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The Effects of Tidal-volume Change with Positive End-expiratory Pressure in Pulmonary Edema

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The effects of variation in tidal volume were studied in 14 dogs with pulmonary edema during mechanical ventilation with a constant positive end-expiratory pressure (PEEP) of 10 cm H_2O. Tidal volumes (V_T) of 5 ml/kg with PEEP improved Pa_{O_2} over that seen with a V_T of 15 ml/kg without PEEP. Oxygenation improved with PEEP as V_T was increased stepwise from 5 to 25 ml/kg. The greatest improvement in oxygenation and ventilation with PEEP occurred when V_T was increased from 5 to 10 ml/kg. Thereafter, as V_T was increased, improvement in oxygenation was small and was accompanied by a gradual decline in cardiac output. A tidal volume of 10 ml/kg and a positive end-expiratory pressure of 10 cm H_2O produced the most effective gas exchange with the least impairment of cardiac output. (Key words: Shunt; Oleic acid-induced pulmonary edema; Functional residual capacity.)

IT HAS BEEN well documented that in both animals[1] and man[2] continuous mechanical ventilation with positive end-expiratory pressure (PEEP) improves gas exchange in pulmonary edema. These studies have not indicated what effect variation in tidal volume would have on gas exchange with PEEP in these circumstances. The following study was done to determine the magnitude of tidal volume needed during continuous mechanical ventilation with 10 cm H_2O PEEP for optimal oxygenation of dogs with experimentally-induced pulmonary edema.

Materials and Methods

Fourteen mongrel dogs (body weights 23–28 kg, mean 25 kg) were anesthetized with pentobarbital, 30 mg/kg iv, paralyzed with 60 mg succinylcholine chloride, and the tracheas were intubated with cuffed endotracheal tubes. Pentobarbital and succinylcholine were given as needed to maintain apnea. The dogs were placed supine and ventilated with a volume-cycled piston respirator (Harvard pump) which delivered 100 per cent oxygen at an inspiratory–expiratory ratio of 1:1. A catheter was placed in the aorta via the femoral artery for pressure monitoring and blood sampling. The pulmonary artery was catheterized by means of a flow-directed balloon-tipped catheter[3] inserted through the external jugular vein. Airway, pulmonary arterial, and arterial blood pressures were monitored throughout the experiment.

Cardiac output ($\dot{Q}_t$) was measured by the Fick principle with measured oxygen consumption and arterial and mixed venous oxygen contents. In order to validate our methods, simultaneous measurements of $\dot{Q}_t$ by the method used in this study and by dye dilution were made in three normal anesthetized dogs. Sixteen determinations of $\dot{Q}_t$ yielded a highly significant correlation ($r = +0.93$) between the two methods. Oxygen consumption ($\dot{V}o_2$) was measured with a closed-circuit method (fig. 1). The ventilator and breathing circuits were tested at the beginning and end of each study for 10 minutes, under a pressure of 50 mm Hg. The system was leak-free under these conditions. Oxygen consumption was measured over a five- to seven-minute period as the loss of volume from the Collins spirometer, corrected to STPD. Between measurements the spirometer was taken out of the breathing circuit. In order to monitor possible contamination of the breathing circuit by room air, the percentage of inspired oxygen was measured continuously with a Biomarine 202R oxygen analyzer.† Blood was analyzed for Pa_{O_2}, Pa_{CO_2}, and *p*H on an Instrumentation Laboratories 113 blood–gas analyzer, with appropriate corrections for temperature of the

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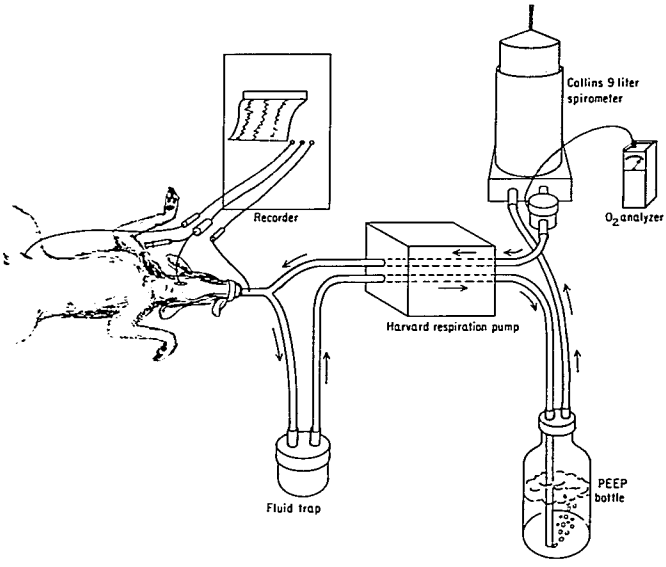

