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Research Article

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Uneven Distribution of Maternal and Fetal Placental Blood Flow, as Demonstrated Using Macroaggregates, and Its Response to Hypoxia *

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Abstract. **A technique is described for studying the distribution of blood flow to the maternal and fetal placental vessels in sheep and dogs with radioactive labeled macroaggregates of albumin.**

When the maternal animal breathed room air the distribution of maternal placental blood flow was uneven among the cotyledons as well as within a given cotyledon. Fetal blood flow was also distributed nonuniformly among and within the cotyledons. The relation of maternal to fetal placental blood flow was also markedly uneven (coefficient of correlation, $r = 0.066$). After the animal was made hypoxic by breathing 10–12% O_2 the distribution of maternal, fetal, and maternal/fetal placental flows became more uniform. The coefficient of correlation of maternal to fetal flow was high ($r = 0.53$, $P < 0.01$). While the maternal animal breathed room air, after ligation of a major branch of the umbilical artery the distribution of maternal, fetal, and maternal/fetal flows in the remaining two-thirds to three-fourths of the placenta became more uniform. The correlation coefficient for maternal to fetal flow was high ($r = 0.35$, $P < 0.01$).

It appears that under normal circumstances with uneven distribution of blood flows there is a considerable portion of the placenta that does not receive blood flow in optimum quantities to promote efficient O_2 exchange. Failure to consider the influence of nonuniform maternal flow/fetal flow will result in overestimation of mean maternal–fetal oxygen tension gradients, and thus underestimation of the placental diffusing capacity for oxygen.

In response to maternal hypoxia or compromise of the fetal placental circulation the distribution of maternal, fetal, and maternal/fetal flows becomes more uniform, thereby increasing the efficiency of placental O_2 exchange.

Introduction

In studies of placental oxygen exchange it has been assumed that maternal and fetal blood flows

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are uniformly distributed to various regions of the placenta. On this basis, the partial pressure of oxygen (Po_2) at the end of the placental capillaries has been inferred from Po_2 tensions in blood draining the entire placenta. Differences in Po_2 for maternal and fetal blood have been used to express the over-all function of the placenta in O_2 exchange. Several recent studies suggest however, that the distribution of maternal placental blood flow and fetal placental flow are not uniform as previously assumed. These are: (*a*) Nonuniform distribution of the arteriolar orifices opening into the human intervillous space (1). (*b*) Cineradioangiographic demonstrations of intermittent surging and blanching of maternal and fetal placental circulations in humans and primates (2–4). (*c*) Comparison of placental exchange of oxygen which is relatively sensitive to uneven flow, and carbon monoxide which is relatively insensitive to uneven flow (5).

The present studies were undertaken to determine quantitatively the distribution of both maternal and fetal blood flows in various regions of the placenta. The effect of uneven distribution of maternal and fetal placental flows on oxygen exchange is described. Furthermore, studies of the redistribution of placental flow during maternal hypoxia and when the placental circulation was compromised by ligation of a major branch of an umbilical artery are included.

Method

The basis of this experimental method was to inject macroaggregates of albumin (MAA) labeled with one isotope into the circulation of a pregnant animal. Simultaneously MAA labeled with a second isotope was injected into the circulation of the fetus-in-utero. The animals were sacrificed and the amount of each isotope in various portions of the placenta was measured. Assuming that the distribution of MAA reflects the distribution of blood flow, the pattern of distribution of the maternal placental flow, fetal flow, and the ratio of maternal to fetal flow were determined from the concentrations of each isotope in these specimens.

Macroaggregates of albumin

Macroaggregates of human serum albumin in aqueous suspension was prepared and labeled with either ^{125}I or ^{131}I by a modification of the method of Taplin (6, 7). The diameter of the particles ranged from 4 to 80 μ. The median particle size was 15.8 μ; 89% of the particles were over 9 μ in diameter. 1 mg of ^{125}I MAA contained about 250,000 particles. The specific activity ranged from 30 μc to 3 mc of isotope per mg. ^{125}I has a half-life of 57.4 days and a principle gamma emission of 35 kev. The specific activity of ^{131}I MAA ranged from 800 μc to 1.5 mc/mg. ^{131}I has a half-life of 8.05 days and 80% of its gamma emission are 364 kev.

Experimental procedures

The distribution of placental blood flow was studied under three experimental conditions.

