The Effect of Changes in Maternal pH and P_{CO_2} on the P_{O_2} of Fetal Lambs

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The effect on the fetus of changes in maternal P_{CO_2} and *p*H were studied in sheep. Maternal hyperventilation without changes in P_{CO_2} and *p*H had no significant effect while hyperventilation associated with hypocapnia and respiratory alkalemia was associated with a consistent decrease in fetal P_{O_2} and S_{O_2}. Fetal P_{O_2} also decreased with maternal metabolic alkalemia indicating that the change in maternal *p*H, rather than P_{CO_2}, was the critical factor influencing fetal P_{O_2}. Maternal hypercapnia with acidemia was associated with a significant increase in fetal P_{O_2} and S_{O_2}. These changes in fetal P_{O_2} and S_{O_2} were the combined effect of alterations in oxygen transfer within the placenta and changes in umbilical blood flow. Prolonged maternal hyperventilation associated with alkalemia resulted in severe fetal hypoxia, metabolic acidosis and fetal distress. Reports concerning parturient women and their fetuses indicate that there is a similar relationship between maternal *p*H and fetal P_{O_2} in man and that this is of clinical importance.

RECENT studies in pregnant animals [1, 2] as well as in parturient women [1, 3] have indicated that the oxygenation of the fetus is significantly influenced by the level of maternal ventilation. This report, based on experimental studies in sheep, presents further data concerning the effects on the fetus of changes in maternal P_{CO_2} and *p*H and an investigation of the mechanisms involved.

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Material and Methods

Material. Studies were carried out in 22 pregnant Dorset-Delaine ewes which had been mated with a pure bred Dorset ram. The gestational age of the fetal lambs was calculated from the mating date which was known within ±2 days and averaged 136 days (range, 130 to 144 days; full-term, 147–150 days).

Preparation. Anesthesia was induced in the pregnant ewe with intravenous sodium pentobarbital (15 to 25 mg./kg. body weight). A cuffed tube was inserted in the trachea and was connected to a respirator to permit intermittent positive pressure breathing (IPPB) with oxygen enriched air. Saline and 5% dextrose in water were administered intravenously throughout the procedure for the control of fluid balance. Additional doses of sodium pentobarbital (1.5 to 2.0 mg./kg.) were given when necessary for the maintenance of anesthesia (every 30 to 120 minutes) and succinylcholine chloride (1.0 to 2.0 mg./kg.) was injected intravenously every 30 to 90 minutes to allow accurate control of maternal ventilation. The end-tidal CO_2 concentration was monitored with an infra-red gas analyzer.

The ewe was positioned on its right side and the left common carotid artery was cannulated so that blood samples could be withdrawn. This cannula also allowed continuous measurement of blood pressure via an inductive transducer and a direct writing oscillograph.

The lamb was exteriorized in the fetal state through a hysterotomy and placed on its right side on a heated table adjacent to the mother. The upper airway was obstructed immediately and the trachea ligated in order to prevent breathing. The umbilical cord was covered with cotton soaked in warm saline and unnecessary manipulation was avoided.

The left common carotid artery of the fetus was cannulated for the continuous measure-

ment of blood pressure in a manner similar to that in the ewe and for serial blood sampling. The external jugular vein was also cannulated for transfusion. In 11 preparations a polyethylene catheter (inside diameter = 1.2 mm.) was placed in one umbilical vein via a tributary and used for obtaining blood samples concomitantly with carotid samples.

Oxygen and carbon dioxide tensions (P_{O_2}, P_{CO_2}) and *p*H were determined at 37° C. within a few minutes of sampling with modified Clark P_{O_2}, Severinghaus P_{CO_2} and Astrup *p*H electrodes and were corrected to body temperature using the factors of Bradley *et al.*[4] and Rosenthal.[5] Oxygen saturation (S_{O_2}) of fetal blood was estimated from P_{O_2} and *p*H values using a nomogram prepared by Meschia *et al.*[6] for S_{O_2} values between 10 and 90 per cent.* Lectic acid concentration was measured in the fetal carotid blood samples by the method of Scholz *et al.*[7] Hemoglobin concentration was estimated by the cyanmethemoglobin method.[8]

In 11 preparations a flowprobe was placed around one of the two umbilical arteries in the cord after careful infiltration with 2 per cent lidocaine to minimize vasospasm. Changes in umbilical blood flow were measured with a gated sine-wave electromagnetic flowmeter † and the results were expressed as percentage of the control value.

When the surgical procedure had been completed (usually about 60 minutes from the time of induction of anesthesia), 2.5 ml. samples of blood were taken simultaneously from maternal and fetal carotid arteries and, in some, from the umbilical vein to obtain the control values for P_{O_2}, P_{CO_2} and *p*H. After each sampling, the fetus was transfused with an equal amount of heparinized maternal blood.

The animals included in this report remained viable and responsive for 5 to 6 hours and a number of different experiments were performed in most of these 22 preparations. The data presented here, however, were usually obtained within 3½ hours from the time of exteriorization of the fetus to avoid the effect of deterioration of the fetus.

