The Effects of Prophylactic Expiratory Positive Airway Pressure on the Resolution of Oleic Acid-Induced Lung Injury in Dogs

JOHN M. LUCE, M.D.,* THOMAS W. HUANG, M.D., PH.D., H. THOMAS ROBERTSON, M.D., PETER S. COLLEY, M.D., RODNEY GRONKA, B.A., MICHAEL L. NESSLY, B.S., FREDERICK W. CHENEY, M.D.

It is not known whether positive end-expiratory airway pressure (PEEP) merely improves gas exchange in patients with the adult respiratory distress syndrome (ARDS) or if it also affects the resolution of their lung injury. The present investigation was performed to determine whether expiratory positive airway pressure (EPAP), a form of PEEP, is prophylactic in preventing the lung injury induced by oleic acid in dogs or in enhancing its resolution. Arterial and mixed venous blood gases and functional residual capacity (FRC) were measured in 14 pairs of mongrel dogs with indwelling catheters and permanent tracheostomies. One member of each pair was treated with 10 cm H_2O EPAP through a valve attached to the tracheostomy tube. Both dogs received 0.06 ml/kg oleic acid intravenously at hour 0. Measurements were made at three, 12, and 24 hours, when EPAP was discontinued, and over the next six days. Five dog pairs were sacrificed at 72 hours; the other surviving animals were sacrificed at 168 hours. FRC was higher at three, 12, and 24 hours in dogs receiving EPAP than in the untreated dogs. The arterial oxygen tension (PaO_2) was higher and the venous admixture ($\dot{Q}va/\dot{Q}t$) was lower at three and 12 hours in the dogs receiving EPAP than in the untreated dogs. However, after 24 hours, no differences were noted between the two groups in FRC, PaO_2, $\dot{Q}av/\dot{Q}t$, mortality, final lung compliance to initial lung compliance differences, lung water to dry lung weight ratios, or histology. It is concluded that EPAP improves gas exchange during its administration, but has no demonstrable prophylactic effect on the resolution of lung injury in the oleic acid model of human ARDS.

From the Department of Medicine, Division of Respiratory Diseases, the Department of Anesthesiology, and the Department of Pathology, University of Washington School of Medicine, Seattle, Washington

POSITIVE END-EXPIRATORY pressure (PEEP) may be used to decrease intrapulmonary shunt and increase the arterial oxygen tension (PaO_2) of patients with the adult respiratory distress syndrome (ARDS). This permits the use of a lower inspired O_2 concentration in such patients while allowing time for their underlying disorder to heal.[1,2] However, some investigators consider PEEP useful "not only in avoiding pulmonary oxygen toxicity but as a fundamental means of aborting or reversing the primary pathophysiologic processes producing acute respiratory failure."[3] In keeping with this view, PEEP may be applied before oxygenation is impaired in patients at risk of developing ARDS under the explicit or implicit assumption that lung healing will be enhanced. Although several clinical series[4–6] support this approach, PEEP may increase shunt[7] and worsen oxygenation[8] in some circumstances. Furthermore, little data exist regarding the impact of PEEP on the natural history either of human ARDS or of animal models of this condition. In a previous study,[9] it was demonstrated that expiratory positive airway pressure (EPAP), a form of PEEP, administered to dogs three hours after lung injury from oleic acid and continued for 21 hours, improved gas exchange during its administration but not over the subsequent six days. The present study was performed to determine whether EPAP is prophylactic in preventing or ameliorating lung injury if administered before oleic acid and continued for 24 hours.

Methods

This experiment involved 14 pairs of mongrel dogs (mean weight of 21.9 ± 2.7 kg) chosen at random from a vivarium population. One of each pair received no treatment, and one was treated with EPAP for 24 hours. The dog pairs were studied sequentially before and for 168 hours after the intravenous administration of oleic acid (Fig. 1). Treated and untreated animals were studied at the same time in pairs to provide better control for the seasonal respiratory illness in the vivarium ani-

Presented in part at the Annual Meeting of the American Thoracic Society, Los Angeles, California, May 15, 1982.

Supported by NIH Grants HL 24163-02 and HL 06155-01.

* Current Address: John M. Luce, M.D., Chest Service, San Francisco General Hospital, San Francisco, California 94110.

Reprint Requests: Frederick W. Cheney, M.D., Department of Anesthesiology, RN-10, University of Washington School of Medicine, Seattle, Washington 98195.

Submitted for publication August 17, 1982

0003-4932/83/0300/0327 $01.30

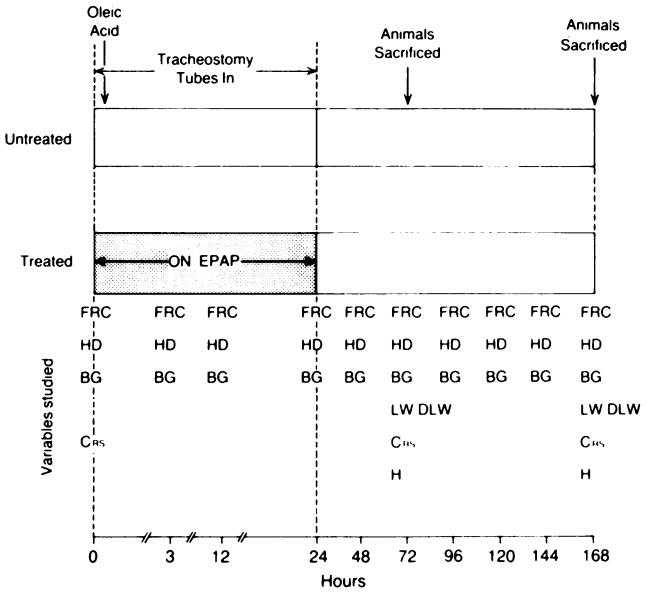


FIG. 1. Experimental protocol. See text for further explanation. EPAP = Expiratory positive airway pressure, FRC = Functional residual capacity, HD = Hemodynamic data, BG = Arterial and mixed venous blood gases, CRS = Respiratory system compliance, LW/DLW = lung water/dry lung weight ratios, H = Histological analysis.

mals. The following variables were examined: functional residual capacity (FRC); hemodynamic parameters including mean arterial pressure ($\bar{P}a$), mean pulmonary pressure ($\bar{P}pa$), pulmonary arterial wedge pressure (Ppaw), and cardiac output ($\dot{Q}t$); arterial and mixed venous blood gases and venous admixture ($\dot{Q}va/\dot{Q}t$); respiratory system compliance (C_{RS}) and lung water to dry lung weight (LW/DLW) ratios; and histology following sacrifice at 72 and 168 hours. Resolution was judged to have been influenced beneficially by EPAP if any of the variables affected by lung injury were significantly different between EPAP-treated and untreated dogs following the period of treatment, or if these variables returned to preinjury values in the EPAP treated dogs before they did in the untreated dogs.