Breathing room air. Studies were carried out in eight near term ewes and their lambs, and in three pregnant mongrel dogs and their pups. A cardiac catheter was introduced through the right carotid artery under local anesthesia (lidocaine hydrochloride) and its tip positioned in the left ventricle. The animals were anesthetized (sodium pentobarbital, 20 mg/kg) and the gravid uterus was exposed through a right flank incision. In ewes a small branch of the umbilical vein was exposed by an incision through the myometrium but not into the amniotic cavity. MAA was injected simultaneously into the maternal left ventricle and fetal umbilical vein (Sheep 15, 25, 30, and 32) (Dogs 13 and 15). In Sheep 12 and 14 we injected the MAA into the maternal left ventricle while the ewe was standing quietly, before anesthetizing the ewe and injecting the fetus. From 200 to 670 μc of MAA was given to the ewes and from 100 to 500 μc to the fetuses. From 100 to 140 μc of MAA was given to the bitches and from 40 to 50 μc to their pups. Injections were made slowly over a period of 30–60 sec and the catheters were flushed with saline. Immediately after the injections blood from a maternal artery, uterine vein, umbilical artery, and vein was collected in greased heparinized syringes and analyzed for the partial pressure of oxygen (Po_2), carbon dioxide (P_{CO_2}) and pH. In Sheep 15 and Dog 14 uterine venous blood was serially sampled during and immediately after the injection period in an attempt to estimate the extraction efficiency of the uterus and placenta. About 5 min after the injection of MAA we sacrificed the animals by injecting a saturated solution of potassium chloride into their left ventricles.

Breathing 10–12% oxygen. Similar studies were carried out in five anesthetized sheep after breathing 10–12% O_2 for 10 min. The injections of 500 μc of ^{131}I MAA into the maternal and 500 μc of ^{125}I MAA into the fetal circulations were made simultaneously.

Compromise of the fetal circulation. In two sheep, while the ewes breathed room air, a major branch of the umbilical artery was ligated. The distribution of blood flows in the remaining two-thirds to three-fourths of the placenta was studied.

Analytical procedures

The uterus and attached placenta were removed from the animal and photographed. A scintillation scan of the distribution of each isotope was made over the entire placenta.[1] From 10 to 110 samples weighing about 1 g

[1] Nuclear-Chicago model 1735 Photo-Dot Scanner with a 19 hole focused collimator. Nuclear-Chicago Corporation, Des Plaines, Ill.

were taken from the cotyledons selected randomly over the entire uterine wall. Full thickness sections were cut through the center axis of the cotyledons after they were separated from the underlying myometrium. These sections thus contained the maternal and fetal gas exchanging vessels. Samples of the underlying uterine wall were obtained separately. The tissue samples were weighed and placed in a well-type scintillation detector. The emissions at the photopeak for each individual isotope were counted for 30 sec with a scaler. We prepared radioautographs of the cotyledons and uterine wall, after the injection of ^{125}I MAA.

The placental cotyledons and the uterine wall were weighed separately. In some cases the fraction of the placental weight contributed by fetal membranes and the cotyledons were also determined. Total radioactivity in the placenta was calculated by multiplying the average microcuries per gram of tissue by the total placental weight.

Calculations

The counts of the placental samples were expressed as microcuries after correction for background radiation, for overlap of ^{125}I and ^{131}I counts, and for internal absorption.

The percentages of the total microcuries recovered in each specimen were calculated by the formula:

per cent of total μc = (μc in the sample/total μc in the placenta) × 100.

The per cent of placental weight that each sample represented was calculated by the formula:

per cent of total weight = (sample weight/total placental weight) × 100.

The relative activity for each sample was expressed as follows:

relative activity = per cent of total μc/per cent of total weight.

For example, if a tissue sample representing 2% of the total placental weight had 2% of the total radioactivity, its relative activity would be 2/2 or 1.0.

The ratio of maternal to fetal activity in a given sample was determined simply as: per cent of total μc_M/per cent of total μc_F where the subscripts M and F refer to maternal and fetal values, respectively.

The fraction of the placenta by weight having a given relative activity was calculated as follows. The specimens were divided according to their relative activities into groups having increments of 0.1. The total weight in each group was expressed as a fraction of total placental weight. A cumulative frequency curve of placental weight for the various relative activities was plotted. To avoid errors introduced in selecting arbitrary boundaries for a group of specimens, we smoothed the curve and re-

TABLE I

Vital statistics

Animal	No.	Maternal wt	Fetal wt	Placental wt	Number of placental samples	Isotope to mother*	Isotope to fetus*	Percentage of maternal isotope recovered in uterus and placenta	Maternal isotope in placenta as percentage of the total uterus and placenta	Percentage of fetal isotope recovered in placenta
		Kg				*C*				
Breathing room air										
Sheep	12	50	—	—	10	^{125}I, 541	0	22	93	—
	13	62	2.6	0.76	10	0	^{125}I, 130	—	—	60
	14	65	3.3	0.73	17	^{125}I, 670	^{131}I, 190	17	96	35
	15	65	0.71	0.44	110	^{125}I, 640	^{131}I, 100	6	90	23
			0.63	0.45	110		^{131}I, 100	—	—	—
	19	60	—		50	^{125}I, 200	0	—	—	—
	25	60	3.9	0.51	80	^{131}I, 310	^{125}I, 330	—	—	—
	30	58	4.1	0.46	102	^{131}I, 440	^{125}I, 460	18	97	24
	32	67	4.5	0.63	98	^{131}I, 450	^{125}I, 440	21	93	31
Dog	13	10	—	—	27	^{125}I, 110	^{125}I, 50	15	95	—
	14	15	—	—	12	^{131}I, 140	^{125}I, 50	5	63	—
	15	12	—	—	32	^{131}I, 100	^{125}I, 40	—	—	—
Breathing 10–12% O_2										
Sheep	23	57	3.0	0.45	80	^{131}I, 500	^{125}I, 500	—	88	—
	26	72	3.8	0.47	88	^{131}I, 500	^{125}I, 500	—	92	—
	27	63	4.6	0.49	87	^{131}I, 500	^{125}I, 500	—	96	—
	28	68	4.2	0.44	99	^{131}I, 500	^{125}I, 500	—	—	—
	31	71	3.5	0.38	85	^{131}I, 500	^{125}I, 500	—	89	—
Ligation of branch of umbilical artery										
Sheep	21	65	3.6	0.46	60	^{125}I, 500	^{131}I, 500	—	94	—
	33	58	2.7	0.41	66	^{131}I, 500	^{125}I, 500	—	97	—

