Anesthesiology
V 37, No 5, Nov 1972

End-expiratory Pressure in Dogs with Pulmonary Edema Breathing Spontaneously

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Positive end-expiratory pressure (PEEP) was applied to anesthetized dogs breathing spontaneously before and after oleic acid-induced pulmonary edema. The effects of PEEP on gas exchange and cardiac index were compared with values obtained during spontaneous breathing at zero end-expiratory pressure (ZEEP). Before pulmonary edema, PEEP decreased intrapulmonary shunt and cardiac index, compared with ZEEP. During pulmonary edema, positive end-expiratory pressures of 5, 10, and 15 cm H_2O caused progressive decreases in shunt with parallel increases in Pa_{O_2}. Cardiac index decreased significantly from the values seen during spontaneous respiration with ZEEP at the 15-cm H_2O level of PEEP only. A marked decrease in respiratory rate with no change in tidal volume was also observed with the application of PEEP, resulting in a decreased minute volume and increased Pa_{CO_2}. It is concluded that since PEEP imposed during spontaneous respiration in experimental pulmonary edema improved arterial oxygenation, clinical trials of the technique are indicated. (Key words: Positive end-expiratory pressure; Oleic acid-induced pulmonary edema; Venous admixture.)

CONTINUOUS mechanical ventilation with positive end-expiratory pressure (PEEP) improves arterial oxygenation in patients with the adult respiratory distress syndrome characterized by interstitial pulmonary edema and alveolar collapse.[1] An experimental model which has features similar to the respiratory distress syndrome seen in humans has been developed in the dog.[2] Injection of oleic acid into the dog produces tachypnea, hypoxemia, decreased lung compliance, and interstitial hemorrhage and edema. Studies using this model have also shown that PEEP used in conjunction with continuous mechanical ventilation produces better arterial oxygenation than either intermittent positive-pressure ventilation or spontaneous respiration.[3, 4] The following study was done during oleic acid-induced respiratory distress to see whether PEEP, when used with spontaneous ventilation, was effective in improving oxygenation.

Methods

Twelve mongrel dogs (each weighing 20.7 ± 0.7 kg SE) were anesthetized with 30 mg/kg pentobarbital. The trachea of each dog was intubated with a cuffed endotracheal tube, and the dog was placed in the supine position and allowed to breathe spontaneously. Throughout the entire period of study the dog inhaled 100 per cent oxygen from a reservoir bag through a nonrebreathing valve (Collins "J" valve) modified with a baffle to reduce deadspace (fig. 1). Polyethylene catheters were placed in the aorta via the femoral artery and in the right ventricle or pulmonary artery via the right jugular vein. Physiologic saline solution was infused at 5 ml/kg/hr, iv; the volume of blood withdrawn for samples was replaced by three times as much saline solution. A Collins 9-liter spirometer measured expired volumes. Airway pressures were measured from a side tap at the proximal end of the endotracheal tube. Appropriate electronic equipment was used to measure and record the ECG and pulmonary arterial and aortic pressures. Mean pressures were obtained by electronic damping of the pressure waves. Cardiac output was measured by the dye-

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Received from the Department of Anesthesiology and the Anesthesia Research Center, University of Washington School of Medicine, Seattle, Washington 98195. Accepted for publication May 11, 1972. Supported by the Anesthesia Research Center Grant GM 15991-04 and Anesthesia Research Training Grant GM 01160-08 from the National Institute of General Medical Sciences, National Institutes of Health.

dilution technique using indocyanine green. Electrodes were used to measure P_{O_2}, P_{CO_2}, and *p*H of arterial and mixed venous blood, with corrections applied for the temperature of the dog.[5, 6] The hematocrit of each sample was measured, and oxygen saturation was calculated from the Severinghaus blood–gas calculator.[6]

Base deficit was calculated from *in-vivo* CO_2 titration curves.[7] Intrapulmonary shunt ($\dot{Q}_s/\dot{Q}_t$) was calculated from the standard mixing equation.[8] Oxygen content, oxygen consumption, and body surface area were calculated by the following formulas:

Arterial O_2 content (Ca_{O_2}) in ml/100 ml = (arterial O_2 saturation) (Hct/3) (1.34) + 0.003 (Pa_{O_2})

O_2 consumption ($\dot{V}_{O_2}$) in ml O_2/min/m^2 = ($Ca_{O_2} - C\bar{v}_{O_2}$) (cardiac index)

