Experimental Pulmonary Edema due to Intermittent Positive Pressure Ventilation with High Inflation Pressures. Protection by Positive End-Expiratory Pressure[1-4]

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SUMMARY

We used a small animal respirator to ventilate normal, anesthetized rats with room air at peak inspiratory pressures of 14, 30, or 45 cm H_2O and no added end-expiratory pressures (intermittent positive pressure breathing [IPPB] 14/0, high inspiratory positive pressure breathing [HIPPB] 30/0, HIPPB 45/0). Other rats were ventilated with the same high inspiratory pressures but with an added end-expiratory pressure of 10 cm H_2O (positive end-expiratory pressure [PEEP] 30/10, PEEP 45/10). Control rats that were not ventilated and the IPPB 14/0 group showed no pathologic lung changes. The HIPPB 30/0 and PEEP 30/10 groups had perivascular edema but no alveolar edema. The HIPPB 45/0 animals had alveolar and perivascular edema, severe hypoxemia, and decreased dynamic compliance and died within one hour. In contrast, the PEEP 45/10 animals had no alveolar edema and survived. We postulate that interstitial perivascular edema develops from ventilation with high inflating pressures by mechanisms of lung interdependence, which decrease the pressure in the perivascular tissues. Alveolar edema induced by HIPPB 45/0 may result from surfactant depletion because of large excursions of alveolar surface area and a low surface tension at end-expiration.

Introduction

Intermittent positive pressure breathing of air with inspiratory pressures less than 15 cm H_2O (IPPB) does not injure lungs (1, 2). However, there is limited clinical or experimental data regarding possible lung injury from positive pressure breathing with inspiratory pressures of 30 cm H_2O or greater (HIPPB). Some patients with adult respiratory distress syndrome (ARDS) may require pressures of 40 to 80 cm H_2O to deliver a normal tidal volume (V_T); few investigations have been done to determine if the only complications of these pressures involve lung rupture with interstitial emphysema or pneumothorax.

Lungs from patients with ARDS and those from animals with experimental pulmonary edema (3) have some relatively normal alveoli scattered among collapsed or fluid-filled alveoli. The abnormal alveoli may be relatively pro-

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tected from overinflation during HIPPB, but we were concerned that the normal alveoli may be overinflated and damaged by ventilation with high pressures.

We postulated that HIPPB could induce increased alveolar surface forces *in vivo* as it does in excised lungs (4, 5) and might, therefore, cause alveolar pulmonary edema (6).

Materials and Methods

Procedures: We used male rats that were free of specific pathogens (Hilltop HLA-W) and weighed 200 to 250 g (table 1). Before injecting sodium pentobarbital into the peritoneal cavity, we lightly anesthetized the rats with halothane (Fluothane, Ayerst Laboratories, Inc., New York). The initial dose of sodium pentobarbital was 78 to 91 mg per kg of body weight; additional doses were given as required to maintain anesthesia. The total dosage and duration are listed in table 1. A tracheostomy was performed with polyethylene tubing (internal diameter, 1.57 to 1.68 mm) as the tracheostomy tube.

After tracheostomy the rats were maintained in a supine position throughout the experiment. They were initially ventilated for 2 to 4 min with a VT and frequency that we had observed previously would result in normal arterial blood gases. The frequency and VT were then altered to achieve the desired airway pressure, and large bore tubing (dead space) was added to the airway to maintain relatively normal arterial P_{CO_2} (Pa_{CO_2}). A constant volume respirator (Harvard Apparatus Co., Millis, Mass.) delivered room air for the duration of the experiment, which was 60 min unless death occurred earlier. A positive end-expiratory pressure (PEEP) was generated by submerging the open end of the expiratory tube under water to a depth of 10 cm. The airway pressure in the respirator tubing was determined with a pressure transducer (PM 6, Statham Instruments, Inc., Oxnard, Calif.) and continuously recorded. The mean airway pressure at the end of the experiment was calculated from the recordings. VT was corrected for gas compression and respirator tubing expansion. Total thoracic dynamic compliance (Cdyn) at the beginning and end of the experiment was calculated from the corrected VT and peak inspiratory and expiratory pressures.