* Only one isotope was injected in those experiments indicated by a zero.

plotted the per cent of total weight for each of the various activity ratios from this smoothed curve.

Results

Table I gives the weights of each mother, fetus, and placenta, the isotope given to each mother and fetus, and the per cent of recovered radioactivity in the uterus and placenta.

Breathing air. Fig. 1 *a* shows an ewe's opened uterus with its attached cotyledons of twin placentas. Scintillation scans of isotopes injected into the circulations of the mother and one of the fetuses are shown in Fig. 1 *b* and *c*, respectively. The scans demonstrated greater number of particles from both circulations within the cotyledons as contrasted with the surrounding uterine wall. But since some cotyledons are larger than others these scans do not accurately reflect blood flow per gram of tissue. It was for this purpose that the tissue samples were weighed and counted individually.

About 18% (range 6–22%) of the isotope injected into the ewes and bitches was recovered in the uterus and placenta (Table I). Of the total amount of isotope recovered from the uterus and placenta about 90% (range 63–97%) was in the placenta, a value probably approximating that part of the total uterine flow received by the cotyledons. The remaining fraction, about 10%, was in the uterine wall. About 30% of the isotope injected into the fetal umbilical vein was recovered from the placenta. In two sheep (30, 32) about 3% of the total fetal placental activity was located in the fetal membranes. Only a minute quantity of maternal or fetal isotope was found to have crossed the placental barrier.

Fig. 2 shows the distribution of maternal, fetal, and maternal/fetal relative activities in Sheep 15. In these histograms the per cent of placental weight is plotted for each 0.1 increment of relative activity. The activity ratio 1.0 represents the mean value that would have been observed if the activity had been distributed uniformly.

The radioactivity injected into the maternal placental circulation was distributed unevenly. A markedly skewed unimodel pattern was seen. This is reflected in the finding that only about 50% of the placenta had a relative activity of within ± 50% of its mean value (Table II). 30% of the placenta had a relative activity less

