ONSET OF RESPIRATION IN THE VENTILATED SHEEP FETUS IN UTERO

by

Dale M. Willis

A THESIS

Presented to the Department of Physiology and the Graduate Division of Oregon Health Sciences University in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE
June 1982

APPROVED:

[redacted]

(Professor in Charge of Thesis)

[redacted]

(Chairman, Graduate Council)

ACKNOWLEDGMENTS

I wish to thank Dr. J. Job Faber, Dr. Kent L. Thornburg, Dr. Debra F. Anderson, and Mr. Thomas Jefferson Green for their advice, assistance, and encouragement.

I am also grateful to the Steinberg Scholarship Committee and the Tartar Trust Fellowship Committee for the monetary support given for my graduate work.

AN ABSTRACT OF THE THESIS OF

Dale M. Willis for the Master of Science Degree in Physiology. Date of receiving this degree: June 1982. Title: Onset of Respiration in the Ventilated Sheep Fetus In Utero. Approved:

Surgery was performed on pregnant ewes and their fetuses at 135 days gestation. Term is 151 days. Fetal tracheal, brachial artery, jugular vein, and amniotic fluid catheters were placed. An inflatable occluder was tied around the umbilical cord. Four days after surgery the lungs were gradually expanded by positive pressure ventilation.

A fetal response of respiratory movement or apnea was recorded immediately after ten minutes of ventilation with varying mixtures of O_2, CO_2, and N_2 in unanesthetized fetus in utero. This protocol was repeated while umbilical blood flow was occluded.

Despite lung expansion and variations in $P_{a_{O_2}}$ between 10 mm Hg and 70 mm Hg and $P_{a_{CO_2}}$ between 35 mm Hg and 95 mm

Hg continuous respiration was not initiated, although intermittent respiration was often seen. This was still true during cord occlusion.

All fetuses delivered by caesarean section after the experiment initiated continuous respiration at arterial P_{O_2}'s and P_{CO_2}'s well within the ranges observed during in utero ventilation. We therefore conclude that occlusion of the cord and expansion of the lung are insufficient stimuli to initiate continuous respiration at birth.

TABLE OF CONTENTS

INTRODUCTION

Many physiological changes occur in the fetus at birth. Changes in circulatory pattern (e.g. loss of foramen ovale flow and an increase in pulmonary blood flow), loss of placental exchange of wastes and nutrients, and loss of the hospitable intrauterine environment all accompany the transition by which the fetus becomes a more independently functioning organism. The dramatic nature of birth is nowhere more evident than in the transition from the placenta to the lung as the functional organ of gas exchange. This transition includes a decrease in pulmonary vascular resistance upon inflation of the lung, a concomitant large increase in pulmonary blood flow and the onset of regular cyclical breathing characteristic of postnatal life. The mechanisms responsible for the transition from prenatal intermittent breathing movements to the regular postnatal pattern are unknown.

During birth numerous stimuli act upon the fetus. Chemical stimuli (hypoxia, hypercapnia, acidosis) and non-chemical stimuli (proprioception, cold, pain, light, lung inflation) all have been suggested as contributors to the "awakening" of the fetus which accompanies the onset of continuous respiration (Dawes, 1968; Harned, 1970). This change from the intermittent breathing movements of the fetus to continuous regular respiration occurs despite changes from "hypoxic" fetal arterial blood oxygen tensions (approximately 25 mm Hg) to the much higher

arterial oxygen tensions that are typical of the neonate (approximately 70 mm Hg) (Dawes, 1972; Boddy, 1974).

Non-chemical stimuli as potential initiators of breathing have received little investigative attention in recent years. Tactile and painful stimuli initiate respiratory responses in the sheep and rabbit (Dawes, 1959; Moss, 1979). However, sustained respiratory movements in response to these stimuli have not been elicited without alteration of blood gas tensions (Harned, 1964; Moss, 1979). This has led most investigators to doubt a major role for non-chemical stimuli in initiating the onset of respiration at birth.

Many investigators have focused on the arterial blood gas tensions and pH as possible initiators of newborn respiration. The fetus is, however, largely unresponsive to chemical stimuli that would cause respiratory responses in the adult or newborn. For example, with an arterial P_{O_2} around 25 mm Hg and an arterial P_{CO_2} of approximately 45 mm Hg, the sheep fetus makes breathing movements only intermittently (Dawes, 1972; Boddy, 1974). Whereas in a newborn lamb, an arterial P_{O_2} of 25 mm Hg would elicit gasping or rapid breathing until a more normal newborn arterial P_{O_2} of approximately 60 mm Hg was reached. The fetal respiratory response to an intravenous injection of cyanide is also diminished or totally absent in comparison to a newborn lamb's response of increased rate and depth of respiration following such an injection (Reynolds,

1961; Biscoe, 1969). If chemical stimuli are, indeed, important initiators of breathing, a change in fetal sensitivity to these stimuli must occur at birth. A brief summary of published work on the subject of fetal breathing movements and the onset of respiration at birth follows.

FETAL BREATHING MOVEMENTS

With normal fetal arterial blood gas tensions and pH ($P_{a_{O_2}}$ = 22 mm Hg, $P_{a_{CO_2}}$ = 47.5 mm Hg, pH = 7.32 (control values, Dawes, 1972))the sheep fetus displays respiratory movements only 40% of the time in the last third of gestation (Dawes, 1972). These respiratory movements have been divided into two kinds of regular deflections recorded from tracheal catheters. Small regular deflections from approximately 0.5 Hz to 3 Hz, breathing, and less rapid, but deeper, tracheal deflections at less than 0.3 Hz. These less rapid deflections have been divided into two categories, augmented breaths, when occuring with the more rapid breathing, and gasping, when occuring by themselves (Bystrzycka, 1975; Patrick, 1976; Kendall, 1977). Spontaneous fetal breathing has been found to be associated with low voltage EEG, and maternal feeding but not with spontaneous variations in fetal arterial P_{O_2}, P_{CO_2} or pH, provided they remain within the normal limits of the uncompromised fetus (Dawes, 1972). Gasping has been correlated with compromises in fetal blood gas tensions and fetal well being (Harned, 1964; Towell, 1974; Patrick, 1976).

Variations in fetal blood gas tensions induced experimentally have been shown to influence the frequency of fetal breathing movements. For example, breathing movements become minimal when the fetus is made more hypoxic (Pa_{O_2} ~ 16 mm Hg) by giving the ewe a 10% O_2 gas mixture to breathe (see Figure 1) and are increased by hypercapnic arterial blood (Pa_{CO_2} above 50 mm Hg) even when arterial PO_2's are normal (see Figure 2) (Boddy, 1974). Severe hypoxic changes caused by cord compression in acutely and chronically prepared fetuses have been shown to initiate gasping when arterial PO_2's fall below 10 mm Hg (Harned, 1964; Towell, 1974). This initiation of gasping has preceded the onset of regular respiration in exteriorized fetuses. Because of the relationship between gasping and the onset of breathing at birth, considerable investigative interest has centered on the interaction of hypoxic gas tensions and cord occlusion as initiative factors of fetal breathing.

Because the intermittent nature of fetal breathing movements has raised questions about their chemical control, experiments on peripheral and central reactivity of the fetus to various chemical stimuli have been performed. However, many of these experiments were conducted on anesthetized fetuses, which are known to have a depressed response to respiratory stimuli (Dawes, 1972). Nevertheless, several studies point to a generally unresponsive carotid chemoreflex

in the fetus which increases in activity with cord occlusion but not with intravenous injection of sodium cyanide (Reynolds, 1961; Biscoe, 1969).

The seemingly depressed response of the carotid body *in utero* may be partially overcome by injection of 3 mg/kg naloxone, a dose 300 times greater than the antiopiate dose of 0.01 mg/kg (Harper, 1974; Moss, 1979). Stimulation of intact cervical sympathetic nerves also increases carotid chemoreceptor activity (Biscoe, 1969). This increase in cervical sympathetic postganglionic traffic has been demonstrated to occur with cord occlusion and may be important in assisting the change in respiratory control at birth (Biscoe, 1969).

Vagal afferent activity in the fetus includes the Hering-Breuer Reflex, a reflex inhibition of inspiration or expiration resulting from stimulation of pressor receptors by deflation or inflation of the lung, and Head's Paradoxical reflex, a reflex inspiratory movement resulting from stimulation of pressoreceptors on inflation of the lung (Widdicombe, 1964; Ponte, 1973). This vagal afferent activity may be increased by cord occlusion and could be an important mechanism causing lung inflation at birth (Ponte, 1973).

Dawes performed brain sections on fetal lambs at the pontine level which caused continuous fetal breathing movements (Dawes, 1980). This suggests that the lack of

continuous movements in utero is due to suprapontine inhibition. One reason proposed for this higher inhibition in the fetus is a "diving reflex" which operates while the fetus is submerged in amniotic fluid (Tchobroutsky, 1969; Harned, 1970). Despite a tracheostomy providing access to air, unanesthetized fetuses do not initiate respiration with occluded umbilical cords when their heads are immersed in water (Tchobroutsky, 1969; Harned, 1970; Johnson, 1973). However, when the head is immersed in normal saline or amniotic fluid a gasping response occurred after cord occlusion in fetal sheep or goats (Towell, 1974; Johnson, 1973). This gasping response progressed to normal newborn respiration in the fetal sheep whose tracheal catheters were exposed to air (Johnson, 1973).

Evidently, the newborn lamb has overcome these fetal inhibitions, if they exist, and maintains regular respiration at O_2 tensions well above previous fetal levels. The carotid chemoreceptor in the newborn does show a dampened response compared to the response of the adult animal. Hypoxia produces an initial increase in ventilation and then a depression in both newborn rabbits and human neonates (Dawes, 1959; Belenky, 1979). Also, the increased ventilatory response to hypoxia is of smaller magnitude on the first day of life in the lamb than the response of older neonates (Belenky, 1979). The full maturation of the response to hypoxia takes at least the

first two weeks after birth in neonates born at term (Wyszogrodski, 1978; Belenky, 1979).

The large differences in respiratory movements between the fetus and the neonate lead one to hypothesize that a mechanism is activated at birth that initiates a change in respiratory control. Reflexes present in the fetus may help explain this onset of respiration. Gasping in response to hypoxia and vagal reflexes augmenting inspiration at birth may be important in initiating lung inflation. Lung inflation has been proposed as a factor important in the change in chemical control at birth (Chernick, 1976).

ONSET OF RESPIRATION

The mechanism which initiates respiration is a mystery. Many different fetal preparations have been used to study the mechanism. Because these preparations have altered the birth process from its normal course, it is necessary to define when birth has taken place, i.e. when the "fetus" becomes a "lamb." For convenience, I will define a fetus as a lamb once the umbilical cord is severed and the lamb has initiated regular spontaneous respirations.

Harned (1964) studied the effect of arterial blood gas tensions in exteriorized fetal sheep by forcing ewes to breathe various mixtures of oxygen, carbon dioxide and nitrogen. Harned could not produce fetal gasping at fetal arterial Po_2's

as low as 10 mm Hg or arterial P_{CO_2}'s as high as 50 mm Hg. Forcing the ewe to breathe 100% O_2 increased fetal arterial P_{O_2} to as high as 32 mm Hg but did not result in regular respiration either. Cord occlusion did provoke gasping in the fetus when arterial P_{O_2}'s had fallen below 9 mm Hg. Harned also noted that while forcing a ewe to breathe gases high in CO_2 and low in O_2 severe spasm of the umbilical cord occurred. He proposed this deterioration of umbilical blood flow as a limitation of acute studies on fetal blood gas tensions (Harned, 1964). This deterioration of umbilical blood flow may result from impairment of placental perfusion over time due to placental exposure during the acute experiment[1] (Harned, 1964).

Avery and Chernick (1965) infused into the carotid artery of a fetal lamb and two fetal guinea pigs boluses of blood with varying gas tensions. Blood with a CO_2 tension of 460 mm Hg brought the peripheral P_{aCO_2} to 77 mm Hg and caused gasping in these animals (Avery, Chernick, 1965). Interpretations from this study should be guarded because of its acute nature and the limited number of guinea pigs (2) and ewes (1) studied.

Herrington and Harned (1971) pursued the relationship between the peripheral and central chemoreceptors and the onset of breathing with further studies on anesthetized sheep fetuses. Using mock operated fetuses and fetuses with

---

[1]"Acute experiment" is used to denote an experiment performed within a few hours of surgery on an exteriorized fetus.

sectioned carotid sinus nerves and/or cervical vagi they recorded the response to cord occlusion at birth. All fetuses began breathing within 15 seconds of cord occlusion. Those with sectioned carotid sinus nerves alone breathed like the mock operated controls. The fetuses with bilaterally sectioned vagi maintained respiration at a decreased rate as did the fetuses with carotid sinus nerves and vagi sectioned (Herrington, 1971). This may be the same response of decreased rate and increased depth of respiration as seen in the adult with bilaterally sectioned vagi. However, tidal volumes were not measured in this experiment. All fetuses responded with hyperventilation when given hypercarbic gas mixtures (Herrington, 1971). Jansen confirmed Herrington's findings from fetuses with sectioned carotid sinus nerves by bilaterally sectioning the sinus nerves in sheep fetuses and allowing them to undergo a normal delivery. Like Herrington's fetuses, Jansen's were all born alive, breathed, and the lambs showed no carotid nerve activity when later tested (Jansen, 1981).

Pagtakhen, Fariday and Chernick (1971) cross circulated fetuses with clamped cords with blood from ventilated newborn lambs in order to study the interaction of arterial P_{O_2} and P_{CO_2} in the initiation of gasping. They demonstrated that no respiration is initiated, breathing or gasping, in acutely anesthetized fetuses with occluded umbilical

circulation if "normal" blood gas tensions are maintained. They found a linear relationship between the arterial P_{O_2} and P_{CO_2} at the time of the first gasp (Pagtakhan, 1971). Their use of pentobarbital anesthesia and the low pH of their preparation ($\bar{x}$= 7.23; range 6.7 - 7.4), however, put into question any quantitative interpretations one may wish to derive from their experiment.

Woodrum (1972) performed similar experiments in partially exteriorized fetuses under local anesthesia. He found that by injecting tonometered blood into the carotid artery proximal to the carotid sinus gasping was initiated 9 seconds after decreasing arterial blood P_{O_2} by 10 mm Hg or 29 seconds after increasing arterial P_{CO_2} by 26 mm Hg. Time of onset and duration of respiratory response did not depend on the rate of infusion of hypoxic or hypercapnic blood (Woodrum, 1972). The use of exteriorized fetuses recently operated on, as well as the low mean control pH (7.27) of the fetal arterial blood justifies caution in interpretation of their results.