Procedures. After the level of maternal respiration had been kept constant for at least 15 minutes, arterial carbon dioxide tension (Pa_{CO_2}) and *p*H of the ewe were varied 47 times in the 22 preparations by changing ventilation by varying amounts and/or the concentration of inspired CO_2 from 0 up to 5 per cent. This new level of respiration was maintained for an average of 29 minutes (range, 14 to 60). Blood samples were drawn simultaneously from the carotid arteries of the ewe and fetus (and 22 times from the umbilical vein) before and during the period of altered respiration. On 21 occasions, umbilical blood flow was also measured before and during altered maternal Pa_{CO_2} and/or *p*H. In all studies, maternal arterial oxygen tension (Pa_{O_2}) was kept above 80 mm. Hg and as constant as possible during the procedure.

Maternal metabolic alkalemia was induced on 10 occasions with intravenous infusion of 5 per cent sodium bicarbonate solution (average, 420 ml.; range, 120 to 860) for an average of 28 minutes (range, 13 to 61). Blood samples were taken from the carotid arteries (and on 7 occasions from the umbilical vein) before and during the period of metabolic alkalemia. Umbilical blood flow was also measured on 4 occasions before and during altered maternal *p*H.

After each acute change in maternal Pa_{CO_2} and/or *p*H away from normal, whether produced by varying respiration or by infusing sodium bicarbonate, maternal Pa_{CO_2} and *p*H were returned toward normal. In order to avoid the possible effects of deterioration, the data were discarded unless the secondary

* Since the affinity for oxygen of red blood cells from the adult differs from that of the fetus, transfusion of the fetus with maternal blood would cause a shift to the right of the fetal oxyhemoglobin dissociation curve. This could, in turn, cause an error in estimating fetal So_2 from the nomogram for fetal blood. In the present studies, in which changes in So_2 were calculated and were compared before and during procedures lasting an average of 29 minutes, the amount of fetal blood replaced by maternal blood in this interval was only 2.5–10 ml. or less than 3% of th total circulating blood volume. The error in comparison of So_2 would therefore be negligible although calculated values by the end of an entire series of studies in one fetus might erroneously be high by as much as 3 per cent saturation.

† A Medicon flowmeter, Model K-2000, with 4 and 5 mm. flowprobes was used. There was a linear response in the range observed and the electronic baseline corresponded well with zero flow at the end of each experiment.

changes in the fetus were readily reversible. When there was a significant change in maternal arterial blood pressure during these procedures, the data were also excluded from the present analysis to avoid additional factors affecting the fetus. Preliminary attempts to study the effect on the fetus of metabolic acidemia had been made in 2 preparations. However, the results are not included in the present report since a stable maternal hemodynamic state could not be maintained.

In order to differentiate the effect on the fetus of changes in maternal P_{CO_2} and *p*H from the mechanical effect per se of hyperventilation with IPPB, 4 ewes were initially hyperventilated for 20 minutes with gas mixtures containing from 3.6 to 7.0 per cent CO_2. Acute hypocapnia (respiratory alkalemia) was then induced without changes in the level of ventilation by substituting a gas mixture with no CO_2.

The effect on the fetus of prolonged maternal hyperventilation for 3½ hours and the resulting respiratory alkalemia was studied in one lamb of 132 days gestation. In this animal blood samples were taken at frequent intervals and umbilical blood flow was monitored throughout the procedure. Six previously reported [9] experiments, indicating that such prolonged exteriorization of the fetal lamb was not associated with deterioration of gas exchange, were used as controls.

TABLE 1. Control Values for Maternal and Fetal Blood Gases, *p*H and Umbilical Blood Flow*

	N	Mean	S.E.
Maternal arterial blood			
P_{O_2} (mm. Hg)	21†	213.2	17.8
P_{CO_2} (mm. Hg)	22	39.6	1.1
*p*H	22	7.38	0.01
Fetal carotid blood			
P_{O_2} (mm. Hg)	21†	26.9	1.1
S_{O_2} (%)‡	21†	71.1	2.5
P_{CO_2} (mm. Hg)	22	49.9	1.3
*p*H	22	7.31	0.01
Umbilical vein blood			
P_{O_2} (mm. Hg)	11	45.3	2.6
S_{O_2} (%)‡	11	>90	
P_{CO_2} (mm. Hg)	11	44.3	1.8
*p*H	11	7.35	0.02
Umbilical blood flow§ ml./kg./min.	11	174	43.5

* In most of the preparations maternal and fetal blood gases and *p*H were measured two to three times during the control period and minimal variations found. The values used in this table are the last measurements during the control period.

† In one preparation the P_{O_2} electrode was not available at the time of the initial control measurement.

‡ Determined from the data of Meschia *et al.*[8] No data are available for determination of S_{O_2} values over 90 per cent.

§ Estimated by multiplying the flow measured in one umbilical artery by 2.

Results

The data from the control period of the 22 preparations are shown in table 1. The

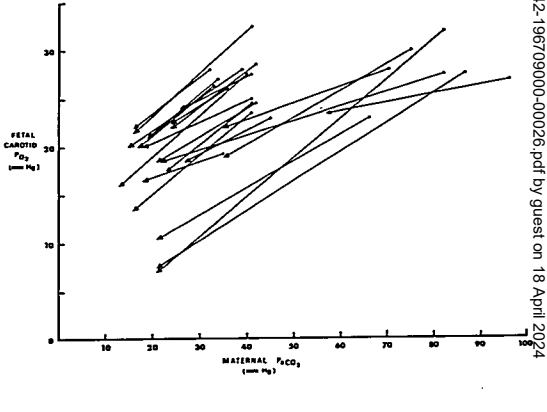

FIG. 1. Effect on fetal carotid P_{O_2} of decreases in maternal P_{aCO_2} by hyperventilation in sheep. Closed circles and triangles connected by solid lines indicate values before and during maternal hyperventilation, respectively. See text and table 2.

