A NEW ARTIFICIAL PLACENTA WITH A CENTRIFUGAL PUMP: LONG-TERM TOTAL EXTRAUTERINE SUPPORT OF GOAT FETUSES

Masahiro Sakata, MD
Katsuya Hisano, MD
Masayoshi Okada, MD
Masao Yasufuku, MD

Purpose: We tried long-term total extrauterine support of goat fetuses at high pump flow, which was pulsatile and synchronized with the cardiac cycle and at low oxygen tension in the umbilical artery and vein by use of the new artificial placenta. **Method:** This system consisted of an arterio-venous extracorporeal membrane oxygenation using umbilical artery and vein and a thermoregulated water bath. Five goat fetuses (125 ± 0.7 days of gestation, 2.0 ± 0.9 kg) were incubated in lactated Ringer's solution. Mean pump flow rate ranged from 113 ± 16 to 193 ± 13 ml/min/kg, and umbilical arterial oxygen tension was maintained at 20 ± 3 to 23 ± 5 mm Hg for five fetuses. **Result:** Blood gas analysis echocardiogram showed that fetal circulation and sufficient oxygen consumption could be maintained, and fetal extrauterine support conditions were made as similar as possible to physiologic circulatory conditions. We achieved long-term extrauterine support of goat fetuses up to 237 hours (mean 137 ± 58 hours). **Conclusion:** We believe that this system can be used for experimental models of the fetus and will come into clinical application for fetal extrauterine support systems and backup systems for fetal operations. (J Thorac Cardiovasc Surg 1998;115:1023-31)

Preterm labor is the leading cause of perinatal morbidity and mortality and remains a great challenge for fetal intervention. It occurs 100% of the time after hysterotomy, and tocolytic therapy has been distressingly unsuccessful. Development of an artificial placenta was initiated in the late 1950s and Zapol and colleagues¹ reported 2 days of total extrauterine support of the isolated immature lamb fetus. In 1993 Unno and colleagues² reported 3 weeks of total extrauterine support. We developed a new artificial placenta with a centrifugal pump to support immature fetuses.

The umbilical blood flow accounts for 41% of the combined output of both ventricles, and fetoplacental circulation consists of an arteriovenous shunt. Furthermore, fetal oxygen tension (Po_2) in arterial

blood is extremely low,³ and a rise in arterial Po_2 causes constriction of the ductus arteriosus and interruption of fetal circulation.

By use of a artificial placenta with a centrifugal pump, we attempted long-term extrauterine support of goat fetuses under nearly physiologic fetoplacental circulatory conditions. Then we examined maintenance of fetal circulation and oxygen consumption under total extrauterine support. We were convinced that this study is not only for laboratory models but also contributed to an advance in the fetal therapy for immature fetuses and fetal operations.

Materials and methods

Animal preparation. Five pregnant Sanen goats with time-dated gestations of 125 ± 0.7 days (full term 148 days) were fasted for 24 hours. Atropine sulfate, 0.5 mg, was injected 30 minutes before the operation. After a slow induction with inhalation of 4% halothane and 50% nitrous oxide, the animals were placed in the supine position on the operating table and intubated. Anesthesia was then maintained with inhalation of 1.5% to 2% halothane and 50% nitrous oxide. All the following procedures were performed under sterile conditions. After a lower midline laparotomy, the uterus was exposed. The fetal hind limbs, the lower part of the body, and the umbilicus were exteriorized through a small hysterotomy. Papaverine was injected around the umbilical arteries to

From the Kobe University School of Medicine, Department of Surgery, Division II, Kobe, Japan.

Received for publication April 30, 1997; revisions requested June 17, 1997; revisions received Nov. 11, 1997; accepted for publication Nov. 11, 1997.

Address for reprints: Masahiro Sakata, MD, Department of Surgery, Division II, Kobe University School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650, Japan.

Copyright © 1998 by Mosby, Inc.