The rats were continuously ventilated while we opened the abdomen after 60 min of experimental conditions (or earlier in the HIPPB 45/0 group when the rat appeared to be near death). We rapidly obtained a 2- to 3-ml arterial blood sample from the aorta before exsanguinating the rat. Arterial blood gas determinations were made with a blood gas analyzer (Radiometer, Inc., Copenhagen, Denmark) and the values were corrected for the animal's rectal temperature (7).

After removing the heart and lungs *en bloc*, we dissected the lungs from the hilar structures and weighed them. Lung weight as a percentage of body weight indicated the degree of pulmonary edema (table 2). A 5-mm-wide transverse section of the left lung was then cut through the hilum and placed in a fixative (Technicon Fixative, Technicon Instruments Co., Terrytown, N. Y.).

Without knowledge of the experimental conditions, we examined a minimum of 4 histologic sections from each animal. The degree of perivascular interstitial edema was graded subjectively on a scale of 0 to 4. Alveolar edema was recorded as present or absent.

TABLE 1

EXPERIMENTAL CONDITIONS

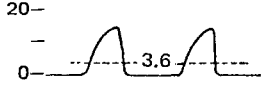
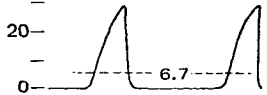
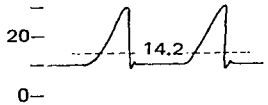
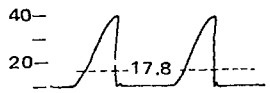
Group	Weight (g)	Pentobarbital Dose (mg/kg)	Pentobarbital Duration (min)	Duration of Experimental Conditions (min)	Mean Airway Pressure (cm H_2O)	VT (ml)	f (min^{-1})	Added VD (ml)	Inspiratory Phase (% of total)
Controls	224	80	81	—	—	—	—	—	
n = 20	(±16.1)*	(±6.7)	(±4.8)						
IPPB 14/0	232	83	70	61	3.6	2.9	49	—	40
n = 6	(±12.7)	(±5.6)	(±2.8)	(±1.6)	(±0.3)	(±0.12)	(±1.0)	—	(±1.6)
HIPPB 30/0	227	85	74	60	6.7	6.8	29	3.0	41
n = 5	(±7.8)	(±4.4)	(±2.4)	(±0.5)	(±0.2)	(±0.17)	(±2.4)		(±0.5)
PEEP 30/10	240	82	87	63	14.2	2.8	48	—	39
n = 5	(±9.1)	(±7.2)	(±8.0)	(±6.2)	(±0.4)	(±0.4)	(±0.9)		(±0.5)
HIPPB 45/0	230	79	48	25	9.7	10.1	23	3.0	43
n = 6	(±6.6)	(±2.8)	(±8.1)	(±7.6)	(±0.3)	(±0.65)	(±2.7)		(±1.5)
PEEP 45/10	237	80	80	62	17.8	3.7	31	0	40
n = 5	(±16.7)	(±5.4)	(±4.9)	(±2.2)	(±0.4)	(±0.48)	(±1.8)		(±0.4)

Definitions of abbreviations: IPPB = intermittent positive pressure breathing; HIPPB = high inspiratory positive pressure breathing; PEEP = positive end-expiratory pressure; VT = tidal volume; f = frequency of ventilation; VD = dead space.

*Standard deviation.

