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THE EFFECTS OF MATERNAL HYPERCAPNIA ON FOETAL OXYGENATION AND UTERINE BLOOD FLOW IN THE PIG

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SUMMARY

1. The purpose of this investigation was to determine the effects of maternal hyperoxaemia and hypercapnia on the uterine vascular bed and foetal oxygenation in the large white sow at 80–90 days gestation.

2. When maternal hyperoxaemia was induced with 100 % oxygen, there was a highly significant rise in the maternal arterial oxygen tension, but no other significant blood gas or vascular changes were observed.

3. When mild maternal hypercapnia was superimposed on maternal hyperoxaemia (oxygen plus 6 % carbon dioxide), the oxygen tension and saturation of both the maternal uterine venous and foetal umbilical venous bloods were significantly increased. Similar but more pronounced increases were found when severe hypercapnia was induced (oxygen plus 50 % carbon dioxide) but in this case all blood samples showed dramatic changes in P_{CO_2} and pH. These changes were accompanied by an increase in the systemic blood pressure and uterine blood flow, and a decrease in uterine vascular resistance.

4. When mild hypercapnia was induced without hyperoxaemia (air plus 5 % carbon dioxide) significant increases were recorded in the oxygen tension and saturation of uterine venous and foetal umbilical venous bloods. Systemic and uterine arterial blood pressure rose, the uterine blood flow increased, and uterine vascular resistance fell.

5. It was concluded that the increased foetal oxygen tension during maternal hypercapnia was the result of the increased uterine blood flow and greater mass delivery of oxygen to the placenta, so that once the oxygen requirements of the placental tissues themselves were exceeded there would be an increased oxygen gradient at the site of gas exchange.

6. Carbon dioxide concentration in arterial blood plays an important role in determining blood flow through the pregnant uterus in the sow.

INTRODUCTION

It is almost half a century since Huggett (1927) demonstrated a considerable oxygen tension gradient between maternal and foetal blood streams in the goat. Since then this gradient has been studied in other animals and in man, and extensively reported in the literature. Meschia, Cotter, Breathnach & Barron (1965) studied the sheep and Barron & Battaglia (1955) the rabbit. The condition in the rhesus monkey was described by Hellegers, Meschia, Prystowsky, Wolkoff & Barron (1964) and that of the human by Prystowsky (1957).

Maternal hyperoxaemia following the administration of 100% oxygen, seems to have a limited effect on foetal oxygenation, though the response varies in different species. Comline & Silver (1968) showed that in the ewe, such conditions raised the foetal oxygen tension from 33 to 38 mmHg, but in the mare, there was a greater increase, from 66 to 82 mmHg. Steven (1968) suggested that this difference could be explained by the different arterial arrangements supplying blood to areas of placental exchange in the two species.

In the human, Rorke, Davey & Du Toit (1968) showed that at Caesarean section, the foetal umbilical arterial oxygen tension was lower when the mother was ventilated with 100% oxygen, than when ventilated with 66·6% oxygen. Baraka (1970) found that the foetal oxygen tension correlated well with the maternal when the P_{CO_2} was in the range 78–200 mmHg, but not when it was in the range 200–500 mmHg.

Dawes (1968) maintained maternal arterial oxygen tension constant in anaesthetized ewes breathing spontaneously, and found that the administration of 3–10% carbon dioxide produced a rise of 6–8 mmHg in foetal arterial oxygen tension. This could not be explained by the Bohr shift or a change in umbilical circulation.

The present study follows an observation that during hypoventilation in a pregnant sow administration of 100% oxygen led to a high oxygen tension in the foetal umbilical venous blood. The study investigated the effect of increasing carbon dioxide in the maternal inspired gas on the oxygenation of the foetus. It confirms the preliminary results we previously reported (Lawn, Mills & Prior, 1970) and indicates a relationship between maternal uterine blood flow and foetal umbilical oxygenation.

METHODS

In-pig sows at 80–90 days gestation (gestation period 122 days) were tranquillized with an intramuscular injection of Phencyclidine 2·2 mg/kg body wt. Anaesthesia was induced with an I.V. injection into the ear of 5 ml. pentobarbitone sodium (100 mg/ml.).