The experimental protocol was as follows: during the week prior to study, the dogs were anesthetized with intravenous pentobarbital (30 mg/kg) and intubated by the endotracheal route. Under sterile conditions, they received permanent tracheostomies by a process in which the cervical strap muscles were tied underneath the trachea and its anterior surface was exteriorized. They were instrumented with forepaw arterial catheters for collection of arterial blood samples and $\bar{P}a$ recordings. Triple lumen Swan–Ganz thermodilution catheters were placed in the pulmonary artery via the external jugular vein for subsequent collection of mixed venous blood samples and for $\bar{P}pa$, $\dot{Q}t$, and Ppaw recordings. The catheters were filled with heparin and wrapped with sterile dressings so that the animals could not dislodge them. The animals were paralyzed with intravenous succinylcholine (5 mg) and ventilated with a Harvard apparatus. Respiratory system compliance was determined by measuring airway pressure (Paw) with the ventilator in the expiratory hold position at successive 100 ml tidal volume increments between 200 ml and 600 ml. This method is similar to that used in patients with ARDS but is not the standard laboratory way of determining lung mechanics. Following this procedure, the dogs were ventilated until they recovered from anesthesia and were extubated. The tracheostomies were covered with sterile pads and the animals' necks were wrapped, permitting them to breathe through their upper airways. The dogs were returned to their cages and allowed food and water as desired. They did not experience obvious discomfort from the tracheostomies.

The animals next were studied three to five days after instrumentation. Each study was carried out with the animals awake and spontaneously breathing room air. On the first day of the study, the neck wraps were removed and tracheostomy tubes were inserted. Functional residual capacity was determined in duplicate by the closed circuit helium dilution method using a Collins water spirometer and helium analyzer; the mean of the two values was taken as FRC. Mean arterial pressure, $\bar{P}pa$, and Ppaw were recorded on a strip chart recorder. Cardiac output was determined as the mean of three measurements made with an Edwards thermodilution computer; standard deviations were in the range of 250 ml. Samples of arterial and mixed venous blood were collected for blood gas determination using a Radiometer blood gas analyzer. Arterial and mixed venous oxygen contents were calculated with the measured hemoglobin and hemoglobin saturations derived from blood gas values using a computer program developed by Ruiz et al.[10] Venous admixture was calculated with the standard equation.

One member of each animal pair was selected by coin toss to receive EPAP therapy. This was accomplished by attaching a special valve, containing a spring-loaded expiratory resistance but minimal inspiratory resistance, to the tracheostomy tube (Fig. 2). The valve was set to deliver 10 cm H_2O of EPAP (Fig. 3). This setting was chosen because it was comparable with that in the other studies discussed below and because it consistently raised FRC to or above preinjury values in all of the treated animals. Strictly speaking, EPAP is not the same as the PEEP provided mechanically ventilated patients or the continuous positive airway pressure (CPAP) used in spontaneously breathing patients, since with both PEEP and CPAP Paw never returns to zero, as it does with EPAP. Nevertheless, all three methods are thought to derive their therapeutic benefit from increasing FRC

and reducing the shunt fraction. As noted above, 10 cm H_2O of EPAP consistently raised the FRC of these animals. Because of this, the term PEEP is used in its generic sense to describe the action of the EPAP valve.

The amount of EPAP and the respiratory waveform produced by the valve were documented by Paw readings immediately after the valve was in place. To prevent occlusion with hemorrhagic pulmonary edema fluid, a frequent problem several hours after oleic acid administration, the tracheostomy tubes and the valve were changed every two to four hours. These changes occurred with equal frequency in the treated and untreated dogs, and significant airway obstruction was not observed. Airway pressure was checked after every change of the valve, and the animals were supervised continuously during the 24 hours of EPAP therapy.

In the 15 minutes after EPAP was initiated, FRC, arterial and mixed venous blood gasses, and hemodynamic data were collected in the treated animals while they were on EPAP. Measurements of FRC were made in the animals on EPAP by incorporating the valve into a closed system and then subtracting the dead space of the valve. The validity of this technique was confirmed in the first six EPAP-treated animals by measuring FRC off EPAP, on EPAP, and with the valve in place but the expiratory resistance mechanism removed. There was no increase in FRC in the latter circumstances, suggesting that the increase in FRC observed when the expiratory resistance was present was due to the resistance itself and was not an artifact created by the closed system.

Immediately after measurements were made at hour zero, the conscious dogs received oleic acid, 0.06 ml/kg (reagent grade), through the right atrial port of the triple lumen catheter. This dose was selected after a dose of 0.09 ml/kg produced an unacceptable mortality during the first 48 hours in a pilot study of six animals. The oleic acid was injected continuously at a rate of 0.4 ml/min using a Harvard pump. During the oleic acid infusion, the animals coughed and vomited occasionally but subsequently showed no other signs of discomfort.

Three hours later, and at 12 hours, FRC, arterial and mixed venous blood gases and hemodynamic data were collected from all the animals. The EPAP valve was removed from the untreated dogs for ten to 15 minutes and these variables were measured again in the treated dogs off EPAP. End positive airway pressure then was reinstituted.

At 24 hours, FRC, arterial and mixed venous blood gasses, and hemodynamic data were collected in all dogs. The valve was removed, and after ten to 15 minutes, these variables were measured again in the treated animals off EPAP. The tracheostomy tubes were removed, and the dogs' necks wrapped to allow them to breathe through the upper airway except during subsequent test periods.

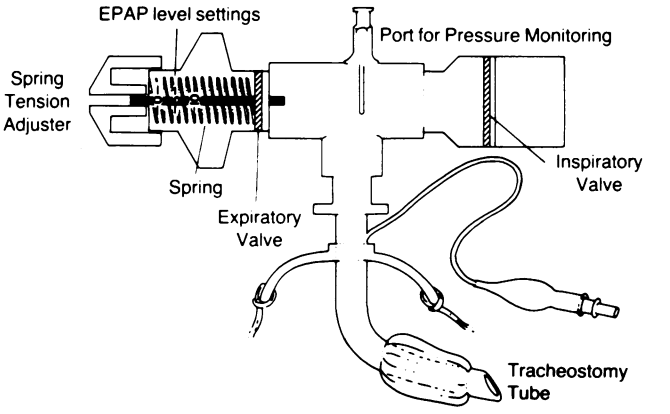


FIG. 2. Valve for delivering expiratory positive airway pressure (EPAP).

Functional residual capacity, arterial and mixed venous blood gases, and hemodynamic data were collected daily over the next seven days in the surviving animals. Five dog pairs were sacrificed at 72 hours; the remaining dogs were given intravenous pentobarbital (30 mg/kg) and succinylcholine (5 mg) and were intubated, and C_{RS} was determined as described above. Final and initial C_{RS} at each tidal volume were calculated for each animal. Next, a sternal thoracotomy was performed and the ribs were spread. The heart and lungs were removed from the thoracic cavity; the pulmonary artery and veins were ligated at the hilum; the heart and lungs were separated. The right lung was weighed, 1 ml of distilled water was added for each gram of lung weight, and the mixture was homogenized in a blender. Weighed aliquots of the mixture were heated at 80 C in a vacuum for seven days until the weights on successive days were within 2–3% of each other. The left lung was transbronchially perfused with phosphate buffered, pH 7.4, 10% formalin solution. The perfusion pressure was maintained at 25 cm H_2O for 30 minutes. The lungs were further fixed in the same fixative overnight following ligation of the bronchi at the 25 cm H_2O filling pressure. The lungs

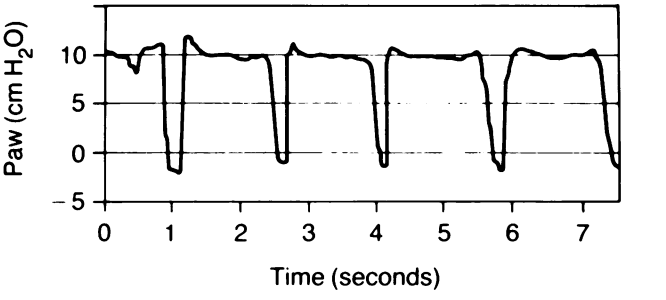


FIG. 3. Recorder tracing of waveform produced by EPAP valve. EPAP = Expiratory positive airway pressure, Paw = Airway pressure.

