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FOETAL PLACENTAL BLOOD FLOW IN THE LAMB

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SUMMARY

1. Fifteen sheep foetuses of 1·5–5·2 kg body weight were prepared with indwelling arterial and venous catheters for experimentation one to six days later.

2. Unanaesthetized foetuses were found to have mean arterial and central venous blood pressures of 40 ± 1·5 (S.E. of mean) and 2·0 ± 0·3 (S.E. of mean) mm Hg respectively, compared to intra-uterine pressure. Intra-uterine pressure was 16 ± 0·8 (S.E. of mean) mm Hg with respect to atmospheric pressure at mid-uterine level.

3. Mean placental blood flow of the foetuses was 199 ± 20 (S.E. of mean) ml./(min.kg body wt.). Mean cardiac output in eleven of the foetuses was 658 ± 102 (S.E. of mean) ml./(min.kg).

4. Mean foetal and maternal colloid osmotic pressures were 17·5 ± 0·7 (S.E. of mean) and 20·5 ± 0·6 (S.E. of mean) mm Hg respectively at 38° C.

5. Intravenous infusions into six ewes of 1·8 mole of mannitol and 0·4 mole of NaCl resulted in significant increases in foetal plasma osmolarity, sodium, potassium, and haemoglobin concentrations, without detectable transfer of mannitol to the foetal circulation.

6. In the sheep placenta there is osmotic and hydrostatic equilibration of water. As a consequence, there should be an interaction between foetal placental blood flow and foetal water exchange with the maternal circulation. It was concluded that this interaction tends to stabilize foetal placental blood flow.

INTRODUCTION

Barcroft (1947) hypothesized that the transfer of water between foetal and maternal plasmas depends on the difference in pressure in the foetal and maternal placental capillaries and the hydraulic permeability of the

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placental barrier, a difference in osmotic pressures to be included in the pressure difference. Foetal placental capillary blood pressure is not only one of the variables determining the flow of water between the foetus and its mother, but also a term in the equations that describe foetal blood flow in the placenta. For the present purpose, it is useful to focus on the post-capillary resistance to flow. Placental blood flow is equal to the difference between the blood pressure in the foetal placental capillaries and the foetal central venous pool, divided by the post-capillary resistance to flow. Foetal placental blood flow and the rate at which water is transferred between the foetal and maternal plasmas are therefore related.

The consequences of this relation appear in their most simple form in the steady state, which is defined as the situation in which there is no net transfer of water between foetus and mother. In the steady state, the algebraic sum of hydrostatic and osmotic pressures acting across the placental barrier is equal to zero.

$$P^{Fpc} - P^{Mpc} - \Pi^F + \Pi^M = 0 \text{ mm Hg.} \qquad (1a)$$

The symbols P^{Fpc} and P^{Mpc} stand for foetal and maternal placental capillary blood pressures and the symbols Π^F and Π^M for foetal and maternal osmotic pressures, respectively.

It is necessary, of course, to refer all hydrostatic pressures to the same reference pressure. But it is practical to refer all foetal hydrostatic pressures to intra-uterine pressure and to refer maternal hydrostatic pressures to atmospheric pressure at mid-uterine level. This requires a correction term P^{Ut} (intra-uterine pressure) in eqn. (1*a*), so that

$$P^{Fpc} - P^{Mpc} + P^{Ut} - \Pi^F + \Pi^M = 0 \text{ mm Hg.} \qquad (1b)$$

According to the reasoning in the first paragraph, foetal placental blood flow, $\dot{Q}^{Fp}$ is given by

$$\dot{Q}^{Fp} = (P^{Fpc} - P^{Fcv})/R_2 \text{ ml./min} \qquad (2)$$

The symbol R_2 stands for the post-capillary resistance to flow in the foetal placental bed and P^{Fcv} for foetal central venous pressure. Combination of eqns. (1*b*) and (2) gives

$$\dot{Q}^{Fp} = (P^{Mpc} - \Pi^M + \Pi^F - P^{Ut} - P^{Fcv})/R_2 \text{ ml./min.} \qquad (3)$$

None of the terms of this equation are known to be under direct control of the regulatory mechanisms of the foetal cardiovascular system, with the possible exception of foetal central venous pressure. We will show that the variations in foetal central venous pressure are too small to be of much consequence.

Eqn. (3) is based on the assumption that there is an equilibrium of hydrostatic and osmotic pressures across the placental barrier, in other words, that the hydraulic conductivity of the barrier is appreciable. The

experiments were designed to prove this point and further to enable us to assess the approximate magnitudes of the constants and variables in eqn. (3) under conditions as close to normal as could be obtained.

METHODS

Animals and surgery

Suffolk ewes and ewes of various local cross-breeds were obtained from an animal dealer. The ewes were X-rayed and if pregnant scheduled for surgery at an estimated 110 to 135 days gestational age. The ewes were kept in a small pen in the laboratory from a few days before surgery until after the completion of the last experiment. They were given food and water *ad libitum*, except that the ewes were fasted 1 day before surgery.

