Time Dependence of Lung Mechanics in Preterm Lambs

PETER RICHARDSON, W. ROBERT PACE, ERNESTO VALDES, SCOTT JARRIEL, AND
THOMAS N. HANSEN

Departments of Pediatrics and Medicine, Baylor College of Medicine, Houston, Texas 77030

ABSTRACT. The passive exhalation flow-volume plots of preterm lambs exhibit curvature. To explain this curvature, we proposed two mathematical models that could predict the measured passive exhalation flow-volume data well. One model takes into account the flow and volume dependence of resistance and compliance. The second model emphasizes the time dependence of lung mechanics and considers the respiratory system viscoelastic properties and the analogy of the lung to two electronic resistor-capacitor circuits connected in parallel. We attempted to determine which of the two models is more valid by analyzing passive exhalation flow-volume data that were obtained while briefly obstructing flow midway through deflation. In 14 preterm lambs (130 d gestation), the flow of exhaled gas increased from 76 ± 35 mL/s when measured just before obstruction to 90 ± 30 mL/s when measured immediately after release of the obstruction ($p < 0.0001$). This finding suggests that a time-dependent phenomenon was taking place during obstruction and is inconsistent with the model based upon the flow and volume dependence of resistance and compliance. We made similar measurements in four near-term (143–146 d gestation) and four full-term lambs (9–12 d of age). Their flow-volume curves were relatively linear, and they showed no increases in flow after removal of the obstruction. The results of this study strongly suggest that time-dependent phenomena caused the curvilinearity in the passive exhalation flow-volume plots of preterm lambs. We suspect that the time-dependent phenomena is associated with the premature lung and with parenchymal lung disease. The models of viscoelastance and of parallel inhomogeneities in the lung are consistent with our observations. (*Pediatr Res* 31: 276–279, 1992)

Abbreviations

τ , expiratory time constant
C, compliance
R, resistance

We have previously reported that in preterm lambs (130 d gestation) the flow-volume plots during passive exhalation are curvilinear (with concavity toward the flow and volume axes (1)). For the flow-volume curve to remain linear during exhalation, the product of C and R must remain constant; under these conditions, passive exhalation is well described using a single τ . To explain the departure from linearity in the flow-volume plots of the preterm lamb, we proposed two possible explanations.

First, the respiratory system C or R might have been volume- and flow-dependent (2), causing the τ to increase during exhalation or, second, time-dependent factors could cause τ to increase during passive exhalation. The time-dependent factors that we considered were 1) the viscoelastic (3) properties of the lung and chest wall, 2) parallel inhomogeneities (4) in the lung, and 3) the compliance of the large airways.

To distinguish between volume- and flow-dependent and time-dependent factors, we obstructed the flow briefly part way through exhalation. We reasoned that, if the curvature in the flow-volume plot was due to the volume and flow dependence of C and R, then the flow-volume plot after release of the obstruction should continue as if no obstruction had occurred. However, if the curvature was the result of time-dependent factors influencing τ , then after the release of the obstruction the flow would jump to a peak flow greater than the flow just before the obstruction of flow. Such an increase in flow could be explained by stress recovery during the period of obstruction or, if parallel inhomogeneities exist, by the slowly emptying lung units recharging the rapidly emptying lung units during the period of obstruction.

We measured flow during passive exhalation of preterm lambs, and we obstructed flow briefly at about midexhalation. We then conducted similar studies using near-term lambs and 9- to 12-d-old lambs and compared their results with the results obtained from the preterm lambs.

MATERIALS AND METHODS

Animal preparation. We studied 14 preterm lambs (range 129–133 d gestation) that weighed 2.0 to 2.7 kg (mean 2.2 kg), four near-term lambs (143 and 146 d gestation) that weighed 2.4 to 2.8 kg, and four 9- to 12-d-old lambs that weighed 6.2 to 9.5 kg.