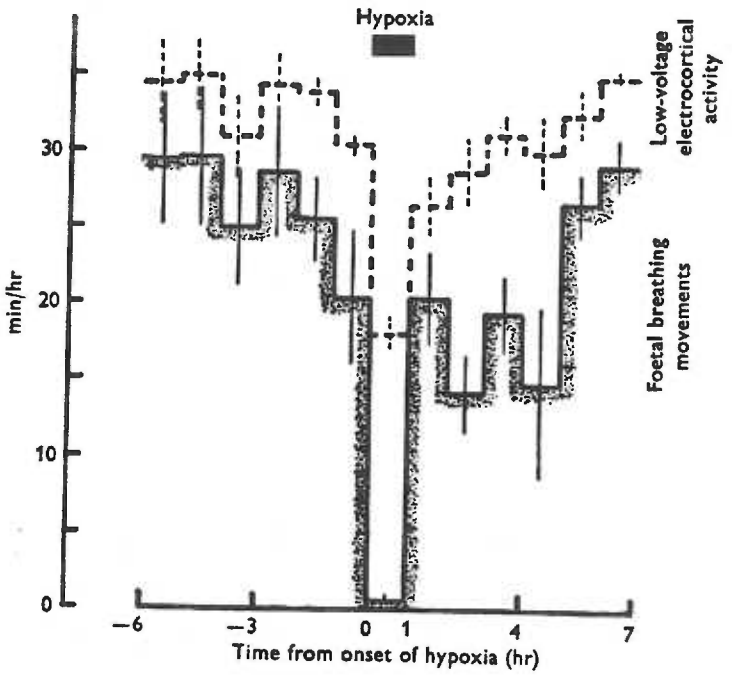
Chernick (1975) performed further experiments on cross circulation preparations of anesthetized fetal and newborn lambs. Fetuses with intact chemoreceptors showed a linear relationship between arterial P_{O_2} and P_{CO_2} at the time of the first gasp. In fetuses with bilateral carotid sinus denervation and in fetuses with both carotid nerves and

cervical vagi sectioned, the onset of respiration depended only on arterial P_{O_2}. From these experiments Chernick inferred that gasping is a central response to hypoxia. No mention was made of the type of respiration established after the onset of gasping. The mean fetal arterial pH was also well below the normal range at the time of exteriorization (7.26) and after denervation had fallen to 7.15 (Chernick, 1975).

From examinations of these experiments on onset of respiration one can devise an experiment that circumvents some of their limitations as well as tests some of the hypotheses on initiation of respiration at birth. First, a chronically prepared fetus allows not only experimentation in the unanesthetized state, but also guarantees a normal blood pH. Second, a chronically prepared fetus allows an experiment to be performed in utero so any effect of exteriorization of the fetus is eliminated. Third, ventilation in utero tests the importance of lung inflation as an isolated factor in initiating the change from fetal to newborn responses to various gas tensions. Fourth, one can change blood tensions over a much wider range than is possible by administration of abnormal gas mixtures to the ewe. Fifth, occlusion of umbilical blood flow tests the importance of maternal-fetal or placental-fetal connections in the onset of respiration. Sixth, lung inflation and umbilical cord occlusion lets one

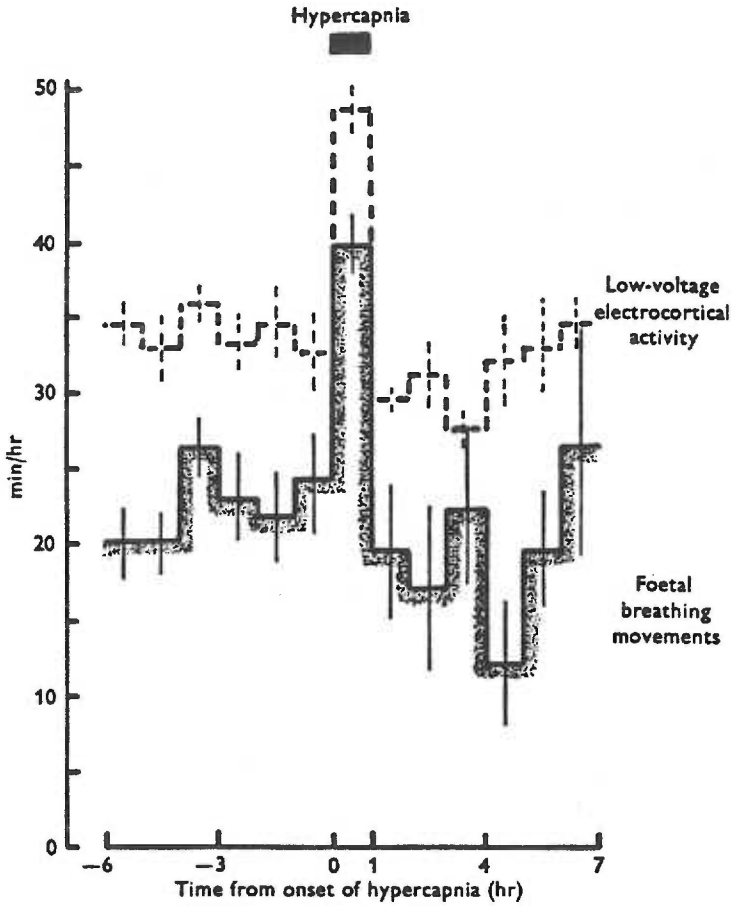
test the importance of the change from fetal to neonatal circulatory patterns in the response of the fetus to chemical stimuli. These parameters were all tested in this study on chronically prepared fetal lambs.

Figure 1. The variation of fetal breathing movements with hypoxia. From Boddy, K., Dawes, G.S., Fisher, R., Pinter, S., and Robinson, J.S. Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxaemia and hypercapnia in sheep. J. Physiol., 1974. 243, 599-618.



The min/hr of foetal breathing movements (▒) and low voltage electrocortical activity (– – –) in five experiments on three lambs, 119–133 days. Hypoxia (9 % O_2, 3 % CO_2 in N_2) is represented by the solid bar.

Figure 2. The variation of fetal breathing movements with hypercapnia. From Boddy, K., Dawes, G.S., Fisher, R., Pinter, S., & Robinson, J.S. Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxaemia and hypercapnia in sheep. J. Physiol., 1974. 243, 599-618.



The min/hr of foetal breathing movements (▒) and the low voltage electrocortical activity (– –) in eight experiments on seven foetuses, 126–138 days. Hypercapnia is shown as a solid bar.

MATERIALS AND METHODS

ANIMALS:

Pregnant timebred ewes of mixed western breeds and three non-timebred gravid ewes whose fetal gestational age was estimated by x-ray were obtained from the Animal Care Department. Surgery was performed on the ewes and their fetuses at approximately 135 days gestation (term in sheep is 151 days). At a gestational age of 135 days the fetal lungs are sufficiently mature for gas exchange during positive pressure ventilation at low pressures (Faber, unpublished).

SURGICAL PREPARATION OF SHEEP:

The sheep were taken off food for one day. They were anesthetized with a NO_2, O_2 and halothane mixture. This ensured proper anesthesia for the fetuses also. The ewes were placed in a supine position and the abdomen scrubbed with Betadine surgical scrub soap and shaved. They were then prepped and draped for sterile surgery.

An abdominal incision was made to expose the gravid uterus. The number of fetuses and their positions were determined. A fetal head was exposed by a uterine incision and delivered from the uterus. A midline neck incision was made, the trachea isolated and a slit made between two tracheal rings. A large bore double lumen catheter was inserted proximally into the trachea and tied in

place. A jugular vein was catheterized with a polyvinyl catheter (I.D. = 0.86 mm, O.D. = 1.32 mm). The skin was closed and a large bore catheter was anchored to the skin for later access to the amniotic fluid.

A forelimb was removed from the uterus for insertion of a brachial artery catheter. This catheter was used during the experiment for obtaining blood for blood gas determinations. The other forelimb was then removed from the uterus and the fetus was pulled out until the umbilical cord was exposed. An inflatable occluder was quickly tied around the umbilical cord, near the body wall, in such a manner that umbilical circulation was not compromised. The fetus was reinserted into the uterus and the lost amniotic fluid replaced by sterile saline to help expand the uterus. The uterus was closed with a purse string suture. In some fetuses an additional small incision was made in the uterus for placement of a lower limb venous catheter for microsphere injection (see Figure 3).

The peritoneum was closed and one million units of penicillin flushed through the amniotic catheter. The tracheal and amniotic catheters were connected so normal outflow of tracheal fluid into the amniotic fluid cavity would not be obstructed. The vascular catheters were flushed with heparinized saline, and a knot was tied in their ends. All catheters were run subcutaneously to

the flank of the ewe where they exited into a nylon pouch sutured to the ewe's side. The maternal skin was closed with wound clips and anesthesia discontinued.

MICROSPHERES:

Fifteen micron plastic microspheres labelled with Ce-141, Cr-51, Nb-95 or Sr-85 were used in three preparations to confirm umbilical occlusion. Microspheres were purchased from the 3M Company.

PROCESSING OF SAMPLES:

Blood for blood gas analysis was obtained from a brachial artery following withdrawal of a 3 ml volume to clear the dead space of the catheter. A Radiometer BMS 3 MK2 blood microsystem was used to determine the pH, P_{O_2} and P_{CO_2} on a 0.7 ml sample of anaerobically drawn blood.

Microsphere counts were determined in fetus and placenta by ashing the fetus and uterus and counting three representative samples from each in a Nuclear Data Model ND 600/660 multichannel analyzer with a Packard Instruments Company sample changer. Fetal and placental counts were compared to verify the completeness of umbilical occlusion.

EXPERIMENTAL PROTOCOL:

Three to seven days postoperatively (mean = 4 days) an experiment was performed on the unanesthetized fetus

in utero. Catheters were opened under sterile conditions and connected to pressure gauges and a calibrated polygraph. An arterial blood sample was taken for reference gas tension analysis from the fetal brachial artery.

After a second reference arterial blood gas tension had been taken the tracheal catheter was drained, connected to a Harvard respirator and the lungs were gradually expanded until minute ventilation was approximately 1 liter per minute of room air (20 to 30 ml. stroke volumes at a rate of 40 to 60 per minute) with a positive end expiratory pressure of 10 to 20 cm. water (see Figure 4). After a period of 30 minutes had been allowed for lung expansion, the fetus was ventilated for ten minutes with various mixtures of O_2, N_2 and CO_2. The pump was then stopped during inflation and an arterial blood gas sample was taken. Tracheal pressures were recorded at the time the blood gas sample was taken to detect the presence or absence of breathing. These pressure changes reflect intratracheal pressures since the respirator expiration line valve was shut during inflation.

After the fetal response to various blood gas tensions was determined in the fetus with an intact umbilical circulation, the umbilical occluder was inflated under a constant pressure of 120 mm Hg. Responses at various gas tensions were recorded as before while there was no umbilical circulation. On a few occasions more than one

blood gas sample was taken after a ten minute ventilation period as a check on umbilical occlusion or to obtain low arterial P_{O_2} values without the damage to the fetus that a ten minute hypoxic period would cause. The in utero positive pressure ventilation insured the survival of the fetus when no placental circulation was present.

In three fetuses radioactive microspheres were injected into the hindlimb venous catheter to verify that inflation of the occluder did indeed cause occlusion of umbilical circulation. In one fetus arterial blood samples were taken during and after injection to determine lower and upper body flows. Placental flow was then calculated before and after inflation of the umbilical occluder. In two fetuses no blood samples were taken to determine blood flows. In these animals the radioactivities of the combined uterine and placental tissue was compared to that of the fetal carcass after inflation of the occluder to verify umbilical occlusion.

Some fetuses were delivered by caesarean section after several hours of experimentation. These fetuses were all born alive, gasped and breathed as newborn lambs. A few blood samples were taken from these animals after birth for blood gas measurements.

Figure 3. Fetal lamb preparation *in utero*.