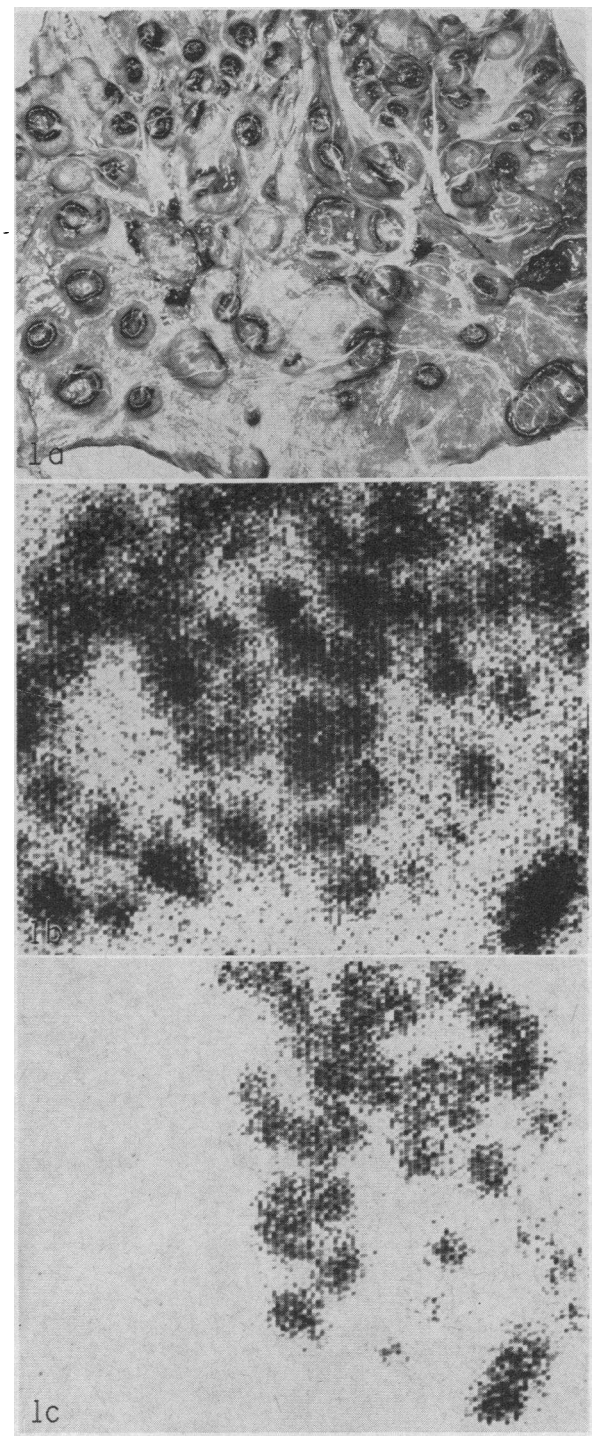

FIG. 1 *a*. OPENED UTERUS OF EWE AND ATTACHED TWIN PLACENTAS. The placental cotyledons on the right are those of the injected lamb (×16). 1 *b*. Scintillation scan of the uterus and placentas pictured in 1 *a*, showing the pattern of maternal distribution of blood flow (^{131}I-MAA). 1 *c*. Scintillation scan showing the pattern of fetal blood flow distribution (^{125}I-MAA) to the placenta on the right.

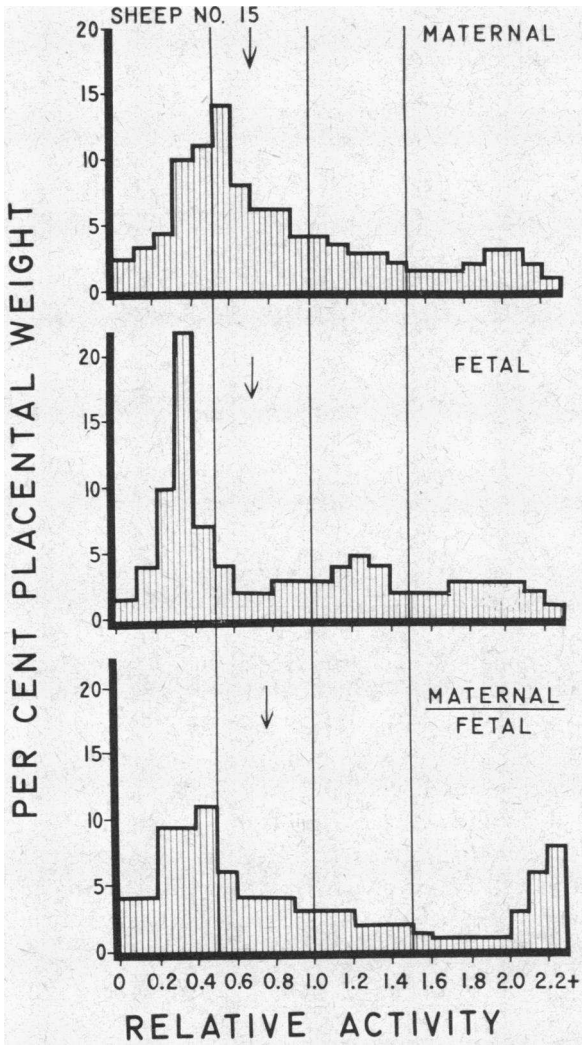

FIG. 2. DISTRIBUTION OF MATERNAL RELATIVE ACTIVITY (^{125}I), FETAL RELATIVE ACTIVITY (^{131}I), AND RATIO OF MATERNAL ACTIVITY TO FETAL ACTIVITY IN SHEEP 15, WHILE BREATHING AIR. The per cent of the placenta with various relative activities is shown. The activity ratio 1.0 represents the mean values that would be observed if the activity had been distributed uniformly. The arrows indicate the median relative activities. The absence of a normal distribution pattern indicates grossly uneven distribution of maternal, fetal, and the ratio of maternal/fetal placental blood flow.

than 0.5. About 17% of the placenta had a relative activity of greater than 1.5. The median value of relative activity for the maternal distribution was about 0.75, another indication that the curve was skewed to the left. We emphasize that the uniformity of distribution of flows is not a function of the distribution of the size of the cotyledons, but rather of the distribution of activity per gram of cotyledon.

The fetal distribution of activity was also distributed nonuniformly. About 40% of the placenta had a relative activity within ± 50% of its mean value. About 40% had a relative activity less than 0.5, and 20% had a relative activity of greater than 1.5. The median value of relative activity for fetal distribution was 0.7.

Regions of high maternal activity were not necessarily regions of high fetal activity. As Fig. 2 shows, the relation of maternal to fetal activity was markedly uneven. About one-third of the placenta had an activity ratio within ± 50% of the mean value. One-third had an activity ratio of less than 0.5, while another third had a ratio of more than 1.5. The median value of relative activity was 0.8. The correlation coefficient of maternal to fetal flow was low, ($r = 0.066$). The distribution of the maternal, fetal, and the ratio of maternal to fetal activity for the other sheep was also markably uneven. (Table II).

