

# Ventilation with End-Expiratory Pressure in Acute Lung Disease

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**ABSTRACT** In 10 patients with severe, acute respiratory failure we studied the effects of positive end-expiratory pressure when intermittent positive pressure ventilation (IPPV) with inspired oxygen ( $F_{I_{O_2}}$ ) up to 0.5 failed to maintain arterial oxygen tension ( $P_{a_{O_2}}$ ) above 70 torr.

Positive end-expiratory pressures (PEEP) of 0, 5, 10, and 15 cm  $H_2O$  were applied for 30-min periods each and in random order. Blood gas exchange, lung volumes, compliance, and hemodynamics were studied at each level of PEEP.  $P_{a_{O_2}}$  ( $F_{I_{O_2}} = 1.0$ ) rose linearly with elevation of PEEP, the mean increase being from 152 to 347 torr, or 13 torr/cm  $H_2O$  PEEP. Mean functional residual capacity (FRC) was  $1.48 \pm 0.78$  liters at zero PEEP (i.e., IPPV) and the increase was essentially linear, reaching 2.37 liters at 15 cm  $H_2O$  PEEP.  $P_{a_{O_2}}$  and FRC showed a close correlation. Total and lung static compliance were greater during ventilation with high than with low levels of PEEP. The increase in  $P_{a_{O_2}}$  correlated with the specific lung compliance. Dynamic lung compliance decreased progressively with rising levels of PEEP except for an increase with 5 and 10 cm  $H_2O$  PEEP in patients with initial values of 0.06 liter/cm  $H_2O$  or higher. Cardiac index fell in some patients and rose in others and there was no correlation of mean cardiac index, systemic blood pressure, or peripheral vascular resistance with level of PEEP. The most probable explanation for the effect of PEEP on  $P_{a_{O_2}}$  and compliance is recruitment of gas exchange airspaces and prevention of terminal airway closure.

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## INTRODUCTION

The effectiveness of ventilation with positive end-expiratory pressure (PEEP)<sup>1</sup> in raising arterial oxygen tension ( $P_{a_{O_2}}$ ) in patients with severe, acute respiratory failure has been increasingly recognized since the report by Ashbaugh, Petty, Bigelow, and Harris (1). It is generally agreed that improvement in oxygenation and the effect on cardiac output appear to be related to the magnitude of PEEP and the resultant increase in functional residual capacity (FRC) (2, 3). However, the response of the individual patient to different levels of PEEP has not previously been reported and data are lacking on the associated changes in pulmonary compliance. Thus, if the increase in FRC results from recruitment of terminal airspaces (alveoli or small airways, or both) one would expect lung compliance to rise (4). Conversely, if overdistention of open airspaces is the predominant event, then no change or even a fall in pulmonary compliance should become apparent.

This study was carried out to clarify qualitatively and quantitatively the effects of mechanical ventilation with different levels of end-expiratory pressure on the circulation, lung volume, and blood-gas exchange in patients with severe respiratory failure. Based on these findings, it was our intent to characterize an optimal magnitude of end-expiratory pressure for the individual patient that will result in a minimal disturbance to cardiopulmonary function.

<sup>1</sup> Abbreviations used in this paper:  $C_{dyn}$ ,  $C_{stat}$ , dynamic and static lung compliance;  $C_{dynT}$ ,  $C_{statT}$ , total dynamic and total static lung compliance; CVP, central venous pressure;  $F_{I_{O_2}}$ , inspired fraction of oxygen; FRC, functional residual capacity; IPPV, intermittent positive pressure ventilation;  $P_{a_{O_2}}$ ,  $P_{a_{CO_2}}$ , arterial oxygen and carbon dioxide tension;  $P_{aw}$ ,  $P_{es}$ ,  $P_i$ , airway, esophageal, and transpulmonary pressure; PEEP, positive end-expiratory pressure;  $V_T$ , tidal volume.

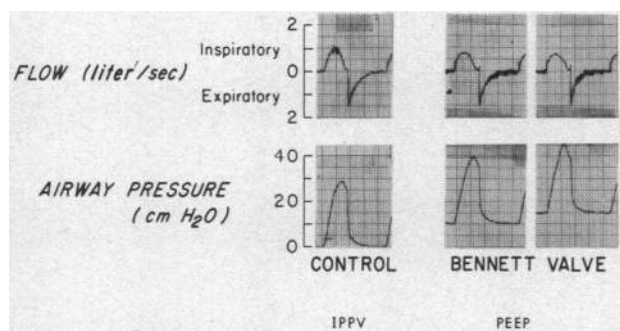


FIGURE 1 Typical flow and airway pressure patterns obtained with and without PEEP. The patient was being ventilated with an Emerson postoperative ventilator and ventilation with PEEP was instituted by addition of a special device to the expiratory port of the ventilator providing a positive expiratory pressure plateau (Bennett No. 3434 gas collecting manifold). Note difference to the pattern used by Kumar et al. (3).

## METHODS

**Selection of patients.** Data were obtained in 10 patients<sup>3</sup> all of whom had severe respiratory failure necessitating mechanical support of ventilation. The criteria for considering the use of PEEP in the pattern of ventilation were as previously described (3), i.e., inability to maintain  $Pa_{O_2}$  at acceptable<sup>3</sup> levels during IPPV when the inspired fraction of oxygen ( $FI_{O_2}$ ) was 0.5 or higher. The initial  $Pa_{O_2}$  during IPPV (i.e., with zero end-expiratory pressure) and an  $FI_{O_2}$  of 1.0 was less than 300 torr in all patients and less than 65 torr in six. All patients were ventilated with a volume preset ventilator<sup>4</sup> through a cuffed endotracheal or tracheostomy tube. Each patient was studied in the semirecumbent position with the trunk elevated approximately 35° from the horizontal plane. The inspiratory-to-expiratory time ratio ranged from 0.3 to 0.9, the respiratory frequency from 9 to 18/min and the tidal volume from 8.9 to 24.1 ml/kg body wt (2.9 to 6.2 ml/cm height). A positive end-expiratory plateau pressure was pro-

<sup>3</sup> Characteristic for all patients included in this study was a marked improvement in  $Pa_{O_2}$  when PEEP was added to the regimen with intermittent positive pressure ventilation (IPPV). They are representative of the approximately 100 patients per year who require treatment with mechanical ventilation and added PEEP or 10% of the total number of patients treated yearly with prolonged mechanical ventilation in our institution. A small number of patients with severe, acute respiratory failure and a large right-to-left shunt respond to mechanical ventilation with PEEP by showing no change or even a fall in  $Pa_{O_2}$ . Three such patients have been described (3); three additional patients have been seen who have failed to show an improvement of oxygenation when high levels of PEEP were applied. We have not been able to identify a common clinical or pathological denominator.

