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Respiratory Function in Lambs after Prolonged Oligohydramnios during Late Gestation

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ABSTRACT. **Our aim was to determine the effects of oligohydramnios during the last third of ovine gestation on respiratory function in lambs during their first postnatal month. To induce oligohydramnios, amniotic and allantoic fluids were drained from pregnant ewes, starting at 109.0 ± 2.3 d of pregnancy (term ≈ 148 d). In 10 lambs born at term, respiratory function was studied four times at weekly intervals; a group of nine lambs from normal pregnancies served as controls. Over the 4-wk study period, treated lambs had significantly higher breathing rates and smaller tidal volumes than controls, although the differences diminished with age. Minute ventilation and O_2 consumption were the same in each group, and when related to body weight, both declined with age. Treated lambs were normoxemic but were hypercapnic compared with controls for up to 4 wk. Functional residual capacity, measured by helium dilution, was the same in each group and increased with age. Static compliance of the respiratory system was lower in treated lambs up to 4 wk; lung compliances were the same in each group, but chest wall compliance was lower in treated lambs than in controls for 4 wk. Postmortem measurements, at 27–28 d, of pulmonary dry weights, DNA contents, and protein contents suggest that the lungs of treated lambs may have been mildly hypoplastic. We conclude that oligohydramnios causes a decreased chest wall compliance, which leads to rapid, shallow breathing and a mild hypercapnia lasting for at least 4 postnatal wk. (*Pediatr Res* 34: 611–617, 1993)**

Abbreviations

Pa_{O_2}, arterial partial pressure of oxygen
Pa_{CO_2}, arterial partial pressure of carbon dioxide
f, respiratory frequency
V_T, tidal volume
MV, minute ventilation
$\dot{V}_{O_2}$, oxygen consumption
Ppl, intrapleural pressure
Crs, total respiratory system compliance
Cl, lung compliance
Cw, chest wall compliance
Pm, mouth pressure

It is well established that a reduced volume of amniotic fluid during pregnancy can impair development of the fetal lungs, leading to pulmonary hypoplasia (1, 2). Oligohydramnios can occur if amniotic fluid production is diminished, as with renal agenesis or obstruction of the urinary tract, or if the fluid escapes from the amniotic cavity, as with prolonged rupture of the fetal membranes (2–4). In sheep, removal of amniotic fluid during the last third of pregnancy leads to a reduction in fetal lung expansion of approximately 20% (5, 6), which, if sustained, leads to fetal lung hypoplasia (7, 8). Our recent studies indicate that oligohydramnios leads to reduced fetal lung expansion due primarily to an alteration in fetal posture imposed by reduced uterine dimensions (6) and by a narrowing of the fetal thorax (9). Depending on its severity, pulmonary hypoplasia after oligohydramnios can cause death from respiratory insufficiency (10), or it may lead to survivable, possibly undetected, respiratory insufficiency in the newborn (11).

As well as causing pulmonary hypoplasia (*i.e.* reduced lung tissue weight and/or pulmonary DNA content relative to body weight), oligohydramnios has been reported to cause a range of structural and maturational changes in the fetal lungs. A reduced number of alveoli, with no evidence of alveolar immaturity, has been reported in human infants dying soon after birth following oligohydramnios (4, 12) and in fetal monkeys after amniotic fluid removal (13). Other studies have provided evidence of pulmonary immaturity after oligohydramnios, such as impaired epithelial maturation in the peripheral parts of the lungs (14) and reduced pulmonary collagen and elastin contents (15, 16). The phospholipid content of hypoplastic fetal lungs after oligohydramnios was unchanged in the sheep (17) and rat (18) and was increased in rabbits (19). Thus, oligohydramnios, depending on species and gestational age of occurrence, may be followed by differing degrees of lung hypoplasia and lung immaturity in the fetus or neonate.

It is evident that infants with hypoplastic lungs may survive birth but that respiratory insufficiency may persist during the neonatal period (1, 4, 12). However, apart from one study in the guinea pig (11), there appears to be little systematic documentation of the effects of oligohydramnios on respiratory function in surviving newborns or on how long respiratory deficits persist. Therefore, the aims of this study were to define the effects of prolonged oligohydramnios during late pregnancy on respiratory function during the first postnatal month and to determine the cause and duration of any abnormalities observed. To produce oligohydramnios, we continuously drained amniotic and allantoic fluids surrounding fetal sheep during the last third of gestation and allowed the pregnancies to continue to term. After birth, the lambs were studied at weekly intervals for 4 wk. Our study revealed the presence of changes in respiratory function that persisted for at least 4 wk after birth.

