

## *Halothane Anesthesia Reduces Pulmonary Function in the Newborn Lamb*

Scott L. Robinson, M.D.,\* Charles A. Richardson, Ph.D.,† Mary M. Willis, B.S.,‡ George A. Gregory, M.D.§

To study the effects of anesthesia on respiratory function of the neonate, the authors investigated the effect of breathing 100% oxygen and of breathing oxygen plus 0.75 MAC halothane on functional residual capacity, lung and airway resistance, expired minute volume, work of breathing, lung compliance, and blood gases and pH in nine 5-8-day-old, 4.6-7.7-kg lambs. Breathing 100% oxygen increased Pa<sub>O<sub>2</sub></sub> but had no effect on Pa<sub>CO<sub>2</sub></sub>, minute ventilation, or lung mechanics. Three-fourths MAC halothane depressed minute ventilation 34% ± 13% (*P* < 0.05) and increased Pa<sub>CO<sub>2</sub></sub> 50% ± 5% (*P* < 0.05). Lung and airway resistance increased 59% ± 26% (*P* < 0.05); work of breathing decreased (*P* < 0.05); and lung compliance was unchanged. Functional residual capacity was reduced 32% ± 6% (*P* < 0.05), which may be due to loss of diaphragm and intercostal muscle function and to an inability to take deep breaths. The authors conclude that 0.75 MAC halothane significantly impairs the pulmonary function of lambs who breathe spontaneously. Similar changes in human infants could account for the hypoxemia and hypercarbia that often are seen during anesthesia. (Key words: Anesthesia; pediatric. Anesthetics, volatile; halothane. Ventilation: anesthetics, effect of.)

HALOTHANE DECREASES functional residual capacity (FRC) 10-50% and increases the alveolar-arterial oxygen gradient of adult humans.<sup>1,2</sup> These changes have been attributed to airway closure, loss of elastic recoil of the lung, and obesity. Similar studies have not been done in the newborn. The lungs and chest wall of the newborn are less well developed than those of the adult; the Pa<sub>O<sub>2</sub></sub><sup>3</sup> is lower, the FRC<sup>4</sup> smaller, and the oxygen consumption (ml · kg<sup>-1</sup> · min<sup>-1</sup>) greater<sup>5</sup> than those of awake adults. Elastic recoil of the lungs and chest wall of the newborn also are reduced.<sup>6</sup> Because of these differences and the impression that anesthesia has exaggerated effects on respiratory function of the neonate, we studied the consequences of breathing 100% oxygen

and of breathing halothane-plus-oxygen on lung mechanics, functional residual capacity (FRC), arterial blood gases, pH<sub>a</sub>, and the alveolar-arterial oxygen pressure gradient [(A-a)D<sub>O<sub>2</sub></sub>] of spontaneously breathing newborn lambs.

### Methods

We studied nine healthy, unmedicated 5-8-day-old, 4.6 to 7.7-kg lambs. Minimum alveolar concentration (MAC) for halothane was determined at 1-3 and 7-8 days of age. On a separate day, the animals were brought to the laboratory, blindfolded to reduce anxiety, and lightly restrained in the left lateral decubitus position. A 22-gauge polyethylene catheter was inserted into a small, superficial artery to monitor blood gases. A 16-gauge angiocath (Deseret Co., Sandy, Utah) was inserted into the pleural space through a small intercostal incision and any residual pleural air evacuated. We connected the pleural catheter to a pressure transducer and displayed its output on a polygraph. To obtain end-tidal gas samples, a 20-gauge polyethylene catheter was inserted into the trachea through the cricothyroid membrane. Ten 1-2-ml samples of gas were taken from the trachea during the last half of exhalation, and the entire 10-20-ml gas sample injected into a Beckman LB-2<sup>®</sup> infrared analyzer that previously had been calibrated with known concentrations of halothane. The analyzer head was filled with CO<sub>2</sub> to prevent CO<sub>2</sub> from interfering with the determination of halothane concentrations. All vascular, pleural, and tracheal catheter insertion sites were anesthetized with 0.5-0.75 ml of 1% lidocaine before the catheters were inserted.