TABLE 2

AIRWAY PRESSURE, COMPLIANCE, Pa_{O_2}, Pa_{CO_2}, LUNG WEIGHT PER BODY WEIGHT, AND HISTOLOGY

Group	PAW (cm H_2O)	Cdyn (ml/cm H_2O) Start	Cdyn (ml/cm H_2O) End	Pa_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)	L/B X 100 (%)	Histology PVE 0	PVE 1+	PVE 2+	PVE 3+	PVE 4+	ALE
Controls	—	—		59 (±7.4)	60 (±5.3)	0.46 (±0.005)	19/20	1/20	—	—	—	—
n = 20				NS	P < 0.01	NS						
IPPB 14/0		0.21 (±0.01)	0.17 (±0.01)	75 (±3.5)	36 (±1.9)	0.44 (±0.021)	3/6	3/6	—	—	—	—
n = 6				P < 0.001	NS	P < 0.01						
HIPPB 30/0		0.23 (±0.00)	0.23 (±0.00)	99 (±2.4)	35 (±3.8)	0.56 (±0.014)	—	—	3/5	2/5	—	—
n = 5				NS	NS	NS						
PEEP 30/10		0.14 (±0.00)	0.15 (±0.00)	95 (±3.2)	39 (±2.0)	0.55 (±0.000)	—	—	4/5	1/5	—	—
n = 5												
HIPPB 45/0		0.22 (±0.01)	0.18 (±0.01)	43 (±3.2)	29 (±2.1)	1.36 (±0.10)	—	—	—	2/6	4/6	6/6
n = 6				P < 0.001	P < 0.05	P < 0.001						
PEEP 45/10		0.11 (±0.01)	0.12 (±0.01)	90 (±3.6)	40 (±2.8)	0.59 (±0.01)	—	—	—	4/5	1/5	—
n = 5												

Definitions of abbreviations: PAW = Airway pressure; L/B X 100 = ratio of lung weight to body weight; PVE = Perivascular edema; ALE = Alveolar edema. For definitions of other abbreviations, see table 1.

Experimental grouping: Controls included animals anesthetized and immediately exsanguinated and others anesthetized and allowed to breathe spontaneously through a tracheostomy for 60 min. The results from the control groups are similar and are presented together as one control group.

We have designated experimental groups by the peak inspiratory airway pressure (Pinsp) and the end-expiratory airway pressure. The groups without added end-expiratory pressure but with inspiratory pressures of 14, 30, and 45 cm H_2O are IPPB 14/0, HIPPB 30/0, and HIPPB 45/0. The animals ventilated by positive pressure inflation with a concomitant PEEP of 10 cm H_2O are designated PEEP 30/10 and PEEP 45/10.

Results

The VT, frequency, added dead space, and mean airway pressure for all groups are presented in table 1. The inspiratory phase occupied about 40 per cent of the respiratory cycle in all experimental groups. There were no significant differences of body weight or pentobarbital dosage between groups (table 1). Duration of anesthesia and of the experimental and control conditions were similar in all groups except those animals in the HIPPB 45/0 group (table 1), which died within 60 min.

Experimental results are shown in table 2 in conjunction with scaled replications of the airway pressure curves. The control and the IPPB 14/0 groups had the same lung weights and similar microscopic appearances of the lungs (table 2 and figure 1). Cdyn decreased in the IPPB 14/0 group probably because of the absence of deep breaths or sighs (8); the hypoxemia and essentially normal histology found in this group are consistent with the presence of atelectasis. The grade 1 perivascular edema in