MATERIALS AND METHODS

Surgical preparation. At 92–113 d after mating (mean 103 ± 2 d), 10 pregnant ewes underwent aseptic surgery under general anesthesia for the implantation of two drainage catheters in the amniotic sac and one into the allantoic sac (5). Anesthesia was induced with sodium thiopentone (1 g, i.v.) and maintained,

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after tracheal intubation, with halothane (1.5–2% vol/vol) in an equal mixture of O_2 and N_2O. Catheters were inserted through small incisions in the uterus and the fetuses were not exposed. Antibiotics (ampicillin, 500 mg) were added to the amniotic fluid before the uterine incision was closed. After recovery from surgery (4–7 d), fluids were drained continuously by gravity from both sacs into sterile bags until about 6 d before the time of expected delivery. Drainage was discontinued before term to allow accumulation of sufficient amniotic fluid to facilitate birth of the lamb. Nine normal pregnant ewes carried lambs that were not exposed to oligohydramnios and that formed the control group. Two of these ewes had undergone a sham surgical procedure. All lambs were born at term, the mean gestational age at delivery being 148.3 ± 0.8 d. All but one lamb were born vaginally. One of the treated lambs required cesarean delivery due to obstructed labor. None of the lambs required resuscitation after birth.

At 1–3 d after birth, both treated ($n = 10$) and control ($n = 9$) lambs underwent aseptic surgery (halothane anesthesia, 1–2% in O_2/N_2O) for the implantation of catheters into the carotid artery for blood sampling and into the jugular vein for drug administration. In all lambs, a saline-filled rubber balloon (1–2 mL) for recording changes in intrapleural pressure was introduced into the dorsolateral pleural cavity through a small midthoracic thoracotomy (20). All catheters were tracked subcutaneously, exiting over the midthoracic spine. All lambs were given intramuscular antibiotics (procaine penicillin, 200 mg; dihydrostreptomycin, 250 mg) at surgery and for 3 d afterwards. Externally, the catheters were sutured to the skin, fitted with stopcocks, and placed in a plastic bag held in place beneath elasticized netting around the animal's trunk. Vascular catheters were flushed daily with heparinized saline. After surgery, each lamb was housed in a pen with its mother.

Measurements of respiratory function. Beginning at least 2 d after surgery, weekly studies were carried out while the lambs, which had been weighed, lay prone in a canvas sling with openings for their legs. The mean postnatal ages at which the studies were performed in both groups of lambs were 4.2 ± 0.4 d (wk 1), 11.0 ± 0.5 d (wk 2), 18.6 ± 0.4 d (wk 3), and 26.4 ± 0.4 d (wk 4); there was no difference between the ages at which treated and control lambs were studied. The first postnatal study was delayed to allow time for the lambs to recover from birth and surgery. The laboratory temperature was 22–23°C, which is close to the thermoneutral range for lambs up to 1 mo of age (21). An arterial blood sample (1 mL) was taken to measure pH, $Paco_2$, Pao_2, O_2 saturation, and Hb content using blood gas analyzers (ABL-30 and OSM2, Radiometer, Copenhagen, Denmark). Samples were analyzed within 5 min of collection and values were corrected for the rectal temperatures of the lambs. A face mask incorporating nasal tubes was then made to permit measurements of f, V_T, and MV. The face mask was made with a rapid-setting molding material (vinyl polysiloxane, Reprosil; Denstply Inc., Milford, DE) after insertion of silicone rubber nasal tubes (3 or 4 mm internal diameter) and could be painlessly removed after the study period (20).

Ventilatory studies were performed while the lambs were resting awake. Tidal flow, V_T, and MV were measured using a pneumotachograph (Fleisch, size 0) connected, via a Y-piece, to the nasal tubes; the lambs were unable to breathe via the mouth. Tidal flow was recorded from the signal generated by a differential pressure transducer (Grass, Instrument Co., Quincy, MA) and volume was obtained by electrical integration of this signal. We measured changes in Ppl by connecting the intrapleural balloon to a pressure transducer held at the midthoracic level (22). All signals were recorded on an eight-channel polygraph (Graphtec, Tokyo, Japan).

After ventilatory measurements were made, the nasal tubes were removed and 11 of the lambs (six treated and five control) were lightly anesthetized with Saffan (Alphaxalone/alphadolone acetate; Pitman Moore, Sydney, Australia) administered i.v. at 15 mg/h/kg. A cuffed endotracheal tube (5 mm diameter) was inserted into the trachea. Anesthesia was used so that lambs could be studied while intubated; initial studies on unanesthetized lambs using a face mask were unsuccessful owing to gas leakage. Lambs continued to breathe spontaneously and maintained arterial gas tensions and pH within the normal range. Lung volume at FRC was measured by a helium washout technique modified for neonatal use (23). For this purpose, we used a water-sealed spirometer (Godart, Paeditest, Bilthoven, The Netherlands, 200-mL bell, 1080 mL of dead space) containing a blower and CO_2 absorber; O_2 was bled into the system to maintain a constant spirometer volume. After the FRC determination, the flow of O_2 was stopped and the change in spirometer volume over 1 min was used to measure $\dot{V}O_2$.

While the lambs were still intubated and anesthetized, using the spirometer, we made measurements of static respiratory compliances (Crs, Cl, and Cw) in six treated and five control lambs. To make these measurements, we continuously recorded Pm via a side port on the endotracheal tube, Ppl, and respired volume while the lambs breathed quietly into and out of the spirometer. A modified weighted spirometer technique was used (24, 25); when the end-expiratory level was constant, four different weights (35, 45, 57, and 70 g) were placed, in a randomized order, onto the spirometer bell. When a new end-expiratory level had been constant for at least five to eight breaths, the weight was removed (Fig. 1). The measurements were repeated in triplicate. After the measurements on the lambs were completed, the pressure and volume transducers were calibrated. The compliance of the spirometer circuit alone was measured from the change in spirometer volume and pressure by applying the same weights to the bell with the circuit sealed.