After a 30-min recovery period, a closely fitting face mask was applied to the animal's snout. To reduce the dead space of the mask, we attached a rubber sleeve inside the conical mask and fixed the sleeve to both ends of the mask. When the mask and sleeve were applied to the animal, the sleeve fit tightly against the animal's face. The only dead space external to the animal was between the tip of the snout and the mask adaptor. At the end of the experiment, we measured this dead space by occluding the nostrils of the animals and filling the space with water. The mask had not been

\* Assistant Clinical Professor of Anesthesia.

† Adjunct Assistant Professor of Anesthesia, Physiology, and CVRI.

‡ Staff Research Associate.

§ Professor of Anesthesia and Pediatrics.

Received from the Department of Anesthesia, Pediatrics, and the Cardiovascular Research Institute, University of California, San Francisco, California. Accepted for publication November 12, 1984. Supported in part by a grant from Ohio Medical Products. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, Chicago, 1978.

Address reprint requests to Dr. Gregory: Department of Anesthesia, University of California, San Francisco, Room S436, Third and Parnassus Avenues, San Francisco, California 94143.

removed from the animal's face. The measured volume was subtracted from the measured FRC.

FRC was measured by the rebreathing helium dilution technique.<sup>7</sup> The pleural pressures and the respiratory gas flow<sup>8</sup> were recorded on electromagnetic tape and a polygraph. Tidal volume, minute ventilation, lung and airway resistance, lung compliance, and total work of breathing were calculated with a PDP-8 digital computer and standard algorithms. The pneumotachograph was calibrated with a calibrated syringe. The length of the connecting tubing of the differential strain gauge was adjusted to make the electrical output of the strain gauge zero when a pressure simultaneously was applied to both sides of the strain gauge. The pneumotachograph output was corrected for changes in carbon dioxide and oxygen concentrations and for water content of the gas. The amplitude-frequency response of the strain gauges and connecting tubes used to measure pressures were flat to 15 Hz. Rectal temperature was monitored with a Yellow Springs® thermistor and maintained at 38.5°–39.5° C (the normal temperature of the lamb) with a heat lamp and water mattress.

We assessed pulmonary function while the lambs were 1) awake and spontaneously breathing air; 2) awake breathing 100% oxygen; and 3) anesthetized, spontaneously breathing oxygen plus 0.75 MAC halothane. This dose of halothane was chosen because it is sedative, causes major changes in the breathing pattern of lambs, and is similar to the concentration used to anesthetize many sick human infants. Measurements were made 15 min after the pleural pressure, and tidal volume tracings were stable. Arterial blood gases were measured just before making each set of lung function measurements. Data were analyzed by repeated measures analysis of variance and the Student-Newman-Keuls test. A level of  $P < 0.05$  was accepted as statistically significant. These studies were approved by the Animal Care Committee.

### Results

The average MAC value for halothane was 1.09% ± 0.03%. Figure 1 shows the changes in FRC per kilogram of body weight. Breathing 100% oxygen did not change FRC significantly. The addition of 0.75 MAC halothane decreased FRC 32% ± 6% below the control value ( $P < 0.05$ ).

Table 1 shows the changes in minute ventilation, lung and airway resistance, lung compliance, and work of breathing as a per cent of the awake, control values. Tidal-volume, respiratory rate, minute ventilation, lung compliance, lung and airway resistance, and work of breathing were unchanged by oxygen breathing. Respiratory rate, tidal volume, minute ventilation, and work of breathing decreased significantly during anesthesia

