Chest wall restriction limits high airway pressure-induced lung injury in young rabbits

LUCRECIA A. HERNANDEZ, KEITH J. PEEVY,
ALICIA A. MOISE, AND JAMES C. PARKER
Departments of Physiology and Pediatrics, College of Medicine, University of South Alabama, Mobile, Alabama 36688

HERNANDEZ, LUCRECIA A., KEITH J. PEEVY, ALICIA A. MOISE, AND JAMES C. PARKER. *Chest wall restriction limits high airway pressure-induced lung injury in young rabbits.* J. Appl. Physiol. 66(5): 2364–2368, 1989.—High peak inspiratory pressures (PIP) during mechanical ventilation can induce lung injury. In the present study we compare the respective roles of high tidal volume with high PIP in intact immature rabbits to determine whether the increase in capillary permeability is the result of overdistension of the lung or direct pressure effects. New Zealand White rabbits were assigned to one of three protocols, which produced different degrees of inspiratory volume limitation: intact closed-chest animals (CC), closed-chest animals with a full-body plaster cast (C), and isolated excised lungs (IL). The intact animals were ventilated at 15, 30, or 45 cmH_2O PIP for 1 h, and the lungs of the CC and C groups were placed in an isolated lung perfusion system. Microvascular permeability was evaluated using the capillary filtration coefficient (K_{fc}). Base-line K_{fc} for isolated lungs before ventilation was 0.33 ± 0.31 $ml \cdot min^{-1} \cdot cmH_2O^{-1} \cdot 100\ g^{-1}$ and was not different from the K_{fc} in the CC group ventilated with 15 cmH_2O PIP. K_{fc} increased by 850% after ventilation with only 15 cmH_2O PIP in the unrestricted IL group, and in the CC group K_{fc} increased by 31% after 30 cmH_2O PIP and 430% after 45 cmH_2O PIP. Inspiratory volume limitation by the plaster cast in the C group prevented any significant increase in K_{fc} at the PIP values used. These data indicate that volume distension of the lung rather than high PIP per se produces microvascular damage in the immature rabbit lung.

mechanical ventilation; peak inspiratory pressure; capillary filtration coefficient; barotrauma

INTERMITTENT POSITIVE-PRESSURE ventilation (IPPV) is frequently used in nurseries and adult intensive care units as a means of ventilatory support during respiratory failure. High peak inspiratory pressures (PIP) are often required to maintain adequate blood oxygenation in these patients. However, there is a growing body of experimental evidence that suggests a high PIP may produce both epithelial and endothelial damage in normal lungs. Greenfield and co-workers (12) ventilated dogs for 2 h with 26–32 cmH_2O PIP and observed significant bilateral pulmonary atelectasis at 24 h. Dogs ventilated for 22–70 h at 34 cmH_2O PIP by Barsch et al. (2) showed morphological evidence of vascular injury, hyaline membranes, atelectasis, alveolar edema, and hemorrhage in their lungs. An increase in permeability of the alveolar epithelium was demonstrated by Egan et al. (6–9) when lung lobes were statically inflated to 40 cmH_2O PIP for 20 min, whereas an increased permeability of microvascular endothelium as evidenced by an increased capillary filtration coefficient (K_{fc}) was observed by Parker et al. (15) when dog lung lobes were ventilated at >42 cmH_2O PIP for only 20 min.

The mechanism by which high PIP induces microvascular damage and pulmonary edema could relate to the high tidal volumes attained as PIP increases or to regional distortion produced by the high pressure itself. In the present study, we measured the degree of microvascular damage in the lungs of immature rabbits under conditions that allowed inflation volume and pressure to be varied independently of each other. The volume limitations produced by the lung parenchyma alone, the lung plus chest wall, and a completely rigid body cast were compared during ventilation with 15–45 cmH_2O PIP.