Anaesthesia was begun with an intravenous injection of 6 mg atropine and a 5% solution of sodium-thiamylal until the ewe lost consciousness. The animal was transferred to a surgery table and quickly intubated. Anaesthesia was continued with halothane in oxygen.

The foetuses were prepared for later experimentation according to methods established by Meschia, Cotter, Breathnach & Barron (1965) and later modified by Smeaton, Cole, Simpson-Morgan & Morris (1969); Willes, Boda & Manns (1969) and Comline & Silver (1970). Uterus and foetus were left *in situ*. A purse string suture in the myometrium, drawn tight around the foetal limb, prevented leaking of amniotic fluid. Foetal anaesthesia could be regulated easily with halothane administered to the ewe; no local anaesthetics were therefore necessary. The use of tapered catheters permitted catheters of outside diameter of 1·3 mm to be used on all foetuses (Bolab, vinyl size V-5). Fifty units of heparin per millilitre of saline were used to keep the catheters open; the foetus and the ewe were not heparinized. A catheter was inserted into a leg vein and advanced until thought to lie close to the foetal heart. Arterial catheters were inserted into a hind limb and a forelimb artery, the latter through a separate incision in the uterus. One catheter was left in the amniotic fluid for later measurement of intra-uterine pressure. Membranes and uterus were carefully closed at the end of the surgery and tested for leaks. The catheters were brought out to a pouch attached to the flank of the ewe. The duration of anaesthesia was generally less than 2 hr and the ewes would stand in the pen less than an hour later.

The ewes were kept in the pen in the laboratory until ready for experimentation. In the meantime, the catheters were flushed at 48 hr intervals. During the experiment, the ewes were put in a small squeeze cage in a corner of the pen. They remained in the company of other ewes and perhaps for that reason appeared to be at ease during the experiments.

The numbers of ewes used for each experiment are listed in the tables in the Results section. Experiments were done without anaesthesia on these chronically prepared ewes and foetuses.

All foetuses were dissected after death to verify the positions of the catheters and to recover parts for isotope analysis.

Administration of hypertonic solutions

The osmolarity of the maternal plasma was increased by infusing a solution containing mannitol and sodium chloride into a jugular vein. The composition and amount of the fluid are listed in the Results section. The infusions required from 20 to 60 min to complete. The water pails were removed during this experiment.

Measurements

Pressures

Pressures were measured with Statham pressure transducers (models Gb and Db) and a Grass P7 or Beckman-Offner RB polygraph. Before every experiment, all gauges were calibrated against a water manometer to an accuracy of $\pm 0{\cdot}5$ mm Hg. Zeros were set at 57 cm above the laboratory floor and checked regularly during the experiment (Fig. 1). Mid-uterine level was estimated by sighting the sheep along a makeshift transit, and with the help of previously made X-ray photographs. Only intra-uterine pressure was affected by the accuracy of this estimate since all other pressures were recorded with reference to intra-uterine pressure. Foetal arterial, foetal central venous, and intra-uterine pressures were continuously recorded during each experiment.

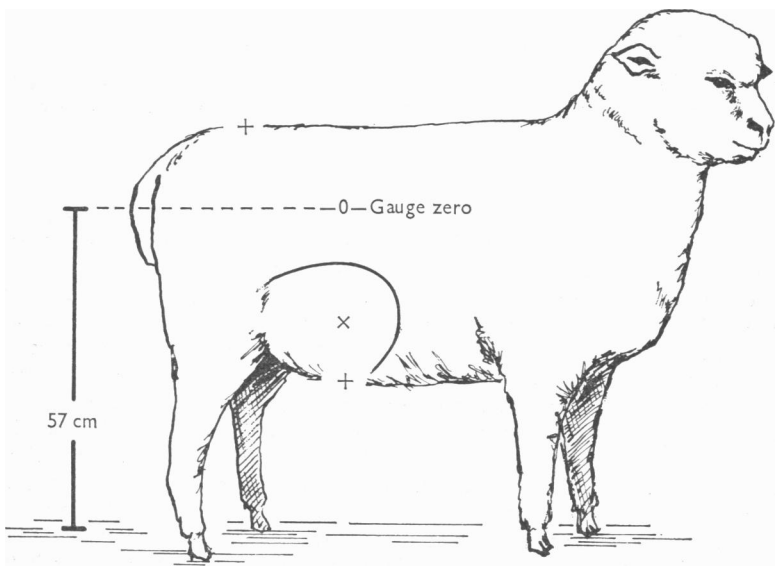

Fig. 1. Pressures were initially recorded against a zero set at 57 cm above the laboratory floor. In the analysis of the records, intra-uterine pressure was subtracted from the foetal intravascular pressures. Intra-uterine pressure itself was corrected to atmospheric pressure at mid-uterine level. Mid-uterine level (indicated by an ×) was estimated during the experiments, with the aid of previously made X-ray photographs of the standing ewe. Mid-abdominal contour served as reference.