<sup>3</sup> An acceptable  $Pa_{O_2}$  is an arbitrary value determined for each patient on the basis of age, systemic disease, cardiovascular performance and, above all, stability of arterial oxygenation. We have considered a value below 70 torr as unacceptable.

<sup>4</sup> The Emerson Postoperative Ventilator (Emerson Respirator Iron Lung Co., Cambridge, Mass.) was used in eight patients and the Bennett MA-1 ventilator (Bennett Respiration Products, Inc., Santa Monica, Calif.) in two patients (Nos. 3 and 4).

duced with a gas-collecting manifold<sup>5</sup> attached to the expiratory port of the ventilator (Fig. 1). All patients received intermittent sedation as indicated by clinical criteria. Attempts to interpose respiratory effort during mechanical ventilation was suppressed either with i.v. morphine (approximately 15  $\mu$ g/kg per hr) or fentanyl (approximately 1–2  $\mu$ g/kg per hr). Occasionally a muscle relaxant, e.g., *d*-tubocurarine, (60  $\mu$ g/kg per hr) was added to facilitate control of ventilation.

Except for the change in end-expiratory pressure as required by the protocol, the ventilator settings remained unchanged throughout the study. Control measurements were obtained during IPPV (zero end-expiratory pressure) to which PEEP of 5, 10, and 15 cm H<sub>2</sub>O was added in random order, each being sustained for 30–35 minutes. During the last 10 min of each phase, arterial blood gases, pH, cardiac output (dye-dilution technique), systemic blood pressure, central venous pressure, and pulmonary compliance were measured. Positive end-expiratory pressure was discontinued briefly at the end of each period and the change in FRC ( $\Delta$ FRC) calculated as follows:  $\Delta$ FRC =  $V_E - V_I$ , where  $V_E$  equals first exhaled tidal volume after discontinuation of PEEP,  $V_I$  equals last inspired volume with PEEP. ( $\Delta$ FRC could not be measured accurately at the beginning of each period because the end-expiratory pressure was usually increased slowly over a period of about 2 min to allow for hemodynamic adjustment.) In two patients  $\Delta$ FRC was compared with the change in FRC calculated from the difference of two measurements obtained with helium dilution, one with PEEP and another 30 min after PEEP was discontinued. Comparison revealed a difference which was smaller than the error inherent in the helium method. Control FRC at zero end-expiratory pressure was measured in all cases with the closed circuit helium dilution method (5) either immediately before or after completion of the study. During the helium equilibration period adequate tidal exchange was effected by manual compression of a rebreathing bag to generate pressures and volumes similar to those produced by the ventilator.

Airway, esophageal, and transpulmonary pressures ( $P_{aw}$ ,  $P_{es}$ , and  $P_i$ ) were measured with transducers<sup>6</sup> calibrated with a water manometer.  $P_{es}$  was recorded with an esophageal balloon (10 cm) with the tip placed in the lower portion of the esophagus and inflated with 0.4 ml of air (6, 7). Tidal volume was obtained from integration of flow<sup>7</sup> through a heated Fleisch pneumotachograph. Inphase rejection of the differential pressure transducers was tested by applying up to 50 cm H<sub>2</sub>O pressure simultaneously to both sides of the transducers. The recorded differential pressure was always zero. All signals were recorded on an eight-channel recorder.<sup>8</sup> The volume channel was calibrated by displacing known volumes of air through the pneumotachograph. Accuracy of the gas volume measurements was tested according to the principles established by Grenvik et al. (8, 9). Pressure volume loops were obtained from photographs of the graphical display on the screen of a storage oscilloscope.<sup>9</sup> The following calculations were made:

<sup>5</sup> Bennett No. 3434.

<sup>6</sup> Sanborn Model 270 (Sanborn Div., Hewlett-Packard Co., Waltham, Mass.).

<sup>7</sup> Sanborn Model 330–1100B and Model 350–5000A.

<sup>8</sup> Hewlett-Packard Model 7868A (Hewlett-Packard Co., Palo Alto, Calif.).

<sup>9</sup> Tektronix type RM 564 with amplifiers Type 3AT2 (Tektronix, Inc., Beaverton, Ore.).

TABLE I  
Clinical Data

Patient No.	Age	Sex	Height	Weight	Primary disease diagnosis	X-ray findings	Initial PaO <sub>2</sub> F <sub>I</sub> O <sub>2</sub> = 1.0 on IPPV
			<i>cm</i>	<i>kg</i>			<i>torr</i>
1	42	F	165	54	Viral pneumonia, gram negative pulmonary superinfection	Bilateral diffuse infiltrates	55
2	52	M	185	93	Viral infection, gram negative pneumonitis	Left lower lobe infiltrate	58
3	51	M	180	73	Salt water aspiration, bronchiectasis, gram negative pneumonitis	Evidence for pulmonary edema	110
4	50	M	170	73	Hx. of smoking, pulmonary hypertension, congestive heart failure, gram negative pulmonary infection. Ventilated with 100% O <sub>2</sub> for 10 days.	Evidence for interstitial pulmonary edema	63
5	54	M	183	90	Acute anterior myocardial infarction with left ventricular failure (episodes of ventricular fibrillation)	Pulmonary vascular congestion, left lower lobe infiltrate, pleural effusion	55
6	61	F	152	73	Acute myocardial infarction with shock; elevated pulmonary capillary wedge pressure	Pulmonary vascular congestion	42
7	41	F	162	43	Status post implantation of coronary artery by-pass grafts; acute tubular necrosis, gram negative pulmonary infection	Pulmonary vascular congestion	119
8	57	F	147	73	Status post Starr-Edwards, aortic valve replacement with subsequent repair of para-valvular leak; gram negative pulmonary infection	Pulmonary vascular congestion	78
9	49	M	185	58	Gastrointestinal bleeding, aspiration, coma, right pneumothorax with IPPV, tracheostomy, staphylococci pulmonary infection	Middle lobe infiltrate	36
10	56	M	191	100	Extensive body trauma with fractures, upper gastrointestinal bleeding; status post gastrectomy, cardiac arrest, acute tubular necrosis, and abdominal sepsis	Basal atelectasis, pulmonary vascular congestion	235