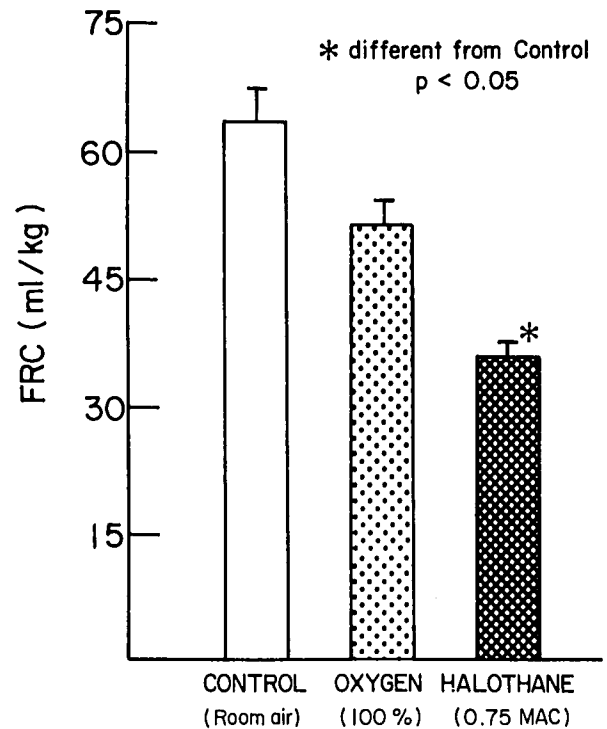


FIG. 1. Changes in FRC/kg body weight in 1–3-day-old lambs with breathing room air, 100% oxygen, and 100% oxygen plus 0.75 MAC halothane. Values are mean ± 1 SD.

( $P < 0.05$ ). Lung and airway resistance increased 59% ± 26% with anesthesia ( $P < 0.05$ ); lung compliance was unchanged.

Table 2 shows the arterial blood gas values in the three conditions. Breathing 100% oxygen increased  $P_{aO_2}$  ( $P < 0.01$ ) without changing  $P_{aCO_2}$ ;  $pH_a$  decreased

TABLE 1. Pulmonary Function Changes with Anesthesia

	Control ( $F_{IO_2} = 0.21$ )	Per Cent of Control	
		Awake ( $F_{IO_2} = 1.0$ )	Anesthetized (0.75 MAC Halothane + $F_{IO_2} = 1.0$ )
Respiratory rate (breaths/min)	79 ± 25	100 ± 5	80 ± 9*
Tidal volume (ml/kg)	5.3 ± 1.3	105 ± 3	81 ± 7*
Minute ventilation ( $l \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ )	0.43 ± 0.11	104 ± 6	66 ± 13*
Lung compliance (ml/cm H <sub>2</sub> O)	4.04 ± 1.07	109 ± 25	113 ± 12
Lung and airway resistance ( $\text{cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$ )	9.8 ± 4.7	113 ± 6	159 ± 26*
Work of breathing (J)	38 ± 5	130 ± 20	80 ± 4*
Functional residual capacity (ml/kg)	64 ± 8	93 ± 5	68 ± 6*

\*  $P < 0.05$ .

TABLE 2. Arterial Blood Gases\*

	Awake (F <sub>I</sub> O <sub>2</sub> 0.21)	Awake (F <sub>I</sub> O <sub>2</sub> 1.0)	0.75 MAC Halothane (F <sub>I</sub> O <sub>2</sub> 1.0)
Pa <sub>O</sub> <sub>2</sub> (mmHg)	73 ± 10	331 ± 103†	241 ± 109†
Pa <sub>CO</sub> <sub>2</sub> (mmHg)	38 ± 3	43 ± 5	57 ± 4†
pH	7.45 ± .03	7.37 ± .03†	7.22 ± 0.4†
(A-a)D <sub>O</sub> <sub>2</sub> (mmHg)	34 ± 8	321 ± 85	406 ± 92

\* Mean ± SD.

† Significantly different from awake (F<sub>I</sub>O<sub>2</sub> 0.21). *P* < 0.05.

slightly. Anesthesia increased Pa<sub>CO</sub><sub>2</sub> to 57 ± 4 mmHg (*P* < 0.05) and decreased p<sub>H</sub><sub>a</sub> to 7.22 ± 0.40 (*P* < 0.05). There was no effect on the alveolar-arterial gradient for oxygen ((A-a)D<sub>O</sub><sub>2</sub>).