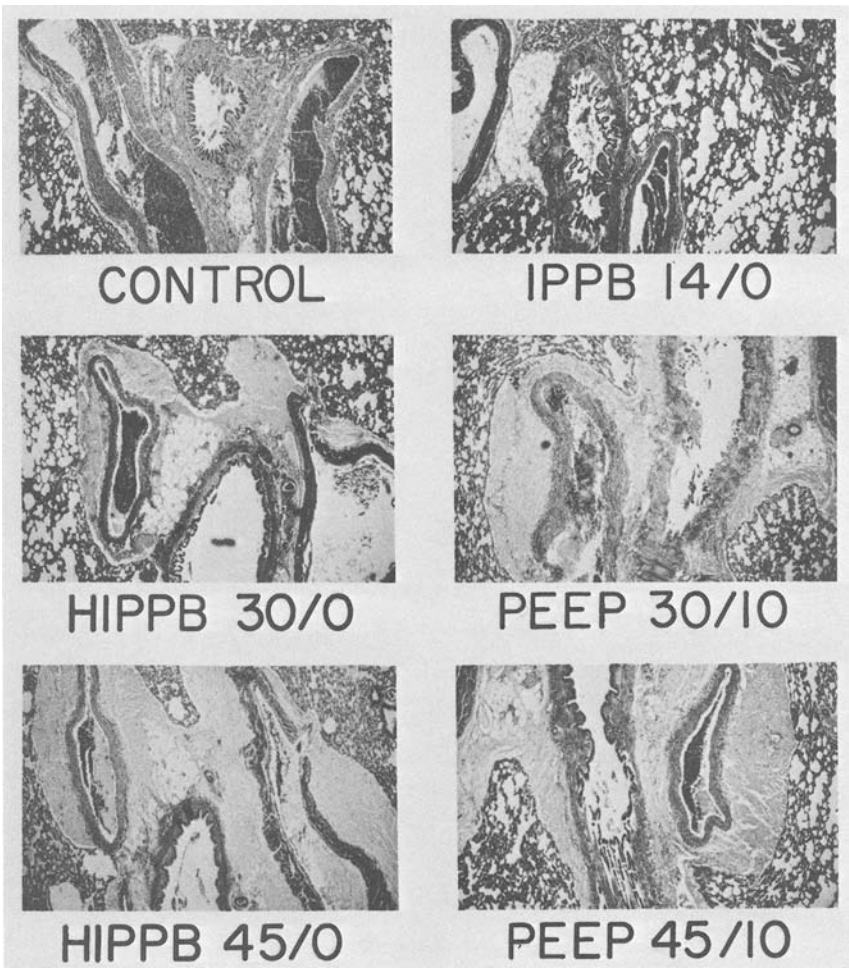


Fig. 1. Appearance of lungs near the hila. The control and IPPB 14/0 have some adipose tissue in the interstitial space but no perivascular edema. The other 4 lungs had extensive perivascular edema. (Original magnification: × 50.)

these rats consisted of only one or two isolated collections of edema, never enough to surround the vessel.

The HIPPB 30/0 and PEEP 30/10 groups had Pa_{O_2} and Pa_{CO_2} that were probably normal for the rat (table 2), stable Cdyn, and perivascular edema, which was present in varying degree in all animals (table 2). Lung weights were the same in these two groups but different from those in the control and IPPB 14/0 groups ($P < 0.01$).

The rats in the PEEP 45/10 group also had a stable Cdyn and normal blood gases (table 2). Although these rats had a slightly greater degree of perivascular edema by subjective histologic grading, the lung weights were not significantly different from the HIPPB 30/0 and PEEP 30/10 groups. Alveolar edema was not observed in these rats (figure 2). Cdyn was lower initially in PEEP 45/10 and 30/10 because these animals were ventilated at the higher range of the pressure-volume curve, where the compliance is low in normal lungs.

The effect of HIPPB 45/0 was striking. The Cdyn decreased an average of 18 per cent, and all rats in this group became cyanotic and were moribund or dead after 13 to 35 min. Colorless froth consisting of minute bubbles that were stable for many hours appeared in the tracheostomy tube of all animals in this group. Two rats died before we obtained arterial blood, but the Pa_{O_2} in the other 4 rats ranged from 34 to 48 mm Hg. The arterial blood pH was 7.39 to 7.45. The lungs were large and heavy, and their surfaces were dark red (figure 3). Marked perivascular edema surrounded all vessels and many bronchi (figure 2), and perivascular and alveolar hemorrhages were present in some histologic sections. Marked alveolar edema, mostly nonhemorrhagic, also occurred in all lungs in this group in a nonuniform, apparently random distribution throughout the lung sections. We did not observe interstitial emphysema or pneumothorax in any of these studies.

Discussion

Our results in the IPPB 14/0 group are consistent with previous experimental studies (1, 2) that reported that the normal lung was not injured by ventilation with room air at Pinsp less

