 1969; revised 29 July 1969

Artificial Placenta: Two Days of Total Extrauterine Support of the Isolated Premature Lamb Fetus

Abstract. *A premature lamb fetus was totally sustained by extracorporeal perfusion with the use of a silicone-membrane blood oxygenator and parenteral nutritional support. The fetus remained in a metabolically stable state lasting several days.*

The fetus is an unstable subject for isolated physiological and biochemical study (*1*). Data on the fetal metabolic state have previously resulted from analyses of blood obtained from an indwelling catheter placed in an umbilical artery or vein (*2*). Data so obtained on oxygen saturation of arterial blood, oxygen consumption, and lactate in the plasma differ from measurements obtained at cesarean section or delivery (*3*).

To study the fetus in a controlled, stable environment, we devised a total support system for isolated fetal perfusion (*4*). The system consisted of (i) a silicone membrane lung which had a constant volume of 70 ml and a gas-exchange area of 0.4 m^2 (the lung was in the form of a spiral coil), (ii) a continuously infused (8.4 ml/hour) nutritional support, and (iii) a thermoregulated (40° to 41°C) bath of synthetic amniotic fluid (*5*).

Using spinal anesthesia and clean but not sterile surgical techniques, we exposed fetal umbilical cords by cesarean section from Hampshire and Corriedale ewes of known gestation age. After the fetus was given heparin (500 U.S.P. units per kilogram), we cannulated one umbilical artery to the level of the renal artery. The cannulas were made to our specifications: outside diameter, 2.6 mm; inside diameter, 2.1 mm; segmented polyurethane reinforced with steel spring wire, 0.10 mm in diameter (*4, 6*). Umbilical arterial blood drained into an expandable silicone reservoir bag 35 cm below the fetus. Blood was then pumped by a large-bore, occlusive roller pump at 26 ml per revolution through the membrane lung and returned to the fetal umbilical vein by a wire-reinforced cannula (3.8 mm outside diameter, 3.3 mm inside diameter). After partial bypass was instituted, the second umbilical artery was similarly cannulated, and the fetus was maintained completely separate from the ewe. After cannulation, the fetus was transferred to the bath of synthetic amniotic fluid (Fig. 1).

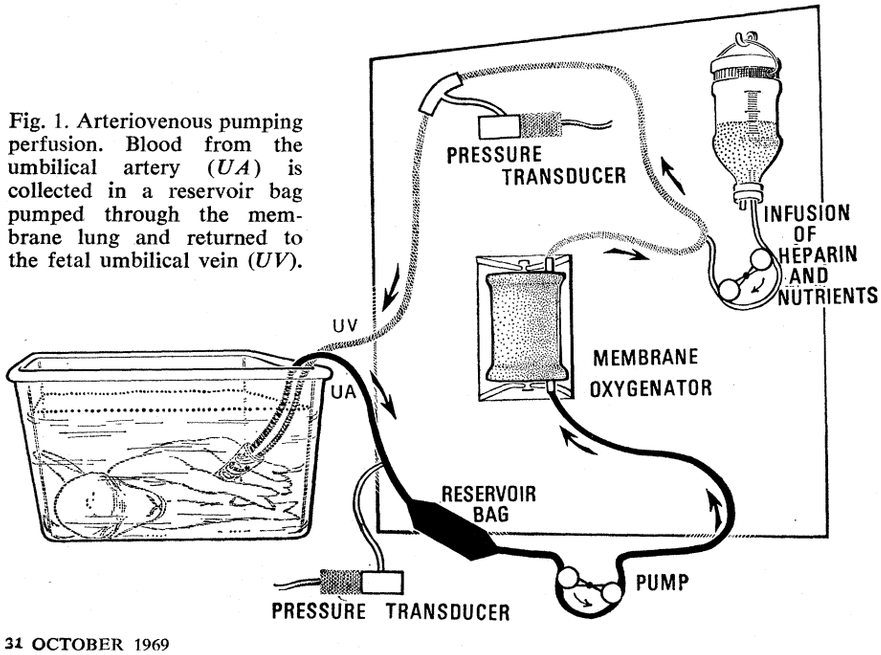

Fig. 1. Arteriovenous pumping perfusion. Blood from the umbilical artery (*UA*) is collected in a reservoir bag pumped through the membrane lung and returned to the fetal umbilical vein (*UV*).