TABLE 1. *Comparison of EPAP-treated Dogs (N = 10) Off and On EPAP*

		Preinjury $\bar{x} \pm$ S.D.	3 Hours $\bar{x} \pm$ S.D.	12 Hours $\bar{x} \pm$ S.D.	24 Hours $\bar{x} \pm$ S.D.
pHa (units)	off EPAP	7.36 ± 0.05	7.38 ± 0.03	7.38 ± 0.03	7.39 ± 0.04
	on EPAP	7.38 ± 0.04	7.36 ± 0.04*	7.36 ± 0.03	7.37 ± 0.03
$PaCO_2$ (torr)	off EPAP	31 ± 3	31 ± 5	29 ± 4	31 ± 4
	on EPAP	34 ± 5	35 ± 5*	33 ± 4*	34 ± 5*
$P\bar{v}CO_2$ (torr)	off EPAP	35 ± 4	38 ± 5	37 ± 4	36 ± 4
	on EPAP	39 ± 4*	41 ± 5*	38 ± 4	39 ± 4*
$P\bar{v}O_2$ (torr)	off EPAP	40 ± 6	37 ± 13	39 ± 5	38 ± 5
	on EPAP	41 ± 4	35 ± 12	38 ± 6	36 ± 6
PA-aO_2 (torr)	off EPAP	15 ± 11	29 ± 15	41 ± 10	41 ± 14
	on EPAP	15 ± 10	22 ± 14*	33 ± 11*	40 ± 18
$\dot{Q}va/\dot{Q}T$ (%)	off EPAP	4 ± 3.2	11 ± 7.3	16 ± 7.5	14 ± 6.3
	on EPAP	5 ± 3.5	8 ± 7.2*	13 ± 6.6	13 ± 5.8
FRC (ml/kg)	off EPAP	49 ± 13.2	37 ± 11.9	40 ± 15.3	39 ± 16.8
	on EPAP	62 ± 14.9*	55 ± 18.7*	55 ± 19.7*	54 ± 17.0*
PaO_2 (torr)	off EPAP	97 ± 9.8	82 ± 12.7	73 ± 9.3	75 ± 10.1
	on EPAP	94 ± 8.0	85 ± 10.3	77 ± 10.5	75 ± 9.6
$\dot{Q}t$ (L/min)	off EPAP	4.08 ± 0.93	2.15 ± 0.55	3.02 ± 0.46	3.41 ± 0.72
	on EPAP	4.15 ± 0.73	3.15 ± 0.44	3.15 ± 0.52	3.50 ± 0.35

* $p < 0.05$ on EPAP compared with off EPAP at same time interval.
EPAP = Expiratory positive airway pressure.
pHa = Arterial pH.
$PaCO_2$ = Arterial carbon dioxide tension.
$P\bar{v}CO_2$ = mixed venous carbon dioxide tension.
$P\bar{v}O_2$ = mixed venous oxygen tension.
PA-aO_2 = Alveolar to arterial oxygen tension difference.
$\dot{Q}va/\dot{Q}t$ = Venous admixture.
FRC = Functional residual capacity.
PaO_2 = Arterial oxygen tension.
$\dot{Q}t$ = Cardiac output.

were then sliced at 2 mm intervals and samples for histologic sections were taken from both normal and abnormal-appearing portions of the lungs. Paraffin sections were routinely stained with hematoxylin and eosin. A pathologist who was unaware of the animal's treatment status evaluated the sections for thickening of alveolar septa, prominence of Type II pneumocytes, alveolar and interstitial edema, and numbers of granulocytes and alveolar macrophages using the qualitative criteria described in a previous study.[9]

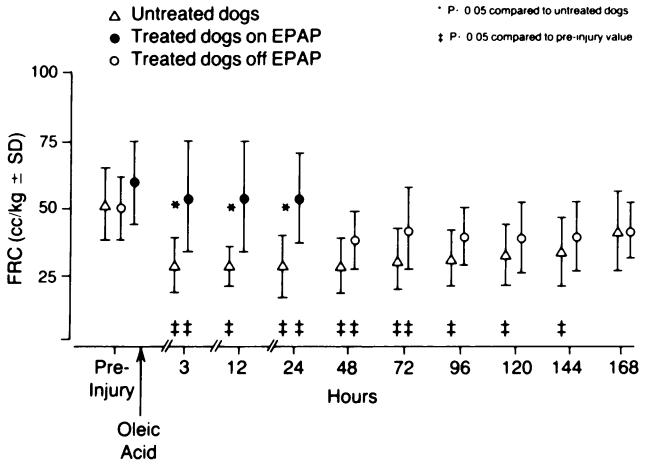


FIG. 4. Changes in functional residual capacity (FRC) in untreated dogs (N = 12) and treated dogs (N = 10) on and off expiratory positive airway pressure (EPAP).

Student's unpaired t-test was used for comparisons between the EPAP-treated and untreated animals. The paired t-test was used for comparisons between treated animals on and off the EPAP valve. The paired t-test also was used to determine when the variables studied in all dogs no longer were different than preinjury values. This was taken as the point at which the effects of injury on a given variable were resolved. Differences were considered significant at a p level of less than 0.05.

Results

No significant differences in preinjury values were noted between the 14 dogs treated with EPAP and the untreated dogs. Ten of the 14 treated animals and 12 of the 14 untreated animals survived 72 hours of the study; five from each group were electively sacrificed at this point. Five of the treated animals and seven of the untreated animals survived to 168 hours and were electively sacrificed. Two treated animals and one untreated animal died with severe hypoxemia during the first 48 hours and had no evidence of pneumonia; the deaths of these animals was attributed to diffuse lung injury

TABLE 2. *Comparison Between EPAP-treated Dogs (N = 10) and Untreated Dogs (N = 12), and Comparison of Values in Each Group with Pre-injury Values*

