Studies in the Development of an Artificial Placenta

The Possible Use of Long-Term Extracorporeal Circulation for Respiratory Distress of the Newborn


The first interest of this group in the development of an artificial placenta was to provide a means of testing the long-term use of an oxygenator in an unanesthetized animal in a readily controlled state. Secondly, the possibility was considered of supporting the newborn child in respiratory distress syndrome with oxygenated blood delivered into the umbilical vein on a long-term basis.

In 1958, Westin studied seven previable human fetuses which he kept alive between 5 and 12 hours by perfusion of the umbilical vein, in association with hypothermia. In choosing the lamb as the experimental animal, we were guided by the excellent studies by Dawes. Much of our early physiological information came from the work of Barcroft and Barron. Barclay et al. provided information concerning the fetal circulation in lambs. Harned et al. suggested supportive circulation by a pump oxygenator in neonatal respiratory distress syndrome, but did not appear to publish details of the study in which they were able to maintain life in newborn lambs for up to an hour.

Methods

This study is based on 10 of 28 lambs removed by Cesarean section from 24 Suffolk ewes between 80 and 134 days of gestation (normal gestation period in this breed is 144 to 147 days) and placed in the artificial placenta. Seventeen ewes received intravenous Nembutal (1,500 mg.) as an anesthetic. With the ewe lying on the right side, a left muscle-splitting incision provided access to the abdomen. The cord and various extremities of the fetus were identified through an incision in the uterus, and the hind end was brought out just far enough to permit dissection of the groin. A polyethylene catheter was inserted into the femoral artery for pressure studies and biochemical study. Fine scissors were used to dissect the two umbilical veins and arteries. With extreme care, two no. 4 silk sutures were placed around each vessel at either end of the 25-mm. length of cleared vessel, some 5.0 cm. from the skin margin.

A specially constructed stainless steel holding device (fig. 1, 2) containing the polyvinyl catheters (Bardie) of the appropriate sizes already connected to the perfusion apparatus (fig. 1) primed with 1,400 to 1,500 ml. of donor blood was used. Heparin, 2 mg. per Kg. body weight, was given into the umbilical vein.

A single umbilical venous catheter was inserted about 5.0 cm. from the skin margin and passed to approximately 5.0-cm. deep to the skin level. The umbilical arteries were cannulated as rapidly as possible and the catheters inserted as far as possible until resistance to passage was felt. If the animal deteriorated after the insertion of the first umbilical arterial catheter, perfusion would be started at once and the second arterial catheter inserted thereafter. Umbilical venous and arterial blood was sampled at 10-, 20-, 30-, and 40-minute periods during the perfusion and when the animal was delivered to the atmosphere.

The artificial circulation was effected by equipment demonstrated in figure 1. The legend under the figure identifies the various component parts.

The fetus was permitted to pump desaturated blood to the umbilical arterial reservoir. The fetus was then transferred to the placental chamber with care being taken to prevent the head of the fetus from being exposed to the atmosphere. The animal was then submerged in artificial amniotic fluid of 5 per cent glucose in normal saline at 35 to 39 C.

Needle electrocardiographic and electroencephalo-
graphic electrodes were placed subeutaneously. Flow rates in the umbilical vein and artery were monitored by an electromagnetic blood flowmeter° with a separate channel for each line. Pressures in the femoral artery, umbilical artery, and umbilical vein were continuously measured by Statham pressure transducers° and recorded on an eight-channel macropolygraph‖ along with electroencephalogram and electrocardiogram. Observations of movements of the fetus and of respiratory and swallowing efforts were recorded. Oxygen saturation in the blood was measured by the Thomas–Van Slyke manometric method and, as well, studied by the microelectrode and the Beckman Spinco physiological gas analyzer, Model 160.† Carbon dioxide content was studied by the Natelson microgasometer,§ and the pH by the Photovolt pH meter.‖ Hematoerit was measured by the Wintrobe method and hemoglobin, plasma hemoglobin, blood urea, and blood sugar estimations made on the Klet colorimeter.[‡]

Results

In the 10 animals in this portion of the study, the weights of the lambs varied between 0.6 and 4.0 Kg., and the period of gestation between 80 and 140 days.

It was possible to obtain a satisfactory perfusion of at least 40 minutes in seven of these animals, and three of these were delivered to the atmosphere. One of these animals (experiment 304—see figs. 1 and 2) was a long-term survivor and is now, three months later, a guest at the Children’s Zoo, apparently thriving. One animal lived eight hours and died of diffuse hemorrhage; the other animal was sacrificed and autopsied at six hours after delivery because of the lack of fresh ewe milk so essential immediately after birth.

The time for insertion of all catheters varied between 3 and 24 minutes, with an average of 8 minutes. In the sole long-term survivor the time was 5 minutes.