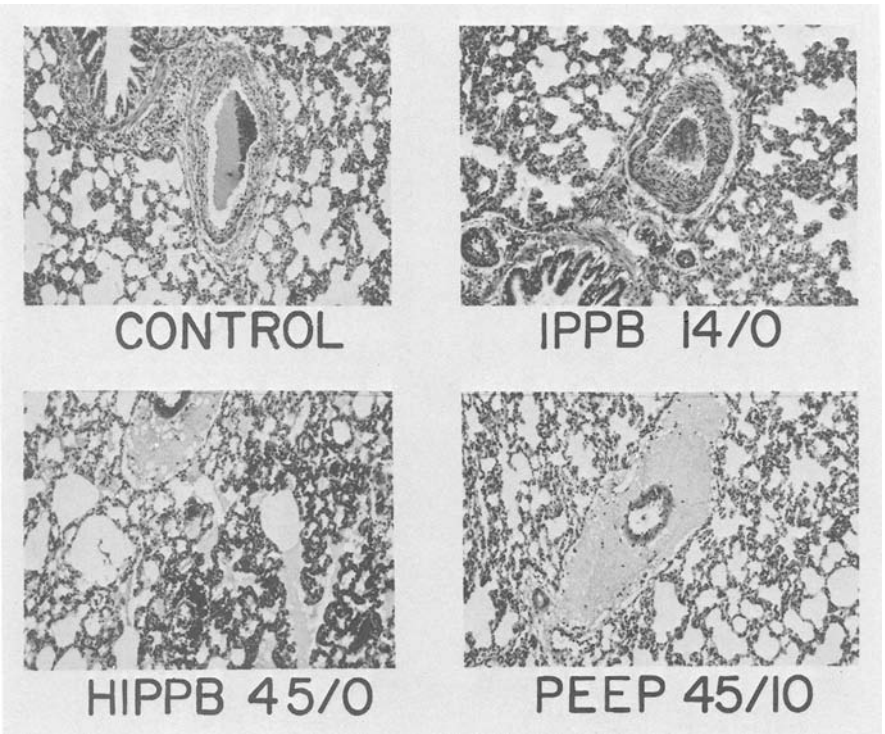


Fig. 2. Peripheral lung tissue. Control and IPPB 14/0 have no perivascular or alveolar edema. The HIPPB 45/0 has alveolar and perivascular edema but PEEP 45/10 has only perivascular edema. (Original magnification: × 125.)

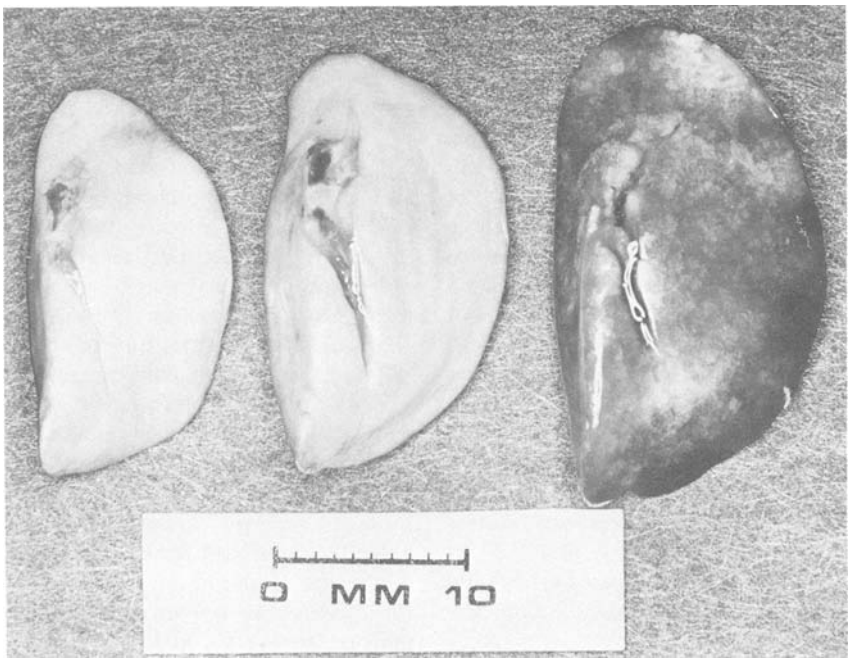


Fig. 3. Comparison of left lungs from rats ventilated with IPPB 14/0, PEEP 45/10, and HIPPB 45/0 (left to right). The perivascular groove is distended with edema in the lungs from rats ventilated with inspiratory pressure of 45 cm H_2O. The dark congested appearance of the lung ventilated with 45/0 is apparent.

than 15 cm H_2O. Recently, Nash and associates (1) used light and electron microscopy to study lungs of goats ventilated with air at Pinsp of 13 cm H_2O and found no abnormalities. They concluded from their studies and review of the literature that the term "respirator lung" was a misnomer.