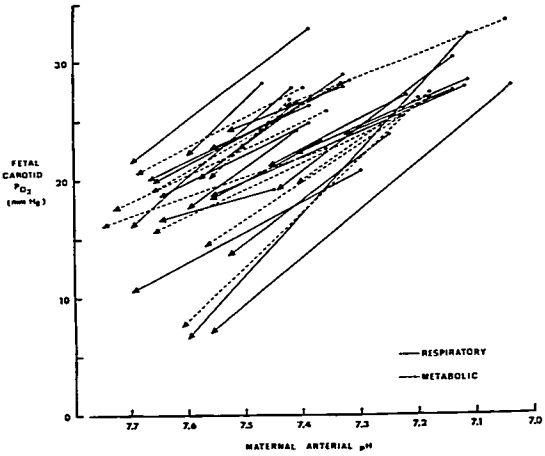

FIG. 2. Effect on fetal carotid P_{O_2} of increases in maternal arterial *p*H in sheep. Closed circles and triangles indicate values before and during elevation in maternal *p*H, respectively. Solid lines indicate increases in maternal *p*H by hyperventilation (respiratory alkalemia) and broken lines by infusion of sodium bicarbonate (metabolic alkalemia). See text and table 2.

changes in the fetus resulting from alterations in maternal ventilation, P_{CO_2} and *p*H are presented under the following headings: (a) changes in fetal carotid blood gases and *p*H, (b) changes in umbilical vein blood gases and *p*H, (c) changes in umbilical blood flow, (d) mechanical effect of hyperventilation per se, (e) changes in blood pressure and heart rate, and (f) changes resulting from prolonged maternal hyperventilation.

(a) *Changes in Fetal Carotid Blood Gases and pH.* The relation between maternal Pa_{CO_2} and fetal carotid P_{O_2} before and during a decrease in maternal Pa_{CO_2} is shown in figure 1 and table 2. A reduction of maternal Pa_{CO_2} was invariably associated with a decrease in the fetal carotid P_{O_2} and S_{O_2}. These hypoxemic changes in the fetus were noted within a few minutes of the decrease in maternal Pa_{CO_2}. The same changes in fetal carotid P_{O_2} are shown with respect to maternal arterial *p*H in figure 2 and table 2. A rise in maternal arterial *p*H was, in each experiment, associated with a decrease in fetal P_{O_2} and S_{O_2}. The average decrease in fetal carotid P_{O_2} was 2.9 mm. of mercury per 0.1 *p*H unit change in maternal arterial blood when calculated from the individual relationships. These changes were readily reversible when maternal *p*H was decreased.

The effect on the fetus of maternal metabolic alkalemia was studied ten times and the results are also shown in figure 2 and table 2. The increase in maternal *p*H was associated in four of these studies with a minimal change in maternal Pa_{CO_2} (*i.e.*, less than ±5 mm. of mercury) while in five, Pa_{CO_2} was intentionally increased (7 to 28 mm. Hg) and in one decreased (−19 mm. Hg). Fetal carotid P_{O_2} and S_{O_2}, however, invariably decreased with the increase in maternal *p*H. The average decrease in fetal carotid P_{O_2} was 2.6 mm. of mercury/0.1 *p*H unit change in maternal blood. This decrease was not significantly ($P > 0.20$, based on an analysis of variance) different from the changes observed with maternal respiratory alkalemia. On the other hand, the decrease in fetal carotid S_{O_2} with maternal metabolic alkalemia was, on the average, significantly ($P < 0.05$) greater than that seen with maternal respiratory alkalemia (12.6 per cent versus 5.7 per cent/0.1 *p*H unit change) due to the different changes in fetal *p*H and the resulting shifts in oxyhemoglobin dissociation curve (see section (b) and table 2).

A decrease in maternal *p*H resulting from an increase in P_{CO_2} (respiratory acidemia) was

invariably associated with an increase in fetal carotid P_{O_2} irrespective of the initial *p*H (figure 3, table 2). The average increase in fetal carotid P_{O_2} was 3.4 mm. of mercury/0.1 *p*H unit change in maternal blood. This corresponds to a significant ($P < 0.01$) increase in fetal carotid S_{O_2} from an average of 58 to 66 per cent (a 14 per cent increase). These changes were also readily reversible.

(b) *Changes in Umbilical Vein Blood Gases and pH.* When blood from the umbilical vein was examined, a decrease in P_{O_2} invariably followed an elevation of maternal *p*H whether of respiratory or metabolic origin (figure 4, table 2). The average change in umbilical vein P_{O_2} during respiratory alkalemia was significantly ($P < 0.05$) greater than the change during metabolic alkalemia (average decrease, 6.3 versus 4.4 mm. of mercury/0.1 *p*H unit change in maternal blood). On the other hand, the average decrease in S_{O_2} was significantly ($P < 0.001$) smaller with respiratory than with metabolic alkalemia (3.5 versus 10.7 per cent saturation/0.1 *p*H unit change). This apparent paradox was primarily due to the effect of the different fetal *p*H values on the oxygen dissociation curve of fetal blood. Thus, acute respiratory alkalemia was always associated with an increase in umbilical vein *p*H (average increase, 0.16 ± 0.03 *pH* unit, $P < 0.001$) whereas the metabolic alkalemia was associated with a decrease in umbilical vein *p*H (average decrease, 0.05 ± 0.02 *p*H unit, $P < 0.05$).