		Treated Dogs off EPAP	Treated Dogs On EPAP								
		Pre-injury $\bar{x} \pm$ S.D.	Pre-injury $\bar{x} \pm$ S.D.	3 Hours $\bar{x} \pm$ S.D.	12 Hours $\bar{x} \pm$ S.D.	24 Hours $\bar{x} \pm$ S.D.	48 Hours $\bar{x} \pm$ S.D.	72 Hours $\bar{x} \pm$ S.D.	96 Hours $\bar{x} \pm$ S.D.	120 Hours $\bar{x} \pm$ S.D.	144 Hours $\bar{x} \pm$ S.D.	168 Hours $\bar{x} \pm$ S.D.
pHa (units)	untreated	7.38 ± .06	—	7.37 ± .04	7.37 ± .06	7.38 ± .04	7.39 ± .04	7.41 ± .03	7.38 ± .05	7.39 ± .06	7.39 ± .03	7.40 ± .05
	treated	7.38 ± .05	7.36 ± 0.4	7.36 ± .04	7.35 ± .03	7.37 ± .03	7.40 ± .04	7.39 ± .04	7.39 ± .04	7.39 ± .04	7.40 ± .03	7.38 ± .02
$PaCO_2$ (torr)	untreated	33 ± 4	—	32 ± 4	31 ± 3	31 ± 3	30 ± 5	29 ± 4†	30 ± 4	30 ± 5	31 ± 4	31 ± 7
	treated	31 ± 3	34 ± 5	35 ± 5	33 ± 4	34 ± 5	31 ± 6	29 ± 5†	29 ± 5	28 ± 3	32 ± 6	30 ± 4
Pa-aO_2 (torr)	untreated	14 ± 10	—	38 ± 16†	48 ± 15†	44 ± 13†	48 ± 17†	41 ± 15†	37 ± 9†	39 ± 11†	30 ± 9	34 ± 9†
	treated	15 ± 11	15 ± 10	22 ± 14*	33 ± 11*†	40 ± 18†	42 ± 13†	43 ± 17†	39 ± 10†	37 ± 10†	27 ± 11	35 ± 17
$P\bar{v}O_2$ (torr)	untreated	42 ± 5	—	35 ± 5†	36 ± 6†	36 ± 4†	35 ± 4†	38 ± 6†	34 ± 2†	36 ± 5	37 ± 7	40 ± 6
	treated	40 ± 6	41 ± 4	38 ± 4	38 ± 6	36 ± 6	36 ± 5	34 ± 9†	34 ± 4	37 ± 6	36 ± 3	40 ± 3
$P\bar{v}CO_2$ (torr)	untreated	37 ± 4	—	38 ± 4	38 ± 4	36 ± 2	36 ± 6	37 ± 4	36 ± 3	36 ± 4	36 ± 4	37 ± 3
	treated	35 ± 4	39 ± 4	38 ± 5	38 ± 4	39 ± 4†	37 ± 4	37 ± 5	36 ± 5	37 ± 4	37 ± 5	36 ± 4
$\dot{Q}t$ (L/min)	untreated	4.96 ± 1.62	—	3.25 ± 0.8†	3.09 ± 0.48†	3.07 ± 0.75†	3.49 ± 0.90†	3.12 ± 0.58†	3.73 ± 0.56	3.61 ± 0.46	3.77 ± 0.64	3.65 ± 0.42
	treated	4.08 ± .93	4.15 ± 0.73	3.15 ± 0.44	3.29 ± 0.59	3.57 ± 0.39	3.28 ± 0.6†	3.22 ± 0.35	3.34 ± 0.36	3.26 ± 0.51	3.66 ± 0.78	3.54 ± 1.02
$\bar{P}a$ (torr)	untreated	120 ± 10	—	—	—	93 ± 11†	97 ± 9†	96 ± 11†	94 ± 7†	86 ± 10†	89 ± 7†	82 ± 15
	treated	113 ± 16	114 ± 21	—	—	102 ± 21	104 ± 19†	94 ± 17†	99 ± 11	99 ± 14	100 ± 19	106 ± 21
$\bar{P}pa$ (cmH_2O)	untreated	21 ± 5	—	—	—	21 ± 10	19 ± 4	17 ± 4†	17 ± 3†	20 ± 6	19 ± 8	21 ± 9
	treated	20 ± 9	26 ± 7	—	—	15 ± 4	18 ± 2	17 ± 6	23 ± 9	18 ± 6	16 ± 6	19 ± 6
$\bar{P}paw$	untreated	8 ± 4	—	—	—	4 ± 3†	4 ± 3†	3 ± 3†	4 ± 3†	6 ± 1	6 ± 3	4 ± 3
(CmH_2O)	treated	8 ± 2	12 ± 7	—	—	3 ± 3†	4 ± 4	3 ± 5†	5 ± 7	3 ± 3*	3 ± 2	6 ± 6

* $p < 0.05$ in EPAP-treated dogs compared to untreated dogs at same time interval.
† $p < 0.05$ compared with pre-injury values.
EPAP = Expiratory positive airway pressure.
pHa = Arterial pH.
$PaCO_2$ = Arterial carbon dioxide tension.
$P\bar{v}O_2$ = Mixed venous oxygen tension.
$P\bar{v}CO_2$ = Mixed venous carbon dioxide tension.
$\dot{Q}t$ = Cardiac output.
$\bar{P}a$ = Mean arterial pressure.
$\bar{P}pa$ = Mean pulmonary arterial pressure.
$\bar{P}paw$ = Pulmonary arterial wedge pressure.

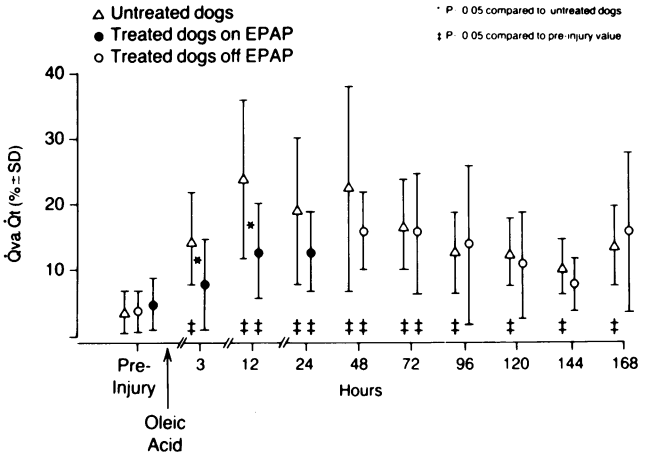


FIG. 5. Changes in venous admixture (Q̇va/Q̇t) in untreated dogs (N = 12) and treated dogs (N = 10) on and off expiratory positive airway pressure (EPAP).

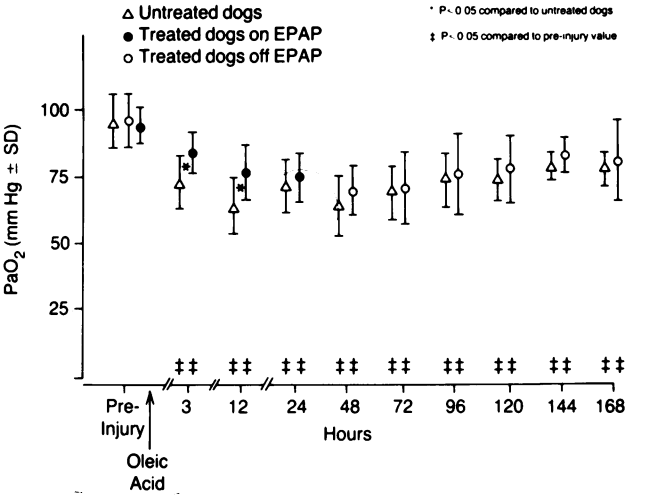


FIG. 6. Changes in arterial oxygen tension (PaO_2) in untreated dogs (N = 12) and treated dogs (N = 10) on and off expiratory positive airway pressure (EPAP).