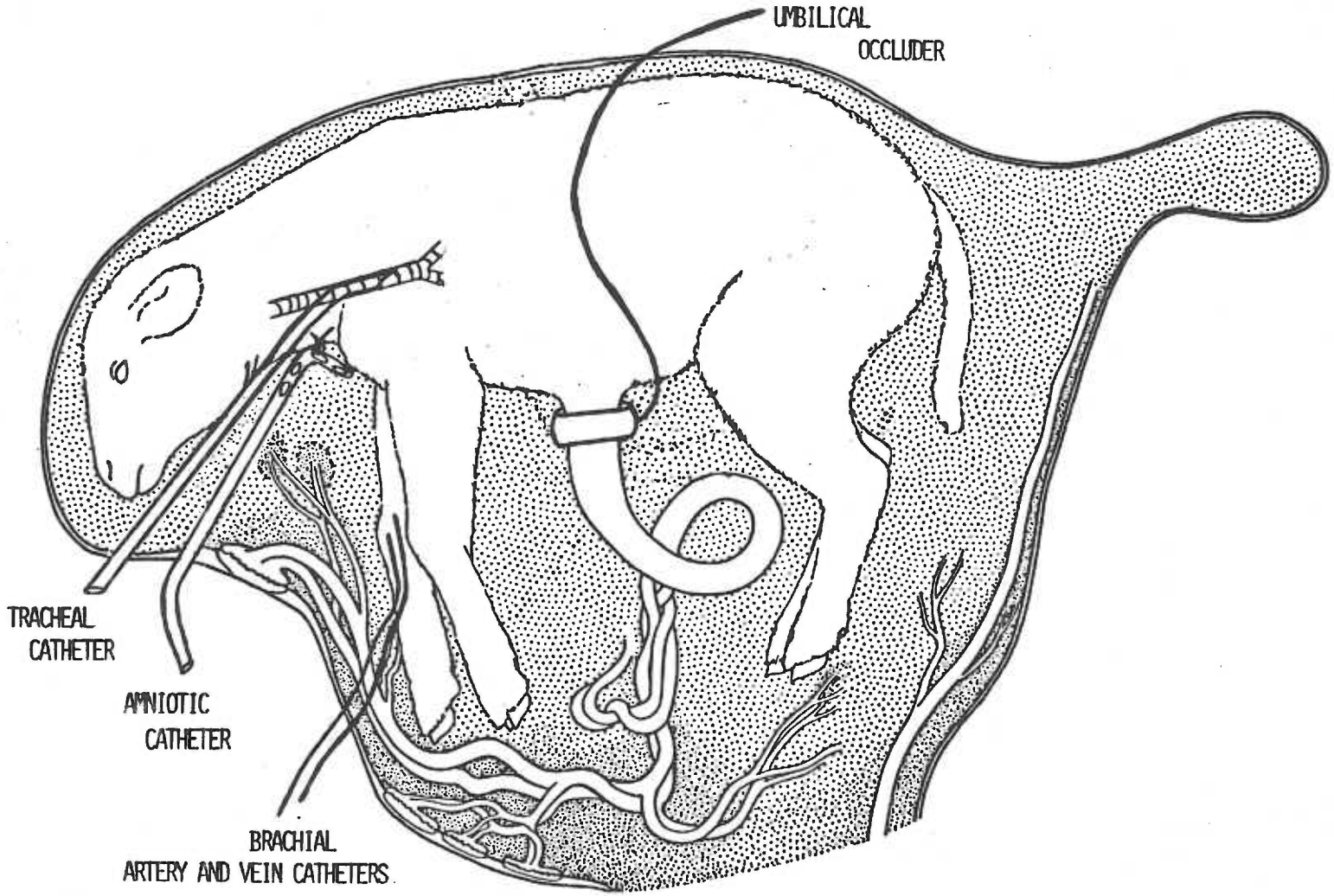
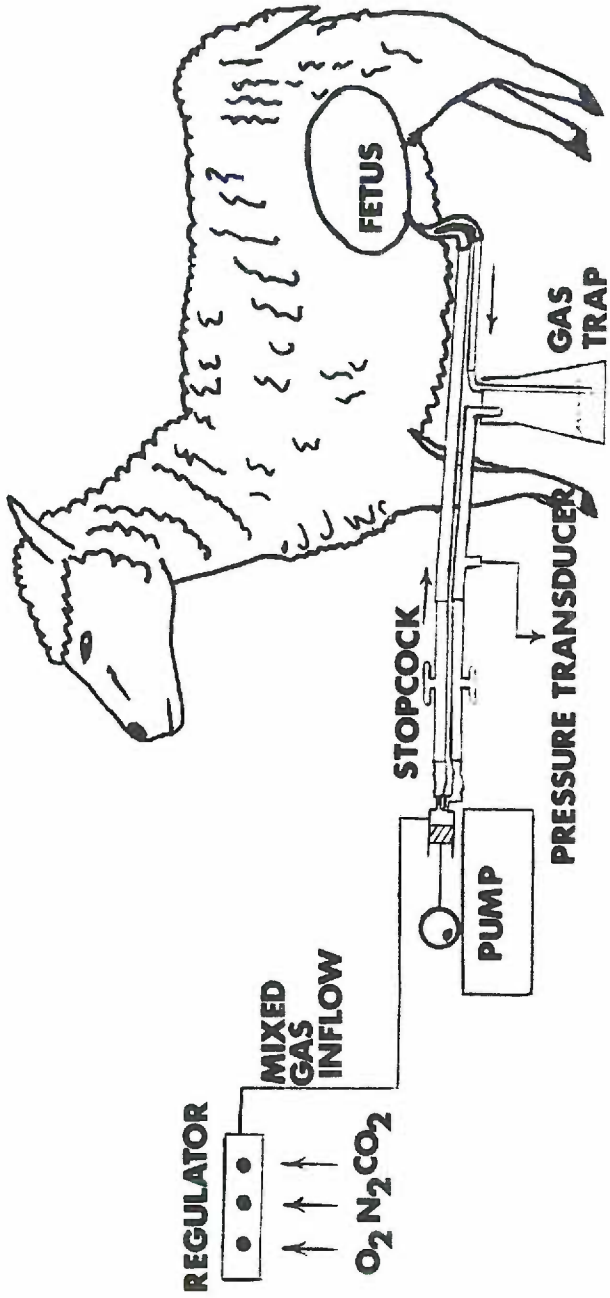

UMBILICAL
OCCLUDER
TRACHEAL
CATHETER
AMNIOTIC
CATHETER
BRACHIAL
ARTERY AND VEIN CATHETERS

Figure 4. Fetal respiratory preparation during the experiment.


FETUS
GAS TRAP
PRESSURE TRANSDUCER
STOPCOCK
PUMP
MIXED GAS INFLOW
REGULATOR
O_2 N_2 CO_2

RESULTS

Eighteen of thirty fetal sheep preparations survived until an experiment was carried out approximately four days after maternal hysterotomy. Of these eighteen fetuses, three were discarded from the study. One was discarded because of extreme acidosis during the control period (pH = 6.9). Two were discarded because of demise during initial lung inflation (experimental error). The fifteen fetuses remaining satisfied the conditions preset for an acceptable fetus. These were an arterial blood pH $\geq$ 7.35, a heart rate < 200, and a recovery period after surgery of at least three days. Little attention was paid to arterial P_{O_2} and P_{CO_2} if the fetuses met the other criteria of normality since blood gas tensions were altered during the experiment and did not remain at control levels.

Of the fifteen fetuses studied *in utero*, eleven showed breathing movements at one time or another after ventilation, Thirteen of the fifteen fetuses were studied before and after umbilical blood flow was occluded. Data on gestational age, weight, days post operation and control blood gases prior to ventilation are included in Table 1.

Each fetus was studied after being ventilated with varying mixtures of O_2, CO_2 and N_2. A composite graph of arterial P_{O_2} vs. arterial P_{CO_2} for all fetuses studied

is shown in Figure 5. Graphs of individual fetuses follow as examples of the range of arterial P_{O_2}'s and P_{CO_2}'s studied in a typical fetus (Figures 6, 7, and 8).

For each point shown in Figure 5, a polygraph recording of tracheal pressure was taken to determine the presence or absence of respiratory movement during the time the respirator was stopped in inflation. A downward deflection on the tracheal polygraph record greater than 3 mm Hg that was easily distinguishable from noise seen in the amniotic fluid pressure record was defined as respiratory movement (Figures 9, 10, and 11). Any recording of tracheal pressure that left in question the presence or absence of respiratory movement was discarded from the study. These distinctions were made for fetuses with unoccluded umbilical blood flow and with occluded umbilical blood flow.

A graph of those points with respiratory movement and apnea at various arterial P_{O_2}'s and P_{CO_2}'s in fetuses with intact umbilical blood flow is shown in Figure 12. As a consequence of the effectiveness of placental exchange, only a few points were obtained at arterial P_{CO_2}'s above 95 mm Hg in fetuses with unoccluded umbilical circulation. For statistical comparisons, therefore, only those data points of arterial P_{CO_2}'s between 35 mm Hg and 95 mm Hg were considered. The range of arterial P_{O_2}'s considered for statistical comparisons was limited to 10 mm Hg to 70 mm Hg since few points were

recorded outside this range in fetuses with unoccluded umbilical blood flow.

Figure 12 is divided into quadrants to test the effect of blood gas tensions on respiratory movement in the ventilated fetus. Quadrant B with increased arterial P_{O_2} and increased arterial P_{CO_2} shows a significantly increased percentage of breathing points ($p < 0.005$) when compared to Figure 12 as a whole by chi-square test (Table 2).

The same range of gas tensions was graphed for those fetuses with occluded umbilical blood flow (Figure 13). Division into quadrants showed no statistical differences in the incidence of respiratory movement due to changes in arterial P_{O_2} or arterial P_{CO_2} (Table 3). When a larger range was considered, arterial P_{CO_2}'s between 35 mm Hg and 155 mm Hg and P_{O_2}'s between 10 mm Hg and 80 mm Hg, there was still no statistical difference seen in the incidence of breathing due to changes in blood gas tensions (Figure 14 and Table 4).

Ratios of placental to carcass radioactivity demonstrated the presence of occlusion in three fetuses injected with radioactive microspheres (Table 5). Fetuses not injected with microspheres showed transient increases in arterial and venous pressures when the umbilical cord occluder was inflated and a rise in arterial P_{CO_2} when the respirator was stopped after occlusion. These were the

same responses seen in the fetuses whose occlusion was demonstrated by radioactive microsphere injection (Figure 15).

A chi-square test was used to compare the incidence of respiratory movement in fetuses with intact umbilical blood flow to the incidence in fetuses with occluded umbilical blood flow for arterial P_{O_2}'s between 10 mm Hg and 70 mm Hg and arterial P_{CO_2}'s from 35 mm Hg to 95 mm Hg. Fetuses with occluded umbilical flow had a higher incidence of breathing ($p < 0.025$) than expected from a pooled sample of all data points of Figures 12 and 13 (Table 6).

This increased incidence of fetal respiratory movement was not due to a greater occurence of metabolic acidosis in fetuses with occluded umbilical blood flow. An unpaired t-test shows no difference ($p > 0.05$) between the bicarbonate concentrations calculated from arterial blood pH and P_{CO_2} values of fetuses with unoccluded and fetuses with occluded umbilical blood flow (Table 7).

The rates of all respiratory movements were measured in the tracheal pressure recordings. Figure 16 shows that the histogram of the number of occurrences of each respiratory rate plotted against respiratory rate is bimodal. No instances were found of respiratory rates between seventeen and twenty-eight breaths per minute. Therefore, a rate below eighteen was defined as "gasping" and a rate greater than twenty-seven as "breathing."

Gasping was recorded in fetuses with unoccluded umbilical blood flow and with occluded umbilical blood flow (Figures 10 and 17). Gasping in fetuses with occluded umbilical blood flow occurred primarily at arterial P_{O_2}'s less than 10 mm Hg. Fetuses with intact umbilical blood flow often gasped at arterial P_{O_2} values well above those thought normal for a fetus. No fetuses with intact umbilical circulations had arterial P_{O_2}'s less than 10 mm Hg, and a comparison with the fetuses with occluded umbilical blood flow is thus impossible in this range of P_{O_2}.

For those fetuses with occluded umbilical circulation, a comparison of the incidences of gasping and respiratory movement at arterial P_{O_2}'s above and below 10 mm Hg was possible. The incidence of respiratory movement in fetuses with occluded umbilical blood flow at arterial P_{O_2} levels less than 10 mm Hg was not different ($p > 0.07$) from the incidence of respiratory movement of fetuses with arterial P_{O_2} levels between 10 mm Hg and 80 mm Hg when compared over arterial P_{CO_2} levels between 35 mm Hg and 155 mm Hg (Table 8). The incidence of gasping was, however, increased ($p < 0.0005$) in the fetuses with arterial P_{O_2}'s less than 10 mm Hg (Table 9).

Figure 18 shows arterial P_{O_2} and P_{CO_2} values for newborn lambs in our laboratory. These lambs were either newborn instrumented lambs, a few minutes to five hours after birth,

or lambs delivered by caesarian section after the experiment. All these newborns were breathing or gasping in a continuous manner to sustain their own blood gas tensions. In some instances CO_2 or O_2 was blown by their nose or tracheal catheter to achieve altered gas tensions.

TABLE 1 -- CONTROL VALUES

Sheep #	Gestational age at experiment	Days post operation	Wt. at necropsy (Kg)	pH	Arterial Blood P_{CO_2} (mm Hg)	Arterial Blood P_{O_2} (mm Hg)
79-114	131	4	4.115	7.413	45.9	19.7
79-123	137	5	4.224	7.408	43.0	24.5
79-127	134	4	3.530	7.412	46.6	23.6
80-11	139	3	5.550	7.415	42.8	17.5
80-15	139	4	3.465	7.440	54.6	15.6
80-19	141	4	4.700	7.362	49.1	14.3
80-20	139	3	4.53	7.391	48.6	21.4
80-27	non time bred	7	3.20	7.38	45.8	18.3
80-34	non time bred	5	4.48	7.401	45.0	15.0
80-102	137	4	4.52	7.402	50.9	21.5
80-104	139	4	5.670	7.379	46.7	15.2
80-108	139	4	5.670	7.387	44.4	12.5
81-011	139	4	3.685	7.376	51.6	15.1
81-013	140	4	3.430	7.418	45.4	20.0
81-24	non time bred	3	4.196	7.349	48.7	12.9
$\bar{x}$	138	4.1	4.24	7.40	47.2	17.8
S.D.	3	1.0	0.73	0.02	3.4	3.8
n	12	15	15	15	15	15

TABLE 2

Nonoccluded Umbilical Blood Flow

Chi-squared test using Yates' correction on the incidence of respiratory movement in fetuses with non-occluded umbilical circulation. Expected values were calculated from pooled data of all quadrants in Figure 12.

quadrant		observed values	expected values	χ^2	p
A	Respiratory movement	3	5.1	0.73	> 0.25
	Apnea	15	12.9		(n.s.)
B	Respiratory movement	11	4.6	10.77	< 0.002
	Apnea	5	11.4		
C	Respiratory movement	16	21.1	1.43	> 0.20
	Apnea	58	52.91		(n.s.)
D	Respiratory movement	8	7.1	0.02	> 0.90
	Apnea	17	17.9		(n.s.)

TABLE 3

Occluded Umbilical Blood Flow

Chi-square test using Yates' correction on the incidence of respiratory movement in fetuses with occluded umbilical circulation. Expected values were calculated from pooled data of all quadrants in Figure 13.

quadrant		observed values	expected values	χ^2	p
A	Respiratory movement	3	3.0		> 0.50
	Apnea	3	3.0	0.17	(n.s.)
B	Respiratory movement	2	1.5	0	> 0.90
	Apnea	1	1.5		(n.s.)
C	Respiratory movement	7	6.5	0	> 0.90
	Apnea	6	6.5		(n.s.)
D	Respiratory movement	10	11.0	0.17	> 0.50
	Apnea	12	11.0		(n.s.)

TABLE 4

Occluded Umbilical Blood Flow

Chi-square comparison using Yates' correction of the incidence of respiratory movement in fetuses with occluded umbilical blood flow at various arterial P_{O_2}'s (0 mm Hg to 80 mm Hg) and P_{CO_2}'s (35 mm Hg to 155 mm Hg). Quadrants from Figure 14 were pooled to calculate expected incidences of respiratory movement and apnea.

quadrant		observed incidence	expected incidence	χ^2	p
E	Respiratory movement	5	6.7	0.51	> 0.40
	Apnea	7	5.3		(n.s.)
F	Respiratory movement	6	3.9	1.44	> 0.20
	Apnea	1	3.1		(n.s.)
G	Respiratory movement	24	25.2	0.051	> 0.75
	Apnea	21	19.8		(n.s.)
H	Respiratory movement	11	10.1	0.036	> 0.75
	Apnea	7	7.9		(n.s.)