TABLE 2. Values for Maternal and Fetal Blood Gases, *p*H and Umbilical Blood Flow Before and During Changes in Maternal *p*H

	Respiratory Alkalemia			Metabolic Alkalemia			Respiratory Acidemia		
	N	Before* Mean (S.E.)	During Mean (S.E.)	N	Before* Mean (S.E.)	During Mean (S.E.)	N	Before* Mean (S.E.)	During Mean (S.E.)
Maternal arterial blood									
P_{O_2} (mm. Hg)	22	202.1 (17.5)	212.9 (21.3)	10	211.2 (30.8)	186.1 (27.4)	25	212.3 (23.1)	213.8 (20.5)
P_{CO_2} (mm. Hg)	22	51.6 (4.4)	22.7† (2.0)	10	48.5 (3.4)	53.6 (4.7)	25	31.8 (2.5)	68.4† (3.7)†
*p*H	22	7.30 (0.03)	7.57† (0.03)	10	7.23 (0.04)	7.61† (0.04)	25	7.48 (0.03)	7.18† (0.02)
Fetal carotid blood									
P_{O_2} (mm. Hg)	22	26.5 (1.7)	18.3† (1.0)	10	27.3 (0.2)	17.4† (1.5)	25	20.4 (1.0)	29.3† (1.0)
S_{O_2} (%)‡	22	66.8 (1.7)	54.8† (4.0)	10	65.6 (4.0)	38.3† (6.3)	25	57.6 (1.1)	65.6† (2.2)
*p*H	22	7.24 (0.02)	7.40† (0.03)	10	7.21 (0.04)	7.17 (0.04)	25	7.34 (0.03)	7.14† (0.02)
Umbilical vein blood									
P_{O_2} (mm. Hg)	11	45.1 (3.3)	29.9† (2.9)	7	39.6 (2.1)	22.1† (2.1)	11	35.6 (2.9)	47.4† (3.4)
S_{O_2} (%)‡	11	85.8 (1.7)	76.7† (5.4)	7	83.0 (3.5)	48.0† (9.3)	11	82.1 (2.4)	84.1 (2.6)
*p*H	11	7.30 (0.04)	7.46† (0.03)	7	7.24 (0.02)	7.20† (0.05)	11	7.39 (0.04)	7.15† (0.03)
Umbilical blood flow§ % of control	12	100	82.5† (2.8)	4	100	76.3† (5.8)	9	100	117.6† (2.4)

* The mean values "before" each procedure are different from the mean control values shown in table 1 because these procedures were started from varying maternal *p*H values. The magnitude of the changes in fetal P_{O_2} with shifts in maternal *p*H was similar whether the maternal *p*H was changed toward or away from the control values and independent of the initial *p*H (*cf.* figs. 1–5).

† The average change is statistically significant ($P < 0.05$) based on the analysis of variance and *t* test.

‡ Determined from the data of Meschia *et al.*[6]; since no data are available for determination of S_{O_2} above 90 per cent, 91 per cent is used for those above 90 per cent for statistical analysis.

§ Estimated by multiplying the flow measured in one umbilical artery by 2.

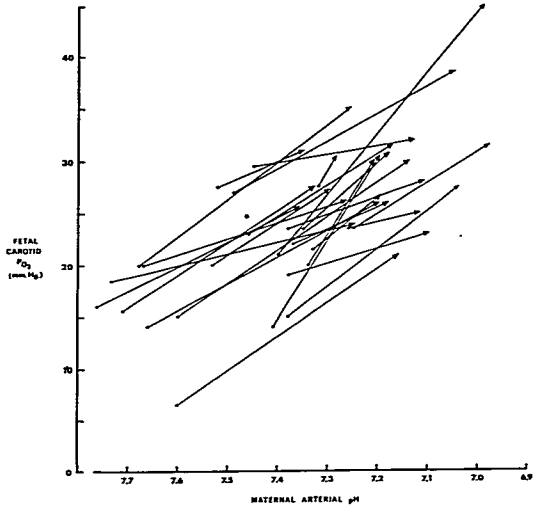

FIG. 3. Effect on fetal carotid P_{O_2} of decreases in maternal arterial *p*H by hypercapnia. Closed circles and triangles indicate values before and during hypercapnia, respectively. See text and table 2.