Dynamic lung compliance ( $C_{dyn}$ ):

$$C_{dyn} = \frac{V_T}{\Delta P_1} \quad (1)$$

where  $V_T$  = tidal volume (liters);  $\Delta P_1$  = change in transpulmonary pressure between points of zero flow (cm H<sub>2</sub>O).

Static lung compliance ( $C_{stat}$ ):

$$C_{stat} = \frac{\Delta FRC}{\Delta P_1} \quad (2)$$

where  $\Delta FRC$  = change in functional residual capacity between 0 and 5 or 0 and 15 cm H<sub>2</sub>O PEEP. Total dynamic ( $C_{dyn}$ ) and static compliance ( $C_{stat}$ ) were calculated in a similar manner using transrespiratory system pressure changes.

Cardiac output, inspired oxygen concentrations, and arterial blood gases were measured as previously described (3).

## RESULTS

The clinical details are listed in Table I; mean values for gas exchange, hemodynamic performance, and

pulmonary mechanics are given in Table II; while data from individual patients are shown in Figs. 2-7 and in Table III.

### Effect of PEEP on hemodynamic performance

The hemodynamic response to ventilation with PEEP varied from patient to patient, as shown in Fig. 2. Mean values for cardiac index, systemic arterial blood pressure, and systemic vascular resistance showed no correlation with the level of PEEP or mean airway pressure. Central venous pressure (CVP) did show a small but significant increase with each rise in end-expiratory pressure (Table II). Cardiac index fell progressively with each level of PEEP in one patient (No. 7, Fig. 2) with severe pneumonia and marked limitation of myocardial function (Table I). Patient No. 6, with a diagnosis of cardiogenic shock, who was receiving an i.v. infusion of isoproterenol and metaraminol at the time of study, demonstrated a fall in systemic blood pressure and cardiac index when 5 cm H<sub>2</sub>O PEEP was

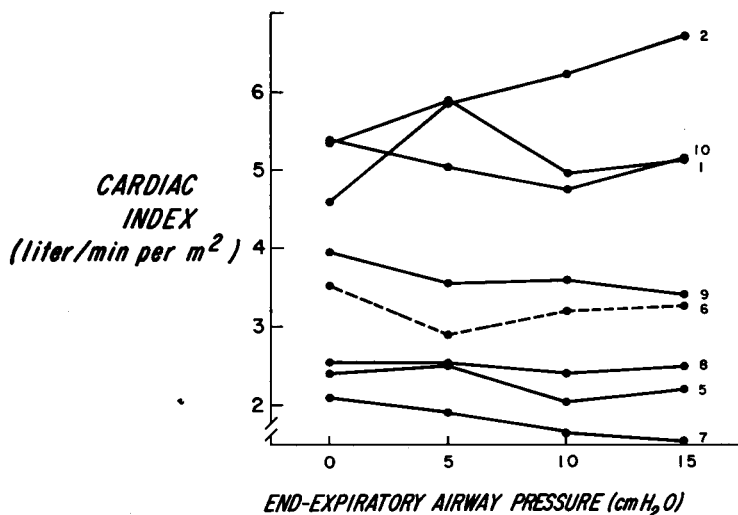


FIGURE 2 Cardiac index recorded at four different levels of end-expiratory pressure, each used for a period of 30 to 35 min. Patient number is entered at right (see Table I). Patient No. 6 received metaraminol 8  $\mu\text{g}/\text{min}$  and isoproterenol 8  $\mu\text{g}/\text{min}$  as i.v. infusion during IPPV. The infusion rate for metaraminol was increased to 75  $\mu\text{g}/\text{min}$ , 150  $\mu\text{g}/\text{min}$ , and 204  $\mu\text{g}/\text{min}$  during ventilation with PEEP at 5, 10, and 15 cm H<sub>2</sub>O, respectively.

applied. This effect was subsequently reversed by an increase in the vasopressor infusion rate during ventilation with 10 and 15 cm H<sub>2</sub>O PEEP.

#### Effect of PEEP on blood gas exchange

Arterial Po<sub>2</sub> rose linearly with each step increase in end-expiratory pressure (mean increase: 13 torr/cm H<sub>2</sub>O PEEP) (Table II). A small, but significant rise in PaCO<sub>2</sub> (2.2 torr) was recorded when PEEP was increased from 10 to 15 cm H<sub>2</sub>O and corresponded to a simultaneous small decrease in minute ventilation due probably to an increased gas leak from the ventilator.

*Effect of PEEP on FRC (Fig. 3, Table III).* Control FRC (in per cent of predicted normal for the supine position and assumed to equal 80% of the value in the upright position [10]) was low in six of the seven patients in whom it was measured (mean  $\pm$  SD: 1.48  $\pm$  0.78 liters) and rose essentially linearly with PEEP. The mean rise at 15 cm H<sub>2</sub>O PEEP was 0.84  $\pm$  0.33 liter or 0.056 liter/cm H<sub>2</sub>O PEEP. In two patients (Nos. 4 and 6) FRC reached its predicted value at 15 cm H<sub>2</sub>O PEEP. One patient with chronic bronchitis and bronchiectasis had a normal FRC despite a low PaO<sub>2</sub>.

In all patients studied, each step increase in FRC was followed by a rise in PaO<sub>2</sub> (Fig. 3).