Flows

Measurements of umbilical blood flow were made with a method adapted from Makowski, Meschia, Droegemueller & Battaglia (1968), an indicator dilution method in which radioactive microspheres were used as indicator. About 50,000 spheres of 50 μ diameter were injected into the venous catheter. Arterial blood was simultaneously sampled from the arterial catheters. Since these spheres have been shown not to recirculate (Rudolph & Heymann, 1967; Makowski *et al.* 1968; Faber & Stearns, 1969) the arterial concentration time integrals were obtained by collecting arterial blood during the injection of the microspheres for a known period of at least

several circulation times, usually 5 min. The injected amounts were obtained by post mortem analysis of the target organs. The calculations have been discussed by Makowski *et al.* (1968).

The microspheres have been shown to mix thoroughly with arterial blood (Rudolph & Heymann, 1967; Neutze, Wyler & Rudolph, 1968; Phibbs, Wyler & Neutze, 1967; Rankin, Meschia, Makowski & Battaglia, 1970; Buckberg, Luck, Payne, Hoffman, Archie & Fixler, 1971). The concentrations of microspheres in the bloods ejected by the right and left foetal ventricles were not the same since the microspheres mix with blood in the ventricles and arteries but probably not in the venous system. The sample from the arterial catheter in a forelimb artery was used to measure the concentration time integral of microspheres in left ventricular blood, that perfused brain, myocardium and the upper part of the foetal body. The sample from the arterial catheter in a hind-limb artery was used to measure the concentration time integral in the blood in the descending aorta past the entrance of ductus arteriosus blood. The former must be used to compute blood flow in brain, heart and upper half of the body, the latter to compute blood flow in the placenta and the remainder of the foetal body. The total of placental blood flow and organ flows constituted foetal cardiac output.

Isotope analysis

The microspheres were labelled with ^{46}Sc, ^{85}Sr, or ^{125}I. It was verified in each experiment that the isotopes did not leach into the plasma. Each batch was microscopically inspected to verify the size distribution of the microspheres.

Foetal tissues were collected post mortem. The tissues of each organ were incinerated separately to increase the concentration of the radioactive material. Incineration for 24 hr at 350° C did not reduce the radioactivity of the microspheres or destroy the visible integrity of the spheres. The ashes were homogenized in a blender and weighed. Aliquots of the ashes, and the entire arterial blood samples were counted in test tubes in a Nuclear Chicago Ultrascalar II or a Packard 3004 well type scintillation spectrometer. Occasionally, three aliquots of the ashes were counted for each organ to verify that the differences between their concentrations did not exceed 1%. Some of the foetal catheters were removed and counted at the end of the experiment. They did not contain activity approaching 1% of the activity of the integrated arterial samples. Generally, samples yielded more than 10,000 counts above background in the time available for analysis.

Tritiated mannitol was counted in a Packard Tri-Carb liquid scintillation spectrometer model 314EX by routine methods (Faber *et al.* 1968).

Chemical determinations

All foetal blood samples were collected after at least three times the volume of the dead space of the catheters had been discarded, a total of about 2 ml.

Osmolarity

Osmolarities of plasma samples were measured by freezing point depression in an Advanced Instruments Inc. osmometer. The osmometer was standardized with solutions of 100, 200 and 500 m-osmole.

Colloid osmotic pressure

Colloid osmotic pressures of plasma samples were measured with the method of Prather, Gaar & Guyton (1968) against a commercial Ringer solution at room

temperature. The apparatus consisted of a space filled with Ringer solution enclosed between a pressure gauge and a membrane (Amicon Corp. UM-10). The plasma sample was placed at the other side of the membrane. It attracted Ringer solution until the pressure drop in the space between the membrane and the gauge compensated the colloid osmotic pressure (Fig. 2). The measurements were reproducible to ±1 mm Hg and required about 10 min.

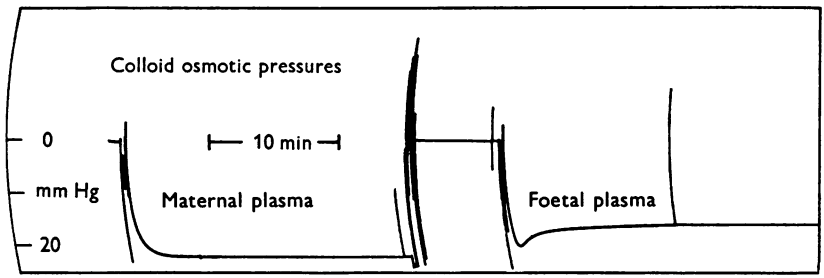

Fig. 2. Recording of colloid osmotic pressures of typical maternal and foetal plasmas. The gauge was calibrated against a water manometer with the membrane in place. A base line (labelled with the 10-min marks) was obtained with Ringer solution. The rapid deflexions indicate the pressure fluctuations associated with the purging of the Ringer solution and the introduction of a maternal plasma sample into the chamber with the help of a syringe. The osmotic pressure rose to its equilibrium value in about 3 min. After 20 min, the sample was replaced with Ringer solution to verify the base line and then the next (foetal) sample was introduced and so on until all samples had been analysed. A diagram of the apparatus has been published by Prather *et al.* (1968).