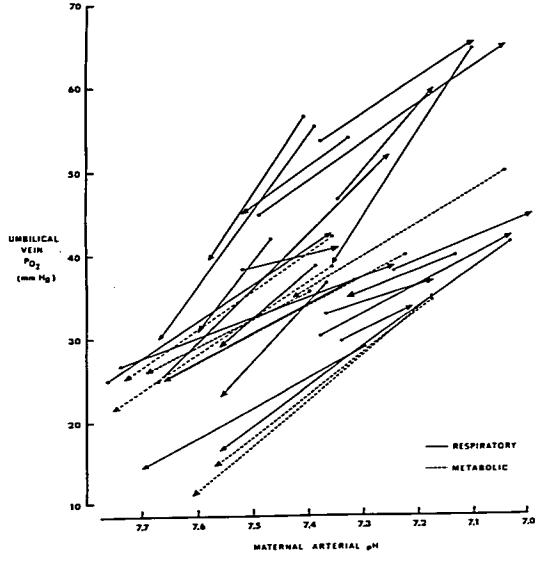

FIG. 4. Effect on umbilical vein P_{O_2} of changes in maternal arterial *p*H. Closed circles and triangles represent values before and during changes in maternal *p*H, respectively. Solid lines indicate *p*H changes produced by respiratory alkalemia or acidemia, and broken lines, by metabolic alkalemia. See text and table 2.

Respiratory acidemia of the ewe resulted in an elevation of umbilical vein P_{O_2} in all instances within a wide range of maternal *p*H studied. There was no end point for the fetal P_{O_2} response within this range. The average change in P_{O_2} (3.4 mm. of mercury/0.1 *p*H unit change in maternal blood) was less ($P < 0.05$) than that observed during both respiratory and metabolic alkalemia. The increase in umbilical vein S_{O_2} during maternal respiratory acidemia was not significant. This was apparently the result of the higher initial P_{O_2} and S_{O_2} in the fetal blood and the shift to the right of the dissociation curve due to respiratory acidemia of the fetus.

(c) *Changes in Umbilical Blood Flow.* The effect on the umbilical arterial blood flow of changes in maternal *p*H is shown in figure 5 and table 2. An increase in maternal *p*H produced by hyperventilation was invariably associated with a decrease in umbilical flow, averaging 7.1 per cent/0.1 *p*H unit change. A similar reduction (average, 5.5 per cent/0.1 *p*H unit change) in flow was also observed during metabolic alkalemia. In addition, placental umbilical vessels appeared constricted during maternal respiratory alkalemia. A decrease in maternal *p*H with hypercapnia produced an increase in umbilical flow (average, 7.9 per cent/0.1 *p*H unit change). There was no significant difference ($P > 0.20$) in the magnitude of the changes in flow during maternal respiratory and metabolic alkalemia and respiratory acidemia.

The decrease in oxygen supply to the fetus during maternal alkalemia was calculated from the average changes in umbilical blood flow and oxygen content of the umbilical vein blood. A 0.1 *p*H unit increase in maternal arterial blood resulted in a decrease of more than 10 per cent in oxygen supply to the fetus with respiratory alkalemia and a decrease of more than 15 per cent with metabolic alkalemia.

(d) *Mechanical Effect of Hyperventilation Per Se.* Hyperventilation without hypocapnia produced, in all four experiments, no significant changes in umbilical and fetal carotid P_{O_2} or umbilical blood flow. However, when maternal hypocapnia (average decrease, 30.4 mm. of mercury) and respiratory alkalemia (average increase, 0.33 *p*H unit) were induced without changes in the level of ventilation, a reduction in fetal carotid P_{O_2} (average, 5.4 mm. of mercury), umbilical vein P_{O_2} (average, 10.0 mm. of mercury) and umbilical flow (average, 15.4 per cent) were observed.

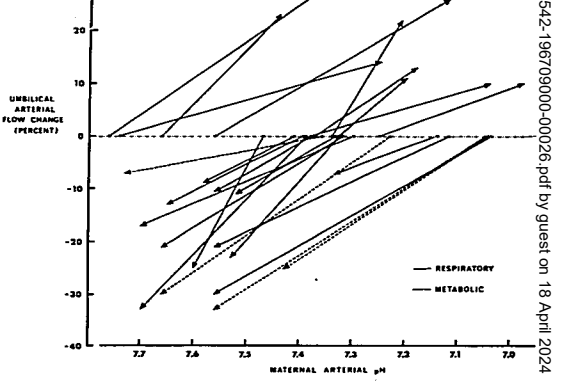

Fig. 5. Effect on blood flow in one umbilical artery of changes in maternal arterial *p*H expressed as per cent change of initial flow. Closed circles and triangles represent values before and during changes in maternal *p*H, respectively. Solid lines indicate *pH* changes produced by respiratory alkalemia and acidemia, and broken lines, by metabolic alkalemia. See text and table 2.

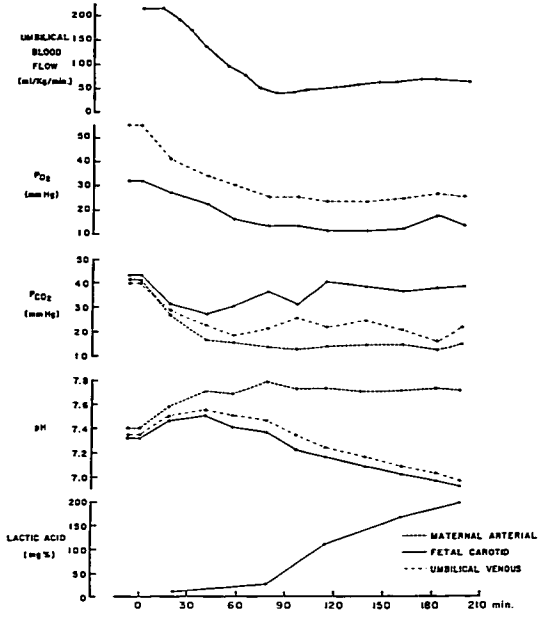

FIG. 6. Effect on the fetal lamb of prolonged maternal hyperventilation. See text.