The umbilical arterial reservoir levels varied between 35 and 75 cm. above the fetus. The height of the umbilical venous reservoirs varied between 0 and 60 cm.

The umbilical arterial flow rates as measured in six of the animals are shown in figure 2A. The long-term-survival animal (experiment 304) is compared with five other similar experimental animals which failed to survive. Flow rates varied between 13 and 50 ml. per Kg. per minute at the start of perfusion. In the survivor, the flow rates never fell below 30 ml. per Kg. per minute, whereas in each of the others lower flow rates did occur.

The pulse rate during perfusion is shown in figure 2E, where again there is a comparison with experiment 304. The pulse rates in the early minutes of perfusion varied between 120 and 240 per minute. A severe fall in pulse rate, if it occurred, heralded the demise of the animal in all instances. The three animals (experiments 304, 305, 307) that lived for a period in the atmosphere had pulse rates higher than 160 per minute at all times.

The oxygen tension in both umbilical arterial and umbilical venous blood is shown in figure 2F. The umbilical artery pO2 remained below 50 mm. Hg in all animals. The wide variation in the oxygen tension of the umbilical venous blood reflected the varying flow rates through the oxygenator.

The carbon dioxide content in volumes per cent is shown in figure 2C, where the umbilical venous and umbilical arterial values in experiment 304 are compared with similar, but unsuccessful, experiments. There was a gradual fall in umbilical arterial carbon dioxide in all the animals.

The pH values shown in figure 2B remained remarkably constant in the surviving animal (experiment 304), but at a slightly lower level than in the animals that failed to survive.

Blood glucose levels varied between 74 and 80 mg. per cent and remained constant throughout this period of perfusion.

The electrocardiogram demonstrated anoxic changes as the pulse rate fell. Widening of the complex T-wave changes and decrease of voltage were seen as the animals deteriorated.
Difficulty occurred in obtaining a really good tracing when the animal was submerged, although the cardiac rate could always be determined from the electrocardiogram.

The electroencephalogram was extremely difficult to visualize in the submerged animals, and the electrocardiogram appeared on it due, presumably, to failure to prevent conduction of currents in the fluid medium even with deeply planted needle electrodes in the scalp.

The femoral arterial pressure in utero varied between 60 and 140 mm. Hg in six lambs studied, as demonstrated in figure 2D. There was a gradual fall in all animals as perfusion continued. The surviving animal (experiment 304) maintained a pressure of 60 mm. Hg after breathing air.

In a control animal (experiment 308) not included in this series, pressures were taken in the umbilical vein and artery under intrauterine conditions. The umbilical venous pressure was 20 mm. Hg with the femoral arterial...
pressure 85/65 mm. Hg. Flow rates in the umbilical arteries in this animal varied between 48 and 60 ml. per Kg. per minute, with femoral arterial pressure 90/60 mm. Hg, umbilical arterial pressure 50/40 mm. Hg, and the umbilical venous pressure 20 mm. Hg.

**Discussion**

In our earlier study, we were able to keep eight lambs alive in the placenta for periods longer than eight hours. The longest survivor was 19 hours, but it was not felt, after postmortem studies that survival in air would have been possible for any of these animals.

There are undoubtedly many reasons why these animals deteriorate in even a short period in the placenta. The time for cannulation, if prolonged, is indeed a common cause of failure. Harned et al. made a point of this, and we certainly agree.

Our flow rates, as soon as the animal was perfused, and presumably at a time when his circulation was at its best and bearing the closest similarity to normal intrauterine conditions, varied between 13 and 50 ml. per Kg. per minute.

Adams and Lind found flow rates in the human fetus to change from 60 ml. per Kg. per minute just before birth to 273 ml. per Kg. per minute just after birth. Dawes, in his study, demonstrated umbilical flows of 100 to 180 ml. per Kg. per minute as an average in six mature lambs. He created a study with an artificial lung in the circuit with a heart-lung preparation of a lamb and demonstrated a decrease in size of the ductus arteriosus if arterial oxygen saturation rose as high as 76 per cent. In none of our animals did the peripheral arterial tension rise to 50 mm. Hg.

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Dawes calculated mean cardiac output in the fetal lamb at 115 ml. per Kg. per minute just before birth, rapidly rising to 325 ml. per Kg. per minute. These values are higher than we have been able to obtain in our perfusion and undoubtedly will be required before a physiologically stable preparation can be assured.

In postulating a clinical application, we have perfused dogs, with survival for periods up to two and a half hours,9,10 by a venovenal-type circulation similar, in certain respects, to fetal circulation allowing for a closed ductus. However, a great deal of further study is anticipated before this becomes a practical method of clinical management of respiratory distress syndrome of the newborn.

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