### Discussion

Halothane has several effects on breathing. It increases the threshold voltage required to stimulate central respiratory neurons<sup>9</sup> and diminishes the contribution of intercostal muscles to ventilation.<sup>10</sup> The latter is of more significance to infants than adults because the intercostal muscles of infants contribute significantly to ventilation.<sup>11</sup> Clinically, our lambs appeared to use their intercostal muscles to breath when awake but not when anesthetized. Rapid eye movement sleep produces similar effects in neonates, *i.e.*, it decreases intercostal nerve and muscle activity, decreases FRC, and tidal volume, and causes inspiratory retractions.<sup>11</sup>

The FRCs of our lambs are slightly larger than those reported by Shaffer *et al.*,<sup>12</sup> which may be explained by the fact that they measured FRC in tracheostomized, premature lambs. Our animals breathed through a tight-fitting mask and were born at term. Therefore, our FRCs included the volume of the upper airway as well.

There was a nonsignificant (7.5%) decrease in FRC when our lambs breathed 100% oxygen, which is similar to the decrease reported by Don<sup>1</sup> and Hickey *et al.*<sup>2</sup> and their co-workers in adult humans. This decrease, if real, presumably is due to resorption atelectasis. Three-fourths MAC halothane decreased the FRC of our lambs 32% from control.

In our animals, the changes in FRC during anesthesia are probably due to reduced intercostal muscle function, abolition of periodic deep breaths, and shallow breathing in subjects whose ratio of FRC to closing volume is low. Since it has not been possible to measure closing volume accurately in newborn animals or humans, the effects on closing volume are speculative. The decrease in FRC in our animals is about twice that reported by Hickey *et al.*<sup>2</sup> in adult humans. The (A-a)D<sub>O</sub><sub>2</sub> is much larger in our awake, air- and oxygen-breathing lambs and in

human infants than it is in adults,<sup>2</sup> which may explain why there was no significant change in (A-a)D<sub>O</sub><sub>2</sub> in our lambs during anesthesia.

Anesthesia produced a 59% increase in lung and airway resistance in our animals. Respiratory work did not increase to compensate for the increased airway resistance. Respiratory rate, tidal-volume, and minute ventilation decreased. Consequently, Pa<sub>CO</sub><sub>2</sub> increased. The increase in lung and airway resistance in our lambs is very different from the findings in adult animals and humans, where resistance is unchanged<sup>13,14</sup> or decreased<sup>15-18</sup> from control. Previous studies were done in tracheostomized or tracheally intubated subjects, which measured the resistance of the trachea and intrapulmonary airways. Our studies were done with a close-fitting face mask. Because of this, our measurements included the resistance of the nose and pharynx. It is probable that some upper airway obstruction occurred during anesthesia, despite attempts to prevent it from occurring. A second difference between our studies and those of others is the magnitude of the decrease in FRC. Halothane reduces the FRC of healthy adults by 3-20%,<sup>1,2</sup> the average decrease being about 10%. The FRC of our lambs decreased an average of 32%. This degree of atelectasis increases lung and airways resistance.<sup>19</sup> From Dubois' data,<sup>19</sup> nearly all of the increase in resistance can be accounted for by the decrease in FRC.

Graff *et al.*<sup>20</sup> increased resistance to breathing by reducing the size of the endotracheal tube in 10 anesthetized (halothane), tracheally intubated 2-4-week-old infants. Their average Pa<sub>CO</sub><sub>2</sub> initially was >50 mmHg. Their work of breathing increased and their Pa<sub>CO</sub><sub>2</sub> remained constant during anesthesia. We are uncertain why these infants could maintain their Pa<sub>CO</sub><sub>2</sub> at this elevated level. The Pa<sub>CO</sub><sub>2</sub>s and lung and airway resistance of our lightly anesthetized lambs were consistently elevated—our lambs did not increase their work of breathing.

Despite the decrease in FRC and the increase in lung and airway resistance, lung compliance did not change. This lack of change is probably due to the fact that tidal volumes and inspiratory pressures decreased a similar amount (19% ± 7% and 23% ± 8%) during anesthesia.

The 20% decrease in work of breathing during anesthesia was associated with a 34% decrease in minute ventilation and a 23% decrease in pleural pressure change during inspiration, which accounts for the decrease in work.

Steward<sup>21</sup> found that some preterm infants who spontaneously breathed a mixture of nitrous oxide, halothane, and oxygen developed respiratory complications, including apnea. Since human infants and lambs have similar chest walls and lungs, we speculate that the preterm

infants studied by Steward may have experienced similar decreases in FRC to those seen in our lambs.