However, our observations with 4 other groups contrast with the conclusions reached by ventilation with IPPB 14/0. Our results with HIPPB 30/0, HIPPB 45/0, PEEP 30/10, and PEEP 45/10 constitute pathologic evidence of lung injury produced in rats by pressures comparable to those used to ventilate patients with the ARDS. Because the design of our study precludes oxygen toxicity or fluid overloading as mechanisms for the lung damage, we conclude that the pulmonary edema was induced directly by the ventilation.

Few previous investigators have studied the effects of mechanical ventilation with Pinsp greater than 30 cm H_2O. Ovenfors (9) used inflation pressures of 60 to 80 cm H_2O with dogs and produced interstitial emphysema associated with perivascular and alveolar hemorrhage and, in some cases, with alveolar edema. It is possible that the hemorrhage and edema were secondary to vessel damage because the interstitial emphysema probably resulted from alveolar rupture at these high inflating pressures. In contrast, we found no interstitial emphysema, pneumothorax, or air embolism; furthermore, the perivascular edema was mostly nonhemorrhagic and the degree of alveolar edema in the HIPPB 45/0 group greatly exceeded the hemorrhage. In addition, a Pinsp of 45 cm H_2O did not produce alveolar edema when we added 10 cm H_2O end-expiratory pressure (PEEP 45/10). Therefore, the high inflating pressures we used were not solely responsible for the alveolar edema. We concluded that tissue disruption secondary to a high Pinsp is probably not the mechanism of the changes we observed.

Greenfield and co-workers (10) performed biopsies on dog lungs ventilated with Pinsp of 26 to 32 cm H_2O, and determined the surface tension characteristics of lung extracts. Seven dogs were ventilated for 2 hours and had diffuse atelectasis associated with abnormal surface tension characteristics. These investigators also reported that 3 dogs ventilated for 2 to 5 hours showed "signs of pulmonary edema and right heart failure" immediately after the ventilation period, but the lung extracts exhibited normal

surface tension characteristics. No histologic information was published with their investigation. More recently, Barsch and associates (11) ventilated dogs with air at Pinsp of 20 to 34 cm H_2O and found morphologic evidence of lung damage (histology not described in abstract) and evidence of decreased surfactant activity in 4 of 5 dogs. However, no evidence of abnormal pulmonary surface forces was observed in two studies (12, 13) with intact dogs ventilated with a high VT of 50 ml per kg with (13) or without (12, 13) PEEP of 10 cm H_2O. Unfortunately, the Pinsp was not reported. We used a VT that averaged 43 ml per kg with the HIPPB 45/0 group. It may appear from these observations that the rat is more likely to develop respirator-induced alveolar edema than the dog; however, the studies done in the two species were not at the same frequency of breathing, and changes in surface forces induced *in vitro* by large VT ventilation are highly dependent upon the respiratory frequency (4, 5).

The detailed studies by Faridy and associates (4) and by McClenahan and Urtnowski (5) with excised dog and rat lungs stimulated our *in vivo* studies. Using pressure-volume curves, as well as surface tension measurements of lung extracts, these investigators demonstrated that ventilation of excised dog and rat lungs can progressively decrease lung compliance because of an increase of the surface forces (4, 5). They showed that this effect of ventilation was directly related to the VT, the frequency of breathing, and the duration of ventilation, but the effect was inversely related to the end-expiratory transpulmonary pressure (4). An end-expiratory pressure of 3 cm H_2O prevented abnormal shifts in pressure-volume curves in the ventilated lungs. These investigators also concluded that recovery of normal pressure-volume relationships after ventilation was dependent upon metabolism and probably involved surfactant secretion (4, 5). One advantage of the excised lung in these studies was that pulmonary edema could not develop while the vascular bed was not perfused. Regardless of the initiating mechanism, once alveolar edema becomes prominent, the pressure-volume curves are altered and the surface activity of lung extracts may be inhibited (14). In preliminary studies with 3 rats ventilated with HIPPB 45/0 for 5 to 10 min we were unable to detect differences in the pressure-volume relationships of the excised lung when compared with excised lungs from control rats. We concluded that alveolar edema may develop as the surface forces increase or that possibly surfactant may be replenished upon the alveolar surface during the time required for excising the lungs. However, rabbit lungs ventilated *in vivo* with a large VT have been reported to have a change of pressure-volume relationships consistent with increased surface forces with little or no edema (15).