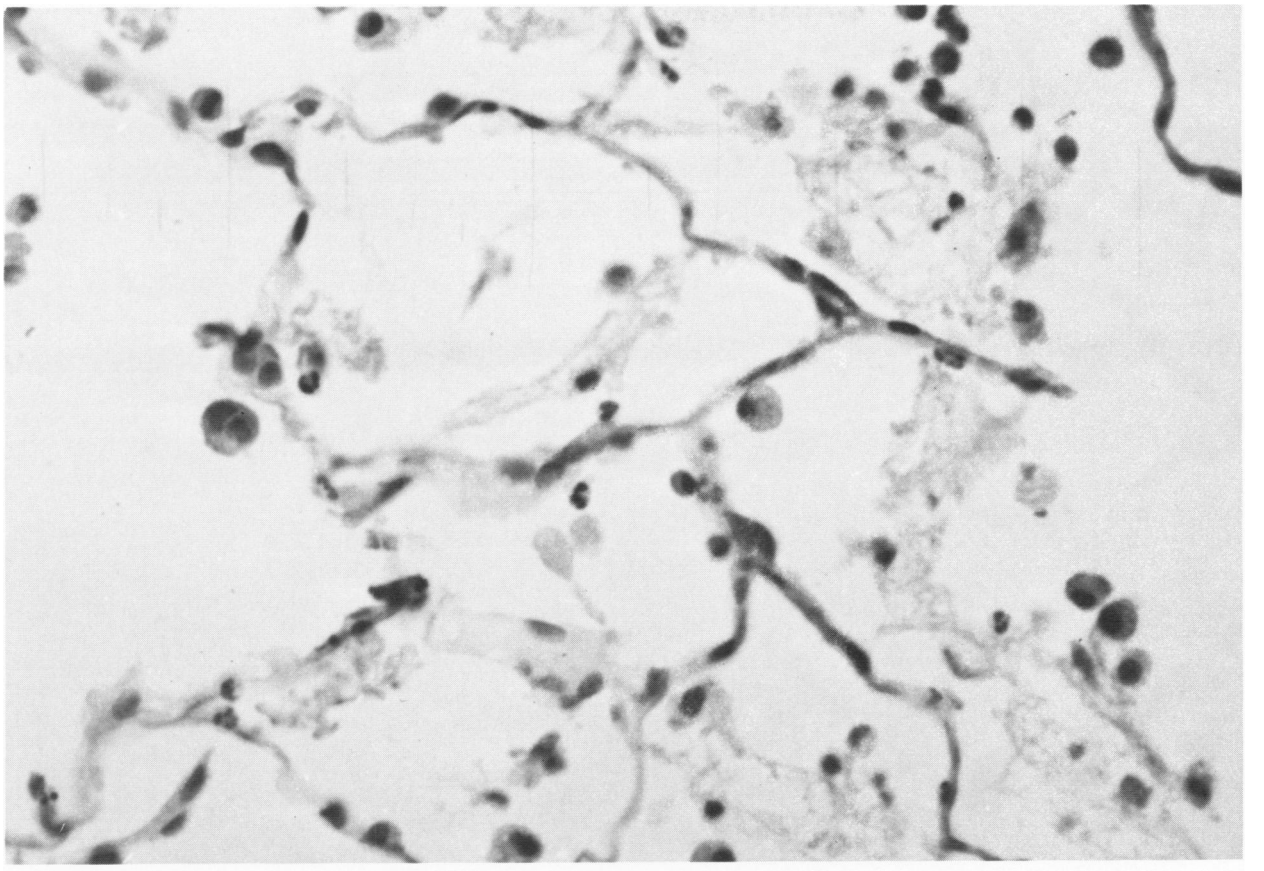
from oleic acid. Two treated animals and one untreated animal died with pneumonia after 48 hours. Data on surviving, that is, electively sacrificed animals only, were included in the results.

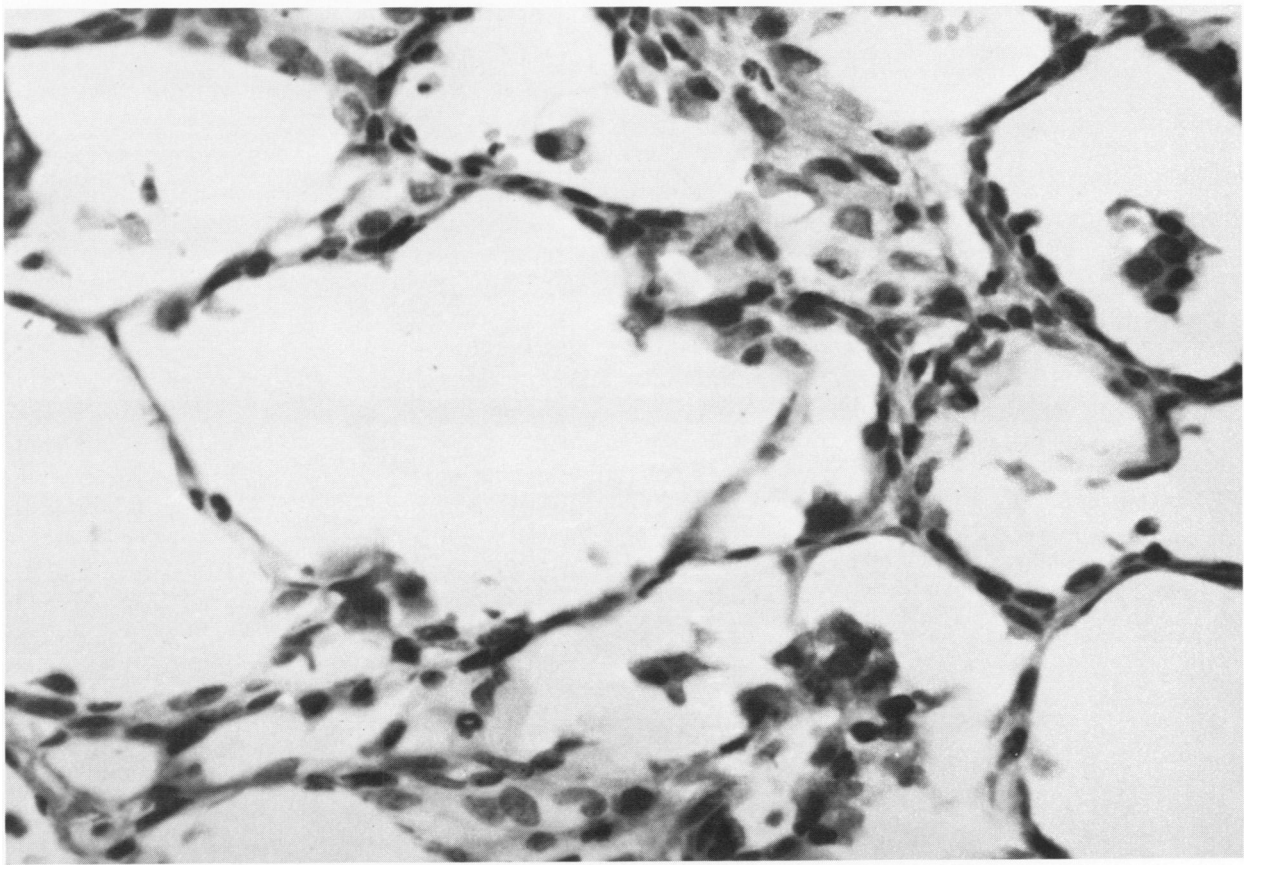
Comparison of the ten surviving treated dogs on and off EPAP showed that EPAP significantly increased FRC before injury and at 3, 12, and 24 hours, and decreased Q̇va/Q̇t at three hours. The alveolar to arterial PO_2 gradient was significantly decreased by EPAP at three and 12 hours. Cardiac output was not affected significantly by EPAP; $PaCO_2$ rose slightly at three, 12, and 24 hours (Table 1).