FIG. 1. Circuit for measurement of oxygen consumption during continuous mechanical ventilation with positive end-expiratory pressure. Arrows indicate the direction of air flow. Carbon dioxide absorbent (soda lime) is inside the spirometer.

animal.[4,5] Oxygen content was derived from the calculated saturation,[5] dissolved oxygen, and measured hemoglobin concentration. Shunt ($\dot{Q}_s/\dot{Q}_t$) through the lungs was determined with the standard formula.[6] Expired volumes were measured with the Collins spirometer. Mixed expired carbon dioxide was monitored during PEEP with a Beckman LB-1 CO_2 analyzer for calculation of dead-space-to-tidal volume ratio (V_D/V_T). The increase in end-expiratory lung volume (ΔFRC) brought about by the positive end-expiratory pressure was measured by allowing the animal to exhale passively into the spirometer until there was no further volume change from 10 cm H_2O positive pressure to atmospheric pressure.

Baseline measurements of all variables were made during intermittent positive-pressure ventilation (IPPV) at a tidal volume of 15 ml/kg without positive end-expiratory pressure and at a respiratory rate of 16/min. Oleic acid, 0.2 ml/kg, was injected into the right ventricle during a four-minute period. Sixty to 90 minutes were allowed after injection of oleic acid before proceeding with the study to permit full development of the pathophysiologic picture of respiratory distress. Measurements made during IPPV were repeated. PEEP was then produced by placing the expiratory tubing under 10 cm of water. Measurements were carried out 20 minutes after stepwise changes of V_T in the following order:

Seven odd-numbered dogs: 5, 10, 15, 20, 25, 25, 20, 15, 10, and 5 ml/kg
Seven even-numbered dogs: 25, 20, 15, 10, 5, 5, 10, 15, 20, 25 ml/kg

The orders of V_T changes were varied to take into account the continued deterioration in

TABLE 1. Mean Values for 14 Dogs ± SD before and after Pulmonary Edema without PEEP

IPPV (V_T = 15 ml/kg)	$\dot{Q}_s/\dot{Q}_t$ (Per Cent)	Pa_{O_2} (mm Hg)	$\dot{Q}_t$ (l/min)	Pa_{CO_2} (mm Hg)	pH	Base Excess (mM/l)	Mixed Venous Oxygen Tension (mm Hg)	Mixed Venous Oxygen Saturation (Per Cent)	Mean Airway Pressure (cm H$_2$O)	Mean Arterial Blood Pressure (mm Hg)	Pulmonary Arterial Pressure (cm H$_2$O)	Heart Rate (beats/min)	$\dot{V}_{O_2}$ (ml/min) (STPD)	Hgb (gm/100 ml)
Before oleic acid	12 ±4	107 ±20	3.01 ±1.21	32 ±4	7.43 ±0.07	−3.7 ±2.5	51 ±14	79 ±10	3 ±1	117 ±21	25 ±0 10 ±3	147 ±33	191 ±21	13 ±1
After oleic acid	*41 ±12	*70 ±27	2.72 ±0.88	*39 ±9	*7.31 ±0.07	* −6.8 ±3.5	*38 ±9	*61 ±14	*7 ±3	112 ±22	*39 ±8 *17 ±10	148 ±26	146 ±20	15 ±2

* $p < 0.05$ compared with IPPV before injection of oleic acid.

cardiopulmonary status after injection of oleic acid.[7] Respiratory rate was changed with V_T in order to maintain a constant minute volume ($\dot{V}_E$) for each animal. In order to maintain cardiac output in the face of fluid loss into the lung, physiologic saline solution was infused at the rate of 250 ml/hr during the course of the study. In addition, 250 ml of Dextran 70 were infused in the two-hour period following injection of oleic acid. In order to monitor the fluid loss from the lungs, pulmonary edema fluid was collected throughout the experiment in a trap on the expiratory side of the circuit (fig. 1). At the conclusion of the experiment, after the heart had stopped from hypoxic arrest, the fluid which issued from the airways was measured and added to the total.

Statistical analysis of the data obtained during IPPV before and after pulmonary edema was carried out with the Student t test for paired data. Mean values ±1 SD are given.

Results

During IPPV at a tidal volume of 15 ml/kg, significant deterioration in all measurements of gas exchange occurred after injection of oleic acid (table 1). Cardiac output decreased slightly in spite of the infusion of approximately 500 ml of physiologic saline solution and 250 ml of Dextran 70. Pulmonary arterial pressure increased significantly as a result of oleic acid embolism. The significant decrease in mixed venous oxygen saturation (Sv_{O_2}) with pulmonary edema was primarily due to a significant decrease in Pa_{O_2}. The small decrease in cardiac output and increase in $\dot{V}_{O_2}$ with pulmonary edema also contributed to the change in Sv_{O_2}.