Body surface area (BSA) in m^2 = (0.112) (wt in kg)$^{2/3}$

Positive end-expiratory pressure was produced by attaching to the expiratory line a 2-cm-ID tube, which was immersed in water. The depth of immersion controlled the end-expiratory pressure. Baseline measurements were made at end-expiratory pressures of 0 (control), 5, 10, and 15 cm H_2O. Hemorrhagic pulmonary edema was induced by rapid injection of 0.15 ml/kg of oleic acid into the pulmonary artery or right ventricle.[2] In order to reduce the base deficit which occurs with administration of oleic acid,[2, 3] 2 mEq/kg of sodium bicarbonate were given to each animal. An hour elapsed before further measurements to allow development of significant pulmonary edema. Small doses of pentobarbital, 5 to 15 mg/kg, as necessary to maintain anesthesia, were given before this interval. All variables were measured at ZEEP before every measurement at 5, 10, and 15 cm H_2O PEEP. The animals breathed for 15 minutes at each level of the end-expiratory pressure. The order of these measurements was randomized to obviate the effect of time on the values reported. Paired t tests were used for statistical analysis. *P* values greater than 0.05 were considered not significant.

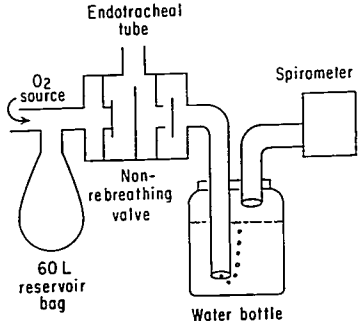

FIG. 1. Schematic diagram of apparatus used to produce PEEP in dogs breathing spontaneously.

Results

Effects of PEEP before Pulmonary Edema (Table 1)

The $\dot{Q}_s/\dot{Q}_t$ fraction showed a small but significant decrease from zero end-expiratory pressure (ZEEP) at 5, 10, and 15 cm H_2O PEEP. Pa_{O_2} increased slightly at all values of PEEP, but the change was significant at 5 cm H_2O only. Cardiac index was significantly decreased at 10 and 15 cm H_2O PEEP. There was a small but significant decrease in mixed venous oxygen saturation at 5 and 10 cm H_2O PEEP. Pa_{CO_2} increase was significant at 15 cm H_2O PEEP only. Respiratory rate decreased slightly but significantly at all values of PEEP.

Effects of PEEP after Pulmonary Edema (Tables 2 and 3)

The circulatory and respiratory effects of oleic acid varied considerably from animal to animal. Four dogs died of hypoxia caused by pulmonary edema within an hour of injection of oleic acid. The data from these dogs are not reported. Other animals had Pa_{O_2} values ranging from 44 to 214 torr for several hours following injection of oleic acid. Table 2 summarizes the changes produced at ZEEP by oleic acid. Table 3 shows the changes produced by PEEP. The application of PEEP

TABLE 1. Mean Values in 12 Dogs (±1 SEM) before Pulmonary Edema at 0, 5, 10, and 15 cm H_2O End-expiratory Pressure

	End-expiratory Pressure			
	0	5 cm H_2O	10 cm H_2O	15 cm H_2O
Pa_{O_2} (torr)	435 ± 17	455 ± 17*	460 ± 11	445 ± 14
$\dot{Q}_s/\dot{Q}_t \times 100$	15 ± 1	12 ± 1*	12 ± 1*	11 ± 1*
$P\bar{v}_{O_2}$ (torr)	76 ± 4	72 ± 6*	71 ± 4*	72 ± 5
$S\bar{v}_{O_2}$ (per cent)	85.6 ± 1.7	82.7 ± 2.1*	83.0 ± 1.8*	82.3 ± 2.0
$C\bar{v}_{O_2}$ (ml O_2/100 ml)	15.8 ± 0.6	15.9 ± 0.7	16.0 ± 0.5	15.6 ± 0.6
CI (l/min/m²)	2.46 ± 0.20	2.23 ± 0.17	1.97 ± 0.15*	2.01 ± 0.13*
$\dot{V}_{O_2}$ (ml/min/m²)	83 ± 5	90 ± 5	89 ± 4	92 ± 5
Pa_{CO_2} (torr)	55 ± 4	52 ± 5	58 ± 6	66 ± 6*
$\dot{V}_E$ (l/min)	2.49 ± 0.45	2.50 ± 0.48	2.01 ± 0.42	2.09 ± 0.44
Respiratory rate (breaths/min)	11 ± 2	9 ± 2*	8 ± 2*	8 ± 2*
V_T (ml/breath)	235 ± 30	288 ± 23	258 ± 23	261 ± 27
Mean arterial pressure (torr)	136 ± 4	144 ± 4*	139 ± 4	135 ± 5
Pulse (beats/min)	157 ± 6	156 ± 7	155 ± 7	152 ± 8
Arterial *p*H	7.21 ± 0.03	7.23 ± 0.03	7.19 ± 0.03	7.15 ± 0.04*
Arterial base deficit (mEq/l)	5.5 ± 1.2	6.2 ± 0.9	5.9 ± 1.0	6.2 ± 1.0
Arterial hematocrit (per cent)	41 ± 2	42 ± 2	42 ± 2	43 ± 2*