A size 9 Magill endotracheal tube was introduced and connected to a Cape ventilator, by means of which the respiratory rate and the tidal volume were regulated. In the larger sows, this ventilator was unable to maintain the P_{CO_2} of maternal arterial blood at normal values.

Isotonic saline was infused into an ear vein at approximately 1 ml.min^{-1} together with pentobarbitone sodium at 10 mg/min to maintain anaesthesia.

An arterial cannula was passed through the femoral artery into the aorta to monitor blood pressure and pulse rate by a Statham pressure transducer P23AC on a Brush Celvite Recorder 260.

The sow was placed in the left lateral position and an L-shaped incision made in the right side extending from the groin out to, and parallel with the linea alba. The layers down to the peritoneum were divided, haemostasis secured and the peritoneum opened. Since handling and exposure of the uterus and foetus may alter blood gas values, all these procedures were kept to a minimum.

Two series of experiments were carried out:

(1) The analysis of foetal and maternal blood gas changes during alterations of maternal ventilating gases.

(2) The measurement of uterine blood flow changes and uterine vascular resistance under the same conditions as (1).

Blood samples were analysed for P_{O_2}, pH and P_{CO_2} using the Radiometer Gas Monitor and pH meter 27. The percentage saturation was calculated from the oxygen dissociation curves of Tweeddale (1973). These had been determined over the pH range 7·00–7·60 for both maternal and foetal bloods. The P_{50} values at 37° C and pH 7·4 were 34·2 and 22 mmHg respectively, and the Bohr effects, $\Delta \log P_{50}/\Delta$ pH were $-0{\cdot}43$ and $-0{\cdot}45$ for maternal and foetal blood. The haemoglobin concentration was determined by the cyanmethaemoglobin method.

Measurement of uterine blood flow and resistance

After opening the peritoneum, the right uterine artery or one of its main branches was palpated at the posterior end of the incision. Peritoneum was then stripped off the vessel which was separated from the accompanying venous plexus for about one inch. A Statham cuff electromagnetic flowmeter S.P. 2202 was then applied.

By further palpation part of the uterus supplied by that artery was identified, and through a small arterial branch a catheter was introduced to a point close to the flowmeter head. This was then connected to a Statham pressure transducer to measure uterine arterial blood pressure. This catheter was flushed continuously with heparinized saline at a slow rate. No attempt was made to cut off collateral circulation from ovarian vessels. Periods of about an hour were allowed for the sow to adjust to these procedures.

The uterine blood flow, although affected by changes in blood pressure, is also affected by changes in resistance of the uterine vascular bed. A small analog computer (Vidac) was therefore used to compute continuously the uterine resistance during experiments from the expression:

$$Zu(t) = \frac{Pu(t)}{Fu(t)},$$

where $Zu(t)$ = resistance, $Pu(t)$ = pressure and $Fu(t)$ = flow. In later experiments, the computer was replaced by a Statham Cardiovascular Analyser SP 1011.

Sows were initially given air to breathe and blood samples were taken to measure maternal arterial pH and blood gas tensions. Following this the sows were ventilated with each of the following gases (not necessarily in this order): 100 % oxygen, oxygen plus 6 % carbon dioxide, oxygen plus 50 % carbon dioxide and air plus 5 % carbon

dioxide. Maternal and foetal blood samples were not taken until blood pressure and blood flow readings were steady under each of the new conditions. In the case of a ventilating mixture of 50% oxygen and 50% carbon dioxide, this state was reached in about 10 min.

For foetal sampling, a foetal sac was identified and a small incision made over it in the uterus. A loop of umbilical cord was brought out and samples drawn from both the umbilical artery and vein. Maternal samples were drawn simultaneously from a vein draining the uterus in the region of the foetus being sampled, and from the femoral artery catheter. All samples were drawn into heparinized syringes. After sampling, each foetus was discarded and the uterus sutured. Since sampling occurred only once from each foetus, subsequent foetal sampling involved progressive exteriorization of the uterine horn, which was kept moist with warm saline packs.

Fourteen studies of changes in maternal and foetal blood gases were carried out in fourteen sows. Sixteen studies of changes in uterine flow and vascular resistance were carried out in eleven sows. Four animals were common to the two groups. Maternal blood gases in the animals used for haemodynamic studies were within the range shown in Table 1.