METHODS

New Zealand White rabbits 4–6 wk old (0.7–1.2 kg) were anesthetized with pentobarbital sodium (30 mg/kg) via an ear vein. A tracheostomy was performed, and the animals were ventilated with a neonatal Healthdyne 105 respirator with room air. The right carotid artery was cannulated for monitoring the systemic arterial pressure and for fluid ($0.5\ ml \cdot 100\ g^{-1} \cdot h^{-1}$) and heparin administration (200 U/100 g). The intact animals were ventilated for 1 h in the supine position, and the respirator was set at 25 breaths/min, 0 cmH_2O positive end-expiratory pressure (PEEP), and inspiratory time of 0.6 s. Airflow ranged between 1 and 6 l/min and was adjusted to achieve 15, 30, or 45 cmH_2O PIP. PIP measurements were obtained at end inspiration and are independent of inspiratory flow rate.

Experimental Protocols

A total of 40 rabbits were divided into 8 groups of 5 rabbits each. Three protocols were used: intact closed-chest rabbits (CC), closed-chest rabbits with full-body cast (C), and isolated excised rabbit lungs (IL).

Closed-chest protocol. In this protocol, groups of intact closed-chest rabbits were ventilated for 1 h at three different peak airway pressures. Closed-chest rabbits were ventilated at 15 cmH_2O PIP in CC-15 ($n = 5$), 30

cmH_2O PIP in CC-30 ($n = 5$), and 45 cmH_2O PIP in CC-45 ($n = 5$). The lungs of the animals were then excised and perfused for measurement of K_{fc} as described below.

Body cast protocol. Young rabbits were prepared before ventilation with a full-body plaster cast placed around the chest and abdomen and allowed to dry completely during normal tidal volume breathing. The animals were then ventilated for the 1-h period at 15 cmH_2O PIP in C-15 ($n = 5$), 30 cmH_2O PIP in C-30 ($n = 5$); and 45 cmH_2O PIP in C-45 ($n = 5$). Lungs were then excised and perfused as described below.

Isolated lung ventilation protocol. In this group, the lungs were removed from the chest cavity and placed in the isolated lung perfusion system before the period of ventilation. After two base-line measurements of K_{fc}, the isolated lungs were ventilated for 1 h with 15 or 30 cmH_2O PIP and two more K_{fc} measurements were made. The IL-15 group ($n = 5$) was ventilated at 15 cmH_2O PIP, and the IL-30 group ($n = 5$) was ventilated at 30 cmH_2O PIP. In both groups a PEEP of 4 cmH_2O was used. In each of these experiments, the base-line K_{fc} served as an internal paired control before PIP ventilation and a PIP of 45 cmH_2O was not used because of the severe damage produced at lower PIP values.

The lungs from rabbits in protocols CC and C were removed after ventilation and mounted in the perfusion system. To accomplish this, the animals were exanguinated through the carotid cannula, and the blood removed (~25–30 ml) was added to 200 ml of 5% bovine albumin in Krebs solution and used to prime the constant-flow perfusion circuit shown in Fig. 1. Papaverine (6 mg) was added to the perfusate to maximally dilate blood vessels and ensure homogenous perfusion. After exanguination, the heart-lung block was removed and weighed, and cannulas were placed in the pulmonary artery and the left atrium. Perfusion of the lung was begun within 10 min after removal of the lungs from the chest cavity. The lungs and heart were placed on a weighing pan suspended from a spring-counterbalanced force transducer (Grass FT03C) and covered with Saran Wrap to prevent water evaporation. The sensitivity of the weight-recording system was calibrated to provide a pen deflection of 5 cm/g wt. Arterial and venous pressures were continuously monitored via a Statham P23 pressure transducers through saline-filled catheters inserted in the inflow and outflow cannulas. Venous outflow was directed to the reservoir for recirculation. The vertical height of the outflow tubing was adjusted to regulate venous pressure. Weight and pressures were continuously recorded on a Grass polygraph (model 7D), and flow was obtained from a calibrated pump scale. Venous pressure was set at 5 cmH_2O, and flow rate was adjusted until the lung attained an isogravimetric state. Lungs were gently hyperinflated periodically during each experiment to prevent atelectasis, and airway pressure was maintained at a constant 3 cmH_2O.