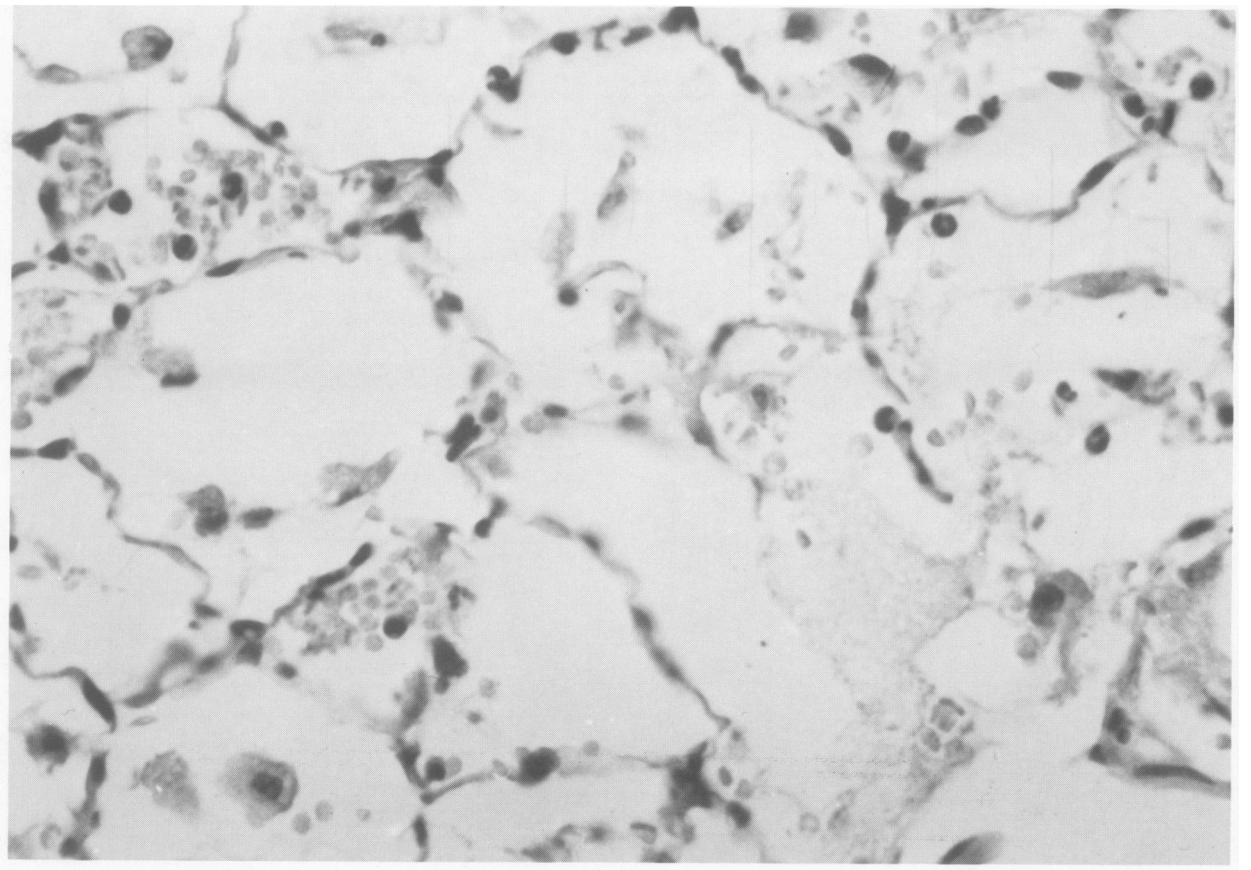
Comparison of the ten surviving treated animals on EPAP with the 12 surviving untreated animals revealed that EPAP increased FRC at 0, 3, 12, and 24 hours (Fig. 4), decreased Q̇va/Q̇t at three and 12 hours (Fig. 5), and increased PaO_2 at three and 12 hours (Fig. 6). After EPAP was discontinued, however, no significant differences were noted between the two groups in any of these variables. Functional residual capacity returned to preinjury values by 96 hours in the treated animals and by 168 hours in the untreated animals. Venous admixture returned to preinjury values by 96 hours in the treated animals and did not return to preinjury values in the untreated animals. However, the PaO_2 did not return to preinjury values in either group. No significant differences were noted in Ppaw, $\bar{P}pa$, $\bar{P}a$, mixed venous PO_2 or PCO_2 or Q̇t between the two groups at any time in the study, and all of these variables returned to preinjury values in both groups before the end of the study (Table 2). No significant distinction was noted in the differences between initial and final C_{RS} (Table 3). The final mean lung water to dry lung weight ratios ± standard deviation were similar in both groups at 72 hours (treated [N = 5] 5.05 ± 0.55, untreated [N = 4] 5.99 ± 2.03) and at 168 hours (treated [N = 5] 4.94 ± 0.83, untreated [N = 7] 4.99 ± 0.58), although both were higher than the laboratory values for normal dry lungs (3.92 ± 0.49).

Finally, no difference in morphologic parameters was observed between the EPAP-treated and untreated dogs. At 72 hours, the lung parenchyma showed focal areas of mild thickening of alveolar septa due to expansion of interstitial space, presumably caused by interstitial edema. Occasional prominent low cuboidal pneumocytes containing abundant basophilic cytoplasm were noted. The alveolar space was filled with proteinaceous alveolar edema fluid containing various amounts of red blood cells. Increased numbers of alveolar macrophages and rare, polymorphonuclear leukocytes also were noted in the area of alveolar edema. There appeared to be more alveolar extravasation of red blood cells in the treated group; otherwise, there was no appreciable difference between the treated and untreated groups. At 168 hours, the alveolar septae were also focally thickened as at 72 hours. However, more low cuboidal pneumocytes, presumably Type II pneumocytes, were seen

FIG. 7. Representative morphology from untreated (I) and treated dogs (II) studied at 72 (a) and 168 (b) hours (125× power). Focal septal thickening is more prominent at 168 hours, and more cuboidal pneumocytes are present. Edema fluid is evident at both 72 and 168 hours. More red blood cells are evident in the alveoli of the treated dog than the untreated dog at 168 hours. No other differences were observed between treated and untreated animals.