0022-5223/98 \$5.00 + 0 12/1/87525

Fig. 1. The system of the fetal AV-ECMO. The circuit consists of a centrifugal pump (HPM-15, Nikkiso Ltd.), a membrane oxygenator (Menox 2000 Kurare), an in-line electromagnetic blood flowmeter (MFV 1100, Nihon Kohden Co.), and an optical fluorescence blood gas monitor (CDI 300, Cardiovascular Devices Inc.). Ao, Aorta; PA, pulmonary artery; UA, umbilical artery; UV, umbilical vein; DA, ductus arteriosus; DV, ductus venosus; IVC, inferior vena cava; SVC, superior vena cava; RV, right ventricle; LV, left ventricle; LA, left atrium; RA, right atrium; FO, foramen ovale.

prevent arterial constriction. One polyvinyl cannula (9F, adapted from the suction tube inside diameter at the catheter tip 2.5 mm, length 25 cm; Japan Sherwood, Ltd., Tokyo, Japan) for drainage was inserted into the umbilical artery 2 cm from the fetal abdominal wall beyond the aortic bifurcation, and a 10F or a 12F cannula (inside diameters 2.7 mm and 3.4 mm, respectively, length 15 cm; Kurare, Ltd., Tokyo, Japan) was inserted into the umbilical vein for return, and fetal arteriovenous extracorporeal membrane oxygenation (AV-ECMO) was started. Another cannula for drainage was inserted into the other side of the umbilical artery. After all cannulations, the fetus was isolated from the placenta and transferred to an incubator filled with 40° C lactated Ringer's solution. It takes about 2 hours to prepare the experiments from the beginning to the establishment of the fetal AV-ECMO. The mother goats were returned to the farm after recovering from the operation. All animals received humane care according to the "Guidelines for Animal Experimentation of the Kobe University School of Medicine."

Incubation system. The extracorporeal closed circuit consisted of a centrifugal pump (HPM-15, priming volume 25 ml; Nikkiso, Ltd., Tokyo, Japan), a membrane oxygenator consisting of double-layered polyolefin hollow

fiber (Menox 2000, Kurare), an in-line electromagnetic blood flowmeter (MFV 1100, Nihon Kohden Co., Tokyo Japan), and an optical fluorescence blood gas monitor (CDI 300, Cardiovascular Devices, Inc., Calif.) (Fig. 1). Fetal blood from the umbilical arteries was oxygenated and returned to the umbilical vein. Blood oxygenation was achieved with air blended with either 100% oxygen or 100% nitrogen, so that the P_{O_2} of the umbilical arterial blood could be maintained at 20 mm Hg. The extracorporeal circuit and membrane oxygenator were primed with 95 ml of maternal blood with heparin. Glucose (10% solution), heparin, and prostaglandin E_2 (Ono, Tokyo, Japan) were infused continuously into the extracorporeal circuit at rates of 3 to 8 mg/min/kg, 0.8 U/min/kg, 3 μ g/min/kg, respectively. Hyperalimentation fluid was also infused 3 days after initiation of AV-ECMO. Activated coagulation time was kept between 180 and 200 seconds. Prostaglandin E_2 was infused to prevent ductal constriction. Fetal arterial blood glucose concentration was maintained at more than 20 mg/dl.⁴ Maternal blood or fetal blood with ethylenediaminetetraacetic acid was infused to substitute blood samples. The lactated Ringer's solution with antibiotics (moxalactam) in the bath was thermoregulated at 40° C.

Fig. 2. Interrelationship between carotid arterial pressure and pump flow rate. The pump flow featured a pulsatile high flow and was matched in pulsation and shape with the cardiac cycle.