TABLE 5

Ratio of Placenta-Uterine Counts/g/min to Fetal Carcass Counts/g/min.

fetus number	umbilical blood flow	ratio of placental counts to fetal carcass counts
79-114	occluded	-0.086
80-15	occluded	0.0023
81-24	unoccluded	0.427
	occluded	0.0168

TABLE 6

Comparison of the incidence of respiratory movement in fetuses with nonoccluded umbilical blood flow (Figure 12) to the incidence of respiratory movement in fetuses with occluded umbilical blood flow (Figure 13). A pooled sample was used to calculate expected values.

		observed values	expected values	χ^2	p
Figure 12	Respiratory movement	38	45.1	1.66	> 0.20
	Apnea	95	87.9		(n.s.)
Figure 13	Respiratory movement	22	14.9	4.54	< 0.05
	Apnea	22	29.1		

TABLE 7

Comparison of calculated bicarbonate concentrations of all arterial blood gas determinations from fetuses with unoccluded umbilical blood flow to fetuses with occluded umbilical blood flow.

Calculated HCO_3^- from points on Figure 12

(unoccluded umbilical blood flow)

$\bar{x}$	S.D.	n
26.2	2.7	133

Calculated HCO_3^- from points on Figure 13

(occluded umbilical blood flow)

$\bar{x}$	S.D.	n
24.9	4.3	44

Unpaired t test of values

$t=2.29$ $p>0.20$ (n.s.)

TABLE 8

Chi-square comparison using Yates' correction of the incidence of respiratory movement in fetuses with arterial P_{O_2} levels less than 10 mm Hg and fetuses with arterial P_{O_2} levels between 10 mm Hg and 80 mm Hg. All fetuses had occluded umbilical blood flow and arterial P_{CO_2} levels between 35 mm Hg and 155 mm Hg. A pooled sample of all fetuses with occluded umbilical blood flow was used to calculate the expected incidences of respiratory movements and apnea.

Fetal arterial P_{O_2} levels between 10 mm Hg and 80 mm Hg.

	Observed Values	Expected Values	χ^2	p
Respiratory movement	33	37.0	0.764	> 0.25
Apnea	33	30.0		(n.s.)

Fetal arterial P_{O_2} levels less than 10 mm Hg.

	Observed Values	Expected Values	χ^2	p
Respiratory movement	13	9.0	3.15	> 0.07
Apnea	3	7.0		(n.s.)

TABLE 9

Chi-square comparison using Yates' correction of the incidence of gasping in fetuses with arterial P_{O_2} levels less than 10 mm Hg and fetuses with arterial P_{O_2} levels between 10 mm Hg and 80 mm Hg. All fetuses had occluded umbilical blood flow and arterial P_{CO_2} levels between 35 mm Hg and 55 mm Hg. A pooled sample of all fetuses with occluded umbilical blood flow was used to calculate the expected incidences of gasping and nongasping (breathing or apnea).

Fetal arterial P_{O_2} levels between 10 mm Hg and 80 mm Hg.

	Observed Values	Expected Values	χ^2	p
gasping	3	12.9	20.18	< 0.0005
nongasping	79	53.1		

Fetal arterial P_{O_2} levels less than 10 mm Hg.

	Observed Values	Expected Values	χ^2	p
gasping	11	3.1	21.7	< 0.0005
nongasping	5	12.9		

Figure 5. Graph of all arterial blood gas tensions obtained in ventilated fetuses before and during umbilical cord occlusion. The abscissa, P_{aCO_2}, begins at 35 mm Hg.

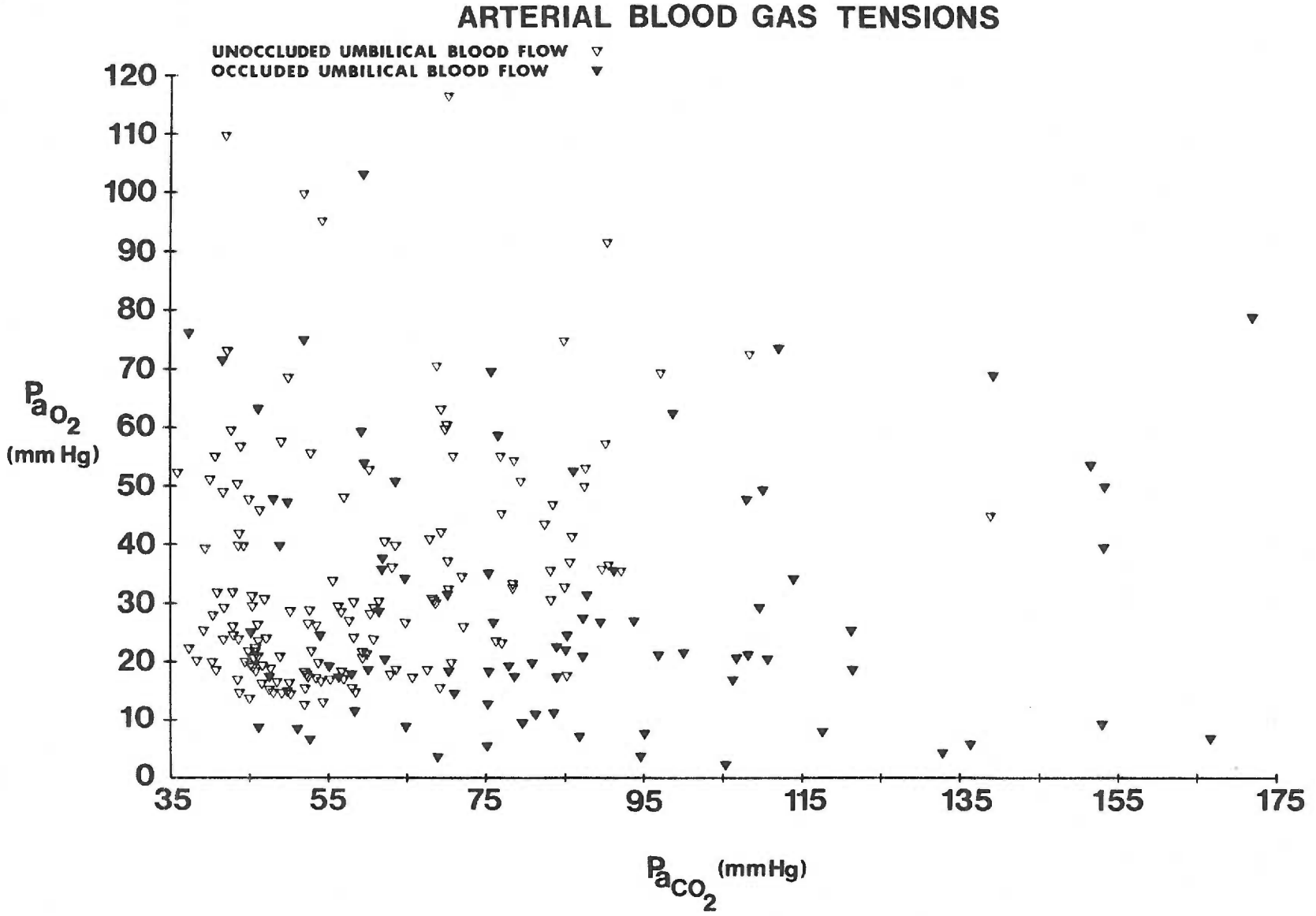

ARTERIAL BLOOD GAS TENSIONS
UNOCCLUDED UMBILICAL BLOOD FLOW
OCCLUDED UMBILICAL BLOOD FLOW
120
110
100
90
80
70
60
50
40
30
20
10
0
$P_{a_{O_2}}$ (mm Hg)
35
55
75
95
115
135
155
175
$P_{a_{CO_2}}$ (mm Hg)

Figure 6. Blood gas tensions and respiratory response in a typical ventilated fetus. Fetus 80 - 15 is shown. The abscissa, P_{aCO_2}, begins at 35 mm Hg.

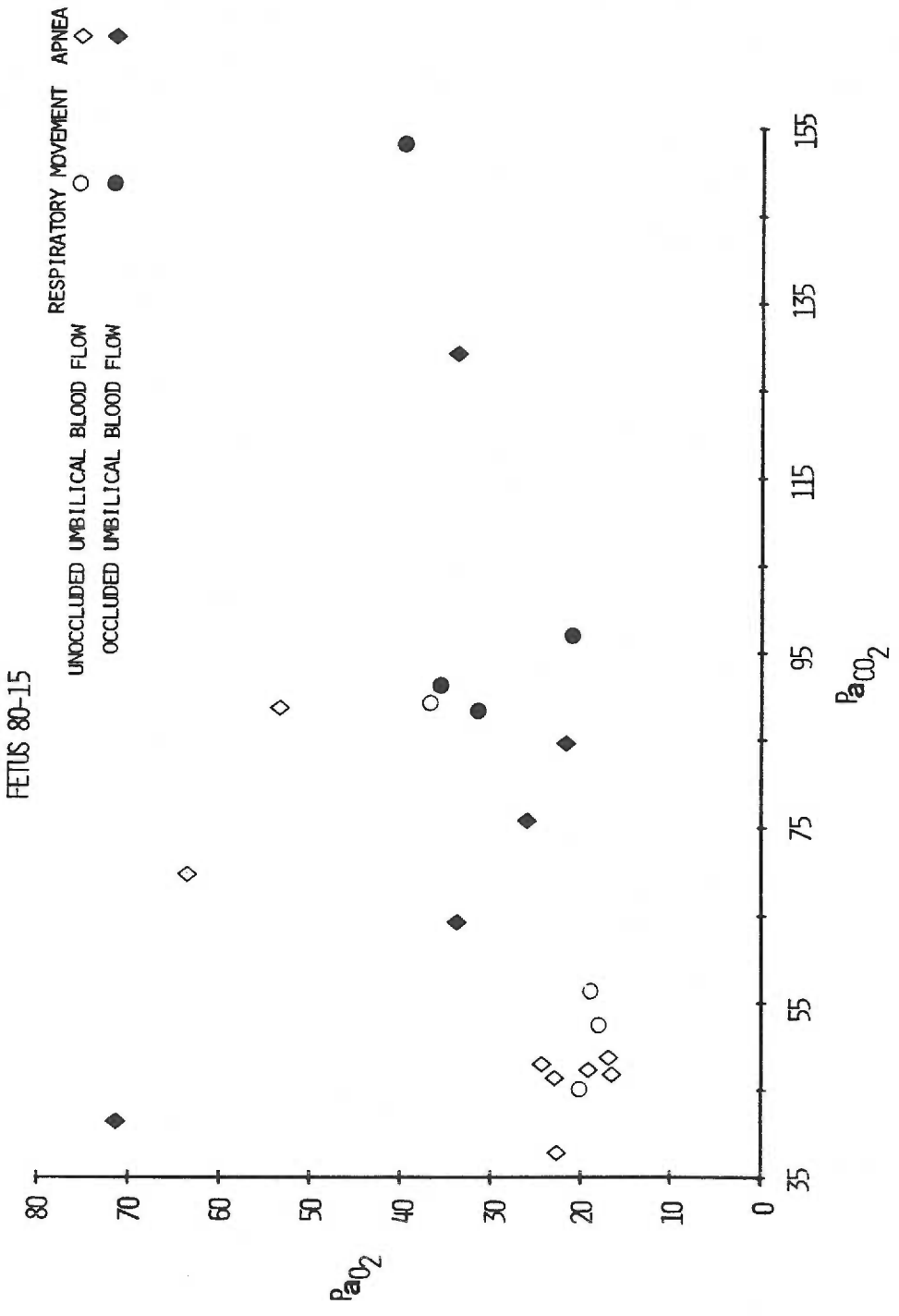

FETUS 80-15
UNOCCLUDED UMBILICAL BLOOD FLOW
OCCLUDED UMBILICAL BLOOD FLOW
RESPIRATORY MOVEMENT
APNEA
Pa_{O_2}
Pa_{CO_2}
80
70
60
50
40
30
20
10
0
35
55
75
95
115
135
155

Figure 7. Blood gas tensions and respiratory response in a typical ventilated fetus. Fetus 80 - 19 is shown. The abscissa, Pa_{CO_2}, begins at 35 mm Hg.

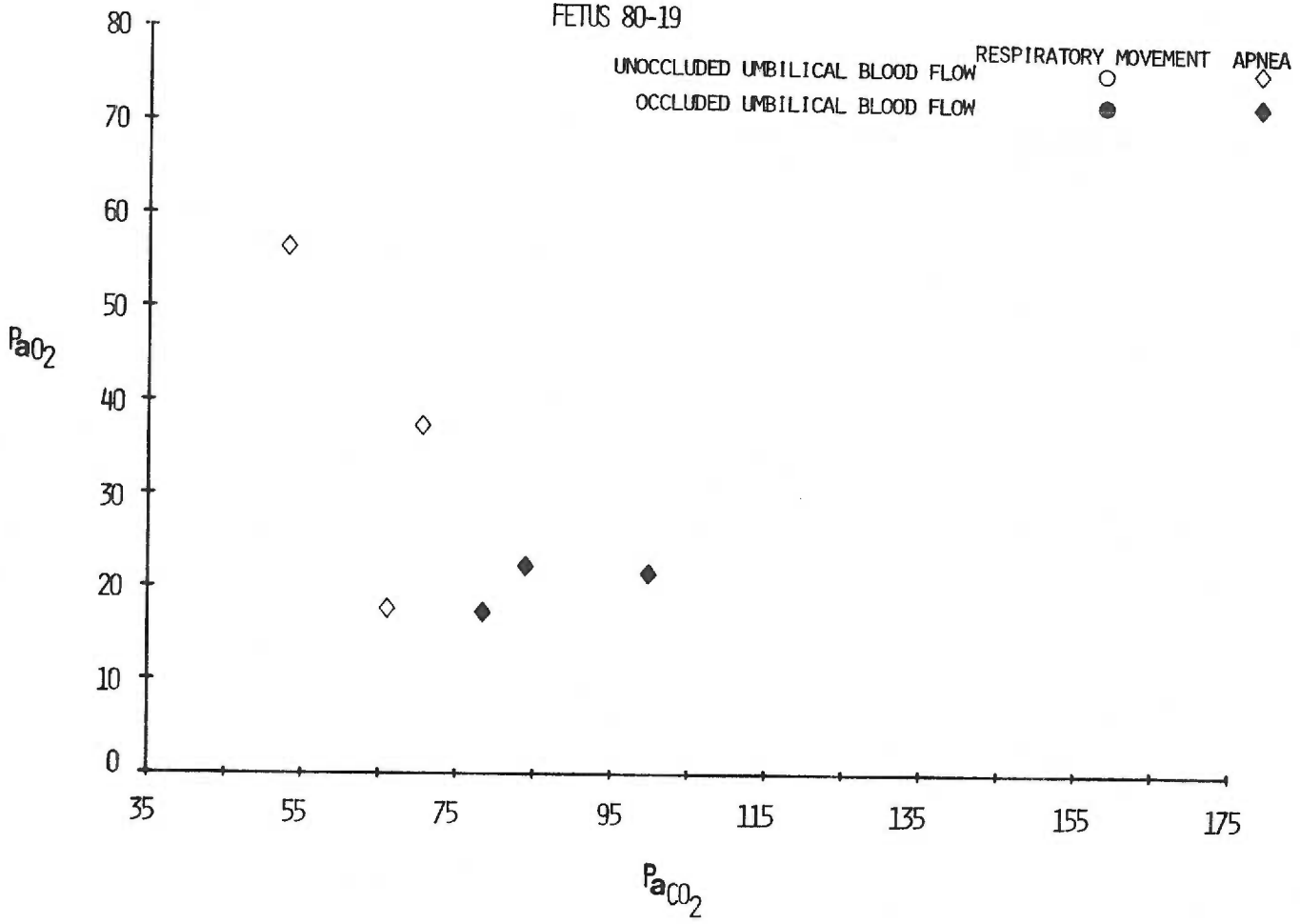

FETUS 80-19
UNOCCLUDED UMBILICAL BLOOD FLOW
OCCLUDED UMBILICAL BLOOD FLOW
RESPIRATORY MOVEMENT
APNEA
80
70
60
50
40
30
20
10
0
P_{aO_2}
35
55
75
95
115
135
155
175
P_{aCO_2}

Figure 8. Blood gas tensions and respiratory response in a typical ventilated fetus. Fetus 81 - 13 is shown. The abscissa, $P_{a}CO_2$, begins at 35 mm Hg.