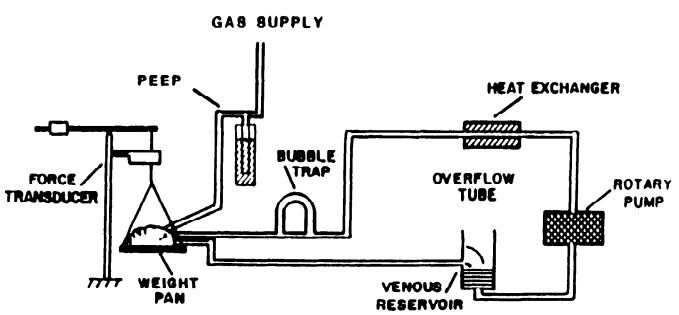

FIG. 1. Apparatus used for constant-flow perfusion of heart-lung preparation. Vascular pressures, airway pressure, and lung weight were continuously monitored. PEEP, positive end-expiratory pressure.

Estimation of Isogravimetric Capillary Pressure

Isogravimetric capillary pressure (Pc,i) was measured using the double-occlusion technique previously described (15, 18). When the lung was neither gaining nor losing weight, the arterial inflow and venous outflow tubing were rapidly occluded upstream to the opening of the pressure catheters while the pump was stopped. Arterial pressure decreased, and venous pressure increased to a pressure that has been shown to equal capillary pressure (18).

Estimation of K_{fc}

The filtration coefficient was assessed by observing the increase in lung weight recorded after venous pressure was increased suddenly by 8–10 cmH_2O from an isogravimetric state. The sudden increase in vascular pressures induced an initial rapid weight gain of the lobe due to the blood volume increase and a slower more prolonged phase of weight gain due to transcapillary filtration of fluid (4, 10, 11). The K_{fc} was calculated using the average rate of weight gain between 3 and 5 min after the pressure increase, since this value was found empirically to predict the extrapolated zero time rate of weight gain closely (17). Total vascular resistance (Rt) was calculated by

$$Rt = (Ppa - Pv)/\dot{Q}$$

where Ppa is volume arterial pressure, Pv is venous outflow pressure, and $\dot{Q}$ is blood flow.

Statistics

All values are expressed as means ± SE. Comparisons were performed using one-way analysis of variance with Scheffé as the post hoc test. Significance was determined when $P < 0.05$ was obtained.

RESULTS

All the animals included in this study survived the 1-h period of ventilation, but two of the CC-45 group developed a tension pneumothorax with subsequent pneumoperitoneum. In addition, all the CC-45 lungs had edema fluid in the trachea by the end of the 1 h of ventilation.

The general appearance of the lungs was observed immediately after the chest cavity was opened. The lungs of the CC-15 group appeared grossly normal, with a pink color and no areas of hemorrhages or atelectasis. The CC-30 lungs showed a few spotty areas of hemorrhage and localized areas of atelectasis but no regions of obvious consolidation. The CC-45 group appeared grossly

consolidated in the dependent regions of both lungs, and there were three to four localized air leaks. The C-15, C-30, and C-45 lungs appeared completely normal with no hemorrhage, atelectasis, or areas of consolidation. None of the casted animals had edema fluid in the trachea, and none developed a pneumothorax.