Monitoring. Blood flow rates (in milliliters per minute) were determined with an in-line electromagnetic flow sensor. Umbilical artery (preoxygenator) and umbilical vein (postoxygenator) blood gas samples were aspirated from sampling ports of the circuit. The pH, blood gas tensions (P_{O_2} , P_{CO_2} , mm Hg), hemoglobin concentration (Hb, gm/dl), oxygen saturation of the blood (percent), and electrolyte concentrations (sodium, potassium, chloride, mEq/L) were immediately analyzed on an ABL 501 (Radiometer A/S, Copenhagen, Denmark) and an OSM-3 (Radiometer) every 4 to 8 hours. The umbilical arterial blood gas values were also continuously measured at the actual blood temperature on an in-line optical fluorescence blood gas monitor (CDI 300). The CDI 300 was calibrated with values obtained from the ABL 501 and OSM-3.

Hemodynamic measurements were carried out 24 hours after the initiation of AV-ECMO, when the fetal circulation had stabilized. A 3F catheter was introduced into the carotid artery of all the fetuses through a small incision in the neck for fetal heart rate, arterial blood pressure, and gas monitoring. In two fetuses (cases 1 and 2) a 3F balloon-tipped catheter (Baxter Healthcare Corp., Santa Ana, Calif.) was inserted through the jugular vein into the right atrium for right atrial pressure monitoring and into the other three fetuses (cases 3 through 5) into the right ventricle for gas monitoring. The heart rate, carotid

arterial pressure, and right atrial pressure were monitored with a polygraph system (Nihon Kohden Co., Tokyo, Japan). The heart rate was measured with a cardiota-chometer triggered from the phasic systemic arterial pressure pulse wave.

The fetal whole-body oxygen consumption (OC, ml/min/kg) was calculated as follows:

$$\text{Blood oxygen content (ml/dl)} = 1.34 \times \text{Hb} \times \frac{\text{oxygen saturation}}{100} + 0.003 \times P_{O_2}$$

$$\text{OC} = \frac{(\text{Umbilical venous blood oxygen content} - \text{Umbilical arterial blood oxygen content}) \times \text{ECMO flow}}{100/\text{body weight}}$$

The fetal blood lactate and pyruvate concentrations were measured every 24 hours. The diameter of the ductus arteriosus was measured with two-dimensional echocardiography. Pulse Doppler ultrasound blood velocity waveforms of the ductus arteriosus were evaluated with a 5 MHz transducer PSF 50 FT and an SSH140AHG (Toshiba, Ltd., Tokyo, Japan) by placing the Doppler sample volume in the ductus arteriosus.

Results

Case. Mean weight of the five goat fetuses was 2.0 ± 0.1 kg at the initiation of AV-ECMO. The

Table I. Duration of perfusion and total extrauterine support condition

Case	Case 1	Case 2	Case 3	Case 4	Case 5
Duration of perfusion (hr)	133	237	87	117	112
Pump flow rate (ml/min/kg)	145 $\pm$ 20	171 $\pm$ 17	113 $\pm$ 16	193 $\pm$ 13	186 $\pm$ 19
Heart rate (beats/min)	163 $\pm$ 30	156 $\pm$ 15	144 $\pm$ 18	153 $\pm$ 16	154 $\pm$ 15
Blood pressure (mm Hg)					
Systolic	56 $\pm$ 10	73 $\pm$ 8	75 $\pm$ 9	64 $\pm$ 6	85 $\pm$ 7
Diastolic	30 $\pm$ 8	41 $\pm$ 5	43 $\pm$ 5	38 $\pm$ 4	45 $\pm$ 6
Mean	43 $\pm$ 9	57 $\pm$ 6	58 $\pm$ 6	51 $\pm$ 5	64 $\pm$ 6
Electrolyte concentration (mEq/L)					
Na	138 $\pm$ 5.1	138 $\pm$ 4.5	141 $\pm$ 5.2	143 $\pm$ 3.6	141 $\pm$ 4.7
K	3.6 $\pm$ 0.4	3.6 $\pm$ 0.5	3.4 $\pm$ 0.2	3.5 $\pm$ 0.4	3.4 $\pm$ 0.2
Cl	107 $\pm$ 4.9	107 $\pm$ 3.4	108 $\pm$ 5.1	109 $\pm$ 3.9	108 $\pm$ 3.2

fetal body weight at autopsy was 2.7 ± 0.4 kg. Values are expressed as mean $\pm$ standard deviation. The cause of death was circulatory failure.