(e) *Changes in Blood Pressure and Heart Rate.* Although the average changes were small, there was a significant ($P < 0.05$) decrease in maternal and fetal mean arterial blood pressures ($\overline{BP}$) during respiratory alkalemia (98 to 94 and 53 to 50 mm. of mercury, respectively). During metabolic alkalemia there was no significant change in $\overline{BP}$ in the ewe or fetus. There was a slight but significant ($P < 0.05$) increase (97 to 101 mm. of mercury) in maternal $\overline{BP}$ with respiratory acidemia while no significant difference was observed in the fetus. There was no significant average change in maternal and fetal heart rate during these experiments.

(f) *Changes Resulting from Prolonged Maternal Hyperventilation.* Figure 6 shows the experiment in which the effects on the fetus of prolonged hyperventilation were studied. During maternal alkalemia produced by hyperventilation, there was a progressive decrease in umbilical vein P_{O_2} and umbilical flow which resulted in a significant decrease in fetal carotid P_{O_2}. The fetal carotid P_{CO_2} was decreased initially (respiratory alkalemia) and then gradually returned to, but did not exceed, the control level while the umbilical vein P_{CO_2} remained low. As a result of fetal alkalemia, umbilical vein S_{O_2} did not decrease significantly at first because of the shift to the left of the oxyhemoglobin dissociation curve. However, as hyperventilation and respiratory alkalemia of the mother were continued, the fetus developed severe hypoxia (carotid P_{O_2} 11–13 mm. of mercury), metabolic acidosis ($pH > 7.0$) with lactic acidemia (195 mg. % 100 ml. of blood versus the control value of 19), and signs of distress as evidenced by restlessness, arrhythmias, gasping and the passage of meconium. Throughout this experi-

ment, the maternal Pa_{O_2} was maintained between 167 and 227 mm. of mercury. There was no significant change in the $\overline{BP}$ of the ewe or fetus.

Discussion

The data obtained in the present study are from the anesthetized ewe and its exteriorized fetus. Under these circumstances, the placental circulation may differ from that of the normal pregnant state. However, blood gases and umbilical blood flow appeared unimpaired when the control values were compared to values from unanesthetized, apparently undisturbed pregnant ewes and their fetal lambs reported by Meschia *et al.*[10, 11] Actually the present control values for fetal P_{O_2} are considerably higher than those reported by other authors.[12, 13] This is primarily due to adequate control of maternal ventilation and *p*H rather than to the relatively high maternal P_{O_2} since the latter has been shown to have a limited effect.[14] In previous reports, various combinations of maternal hypoxemia, hyper- and hypoventilation have usually been present and, as indicated by the present data, fetal and placental physiology has undoubtedly been disturbed.

The results of the present experiments show that changes in fetal P_{O_2} correlate positively with changes in maternal Pa_{CO_2} and negatively with changes in maternal arterial *p*H during alterations in maternal respiration regardless of the initial P_{CO_2} and *p*H. The data further indicate that these changes are the combined result of changes in maternal-fetal oxygen transfer within the placenta and changes in fetal-placental blood flow. Since fetal P_{O_2} decreased during maternal metabolic alkalemia regardless of changes in maternal Pa_{CO_2}, it appears that under these circumstances the findings are primarily the result of variations in maternal *p*H rather than Pa_{CO_2} *per se*.

These changes in fetal P_{O_2} associated with alterations in maternal *p*H were not due to the deterioration of the exteriorized fetus since the alteration in fetal P_{O_2} was readily reversible when the maternal *p*H change was reversed. Furthermore, in an earlier report,[9] blood gas tensions, *p*H and lactic acid concentrations in the exteriorized fetal lambs were unchanged for at least 3 to 3½ hours when the maternal respiration was maintained within normal limits. This indicates that the severe fetal asphyxia observed during prolonged maternal hyperventilation was primarily the result of alkalemia of the ewe rather than of deterioration.

Factors Which Influence Fetal P_{O_2} and S_{O_2}

Acute changes in the oxygen supply through the umbilical vein to the fetus may result from variations in the oxygen tension and content of maternal arterial blood [14] and alterations in uterine blood flow, diffusion across the placental membranes, shunting of blood on either the maternal or fetal side of the placenta, or umbilical blood flow. The effect of variations in *p*H on the oxyhemoglobin dissociation curve (the Bohr effect) may also influence fetal P_{O_2} and S_{O_2}. Since, in the present study, maternal Pa_{O_2} was controlled, the findings must be based on other factors. Likewise, the rapidity and reversibility of the changes suggest that an alteration in diffusion across the placental membranes is not an important factor in these experiments.

(1) *The pH Effect on the Oxyhemoglobin Dissociation Curve.* Maternal alkalemia increases the affinity of the maternal blood for oxygen (with the shift to the left of the oxyhemoglobin dissociation curve) and this would decrease the amount of oxygen released at the capillary level from hemoglobin. Oxygen available for the fetus would thus be decreased, unless there was an accompanying reduction in tissue P_{O_2}, and might account for a part of the observed changes in fetal P_{O_2} and S_{O_2}.