In two of these studies the origins of placental specimens were located on a tracing of the entire placenta. Regions of high and low activity were interspersed in a random manner. Furthermore, the variation of activity among specimens from a single cotyledon was almost as great among the various cotyledons. For example, among six specimens from a single cotyledon in Sheep 15, maternal relative activity varied from 0.3 to 1.5, fetal relative activity ranged from 1.1 to 2.4, and the maternal fetal activity ratio varied from 0.15 to 0.5. These findings indicate that the uneven distribution of maternal and fetal activity in most experiments was not confined to a localized area as a result of the animal's position, the site of injection, or surgical handling. The one exception was the uterus of Dog 13 which showed decreased maternal activity in a horn of the uterus that had been exteriorized. This finding suggests that extreme care must be taken in studies of uterine placental circulation to avoid changing blood flow.

The average per cent of the placenta with various relative activities was calculated for all the sheep studies while breathing room air (Table II). For the ratio of maternal to fetal activity 30% of the placenta had a relative activity of less than 0.5, 20% had a relative activity of more than 1.5, and only 50% had a relative activity within

TABLE II

Percentage of the placenta with various relative activities for maternal, fetal, and maternal/fetal distribution in sheep breathing room air

	Maternal			Fetal			Maternal/fetal			
	Percentage of placenta with relative activity of:			Percentage of placenta with relative activity of:			Percentage of placenta with relative activity of:			Coefficient of correlation
	<0.5	0.5 to 1.5	>1.5	<0.5	0.5 to 1.5	>1.5	<0.5	0.5 to 1.5	>1.5	
Sheep No.										
12	20	61	19							
13				10	85	5				
14	21	69	10	15	69	16	19	51	30	−0.60
15	30	53	17	40	40	20	33	33	34	0.066
19	21	62	17							
25	43	47	10	18	82	0	41	41	18	0.013
30	16	71	13	16	76	8	19	66	15	−0.122
32	22	64	14	18	73	9	20	62	18	0.078
Average of group	25	58	17	20	66	14	30	50	20	
Dog No.										
13	48	57	5	20	72	8	42	49	9	
14	26	55	19	23	59	18	38	38	24	
15	21	65	4	44	32	24	26	41	33	

± 50% of the mean. Because these distributions are nonsymmetrical ordinary statistical measurements such as standard deviation are not applicable. We have therefore included nonparametric statistics such as the values of relative activity for the median, first and third quartiles, and the interquartile range. (Table IV).

Breathing 10–12% oxygen. In these five studies the maternal arterial Po_2 was 40–47 mm Hg (normal 80–95 mm Hg) and Pco_2 was 25–27 mm Hg (normal 28 mm Hg). The Po_2 of the umbilical vein was 16–20 mm Hg (normal 25–30 mm Hg) and the umbilical artery was 9–15 mm Hg (normal 10–15 mm Hg). About 90% of the isotope recovered from the uterus and placenta was in the placenta (Table I).

Fig. 3 shows the distribution of maternal, fetal, and maternal/fetal relative activities in Sheep 23. The distribution of activity was more uniform during hypoxia. For the maternal distribution, about 75% of the placenta had a relative activity between ± 50% of the mean (Table III). About

TABLE III

Percentage of the placenta with various relative activities for maternal, fetal, and maternal/fetal distribution in sheep breathing 10–12% O_2, and with ligation of a branch of the umbilical artery

	Maternal			Fetal			Maternal/fetal				
	Percentage of placenta with relative activity of:			Percentage of placenta with relative activity of:			Percentage of placenta with relative activity of:			Coefficient of correlation	
Breathing 10–12% O_2	<0.5	0.5 to 1.5	>1.5	<0.5	0.5 to 1.5	>1.5	<0.5	0.5 to 1.5	>1.5		*P* values
Sheep No.											
23	14	75	11	14	75	11	16	70	14	0.30	<0.01
26	11	79	10	9	85	6	12	81	8	0.53	<0.005
27	12	80	8	8	89	3	11	77	12	0.18	<0.01
28	10	74	16	16	79	5	18	71	11	0.31	<0.005
31	17	71	12	14	74	12	20	68	12	0.23	<0.01
Average of group	12	78	10	11	83	6	13	77	10		
Ligation of branch of umbilical artery											
21	17	69	14	7	86	7	14	71	15	0.35	<0.01
33	16	72	12	13	83	4	14	75	11	0.74	<0.005
Average of group	16	71	13	11	82	7	14	74	12		