The pump flow featured a pulsatile high flow and was matched in pulsation and shape with the cardiac cycle (Fig. 2). Pump flow was increased in proportion to the pump revolution rate and also in proportion to the fetal blood pressure.

The duration of incubation was 87 to 237 hours (mean 137 ± 58 hours). The mean pump flow for the five fetus was from 113 ± 16 to 193 ± 13 ml/min/kg. The pump flow in case 3 was low because of stenosis of the cannula for return, but high-flow perfusion could be obtained after elimination of this stenosis (Table I).

Blood gas analysis in the carotid artery, the umbilical vein, and the right ventricle. Acidemia developed in only case 1. P_{O_2} and oxygen saturation of the umbilical artery were maintained at 20 ± 4 to 23 ± 5 mm Hg and $45\% \pm 14\%$ to $59\% \pm 9\%$, respectively. The P_{O_2} of the umbilical veins for the five fetuses ranged from 32 ± 7 to 41 ± 6 mm Hg and the oxygen saturation from $75\% \pm 9\%$ to $84\% \pm 7\%$. The P_{O_2} of the carotid artery ranged from 24 ± 4 to 28 ± 6 mm Hg, and the oxygen saturation from $55\% \pm 8\%$ to $66\% \pm 6\%$ (Table II). The following relationship was always maintained in all cases: P_{O_2} and oxygen saturation of the umbilical vein $>$ those in the carotid artery $>$ those in the umbilical artery.

Hemoglobin concentrations were from 6.5 ± 1.2 to 9.7 ± 0.8 g/dl for each case, but that of case 1 was lower than other cases (Table III). Oxygen consumption was 4.4 ± 1 to 5.3 ± 1.7 ml/min/kg, umbilical arterial lactate concentration was 28 ± 11 to 95 ± 30 mg/dl, and pyruvate concentration was 2.2 ± 0.9 to 4.1 ± 0.9 mg/dl. Lactate concentration in case 1 was higher than the others. In case 1

metabolic acidemia developed after anemia (Table III).

During perfusion, P_{O_2} and oxygen saturation in the right ventricle, the carotid artery, and the umbilical artery and vein were simultaneously measured 20 times in cases 3, 4, and 5. P_{O_2} and oxygen saturation in the right ventricle were 19 ± 4 mm Hg and $43\% \pm 7\%$, respectively; the umbilical venous P_{O_2} and oxygen saturation were 34 ± 7 mm Hg and $76\% \pm 11\%$, the carotid arterial P_{O_2} and oxygen saturation were 25 ± 4 mm Hg and $61\% \pm 9\%$, and the umbilical arterial P_{O_2} and oxygen saturation were 22 ± 4 mm Hg and $51\% \pm 10\%$, respectively. The following relationship was always maintained: P_{O_2} and oxygen saturation in the umbilical vein $>$ those in the carotid artery $>$ those in the umbilical artery $>$ those in the right ventricle.

Echocardiogram. Two-dimensional and pulse-Doppler echocardiogram showed that the ductus arteriosus was wide open and that the direction of the ductus arteriosus waveform was from the pulmonary artery to the descending aorta during fetal extrauterine support (Fig. 3).

Representative case. Fig. 4 shows the biochemical and physiologic effects of 237-hour perfusion on a 2.0 kg fetus of 125 days' gestational age.

Discussion

In 1969 Zapol succeeded in 55-hour extrauterine support of fetal lambs by use of a roller pump, and recently Unno and colleagues achieved 534-hour total extrauterine support of a goat fetus also with a roller pump.^{1,2} To our knowledge there have been no reports concerning total extrauterine support of a fetus under the nearly physiologic circulatory condition by use of a centrifugal pump.