Figure 2 is a comparison of K_{fc} measurements in the CC and C groups at the three different PIP. At 15 cmH_2O PIP the K_{fc} was 0.28 ± 0.02 $ml \cdot min^{-1} \cdot cmH_2O^{-1} \cdot 100\ g^{-1}$ for the CC group and 0.286 ± 0.018 $ml \cdot min^{-1} \cdot cmH_2O^{-1} \cdot 100\ g^{-1}$ for the C group. There was no statistical difference between K_{fc} at 15 cmH_2O in these two groups or between these K_{fc} values and the base-line K_{fc} (0.33 ± 0.031 $ml \cdot min^{-1} \cdot cmH_2O^{-1} \cdot 100\ g^{-1}$) obtained in isolated lungs before ventilation (Fig. 3). K_{fc} in the CC-30 group showed a 54% increase compared with the CC-15 group and a 75% higher K_{fc} in the C group at the same PIP ($P < 0.05$). K_{fc} in the CC-45 group was 650% higher than in the C-45 group ($P < 0.05$), but there were no significant differences between the C groups at either of the three PIP employed.

Figure 3 shows the effect of PIP on K_{fc} in isolated lungs removed from the chest before the 1-h ventilation period. Base-line K_{fc} measurements were determined before and after ventilation with 15 and 30 cmH_2O PIP. K_{fc} increased significantly from base line (0.33 ± 0.031 $ml \cdot min^{-1} \cdot cmH_2O^{-1} \cdot 100\ g^{-1}$) by 890% in the IL-15 group and by 880% in the IL-30 group. The base-line K_{fc} values in this group were not significantly different from previously determined base-line K_{fc} values in similar-sized rabbits (16).

Rt was not different at any peak airway pressure for the CC group (0.012 ± 0.00124 $cmH_2O \cdot l^{-1} \cdot min \cdot 100$ g) or for the C group (0.0108 ± 0.0014 $cmH_2O \cdot l^{-1} \cdot min \cdot 100$ g). However, as shown in Fig. 4, when Rt was compared in the IL-15 group, there was a significant increase in resistance of 240% between the base line and postventilation measurements ($P < 0.05$). In the IL-30 group, there was also an increase in mean resistance of 228%, but this increase did not reach statistical significance (P = 0.08, Fig. 4). Pc,i averaged 6.7 ± 0.24, 6.2 ± 0.3, and 6.25 ± 0.4 cmH_2O at base line in the CC, C, and IL protocols, respectively, but did not change significantly with ventilation.

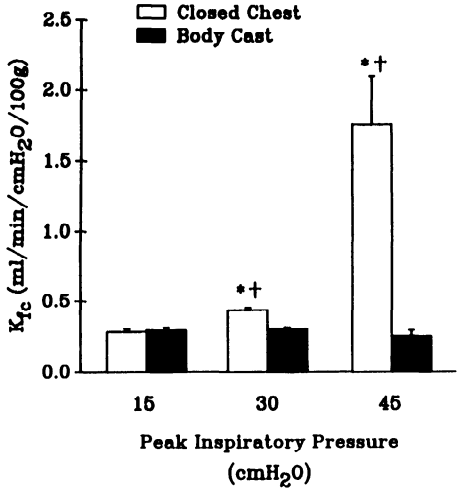

FIG. 2. Comparison of capillary filtration coefficient (K_{fc}) measurements in lungs from closed-chest and body cast experiments after ventilation with 15, 30, and 45 cmH_2O peak inspiratory pressure (PIP) for 1 h. * $P < 0.05$ relative to 15 cmH_2O PIP. † $P < 0.05$ relative to cast group at the same PIP.

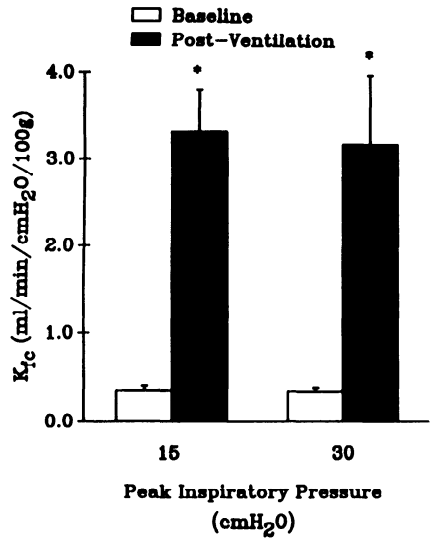

FIG. 3. Comparison of capillary filtration coefficient (K_{fc}) measurements before and after 1 h of ventilation with 15 and 30 cmH_2O peak inspiratory pressure in isolated perfused rabbit lungs. * $P < 0.05$ relative to base-line K_{fc} within the same lung by use of paired t test.