At the end of each weekly study, the lambs were returned to their mothers after recovery from anesthesia. At 27–28 d after birth, the lambs were painlessly killed with an i.v. overdose of pentobarbital and the lungs removed for estimation of pulmonary dry weight, DNA content, and protein content. The DNA content of the lungs was measured using a fluorometric assay (26) after homogenization of the tissue and enzymatic protein degradation with proteinase K (27). Pulmonary protein content was determined by dissolving the tissue in NaOH (1 M) at 90°C, then neutralizing with HCl (1 M), before measuring the protein concentration using a standard protein assay (Bio Rad, Richmond, CA).

Analysis of data. Mean V_T, f, and MV were measured from the polygraph tracings during quiet breathing over 70 to 140 breaths. Crs and Cw were measured directly using an established method (28, 29), and Cl was derived from the relationship $1/Crs = 1/Cl + 1/Cw$. To obtain Crs, the change in spirometer volume (ΔV) caused by each weight at end expiration was divided by the change in Pm (ΔPm), and then the compliance of the spirometer circuit alone was subtracted. The effect of gas compression within

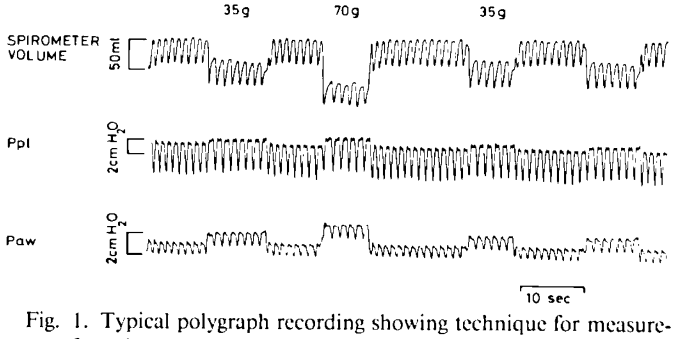

Fig. 1. Typical polygraph recording showing technique for measurement of respiratory compliances by the weighted spirometer method. Changes in spirometer volume, Ppl, and airway (*i.e.* mouth) pressure (*Paw*) in response to weighting the spirometer (35 g, 70 g), measured at end expiration, were used to derive compliances of the respiratory system, lung, and thoracic wall. See text for details.

the lungs was considered negligible and therefore no correction was applied. Static Cw was obtained from the formula $(\Delta V - \Delta V_1)/\Delta Ppl$, where ΔV is the change in volume of the spirometer with the lamb attached, ΔV_1 is the change in volume of the spirometer circuit alone, and ΔPpl is the change in intrapleural pressure (29). Static Cl was then derived from the formula: $Cl = 1/(1/Crs - 1/Cw)$ (29). For each applied weight, the mean change in lung volume was plotted against the associated mean change in pressure (*i.e.* Pm or Ppl) and a line of best fit was drawn to derive the equation describing the pressure-volume relationship. Specific static compliances were calculated by dividing compliance values by the lamb's body weight.

Data obtained from treated and control animals were analyzed using Statistical Analysis System (SAS Inc., Cary, NC) computer software. Differences between measurements of arterial gas tensions and pH, ventilation, FRC, and respiratory compliances were analyzed by one-way analysis of variance with repeated measures. Differences between pulmonary weights and DNA and protein contents at postmortem were analyzed by *t* test. Linear regression analysis was used to determine the degree of association between blood gas values, ventilatory measurements, and respiratory compliances. Values are expressed as mean ± SEM. Respiratory volumes and flow rates are expressed at body temperature, pressure, saturation. This study was approved by the Monash University Committee for Ethics in Animal Experimentation.

RESULTS

The mean period of amniotic and allantoic fluid drainage was 32.9 ± 2.5 d. Over this period, 360 ± 16 mL/d of amniotic fluid and 74 ± 25 mL/d of allantoic fluid were drained. The period between the cessation of fluid drainage and delivery of the lambs was 6.7 ± 1.0 d. The gestational ages of lambs at birth were the same for each group (148.3 ± 0.8 d). Birth weights for treated (4.2 ± 0.2 kg) and control (3.9 ± 0.2 kg) lambs were not significantly different. The postnatal ages and body weights at the time of the weekly studies were not different between the two groups. Mean body weights (both groups) at the time of the four studies were 5.0 ± 0.2 kg (wk 1), 6.6 ± 0.3 kg (wk 2), 8.3 ± 0.3 kg (wk 3), and 10.0 ± 0.5 kg (wk 4). Rectal temperatures of the lambs were not significantly different between the two groups, and the mean value (39.6 ± 0.1°C) did not change with age.