The rate of physiologic umbilical blood flow has

Table II. Blood gas analysis of the umbilical artery, carotid artery, and umbilical vein

Case	Case 1	Case 2	Case 3	Case 4	Case 5
In the umbilical artery					
pH	7.33 ± 0.14	7.45 ± 0.05	7.45 ± 0.04	7.45 ± 0.04	7.41 ± 0.05
Po ₂ (mm Hg)	23 ± 5	20 ± 5	20 ± 4	23 ± 4	23 ± 3
SaO ₂ (%)	45 ± 14	48 ± 13	45 ± 8	59 ± 9	52 ± 8
PCO ₂ (mm Hg)	34 ± 5	34 ± 5	35 ± 2	35 ± 5	38 ± 4
BE (mEq/L)	-7.3 ± 6	-1.6 ± 3	0.7 ± 2	2.3 ± 6	-0.4 ± 3
In the umbilical vein					
Po ₂ (mm Hg)	41 ± 6	32 ± 7	40 ± 10	34 ± 9	34 ± 5
SvO ₂ (%)	77 ± 12	75 ± 9	84 ± 7	80 ± 9	76 ± 10
In the carotid artery					
Po ₂ (mm Hg)	28 ± 6	24 ± 4	27 ± 3	27 ± 5	24 ± 3
SaO ₂ (%)	55 ± 13	56 ± 10	66 ± 6	66 ± 6	55 ± 9

Po₂, Oxygen tension; SaO₂, arterial oxygen saturation; SvO₂, venous oxygen saturation; PCO₂, carbon dioxide tension; BE, base excess.

Table III. Oxygen consumption rate and concentration of lactate and pyruvate under total extrauterine support

	Case 1	Case 2	Case 3	Case 4	Case 5
Hemoglobin (g/dl)	6.5 ± 1.2	8.6 ± 1.2	8.7 ± 0.9	9.7 ± 0.8	7.9 ± 0.6
Oxygen consumption (ml/kg/min)	4.4 ± 0.9	5.3 ± 1.7	4.6 ± 1.4	4.9 ± 1.6	4.6 ± 1.4
Lactate (mg/dl)	95 ± 30	28 ± 11	31 ± 15	24 ± 10	38 ± 16
Pyruvate (mg/dl)	4.1 ± 0.9	2.2 ± 0.9	2.9 ± 1.3	2.5 ± 1.2	3.7 ± 1.1

been show to range from 158 to 251 ml/min/kg for fetal lamb,⁵⁻⁷ so that the precise rate still remains controversial. In our experiment the rate of physiologic umbilical blood flow was assumed to be between 170 and 200 ml/min/kg.

The previous artificial placenta, which we used before and Zapol has used, was a closed circuit that consisted of a roller pump. In all these experiments, however, the pump flow rate was only 60 to 100 ml/min/kg.^{1,8,9} It was difficult to maintain a high physiologic flow rate by this system. When the fetal heart and pump worked independently, imbalance between cardiac output and high pump flow rate easily caused suck of the aortic wall into the drainer, and finally pump flow was reduced or stopped. It was thought that drainage volume must be changed with the fetal cardiac cycle because pump flow at 170 ml/min/kg accounts for 40% of fetal cardiac output. Furthermore, it is thought that any pump is sufficient to assist perfusion pressure against the resistance that was developed by the circuit because fetoplacental circulation is an arteriovenous shunt.