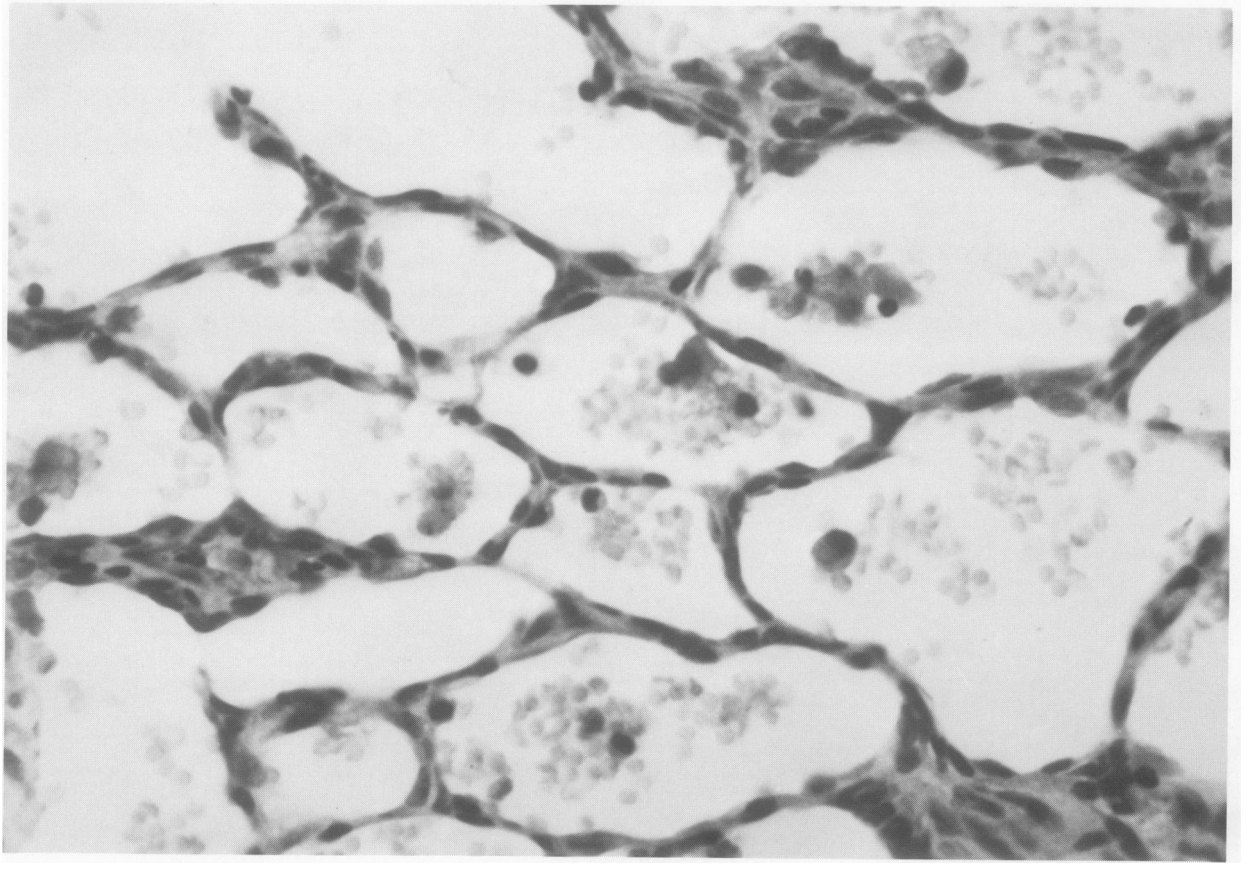


TABLE 3. *Comparison of Initial and Final Respiratory System Compliance (CRS) in ml/cm H_2O at Various Tidal Volumes Between EPAP-treated and Untreated Dogs*

Tidal Volumes (ml)	200 $\bar{x} \pm$ S.D.	300 $\bar{x} \pm$ S.D.	400 $\bar{x} \pm$ S.D.	500 $\bar{x} \pm$ S.D.	600 $\bar{x} \pm$ S.D.
Initial CRS					
Untreated (N = 8)	35 ± 16	36 ± 14	37 ± 14	39 ± 15	40 ± 13
Treated (N = 10)	35 ± 7	36 ± 6	37 ± 7	39 ± 7	42 ± 9
Final CRS @ 72 hours					
Untreated (N = 3)	24 ± 6	27 ± 3	29 ± 2	31 ± 2	34 ± 3
Treated (N = 4)	30 ± 7	32 ± 7	34 ± 8	35 ± 10	36 ± 11
Final CRS @ 168 hours					
Untreated (N = 7)	39 ± 19	39 ± 11	39 ± 9	41 ± 10	41 ± 11
Treated (N = 5)	34 ± 8	36 ± 9	39 ± 10	39 ± 12	41 ± 12

No statistical significance in CRS between groups at above time intervals.

lining the alveolar space. More prominent interstitial fibrosis also was seen. The alveolar proteinaceous edema fluid was no more detectable. Red blood cells and alveolar macrophages were numerous in the areas of alveolar thickening. There was no difference between treated and untreated groups (Fig. 7).

Discussion

Little debate exists regarding the ability of PEEP to decrease intrapulmonary shunt, increase the PaO_2 and thereby permit the use of a lower inspired O_2 concentration in patients with diffuse lung injury. However, the issue of whether PEEP has a therapeutic effect in preventing or reversing the pathologic process responsible for ARDS has not been resolved. Settling this issue is important, for if PEEP truly is curative, it should be applied promptly and even prophylactically despite its possible adverse effects on $\dot{Q}t$ and O_2 transport.

Unfortunately, despite claims that PEEP is potentially therapeutic,[3] a theoretical rationale for this position has not been formulated. Initially, it was hoped that PEEP might limit the formation of pulmonary edema during ARDS. This idea was supported by the demonstration by Webb and Tierney[11] that alveolar edema deposition is prevented by PEEP in rats receiving high inspiratory positive pressure breathing. The authors attributed this finding to PEEP's ability to prevent surfactant inactivation, as demonstrated by Wyszogrodsky et al.[12] Despite this ability, however, Hopewell[13] and Hopewell and Murray[14] have shown that extravascular lung water is not decreased by PEEP in experimental models of diffuse lung injury.

Although PEEP does not prevent the formation of pulmonary edema, it might promote lung healing by aiding cellular maturation. Levine and Johnson[15] have demonstrated that the longer a lung remains collapsed, the more pressure is required for reinflation; they relate this finding to changes in elastic tissue and muscular arteries and to a loss of surface active material. Kilburn[16] has noted that alveolar cell maturation and differentiation may be adversely affected by the exclusion of air from cell surfaces, as may occur in flooded or collapsed alveoli during ARDS. By preventing or reversing such collapse, PEEP possibly could enrich the alveolar microenvironment. However, this possibility has never been proved.