Arterial blood gases and pH. Values obtained at the start of each weekly study are shown in Figure 2. There was no significant difference in Pa_{O_2} between the two groups, and values did not change significantly with age; the combined mean value was 13.46 ± 0.16 kPa (101.2 ± 1.2 mm Hg). Similarly, O_2 saturation values (mean 95.9 ± 0.5%) were not different between the two groups and did not change with age. In treated lambs, mean Pa_{CO_2} (5.33 ± 0.12 kPa, 40.1 ± 0.9 mm Hg) was higher ($p < 0.05$) than in control lambs (5.00 ± 0.08 kPa, 37.6 ± 0.6 mm Hg) and values were not affected by age. Arterial pH was not significantly lower ($0.05 < p < 0.10$) in the treated lambs than in the controls. Arterial pH increased ($p < 0.001$) over the 4 wk from 7.39 ± 0.01 to 7.42 ± 0.01 in treated lambs and from 7.41 ± 0.01 to 7.43 ± 0.01 in the control lambs. In the combined data, arterial pH was negatively correlated with Pa_{CO_2} ($r = -0.4$, $p = 0.001$). There was a reduction with age ($p < 0.001$) in arterial Hb content in both groups (combined), but there was no significant difference between groups. Mean Hb content (both groups) declined from 10.7 ± 0.4 mg/dL at wk 1 to 8.5 ± 0.4 mg/dL at wk 4.

Ventilatory measurements. At all ages, f was significantly greater in treated lambs than in controls; on average, it was 13.3 breaths/min greater in the treated lambs ($p < 0.05$). In both groups, f declined with age ($p < 0.001$); in treated lambs, f declined from 71.3 ± 5.5 (wk 1) to 41.2 ± 3.4 (wk 4) breaths/min, and in controls f declined from 50.1 ± 5.7 (wk 1) to 34.2 ± 3.9 (wk 4) breaths/min (Fig. 3). The difference between the groups diminished with age. When the data were combined, f was inversely correlated with arterial pH ($r = -0.3$, $p = 0.03$), but was not correlated with Pa_{CO_2}.

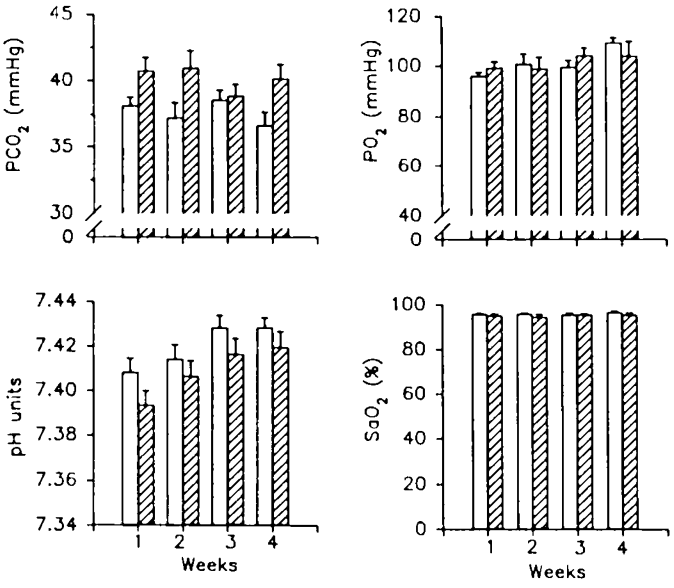

Fig. 2. Gas tensions and pH of arterial blood in control (*open columns*) and treated (*hatched columns*) lambs measured at the time of the weekly studies. SaO_2, - O_2 saturation. Treated lambs had significantly higher P_{CO_2} values than controls ($p < 0.05$), and tended to have lower pH values ($0.05 < p < 0.10$). One mm Hg = 0.133 kPa.

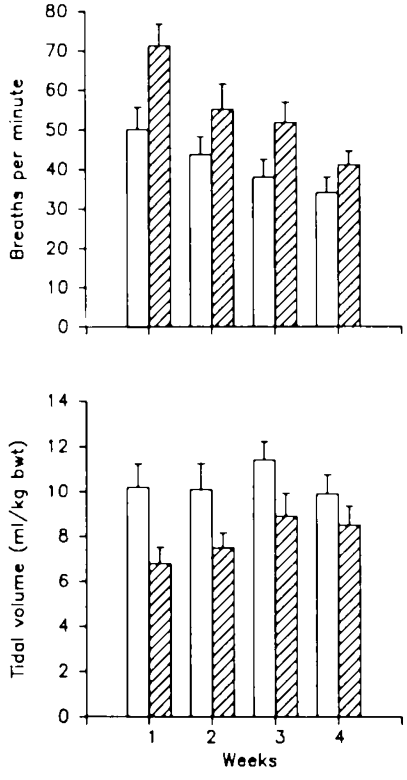

Fig. 3. V_T and f measured at weekly intervals in control lambs (*open columns*) and treated lambs (*hatched columns*). Over the four study periods, treated lambs had higher f ($p < 0.05$) and smaller V_T ($p < 0.05$) than control lambs.

V_T (mL/kg body weight) was smaller in treated lambs than in controls ($p < 0.05$) (Fig. 3). In treated lambs, V_T ranged from 6.8 ± 0.7 mL/kg (wk 1) to 8.5 ± 0.9 mL/kg (wk 4), whereas in control lambs the mean value was 10.4 ± 0.8 mL/kg. V_T was inversely correlated with f ($r = -0.6$, $p < 0.001$).