* Significant ($P < 0.05$) compared with initial control at zero end-expiratory pressure.

progressively decreased the shunt fraction at 5, 10, and 15 cm H_2O PEEP. These changes are reflected in significantly increased Pa_{O_2}'s at 10 and 15 cm H_2O PEEP. Respiratory rate and minute volume decreased significantly at all values of PEEP. No significant changes were observed in oxygen consumption/m². There was a small but significant decrease in cardiac index from control at 15 cm H_2O PEEP. In spite of this decrease in cardiac output, mixed venous oxygen saturation increased significantly at 15 cm H_2O PEEP due to the increase in Pa_{O_2} caused by PEEP. Changes in mean arterial blood pressure, pulse rate, tidal volume, and base deficit were not significant.

Discussion

Oleic-acid embolism caused a marked increase in shunt and decrease in cardiac output during spontaneous ventilation (table 2). The increased shunt and resultant decreased Pa_{O_2} were the result of alveolar collapse from pulmonary edema. The results of this study showed that PEEP imposed during spontaneous ventilation improved arterial oxygenation in pulmonary edema. The proposed mechanism of this improvement is that PEEP maintains unstable alveoli open for gas exchange at end-expiration.[3]

The reduction of cardiac index which developed during pulmonary edema probably resulted from loss of circulating blood volume into the lung. PEEP would also be expected to decrease cardiac output because of interference with venous return.[9] In spite of the presence of hypovolemia, PEEP caused a significant decrease in cardiac index from that seen at ZEEP at the 15-cm H_2O level only. It is noteworthy that in spite of the significant decrease in cardiac index with 15 cm H_2O PEEP, the increased Ca_{O_2} engendered by PEEP caused a significant increase in $C\bar{v}_{O_2}$. As oxygen consumption was essentially unchanged, this increased $C\bar{v}_{O_2}$ suggests that tissue oxygenation was increased with 15 cm H_2O PEEP in spite of decreased cardiac index. It would seem that even in the presence of hypovolemia, if there is significant hypoxia, the improvement in arterial oxygenation brought about by PEEP can more than compensate for the concomitant diminution in

cardiac output. In the clinical situation, if hypovolemia were corrected, then PEEP would have even less effect on cardiac output.[1]

The major drawback to the use of PEEP in the anesthetized animal is the increased Pa_{CO_2} which results from the marked decrease in respiratory rate with little or no increase in tidal volume. During pulmonary edema the amount of wasted or deadspace ventilation increased because of a combination of decreased cardiac output, increased respiratory rate and capillary occlusion due to oleic acid. This is dramatically shown, in that with ZEEP a $\dot{V}_E$ of 2.49 l/min produced a Pa_{CO_2} of 55 mm Hg prior to injection of oleic acid, and after oleic acid a $\dot{V}_E$ of 5.95 l/min was necessary to produce a Pa_{CO_2} of 53 mm Hg. Owing to the increased requirement for ventilation during pulmonary edema, the marked decrease in $\dot{V}_E$ caused by PEEP at the 10- and 15-cm H_2O levels caused clinically unacceptable increases in Pa_{CO_2}.

TABLE 2. Mean Values (±1 SEM) in 12 Dogs at Zero End-expiratory Pressure before Injection of Oleic Acid and an Hour after Production of Pulmonary Edema

	Normal	Pulmonary Edema
Pa_{O_2} (torr)	435 ± 17	97 ± 13*
$\dot{Q}_s/\dot{Q}_t \times 100$	15 ± 1	30 ± 2*
$P\bar{v}_{O_2}$	76 ± 4	40 ± 2*
CI (l/min/m²)	2.46 ± 0.20	1.47 ± 0.09*
$\dot{V}_{O_2}$ (ml/min/m²)	85 ± 5	113 ± 8*
Pa_{CO_2} (torr)	55 ± 4	53 ± 5
$\dot{V}_E$ (l/min)	2.49 ± 0.45	5.95 ± 0.67*
Respiratory rate (breaths/min)	11 ± 2	74 ± 4
V_T (ml/breath)	235 ± 30	97 ± 5*
Mean arterial pressure (torr)	136 ± 4	134 ± 6
Pulse (beats/min)	157 ± 6	143 ± 9
Hematocrit (per cent)	41 ± 2	45 ± 2*

* Significant, $P < 0.05$.