No occlusive site exists in a centrifugal pump. Pump flow was decided by revolution rate of pump head and the transmitted arterial pressure pulse. During perfusion, revolutions per minute of the centrifugal pump were constant from 800 to 1000. The pulsatile nature of pump flow is due to an arterial transmitted inflow pressure pulse. The

pump flow was not gated at all to provide synchronized blood flow. Our system also contained external perfusion-type polyolefin hollow fiber membrane oxygenator. Pressure loss in this artificial lung is very low, and total resistance of the circuit is also low. As a result, pump flow was maintained at high flow synchronized with cardiac cycle at the constant revolution rate of the pump head. By use of a centrifugal pump, no type of reservoir was needed. Our system could be made simple and the prime volume was 95 ml.

Unno and associates² succeeded in reducing the pump implication to fetuses by use of the open circuit system that contained an arterial open-top reservoir with flow detector-controller, roller pump, and venous closed reservoir. In this system drainage blood flow was not regulated by rotation of the roller pump head.

Patency of the ductus arteriosus is a key point in fetal circulation. The constrictor effect of Po₂ on the ductus arteriosus has been demonstrated.¹⁰ It is thus essential to keep arterial Po₂ low to prevent constriction of the ductus arteriosus. Furthermore, it has been shown that the Po₂ of the umbilical artery is about 20 mm Hg (17.3 to 24 mm Hg) and saturated oxygen is 50% to 59% under physiologic conditions in fetal lambs.^{5,6,11-18} For this reason we attempted to maintain Po₂ in the umbilical artery at 20 mm Hg. Because of low arterial Po₂, the ductus

Fig. 3. Echocardiographic findings in the ductus arteriosus during total extrauterine support. **A,** The ductus arteriosus was wide open. Direction of ductal blood flow is right to left shunt. Peak velocity of ductal blood flow is 1.8 msec. Pump flow, 150 ml/min/kg at 800 rpm; heart rate, 134/min; blood pressure, 75/42(54) mm Hg. Ao, Aorta; DA, ductus arteriosus; PA, pulmonary artery. **B,** The ductus arteriosus was wide open. Direction of ductal blood flow is right to left shunt. Peak velocity of ductal blood flow is 1.8 msec. Pump flow, 178 ml/min/kg at 1000 rpm; heart rate, 146/min; blood pressure, 80/47(58) mm Hg.

arteriosus could remain wide open during total extrauterine support.

Under intrauterine physiologic conditions, highly oxygenated umbilical blood passes through the ductus venosus to the heart and the brain and to the upper body.¹³ Poorly oxygenated blood returning to the heart from both the abdominal inferior and the superior vena cava passes through the ductus arteriosus to the lower body and to the umbilical cord. A large part of the right ventricular blood ejected to the descending aorta through the ductus arteriosus is mixed with the blood ejected from the left ventricle in the descending aorta. Under intrauterine physiologic conditions of the fetal lamb, PO_2 of the umbilical artery is 17.3 to 24 mm Hg. PO_2 in the ascending aorta is 24 to 28 mm Hg,^{19,20} whereas in the umbilical vein, PO_2 is 30 to 33 mm Hg.^{6,13,15,21,22} In the right ventricle PO_2 is 16 to 20 mm Hg.^{23,24} These values were in agreement with those obtained under total extrauterine support. These results and echocardiographic findings of the ductus arteriosus indicated that fetal circulation could be maintained under nearly physiologic conditions with this new support system.

Under total extrauterine support, low arterial PO_2 and sufficient oxygen consumption must be surely maintained. The acidemia that develops after hypoxemia, resulting from hemorrhage or reduction of