RESULTS

The initial maternal arterial oxygen tension (P_{a,O_2}) in the sows was $98{\cdot}0 \pm 3{\cdot}6$ mmHg and maternal arterial carbon dioxide tension (P_{a,CO_2}) was $44{\cdot}4 \pm 2{\cdot}6$ mmHg. In spite of this slightly elevated P_{a,CO_2} the pH was $7{\cdot}45 \pm 0{\cdot}04$.

Inhalation of air

In some cases, foetal samples were not taken when the sows were initially breathing air. In Table 1 the maternal gas tensions during air inhalation include some samples taken following high oxygen ventilation, when nitrogen would inevitably be removed.

Clearly the samples taken during air breathing were sometimes obtained before the nitrogen steady state had been fully restored. Consequently the maternal P_{a,O_2} was sometimes higher than would have been expected during air breathing. However since the changes which resulted from alterations of inspired gas were compared with the air breathing values in Table 1, this would lessen the increase in oxygen tension produced. If they were compared with the initial gas tensions in the sows, the statistical significance would be greater.

Inhalation of 100% *oxygen*

When the sows were ventilated with 100% oxygen, in spite of the large increase in maternal P_{a,O_2} (Table 1) there was no significant increase in the P_{O_2} or percentage saturation of either the uterine or the umbilical venous bloods. Since the maternal arterial blood was approximately 98% saturated with oxygen when breathing air, the increase in maternal P_{a,O_2} under 100% oxygen would be associated largely with an increase in oxygen in simple solution and only a small change in oxygen content. This would

TABLE 1. Blood gas and pH values of maternal arterial (M.art.), uterine venous (M.ven.), umbilical venous (F.ven.) and umbilical arterial (F.art.) bloods when sows were ventilated with different gas mixtures

Ventilation		M.art.	M.ven.	F.ven.	F.art.	M.art.	M.ven.	F.ven.	F.art.
		P_{O_2} mmHg				P_{CO_2} mmHg			
Air (n = 14)	Mean	111·5†	54·4	26·1	12·6	45·6	57·8	65·4	78·4
	S.E.	3·7	3·7	1·4	1·4	2·1	2·5	3·5	5·2
Oxygen 100% (n = 13)	Mean	314·4	59·1	31·5	12·1	48·2	57·1	68·9	86·1
	S.E.	33·3	3·0	2·1	2·0	2·6	2·9	3·1	5·0
	Sig.	***	—	—	—	—	—	—	—
Oxygen plus 6% carbon dioxide (n = 7)	Mean	292·6	80·6	54·7	15·3	84·3	97·4	96·4	108·9
	S.E.	51·7	4·5	8·5	3·8	5·8	6·4	7·5	5·5
	Sig.	***	**	**	—	***	***	***	***
Oxygen plus 50% carbon dioxide (n = 7)	Mean	258·3	118·4	67·4	35·6	148·1	148·1	140·6	136·3
	S.E.	33·5	16·3	6·7	5·4	11·3	9·2	8·1	6·7
	Sig.	***	***	***	***	***	***	***	***
Air plus 5% carbon dioxide (n = 6)	Mean	125·2	82·8	48·2	24·2	72·3	78·5	76·5	89·5
	S.E.	4·7	3·6	4·8	4·6	5·2	5·3	3·5	3·3
	Sig.	—	***	***	**	***	***	**	**
Ventilation		pH				% saturation			
Air (n = 14)	Mean	7·431	7·371	7·366	7·303	97·8	74·5	57·4	19·5
	S.E.	0·016	0·013	0·019	0·024	—	4·4	3·3	3·7
Oxygen 100% (n = 13)	Mean	7·413	7·358	7·335	7·247	100·0	78·9	64·5	18·7
	S.E.	0·017	0·019	0·019	0·024	—	2·9	3·8	4·4
	Sig.	—	—	—	—	—	—	—	—
Oxygen plus 6% carbon dioxide (n = 7)	Mean	7·208	7·169	7·206	7·157	100·0	86·5	82·1	22·8
	S.E.	0·023	0·018	0·032	0·022	—	2·9	4·8	7·9
	Sig.	***	***	**	**	—	**	**	—
Oxygen plus 50% carbon dioxide (n = 7)	Mean	7·002	6·996	7·046	7·002	100·0	89·5	85·7	51·9
	S.E.	0·029	0·035	0·026	0·025	—	4·4	3·3	9·1
	Sig.	***	***	***	***	—	**	***	**
Air plus 5% carbon dioxide (n = 6)	Mean	7·272	7·244	7·277	7·210	99·8	91·9	82·5	42·4
	S.E.	0·030	0·035	0·041	0·022	—	1·6	5·2	10·4
	Sig.	***	**	*	*	—	***	**	*