TABLE 3. Mean Values (±1 SEM) in 12 Dogs at 0, 5, 10, and 15 cm H_2O Positive End-expiratory Pressures after Production of Pulmonary Edema

	End-expiratory Pressure					
	0	5 cm H_2O	0	10 cm H_2O	0	15 cm H_2O
Pa_{O_2} (torr)	95 ± 13	111 ± 16	89 ± 11	109 ± 9*	88 ± 13	158 ± 27*
$\dot{Q}_s/\dot{Q}_t \times 100$	32 ± 3	28 ± 3*	36 ± 5	30 ± 5*	32 ± 3	21 ± 3*
$P\bar{v}_{O_2}$ (torr)	37 ± 2	40 ± 3*	37 ± 3	41 ± 3*	37 ± 3	48 ± 3*
$S\bar{v}_{O_2}$ (per cent)	51.8 ± 1.6	54.3 ± 2.7	49.4 ± 4.5	50.6 ± 4.4	52.0 ± 3.0	58.9 ± 2.1*
$C\bar{v}_{O_2}$ (ml O_2/100 ml)	10.6 ± 0.5	11.2 ± 0.7	10.4 ± 1.1	10.9 ± 1.0	10.9 ± 0.9	13.0 ± 0.7*
CI (l/min/m²)	1.40 ± 0.10	1.29 ± 0.08	1.37 ± 0.09	1.24 ± 0.09	1.39 ± 0.07	1.18 ± 0.06*
$\dot{V}_{O_2}$ (ml/min/m²)	113 ± 6	109 ± 5	97 ± 4	100 ± 4	108 ± 6	101 ± 4
Pa_{CO_2} (torr)	47 ± 6	53 ± 5*	52 ± 5	69 ± 7*	45 ± 4	75 ± 7*
$\dot{V}_E$ (l/min)	7.61 ± 0.58	6.53 ± 0.65*	7.41 ± 0.76	4.97 ± 0.46*	7.55 ± 1.12	3.64 ± 0.54*
Respiratory rate (breaths/min)	69 ± 4	50 ± 4*	74 ± 4	42 ± 4*	73 ± 5	31 ± 4*
V_T (ml/breath)	113 ± 9	132 ± 12*	105 ± 5	118 ± 7	117 ± 12	121 ± 12
Mean arterial pressure (torr)	138 ± 6	135 ± 6	137 ± 4	131 ± 6	137 ± 6	128 ± 5
Pulse (beats/min)	151 ± 10	149 ± 10	140 ± 9	139 ± 9	147 ± 9	140 ± 11
Arterial pH	7.31 ± 0.03	7.26 ± 0.03*	7.26 ± 0.03	7.15 ± 0.04*	7.31 ± 0.03	7.13 ± 0.4*
Arterial base deficit (mEq/l)	3.6 ± 1.1	4.1 ± 0.9	3.9 ± 1.1	4.4 ± 1.1	3.5 ± 0.9	4.3 ± 0.9*
Arterial hematocrit (per cent)	45 ± 2	47 ± 2*	46 ± 2	48 ± 2*	46 ± 2	49 ± 2*

* Significant ($P < 0.05$) compared with controls at zero end-expiratory pressure measured before each measurement at PEEP.

Gregory[10] *et al.* have shown that PEEP applied to spontaneously-breathing neonates with RDS improves oxygenation. As the pathophysiology of the animal model used in the present study approximates that of the neonatal respiratory distress syndrome,[2] our results suggest that improvement in oxygenation with PEEP in RDS is due to a marked decrease in shunt accompanied by a small decrease in cardiac output.

Application of PEEP without a ventilator deserves further clinical trial in humans. Arterial oxygen tensions can be held at acceptable levels earlier in the course of weaning a patient from mechanical ventilation if PEEP instead of ZEEP is utilized.[11] For some patients who have difficulty oxygenating without severe problems in their ability to ventilate, a mechanical respirator may not be needed. Since the peak airway pressures needed are lower, tracheal cuff pressures can be reduced and the lung is exposed to lower peak airway pressures than are necessary with mechanical ventilation. With suspected tracheal or pulmonary parenchymal injury, these lower pressures would be a considerable advantage.

A possible disadvantage of producing PEEP in spontaneously-ventilating patients is the increase in $Paco_2$ observed as PEEP was increased. Since oxygen consumption was not significantly changed during PEEP, the high $Paco_2$ was not a result of an increase in CO_2 production from increased work of breathing. Therefore, the ventilatory changes seen in our animal study were probably produced by inflation reflexes, which caused a slower respiratory rate. These changes were not significant in the neonate, as Gregory[10] found no consistent alterations in respiratory rate or $Paco_2$ as PEEP was increased. Fatigue of the patient's respiratory muscles, another possible disadvantage of the technique, can be minimized by careful observation of $\dot{V}_E$ and $Paco_2$.

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