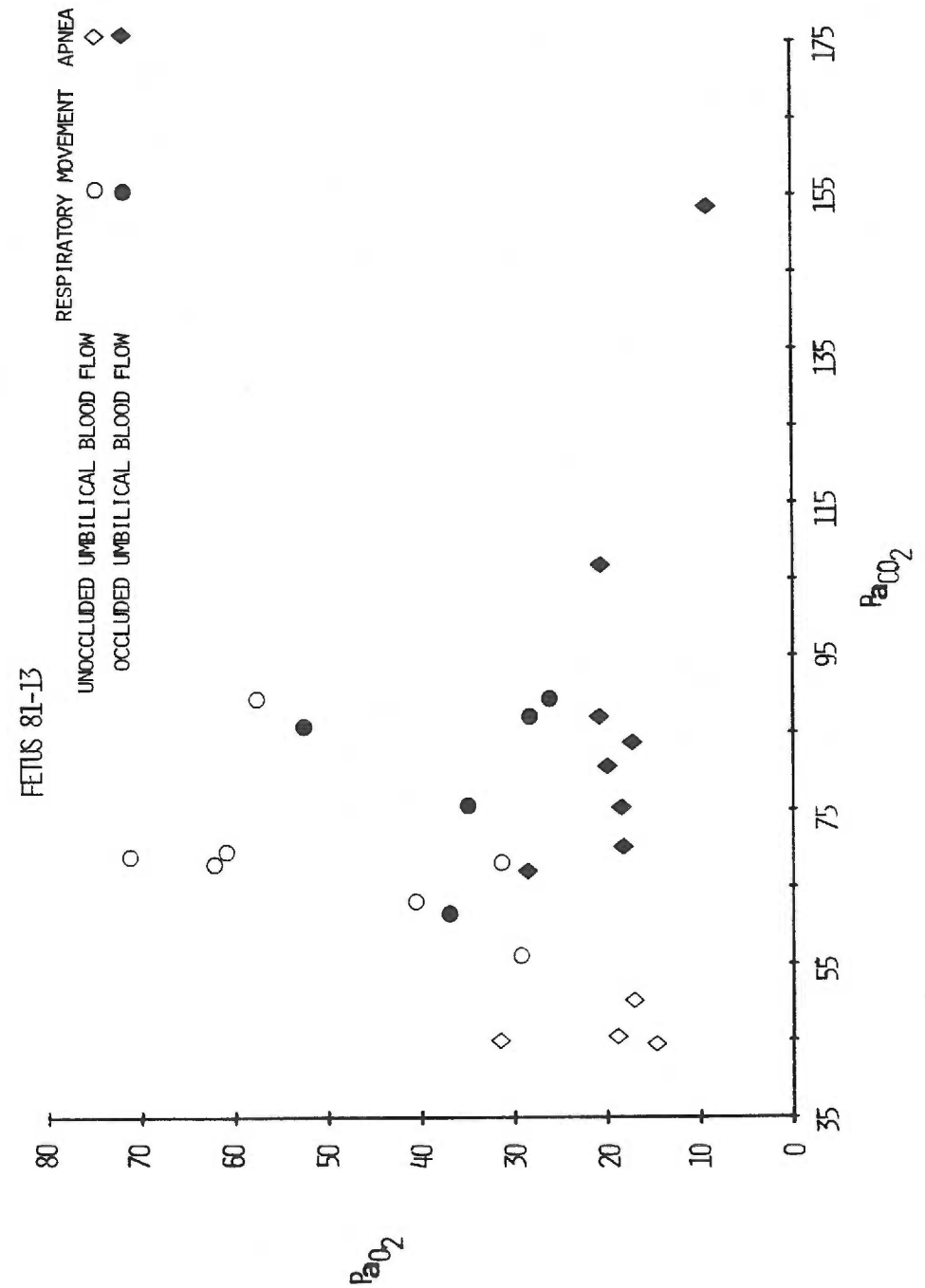

FETUS 81-13
RESPIRATORY MOVEMENT APNEA
UNOCCLUDED UMBILICAL BLOOD FLOW
OCCLUDED UMBILICAL BLOOD FLOW
Pa_{O_2}
80
70
60
50
40
30
20
10
0
Pa_{CO_2}
35
55
75
95
115
135
155
175

Figure 9. Respiratory movement in a sheep fetus. Polygraph record of a sheep fetus *in utero* during an episode of "breathing". An arterial blood sample was drawn, marked "A" on the record.

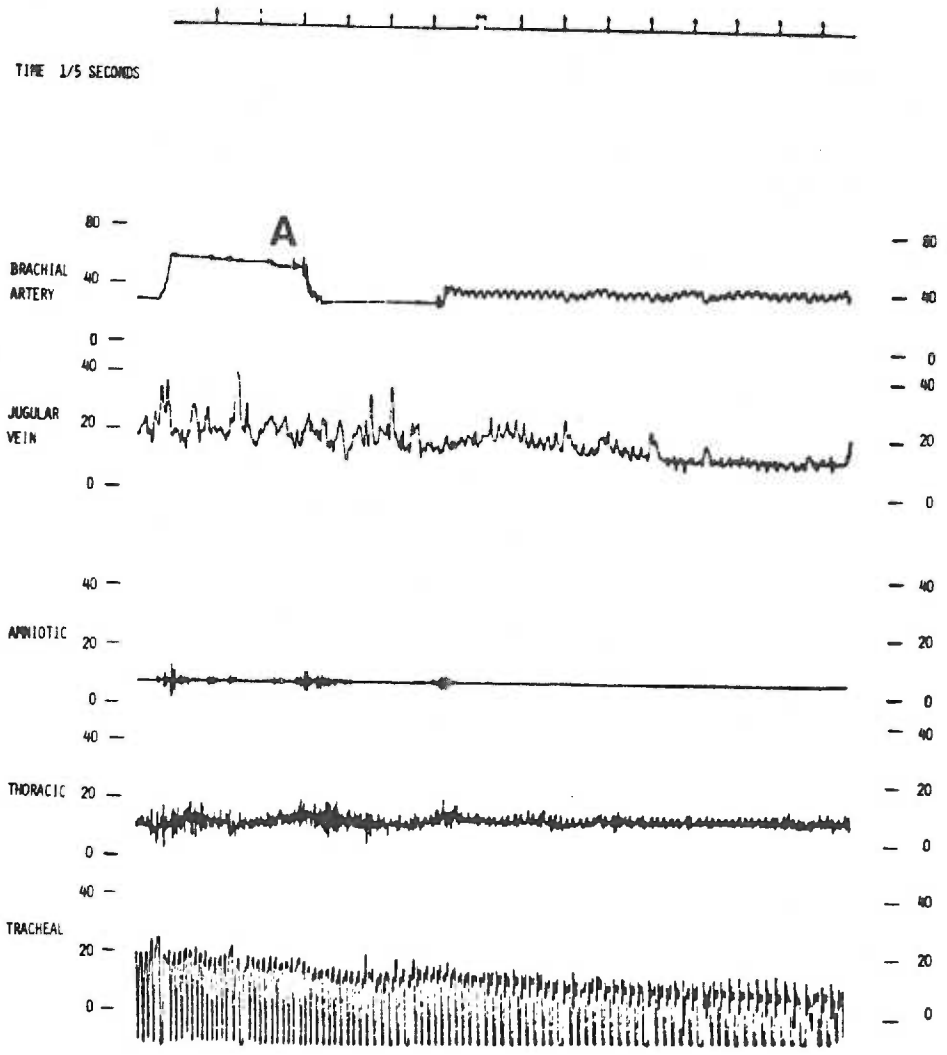

TIME 1/5 SECONDS
A
BRACHIAL ARTERY
JUGULAR VEIN
AMNIOTIC
THORACIC
TRACHEAL
80
40
0
20

Figure 10. Respiratory movement in a sheep fetus. Polygraph record of a sheep fetus *in utero* during an episode of "gasping". An arterial blood sample was drawn, marked "A" on the record.

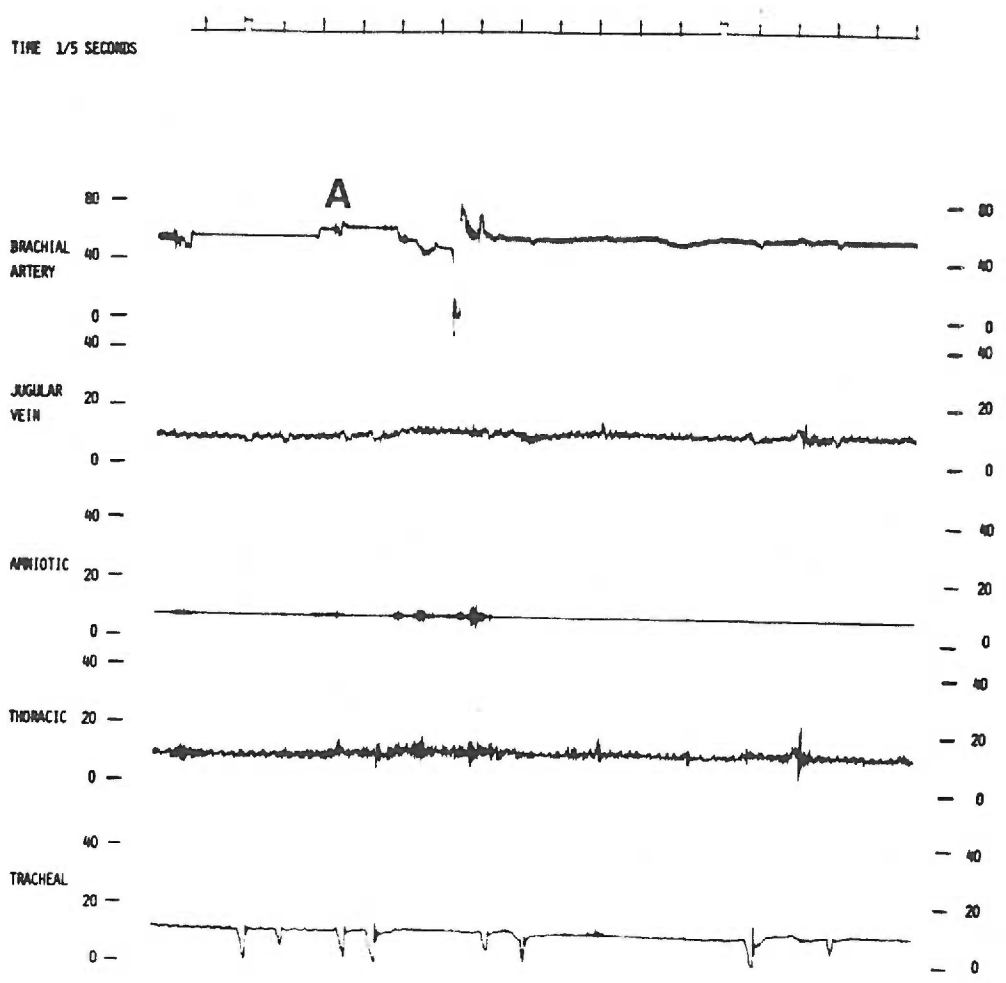

TIME 1/5 SECONDS
A
BRACHIAL ARTERY
JUGULAR VEIN
AMNIOTIC
THORACIC
TRACHEAL
80
40
0
20

Figure 11. Apnea in a sheep fetus. Polygraph record of a sheep fetus *in utero* during an episode of apnea.