In the present study, acute respiratory alkalemia of the ewe was associated with an increase in fetal *p*H due to hypocapnia. The fetal oxyhemoglobin dissociation curve was therefore shifted to the left and thus the decrease in umbilical vein S_{O_2} was limited. On the other hand, metabolic alkalemia of the ewe was associated with a decrease in fetal *p*H and hence the decrease in umbilical vein S_{O_2} was greater than observed with comparable

changes in maternal *p*H due to respiratory alkalemia (cf. table 2).

(2) *Uterine Blood Flow.* Changes in the uterine blood flow alter placental perfusion and, in turn, affect fetal P_{O_2} and S_{O_2}. Uterine blood flow may be influenced indirectly as a result of alternations in maternal cardiac output and directly by the changes in uterine or maternal-placental vascular resistance.

The mechanical effect of different levels of IPPB on maternal hemodynamics or uterine blood flow cannot explain the findings of the present study since maternal hyperventilation without an increase in *p*H did not result in significant changes in fetal P_{O_2}. This conclusion is at variance with that of Morishima *et al.*[15]; the discrepancy appears to be due, at least in part, to the failure of these authors to separate adequately the mechanical effect from that of changes in maternal *p*H. It is possible, however, that an extreme degree of hyperventilation with IPPB may result in a reduction in cardiac output and uterine blood flow.

The influence on uterine blood flow or even cardiac output of hypocapnia or alkalemia is not well established.[16, 17, 18] The study of Andersen and Mouritzen [19] suggests that sodium bicarbonate infusions do not decrease and may indeed increase cardiac output. It therefore seems unlikely that fetal hypoxemia associated with maternal alkalemia results from a reduction of maternal cardiac output. In the present study, changes in maternal cardiac output appear to have been small as judged by blood pressure and heart rate but were not directly measured.

Acute maternal acidemia may be associated with increased cardiac output,[20] but there have been conflicting results reported concerning the effect on the uterine blood flow of maternal hypercapnia.[21, 22] Further studies are needed to see if uterine vascular resistance indeed varies with changes in *p*H during pregnancy.

(3) *Intraplacental Factors.* A change in maternal and/or fetal placental vascular resistance, whether in the larger vessels or at the pre-capillary level, might be associated with varying degrees of shunting. Panigel [23] demonstrated in the human placenta that hypercapnia dilates fetal placental arteries and veins as well as cotyledonary vessels. Bøe [24] has demonstrated, in the villous circulation of the human placenta, that shunts exist which decrease during asphyxia, presumably as a result of acidosis and/or hypoxia; alkalemia might produce the opposite effect. In sheep, intraplacental shunting has also been demonstrated by Metcalfe *et al.*[25] and Campbell *et al.*[13] but without reference to the maternal *p*H as a controlling factor. Additional studies in our laboratory [26] show a direct correlation between maternal arterial *p*H and the maternal arterial-umbilical vein P_{CO_2} gradient and these data support the concept that an increase in maternal *p*H may be associated with an increase in intraplacental shunting. If such changes in shunting do occur, they could account for some of the observed changes in fetal P_{O_2}.

An understanding of the mechanism by which changes in maternal *p*H affect umbilical vein P_{O_2} and umbilical blood flow requires further investigation. Fetal placental vascular resistance may be influenced by variations in maternal placental *p*H per se or by the secondary changes in umbilical blood *p*H. The latter mechanism might explain the effect of respiratory alkalemia and acidemia since parallel changes exist between maternal and fetal *p*H. This mechanism, however, could not explain the effect of maternal metabolic alkalemia because, under these circumstances, fetal *p*H is decreased rather than increased. Thus, factors other than changes in fetal *p*H must be considered. Variations in intraplacental P_{O_2}, in part the result of the Bohr effect, may be one of the factors.

Present studies show that umbilical vein P_{O_2} is more profoundly affected per unit change in *p*H by maternal respiratory alkalemia than by metabolic alkalemia; respiratory acidemia produced an even smaller change. These different responses might be in part due to the different ranges of maternal *p*H for the three types of study. If, however, these findings are secondary to differences in intracellular *p*H of the tissue responsible for changes in vascular resistance and shunting, they would be consistent with the findings of Adler *et al.*[27, 28] and Robin [29] who showed that, in acute ex-

periments, the cell membrane is more resistant to extracellular acidosis than to alkalosis, and that intracellular pH is more readily influenced by extracellular respiratory alkalosis than by metabolic alkalosis. The critical factor affecting fetal P_{O_2} could therefore be the changes in maternal pH alone rather than any combined effect of pH and P_{CO_2}.

Clinical Significance

Transfer of blood gases in the syndesmochorial placenta of sheep may differ from that of the hemo-chorial placenta of humans. The similarities between the present findings in sheep and observations in humans, however, suggest that conclusions based on these experiments may be applicable to pregnant women.

As previously analyzed,[1] the data of Wulf [30] from unanesthetized women and their fetuses delivered vaginally showed a direct correlation between maternal Pa_{CO_2} and umbilical vein P_{O_2}. This correlation existed in spite of the fact that blood samples were taken from the umbilical cords at the time of delivery when fetal blood gas values were undoubtedly influenced by the events of labor and delivery.