Haemoglobin

Haemoglobin was determined by the cyanmethaemoglobin method with commercially available reagents (B.D. Unopette) in 1:250 dilution. Since only relative changes needed to be known, the results will be given in optical densities as measured in a Beckman Instrument Model DB-G spectrometer at a wave-length of 540 nm. The optical densities were shown to be proportional to haemoglobin concentration over the range used.

Sodium and potassium

Sodium and potassium concentrations were determined after a 200 times dilution with a 0·025% solution of lithium (chloride) (per million) in a Baird Atomic Model KY flamephotometer. Since sample size was only 50 µl., the calibration curve was made based on 50 µl. samples of artificially prepared 'plasmas' of known sodium and potassium concentrations. The largest discrepancy between concentrations determined on samples of 50 µl. and samples of several millilitres was 6 m-equiv/l. for sodium and 0·3 m-equiv/l. for potassium.

Hydrogen ion concentrations

The pH of foetal arterial blood was measured with a Radiometer model 27 pH meter with a capillary glass electrode. The samples were drawn under anaerobic conditions from a foreleg or hind-leg arterial catheter and immediately used. The instrument was calibrated with fresh Radiometer buffer before and after each measurement.

RESULTS

Blood pressures and blood flows in unanaesthetized foetuses

Measurements obtained on fifteen foetuses are compiled in Table 1. All measurements were taken with the ewe standing quietly and apparently completely at ease. Fig. 3 shows the recordings of foetal blood pressures and intra-uterine pressures of ewe *m*. Fluctuations in intra-uterine pressure due to coughing or movement were properly transmitted to foetal intravascular pressures. Apart from such fluctuations, foetal pressures were found to be stable over periods of many hours in undisturbed foetuses. Measurement of cardiac output did not affect foetal arterial (or venous) blood pressures when these were recorded simultaneously with cardiac output.

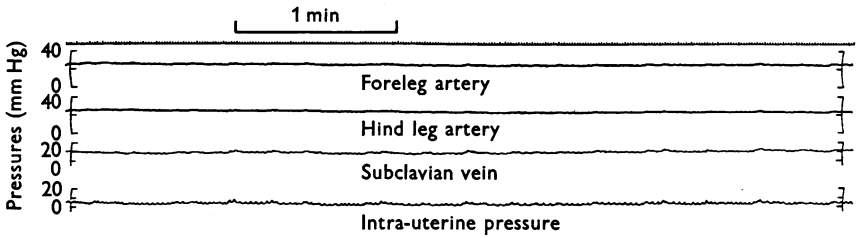

Fig. 3. Pressure recordings from an unanaesthetized foetus and ewe (*m*). Zero pressure corresponds to the gauge zero, at 57 cm above the laboratory floor (see Fig. 1).

Only mean arterial blood pressures were noted since the catheters were too narrow for reliable measurement of systolic and diastolic pressures. Mean arterial blood pressure was $40 \pm 1{\cdot}5$ (S.E. of mean) mm Hg in comparison with intra-uterine pressure. Mean intra-uterine pressure was $16 \pm 0{\cdot}8$ (S.E. of mean) mm Hg with respect to atmospheric pressure at mid-uterine level (Fig. 1). Intra-uterine pressure would have to be added to arterial blood pressure for comparison with data obtained on foetuses *in utero* by other investigators. This would give $56 \pm 1{\cdot}8$ (S.E. of mean) mm Hg with respect to atmospheric pressure at mid-uterine level. Mean foetal central venous pressure was $2{\cdot}0 \pm 0{\cdot}3$ (S.E. of mean) mm Hg, with a range of 0–4 mm Hg, compared to intra-uterine pressure. None of these pressures correlated significantly with foetal weight or with the post-operative interval in the group presented in Table 1.

Foetal cardiac output and foetal placental blood flow were expressed per kilogram foetal body weight to remove an obvious dependence of flow on weight from the data. Cardiac output per kilogram and placental flow per kilogram tended to be somewhat lower in heavy foetuses than in light foetuses but regression analysis showed that there was no significant