Because of the changes seen in lung function and gas exchange in this study, we suggest that ventilation should be controlled in anesthetized infants who are less than 6 months old. Also, perhaps several deep breaths at the conclusion of anesthesia would reexpand atelectatic areas of the lung and reduce the likelihood of postoperative atelectasis.<sup>7</sup>

### References

1. Don HF, Waliba M, Cuadrado L, Kelkar K: The effects of anesthesia and 100% oxygen on the functional residual capacity of the lungs. *ANESTHESIOLOGY* 32:521-529, 1970
2. Hickey RF, Visick WD, Fairley HB, Fourcade HE: Effects of halothane anesthesia on functional residual capacity and alveolar-arterial oxygen tension difference. *ANESTHESIOLOGY* 38:20-24, 1973
3. Koch G, Wendel H: Adjustment of arterial blood gases and acid-base balance in the newborn infant during the first week of life. *Biol Neonate* 12:136-161, 1968
4. Chu J, Clements JA, Cotton EK, Klaus MH, Sweet AY, Tooley WH: Neonatal pulmonary ischemia. Part I: Clinical and physiological studies. *Pediatrics* 40:709-782, 1967
5. Hey EN: The relation between environmental temperature and oxygen consumption in the newborn baby. *J Physiol (Lond)* 200:589-603, 1969
6. Mansell A, Bryan C, Levison H: Airway closure in children. *J Appl Physiol* 33:711-714, 1972
7. Gregory GA, Edmunds LH Jr, Kitterman JA, Phibbs RH, Tooley WH: Continuous positive airway pressure and pulmonary and circulatory function after cardiac surgery in infants less than 3 months of age. *ANESTHESIOLOGY* 43:426-431, 1975
8. Gregory GA, Kitterman JA: Pneumotachograph for use with infants during spontaneous or assisted ventilation. *J Appl Physiol* 31:766-767, 1971
9. Ngai SH, Katz RL, Farhie SE: Respiratory effects of trichlorethylene, halothane and methoxyflurane in the cat. *J Pharmacol Exp Ther* 148:123-130, 1965
10. Tusiewicz K, Bryan AC, Froese AB: Contributions of changing rib cage-diaphragm interactions to the ventilatory depression of halothane anesthesia. *ANESTHESIOLOGY* 47:327-337, 1977
11. Knill R, Bryan C: An intercostal-phrenic inhibitory reflex in human newborn infants. *J Appl Physiol* 40:352-356, 1976
12. Shaffer TH, Delivoria-Papadopoulos M, Arcinue E, Paez P, Dubois AB: Pulmonary function in premature lambs during the first few hours of life. *Respir Physiol* 28:179-188, 1976
13. Brakensiek AL, Bergman NA: The effects of halothane and atropine on total respiratory resistance in anesthetized man. *ANESTHESIOLOGY* 33:341-344, 1970
14. Hickey RF, Graf PD, Nadel JA, Larsen CP: The effects of halothane and cyclopropane on total pulmonary resistance in the dog. *ANESTHESIOLOGY* 31:334-343, 1969
15. Gold MI: Anesthesia for the asthmatic patient. *Anesth Analg* 49:881-887, 1980
16. Schneider SM, Popper EM: Anesthesia for the asthmatic patient. *ANESTHESIOLOGY* 22:886-892, 1961
17. Colgan FJ: Performance of the lungs and bronchi during inhalation anesthesia. *ANESTHESIOLOGY* 26:778-785, 1965
18. Hirshman CA, Bergman NH: Halothane and enflurane protect against bronchospasm in an asthma dog model. *Anesth Analg* 57:629-633, 1978
19. Dubois AB: Resistance to breathing, *Handbook of Physiology: Respiration*. Washington, D. C., American Physiological Society, 1964, pp 451-462
20. Graff TD, Sewall K, Lim HS, Kantto, Morris RE Jr, Benson OW: The ventilatory response of infants to airway resistance. *ANESTHESIOLOGY* 27:168-175, 1966
21. Steward DJ: Preterm infants are more prone to complications following minor surgery than are term infants. *ANESTHESIOLOGY* 56:304-306, 1982