Sig. = Statistical significance compared to the corresponding air values (paired analysis).
*** = $P < 0·001$, ** = $P < 0·01$, * = $P < 0·05$. n = the number of studies. † See note in results.

account for the lack of a significant increase in the oxygenation of venous bloods. No significant differences were found in pH or P_{CO_2} values of any of the blood samples following inhalation of 100% oxygen.

Inhalation of oxygen/carbon dioxide mixtures

Two groups are considered in this section.

(*a*) Oxygen plus 6% carbon dioxide in which the maternal P_{a,CO_2} values were 61–100 mmHg.

(*b*) Oxygen plus 50% carbon dioxide in which the maternal P_{a,CO_2} value were 114–< 190 mmHg.

The changes in blood gas and pH values for both groups are given in Table 1.

Group a. With the sows breathing 94% oxygen and 6% carbon dioxide there was a highly significant rise in maternal oxygen tension comparable with the rise produced by the inhalation of 100% oxygen. However, the addition of 6% carbon dioxide produced a significant rise in oxygen tension in both uterine venous and umbilical venous blood, which was not demonstrated with 100% oxygen. The percentage oxygen saturation of these venous bloods also rose significantly during carbon dioxide inspiration. Although both maternal and foetal P_{CO_2} values rose, compared to air, the arteriovenous differences were maintained. All the bloods showed a decrease in pH corresponding to the P_{CO_2} increases.

Group b. The maternal uterine and umbilical venous P_{O_2} values rose dramatically in this group, although the percentage saturation changes were similar to those of group *a*.

The P_{CO_2} values of the maternal blood rose significantly, the arterial value reaching the same level as the uterine venous. On the foetal side the significant P_{CO_2} rise reversed the normal arteriovenous difference. The foetus was, therefore, still absorbing carbon dioxide from the mother and a steady state had not been reached. The pH of all samples fell markedly, the uterine venous pH reaching the lowest values.

Inhalation of air plus 5% carbon dioxide

The blood gas and pH changes can be seen in Table 1. In spite of the fact that the maternal P_{O_2} was not significantly different from those animals breathing air, there was nevertheless a marked increase in both uterine and umbilical venous blood P_{O_2} values. The % oxygen saturations of these venous bloods also rose significantly. The magnitude of these changes and the changes in P_{CO_2} and pH were similar to those observed when oxygen plus 7% carbon dioxide was administered to the sows.

Figs. 1 and 2 show the P_{O_2} values of the uterine and the foetal venous bloods plotted against the maternal arterial P_{CO_2} values. These figures