TABLE 1. Pressures and flows in unanaesthetized foetuses

Animal	Wt. (kg)	Time (post-operation)	Pressures (mm Hg) P^{Fa}	P^{Fv}	P^{Ut}	H.R. (beats/min)	pH	Blood flows ml./(min.kg) $\dot{Q}^{F}$	$\dot{Q}^{Fp}$
a	5·2	1 day	49	2	15	156	—	—	165
b	3·0	6 hr	44	4	23	130	—	—	156
c	3·0	9 hr	42	1	16	206	—	444	193
d	3·4	3 days	45	2·5	13	160	7·39	384	154
e	2·1	3 days	38	3	16	155	7·31	1408	198
f	3·6	3 days	45	3	18	157	7·40	336	210
g	4·3	3 days	41	1·5	17	160	7·31	359	44
h	2·6	4 days	44	1·5	10	180	7·32	—	371
i	3·2	6 days	39	1·5	21	161	7·37	710	255
j	4·6	5 days	36	2	16	150	7·34	—	145
k	4·5	4 days	48	2	17	165	7·39	473	212
l	1·5	4 days	32	1	12	195	7·38	712	329
m	1·8	4 days	42	3	13	208	7·37	484	170
n	2·1	3 days	31	2	16	240	7·02	904	142
o	3·4	4 days	30	0	16	170	7·42	1028	240
Mean	3·2	3 d., 3 hr	40	2·0	16	173	7·34	658	199
S.D.	1·1	38 hr	6	1·0	3·2	27	0·10	322	76
S.E. of mean	0·3	10 hr	1·5	0·3	0·8	7	0·03	102	20

Abbreviations:

Wt. is foetal body weight.

P^{Fa}, P^{Fcv}, P^{Ut} are the hydrostatic pressures in the foetal artery, the foetal central venous pool, and in the uterus respectively.

H.R. is heart rate.

$\dot{Q}^{F}$ and $\dot{Q}^{Fp}$ are the cardiac output and the blood flow through the foetal placenta, respectively, expressed per kilogram foetal body weight.

correlation between these flows and foetal weight and time after operation. The data were therefore pooled. Mean foetal cardiac output was 658 ± 102 (S.E. of mean) ml./(min.kg) which is about 17% higher than the value found in acute experiments on unanaesthetized foetuses in utero by Rudolph & Heymann (1967) and about 25% higher than the value found in 1970 (Rudolph & Heymann, 1970). Mean foetal placental blood flow was 199 ± 20 (S.E. of mean) ml./(min.kg). Placental blood flow was on the average 34% ± 5% (S.E. of mean) of cardiac output, which is about 12% less than the value reported from acute experiments on unanaesthetized foetuses *in utero* (Rudolph & Heymann, 1970). The only significant correlation found in Table 1 was a decrease in foetal heart rate with an increase in foetal weight ($r = -0{\cdot}56$, $P < 0{\cdot}05$).

In foetuses *a* and *b*, no attempt was made to record cardiac output. In foetuses *h* and *j*, cardiac output could not be measured because of a clogged arterial forelimb catheter. No attempt was made to record foetal arterial pH in the first three foetuses listed in Table 1. A low foetal pH in foetus *n* was obtained in several samples during the experiment and must reflect a foetus in bad condition. At post mortem stained amniotic fluid was found but no other obvious reasons for foetal distress.

Colloid osmotic pressures of foetal and maternal plasmas

Colloid osmotic pressures were recorded in a series of twenty ewes and twenty foetuses. The series partially overlapped the series reported in Table 1, but eight of the samples were from maternal and foetal bloods taken shortly after an anaesthetic had been given. There was no difference between the data from the anaesthetized and the unanaesthetized groups that approached statistical significance. An example of the recording of colloid osmotic pressure is shown in Fig. 2. The measurements were made at room temperature (about 26° C) and were corrected to 38° C by multiplication with the ratios of the absolute temperatures (1·04). The results are summarized in Table 2.

Foetal responses to osmotic transients in maternal plasma

Hypertonic solutions of mannitol and sodium chloride were infused I.V. into six ewes after the measurements reported in Tables 1 and 2 had been obtained (ewes *h*, *j*, *k*, *l*, *m*, and *o*). All ewes responded with a profuse diuresis and sometimes visible loss of body volume. Ewe *o* laid down at the beginning of this part of the experiment; this did not seem to interfere with the measurements. All ewes recovered from the intervention, but one foetus (*o*) was found to have died the following evening. Ewe *h* delivered a healthy lamb 8 days later that lived for 3 weeks in the laboratory.

Fig. 4 shows the responses in ewe and foetus *j*. Table 3 summarizes the results obtained on all animals. The mean amounts of infused mannitol and sodium chloride and their ranges were 1·8 (1·0–2·0) moles and 0·41 (0·26 to 0·51) moles respectively, dissolved in 1–2 l. water. The solutions were autoclaved.

In two ewes, tritiated mannitol was injected I.V. shortly after the infusion of the hypertonic solution. In each instance, foetal levels of tritium were too low to be detected reliably, proving that even after several hours foetal mannitol concentrations were less than 10% of the maternal concentrations at the same time.

TABLE 2. Colloid osmotic pressures of ewes and foetuses of 101–139 days gestational age

Plasma source	Mean colloid osmotic pressure* (mm Hg at 38° C)	S.E. (mm Hg)	No. of samples
Maternal blood	20·5	0·6	20
Foetal blood	17·5	0·7	20
Difference of paired data	2·84	0·93	17

* Eight sample pairs were obtained from ewes and foetuses shortly after these had received an anaesthetic. There was no significant difference between the groups with and without anaesthetic.