The preterm and near-term lambs were the product of twin pregnancies. We delivered these lambs by cesarean section using ketamine for sedation and epidural anesthesia (1). We first placed the ewes supine on the operating table, and after hysterotomy we exteriorized the heads of the fetuses, intubated them with 4.0-mm inner diameter cuffed endotracheal tubes (Mallinckrodt Critical Care, Argyle, NY), suctioned their airways, expanded their lungs with oxygen at a pressure of 35 cm H₂O for 5 s, and then lowered the airway pressure to 5 cm H₂O for 5 s (5). We repeated this lung expansion procedure 10 times and then delivered the fetuses, dried them with towels, and placed them under an infant warmer on a heating pad that was adjusted to maintain their rectal temperature at 39°C. Next, we performed cut downs on the hindlimbs of the lambs, after administering a local anesthetic (1% lidocaine), and placed catheters in a hindlimb artery and vein. After connecting the arterial catheter to a pressure transducer, we sedated each of the lambs with pentobarbital.

We mechanically ventilated the preterm and near-term lambs using a fraction of inspired O₂ of 1.0, a peak inspiratory pressure of 35 cm H₂O, a positive end-expiratory pressure of 5 cm H₂O, an inspiratory time of 0.2 s, and a rate of 60 breaths/min. After

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Correspondence: Peter Richardson, Ph.D., Director of Research and Development, Bunnell, Incorporated, 436 Lawndale Drive, Salt Lake City, UT 84115.

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allowing the lambs to stabilize for 1 h, we adjusted peak inspiratory pressure and fraction of inspired O_2 to maintain arterial CO_2 and O_2 pressures between 35 and 45 mm Hg (5–6 kPa) and 60 and 80 mm Hg (8–11 kPa), respectively. At 4 h postnatal age, we paralyzed the lambs with pancuronium bromide (0.25 mg/kg). We monitored heart rate and blood pressure throughout the experiment. After institution of paralysis, we administered additional pentobarbital when there were increases in the lambs' heart rate or blood pressure.

We sedated the four full-term newborn lambs with 30 mg/kg of pentobarbital sodium, intubated them with 5.0-mm inner diameter cuffed endotracheal tubes, and ventilated them using an animal volume ventilator (Harvard, South Natick, MA). Just before making our measurements, we paralyzed these lambs with 1 mg/kg of succinylcholine.

Instrumentation. The instrumentation for measuring the respiratory system mechanics consisted of a Fleisch "0" pneumotachometer (OEM Medical, Inc., Richmond, VA) placed between the ventilator tubing T connector and the endotracheal tube. To obtain a position for obstructing exhalation flow between the pneumotachometer and the lamb (6), we fabricated a "clamp connector" from a 3-cm length of $\frac{3}{8}$ -inch inner diameter polyvinyl chloride tubing connected to a fitting that was machined to house the large end of an endotracheal tube adapter (similar to a standard ventilator tubing T piece). We inserted an endotracheal tube adapter, which had a side port for sampling airway pressure (Respiratory Support Products, Inc., Costa Mesa, CA), into the clamp connector and then connected the adapter to the endotracheal tube. We attached the other end of the clamp connector to the pneumotachometer. During the measurements, we used forceps (Presbyterian Hospital tube occluding clamp; Miltex Instrumentation Co., Inc., Lake Success, NY) to pinch the tubing and obstruct exhalation.

We used variable reluctance pressure transducer-carrier demodulator systems (MP45-871, CD257; Validyne, Inc., Northridge, CA) to measure airway pressure (± 50 cm H_2O) and the pressure difference across the pneumotachometer (± 2 cm H_2O). We fabricated three 3rd-order low-pass transmission line filters from small pieces of tubing and used solvent to bond them into the middle of three 6-inch lengths of tubing. These three acoustic filters were used to couple the transducers to the pneumotachometer and the endotracheal tube adapter. We also conditioned the pressure signals using 50-Hz low-pass filters (Validyne, Inc.). We then sampled the two signals simultaneously at 5-ms intervals using a 12-bit resolution analog to digital converter (model 570; Keithley, Cleveland, OH) connected to an IBM-PC-XT 16-bit computer that performed numerical analyses on-line. In addition, we used an oscilloscope (model 5111a; Tektronix, Inc., Beaverton, OR) to measure the response times of the flow and pressure transducer systems; the 90% response times were 9 and 8 ms.