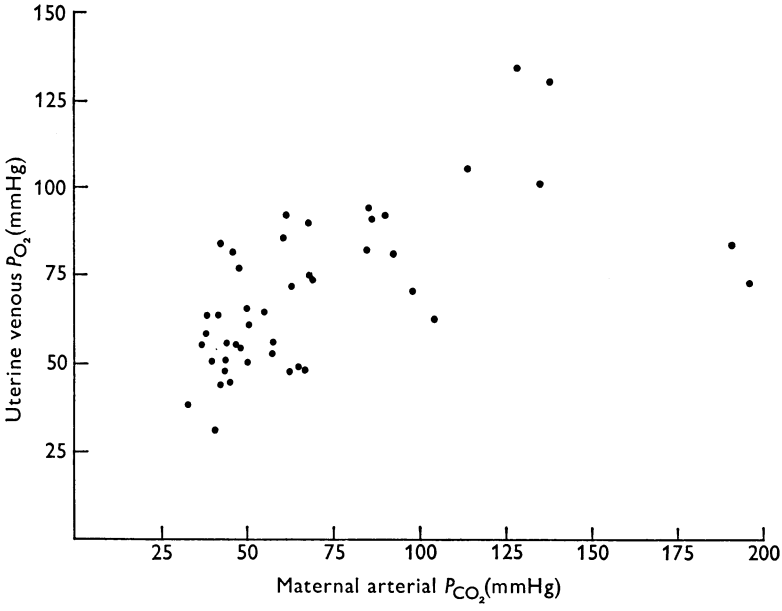

Fig. 1. Uterine venous P_{O_2} plotted against maternal arterial P_{CO_2}: correlation coefficient $r = 0{\cdot}620$, $P < 0{\cdot}001$.

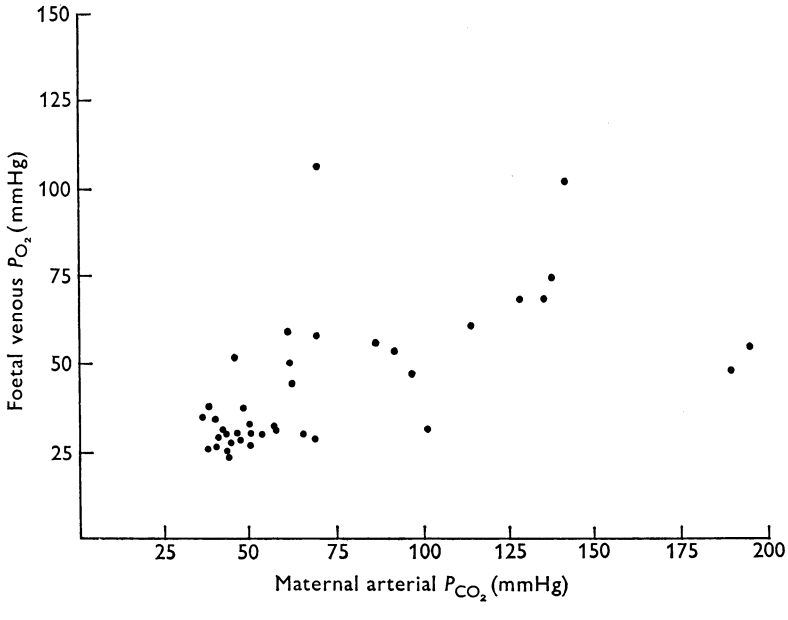

Fig. 2. Foetal umbilical venous P_{O_2} plotted against maternal arterial P_{CO_2}: correlation coefficient $r = 0{\cdot}620$, $P < 0{\cdot}001$.

TABLE 2. Vascular changes when ventilating gases were altered

Ventilating gas comparisons	Numbers showing: Rise	Fall	No change	Mean change	Sig.	Numbers showing: Rise	Fall	No change	Mean change	Sig.
	Systemic pressure					Uterine pressure				
Air to 100% oxygen (n = 11)	4	8	3	−2%	n.s.	6	6	3	+4%	n.s.
Oxygen to oxygen plus 50% carbon dioxide (n = 15)	13	2	0	+20%	< 0·001	10	5	0	0%	n.s.
Air to air plus 5% carbon dioxide (n = 16)	16	0	0	+49%	< 0·001	14	2	0	+46%	< 0·001
	Uterine flow					Uterine resistance				
Air to 100% oxygen (n = 15)	3	9	3	−8%	n.s.	9	3	3	+26%	n.s.
Oxygen to oxygen plus 50% carbon dioxide (n = 15)	12	1	2	+74%	< 0·001	2	12	1	−30%	> 0·001
Air to air plus 5% carbon dioxide (n = 16)	15	0	1	+117%	< 0·01	3	13	0	−25%	< 0·05

n = number of studies. n.s. = not significant.

include the values found in both normally ventilated and hypercapnic sows. The correlation coefficient in each case ($r = 0{\cdot}620$) shows that the relationship is highly significant ($P < 0{\cdot}001$).

Vascular changes

Inhalation of air

The systemic blood pressure was found to remain stable during the inhalation of air. However the uterine blood pressure and in particular the uterine blood flow, showed spasmodic variations related to uterine contractions. When these variations coincided with ventilation changes, they made accurate interpretation of the traces difficult.