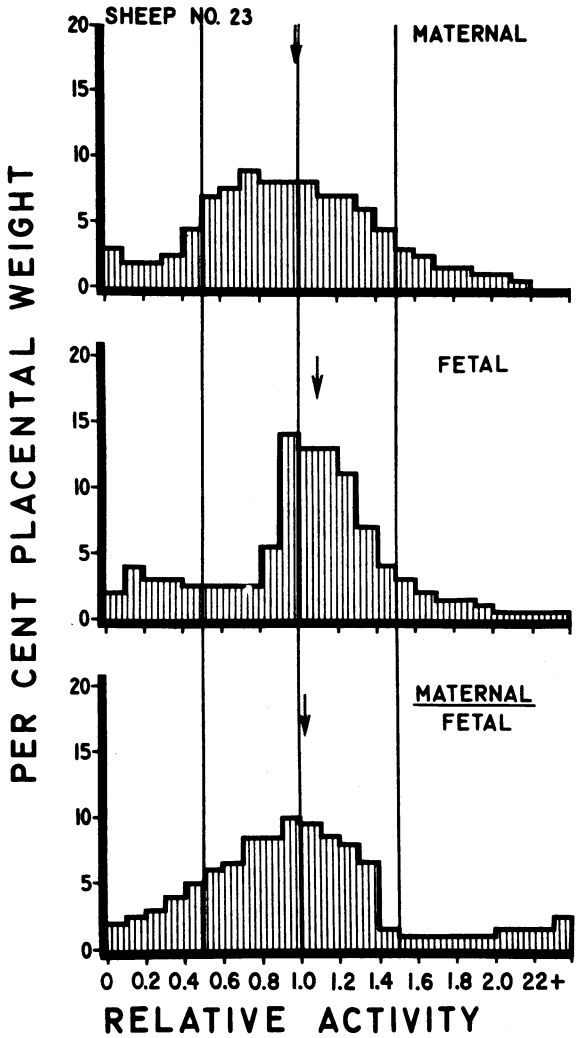

FIG. 3. DISTRIBUTION OF MATERNAL RELATIVE ACTIVITY (^{131}I), FETAL RELATIVE ACTIVITY (^{125}I), AND THE RATIO OF MATERNAL ACTIVITY TO FETAL ACTIVITY IN SHEEP 23 AFTER BREATHING 12% O_2 FOR 10 MIN. The per cent of the placenta with various relative activities is shown. The activity ratio 1.0 represents the mean values that would be observed if the activity had been distributed uniformly. The arrows indicate the median relative activity.

14% had a relative activity less than 0.5, and 11% had a relative activity of more than 1.5.

The fetal distribution of radioactivity was also more uniform with 75% of the placenta having a relative activity within ± 50% of the mean. About 14% had a relative activity of less than 0.5, and 11% had a relative activity of more than 1.5.

The relation of maternal to fetal flow was more uniform. About 70% of the placenta had an activity ratio within ± 50% of the mean value. 16% had an activity ratio less than 0.5, and 14% had an activity ratio greater than 1.5. The coefficient of correlation for this study was high, ($r = 0.30$, $P < 0.01$). In the other animals similar patterns of distribution were seen (Table III).

The average per cent of the placenta with various relative activities was calculated for the sheep in this group (Table III). For the ratio of maternal to fetal activity 13% of the placenta had a relative activity of less than 0.5, 10% had a relative activity of more than 1.5, and 77% had a relative activity within ± 50% of the mean. The median values of relative activity for this group more closely approach 1.0. The first and third quartiles are also closer to the median value and the interquartile range is smaller than in the group breathing room air. (Table IV).

Compromise of the fetal circulation. The scintillation scans of these studies showed that ligation of a major branch of the umbilical artery resulted in no fetal activity in one-fourth to one-third of the placenta.

In the remaining unoccluded regions of the placenta a more uniform distribution of maternal, fetal, and maternal/fetal relative activities was seen.

For the maternal and fetal distribution of Sheep 21, 69 and 86%, respectively, of the placenta had relative activities between ± 50% of the mean

TABLE IV

Values of relative activity for median, first and third quartile, and interquartile range for average of sheep breathing air, 10—12% O_2 and with ligation of a branch of the umbilical artery

	Maternal				Fetal				Maternal/fetal			
	Median	First quartile	Third quartile	Interquartile range	Median	First quartile	Third quartile	Interquartile range	Median	First quartile	Third quartile	Interquartile range
Breathing air	0.7	0.5	1.3	0.8	0.8	0.6	1.3	0.7	0.7	0.4	1.4	1.0
Breathing 10–12% O_2	0.9	0.7	1.1	0.4	1.0	0.7	1.2	0.5	0.9	0.6	1.1	0.5
Ligation of branch of umbilical artery	0.8	0.6	1.1	0.5	1.0	0.7	1.2	0.5	1.0	0.6	1.2	0.6