Experimental protocol. Before making measurements, we calibrated the pneumotachometer using the gas from the ventilator circuit at the concentration that was being used on the animal. We used a water manometer to calibrate the pressure transducer.

For the experiments involving the preterm and near-term lambs, we began to make measurements at 4 h of age. By this time, the animals were relatively stable, that is, they did not require frequent changes in ventilator settings to control arterial blood gas tensions. For the older lambs, we began to make measurements immediately after paralysis.

To have a consistent volume history, we inflated the lungs of each of the lambs to 30 cm H_2O pressure for 1 s just before each measurement. None of the lambs breathed spontaneously during the experimental period.

To perform the passive exhalation maneuver, we first ob-

Fig. 1. Typical passive exhalation flow-volume plots of preterm lambs (A) show curvature, whereas the plots for near-term lambs (B) and 9- to 12-d-old lambs (labeled *post-term*) (C) lambs are relatively linear.

structed respiratory flow (we clamped the tubing in the clamp connector) at end inspiration for approximately 2 s, then released the clamp and allowed the lamb to exhale passively through the pneumotachometer to the atmosphere. At approximately mid-exhalation, we obstructed flow again, allowed pressures within the lungs to equilibrate for about 0.7 s, then released the clamp a second time, and allowed lung deflation to be completed to a resting lung volume at atmospheric pressure.

The study protocol was approved by the Baylor Animal Research Protocol Review Committee.

RESULTS

The passive exhalation flow-volume plots of the preterm lambs (Fig. 1A) were concave toward the flow and volume axes, but the plots for the near-term (Fig. 1B) and newborn lambs (Fig. 1C) were relatively linear. In the preterm lambs (Fig. 2A), flow increased from 76 ± 35 mL/s (mean $\pm$ SD) immediately before the obstruction at midexhalation to 90 ± 30 mL/s immediately after release of the obstruction ($p < 0.0001$). In the near-term lambs (Fig. 2B), flow decreased from 99 ± 33 pre- to 94 ± 31 mL/s postocclusion, and in the full-term newborn (Fig. 2C) the flow decreased from 156 ± 38 pre- to 149 ± 30 mL/s postocclusion.

DISCUSSION

In the preterm lambs, flow increased roughly 18% after release of the obstruction at midtidal volume, whereas in the near-term and full-term newborn lambs flow actually decreased slightly. During obstruction of flow, the lung volume remained constant; therefore, the volume dependence of C and R cannot account for the increase in flow observed in the preterm lambs. During passive deflation of the lung, the flow was decreasing and yet τ , the product of R and C, was increasing. Therefore, the flow dependence of R cannot explain the curvature in the flow-volume plots because that would imply that R increases with decreases in flow rather than the more logical notion that R decreases when flow decreases.

The physiological explanations for the increase in flow after obstruction in the preterm lamb very likely contain parameters that are a function of time. During the 2-s period of obstruction at end inhalation, stress relaxation of the respiratory system was taking place. Stress recovery would then occur during exhalation and continue to occur during the brief 0.7-s period of obstruction at midexhalation. During stress recovery, the elastic properties of the respiratory system would change and pressure in the lung would increase (7), contributing to the jump in flow when the obstruction was removed.

If we accept the notion that stress recovery is the main cause of the jump in flow, then we must attempt to explain why no jump in flow occurred in the near-term and full-term newborn lambs. Stress adaptation has been attributed to molecular rearrangements within the alveolar surface film, exchanges between air-liquid interface and the alveolar subphase, and the viscous sliding of surfactant on alveolar surfaces (3). Because the surfactant system is not fully developed in the preterm lamb, we might expect the viscoelastic properties of the preterm lung to differ from the normal lung or the near-term and full-term newborn lambs. If some respiratory units have a more developed surfactant system than other respiratory units, then we would expect the viscoelastic effects of these units to differ also.