There was no significant difference in MV between the two groups. In both groups, MV, adjusted for body weight, declined with age ($p < 0.001$); combined data showed a reduction from 500 ± 39 mL/min/kg at wk 1 to 323 ± 13 mL/min/kg at wk 4 (Fig. 4). $\dot{V}O_2$, adjusted for body weight, was not significantly different between the two groups. $\dot{V}O_2$ values (combined data, at standard temperature and pressure, dry) declined with age ($p < 0.001$) from 14.8 ± 0.3 mL/min/kg at wk 1 to 9.2 ± 0.3 mL/min/kg at wk 4. There was a significant positive correlation between MV and $\dot{V}O_2$ ($r = 0.5$, $p < 0.001$).

FRC. There was no significant difference in FRC between the two groups of lambs (Fig. 5). FRC (mL) significantly increased with age ($p < 0.001$) in both groups of lambs (Fig. 5). In contrast, combined values of FRC adjusted for body weight declined ($p < 0.05$) with age, from 24.4 ± 1.3 mL/kg (wk 1) to 21.6 ± 0.9 mL/kg (wk 4).

Respiratory compliances. Measurements of static compliances, Crs, Cl, and Cw, per unit body weight (mL/cm H_2O/kg) are shown in Figure 6. Crs was significantly lower in treated lambs than in controls ($p < 0.05$). With increasing age, values declined ($p < 0.05$) from 13.95 ± 2.34 to 9.81 ± 0.86 mL/kPa/kg (1.37 ± 0.23 to 0.96 ± 0.08 mL/cm H_2O/kg) in treated lambs and from 21.47 ± 3.36 to 15.12 ± 2.18 mL/kPa/kg (2.11 ± 0.33 to 1.48 ± 0.21 mL/cm H_2O/kg) in control lambs. There was no significant effect of age or treatment on Cl; the mean value of Cl for combined data for all ages was 29.70 ± 1.97 mL/kPa/kg (2.91 ± 0.19 mL/cm H_2O/kg). In treated lambs, mean Cw (20.43 ± 2.67 mL/kPa/kg, 2.00 ± 0.26 mL/cm H_2O/kg) was approximately half ($p < 0.001$) that in control lambs (42.95 ± 3.57 mL/kPa/kg, 4.21 ± 0.35 mL/cm H_2O/kg). A significant difference was present at each of the four weekly study periods. When data from both groups were combined, Cw declined significantly with age ($p < 0.001$). When analyzed separately, Cw in control lambs declined significantly from 65.31 ± 7.22 mL/kPa/kg (6.40 ± 0.71 mL/cm H_2O/kg) at wk 1 to 37.92 ± 6.45 mL/kPa/kg (3.72 ± 0.63 mL/cm H_2O/kg) at wk 4, but treated lambs maintained the same Cw values up to 4 wk after birth. There was a significant interaction of age and treatment ($p = 0.003$), indicating that the treated and control groups were differently affected by age.

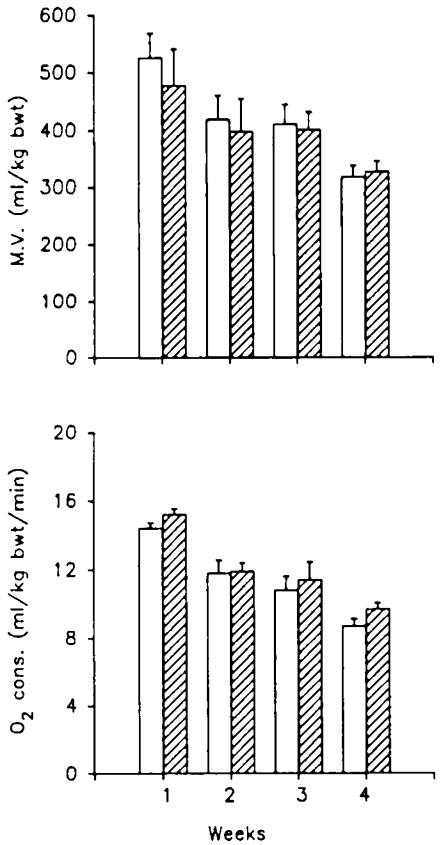

Fig. 4. MV and $\dot{V}O_2$ rates, both shown in relation to body weight, in control (*open columns*) and treated (*hatched columns*) lambs measured at weekly intervals. Both declined with age ($p < 0.001$), and there were no differences between groups.