Although we did not design our studies to determine the mechanism of the perivascular and alveolar edema formation, we can exclude several possible mechanisms for each type of edema. We have assumed that perivascular edema may not be associated in all cases with alveolar edema and that there is the potential for different pathogenetic mechanisms for perivascular and alveolar edema formation. Anesthetic dosage, ratio of inspiratory to expiratory duration, and animal weight (16) were not significantly different among the groups (table 1) and, therefore, cannot be responsible for differences in perivascular edema. Also, perivascular edema is probably not simply a function of change in alveolar surface area per breath or per unit time (table 3). The lack of correlation between VT and degree of perivascular edema is seen, for instance, by comparing groups IPPB 14/0 and PEEP 30/10, which have the same VT and frequency but significantly different amounts of perivascular edema.

The development of perivascular edema without apparent alveolar edema in the HIPPB 30/0, PEEP 30/10, and PEEP 45/10 groups is consistent with the effects of "lung interdependence" (17, 18) during inflation, which may decrease the pressure in the perivascular space surrounding nonalveolar vessels and permit edema fluid to accumulate. This fluid may enter the interstitial space from the alveolar capillaries and pass to the perivascular space around larger vessels, or it may enter the space directly by passing through the wall of these precapillary vessels (19–21). Because the perivascular edema appears to require a high Pinsp and the alveolar vessels must be compressed during inspiration by pressures of 30 to 45 cm H_2O, it is possible that the fluid passes through the walls of arteries or veins. We demonstrated the effects of lung interdependence in a preliminary study by fixing normal rat lungs while they were inflated with fixative. We found greatly expanded perivascular spaces; therefore, to assess the degree of perivascular edema in the current study, we fixed the lungs when they were not inflated. In con-

TABLE 3
SURFACE AREA CHANGES AND PERIVASCULAR EDEMA

Group	△A/br	△A/min	L/B X 100	PVE
IPPB 14/0	100	100	0.44	0 to 1^+
HIPPB 30/0	223	131	0.56	2 to 3^+
PEEP 30/10	85	80	0.55	2 to 3^+
HIPPB 45/0	320	150	1.36	3 to 4^+
PEEP 45/10	112	70	0.59	3 to 4^+

Calculations assume: (*1*) The airspace is a portion of a sphere which changes volume but not shape during the breath. (*2*) The volume change in the airspace is proportional to the volume change of the entire lung. (*3*) The initial volume without added pressure (functional residual capacity) was 4 ml. The change in surface area is expressed relative to an arbitrary value of 100 assigned to the IPPB 14/0 group. The proportional change of radius was calculated from the initial and final volumes (initial volume plus tidal volume) using the equation for a sphere; $(\text{radius})^3 = 3 \times \text{volume}/4\pi$. Thus, the radius of a 4-ml lung after a 4-ml tidal volume would increase by 26 per cent. Although the calculations are approximations, they are intended to illustrate the relative changes of surface area with the various conditions.HC

Definitions of abbreviations: △A = change in surface area; br = breath. For definitions of other abbreviations, see tables 1 and 2.

trast with these normal lungs, which were fixed while inflated and had large clear spaces about the vessels, the perivascular edema of lungs fixed while not distended contained protein, as was evident by its deep eosinophilic staining.

Only those animals in the HIPPB 45/0 group developed alveolar edema. Was this alveolar edema due to the systemic hemodynamic effects of positive pressure breathing with development of "shock lung"? The effect of positive intrathoracic pressure on cardiac output is a function of mean airway pressure (22), which was greater in the PEEP 45/10 group than in the HIPPB 45/0 group (tables 1 and 2); thus, the former group presumably had lower cardiac outputs. If the alveolar edema were related to a lower cardiac output we would have expected it to be most apparent in the 45/10 group.