Inhalation of 100% *oxygen*

When the sows were ventilated with 100% oxygen following a period on air, no significant changes were found in either systemic or uterine blood pressures, or the uterine blood flow, although both upward and downward tendencies were observed (see Table 2). Uterine resistance computations indicated an insignificant mean rise during oxygen inhalation. A trace showing typical changes when sows were ventilated with air, then 100% oxygen, then oxygen plus 50% carbon dioxide is shown in Fig. 3.

Inhalation of oxygen plus 50% *carbon dioxide*

When sows were ventilated with oxygen plus 50% carbon dioxide following 100% oxygen, the systemic blood pressure showed a significant mean rise of 20% (Table 2). The uterine blood pressures showed varying responses, the mean changes observed being not statistically significant. The uterine blood flow rose in nearly all cases, yielding a mean increase of 74%. The recordings of resistance showed a mean fall of 30%.

Inhalation of air plus 5% *carbon dioxide*

When sows were ventilated with air plus 5% carbon dioxide following air only, the systemic and uterine blood pressures and the uterine flows all rose (Table 2), although the individual responses varied in degree, giving mean changes which were of high statistical significance. The uterine resistance showed a mean fall which is significant at the 5% level. A typical trace is seen in Fig. 4. It can be seen from Fig. 4 and Table 2 that the increase in uterine blood flow was in part due to the increase in blood pressure and in part due to the decrease in resistance of the uterine bed.

