PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 154, 606-609 (1977)

High Gain Placental Cardiovascular Control[1] (39728)

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The ventilation-perfusion ratios in the mammalian lung are partially stabilized by local feedback loops so that changes in alveolar ventilation cause changes in the adjacent pulmonary circulation (1) and changes in the pulmonary circulation affect the ventilation of the adjacent alveoli (2). These mechanisms assist in the stabilization of ventilation-perfusion ratios and aid in the transfer of respiratory gases. Like the lung the placenta is an organ of exchange. The uterine blood flow is the analog of the alveolar ventilation and the umbilical blood flow is the analog of the pulmonary circulation. The arguments which apply to the effect of ventilation-perfusion ratios on the pulmonary exchange of respiratory gases also apply to perfusion-perfusion ratios and placental exchange (3). For this reason we attempted to demonstrate the presence of mechanisms linking the uterine and umbilical blood flows. We used a preparation in which the flow in the perfused umbilical circuit was changed while the responses of the adjacent uterine flow were measured.

Methods. Eight near-term goats were used in this study. The gestational ages ranged from 120 to 130 days. The mother was anesthetized with intravenous pentobarbital. A tracheotomy was performed and catheters were placed in a maternal femoral artery and uterine vein. A small incision was made in a relatively cotyledon-free area of the uterus. The umbilical cord was located and the cord vessels were catheterized so that it was possible to pump blood into the umbilical arteries and to recover the venous drainage. In this way the placenta could be perfused for several hours. The mother's body was lowered into a bath containing 150 liters of Krebs saline solution with the bicarbonate replaced by chloride, so that the weight of the uterus and contents did not rest upon the inferior vena cava. The placental perfusion circuit consisted of a primary perfusion pump and an additional pump which lifted the venous drainage into bubble oxygenators which equilibrated the blood with a gas mixture containing CO_2, O_2, N_2, and acetylene (C_2H_2). The mother breathed a gas mixture containing O_2, N_2, and nitrous oxide (N_2O).

The umbilical blood flow ($\dot{Q}_f$) was determined by the setting of the primary perfusion pump, which was calibrated against timed collections of venous outflow. Blood samples were drawn from the maternal artery (MA), uterine vein (MV), umbilical perfusate (FA), and from the umbilical veins (FV). The N_2O and C_2H_2 concentrations (C) in the blood samples were determined by gas chromatography (Beckman GC-2A with blood gas accessory). The uterine blood flow ($\dot{Q}_m$) was calculated according to the equation

$$\dot{Q}_m = \dot{Q}_f(C_{FA} - C_{FV})/(C_{MV} - C_{MA})$$

for both the C_2H_2 data and the N_2O data. Data were considered to be acceptable when the calculated results for $\dot{Q}_m$ from the N_2O and C_2H_2 values differed by no more than 10%. The uterine blood flow was recorded as the mean of the paired N_2O and C_2H_2 data.

The placenta was perfused for 30 min at a fixed rate. Blood samples were then taken from the four sites (MA, MV, FA, FV). The umbilical blood flow was then changed and maintained at its new level for a further 30 min, at which time a second set of blood samples was taken. In some preparations a third umbilical blood flow was studied and a third set of data were obtained.

Full details of the surgery, assay, the per-

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ISSN 0037-9727

fusion circuit, and the maintenance of physiological gas concentrations in the perfusion blood are provided elsewhere (4).

The respiratory gas status of the blood entering the umbilical arteries was: PO_2, 16 mm Hg; PCO_2, 49 mm Hg; and pH, 7.06. The equivalent values for maternal arterial blood were PO_2, 120 mm Hg; PCO_2, 31 mm Hg; and pH, 7.37. These values are similar to established values for the goat (4). The blood in the perfusion circuit was drawn into heparinized containers 12 h before the perfusion. The donors were unanesthetized nonpregnant goats. The average hemoglobin concentration in the blood of the pregnant goats was 10.3 g% and that of the blood from the donor goats was 9.4 g%. The uterine venous pressures were not measured. The umbilical venous pressures were adjusted to a value of approximately 5 mm Hg by raising or lowering the venous reservoir.

All data reported were obtained from preparations in which the maternal and fetal blood values of pH, PO_2 and PCO_2 were within normal limits.

Results. Data from eight animals are presented in Table I. Fourteen changes in umbilical perfusion rate could be correlated with changes in calculated uterine blood flow. In 13 of the 14 observations a change in umbilical perfusion rate induced a change in the same direction in the uterine blood flow. The ratio of the second umbilical flow to the original is also given in Table I, together with the ratio of the corresponding uterine blood flows. The changes in uterine blood flow were quite large in most cases. The χ^2 test was applied against the assumption that, of the 14 changes in uterine blood flow, 7 would change in the same direction as the umbilical flow and 7 would change in the opposite direction. The resultant χ^2 value of 8.64 indicated that changes in the umbilical blood flow caused the uterine blood flow to change in the same direction ($P < 0.005$).

The values labeled 2c and 2d in Table I were obtained simultaneously because goat 2 carried twins and both placentas were perfused. In 2d the umbilical perfusion rate was increased and the uterine flow to that placenta also increased. In 2c, the umbilical perfusion rate was decreased and the uterine flow to that placenta decreased. Hence the maternal flow to these twin placentas followed the umbilical flows even though this required the placentas to react simultaneously in opposite directions.