Moya *et al.*[3] studied maternal pH and umbilical S_{O_2} in humans at the time of delivery. Using their data plus the nomogram of Hellegers and Schruefer,[31] the values for umbilical vein P_{O_2} were estimated and are shown in table 3. During "mild hyperventilation" (maternal pH $\gtreqless$ 7.60), umbilical vein P_{O_2} was already decreased while S_{O_2} did not change because of the elevation of the fetal pH and the resulting shift to the left of the oxyhemoglobin dissociation curve. When the maternal hyperventilation was more severe (average pH, 7.67), marked hypoxia and acidosis of the fetus was found in both cases in spite of otherwise normal pregnancies and deliveries.

Saling [32, 33] showed in his study of arterialized capillary blood obtained from the scalp of the fetus that inhalation of oxygen by the mother did not significantly increase, and sometimes decreased, the fetal S_{O_2} and was accompanied by fetal acidosis. He suggested that maternal hypoventilation with oxygen administration might be one cause of the observed fetal hypoxia. In some of his cases, however, there was an associated decrease in maternal and fetal P_{CO_2} and, in these cases, fetal hypoxia may best be explained by maternal hyperventilation.

Table 3. The Mean Umbilical Vein pH, So_2 and Po_2* Values Corresponding to Varying Levels of Ventilation in Parturient Women Based on data of Moya *et al.*[3]

Group	I	II	III	IV
N	28	18	12	2
Maternal pH	7.42	7.52	7.60	7.67
Umbilical vein pH	7.29	7.35	7.38	7.10
Umbilical vein So_2	58.3	59.6	58.5	14.5
Umbilical vein Po_2*	27	25	17	9

* Estimated from pH and So_2 using the nomogram of Hellegers and Schruefer.[31]

Respiratory alkalemia induced by hyperventilation occurs relatively commonly in women during parturition as a result of pain, apprehension and anxiety.[34, 35] It is observed with improperly conducted natural childbirth and, in at least one series, progressed to tetany in a significant number of mothers.[36] Hyperventilation is also induced intentionally [37, 38] or unintentionally [3] during anesthesia for delivery. In addition, when fetal distress is suspected, the mother is frequently hyperventilated with oxygen-enriched air in an attempt to increase the oxygen supply to the fetus.

From the clinical point of view, it appears, on the basis of published data from humans and in light of the present data from sheep, that hyperventilation (with alkalemia) with or without supplemental oxygen significantly reduces, rather than improves, the fetal P_{O_2} and S_{O_2} and thus should be avoided. On the other hand, hypercapnia (respiratory acidemia) increases fetal P_{O_2} and S_{O_2} but the application of this information to the clinical situation requires further investigation since any additional effects are unknown.

Summary

The effect on the fetus of changes in maternal P_{CO_2} and pH were studied in 22 ewes and their exteriorized fetuses while maternal P_{O_2} was controlled.

Maternal hyperventilation without changes in P_{CO_2} and pH had no significant effect on fetal carotid P_{O_2}. When maternal hyperventi-

lation was associated with hypocapnia and respiratory alkalemia, there was a consistent decrease in fetal P_{O_2} and S_{O_2}.

Maternal metabolic alkalemia with intravenous sodium bicarbonate infusion invariably resulted in decreased fetal P_{O_2} and S_{O_2} irrespective of changes in P_{CO_2} indicating that, under these circumstances, maternal *p*H, rather than P_{CO_2}, was the principal factor influencing fetal P_{O_2}.

Maternal hypercapnia and respiratory acidemia were associated with a significant increase in fatal P_{O_2} and S_{O_2}.

The data furthermore indicated that the changes in fetal P_{O_2} were produced by variations in both oxygen transfer within the placenta and umbilical blood flow.

In all short-term studies, these changes were readily reversible.

Prolonged maternal hyperventilation associated with alkalemia resulted in severe fetal hypoxia, metabolic acidosis and fetal distress.

It is postulated that the changes in fetal P_{O_2} associated with variations in maternal *p*H are primarily the result of alterations in the placental vascular resistance and intraplacental shunting. The Bohr effect on the transfer of oxygen from maternal to fetal blood is an additional factor.

Data from parturient women and their fetuses indicate that there is a similar relationship between maternal *p*H and fetal P_{O_2} and that this is of clinical importance.

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Drugs

CNS AND RELAXANTS The effects of *d*-tubocurarine and decamethonium on the central nervous system were studied in cats. Effects at the spinal and supraspinal levels independent of the peripheral neuromuscular activities were noted. In general *d*-tubocurarine facilitated somatic reflex responses (knee jerks and others) while decamethonium inhibited these responses. Intrathecal injection and topical application had similar effects. Decamethonium antagonized the central effects of *d*-tubocurarine suggesting a common site of action. The excitatory action of *d*-tubocurarine suggesting a common site of action. The excitatory action of *d*-tubocurarine may be due to inhibition of a cholinergic synapse involved in inhibition of a motor neurone response; *i.e.*, it facilitates by inhibiting an inhibitory response. (*Bhargava, K. P., and Srivastava, R. K.: Effects of d-Tubocurarine and Decamethonium on the Central Integration of Somatic Reflexes, Brit. J. Pharmacol. 28: 328 (Dec.) 1966.*)