The results during PEEP are summarized in table 2. Mean $\dot{Q}_s/\dot{Q}_t$ was 26 ± 8 per cent at a V_T of 5 ml/kg and decreased to 19 ± 6 per cent when the tidal volume was increased to 10 ml/kg. Thereafter, mean shunt decreased by 2 per cent for each 5-ml/kg increase in V_T. Although minute ventilation was kept constant by adjustment of the respiratory rate, mean Pa_{CO_2} decreased from 72 ± 14 mm Hg at a V_T of 5 ml/kg to 34 ± 4 at a V_T of 25 ml/kg (table 2). As with $\dot{Q}_s/\dot{Q}_t$, the greatest reduction in mean Pa_{CO_2} was seen between tidal volumes of 5 and 10 ml/kg. The changes in

TABLE 2. Mean Values ± SD for 14 Dogs with Pulmonary Edema Ventilated with a Constant End-expiratory Pressure of 10 cm H_2O

	V_T = 5 ml/kg	V_T = 10 ml/kg	V_T = 15 ml/kg	V_T = 20 ml/kg	V_T = 25 ml/kg
$\dot{Q}_s/\dot{Q}_t$ (per cent)	26 ± 8	19 ± 7	17 ± 7	15 ± 6	13 ± 4
Pa_{O_2} (mm Hg)	181 ± 106	217 ± 128	223 ± 130	241 ± 117	285 ± 131
$\dot{Q}_t$ (l/min)	2.24 ± 0.69	1.84 ± 0.41	1.79 ± 0.49	1.65 ± 0.40	1.49 ± 0.40
Pa_{CO_2} (mm Hg)	72 ± 14	51 ± 9	41 ± 6	37 ± 5	34 ± 4
*p*H	7.08 ± .08	7.21 ± .07	7.28 ± .06	7.32 ± .05	7.35 ± .05
Base excess (mM/l)	−13 ± 4	−9 ± 3	−9 ± 4	−8 ± 3	−7 ± 2
Mixed venous oxygen tension (mm Hg)	52 ± 12	44 ± 8	40 ± 6	38 ± 6	36 ± 5
Mixed venous oxygen saturation (per cent)	67 ± 11	64 ± 9	62 ± 9	61 ± 9	59 ± 8
Airway pressure (cm H_2O)	13 ± 1	15 ± 1	16 ± 1	17 ± 1	18 ± 1
Arterial blood pressure (mm Hg)	142 ± 13	140 ± 13	140 ± 18	136 ± 17	130 ± 16
Pulmonary arterial pressure (cm H_2O)	45 ± 8 28 ± 6	40 ± 7 24 ± 4	39 ± 6 23 ± 3	38 ± 6 22 ± 3	36 ± 6 22 ± 3
Heart rate (beats/min)	136 ± 22	154 ± 21	155 ± 26	156 ± 23	153 ± 23
$\dot{V}_{O_2}$ (ml/min) (STPD)	135 ± 22	139 ± 22	141 ± 24	135 ± 23	132 ± 22
Hgb (gm/100 ml)	17 ± 2	16 ± 2	16 ± 2	16 ± 2	16 ± 2
V_d/V_T (per cent)	81 ± 5	58 ± 10	46 ± 8	40 ± 8	36 ± 9
Respiratory rate/min	47 ± 1.0	23 ± 2.0	16 ± 1.0	12 ± 1.0	10 ± 0.6
$(V_T/P)^*$ (ml/cm H_2O)	16 ± 5	20 ± 4	23 ± 4	24 ± 4	27 ± 4

* "Effective compliance," or ratio of tidal volume to pressure at peak inspiration minus 10 cm H_2O.

Pa_{CO_2} paralleled the changes in V_D/V_T (table 2).

The increase in lung volume caused by the 10-cm H_2O positive end-expiratory pressure varied with the tidal volume used (fig. 2). The higher the tidal volume with which the animal was ventilated, the greater the volume of gas expired on removal of PEEP.

Mean cardiac output and Sv_{O_2} were highest at the 5-ml/kg tidal volume, reflecting both the lower mean airway pressure and the cardiovascular effects of the elevated Pa_{CO_2} (table 2). Mean $\dot{Q}_t$, blood pressure, and Sv_{O_2} decreased as the tidal volume was increased. The mean amount of pulmonary edema fluid collected in the trap during the course of the six-hour experiment was 341 ± 231 ml. Each dog received a total of 250 ml of Dextran 70 and approximately 1,500 ml of physiologic saline solution during this time.