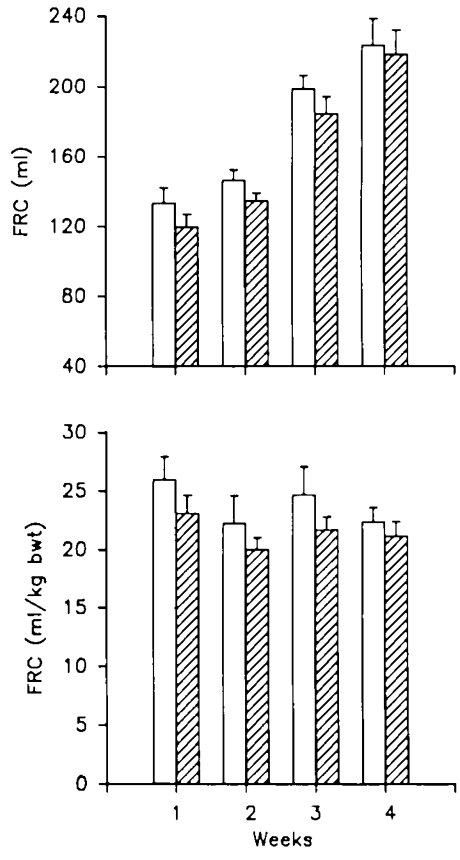

Fig. 5. FRC (body temperature, pressure, saturation) measured by helium dilution at weekly intervals, expressed in mL (*upper graph*) and as mL/kg body weight (*lower graph*). Control lambs, *open columns* and treated lambs, *hatched columns*.

There was a significant positive correlation between arterial pH and both Cw ($p < 0.001$, $r = 0.7$) and Crs ($p < 0.01$, $r = 0.6$) in treated lambs. A significant positive relationship was also present between Cw and P_{ACO_2} ($p < 0.05$, $r = 0.5$) in control lambs (Fig. 7).

Pulmonary weights and DNA and protein contents. The dry lung weights for the two groups, when expressed as a percentage of body weight, were not significantly different, although the mean value for seven control lambs (0.22 ± 0.05%) was greater than that for seven treated lambs (0.18 ± 0.04%). One value in the treated group was more than 3 SD greater than the group mean. If this value was excluded from the analysis, the difference between the two groups became significant ($p = 0.032$); the mean dry lung weight of the six treated lambs was 0.17 ± 0.02% of body weight, which was 23% lower than in control lambs. In treated lambs, the mean total pulmonary DNA content, adjusted for body weight, was 41.8% of that in control lambs; the difference was not significant ($p = 0.076$) due to wide variation between animals. The total pulmonary protein content in the treated lambs (679.0 ± 62.3 mg/kg body weight) was 28% lower than in control lambs (949.4 ± 85.4 mg/kg body weight, $p = 0.034$).

DISCUSSION

This study has shown that oligohydramnios can have lasting effects on the respiratory function of neonatal sheep. The re-

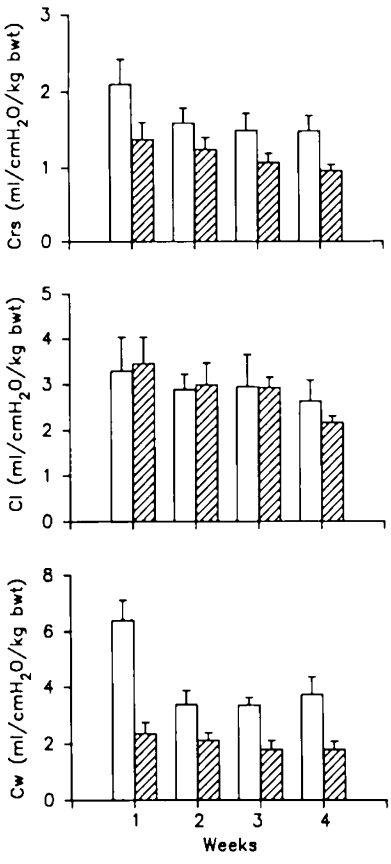

Fig. 6. Static compliances, adjusted for body weight, of the respiratory system (lungs plus chest wall, Crs), lungs (Cl), and chest wall (Cw) in control (*open columns*) and treated (*hatched columns*) lambs measured at weekly intervals. Over the 4-wk study period Crs ($p < 0.05$) and Cw ($p < 0.001$) were lower in treated lambs than in controls. One mL/cm H_2O = 10.2 mL/kPa.