*Effect of PEEP on compliance (Fig. 4).* Static compliance (C<sub>stat</sub>) measured over a change in functional residual capacity ( $\Delta$ FRC) from 0 to 15 cm H<sub>2</sub>O PEEP was greater than that found with a volume change from 0 to 5 cm H<sub>2</sub>O PEEP. Except for patient No. 3, the

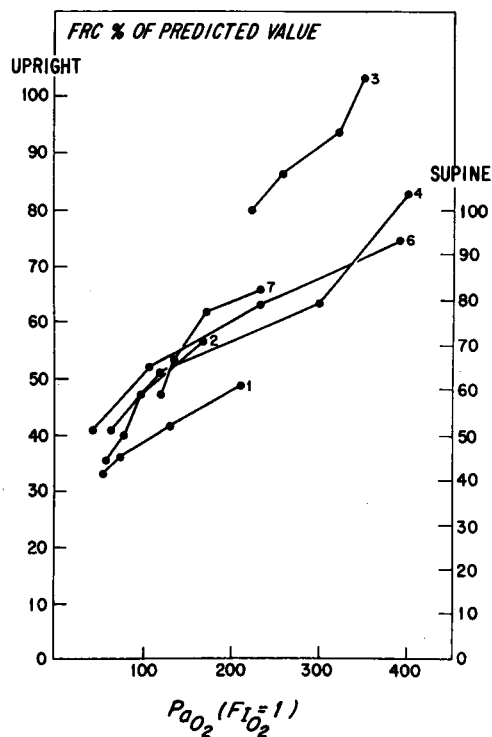


FIGURE 3 Correlation between FRC and the PaO<sub>2</sub> (FI<sub>0</sub><sub>2</sub> = 1.0) at four different levels of end-expiratory pressure. Each lowest point represents the relationship during IPPV, the next at 5 cm PEEP, etc. Note that patient No. 3 had bronchiectasis. Values for the predicted FRC are from Bates, Macklem, and Christie (10).

TABLE II  
Data on Gas Exchange, Hemodynamics, and Respiratory Mechanics

	IPPV control	End-expiratory pressure (cm H <sub>2</sub> O)		
		5	10	15
PaO <sub>2</sub> , torr	152±100	203±120**	279±106**	347±104**
A-aDO <sub>2</sub> , torr	515±101	464±120**	384±106**	323±94**
P <sub>a</sub> CO <sub>2</sub> , torr	40.9±7.7	39.3±7.4	39.4±6.1	41.6±7.2‡
pH	7.42±0.03	7.43±0.04	7.43±0.05	7.40±0.06‡‡
Heart rate/min	95±8	95±8	97±12	100±10
Stroke volume, ml	72.9±29.3	74.5±35.1	71.1±41.5	72.1±43.1
Mean arterial pressure, mm Hg	79±16	81±26	80±20	86±24
Mean central venous pressure, mm Hg	6.7±4.5	7.8±4.3*	8.4±3.6*	10.4±2.9**
Peak airway pressure, cm H <sub>2</sub> O	25.7±3.5	29.3±4.7**	35.0±5.8**	42.0±6.3**
Mean airway pressure, cm H <sub>2</sub> O	8.5±1.7	12.8±2.5**	17.6±2.5**	21.5±3.3**
Peak inspiratory flow, liter/sec	0.76±0.10	0.79±0.06	0.78±0.07	0.74±0.07
Peak expiratory flow, liter/sec	1.19±0.25	1.24±0.20	1.26±0.24	1.29±0.23
Minute ventilation, liter/min	11.57±2.09	11.20±2.08	10.88±1.96	10.29±2.33‡
Dynamic total respiratory compliance, $\frac{\text{liter}}{\text{cm H}_2\text{O}}$	0.041±0.010	0.043±0.010	0.042±0.014	0.037±0.014‡‡
Dynamic lung compliance, $\frac{\text{liter}}{\text{cm H}_2\text{O}}$	0.058±0.017	0.062±0.022	0.060±0.026	0.053±0.024‡

Mean ±SD, correlated *t* test was used to determine the significance of the changes.

\* *P* < 0.05, \*\* *P* < 0.01. Significantly different from value with any other level of end-expiratory pressure, with *P* as indicated.

‡ *P* < 0.05, ‡‡ *P* < 0.01. Significantly different only from value on 10 cm H<sub>2</sub>O end-expiratory pressure, with *P* as indicated.