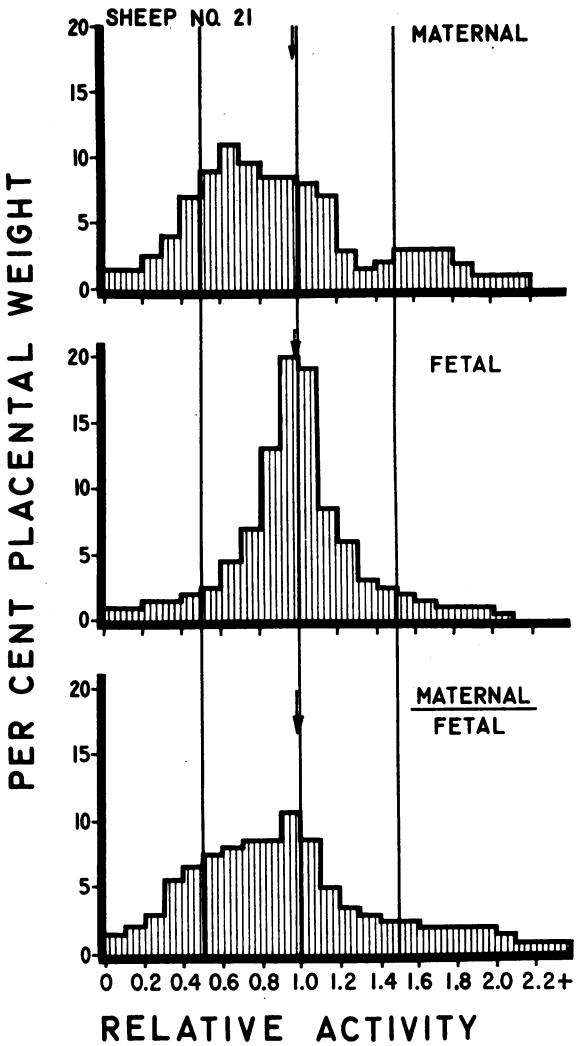

FIG. 4. DISTRIBUTION OF MATERNAL RELATIVE ACTIVITY (^{125}I), FETAL RELATIVE ACTIVITY (^{131}I), AND THE RATIO OF MATERNAL TO FETAL ACTIVITY IN THE REMAINING PLACENTA OF SHEEP 21 AFTER A MAJOR BRANCH OF THE UMBILICAL ARTERY WAS LIGATED. The per cent of the placenta with various relative activities is shown. The activity ratio 1.0 represents the mean values that would be observed if the activity had been distributed uniformly. The arrows indicate the median relative activity.

value (Table III and Fig. 4). For the maternal/fetal distribution the corresponding value was about 71%. The coefficients of correlation between maternal and fetal activities was high, ($r = 0.35$, $P < 0.01$). A similar pattern was seen in the other sheep.

The values of relative activity for the averages are given in Table III and IV. Again the medians and the first and third quartile values are closer to 1.0 and the interquartile range is smaller than in the sheep breathing air.

Discussion

Validity of method

The validity of this technique rests upon the following assumptions: (*a*) The distribution of MAA coincides with the distribution of blood flow. (*b*) The particles lodge in small placental vessels. (*c*) MAA does not obstruct enough blood vessels to cause hemodynamic alterations with redistribution of blood flow. (*d*) The number of aggregates present in each tissue sample is large enough to give statistically valid representation of distribution. (*e*) There was random sampling of the placental cotyledons.

The validity of measuring the distribution of blood flow with MAA has recently been demonstrated by Tow et al. (8). These authors found that the distribution of ^{51}Cr-labeled erythrocytes and ^{131}I-labeled MAA was the same in the lung, ($r = 0.97$) and also demonstrated that MAA particles were distributed normally in the lung with a SD of 20%. Other authors have also demonstrated a high correlation in the distribution of microspherules of different densities in the gastric circulation (9). The diameter of the macroaggregates follows a log normal distribution (8). However, this variation in size would not in itself be responsible for the skewed distribution curves seen in our experiments at normal oxygen tensions since the particles above a critical size, presumably the blood vessel diameter, lodge irrespective of how much larger they are.

The size of MAA relative to placental vessels is critical since the aggregates must be filtered out on their first passage to reflect accurately the distribution of blood flow. Particle trapping seems likely on an anatomic basis since blood flow in both the maternal and fetal placental bed of sheep and dogs is within capillaries. Capillaries in the syndesmochorial placenta of sheep are 9–12 μ in diameter (10), and they are about the same size in the endotheliochorial placenta of the dog (11). As noted earlier 89% of the particles were over 9 μ in diameter. In one sheep and one dog uterine venous blood was serially sampled during and after the injection of MAA, and the uterine-placental extraction efficiency was about 89%.

The fetal placental extraction efficiency was 93% in a dog fetus in which MAA was injected into the umbilical artery.

Hemodynamic alterations in the placental circulation due to occlusion of blood vessels by the particles seems unlikely since in the lung no increase in pulmonary artery pressure was observed until the injected dose of MAA was increased to 10 mg/kg body weight (8). This dose contains about 250,000 particles per gram of tissue, to be compared with 100–2000 particles per gram of cotyledon in the present studies.

A further consideration is that the small number of particles injected might limit statistically valid conclusions. However with 100 or more particles in the typical tissue sample a significant deviation from a normal distribution curve is highly unlikely. Injection of the particles into the maternal left ventricle and the fetal umbilical vein insured mixing in the blood before lodging in the placental vessels.