The lack of firm theoretical support for prompt or prophylactic PEEP is offset by the results of several clinical trials.[4-6] Despite their uniform conclusion that PEEP can prevent lung injury, however, these studies differ in their definitions of ARDS, patient selection and allocation, and method of delivering positive airway pressure. Furthermore, because ARDS is a diverse and random condition, the studies include patients with respiratory failure due to multiple etiologies. To overcome this latter factor, other investigators have studied the effects of early or prophylactic PEEP on animal models in diffuse lung injury over brief time periods.[17,18] Yet, although these studies demonstrate the immediate and well known benefits of PEEP, they do not answer the question of how PEEP affects the natural history of acute lung injury over a long period.

The authors sought to study this natural history using the oleic acid model[19,20] of diffuse lung injury that they previously have characterized in this laboratory. Since lung repair was evident after one day in a previous study,[21] it was reasoned that PEEP would affect lung injury only during the first 24 hours following oleic acid administration. The authors chose to initiate therapy at two points: first, three hours after oleic acid to simulate the clinical situation in which early PEEP is begun when the PaO_2 has started to deteriorate but ARDS is not fully established; and second, before oleic acid to simulate the prophylactic administration of PEEP before obvious signs of injury. Although this injury would not be as severe as that in the previous investigation[21] in which a larger dose (0.09 ml/kg) of oleic acid was used, this higher dose caused an unacceptable mortality when it was applied to dogs that were studied repeatedly during

the first 24 hours following injury. A dose of 0.06 ml/kg was considered sufficient to damage the lungs in such a way that the results of therapy would be apparent.

In the studies of early and prophylactic PEEP, EPAP was used rather than CPAP or PEEP with mechanical ventilation because it was hypothesized that all three methods derive their major benefit from increasing FRC. The work of breathing might have been less if CPAP had been used; EPAP increased the $PaCO_2$ in the dogs that received it in the present study, although their $PaCO_2$ was not significantly greater than that of the untreated dogs. Mean Paw and pleural pressures are higher with PEEP and CPAP than with EPAP; this may impede venous return and possibly reduce pulmonary blood volume and extravascular lung water accumulation. The combination of PEEP and mechanical ventilation may have other theoretical advantages over EPAP that the authors did not allow for.

Given these possible limitations of the experimental model, the present investigation and the companion study[9] demonstrated that EPAP improved lung volumes and gas exchange when it was applied before or during the early stages of diffuse lung injury from oleic acid. Despite these immediate effects, however, FRC, $\dot{Q}va/\dot{Q}t$, and PaO_2 were not improved after discontinuation of EPAP in either investigation. End positive airway pressure accelerated the return to preinjury values of FRC and $\dot{Q}va/\dot{Q}t$, but this was not reflected in restoration of the PaO_2. End positive airway pressure did not decrease lung water or alter histology at 72 or 168 hours.

In sum, EPAP, a form of PEEP, improves gas exchange during its administration but has no beneficial effect in preventing the lung injury induced in dogs by oleic acid or enhancing its resolution. Because of these results, the authors cannot recommend the prophylactic or early use of PEEP in patients with ARDS who do not require this modality for reduction of $\dot{Q}va/\dot{Q}t$ and improvement of PaO_2.

References

1. Ashbaugh DG, Petty TL, Bigelow DB, Harris TM. Continuous positive-pressure breathing (CPPB) in adult respiratory distress syndrome. J Thorac Cardiovasc Surg 1969; 57:31–41.
2. Kumar A, Falke KJ, Geffin B, et al. Continuous positive-pressure ventilation in acute respiratory failure: effects on hemodynamics and lung function. New Engl J Med 1970; 283:1430–1436.
3. Kirby RR, Downs JB, Civetta JM, et al. High level positive end-expiratory pressure (PEEP) in acute respiratory insufficiency. Chest 1975; 67:156–163.
4. Valdes ME, Powers JR, Shah DM, et al. Continuous positive airway pressure in prophylaxis of adult respiratory distress syndrome in trauma patients. Surg Forum 1978; 29:187–189.
5. Weigelt JA, Mitchell RA, Snyder WH III. Early positive end-expiratory pressure in the adult respiratory distress syndrome. Arch Surg 1979; 114:497–501.
6. Schmidt GB, O'Neill WW, Kotb K, et al. Continuous positive airway pressure in the prophylaxis of the adult respiratory distress syndrome. Surg Gynecol Obstet 1976; 143:613–618.
7. Powers SR, Mannal R, Neclerio M, et al. Physiologic consequences of positive end-expiratory (PEEP) ventilation. Ann Surg 1973; 178:265–272.
8. Kanarek DJ, Shannon DC. Adverse effect of positive-end expiratory pressure on pulmonary perfusion and arterial oxygenation. Am Rev Respir Dis 1975; 112:457–459.
9. Luce JM, Robertson HT, Huang T, et al. The effects of expiratory positive airway pressure on the resolution of oleic acid-induced lung injury in dogs. Am Rev Respir Dis 1982; 125:716–722.
10. Ruiz BD, Tucker WK, Kirby RR. A program for calculation of intrapulmonary shunts, blood-gas and acid-base values with a programmable calculator. Anesthesiology 1975; 42:88–95.
11. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures: protection by positive end-expiratory pressure. Am Rev Respir Dis 1972; 110:556–565.
12. Wszyogrodski I, Kyei-Aboagye K, Taeusch HW Jr, Avery ME. Surfactant inactivation by hyperventilation: conservation by end-expiratory pressure. J Appl Physiol 1975; 38:461–466.
13. Hopewell PC. Failure of positive end-expiratory pressure to decrease lung water content in alloxan-induced pulmonary edema. Am Rev Respir Dis 1979; 120:813–819.
14. Hopewell PC, Murray JF. Effects of continuous positive-pressure ventilation in experimental pulmonary edema. J Appl Physiol. 1976; 40:568–574.
15. Levine BE, Johnson RP. Effects of atelectasis on pulmonary surfactant and quasi-static lung mechanics. J Appl Physiol 1965; 20:859–864.
16. Kilburn KH. Alveolar microenvironment. Arch Intern Med 1970; 126:435–449.
17. Flint LM, Gosdin GR, Carrico CJ. Ventilatory therapy for acid aspiration. Surg Forum 1975; 78:492–498.
18. Askanazi J, Wax SD, Neville JF Jr, et al. Prevention of pulmonary insufficiency through prophylactic use of PEEP and rapid respiratory rates. J Thorac Cardiovasc Surg 1978; 75:267–272.
19. Derks CM, Jacobovitz-Derks D. Embolic pneumopathy induced by oleic acid: a systematic morphologic study. Am J Pathol 1977; 87:143–151.
20. Uzawa T, Ashbaugh DG, Continuous positive-pressure breathing in acute hemorrhagic pulmonary edema. J Appl Physiol 1969; 20:427–432.
21. Schoene RB, Robertson HT, Springmeyer SC, et al. Evolution of gas exchange, lavage and pathologic patterns in oleic acid injury (abstr). Am Rev Respir Dis 1979; 119:384.