TABLE III  
Individual Data on Respiratory Mechanics

Patient No.	FRC	End-expiratory airway pressure (cm H <sub>2</sub> O)																			
		IPPV 0					5					10					15				
		P <sub>aw</sub>	P <sub>1</sub>	P <sub>es</sub>	V <sub>T</sub>	ΔFRC	P <sub>aw</sub>	P <sub>1</sub>	P <sub>es</sub>	V <sub>T</sub>	ΔFRC	P <sub>aw</sub>	P <sub>1</sub>	P <sub>es</sub>	V <sub>T</sub>	ΔFRC	P <sub>aw</sub>	P <sub>1</sub>	P <sub>es</sub>	V <sub>T</sub>	ΔFRC
1	0.87	$\frac{27}{0}$	$\frac{15}{-5}$	$\frac{6}{4}$	0.58	$\frac{33}{5}$	$\frac{20}{-2}$	$\frac{13}{8}$	0.58	0.08	$\frac{39}{10}$	$\frac{26}{4}$	$\frac{12}{8}$	0.54	0.22	$\frac{45}{15}$	$\frac{31}{7}$	$\frac{12}{8}$	0.48	0.42	
2	1.63	$\frac{24}{0}$	$\frac{10}{-7}$	$\frac{14}{7}$	1.15	$\frac{22.5}{.5}$	$\frac{12}{-2.5}$	$\frac{12}{6.5}$	1.15	0.23	$\frac{36}{10}$	$\frac{18}{2.5}$	$\frac{14}{8}$	1.05	0.55	$\frac{41}{15}$	$\frac{21}{3}$	$\frac{18}{12}$	1.05	1.01	
3	3.19	$\frac{25}{0}$	$\frac{16}{-2}$	$\frac{9}{1}$	1.10	$\frac{29}{5}$	$\frac{17}{0}$	$\frac{11}{4.5}$	1.10	0.25	$\frac{36}{10}$	$\frac{21.5}{5.0}$	$\frac{14}{5.5}$	1.07	0.55	$\frac{42}{15}$	$\frac{25}{8}$	$\frac{16.5}{6.5}$	1.03	0.92	
4	1.38	$\frac{16.5}{1}$	$\frac{5.5}{-5}$	$\frac{11}{6}$	0.86	$\frac{20}{5.5}$	$\frac{6.5}{-2.5}$	$\frac{13}{7.5}$	0.85	0.35	$\frac{25}{10}$	$\frac{9}{0.5}$	$\frac{13.5}{9.5}$	0.84	0.78	$\frac{31}{16}$	$\frac{13}{4}$	$\frac{16}{11}$	0.82	1.45	
5	—	$\frac{20}{0}$	$\frac{11.5}{-3.5}$	$\frac{8}{3}$	1.05	$\frac{21}{5}$	$\frac{14}{0.5}$	$\frac{6}{4}$	1.05	0.20	$\frac{26}{10}$	$\frac{18.5}{4.5}$	$\frac{8}{6}$	1.15	0.44	$\frac{31}{14}$	$\frac{21}{7.5}$	$\frac{8.5}{6.5}$	1.05	0.72	
6	0.95	$\frac{?}{0}$	$\frac{8.5}{-3}$	$\frac{5}{3}$	0.73	$\frac{23}{5}$	$\frac{12}{0}$	$\frac{15}{11}$	0.77	0.25	$\frac{29}{10}$	$\frac{15}{3}$	$\frac{14}{11.5}$	0.73	0.50	$\frac{35}{14}$	$\frac{21}{5}$	$\frac{15}{13}$	0.67	0.78	
7	1.33	$\frac{29.5}{0}$	$\frac{22.5}{2.5}$	$\frac{5.5}{-2}$	0.77	$\frac{35.5}{5}$	$\frac{28}{5.5}$	$\frac{6.5}{-0.5}$	0.76	0.16	$\frac{45}{11}$	$\frac{35.5}{10.5}$	$\frac{5.5}{-0.5}$	0.73	0.40	$\frac{51}{15}$	$\frac{39}{12.5}$	$\frac{10}{2}$	0.62	0.58	
8	1.07	$\frac{26}{0}$	—	—	—	$\frac{31}{5}$	—	—	—	—	$\frac{36}{10}$	—	—	—	—	$\frac{43}{15}$	—	—	—	—	
Mean	1.48								0.22					0.49					0.84		
SD	±0.78								±0.08					±0.17					±0.33		

Pressures in cm H<sub>2</sub>O; V<sub>T</sub>, and ΔFRC in liters. All pressures were obtained in succession; the negative transpulmonary pressures may result from the semirecumbent position of the patient and a balloon volume of 0.4 ml (Milic-Emili et al. [6, 7]).

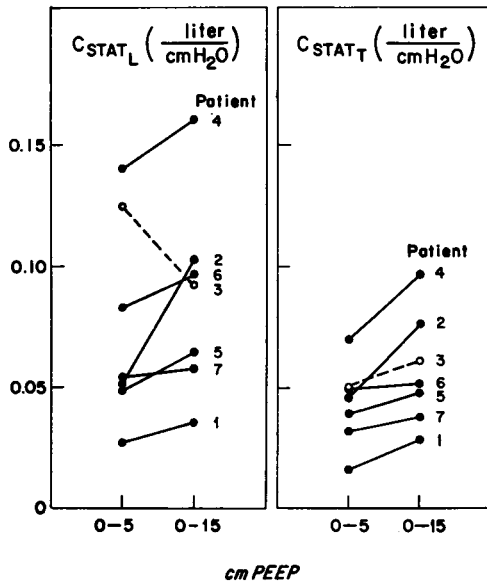


FIGURE 4  $C_{statL}$  and  $C_{statT}$  at volume change corresponding to pressure changes from 0 to 5 and from 0 to 15 cm H<sub>2</sub>O PEEP. There is no satisfactory explanation for the fall in  $C_{statL}$  in patient No. 3. The  $P_{aO_2}$  ( $F_{IO_2} = 1.0$ ) increased in all instances.

same was true for the  $C_{statT}$ . The increase in  $P_{aO_2}$  as a function of specific compliance ( $C_{statL}/\text{control FRC}$ ) is plotted in Fig. 5. It shows that PEEP was more effective in improving  $P_{aO_2}$  in patients with a high lung compliance than in those in whom compliance was low.

Application of PEEP improved  $C_{dynI}$  only when control  $C_{dynI}$  was 0.06 liter/cm H<sub>2</sub>O or higher (Figs. 6A and B). Patients with a lower control  $C_{dynI}$  responded with a further decrease (Fig. 6C). Thus, there were no statistically significant changes in mean  $C_{dynI}$  as compared with the control state. However,  $C_{dynI}$  and  $C_{dynT}$  with 15 cm PEEP was lower in all patients than that observed with 10 cm PEEP.

### Clinical course and complications

In nine patients ventilation with PEEP could be discontinued after 1-11 days. A typical course was shown by Patient No. 1: during spontaneous ventilation with an oxygen face mask,  $P_{aO_2}$  was 33 torr,  $P_{aCO_2}$  28 torr, and pH 7.32. Tracheal intubation and IPPV with 100% oxygen were followed by an increase in  $P_{aO_2}$  to 58 torr, and a further rise to 210 torr when PEEP 15 cm H<sub>2</sub>O was added. The inspired oxygen concentration was reduced to 50% and PEEP was gradually reduced from 15 to 5 cm H<sub>2</sub>O and discontinued on the 6th day. The patient was able to ventilate free of mechanical support on the 10th day when  $P_{aO_2}$  (breathing oxygen) had risen to 375 torr. On the 13th day when

the endotracheal tube was removed,  $P_{aO_2}$  breathing air was 65 torr.