The mechanism of alveolar edema formation during HIPPB 45/0 may be related to the increased surface forces that develop during ventilation of excised lungs with large VT (4, 5). Generally, increased surface forces are associated with atelectasis, but these forces also promote alveolar edema formation (6, 23). Atelectasis may not have been prominent in our studies with HIPPB because the inflating pressures were high. When the lung is inflated with high pressures, the tendency of the airspaces to collapse may be less apparent than during ventilation with low distending pressures.

What is the mechanism by which the surface forces are increased after ventilation with HIPPB 45/0? There are several possibilities, but decreased surfactant synthesis is probably not the sole mechanism of edema formation. The edema occurs rapidly and the rat appears to have an abundance of synthesized surfactant, which is secreted over a period of many hours (24). *In vitro* studies with isolated rat and dog lungs (4, 5) suggest that surfactant is depleted or inactivated in the extracellular surface of the lung and secretion from epithelial cells cannot keep pace with the loss of surfactant from the alveolar surface. The route by which surfactant is lost from the lung is not known, but the surfactant might move along the surfaces of the acinus toward the airways. If this is a pathway for loss of surfactant from the airspace, then ventilation with a large VT and a low end-expiratory pressure may promote surfactant loss. A low end-expiratory pressure would lead to a small alveolar surface area that would compress the molecules on the surface (a low surface tension or a high surface pressure) and force them toward the airways or any segment of the acinus where the concentration of molecules in the surface is less. Inflation of the lung would then replenish the surface with any surfactant molecules that were in the bulk phase below the surface and the cycle would continue. In this fashion, surfactant already secreted onto the alveolar lining may be lost rapidly, although cellular stores of the surfactant may not be depleted if secretion lags behind consumption of surfactant *in vivo* as it does *in vitro* (4, 5). We would predict from this mechanism that the rate of loss of surfactant would be greater when the airspaces are smallest, be-

cause the smaller the airspace the lower the surface tension must be if airspace stability is maintained. The lower surface tension would require closer packing of the molecules in the surface and a greater force driving the surfactant out of the alveolar surface. Therefore, conditions with low lung volumes at end-expiration, i. e., a low closing volume, and a chest wall that does not prevent the lung from collapsing would be most likely to develop alveolar edema with HIPPB. In addition, species with small airspaces would be expected to be more likely to develop alveolar edema than would species with larger airspaces.

A relatively small alveolar volume at end-expiration does appear to be a necessary condition for developing alveolar edema during ventilation with high Pinsp because a PEEP protected against alveolar edema formation in our *in vivo* studies and also protected against increased surface forces *in vitro* (4). The chest wall is an important factor in maintaining the alveolar volume at end-expiration. Several studies have shown that pulmonary edema develops in the open-chest animal during ventilation with relatively large V_T, whereas ventilation of intact control animals with the same V_T and frequency induced no abnormalities (12, 25). We conclude that ventilation-induced alveolar edema depends on a high Pinsp in conjunction with a low end-expiratory volume.

We could also speculate that the alveolar edema may be related to increased pulmonary venous pressure with HIPPB or that inflation releases vasoactive substances from the lung (26), which may promote the edema. We have no information to support these possibilities; however, decreased lymphatic drainage of fluid from the lung is probably not responsible because the edema accumulates much more rapidly than would be expected from decreased lymph flow.

These animal studies have influenced our management of patients requiring ventilatory assistance. We avoid the use of HIPPB when possible, especially if the end-expiratory lung volume is low, as, for example, in patients with ARDS or during thoracotomy. In such situations we strive to avoid very high Pinsp, use a low frequency, and apply PEEP if worsening hypoxemia and decreasing compliance occur. Because the pathologic and physiologic changes of respirator-induced alveolar edema are nonspecific, it may be very difficult to demonstrate whether or not this phenomenon occurs in humans, especially in patients with ARDS. If it does occur in humans, the most likely candidates are those with an abnormally small lung volume at end-expiration.

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