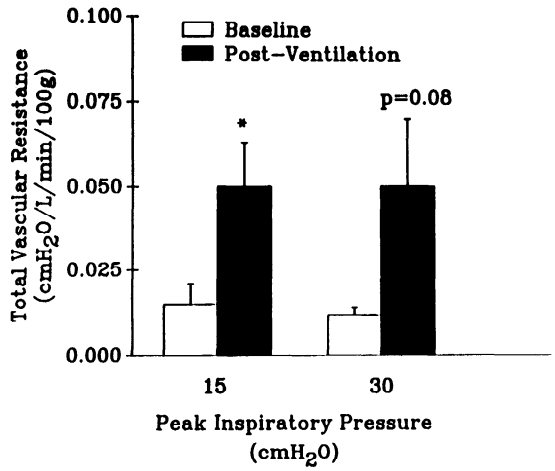

FIG. 4. Comparison of total vascular resistance calculations before and after 1 h of ventilation with 15 and 30 cmH_2O peak inspiratory pressure in isolated perfused rabbit lungs. * $P < 0.05$ relative to base line with the same lung by use of paired t test.

DISCUSSION

High PIP during mechanical ventilation can induce pulmonary edema (5, 14), but the exact mechanisms may include hemodynamic effects as well as damage to the alveolar-capillary barrier. Greenfield and co-workers (12) were the first to show lung damage after the application of a high PIP in mechanically ventilated dogs. At 24 h after ventilation for 2 h at 26–32 cmH_2O PIP, the animals had developed significant bilateral pulmonary atelectasis. The authors postulated that postoperative pulmonary atelectasis seen in surgical patients may also be a consequence of the high PIP used during surgery. Similarly, Barsch and colleagues (2) ventilated dogs for 22–

70 h with room air with 34 cmH_2O PIP and demonstrated pulmonary vascular injury, hyaline membranes, atelectasis, alveolar edema, and hemorrhage in these animals. In a more recent study, Kolobow et al. (13) ventilated healthy sheep over a period of 48 h at 50 cmH_2O PIP and observed progressive impairment in pulmonary mechanics and lung function, acute respiratory failure, and alveolar cellular dysfunction. Webb and Tierney (19) also reported interstitial pulmonary edema and alveolar flooding in rats after mechanical ventilation with 30–45 cmH_2O PIP. They postulated that the interstitial edema might be explained by a very subatmospheric interstitial pressure secondary to pulmonary interdependence and depletion or inactivation of surfactant.

Using an isolated dog lung lobe preparation, Parker et al. (15) showed that mechanical ventilation using >42 cmH_2O PIP significantly increased capillary hydraulic conductivity (K_{fc}), reduced the effective osmotic effect of plasma proteins at the capillary wall (osmotic reflection coefficient), and reduced the total tissue safety factor against edema formation.

In the present study we compared the respective roles of high tidal volume with PIP in the intact young rabbit to determine whether the increase in capillary permeability is the result of overdistension of the lung or direct pressure effects such as increased regional shear forces, which might cause damage independent of overall lung volumes. Microvascular permeability was assessed using the K_{fc}, which is a sensitive indicator of microvascular fluid conductance (4, 10, 15).