Patients Nos. 1-5 were eventually discharged from the hospital. Patients Nos. 6, 7, and 8 died of intractable myocardial failure and its complications. Patient No. 9 developed bilateral bronchopneumonia with a right-sided pneumothorax before PEEP was instituted. A left-sided tension pneumothorax with subcutaneous emphysema and pneumoperitoneum followed after PEEP was added. Bronchopneumonia, ultimately resulting in death, developed in patient No. 10 4 wk after the study.

### DISCUSSION

This study of hemodynamic adjustment and lung function during mechanical ventilation and end-expiratory pressure (PEEP) has shown that moderate levels of PEEP (5 cm H<sub>2</sub>O) have little or no effect on cardiac index in patients with acute respiratory failure. This is consistent with the findings of McIntyre, Laws, and Ramachandran (2) who found no fall in cardiac index in five similar patients with plateau end-expiratory pressure of 5 cm H<sub>2</sub>O. However, the constancy of mean cardiac index when PEEP is elevated further to 10 and 15 cm H<sub>2</sub>O is at variance with our previous findings. Kumar et al. (3) found a reduction in mean cardiac

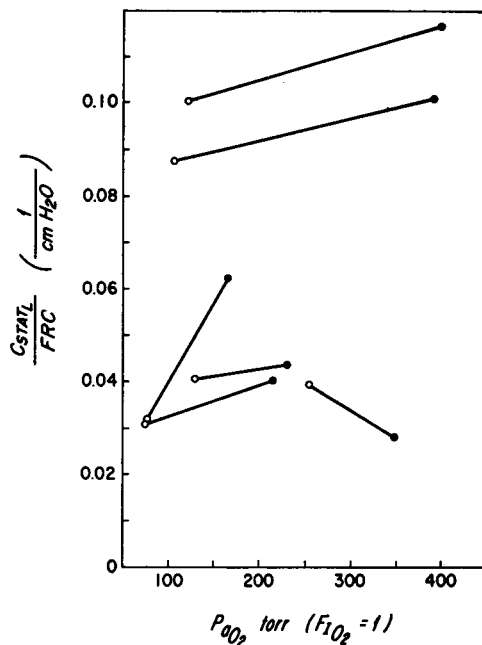


FIGURE 5 The increase in  $P_{aO_2}$  as a function of  $C_{statL}$ . The ratio of  $C_{statL}$  to control-FRC was plotted vs. the  $P_{aO_2}$  to demonstrate that the change in  $P_{aO_2}$  with increase of PEEP from 5 (open circles) to 15 (closed circles) cm H<sub>2</sub>O was larger in the presence of a high lung compliance than in patients with low lung compliance.

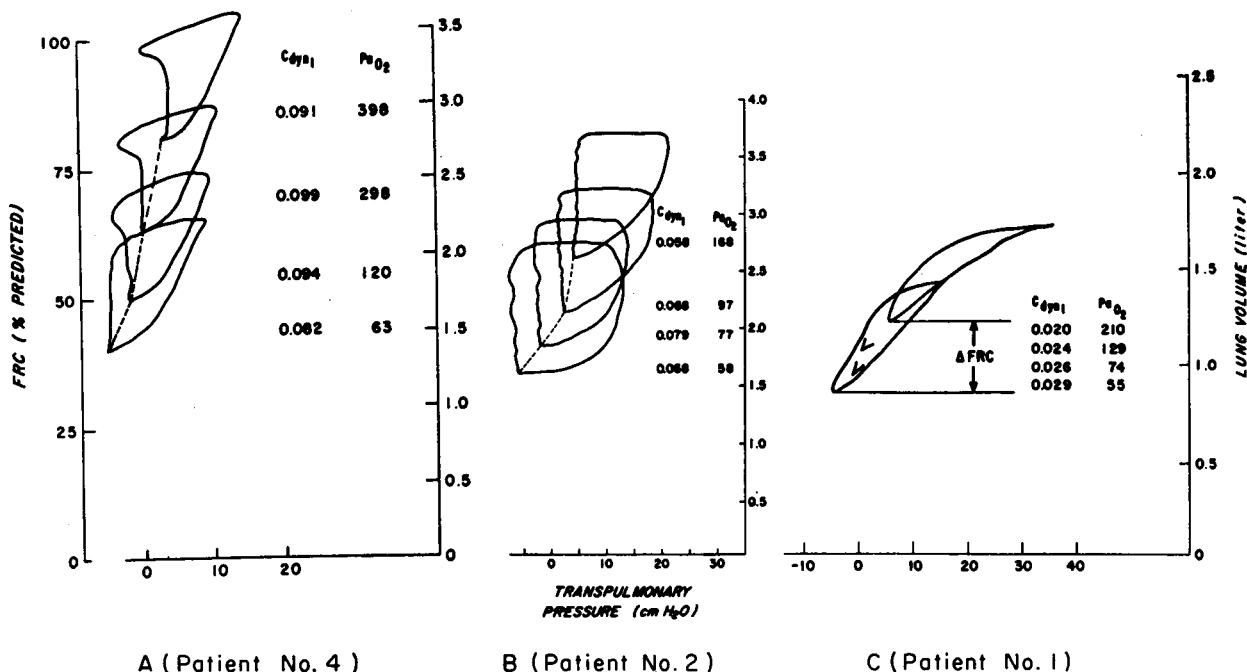


FIGURE 6 Pressure volume loops of the lung with IPPV and different levels of PEEP. The scale marked FRC (per cent of predicted) applies to all three figures; the scale to the right of each figure indicates the actual lung volume in liters. In figures A and B a loop is shown for each level of end-expiratory airway pressure with the lowermost obtained at zero cm H<sub>2</sub>O (IPPV). In figure C most of the pressure volume loops for 5 and 10 cm H<sub>2</sub>O have been omitted for the sake of clarity and only the end-expiratory static part retained. The values for  $C_{dyn}$  (liter/cm H<sub>2</sub>O) are derived from the time tracings (see text and Table III); the values for  $Pa_{O_2}$  (torr) with a  $F_{I_{O_2}} = 1$  are included.