Finally, the observation that with maternal hypoxia the pattern of distribution of maternal and fetal placental blood flows becomes more uniform, approaching a normal curve suggests that the nonuniform patterns seen in the animals breathing air are not an artifact of the method.

Physiologic significance of nonuniform placental blood flow at normal oxygen tensions

An intriguing finding of the present study was that maternal and fetal placental blood flows were distributed unevenly in relation to one another. Thus if diffusion equilibrium was approached in the end capillaries (5) Po_2 must vary throughout the placenta and an uterine vein–umbilical vein Po_2 will be expected. The reasons for this may be illustrated by calculations based on a model of the placenta. Assuming concurrent maternal and fetal placental flow (12, 13) of 500 ml/min in the exchanging capillaries, and two compartments, one with a maternal/fetal ($\dot{Q}_M/\dot{Q}_F$) ratio of 3.0, and another with a ratio of 0.33, in the first compartment the end capillary Po_2 would be 53 mm Hg, and in the second it would be 32 mm Hg. Maternal blood leaving the first compartment would have an O_2 content of 11.4 ml/100 ml while that from the other would have a content of 3.0 ml/100 ml. The compartment with the higher ($\dot{Q}_M/\dot{Q}_F$) ratio and Po_2 of 53 mm Hg would contribute a disproportionately large share to uterine venous blood, raising its Po_2 to 42 mm Hg. On the fetal side the compartment with the low ratio and Po_2 of 21 mm Hg would contribute a disproportionately large share to the mixed umbilical vein decreasing its Po_2 to 24 mm Hg. Thus, despite equilibration of the Po_2 in the individual capillaries a uterine vein–umbilical vein Po_2 gradient of 18 mm Hg would occur as a result of uneven distribution of maternal and fetal placental blood flow.

If the pattern of flow distribution is known for the entire placenta, such as reported in the present study, one may calculate the over-all O_2 tension difference from uterine vein to umbilical vein. This is possible by arbitrarily dividing the placenta into 24 compartments, one for each 0.1 increment of $\dot{Q}_M/\dot{Q}_F$ from 0 to 2.4. Total maternal–fetal O_2 exchanges and total uterine and umbilical flows were obtained from observed values. Changes in oxygen content were calculated for each compartment on the basis of its $\dot{Q}_M/\dot{Q}_F$, arterial O_2 contents, and dissociation curves. The O_2 contents and tensions of the mixed uterine and umbilical venous blood were calculated from the blood flow and O_2 content change in each of the compartments. Our results indicate an average Po_2 difference of 12 mm Hg (range 6–15 mm Hg) between uterine and umbilical veins; this difference is due to uneven maternal/fetal flows in five sheep at normal levels of oxygenation. Further details of these calculations will be presented later.

Physiologic significance of more uniform placental flows during maternal hypoxia and compromise of the fetal placental circulation

A further finding of interest was that during maternal hypoxia the distribution of maternal flow in relation to fetal flow became more uniform. This was also true in the remaining placenta after ligation of a large branch of the umbilical artery. While the exact mechanism of this redistribution is uncertain it would appear that this change is a result of either a decrease in maternal or fetal Po_2 or both. Active vasomotion of arteriolar vessels in response to Po_2 is regarded by observers of the microcirculation as one principal factor of a local

nature regulating blood flow in capillaries (14, 15). A similar mechanism in the placental capillary bed seems reasonable. Of course, other factors probably also influence placental flow distribution, but at least in the present studies Pco_2 and pH are not likely factors since these values were about normal in maternal and fetal blood.

A favorable physiologic effect of more uniform distribution was to achieve a better balance between the oxygen supplied in maternal blood and the transport capacity of fetal blood. In these circumstances the variation of Po_2 is decreased throughout the placenta and less difference due to nonuniform flow is found in uterine vein and umbilical vein. In these ewes breathing 10–12% O_2, the calculated Po_2 difference due to uneven maternal/fetal flows averaged 5 mm Hg.

Clinical significance of placental blood flow pattern

Several pieces of evidence imply that there is normally some reserve capacity of placental exchange such as might be achieved by a redistribution of blood flow. It has been observed in abruptio placenta with one-fourth to one-third of the placenta separated from the uterine wall that the fetus may survive for a limited time (16). Maternal hypotension resulting from blood loss or spinal anesthesia does not necessarily result in fetal death (16). Assali and his coworkers have shown that with spinal shock in pregnant ewes the blood pressure, heart rate, and umbilical venous Po_2 of fetal lambs are relatively unchanged (17). Kaiser et al. showed that the umbilical vein oxyhemoglobin saturation was normal after ewes had been placed in a chamber at a simulated altitude of 22,550 feet (385 mm Hg pressure) and the maternal arterial Po_2 was only 35 mm Hg (18). Metcalfe and his coworkers extended these studies in sheep at 14,900 feet in the Peruvian Andes and found the umbilical venous Po_2 similar to that of normal lamb fetuses at sea level (19). Our studies suggest that these observations may be explained by a more uniform distribution of maternal and fetal blood flow.

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