The second time-dependent explanation for our observation is that the lung of the preterm lamb is made up of units having a wide distribution of passive exhalation time constants (1). In

Fig. 2. Brief obstruction of flow in the preterm lambs (A) caused an increase in flow immediately after removal of the obstruction, whereas in near-term (B) and 9- to 12-d-old (C) lambs the obstruction had little effect on the shape of the plots.

preterm human infants with hyaline membrane disease, inhomogeneities in the distribution of ventilation (8) and in ventilation-perfusion ratios (9) are well known and have been correlated with histopathologic evidence of patchy overdistension and atelectasis (10). It is not unreasonable to assume the existence of inhomogeneities in the lung mechanics of preterm lambs.

If parallel inhomogeneities exist in the lung, then during the time of obstruction of flow at midtidal volume, the slowly emptying lung units would recharge the relatively fast emptying lung units. This phenomenon could be taking place in all three animal models, but would be more pronounced in the preterm lamb, where epithelial damage in respiratory bronchioles and alveolar ducts (10) exists.

An additional time-dependent factor, which seems to be of minor importance, is the reexpansion of large airways (11). During passive deflation against atmospheric pressure, the pressure in the large airways of the lambs decreased and was governed largely by the gas flow and the R of the endotracheal tube. Thus, when flow was obstructed near midtidal volume, the airway pressure would increase and, because of the C of the large airways, the airways would expand. In essence, the large airways would be recharged (analogous to a shunt capacitor) so that when the obstruction was removed the sudden discharging of the large airways would result in a jump in flow.

If the C of the large airways acted as the major contributor to our observation, then the jump in flow should have occurred in all three animal models. If the jump in flow occurred in the preterm lamb and not in the near-term lamb, it would suggest that the large airway C of the preterm lamb must have been much greater than that of the near-term lambs. This is because the same size endotracheal tube was used in both groups of lambs; that is to say, the shunt capacitors of both the near-term and preterm lambs were discharging through the same sized resistors.

We can estimate the C of the shunt capacitor by dividing the time constant of the fast compartment by the R of the endotracheal tube. If we use 0.1 s for τ (1) and 0.013 cm H₂O/mL/s for R (12), then this would require the C of airways to be 7.7 mL/cm H₂O. Because the C of the respiratory system of these lambs is about 1.8 mL/cm H₂O (1), the estimated C required to cause the jumps in flow is much too large. Therefore, we do not believe that the large airway C was a major contributor to either the curvature of the passive exhalation flow-volume plots or the jump in flow observed in the preterm lambs.

Furthermore, we conclude that the volume and flow dependence of R and C are not major factors contributing to the curvature in the passive exhalation flow-volume plots of preterm lambs in the range of volumes studied. We conclude that time-dependent phenomena cause both the curvilinearity in the flow-volume plots and the jump in flow after removal of the obstruction

at midtidal volume in the preterm lambs. The three time-dependent explanations are not mutually exclusive and could well occur simultaneously.

We believe that the question of which time-dependent phenomenon dominates during tidal breathing is fundamental to models for ventilating sick newborn infants and, therefore, it is of clinical importance. If the viscoelastic properties of the lung are a major factor in the pressure-volume-time relationship of the preterm infant with hyaline membrane disease, then perhaps relatively long inhalation times should be used during mechanical ventilation. Increases in inhalation time would allow more time for stress relaxation of lung and chest wall to occur. This would cause an increase in C, which could lead to a reduction in the pressure required to deliver a particular tidal volume. On the other hand, if parallel inhomogeneities play a major role in the mechanics of the lung, then inhalation times could be adjusted to alter the distribution of ventilation, and expiratory times could be adjusted to influence the distribution of end-exhalation alveolar pressures.

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