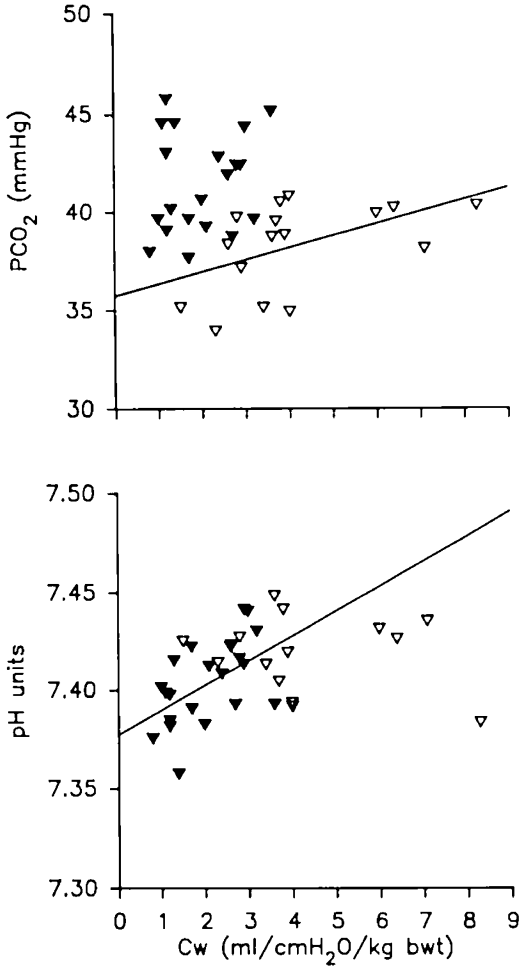

Fig. 7. *Upper panel* shows relationship between static Cw and $Paco_2$ in control lambs. The regression line ($Paco_2$ = 35.7 + 0.6Cw) indicates the significant correlation between Cw and $Paco_2$ ($r = 0.5$, $p < 0.05$) in control lambs only. *Lower panel* shows relationship between Cw and pH in treated lambs. The regression line (pH = 7.4 + 0.6Cw) shows a significant correlation between Cw and arterial pH ($r = 0.5$, $p < 0.05$) in treated lambs only. *Open symbols*, control lambs; *closed symbols*, treated lambs. One mm Hg = 0.133 kPa; 1 mL/cm H_2O = 10.2 mL/kPa.

moval of amniotic fluid over most of the last third of gestation did not affect the length of gestation or the birth weight of lambs. Most of the lambs were born without assistance, and all established ventilation spontaneously. Apart from transient stiffness in the limb joints of two lambs and in the neck of one, all treated lambs were able to walk and feed normally within 24 h of birth, and all grew normally. In observing their behavior, it was not possible to distinguish between treated and untreated lambs.

The most striking effects of oligohydramnios, each of which persisted for the first 4 postnatal wk, were an increased f, reduced V_T, a mild hypercapnia, and a reduced Crs and Cw. It is likely that these effects were causally related, and we propose that the primary cause was the reduction, in treated lambs, of Cw; because Cl was similar in both groups, the reduced Crs was a consequence of the reduction in Cw. A decreased Cw is analogous to a stiff chest wall induced, for example, by a thoracic brace or splint, and would be expected to cause a pattern of rapid, shallow breathing such as we observed after oligohydramnios. A similar pattern of breathing has been shown to occur in newborn guinea pigs (with no change in minute ventilation per unit of body weight) after prolonged oligohydramnios (11). In accordance with our findings, a recent study of human infants born after midtrimester amniocentesis found a lower dynamic compliance of the respiratory system, but normal thoracic gas volumes (30). The increase in $Paco_2$, despite a normal MV, may have resulted from a reduction in alveolar ventilation due to an increased f and a reduced V_T.

The elevation in $Paco_2$ and the tendency for arterial pH to be reduced were also probably caused by the restricted movements of the chest wall. Owing to the chronic nature of the chest wall stiffness, some compensation may have occurred (*e.g.* increased renal H^+ and reduced bicarbonate excretion), such that the arterial pH was only slightly (nonsignificantly) reduced. Apparently, under these conditions, a balance must be reached between the need to maintain a normal $Paco_2$, and pH of cerebrospinal fluid, and the extra work of breathing due to the stiffer chest wall. Respiratory compromise in the neonate with a stiff chest wall may present an apparent paradox. A highly compliant chest wall, as seen in the immediate newborn, can also result in respiratory compromise, as the rib cage readily deforms during each inspiration (31). This effect is supported by our data from control lambs (Fig. 7) in which Cw was significantly correlated with $Paco_2$ ($r = 0.5$, $p < 0.05$). However, it seems likely that an excessively stiff chest wall may also lead to respiratory compromise due to restrictions on the movements of the lung with each inspiratory effort, resulting in an effective reduction in alveolar ventilation. Our finding of a significant correlation between Cw and arterial pH ($r = 0.7$, $p < 0.001$) in the treated lambs (Fig. 7) supports this conclusion.

It is not immediately apparent how oligohydramnios could have lasting effects on the compliance of the chest wall. Previous studies have indicated that the spinal column of fetal sheep (6) and humans (32) subjected to oligohydramnios is more flexed *in utero* than normal, and that the dome of the diaphragm moves

further into the thorax (9, 33). Increased trunk flexion and the resulting reduction in fetal lung expansion (5, 6) may impair the normal development of the rib cage, intercostal muscles, or abdominal walls, each of which could affect Cw. In fetal sheep, it has been found that the rib cage becomes narrower as a result of amniotic and allantoic fluid removal (9) and this may affect the development and mechanical properties of the ribs. Observations of human infants after oligohydramnios have shown a bell-shaped thorax and the oligohydramnios tetrad syndrome suggestive of pressure deformities of the body (4).

Oligohydramnios has frequently been associated with pulmonary hypoplasia and structural and biochemical immaturity of the lungs (3). These changes have usually been assumed to be the cause of postnatal respiratory insufficiency after such pregnancies. A previous study of fetal sheep subjected to a similar period of oligohydramnios showed that the lungs were hypoplastic at postmortem approximately 10 d before term (5). Taken together, our measurements of pulmonary dry weights, DNA contents, and protein contents suggest that the lungs may have still been mildly hypoplastic at 4 wk. However, there was no evidence of structural or maturational retardation of lung development based on our measurements of Cl, which were the same as in control lambs. In these studies, we were unable to measure the surfactant content of the lungs.