In our experiments, there were three degrees of volume restriction of the lung. Since the IL protocol consisted of isolated lungs, there was no volume restriction except that offered by elasticity of the lung parenchyma. These lungs showed the greatest damage of any group with a marked 890% increase in K_{fc} even at the lowest PIP of 15 cmH_2O. K_{fc} did not further increase in isolated excised lungs subjected to 30 cmH_2O PIP. In the closed-chest rabbits, the chest wall as well as lung recoil opposed a lung volume increase with PIP. In this group, 15 cmH_2O PIP produced no significant increase in K_{fc} above control values for unventilated lungs. K_{fc} increased significantly at 30 cmH_2O PIP but only 54%, whereas 45 cmH_2O PIP produced a 580% increase in K_{fc} compared with the 15 cmH_2O PIP group. There was gross macroscopic evidence of hemorrhage and tracheal edema fluid observed in all the animals ventilated with a 45 cmH_2O PIP. Rabbits with a full-body cast had the greatest volume restriction, because the volumes of the chest and abdomen were unable to increase beyond the limits of the rigid plaster cast. This prevented the chest from expanding to significantly larger volumes during inspiration than that present in normal tidal breathing. The lungs of these rabbits showed no significant increases in K_{fc} even at 45 cmH_2O PIP and no macroscopic evidence of lung injury. Thus no vascular damage occurred when overdistension was prevented by the full-body cast.

The base-line K_{fc} values in these immature rabbit lungs were not significantly different from that measured in our laboratory in adult rabbits (1). Matalon and Wangensteen (14) demonstrated a twofold higher K_{fc} in newborn than adult rabbits, but apparently this difference does not persist. The rabbit lungs were also more sensitive to airway pressure injury than adult dog lungs, because Parker et al. (15) observed no increase in K_{fc} at PIP <42 cmH_2O in isolated dog lungs. In contrast, when these isolated immature rabbit lungs were ventilated with only 15 cmH_2O PIP (Fig. 3), massive increases in K_{fc} were produced. We must also consider the length of the ventilation period as a possible explanation for the difference in susceptibility to airway pressure injury, because Parker et al. ventilated the lungs for 20 min, whereas in the present experiments, we ventilated the lungs for 1 h. Complete protection was not afforded even by an intact chest wall, because K_{fc} was significantly increased even after 30 cmH_2O PIP for 1 h.

Recently, Dreyfuss et al. (5) ventilated rats for 20 min and compared the consequences of normal tidal volume ventilation at a high airway pressure with those of high tidal volume ventilated at both high and low airway pressure. They observed that high volume but not low volume-high pressure ventilation produced significant increases in lung edema and transcapillary albumin fluxes. Carlton et al. (3) also studied the effects of high lung inflation pressure and volume on fluid and protein leakage in the pulmonary microcirculation. They found that high pressure ventilation with high volume ventilation caused a sevenfold increase in lung lymph flow and protein clearance, whereas high pressure ventilation with a normal volume produced a 35% decrease in lymph flow and protein clearance.

Although there appears to be considerable species variability in the susceptibility of the lung to mechanical damage by high PIP, we can conclude that such susceptibility is inversely related to chest wall compliance and the static recoil forces opposing volume expansion. The thicker, less compliant chest wall of adults would be expected to afford greater protection than the thinner chest wall of newborns and infants. In addition, the intrinsic determinants of lung compliance, such as collagen, elastin, and surface forces, may also limit damage due to high PIP. However, the extent to which these factors affect species variability and developmental aspects of susceptibility to high PIP damage is currently unknown.

This study was supported by National Heart, Lung, and Blood Institute Grants HL-37341 and HL-24571.

Address for reprint requests: J. C. Parker, Dept. of Physiology, College of Medicine, MSB 3024, University of South Alabama, Mobile, AL 36688.

Received 23 June 1988; accepted in final form 29 November 1988.

REFERENCES

1. ADKINS, K., L. A. HERNANDEZ, A. A. MOISE, K. PEEVY, B. BUCHANAN, AND J. C. PARKER. High peak airway pressures increase microvascular permeability in adult rabbit lungs (Abstract). *Physiologist* 31: A59, 1988.
2. BARSCH, J., C. BIRBARA, AND G. W. N. EGGERS. Positive pressure as a cause of respiratory induced lung disease (Abstract). *Ann. Intern. Med.* 72: 810, 1970.
3. CARLTON, D. P., R. G. SCHEERER, J. J. CUMMINGS, AND R. D. BLAND. Lung overexpansion injures the pulmonary microcirculation in lambs (Abstract). *Pediatr. Res.* 23: 500, 1988.