the umbilical blood flow, is mainly metabolic.^{16,22} Fetal oxygen consumption with our extrauterine support system was 4.4 to 5.3 ml/min/kg. In all cases except case 1 metabolic acidosis did not develop during perfusion. It was therefore thought that oxygen consumption could be maintained with this total extrauterine support. The hemoglobin concentration in the normal late-gestation fetal lamb is 8.9 to 9.9 gm/dl.^{18,25} In case 1 anemia caused by bleeding from the site of catheter introduction caused hypoxemia and lactic acidosis. In case 3 pump flow was 113 ± 16 and duration of incubation was 87 hours. It was shorter than other cases. In Unno's system, the pump flow was low between 60 and 130 ml/min/kg. The optimal condition of the pump flow rate and oxygenation in the artificial placenta is the next problem to be addressed. PO_2 in the umbilical vein was about 40 mm Hg in case 1 and case 3. It was thought that in case 1 it was due to replacement of fetal hemoglobin with adult hemoglobin by transfusion of large amounts of maternal blood for bleeding, and in the case 3 it was due to low pump flow. In the low pump flow such as 60 to 130 in Unno's system, oxygen saturation in the postoxygenerator blood needs to be 100% to maintain oxygen delivery. In our system, however, it needed to be kept 70% to 80% to maintain arterial PO_2 low. It is thought that as pump flow is increased, PO_2 and

Fig. 4. Physiologic and biochemical parameters monitored during a 237-hour perfusion (case 2).

oxygen saturation in the postoxygenerator blood are decreased to keep enough oxygen delivery and low arterial P_{O_2} that fetus is capable of accommodating the pump flow within 60 to 200 ml/min/kg.

The placenta has many functions such as transfer and synthesis of many substances. The arterial placenta mainly substitutes for only respiratory function. Circulatory failure gradually progressed during extrauterine support. All cases had ascites, pulmonary effusion, and peripheral edema at the end of extrauterine support. It is thought that circulatory failure was caused by implication of fetal AV-ECMO to the fetal homeostasis and by deficiency of other placental function. There is much room for further improvement of the contact surface and reduction of prime volume in this system by use of a small prime pump such as an in-line axial flow pump²⁶ and a small artificial lung.

In the artificial placenta the goat fetuses often moved their head, body, and extremities and swam around while making the breathlike movements. These fetal movements could be easily observed during incubation. The next question to be addressed in the artificial placenta concerns fetal nutrition and fetal maturation. In case 2, which was incubated for 237 hours, the eye was at first closed with a thin membrane, but the eyes opened fully during incubation. It was suggested that this was the example of fetal maturation.

To summarize, we showed that it was possible to incubate fetal goats by maintaining fetal circulation similar to that under intrauterine conditions. With this new support system, we achieved long periods, up to 237 hours, of extrauterine support of fetal goats under the nearly physiologic intrauterine circulatory condition. We believe that this system can be used for experimental models of fetuses, and that with further improvements this system will come into clinical application as a fetal extrauterine support system and backup system for fetal operations.