In the light of previous observations on the tissue weights and structural and biochemical indices of lung development after oligohydramnios, we were surprised that our measurements of FRC, as well as Cl were not significantly affected by oligohydramnios. It is possible that FRC was maintained at a higher level than expected in the treated lambs owing to their higher f. It has been proposed that human neonates, which normally have a relatively compliant chest wall, maintain their FRC partly by their high breathing rates (34). It is also possible that a stiff chest wall may more effectively oppose pulmonary recoil at end expiration, resulting in the maintenance of a near normal FRC, because it is known that the elasticity of the thoracic wall plays an important role in determining the resting volume of the lungs (35). In the converse situation seen in premature human infants, a more compliant chest wall, as evidenced by rib cage distortion, may not maintain an adequate transpulmonary pressure at end expiration, resulting in a decreased FRC (31).

The use of anesthesia and tracheal intubation to measure respiratory compliances and FRC may have affected the values obtained. However, our choice of anesthetic agent and dose was such that ventilation was not impaired. Furthermore, because both groups of lambs were anesthetized to the same degree, differences between groups are likely to be representative of differences in the unanesthetized state.

The severity and nature of the effects of oligohydramnios on the fetal and neonatal respiratory system are likely to be related to the timing and duration of the period of amniotic fluid lack (36). None of our lambs died or apparently suffered as a consequence of respiratory insufficiency after oligohydramnios and all grew normally, indicating that the respiratory effects were mild (*i.e.* sublethal or asymptomatic). The period of oligohydramnios began after or late in the canalicular stage of fetal lung development, when the lungs are considered to be highly affected by their physical environment (36); in fetal sheep, the canalicular period begins at about 80 d of gestation (37). Thus, had the period of oligohydramnios started earlier, the respiratory effects may have been more marked. Further experiments are needed to determine whether this is the case. It is also possible that our termination of fluid drainage several days before parturition allowed some reversal of the respiratory effects of oligohydramnios. Our results in the sheep should be related to the human with caution, because the fetal sheep appears to be more resistant to the effects of prolonged oligohydramnios.

The effects of oligohydramnios lasted for up to 4 wk after birth, although there was evidence for amelioration in some of them. Although there was no evidence of a recovery toward control values in chest wall compliance, the breathing pattern (V_T and f) tended to change toward control values by the 4th postnatal week. This occurred in spite of a maintained hypercapnia in the treated lambs. Further studies are needed to determine the postnatal duration of the effects of oligohydramnios.

Our control data showed changes related to postnatal age that provide information on the functional maturation of the respiratory system after birth. For example, as noted in a previous study in lambs (20), there was a significant increase in arterial pH over the 4 wk after birth; this was matched by a tendency for $Paco_2$ to decline and Pao_2 to rise. V_T (mL) increased and f decreased with age, reflecting the increasing dimensions of the lungs and thoracic cage and their changing mechanical properties. MV and $\dot{V}o_2$ (both related to body weight) declined with age, probably due to a weight-related decrease in metabolic rate. The absence of a difference in both of these parameters between the two groups of lambs suggests that metabolically they were similar. The older lambs may have been more affected by the room temperature, which, for their age, was high relative to their thermoneutral zone (21). In both groups of lambs, FRC (mL) increased with age, whereas FRC (mL/kg) decreased with age, indicating that body weight increased more rapidly than FRC. The FRC values in our control lambs (22–24 mL/kg) were similar to those obtained in other studies of human and ovine neonates. In human infants, values of 16–26 mL/kg have been obtained by helium dilution (38–40). A mean value of 31 mL/kg was obtained by helium dilution in lambs 1–2 h after birth (23).

Our control values of Crs (15.1–21.5 mL/kPa/kg) are similar to values obtained in anesthetized newborn mammals [18.5 mL/kPa/kg, (41)] and in unanesthetized newborn lambs [22.2 mL/kPa/kg, (28)]. These values for Crs are higher than those obtained in healthy full-term human infants at 1–28 d of age [11.3 and 10.2 mL/kPa/kg (25, 42)]. Static Crs was high (21.5 mL/kPa/kg) in our control group in the 1st postnatal week compared with subsequent weeks, due largely to a highly compliant chest wall. Overall, Cw was approximately double Cl in control lambs; our mean control values of Cw (37.7–65.3 mL/kPa/kg, 3.7–6.4 mL/cm H_2O/kg) are similar to values obtained in term infants (42.8 mL/kPa/kg, 4.2 mL/cm H_2O/kg) (31). A relatively high Cw is characteristic of newborn dogs (43), goats (44), and lambs (28), in which Cw was 3–4 times greater than Cl. In anesthetized infants (3–105 d) a Cw value of approximately 61.2 mL/kPa/kg (6 mL/cm H_2O/kg) was obtained, which was several times greater than Cl (45) and which is indicative of the very flexible rib cage of the neonate. Soon after birth, the rib cage apparently becomes much stiffer, the mechanism for which is unknown.

We conclude that oligohydramnios in sheep can produce sublethal but lasting effects on the postnatal respiratory system. These effects appear to be due principally to a decreased Cw rather than to changes in the lungs themselves. It seems possible that oligohydramnios-induced respiratory insufficiency previously attributed to pulmonary hypoplasia may be due, at least in part, to increased but undetected stiffness of the chest wall.

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