Table 3 and Fig. 4 indicate that osmotic equilibrium was initially restored by transfer of water through the placenta, rather than by the transfer of solutes. The statistically significant increases in foetal haemoglobin concentrations, and sodium and potassium concentrations all point to a diminishing foetal blood volume due to a loss of foetal water. Maternal concentrations of sodium did not change significantly because of the sodium chloride added to the infused solution. A foetal mannitol diuresis was unlikely because of the small amounts of mannitol found in the foetal circulation. The somewhat greater increase in plasma sodium concentration than in osmolarity of the foetal plasma (Table 3) also argued against the presence of important concentrations of mannitol in the foetal plasma.

The one foetus that died soon after the experiment was grossly dehydrated at autopsy evidenced by shrivelled skin and sunken eyes. In all cases, the ewe was given water *ad libitum* as well as food immediately after the experiment and no abnormalities were noted at autopsies performed 1 or 2 days after the experiments when the ewe and her foetus were killed for isotope analysis.

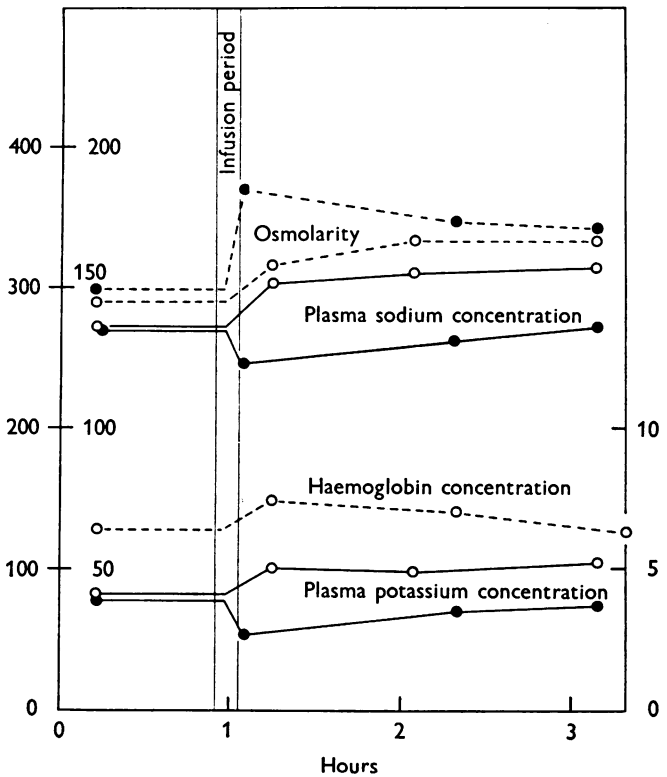

Fig. 4. Filled circles are maternal values, open circles are foetal values. An I.V. infusion of mannitol (2 M) and sodium chloride (30 g) was given during the period indicated by the vertical lines. The osmolarity of the maternal plasma increased immediately, that of the foetal plasma followed more slowly, paralleled by increases in foetal plasma concentrations of sodium, potassium, and haemoglobin. A fall in maternal plasma sodium concentration, as in this ewe (*j*) was not regularly seen. Osmolarity in m-osmole/l. (outer left scale), sodium concentration and potassium concentration in m-equiv/l. (inner left and right scales respectively). Haemoglobin concentration in arbitrary units (optical density × 100) is shown on the right-hand scale.

DISCUSSION

The assumptions made in the derivation of eqn. (3)

According to eqn. (3), foetal placental blood flow, or at least its steady state value, is the ratio of a pressure term consisting of maternal capillary pressure, maternal and foetal osmotic pressures, intra-uterine pressure and foetal central venous pressure, and the post-capillary resistance to foetal placental flow. Three assumptions are made in its derivation.

TABLE 3. Changes in foetal and maternal plasmas after infusion of hypertonic solution into six ewes. Values ±1 S.E. of mean

	Pre-infusion value		First-post-infusion value		Increase (%) (paired data)		*P* value of increase (paired data)	
	Foetal	Maternal	Foetal	Maternal	Foetal	Maternal	Foetal	Maternal
Na^+ concentration	137	138	163	134	21·5	−1·2	< 0·01	n.s.
m-equiv/l.	±3·8	±2·7	±5·1	±5·1	±5·0	±3·1	—	—
K^+ concentration	4·4	4·3	5·2	3·0	22·5	−23·5	< 0·05	n.s.
m-equiv/l.	±0·4	±0·5	±0·2	±0·3	±8·1	±9·8	—	—
Hb concentration	—	—	—	—	17·4*	−9·7*	< 0·01	n.s.
arbitrary units	—	—	—	—	±3·4	±4·7	—	—
Osmolarity	317	305	350	379	10·7	24·0	< 0·01	< 0·1
m-osmole/l.	±11	±2	±10	±18	±2·2	±5·7	—	—

* Data for haemoglobin obtained in five foetuses and only three ewes.

Water movement across the placental barrier takes place under the influence of osmotic and hydrostatic forces.