REFERENCES

1. Zapol WM, Kolobow T, Pierce J, Vurek GG, Bowman RL. Artificial placenta: two days of total extrauterine support of the isolated premature lamb fetus. *Science* 1969;166: 617-8.
2. Unno N, Kuwabara Y, Okai T, Kido K, Nakayama H, Kikuchi A, et al. Development of an artificial placenta: survival of isolated goat fetuses for three weeks with umbilical arteriovenous extracorporeal membrane oxygenation. *Artif Organs* 1993;17:996-1003.
3. Cohn HE, Sacks EJ, Heymann MA, Rudolph AM. Cardiovascular responses to hypoxemia and acidemia in fetal lambs. *Am J Obstet Gynecol* 1974;120:817-24.
4. Fowden AL, Silver M. The effects of thyroid hormones on oxygen and glucose metabolism in the sheep fetus during late gestation. *J Physiol* 1995;482:203-13.
5. Carter AM. Factors affecting gas transfer across the placenta and the oxygen supply to the fetus. *J Dev Physiol* 1989;12: 305-22.
6. Paulick RP, Meyers RL, Rudolph AM. Effect of maternal oxygen administration on fetal oxygenation during graded reduction of umbilical or uterine blood flow in fetal sheep. *Am J Obstet Gynecol* 1992;167:233-9.
7. Carver TD, Hay WW. Uteroplacental carbon substrate metabolism and O_2 consumption after long-term hypoglycemia in pregnant sheep. *Am J Physiol* 1995;269:E299-308.
8. Hisano K, Okada M, Sakata M, Noma O, Yokoyama N, Uetani Y, et al. Experimental study of ECMO for fetus: Doppler echocardiographic evaluation of goat fetal blood flow. *J J Artif Organs* 1993;22:880-4.
9. Sakata M, Yasufuku M, Hisano K, Okada M. Fetal circulation under the condition of artificial placenta with AV-ECMO. *J J Artif Organs* 1996;25:290-3.
10. Born GVR, Dawes GS, Mott JC. The constriction of the ductus arteriosus caused by oxygen and by asphyxia in newborn lambs. *J Physiol* 1956;132:304-42.
11. Dawes GS, Mott JC. Changes in O_2 distribution and consumption in foetal lambs with variations in umbilical blood flow. *J Physiol* 1964;170:524-40.
12. Johnson GH, Kirschbaum TH, Brinkman CR, Assali NS. Effects of acid, base, and hypertonicity on fetal and neonatal cardiovascular hemodynamics. *Am J Physiol* 1971;220:1798-807.
13. Edelstone DI, Rudolph AM. Preferential streaming of ductus venosus blood to the brain and heart in fetal lambs. *Am J Physiol* 1979;237:H724-9.
14. Edelstone DI, Rudolph AM, Heymann MA. Effect of hypoxemia and decreasing umbilical flow on liver and ductus venosus blood flows in fetal lambs. *Am J Physiol* 1980;238: H656-63.
15. Edelstone DI, Rudolph AM, Heymann MA. Liver and ductus venosus blood flows in fetal lambs in utero. *Circ Res* 1978; 42:426-33.
16. Iwamoto HS, Kaufman T, Keil LC, Rudolph AM. Responses to acute hypoxemia in fetal sheep at 0.6-0.7 gestation. *Am J Physiol* 1989;256:H613-20.
17. Kwan E, Rurak DW, Taylor SM. Oxygen consumption, acid-base status, and behavior during and after acute, severe hemorrhage in fetal lambs. *Am J Physiol* 1995;269: R758-66.
18. Hooper SB, Walker DW, Harding R. Oxygen, glucose, and lactate uptake by fetus and placenta during prolonged hypoxemia. *Am J Physiol* 1995;268:R303-9.
19. Jensen A, Roman C, Rudolph AM. Effect of reducing uterine blood flow on fetal blood flow distribution and oxygen delivery. *J Dev Physiol* 1991;15:309-23.
20. Kuipers IM, Maertzdorf WJ, de Joug DS, Hanson MA, Blanco CE. Effect of mild hypocapnia on fetal breathing and behavior in unanesthetized normoxic fetal lambs. *J Appl Physiol* 1994;76:1476-80.

21. Itskovitz J, Goetzman BW, Roman C, Rudolph AM. Effect of fetal-maternal exchange transfusion on fetal oxygenation and blood flow distribution. *Am J Physiol* 1984;247:H655-60.
22. Rurak DW, Richardson BS, Patrick JE, Carmichael L, Homan J. Oxygen consumption in the fetal lamb during sustained hypoxemia with progressive acidemia. *Am J Physiol* 1990;258:R1108-15.
23. Heymann MA. Control of the pulmonary circulation in the perinatal period. *J Dev Physiol* 1984;6:281-90.
24. Reid DL, Thornburg KL. Pulmonary pressure-flow relationships in the fetal lamb during in utero ventilation. *J Appl Physiol* 1990;69:1630-6.
25. Jensen A, Berger R. Fetal circulatory responses to oxygen lack. *J Dev Physiol* 1991;16:181-207.
26. Reddy VM, Liddicoat JR, Klein JR, Wampler RK, Hanley FL. Long-term fetal outcome after fetal cardiac bypass: fetal survival to full term and organ abnormalities. *J Thorac Cardiovasc Surg* 1996;111:536-44.