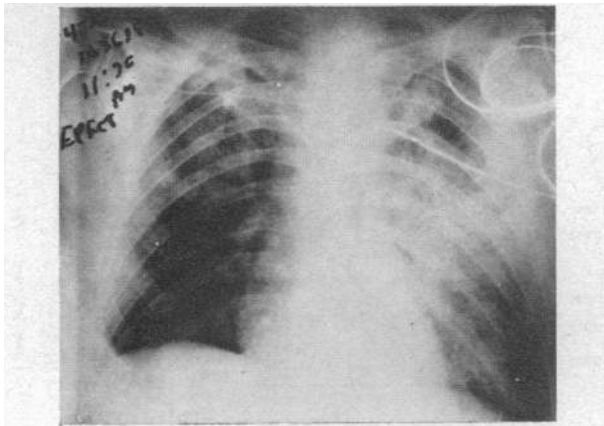
index from 4.5 to 3.6 liters when an average level of 13 cm H<sub>2</sub>O PEEP was reapplied after 30 min of IPPV. In the present study end-expiratory plateau pressures were produced without the use of expiratory flow impedance (Fig. 1) whereas Kumar et al. (3) used expiratory flow impedance for the same purpose. The flow impedance technique might be expected to result in a higher mean airway pressure and more profound circulatory depression, as demonstrated in dogs by Colgan, Barrow, and Fanning (11). In fact, the rise in mean airway pressure (from 11 to 23 cm H<sub>2</sub>O) described by Kumar after 13 cm H<sub>2</sub>O PEEP was no greater than the change extrapolated from the present data for the same level of PEEP, i.e., from 8.5 to 20 cm H<sub>2</sub>O. Thus, the discrepancy cannot be explained solely by differences in technique of generating positive end-expiratory airway pressures.

Inspection of individual changes (Fig. 2) shows that the cardiac index fell in the majority of patients, and that the mean value is raised considerably by the disproportionate increase in cardiac index which occurred in patients Nos. 2 and 10.

A stereotyped hemodynamic response to application of PEEP cannot be expected since both the relationship between available blood volume and capacity of the

intravascular bed (12) as well as the type of underlying lung disease (13) influence this response. Uzawa and Ashbaugh (14) and Cheney and Martin (15) observed large decreases in cardiac index with application of PEEP in dogs with oleic acid induced acute respiratory failure. However, it is likely that acute hypovolemia due to the severe pulmonary edema and massive fluid loss into the lungs was a mitigating factor.

*PEEP and oxygenation.* Mechanical ventilation with PEEP may effect arterial oxygenation by several mechanisms. First, a change in cardiac output will alter mixed venous oxygen content (oxygen consumption and  $\dot{Q}_S/\dot{Q}_T$  assumed constant) and, thus, influence  $Pa_{O_2}$ . Also a change in cardiac output may be associated with a change in pulmonary artery pressure and redistribution of pulmonary blood flow (16). The resultant change in  $Pa_{O_2}$  will depend on the relative perfusion of the nonventilated area, and whether this lesion is in a dependent or nondependent portion of the lung. In our series, two patients with predominantly unilateral disease exhibited a significant rise in  $Pa_{O_2}$  with PEEP only when the better lung was dependent. This phenomenon is illustrated in Fig. 7. We have found no correlation between cardiac index and  $Pa_{O_2}$ ; however, pulmonary artery pressures were not measured. Second,



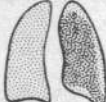


POSITION		PaO <sub>2</sub> (TORR)	
		$\bar{P}$ PEEP	$\bar{C}$ PEEP
Supine		66	97
Left Infiltrate Dependent		?	76
Left Infiltrate Nondependent		65	152

FIGURE 7 Influence of body position on the effect of positive end-expiratory pressure (PEEP) on PaO<sub>2</sub> seen in patient No. 2 with left-sided pulmonary infiltrates, F<sub>I</sub>O<sub>2</sub> = 1.0.

PEEP may produce regional changes in lung volume with redistribution of blood flow to ventilated-perfused and ventilated, nonperfused parts of the lung (17, 18). Third, an alteration of pulmonary mechanics may lead to improved gas distribution.

The low FRC observed in this and other studies (2, 3) is characteristic of patients with acute respiratory failure and large intrapulmonary right-to-left shunt ( $\dot{Q}_S/\dot{Q}_T$ ). It is not known whether the low FRC is an artifact produced by the presence of a small communicating gas volume, i.e., closure of conducting airways with gas trapping, or closure of terminal gas-exchanging air units. Although the evidence is incomplete, we favor the latter for the following reasons. First, as shown by Kumar et al. (3) when PEEP is discontinued abruptly, arterial Po<sub>2</sub> falls sharply within 1 min. Small airway closure (19) with subsequent absorption of trapped gas and atelectasis (20) may explain the subsequent, more gradual diminution in PaO<sub>2</sub>.

Second, if the airway pressure generated exceeds the opening pressure of distal conducting airways during helium equilibration by manual ventilation (see Methods), then intermittent opening would allow helium wash-in to distal airspaces, and this volume will be included in the FRC measurement. Furthermore, during ventilation with 100% oxygen, intermittent airway closure and gas trapping during part of the respiratory cycle will not lead to pronounced right-to-left shunting since fresh oxygen will enter gas-exchanging airspaces with each breath. If, on the other hand, peak inspiratory airway pressures are below critical opening pressures for small, conducting airways, a reduction in  $\dot{Q}_S/\dot{Q}_T$  after the application of 5–10 cm H<sub>2</sub>O PEEP would be difficult to explain. The data are inadequate to resolve the problem.

**PEEP and compliance.** Inspection of the pressure volume loops (Fig. 6A and B) reveals two changes when PEEP is elevated from 0 to 15 cm H<sub>2</sub>O. First, a line joining the end-expiratory, static points of the loops describes a curve with a rising slope. This was apparent in six of seven patients, and is interpreted as evidence for an increase in static compliance with rising levels of PEEP, probably secondary to recruitment of terminal airspaces (4). The consistent increase in C<sub>stat<sub>t</sub></sub> is well illustrated in Fig. 4. It is matched by a similar increase in C<sub>stat<sub>1</sub></sub> with the exception of case No. 3 where an unexplained fall was observed.