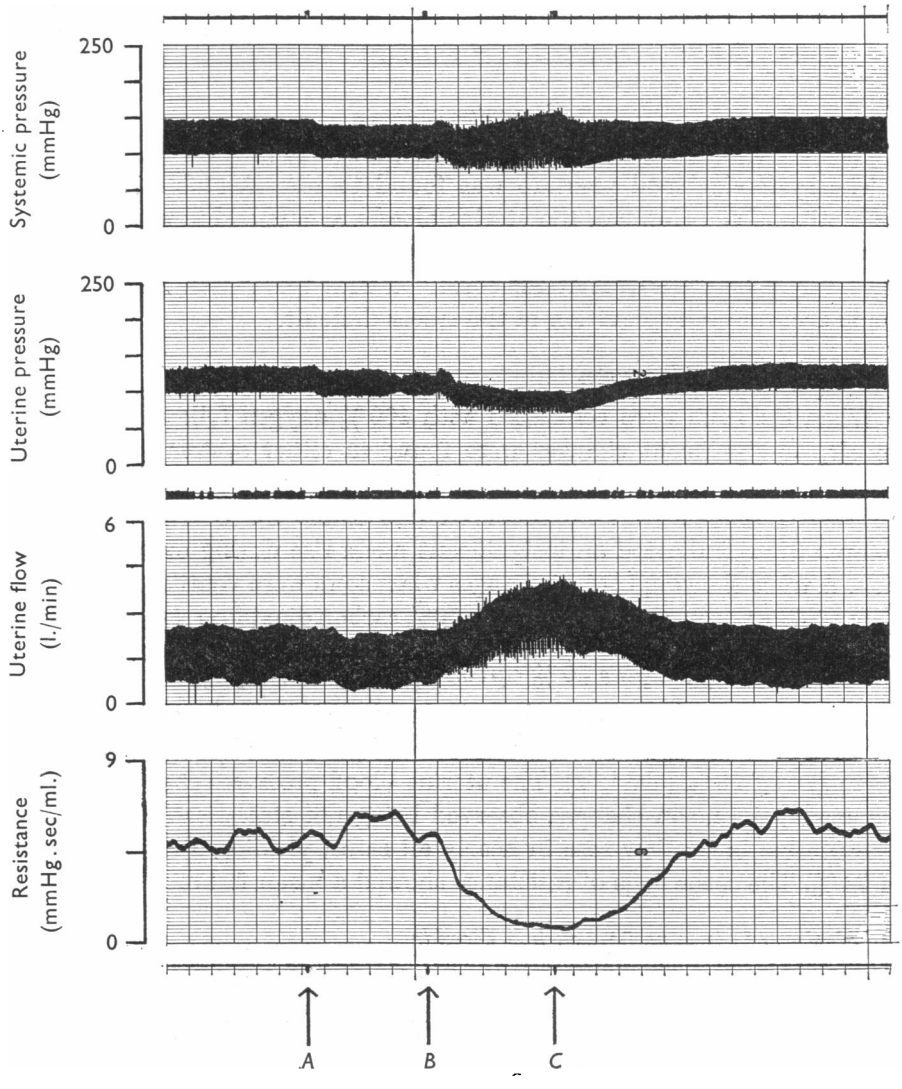

Fig. 3. Tracings of systemic arterial pressure (mmHg), uterine arterial pressure (mmHg), uterine arterial blood flow (l. min^{-1}) and uterine vascular resistance (mmHg.sec.$ml.^{-1}$). At *A* the inspired gas was changed from air to 100% oxygen, followed by oxygen and 50% carbon dioxide at *B* and air again at *C*. Time marker in minutes.

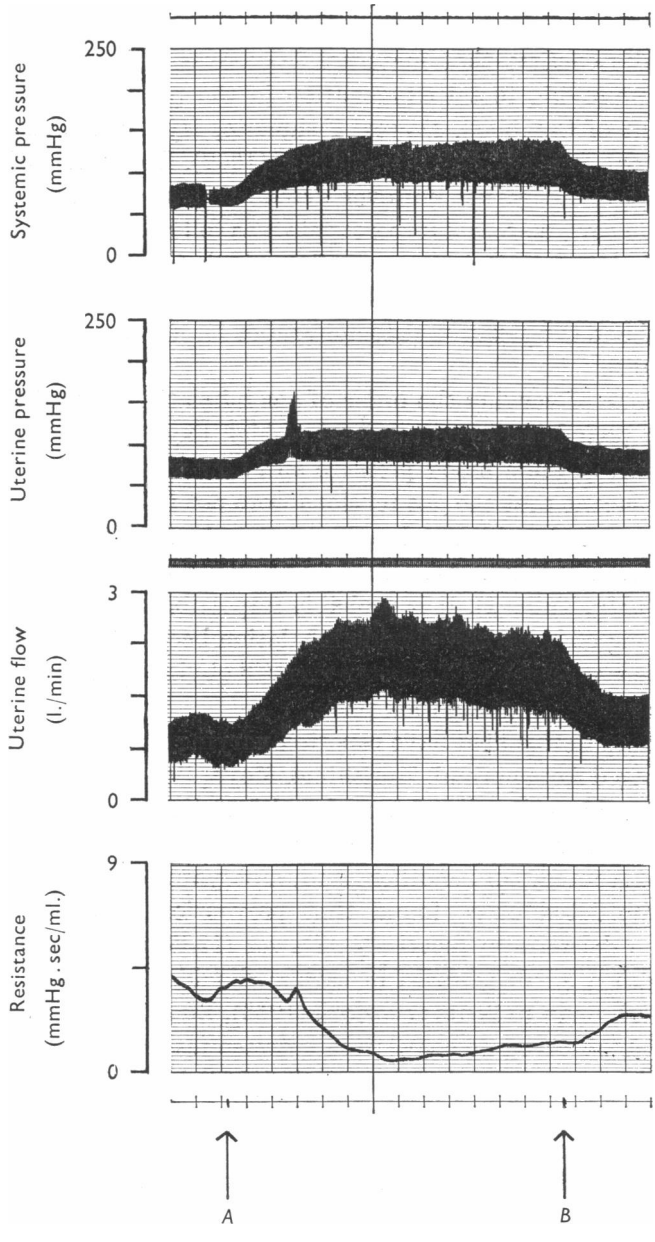

Fig. 4. Tracings of systemic arterial pressure (mmHg), uterine arterial pressure (mmHg), uterine arterial blood flow (l. min^{-1}) and uterine vascular resistance (mmHg . sec . $ml.^{-1}$). At *A* the inspired gas was changed from air to air with 5% carbon dioxide, followed by air again at *B*. Time marker in minutes.

DISCUSSION

These results confirm that maternal hyperoxaemia on its own is ineffective in improving foetal oxygenation in the pig. This conclusion is similar to that of Campbell, Dawes, Fishmann, Hyman & James (1966) and Motoyama, Rivard, Acheson & Cook (1967), from work with ewes.