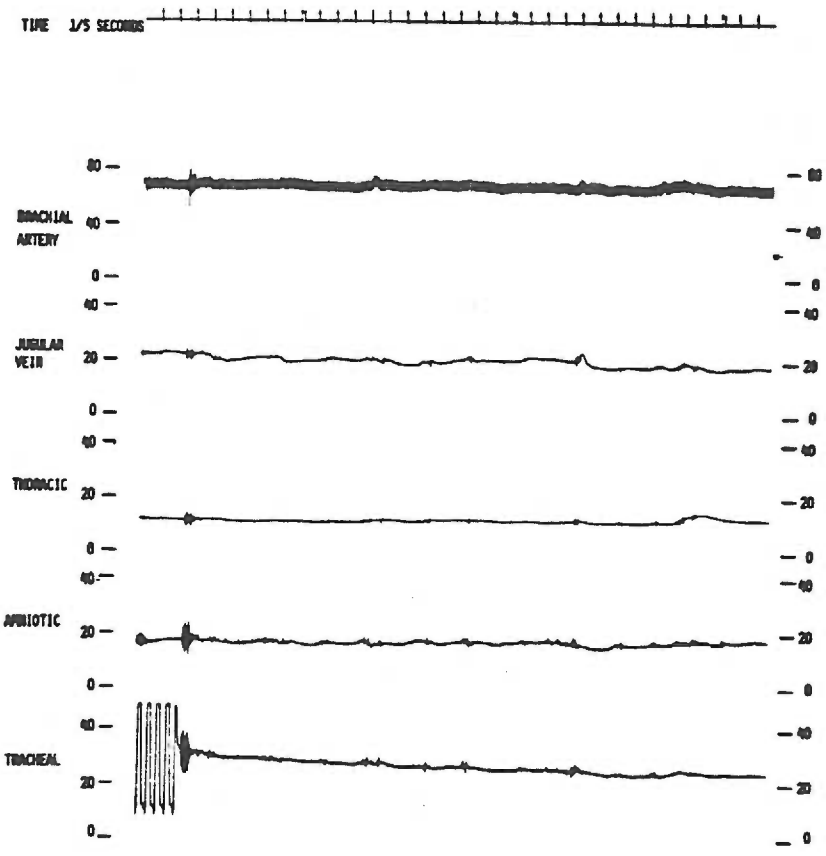

TIME 1/5 SECONDS
BRACHIAL ARTERY
JUGULAR VEIN
THORACIC
AMBIOTIC
TRACHEAL
80
40
0
40
20
0
40
20
0
40
20
0
40
20
0

Figure 12. Respiratory movement and apnea at various arterial P_{O_2}'s and P_{CO_2}'s in a ventilated sheep fetus with intact umbilical blood flow. The abscissa, P_{aCO_2}, begins at 35 mm Hg.

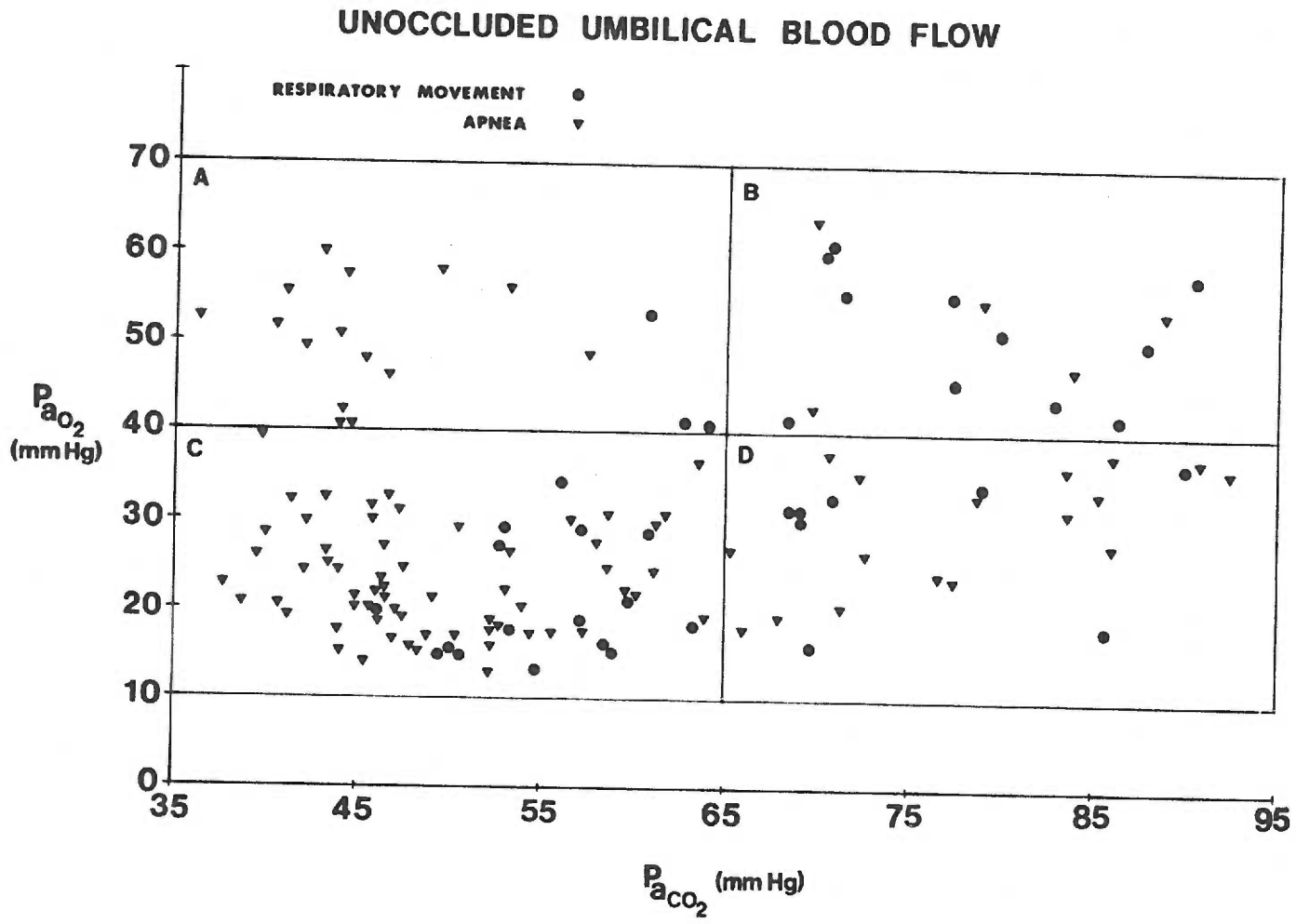

UNOCCLUDED UMBILICAL BLOOD FLOW
RESPIRATORY MOVEMENT
APNEA
A
B
C
D
70
60
50
40
30
20
10
0
35
45
55
65
75
85
95
$P_{a_{O_2}}$ (mm Hg)
$P_{a_{CO_2}}$ (mm Hg)

Figure 13. Respiratory movement and apnea at various arterial P_{O_2}'s and P_{CO_2}'s in a ventilated sheep fetus with occluded umbilical blood flow. The abscissa, Pa_{CO_2}, begins at 35 mm Hg.

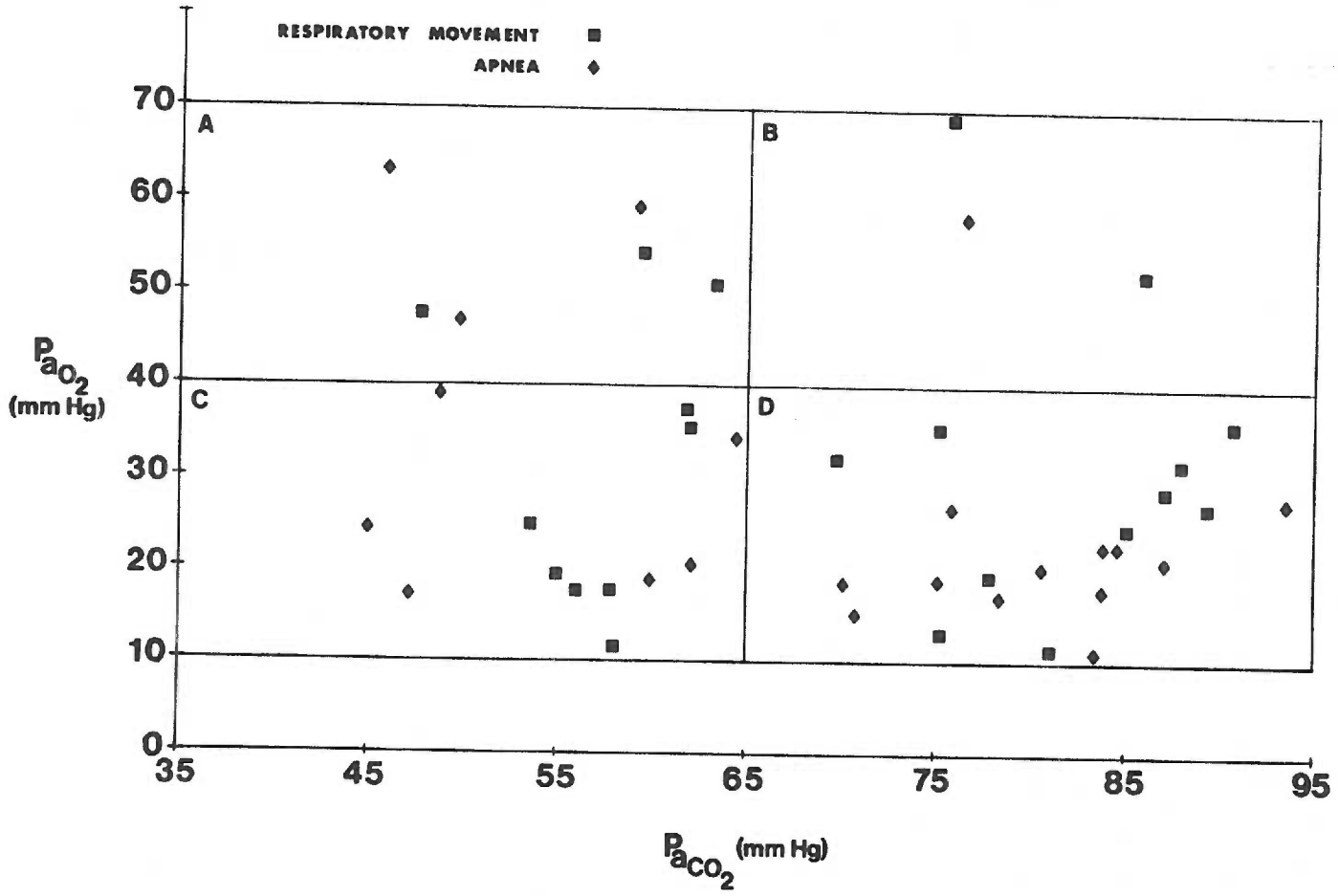

OCCLUDED UMBILICAL BLOOD FLOW
RESPIRATORY MOVEMENT
APNEA
A
B
C
D
70
60
50
40
30
20
10
0
35
45
55
65
75
85
95
P_{aO_2} (mm Hg)
P_{aCO_2} (mm Hg)

Figure 14. Respiratory movement and apnea at various arterial P_{O_2}'s and P_{CO_2}'s in a ventilated sheep fetus with occluded umbilical blood flow. The range of arterial P_{O_2}'s and P_{CO_2}'s is greater than in figure 13. The abscissa, P_{aCO_2}, begins at 35 mm Hg.

OCCLUDED UMBILICAL BLOOD FLOW

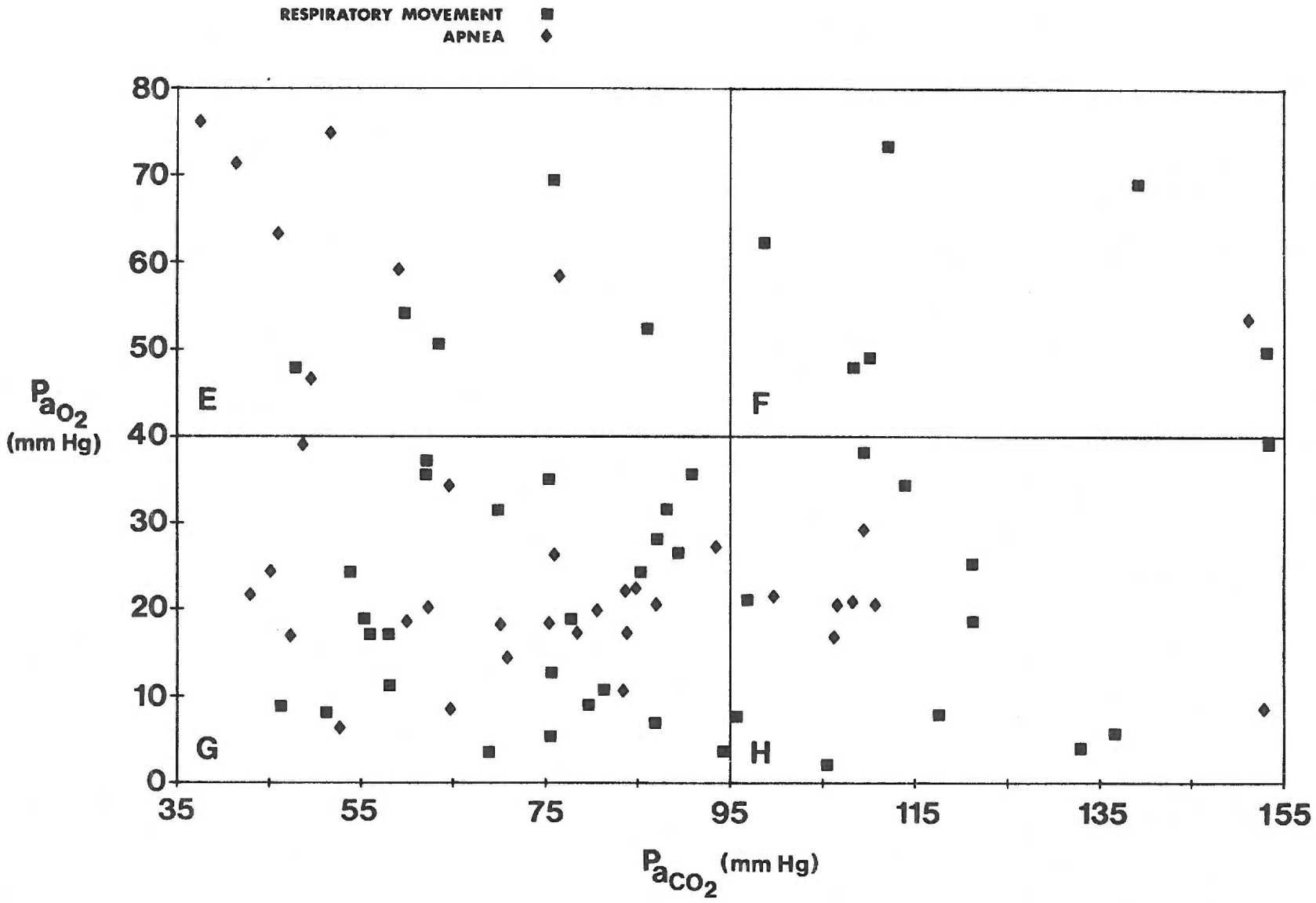


Figure 15. Polygraph record showing the typical increase in arterial and venous pressure with umbilical cord occlusion. The beginning of cord occlusion is marked by an arrow.