Water exchange between foetus and ewe takes place mainly in the placenta.

Foetal capillary blood pressure and foetal central venous blood pressure constitute the driving pressure of the post-capillary resistance of the foetal placental vascular bed.

The present experiments indicate that transfer of water does occur under the influence of osmotic pressures. Acutely provoked increases in the osmolarity of the maternal plasma cause responses in the plasma of the sheep foetus that are like the responses observed in rabbit foetuses (Dancis, Worth & Schneidau, 1957; Bruns, Linder, Drose & Battaglia, 1963) and rat foetuses (Adolph & Hoy, 1963). In the placenta of each of these three species the reflexion coefficients of the placental barrier, even for small solutes, are sufficiently different from zero to cause rapid movement of water across the barrier under the influence of a difference between the osmolarities of the foetal and maternal plasmas. The rabbit placenta, however, is very much more permeable to small solutes such as sodium ion and chloride ion, than the sheep placenta (Flexner & Gellhorn, 1942; Faber, Green & Long, 1971; Faber, Hart & Poutala, 1968; Meschia, Battaglia & Bruns, 1967). Understandably, about half of the increase of plasma osmolarity in the rabbit foetus was found to be due to the transfer of mannitol to the foetal plasma (Bruns *et al.* 1963) whereas the amount of mannitol transferred to the sheep foetus was found to be negligible in the present experiments.

The experiments presented here did not prove that the observed transfer of water from the foetal to the maternal plasma took place in the placenta. The experiments of Friedman, Gray, Hutchinson & Plentl (1959) show that only a few percent of the total diffusional water transfer between foetus and mother takes place directly between amniotic fluid and maternal organism in the monkey and in man. Diffusional exchange of tritiated water can be accounted for only by the blood flow through the placenta in sheep (Meschia *et al.* 1967). It is difficult to envisage how this could be different for hydraulic transfers. The third assumption, that foetal capillary blood pressure and foetal central venous blood pressure are the driving pressure of the post-capillary resistance appears plausible, provided there is no 'sluice flow' mechanism (Power & Longo, 1970), that is an external compression of foetal placental vessels. This seems assured under the conditions of the present experiments (Power, 1971, and following discussion). Until evidence to the contrary is found, the validity of eqn. (3) may, therefore, be accepted.

Numerical evaluation of eqn. (3)

The blood pressure in the maternal placental capillaries of the sheep (P^{Mpc}) has been estimated (Faber, 1971) by the use of isogravimetric perfusions (Pappenheimer & Soto-Rivera, 1948) of the foetal side of the placenta. The mean value found was 34 ± 5 mm Hg, referred to atmospheric pressure at mid-uterine level.

The evaluation of the difference in osmotic pressure between foetal and maternal plasma ($\Pi^F - \Pi^M$) is hampered by our ignorance as to what solutes should be taken into account. The sheep placenta is relatively impermeable to small solutes; the experiments show that substances as small as mannitol (molecular weight 182) can exert consequential osmotic pressures. Unfortunately, osmolarities determined by freezing point depressions are too inaccurate to be of help. At a temperature of 39° C, an error of 1 m-osmole *could* represent an osmotic pressure of 19 mm Hg.

Although the sheep placenta is not known to actively transport sodium, potassium, or chloride between the foetal and the maternal plasma, it is known to actively transport some amino acids (Reynolds & Young, 1971) and it does generate a hitherto unexplained electrical potential (Meschia, Wolkoff & Barron, 1958; Mellor, 1970).

In view of the fact that the sheep placenta is permeable to urea, and to sodium ion, and that differences in sodium ion or in potassium ion concentration in foetal and maternal plasma or in freezing-point depressions could not be proven, we will assume that the only solutes whose concentrations differ in a steady state are plasma proteins, and that therefore only the difference in colloid osmotic pressures needs to be taken into account.

The assumption is made only to illustrate the consequences of eqn. (3) with a numerical example. Although it is conceivably incorrect when applied to the placenta of the sheep, it would almost certainly be correct if made for the placenta of the rabbit which is so permeable (Faber *et al.* 1971) that no concentration differences of small molecules are likely to persist for any length of time and which does not generate an electrical potential (Wright, 1966; Mellor, 1969). The rabbit placenta has a structure (Enders, 1965) that is much more like that of the human placenta than the structure of the sheep placenta (Lawn, Chiquoine & Amoroso, 1969). The size of the rabbit foetus does not allow the experiments that are necessary for the evaluation of eqn. (3). Setting $\Pi^F - \Pi^M$ equal to -3 mm Hg (Table 2) leads to an estimate of foetal placental capillary blood pressure of 31 mm Hg (34 − 3 mm Hg), referred to atmospheric pressure, and of 15 mm Hg (31–16 mm Hg) referred to intra-uterine pressure. This value and a foetal arterial blood pressure of 40 mm Hg and

a foetal central venous blood pressure of 2 mm Hg (Table 1) indicate that 66 % of the placental resistance is pre-capillary and 34 % is post-capillary.