The extracorporeal circuit and one membrane lung were primed with 240 ml of packed, adult-sheep red cells (washed with Ringer solution containing lactate) with 2000 U.S.P. units of heparin added. If two membrane lungs in series were used (fetal weight > 3 kg), the circuit was primed with 310 ml of sheep red cells. All extracorporeal tubing was made of silicone rubber with tetrafluoroethylene connectors. During perfusion, heparin (150 U.S.P. units per kilogram per hour), antibiotics (penicillin, chloramphenicol, and sodium colistimethate), and nutrients (glucose, amino acids, and vitamins) were continuously infused.

Biochemical and physiological effects of prolonged perfusion in a 3.05-kg male Hampshire fetus of 125 days gestation age (term, 147 days) are illustrated in Fig. 2. The *p*H of the blood was stabilized in the range of 7.40 ± 0.05 with P_{CO_2} between 30 and 50 mm-Hg. No buffers were added. Oxygen consumption, monitored continuously by spirometry of the membrane oxygenator gas supply, averaged 6.0 ± 0.5 cm^3 kg^{-1} min^{-1} with fetal rectal temperature varying between $39.2° \pm 0.5°C$. When the rate of flow in the artificial placenta was 70 to 100 ml kg^{-1} min^{-1}, oxygen saturation in the umbilical artery was between 55 and 75 percent. To compensate for early metabolic acidosis, we increased initial blood flow through the membrane oxygenator up to 150 ml kg^{-1} min^{-1}. Fetal blood pressure in the aorta was measured by occluding umbilical arterial inflow for 3 seconds, and thereby we avoided another arterial cannulation in a heparinized fetus.

Fluid volume was initially adjusted with packed, washed, adult-sheep red cells to maintain an umbilical arterial pressure of 85 mm-Hg. No further infusions of red cells or plasma were necessary. Hemoglobin fell from 16 g/100 ml to 8 g/100 ml in 55 hours, an amount consistent with sampling losses of 265 ml. This volume was replaced by Ringer solution containing lactate. Free hemoglobin in the plasma decreased from an initial 100 mg/100 ml

to 13 mg/100 ml at 15 hours of perfusion, and persisted below 10 mg/100 ml for the remaining 40 hours. Platelets measured at 24 hours of perfusion were 199,000 per cubic millimeter. Total bilirubin remained below 1 mg/100 ml. Glucose in the plasma remained at approximately 100 mg/100 ml. Lactic acid rose to a high of 84 mg/100 ml at 5 hours of perfusion, then fell sharply to about 10 mg/100 ml and remained so (see Fig. 2). Potassium in the plasma was stabilized at 6 ± 2 meq/liter. Creatinine fell from an initial value of 2.5 mg/100 ml to less than 1 mg/100 ml.

During perfusion, the fetus rested quietly in the artificial amniotic bath. About once each hour it moved its head or legs spontaneously. It exhibited a strong sucking reflex as well as a withdrawal reflex when pinched. After 55 hours of perfusion, the fetus abruptly underwent cardiac arrest and stopped extracting oxygen from the umbilical arterial blood. Cultures of the fetal blood and the amniotic bath yielded *Klebsiella* and *Aerobacter* species resistant to the infused antibiotics. At autopsy we found a moderately increased amount of peritoneal fluid; hemorrhage and edema were absent.

There was no evidence of hemolysis, an indication that mechanical trauma to red cells was not a problem in long-term maintenance of this preparation. Fetuses in four of eight experiments survived for periods exceeding 20 hours, and we now have two apparently normal long-term surviving lambs after 4 and 10 hours of extrauterine support.