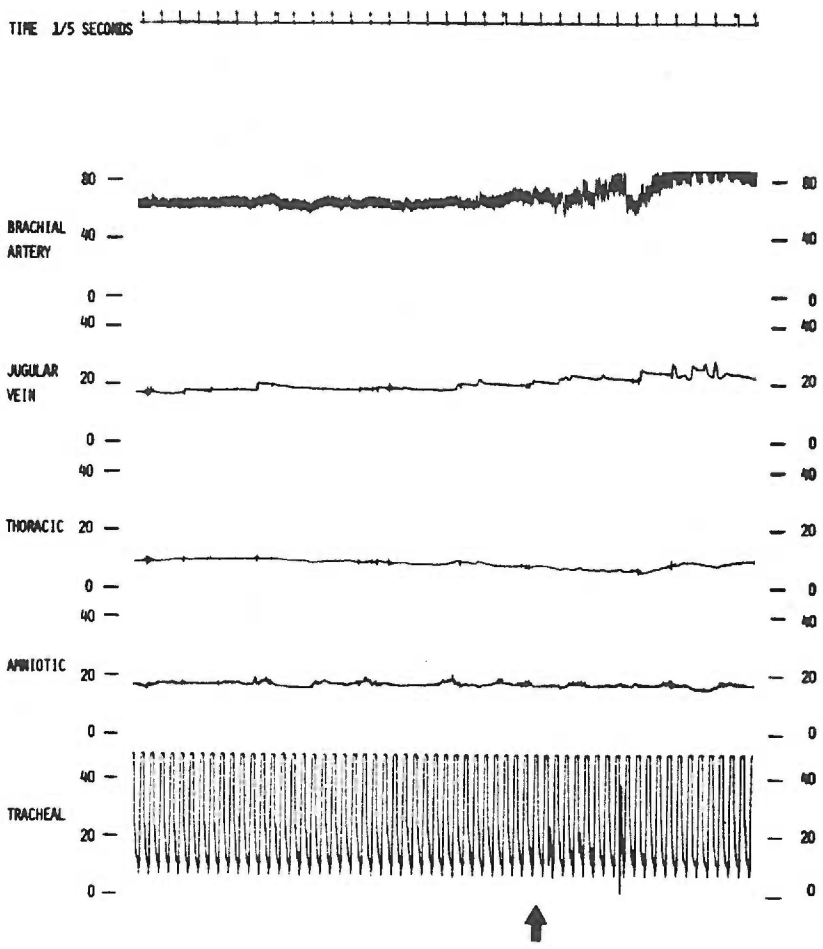

TIME 1/5 SECONDS
BRACHIAL ARTERY
JUGULAR VEIN
THORACIC
AMNIOTIC
TRACHEAL
80
40
0
40
20
0
40
20
0
40
20
0
40
20
0
80
40
0
40
20
0
40
20
0

Figure 16. Histogram showing the number of observations made of each respiratory rate. Respiratory rate is grouped in multiples of nine.

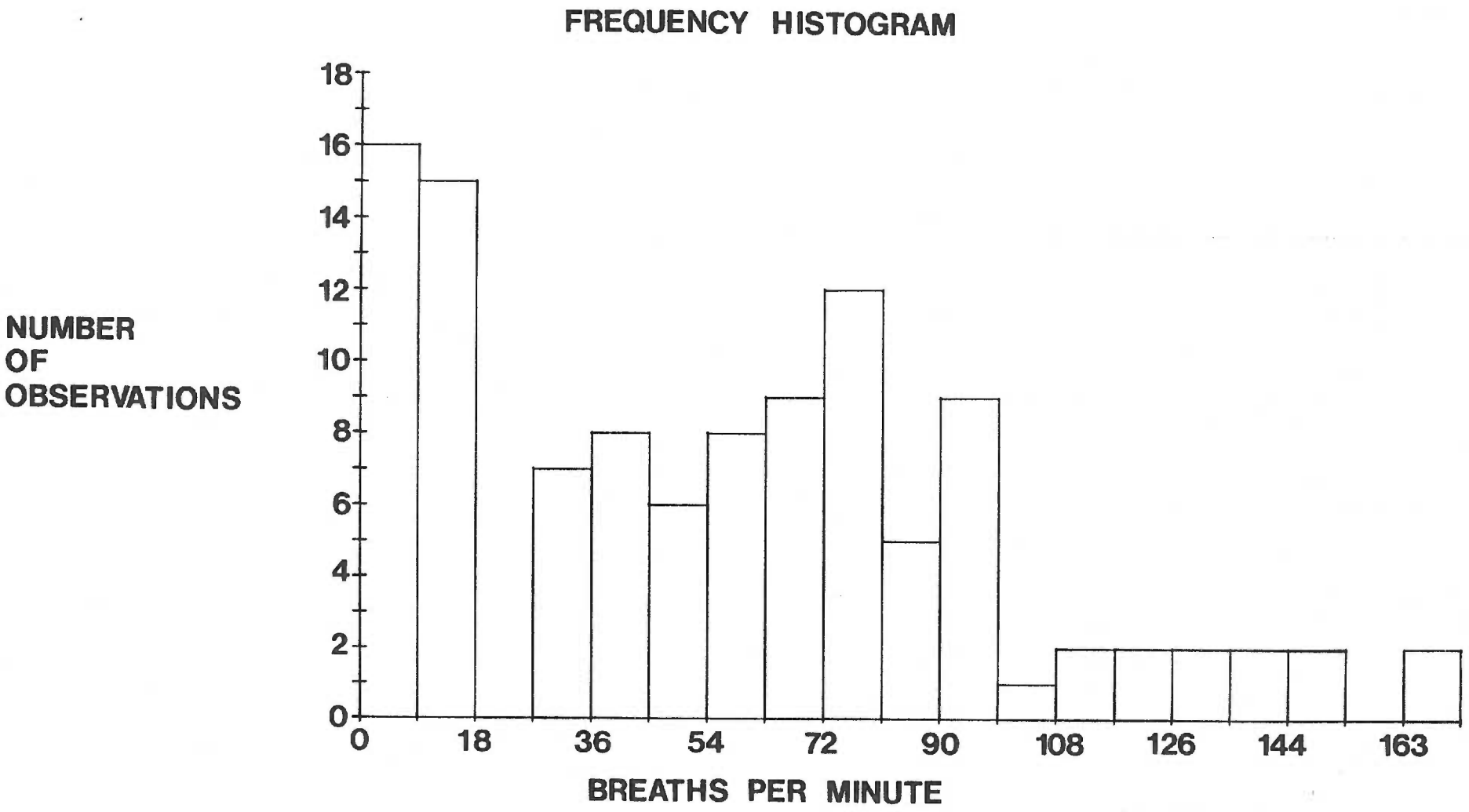

FREQUENCY HISTOGRAM
NUMBER OF OBSERVATIONS
18
16
14
12
10
8
6
4
2
0
0
18
36
54
72
90
108
126
144
163
BREATHS PER MINUTE

Figure 17. Gasping and apnea in fetuses with inoccluded and occluded umbilical blood flow at various arterial blood gas tensions. The abscissa, $P_{a_{CO_2}}$, begins at 35 mm Hg.

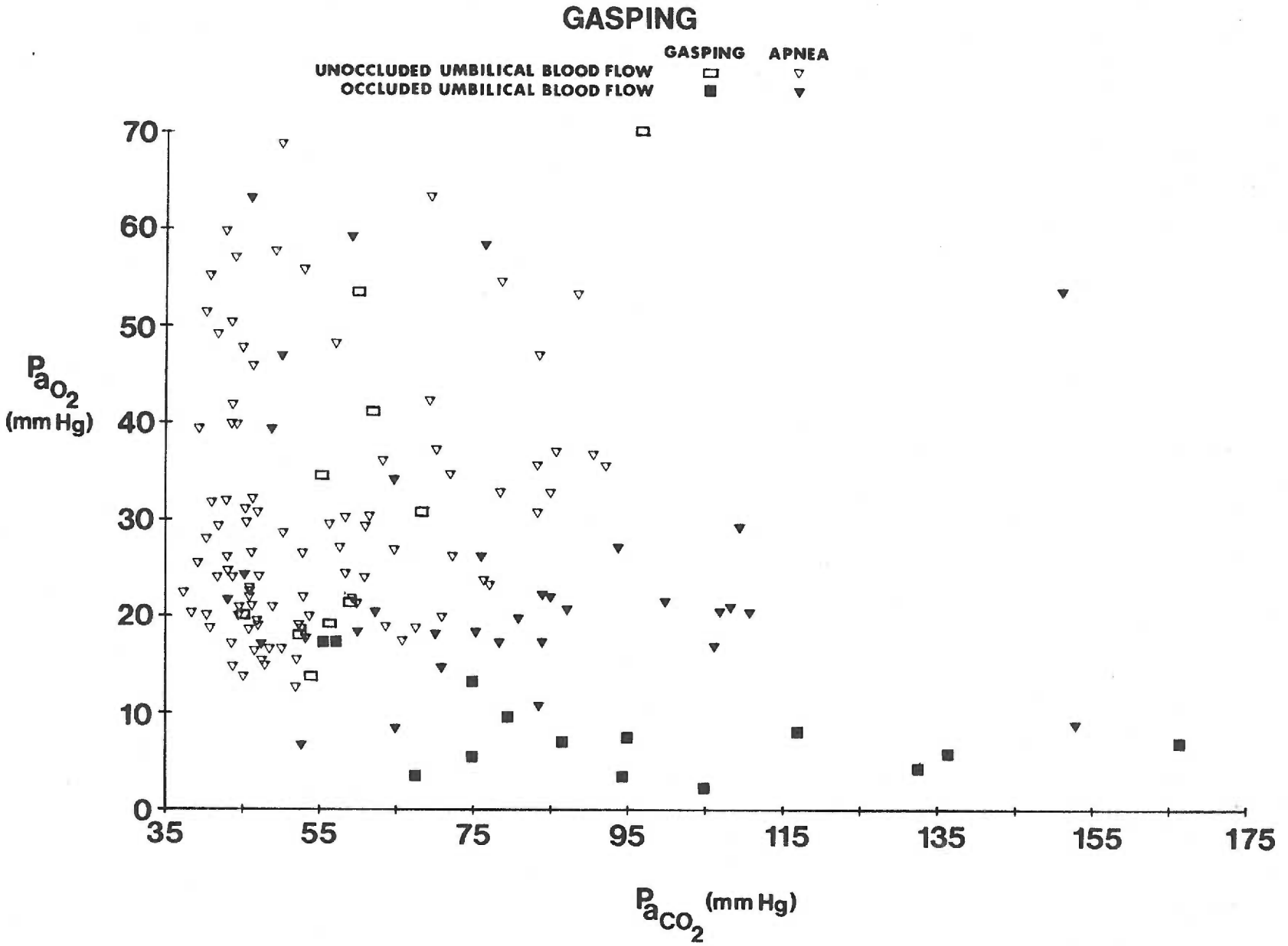
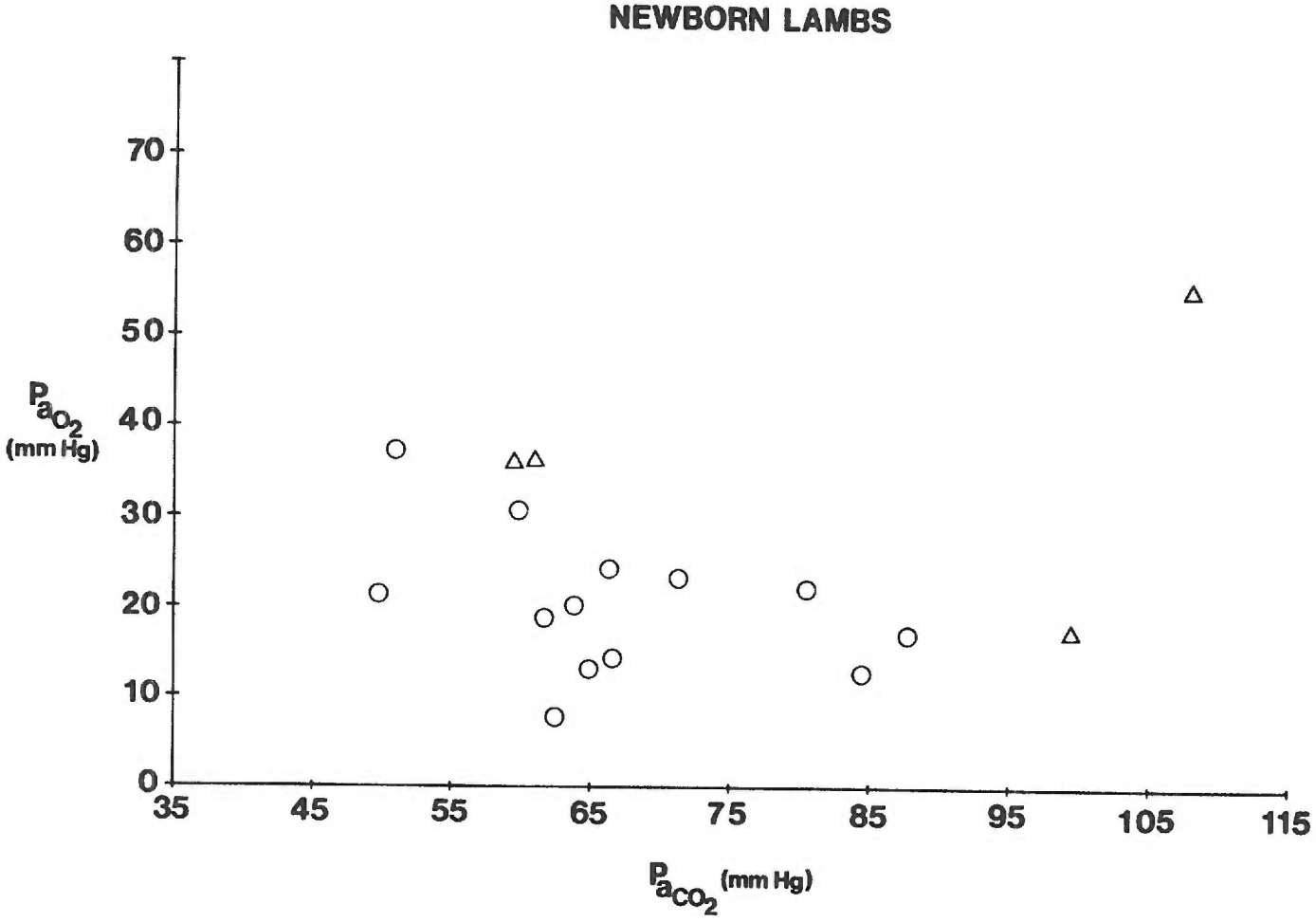

GASPING
GASPING
APNEA
UNOCCLUDED UMBILICAL BLOOD FLOW
OCCLUDED UMBILICAL BLOOD FLOW
70
60
50
40
30
20
10
0
$P_{a_{O_2}}$ (mm Hg)
35
55
75
95
115
135
155
175
$P_{a_{CO_2}}$ (mm Hg)

Figure 18. Arterial blood gas tensions for newborn lambs. Lambs from this experiement are designated ○ . Lambs from other experimental protocols are designated by △ . The abscissa, $P_{a_{CO_2}}$, begins at 35 mm Hg.