Table 1 shows that mean foetal placental blood flow is 199 ml./(min.kg) so that placental resistance to flow is 0·193 mm Hg.min.kg/ml., (40–2)/199, of which 0·128 is the pre-capillary resistance and 0·065 mm Hg.min.kg/ml. is the post-capillary resistance.

According to eqn. (3), foetal placental blood flow is:

$$\dot{Q}^{Fp} = (34\text{–}3\text{–}16\text{–}2)/0{\cdot}065 = 200 \text{ ml./(min.kg)},$$

which agrees of course with the value found in Table 1.

Stabilization of foetal placental blood flow

It is known that even immature foetuses are capable of redistributing their cardiac outputs by selective vasoconstriction (Campbell, Dawes, Fishman & Hyman, 1967; Dawes, Lewis, Milligan, Roach & Talner, 1968; Dawes, Duncan, Lewis, Merlet, Owen-Thomas & Reeves, 1969; Purves & James, 1969; Parker & Purves, 1967). In times of need, arterial blood pressure increases and umbilical blood flow increases proportionally (Dawes, Mott & Rennick, 1956). This indicates that placental vascular resistance of which about one third is post-capillary, is fairly constant, a conclusion reiterated by Dawes (1968, pp. 72–75) on more elaborate evidence than was available in 1956. Unless there is a change in post-capillary resistance, increases in arterial blood pressure and placental flow will lead to a rise in capillary blood pressure in the foetal placenta and a loss of foetal water until foetal placental capillary blood pressure returns to normal. Emergency redistributions of foetal cardiac output accompanied by changes in foetal arterial blood pressure are clearly incompatible with a steady state, even though the process of water loss may be slow enough to permit a deviation from the steady state for several hours without serious foetal dehydration. The values found for foetal cardiac output in Table 1 indicate that substantial increases in foetal placental blood flow must be possible. In the long run, however, a placental blood flow that differs from the flow dictated by eqn. (3) will lead to a loss or gain of foetal water, a decrease or increase of foetal blood volume, central venous pressure, cardiac output, arterial blood pressure and placental blood flow until the steady state is restored and eqn. (3) is once again obeyed. This process we will call the stabilization of foetal placental blood flow.

Although foetal placental blood flow is stabilized, foetal cardiac output is not. The Frank–Starling curves of the foetal heart are so steep that doubling of the cardiac output can occur with minor changes in foetal central venous pressure, P^{Fcv} (Downing, Talner & Gardner, 1965; Fouron & Héber, 1970). In the absence of a significant intrathoracic pressure (Dawes,

1968, p. 129), central venous pressure is the filling pressure of the foetal heart. If, for example, autoregulation of the circulation to the foetal tissues led to a decrease in somatic peripheral resistance, and hence to a decrease in arterial blood pressure, it would also decrease placental blood flow. The stabilization of placental blood flow would then restore the steady-state placental blood flow (and arterial blood pressure) through the absorption of water, an increase in foetal blood volume, and increases in foetal central venous blood pressure, in cardiac output, and in arterial blood pressure. After restoration of the steady state, foetal systemic flow would have increased in proportion to the decrease in systemic resistance, but placental blood flow would have remained the same, except to the extent that the necessary small change in foetal central venous pressure in eqn. (3) (P^{Fcv}) would have affected it.

Foetal control of placental flow

Foetal control of the variables in eqn. (3) would determine foetal placental blood flow in the long term, yet no foetal cardiovascular mechanisms are at present known to do so.

In species with a relatively impermeable placenta, such as the sheep, active transfer of a small solute might affect the difference in osmotic pressures ($\Pi^F - \Pi^M$); this mechanism is improbable in species with relatively permeable placentas such as the rabbit, and probably man. The mechanism of control of *colloid* osmotic pressures (Oratz, Rothschild & Schreiber, 1970) in the foetus is not known although there is good evidence that the foetus generates almost all of its own plasma proteins (Dancis & Shafran, 1958). The resistance of the foetal placental vascular bed, of which the post-capillary resistance is about one third, is known not to respond to any appreciable degree to cardiovascular emergencies (Dawes, 1968, p. 74) although its long-term regulation is uncertain. Maternal capillary blood pressure in the placenta (P^{Mpc}), and intra-uterine pressure (P^{Ut}) are not suspected to be under foetal control. Foetal central venous pressure (P^{Fcv}) has not been observed to fluctuate by more than a few mm Hg in our experiments, and in any case cannot drop by more than 2 mm Hg (Table 1) without causing collapse of the foetal venous system.

Barcroft's hypothesis (1947) that placental water transfer is determined by osmotic and hydrostatic pressures in the placental capillaries leads to the conclusion that long term foetal placental blood flow is not under the control of the well-known cardiovascular regulation mechanisms that operate in the foetus as well as in the adult. Control of foetal placental blood flow appears to lie in the regulation of foetal plasma (colloid) osmotic pressure, in the regulation of foetal placental post-capillary resistance or in foetal mechanisms that influence the maternal circulation.

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