The present investigation however demonstrates conclusively that in the case of the sow, maternal hypercapnia was followed by a marked rise in both the foetal and uterine venous P_{O_2}, whether the maternal arterial P_{O_2} was at normal air values or elevated. The relationship between maternal P_{CO_2} and the uterine and foetal venous P_{O_2} values is demonstrated in Figs. 1 and 2.

The technique of varying the order of gas inhalations meant that some air breathing periods followed a period of high oxygen inhalation. Since sampling occurred when blood pressure and flow were in a steady state, it sometimes meant that the gas tensions were not in a steady state. This explains the somewhat high value for maternal arterial oxygen tension during air breathing without and with additional carbon dioxide (111·5 and 125·2 mmHg, Table 1). It is probably impossible to wait for a steady gas state during 50% carbon dioxide inhalation because the foetus would die before this was reached. The foetus was still obviously taking up carbon dioxide at the time sampling took place.

Other workers in this field have reported varying results when maternal P_{CO_2} was changed from normal. Morishima, Moya, Bossers & Daniel (1964), working with guinea-pigs, found a profound foetal metabolic acidiosis and lowered foetal venous P_{O_2} following hyperventilation even when hypocapnia was prevented. On the other hand, Motoyama *et al.* (1967) working with hyperventilated ewes, found that prevention of the hypocapnia resulted in no decrease in foetal P_{O_2}. Dawes (1968) also found a rise in foetal P_{O_2} with a small increase in carbon dioxide in the inspired gas. Working with human patients Crawford (1966), Lumley, Renou, Newman & Wood (1969) observed no correlation between maternal P_{CO_2} or pH and the state of foetal oxygenation, but Wulf (1964) indicated a decrease in foetal P_{O_2} following maternal hyperventilation. Although these results are variable, the general trend seems to fit in with our observations, namely, that foetal oxygenation is directly related to maternal carbon dioxide tension.

Transfer of oxygen across the placenta is affected by the position of the maternal and foetal oxygen-haemoglobin affinity curves, the foetal curve generally lying to the left of the maternal. A decrease in the blood pH such as that induced during the present investigations, would cause a shift to the right. Transfer of oxygen to the foetuses would then be

facilitated but this effect has been shown by Tweeddale (1973) to account for only 20–25 % of the increase in uterine and umbilical venous oxygen saturations actually observed.

Clearly other factors must play a major part in the transfer of oxygen across the placenta during maternal hypercapnia. This investigation has shown that there is an increase in the uterine blood flow. The increased systemic blood pressure during hypercapnia is one factor which contributed to this, but in addition the uterine vascular resistance was shown to decrease. This opening up of the uterine vascular bed when P_{CO_2} was increased, if taking place in the region of the placenta, would cause an increase in the rate of mass delivery of oxygen to the cotyledons. Once the oxygen requirements of the placental tissues were exceeded, an increased rate of delivery of oxygen would raise the gradient at the point of gas transfer to the foetus.

The increase in uterine blood flow following maternal hypercapnia in sows is complementary to the findings of Leduc (1972). Working with rabbits, he noted a decrease in maternal placental blood flow, when maternal P_{CO_2} levels were decreased to approximately 18 mmHg by hyperventilation. Huckabee (1962), however, working with pregnant ewes, found no relationship between maternal hypercapnia and uterine blood flow, but no values were quoted for maternal P_{CO_2}.

The addition of 6 % carbon dioxide to oxygen, or of 5 % carbon dioxide to air, raised the foetal umbilical P_{CO_2} significantly in each case, and lowered the foetal pH. The effect of 5 % carbon dioxide in air on the foetal pH was only just significant. These changes might be detrimental to the foetus, but perhaps not so detrimental as the effects of hypocapnia on foetal P_{O_2}. It would be of value to assess the effect on foetal well being, of sustaining these changes for longer periods of time.

It has been customary in obstetric practice to administer 100 % oxygen to mothers to alleviate foetal distress. The present findings suggest that a study of the effect on the foetus of the administration of gas mixtures containing low percentages of carbon dioxide would be worth while.

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