NEWBORN LAMBS
70
60
50
40
30
20
10
0
$P_{a_{O_2}}$ (mm Hg)
35
45
55
65
75
85
95
105
115
$P_{a_{CO_2}}$ (mm Hg)

DISCUSSION

Advantages of this experimental protocol over previous studies on the initiation of respiration at birth are the ability to study a chronically prepared fetal sheep that is unanesthetized and recovered from surgery, the ability to isolate the fetus from influences of the external environment during experimentation and the ability to separate some of the physiological changes occurring at birth.

The four days allowed after surgery was an adequate time for recovery prior to an experiment. In four days a fetus returns physiologically to baseline level according to experience in our lab and reports in the literature (Dawes, 1972; Kendall, 1977; Anderson, 1981).

Control arterial blood gas P_{O_2}'s in our fifteen fetuses were lower than control values in the literature for chronically catheterized sheep, a mean of 17.8 mm Hg versus 22 mm Hg (Dawes, 1972). This lower arterial P_{O_2} may be in part due to the older age of the fetuses and in part to our surgery which was more extensive than that done by Dawes. The extensive surgery may have resulted in more trauma to cotyledons, thus less exchange area and a decreased placental flow. The decreased P_{O_2} of our fetuses did not reduce their viability as lambs. All lambs delivered after experimentation were born alive and breathed spontaneously. Also, the arterial blood pH and arterial P_{CO_2} were within the limits of normal for a fetal lamb.

The efficiency of placental exchange limited the variability of arterial blood P_{CO_2} and P_{O_2} in fetuses with unoccluded umbilical blood flow. We were unable to drive arterial P_{CO_2} above 95 mm Hg or drive arterial P_{O_2} below 10 mm Hg by ventilation of the fetus. The range of gas tensions studied were, however, much greater than those achieved in previous studies using chronically prepared fetal sheep.

Arterial blood gases could be altered over a much greater range in fetuses with occluded umbilical blood flow. This allowed the study of respiratory response at higher arterial P_{CO_2}'s and lower arterial P_{O_2}'s than when umbilical blood flow was unoccluded.

Cord occlusion was verified in these fetuses by injection of radioactive microspheres and comparison of counts per gram tissue per minute in placenta to that in fetal carcass. In fetuses with occluded umbilical circulation placental counts are at most one twenty-fifth of the radioactivity in the fetal carcass. What little radioactivity was recorded in placental tissue can be explained by the flow of residual microspheres from the occluded umbilical cord to the placenta during the period when occlusion was released to remove the fetus from the ewe and to random variation in background counts.

The arterial blood P_{O_2} of my newborn lambs was generally much lower than the values of 60 to 70 mm Hg reported in the literature. These lower arterial P_{O_2}'s

are reasonable when one considers that all fetuses were delivered prematurely, the fetuses from this experiment breathed through tracheal catheters, and had all endured positive pressure ventilation *in utero* which may have inflicted damage to the lungs. All fetuses delivered after experimentation did initiate and maintain respiration without assistance.

A newborn lamb initiates and maintains respiration at arterial blood gas tensions that did not initiate respiration as a fetus. This change at birth from the fetal response to chemical stimuli to a response more like that of the adult occurs abruptly. This sudden change in respiratory responsiveness must mean a change in respiratory control characteristics occurs at birth. The mechanism of this sudden change is unknown. However, this experiment has examined and ruled out several proposed hypotheses.

From examination of changes in the incidence of respiratory movement at various arterial P_{O_2}'s and arterial P_{CO_2}'s, we can see that in fetuses with unoccluded umbilical blood flow an increase in the incidence of fetal respiration occurred when both high arterial P_{O_2}'s and high arterial P_{CO_2}'s are present ($p < 0.005$) (Figure 12, Table 2). These changes in blood gas tensions, however, did not initiate newborn-like respiration. We can conclude that it is not the

fetus's more hypoxic blood gas levels or the lack of stimulus from carbon dioxide that makes its respiratory response different from that of a newborn lamb.

The variation of fetal respiratory incidence with changes in arterial P_{O_2} and P_{CO_2} disappeared when the same fetuses were studied with occluded umbilical flow. Though the incidence of fetal respiration was increased over the incidence of respiration when umbilical blood flow was not occluded, umbilical occlusion did not initiate newborn-like respiratory responses in the fetuses, either. From this fact we can deduce that a placental factor, if it exists, is not an important inhibitor to the onset of respiration in fetal lambs.

Cord occlusion and lung inflation change the fetal circulation system to a newborn circulatory pattern. That the fetus did not initiate newborn-like respiration after this pattern was achieved, disproves other hypotheses suggested as important initiators of respiration at birth. Initial lung inflation does not give rise to newborn respiration as hypothesized by Chernick (Chernick, 1976). The change in circulatory pattern and dependence on the lung as the organ of gas exchange did not initiate a change in respiratory control in the fetus. The proposal that oscillatory variation in blood gases provides the stimulus for initiation of respiration was therefore also proved false (Bowes, 1980).

The division of respiratory movements into gasping and breathing was seen by the bimodal distribution of the

frequency of respiration movements as a function of respiratory rate. The presence of this bimodal distribution agrees with other reports in the literature of fetal respiratory movements (Dawes, 1972; Brystrzycka, 1975; Kendall, 1977). The range of this distribution varies between observers. Dawes reported breathing at frequencies of 60 to 240 breaths per minute and gasping at 1 to 3 breaths per minute (Dawes, 1972). Brystrzycka reported ranges in fetal lambs of 32 breaths per minute to 180 breaths per minute and gasping as inspirations of 8 per minute or less (Brystrzycka, 1975). These latter results agree more closely with ours.

The questions arise, however, are gasping and breathing separate respiratory phenomena and does the occurrence of gasping change with cord occlusion? Gasping accounts for approximately twenty percent of the respiratory movement in both the fetus with occluded and unoccluded umbilical circulation. Though most gasping points are present at low arterial P_{O_2}'s, there are insufficient recordings of gasping to show any significant difference with variation of arterial P_{O_2}'s above 10 mm Hg.

Arterial P_{O_2}'s less than 10 mm Hg were obtainable only when umbilical flow was occluded. At these hypoxic P_{O_2} values the incidence of gasping was increased over the incidence of gasping at higher arterial P_{O_2} levels ($p < 0.005$) (Table 9). The incidence of respiratory movement was not

significantly increased at P_{O_2}'s below 10 mm Hg ($p > 0.07$) (Table 8). The importance of this increased incidence of gasping at low arterial P_{O_2}'s is not known. As seen from my data, however, neither the resultant lung inflation caused by a newborn's gasp nor the loss of umbilical blood flow caused by occlusion initiate respiration at birth.

What is the mechanism that initiates respiration at birth? From the results of this data, one can rule out lung inflation, cord occlusion, and variations in arterial P_{O_2} above 10 mm Hg as respiratory initiators even though many of these factors may have some role in the initiation of respiration once the lamb is born.

SUMMARY AND CONCLUSIONS

Onset of continuous respiration did not occur in the ventilated sheep fetus *in utero* after lung expansion, cord occlusion, and variation of blood gas tensions at levels that caused respiration in newborn lambs.

We conclude that a change in respiratory control occurs at birth and that this change in respiratory control is not initiated by lung inflation, cord occlusion, or variations in arterial P_{O_2} above 10 mm Hg. These factors may play some role in initiation of respiration, however, once the lamb is born.

BIBLIOGRAPHY

1. Anderson, D.F., Bissonnette, J.M., Faber, J.J., & Thornburg, K.L. Central shunt flows and pressures in the mature fetal lamb. Am. J. Physiol., 1981. 241, H60-H66.

2. Avery, M.E., Chernick, V., & Young, M. Fetal respiratory movements in response to rapid changes of CO_2 in carotid artery. J. Appl. Physiol., 1965. 20(2), 225-227.

3. Belenky, D. A., Standaert, T.A., & Woodrum, D.E. Maturation of hypoxic ventilatory response of the newborn lamb. J. Appl. Physiol., 1979. 47(5), 927-930.

4. Biscoe, T.J., Purves, M.J., & Sampson, S.R. Types of nervous activity which may be recorded from the carotid sinus nerve in the sheep foetus. J. Physiol., 1969. 202, 1-23.

5. Boddy, K., Dawes, G.S., Fisher, R., Pinter, S., & Robinson, J.S. Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxaemia and hypercapnia in sheep. J. Physiol., 1974. 243, 599-618.

6. Bowes, G., & Phillipson, E.A. CO_2 regulation of respiratory rhythm: implications for the fetus. Seventh International Workshop on Fetal Breathing. Oxford, 1980. 2 (Abstract).

7. Bystrzycka, E., Nail, B.B., & Purves, M.J. Central and peripheral neural respiratory activity in the mature sheep foetus and newborn lamb. Respiration Physiology, 1975. 25, 199-215.

8. Chernick, V. The development of the lung and onset of respiration. In Goodwin, J.W., Godden, J.O., & Chance, G.W. (Ed). Perinatal Medicine, the basic science underlying clinical practice. Baltimore: The Williams & Wilkins Co., 1976. pp. 517 - 536.

9. Chernick, V., Fariday, E. E., & Pagtakhan, R.D. Role of peripheral and central chemoreceptors in the initiation of fetal respiration. J. Appl. Physiol., 1975. 38(3), 407-410.

10. Dawes, G.S. Foetal and neonatal physiology. Chicago: Year Book Medical Publishers, Inc., 1968.

11. Dawes, G.S., Fox, H.E., Leduc, B.M., Liggins, G.C., & Richards, R.T. Respiratory movements and rapid eye movement sleep in the foetal lamb. J. Physiol., 1972. 220, 119-143.

12. Dawes, G.S., Gardner, W.N., Johnston, B.M., & Walker, D.W. Breathing patterns in fetal lambs after mid-brain transection. J. Physiol., 1980. 300, 29P. (Abstract).

13. Dawes, G.S., & Mott, J. Reflex respiratory activity in the newborn rabbit. J. Physiol., 1959. 145, 85-97.

14. Harned, H.S., Jr., Herrington, R.T., & Ferreiro, J.I. The effects of immersion and temperature on respiration in newborn lambs. Pediatrics, 1970. 45(4), 598-605.

15. Harned, H.S., Jr., Rowshan, G., MacKinney, L.G., & Sugioka, K. Relationships of P_{O_2}, P_{CO_2} and pH to onset of breathing of the term lamb as studied by a flow-through cuvette electrode assembly. Pediatrics, 1964. 33, 672-681.

16. Harper, R.G., & Yoon, J. J. Handbook of neonatology. Chicago: Year Book Medical Publishers, Inc., 1974.

17. Herrington, R.T., Harned, H.S., Jr., Ferreiro, J. I., & Griffin, C.A., III. The role of the central nervous system in perinatal respiration: Studies of chemoreceptor mechanisms in the term lamb. Pediatrics, 1971. 47, 857-864.

18. Jansen, A.H., Ioffe, S., Russell, B.J., & Chernick, V. Effect of carotid chemoreceptor denervation on breathing in utero and after birth. J. Appl. Physiol., 1981. 51(3), 630-633.

19. Johnson, P., Robinson, J.S., & Salisbury, D. The onset and control of breathing after birth. In Comline, K.S., Cross, K.W., Dawes, G.S., & Nathanielsz, P.W. (Ed.). Foetal and Neonatal Physiology. Cambridge: University Press, 1973. pp. 217-221.

20. Kendall, J.Z. Respiratory movements in the fetal guinea pig in utero. J. Appl. Physiol., 1977. 42(4), 661-663.

21. Moss, I.R., & Scarpelli, E.M. Generation and regulation of breathing in utero: fetal CO_2 response test. J. Appl. Physiol., 1979. 47(3), 527-531.

22. Pagtakhan, R.D., Faridy, E.E., & Chernick, V. Interaction between arterial P_{O_2} and P_{CO_2} in the initiation of respiration of fetal sheep. J. Appl. Physiol., 1971. 30(3), 382-387.

23. Patrick, J.E., Dalton, K.J., & Dawes, G.S. Breathing patterns before death in fetal lambs. Am. J. Obstet. Gynecol., 1976. 125, 73-78.

24. Ponte, J., & Purves, M.J. Types of afferent nervous activity which may be measured in the vagus nerve of the sheep foetus. J. Physiol., 1973. 229, 51-76.

25. Reynolds, S.R.M., & Mackie, J.D. Development of chemoreceptor response sensitivity: studies in fetuses, lambs, and ewes. Am. J. Physiol., 1961. 201(2), 239-250.

26. Tchobroutsky, C., Merlet, C., & Rey, P. The diving reflex in rabbit, sheep, and newborn lamb and its afferent pathways. Respiration Physiology, 1969. 8, 198-117.

27. Towell, M.E., & Salvador, H.S. Intrauterine asphyxia and respiratory movements in the fetal goat. Am. J. Obstet. Gynecol., 1974. 118(8), 1124-1131.

28. Widdicombe, J.G. Respiratory reflexes. In Fenn, W.O., & Rahn, H. (Ed.). Handbook of Physiology. Section 3. Respiration. Vol. I. Washington, D.C.: American Physiological Society, 1964. pp. 585-630.

29. Woodrum, D.E., Parer, J. T., Wennberg, R. P., & Hodson, W.A. Chemoreceptor response in initiation of breathing in the fetal lamb. J. Appl. Physiol., 1972. 33(1), 120-125.

30. Wyszogrodski, I., Thach, B.T., & Milic-Emili, J. Maturation of respiratory control in unanesthetized newborn rabbits. J. Appl. Physiol., 1978. 44(2), 304-310.