4. DRAKE, R. E., AND J. C. GABEL. Effect of histamine and alloxan on canine pulmonary vascular permeability. *Am. J. Physiol.* 239 (*Heart Circ. Physiol.* 8): H96–H100, 1980.
5. DREYFUSS, D., P. SOLER, G. BASSET, AND G. SAUMON. High inflation pressure pulmonary edema: respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am. Rev. Respir. Dis.* 139: 1159–1169, 1988.
6. EGAN, E. A. Lung inflation, lung solute permeability and alveolar edema. *J. Appl. Physiol.* 53: 121–125, 1982.
7. EGAN, E. A. Alveolar epithelial protein permeability and alveolar edema (Abstract). *Federation Proc.* 40: 447, 1981.
8. EGAN, E. A. Response of alveolar epithelial solute permeability to changes in lung inflation. *J. Appl. Physiol.* 49: 1032–1036, 1980.
9. EGAN, E. A., R. M. NELSON, AND R. E. OLVER. Lung inflation and alveolar permeability to non-electrolytes in the adult sheep in vivo. *J. Physiol. Lond.* 260: 409–424, 1976.
10. GAAR, K. A., JR., A. E. TAYLOR, L. J. OWENS, AND A. C. GUYTON. Pulmonary capillary pressure and filtration coefficients in the isolated perfused lung. *Am. J. Physiol.* 213: 910–914, 1967.
11. GAAR, K. A., JR., A. E. TAYLOR, L. J. OWENS, AND A. C. GUYTON. Effect of capillary pressure and plasma protein on development of pulmonary edema. *Am. J. Physiol.* 213: 79–82, 1967.
12. GREENFIELD, L. J., P. A. EBERT, AND D. W. BENSON. Effect of positive pressure ventilation on surface tension properties of lung extracts. *Anesthesiology* 25: 312–316, 1964.
13. KOLOBOW, T., M. P. MORETTI, R. FUMAGALLI, D. MASCHERONI, P. PRATO, V. CHEN, AND M. JORIS. Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. *Am. Rev. Respir. Dis.* 135: 312–315, 1987.
14. MATALON, S. V., AND O. D. WANGENSTEEN. Pulmonary capillary filtration and reflection coefficients in the newborn rabbit. *Microvasc. Res.* 14: 99–110, 1977.
15. PARKER, J. C., M. I. TOWNSLEY, B. RIPPE, A. E. TAYLOR, AND J. THIGPEN. Increased microvascular permeability in dog lungs due to high peak airway pressures. *J. Appl. Physiol.* 57: 1809–1816, 1984.
16. PEEVY, K., L. A. HERNANDEZ, A. A. MOISE, AND J. C. PARKER. Barotrauma-associated microvascular injury after ventilation with short inspiratory times (IT) and high peak pressures (PIP) (Abstract). *Pediatr. Res.* 23: 567, 1988.
17. RIPPE, B., R. C. ALLISON, J. C. PARKER, AND A. E. TAYLOR. Effects of histamine, serotonin, and norepinephrine on the circulation of dog lungs. *J. Appl. Physiol.* 57: 223–232, 1984.
18. TOWNSLEY, M. I., R. J. KORTHUIS, B. RIPPE, J. C. PARKER, AND A. E. TAYLOR. Validation of double vascular occlusion method for $p_{c,i}$ in lung and skeletal muscle. *J. Appl. Physiol.* 61: 127–132, 1986.
19. WEBB, H. H., AND D. F. TIERNEY. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. *Am. Rev. Respir. Dis.* 110: 556–564, 1974.