Discussion

Positive end-expiratory pressure brings about improvement in oxygenation in pulmonary edema by increasing end-expiratory lung volume.[1] Unstable alveoli, otherwise collapsed at end-expiration, are kept open. The finding in the present study that the volumes engendered by PEEP varied and were directly proportional to tidal volumes (fig. 2) has not been reported previously. As tidal volume increased, so did lung compliance, so that for the 10-cm H_2O end-expiratory

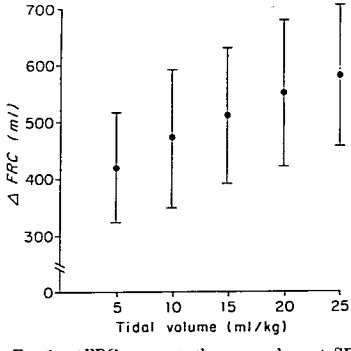

FIG. 2. ΔFRC represents the mean volume ± SD of air expired when 10 cm H_2O positive pressure was removed and the dog was allowed to expire to atmospheric pressure.

pressure there was a greater volume of air in the lung. Further evidence for this improvement in lung compliance with increased tidal volume is that the V_T/P ratio, or "effective compliance," also increased with tidal volume (table 2). Evidently, as tidal volume increased, the opening pressures of more collapsed alveoli were exceeded and compliance increased with the larger lung volume. These alveoli, so opened, must have closed during the one-minute interval it took for complete exhalation from 10-cm H_2O PEEP to atmospheric pressure.

Injection of oleic acid produces in dogs a clinical and pathophysiologic picture similar to the human adult respiratory distress syndrome.[1] Chemical injury of the pulmonary capillaries caused by oleic acid allows fluid leakage into the alveoli, interstitial areas, and airways of the lung.[1] Observations made in the animal model of oleic acid-induced pulmonary edema should have direct clinical applicability to patients with adult respiratory distress syndrome. Continuous mechanical ventilation with PEEP is clearly more effective than IPPV in reducing shunt in pulmonary edema. During IPPV, mean $\dot{Q}_s/\dot{Q}_t$ was 44 ± 12 per cent, while ventilation with the same tidal volume with the addition of PEEP produced a mean shunt of 17 ± 7 per cent. The greatest reduction in shunt during PEEP was seen when tidal volume was increased from 5 to 10 ml/kg. Tidal volumes higher than 10 ml/kg caused only small but progressive decreases in shunt and increases in Pa_{O_2}.

Even though $\dot{V}_E$ was the same with all patterns of ventilation, Pa_{CO_2} was unacceptably high at a V_T of 5 ml/kg. The mean Pa_{CO_2} at 10-ml/kg tidal volume was 51 ± 9 mm Hg, with a respiratory rate of 23/min. Respiratory rate could have been increased during ventilation at a V_T of 10 ml/kg to reduce the Pa_{CO_2} to more normal levels.

In spite of the fact that the end-expiratory lung volume (ΔFRC) caused by the 10-cm H_2O PEEP increased directly with tidal volume, tidal volumes greater than 10 ml/kg seemed to have relatively little effect on shunt. There was a 7 per cent decrease in shunt when V_T was increased from 5 to 10 ml/kg and only a 6 per cent decrease in shunt when V_T was further increased to 25 ml/kg. As tidal volume increased, so did mean airway pressure, which in turn depressed cardiac output by interfering with venous return. Therefore, the advantage of small decreases in shunt seen with tidal volumes of more than 10 ml/kg was offset by similar decreases in cardiac output. While confirmatory studies in humans are needed, the results in the animal model of the respiratory distress syndrome used in this study indicate that 10 ml/kg is the most appropriate tidal volume for use with PEEP. Tidal volumes should be increased if $Paco_2$ cannot be kept within the normal range with a respiratory rate of 20–25/min at a tidal volume of 10 ml/kg. We have previously shown in the animal model used in the present study that increasing PEEP from 5 to 10 cm H_2O at a V_T of 15 ml/kg decreased mean shunt from 24 to 14 per cent.[8] Our clinical experience indicates that in the adult respiratory distress syndrome it may be necessary to increase end-expiratory pressure to as high as 15 cm H_2O to achieve satisfactory oxygenation. Therefore, in the clinical situation, if oxygenation remains impaired due to shunt with a V_T of 10 ml/kg and an end-expiratory pressure of 10 cm H_2O, then consideration should be given to increasing end-expiratory pressure rather than tidal volume.

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