Discussion. In these experiments the uterine blood flow changed in the same direction as the change in umbilical perfusion

TABLE I. EFFECT OF CHANGING FETAL PLACENTAL BLOOD FLOW (F) ON THE MATERNAL PLACENTAL BLOOD FLOW (M).[a]

Goat	Fetal weight (kg)	Blood pressures (mm Hg)			Blood flows (ml/min)				Flow ratios		Direction[b]
		F1	F2	Maternal	F1	F2	M1	M2	F1/F2	M1/M2	
1a	1.93	69	59	65	300	200	397	310	0.67	0.78	Same
1b	1.93	60	90	65	200	350	310	525	1.75	1.69	Same
2a	1.51	94	45	100	154	54	1540	242	0.35	0.16	Same
2b	1.51	45	74	97	54	140	242	507	2.59	2.10	Same
2c	1.51	74	49	88	140	65	507	285	0.46	0.56	Same
2d	1.00	59	85	89	43	118	280	885	2.74	3.16	Same
3a	2.36	89	77	100	190	110	560	525	0.58	0.94	Same
4a	–	95	108	110	138	168	860	1050	1.22	1.22	Same
5a	2.22	78	54	–	290	210	604	122	0.72	0.20	Same
6a	1.49	39	58	81	215	257	423	514	1.20	1.22	Same
6b	1.49	58	75	79	257	303	293	354	1.18	1.21	Same
7a	1.50	50	48	85	100	97	523	508	0.97	0.97	Same
8a	1.84	49	55	84	100	116	602	628	1.16	1.04	Same
8b	1.84	50	68	83	116	213	628	492	1.84	0.78	Opposite

[a] The fetal flow is changed from F1 to F2 and the maternal flow responded by changing from M1 to M2. The fetal weights, perfusion pressures, and maternal arterial pressures are also given.

[b] Same means that the uterine blood flow changed in the same direction as did the fetal blood flow. Opposite means that it did not.

rate. This observation supports the hypothesis that local reflex mechanisms within the placenta stabilize local perfusion–perfusion ratios, and that these mechanisms are analogous to those described as stabilizing ventilation–perfusion ratios in the lung.

Differing results have been reported by other investigators. Raye *et al.* (5) observed no rapid change in uterine blood flow in sheep when the fetus was killed, a result which may be explained by the work of Grant *et al.* (6) who showed that the ability of the local mechanisms to stabilize the ventilation–perfusion ratio in the lung is greatest in the physiological range but is relatively poor outside this range. If such a mechanism exists in the placenta it would not be apparent after fetal death. It is also possible that the mechanism which matches uterine blood flow to umbilical blood flow requires a continued umbilical circulation.

Berman *et al.* (7) reported that they observed no changes in the uterine blood flow in response to changes in the umbilical blood flow. In their experiments the umbilical blood flow was changed by partial occlusion of the umbilical cord and the uterine flow was monitored for 60 sec. It is improbable that responses of the type which are suggested here could be detected in so short a time span. Tucker and Reeves (8) have shown that the resistance of the pulmonary circulation is maximal 4 min after instituting alveolar hypoxia.

Grant *et al.* (6) report the open loop gain for their system. In our preparation such sophisticated calculations are hardly appropriate. The changes we induced were large and the number of observations we could make in one animal were extremely limited. When such calculations are applied to the data given in Table I it becomes apparent that the open loop gains are extremely high. In fact, in many cases the uterine flow appears to overshoot, the compensation being greater than that needed to return the perfusion–perfusion ratio to its control state. The presence of high gain control systems in the placental circulation is an unexpected finding and may reflect the release of the placental vascular bed from fetal control in these perfused preparations. The fetus possesses several mechanisms such as catecholamine release and the renin-angiotensin system (9, 10), whereby cardiovascular control can be achieved. These endogenous control systems may damp out many disturbances initiated from the placental vascular bed but would not be observed in the perfused placenta.

We must, however, add a warning note. These observations were made under very artifical circumstances involving a perfused placenta which means that the blood flows and pressures were different from those observed under physiologic circumstances. Nevertheless, they suggest the existence of a mechanism which, under some conditions, may operate to balance the umbilical and uterine blood flows.

Summary. The placentas of eight near-term goats were perfused with blood containing C_2H_2. The adult goats breathed gas containing N_2O. Catheters were placed in a maternal femoral artery and uterine vein. Knowledge of the perfusion rate and N_2O and C_2H_2 concentrations in the maternal artery, uterine vein, umbilical arteries, and umbilical veins, permitted the calculation of the uterine blood flow.

The uterine flow was calculated before and after a change in the rate of the umbilical perfusion. Fourteen such observations were made. In 13 cases the uterine flow changed in the same direction as did the umbilical flow ($P < 0.005$). The magnitude of the change in uterine flow indicated that the mechanism whereby the change was mediated had a gain of greater than 1.

This work was supported by Grants PHS HE05499, HE06336, and HD2313 and by the Oregon Heart Association.

The authors wish to acknowledge the assistance of Mr. J. E. Welch and Mr. R. Ackley in the conduction of the experimental protocols.

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Received September 2, 1976. P.S.E.B.M. 1977, Vol. 154.