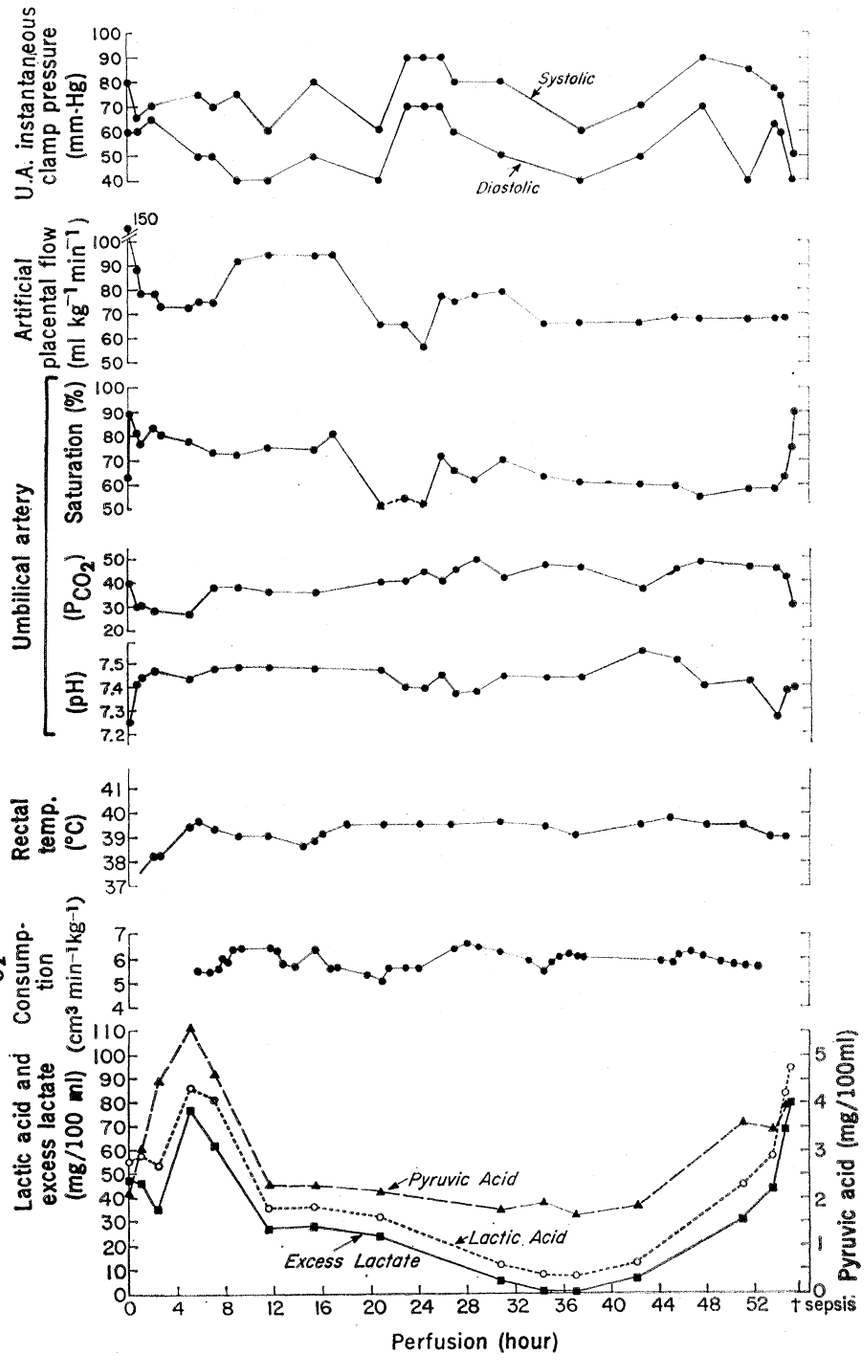

Fig. 2. Physiologic and biochemical parameters monitored during a 55-hour perfusion of a 3.05-kg male Hampshire fetus at 125 days of gestation. Excess lactate was computed by a modification of the method of Huckabee (7).

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15 May 1969; revised 2 July 1969