In five patients the inflation limb of the pressure volume loops recorded during ventilation with PEEP were less convex towards the pressure axis than during IPPV (Fig. 6B). Such changes in convexity probably reflect a diminution in flow-resistive pressure and the altered static pressure-volume behavior of a lung when inflation is associated with recruitment of closed units. We conclude, therefore, that a decrease in airway resistance, or diminished closure of lung units, or both, does take place when FRC is increased with PEEP. Patient No. 4 (Fig. 6A) who demonstrated the greatest rise in PaO<sub>2</sub>, showed no visible change in the inflation portion of his loop and only a small increase of the relatively high C<sub>stat<sub>1</sub></sub>. Another mechanism which may have contributed to the large increase in PaO<sub>2</sub> includes the redistribution of blood flow secondary to regional changes in lung volumes (17, 18), as was discussed above.

The fall in C<sub>dyn<sub>1</sub></sub> and C<sub>dyn<sub>t</sub></sub> observed in all patients when PEEP was increased from 10 to 15 cm H<sub>2</sub>O may reflect increasing stiffness of highly distended airspaces. On the other hand, the continued increase in PaO<sub>2</sub> in the face of reduction in C<sub>dyn<sub>1</sub></sub> and C<sub>dyn<sub>t</sub></sub> may indicate the simultaneous occurrence of airspace recruitment with overdilatation of open alveoli represented by the upper, flatter portion of the pressure volume curve. The relative contribution of each to the change in lung



volume probably modulates the ensuing relationship between FRC and  $PaO_2$ .

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### REFERENCES

1. Ashbaugh, D. G., T. L. Petty, D. B. Bigelow, and T. M. Harris. 1969. Continuous positive-pressure breathing (CPPB) in adult respiratory distress syndrome. *J. Thorac. Cardiovasc. Surg.* **57**: 31.
2. McIntyre, R. W., A. K. Laws, and P. R. Ramachandran. 1969. Positive expiratory pressure plateau: improved gas exchange during mechanical ventilation. *Can. Anaesth. Soc. J.* **16**: 477.
3. Kumar, A., K. J. Falke, B. Geffin, C. F. Aldredge, M. B. Laver, E. Lowenstein, and H. Pontoppidan. 1970. Continuous positive-pressure ventilation in acute respiratory failure. Effects on hemodynamics and lung function. *N. Engl. J. Med.* **283**: 1430.
4. Mead, J., and C. Collier. 1959. Relation of volume history of lungs to respiratory mechanics in anesthetized dogs. *J. Appl. Physiol.* **14**: 669.
5. Laws, A. K. 1968. Effect of induction of anaesthesia and muscle paralysis on functional residual capacity of the lungs. *Can. Anaesth. Soc. J.* **15**: 325.
6. Milic-Emili, J., J. Mead, J. M. Turner, and E. M. Glauser. 1964. Improved technique for estimating pleural pressure from esophageal balloons. *J. Appl. Physiol.* **19**: 207.
7. Milic-Emili, J., J. Mead, and J. M. Turner. 1964. Topography of esophageal pressure as a function of posture in man. *J. Appl. Physiol.* **19**: 212.
8. Grenvik, A., and U. Hedstrand. 1966. The reliability of pneumotachography in respirator ventilation. *Acta Anaesthesiol. Scand.* **10**: 157.
9. Grenvik, A., U. Hedstrand, and H. Sjogren. 1966. Problems in pneumotachography. *Acta Anaesthesiol. Scand.* **10**: 147.
10. Bates, D. V., P. T. Macklem, and R. V. Christie. 1971. *Respiratory Function in Disease*. W. B. Saunders Company, Philadelphia, Pa. 2nd edition. 93.
11. Colgan, F. J., R. E. Barrow, and G. L. Fanning. 1971. Constant positive-pressure breathing and cardiorespiratory function. *Anesthesiology*. **34**: 145.
12. Sykes, M. K., A. P. Adams, W. E. I. Finlay, P. W. McCormick, and A. Economides. 1970. The effects of variations in end-expiratory inflation pressure on cardiorespiratory function in normo-, hypo-, and hypervolaemic dogs. *Brit. J. Anaesth.* **42**: 669.
13. Hedley-Whyte, J., H. Pontoppidan, and M. J. Morris. 1966. The response of patients with respiratory failure and cardiopulmonary disease to different levels of constant volume ventilation. *J. Clin. Invest.* **45**: 1543.
14. Uzawa, T., and D. G. Ashbaugh. 1969. Continuous positive-pressure breathing in acute hemorrhagic pulmonary edema. *J. Appl. Physiol.* **26**: 427.
15. Cheney, F. W., and W. E. Martin. 1971. Effects of continuous positive-pressure ventilation on gas exchange in acute pulmonary edema. *J. Appl. Physiol.* **30**: 378.
16. West J. B. 1970. *Ventilation/Blood Flow and Gas Exchange*, Blackwell Scientific Publications Ltd., Oxford. 2nd edition.
17. Hughes, J. M. B., J. B. Glazier, J. E. Maloney, and J. B. West. 1968. Effect of lung volume on the distribution of pulmonary blood flow in man. *Respir. Physiol.* **4**: 58.
18. Roos, A., L. J. Thomas, Jr., E. L. Nagel, and D. C. Prommas. 1961. Pulmonary vascular resistance as determined by lung inflation and vascular pressures. *J. Appl. Physiol.* **16**: 77.
19. Craig, D. B., W. M. Wahba, H. F. Don, J. G. Couture, and M. R. Becklake. 1971. "Closing volume" and its relationship to gas exchange in seated and supine positions. *J. Appl. Physiol.* **31**: 717.
20. Burger, E. J., Jr., and P. Macklem. 1968. Airway closure: demonstration by breathing 100%  $O_2$  at low lung volumes and by  $N_2$  washout. *J. Appl. Physiol.* **25**: 139.