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Cardiorespiratory Effects of High Positive End-expiratory Pressure

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Five healthy rhesus monkeys were ventilated with intermittent mandatory ventilation and 20 torr positive end-expiratory pressure (PEEP) for 8 hours. PEEP was increased to 25 torr and the monkeys were ventilated for 4 more hours. Lactated Ringer's solution and human salt-poor albumin were used to expand plasma and extracellular fluid volume throughout the entire period of study. Homologous blood was administered to maintain hematocrit at control levels and maintenance fluids were infused to maintain transmural pulmonary capillary wedge pressure at 5 to 15 torr. Although cardiac output, mean aortic blood pressure, oxygen consumption, venous admixture, transmural pulmonary capillary wedge pressure, HCO_3^- and *in-vivo* base excess were not changed when intermittent mandatory ventilation was employed, cardiac output and blood pressure were significantly depressed by brief periods of controlled mechanical ventilation when alternated with intermittent mandatory ventilation. Sporadic increases in arterial–venous oxygen content difference occurred. Arterial carbon dioxide tension was elevated moderately, with a concomitant depression of arterial *p*H. No pneumothorax occurred. High PEEP was well tolerated with intermittent manditory ventilation, intravascular volume expansion, and careful cardiovascular monitoring. (Key words: Ventilation, positive end-expiratory pressure.)

THE EFFICACY of PEEP in reducing atelectasis and right-to-left intrapulmonic shunting in acute respiratory failure is well documented.[1–4] Recently, we have shown that when high PEEP, above 18 torr (25 cm H_2O), is applied in selected cases refractory to conventional therapy, a substantial reduction in mortality can result.[5] It is of particular interest that cardiopulmonary function was unimpaired. However, the wide range of pathologic conditions suffered by these patients and the many therapeutic interventions instituted made it difficult to single out the effects of PEEP. So, we performed a study in normal primates to determine specifically the effects of high PEEP on cardiorespiratory function.

Methods

Five healthy rhesus monkeys (*Macaca mulatta*), ranging in weight from 8.0 to 9.6 kg and in age from juvenile to adult, were anesthetized intramuscularly with ketamine (100 mg) and diazepam (5 mg). Tracheal intubation was performed and the animals

ABBREVIATIONS

$\bar{A}P$	=	mean aortic blood pressure
Ca_{O_2}	=	arterial oxygen content
$Ca\text{-}\bar{v}_{O_2}$	=	arterial–venous oxygen content difference
CMV	=	controlled mechanical ventilation
$C\bar{v}_{O_2}$	=	mixed venous oxygen content
FI_{O_2}	=	fraction of inspired oxygen
IMV	=	intermittent mandatory ventilation
PAP	=	pulmonary artery pressure
PCWP	=	pulmonary capillary wedge pressure
PEEP	=	positive end-expiratory pressure
$\dot{Q}_A/\dot{Q}_T$	=	venous admixture
T_{PCWP}	=	transmural pulmonary capillary wedge pressure (PCWP minus intrapleural pressure)
$\dot{V}_{O_2}$	=	oxygen consumption, ml/min ($Ca_{O_2} - C\bar{v}_{O_2} \times$ cardiac output in l/min $\times$ 10)

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were ventilated with a time-cycled ventilator using IMV[6,7] and zero end-expiratory pressure during the control period. The FI_{O_2} was .30 throughout the study. Anesthesia was maintained with incremental doses of ketamine (10–20 mg) administered intravenously when seemingly purposeful movement occurred. An average of 288 ± 40 mg of ketamine was administered. Catheters were placed in a forelimb vein and in the aorta via a femoral artery cutdown. A thermodilution Swan-Ganz catheter with the CVP injection port 15 cm from the tip was inserted into the femoral vein and advanced through the heart into the right or left pulmonary artery. A Teflon catheter was placed into the pleural cavity through a small intercostal incision. Cardiac output was monitored sequentially in duplicate by thermodilution techniques[8] using 3-ml injections of 5 per cent dextrose in water at 0 C. Systemic arterial, pulmonary artery, pulmonary capillary wedge, intrapleural, and airway pressures were monitored continuously with Statham transducers and a Grass six-channel recorder. Arterial and central mixed venous blood gases and *p*H were measured during the control period and at hourly intervals thereafter with an Instrumentation Laboratories 113 blood–gas analyzer. Corrections were made for temperature and HCO_3^-, *in-vivo* base excess, Ca_{O_2}, $C\bar{v}_{O_2}$, $\dot{V}_{O_2}$, and $\dot{Q}_A/\dot{Q}_T$ were determined using a programmable calculator with special corrections for simian blood.[9] A Foley catheter was placed in the bladder for urinary drainage.

Pooled homologous blood was administered to maintain the baseline hematocrit throughout the study, and all blood withdrawn for sampling or lost during cutdown was replaced. Lactated Ringer's solution and human salt-poor albumin were administered during the control period until T_{PCWP} was 5 to 10 torr, and then continuously thereafter to maintain a minimum T_{PCWP} of 5 to 15 torr.

Following baseline measurements, the end-expiratory pressure was increased rapidly to 20 torr (27 cm H_2O) in increments of 4 to 8 torr. The monkeys were maintained at this level of PEEP for eight hours, after which PEEP was increased to 25 torr (34 cm H_2O) for four more hours. The IMV rate was adjusted to a level that maintained Pa_{CO_2} between 40 and 60 torr¶ (3 to 8 breaths/min). The monkeys breathed spontaneously. During the four-hour period at 25-torr PEEP, IMV and CMV were alternated for periods of two minutes to assess any difference between the effects of the two ventilatory techniques on cardiovascular function. Eighteen such comparisons were made. All changes in cardiopulmonary function were analyzed for significance by Student's t test. After 12 hours, the animals were sacrificed and the lungs, liver, spleen, and kidneys removed for pathologic examination.

Results

Four of five monkeys survived the study. One died suddenly of unrecognized hemorrhage at the site of the arterial and venous cutdown during the eleventh hour of study.

Cardiovascular Function (Table 1)

Cardiac output and $\overline{AP}$ did not change significantly while the monkeys were ventilated with IMV. However, the transition between IMV and CMV (fig. 1) was associated with a significant diminution of cardiac output. In 14 of 18 determinations, cardiac output with CMV decreased; in four determinations no change occurred. The average decrease for all measurements was from 1.02 ± .19 to .78 ± .18 l/min ($P < .005$). The arterial systolic pressures in 17 of 18 determinations decreased; in one case no change occurred. The average decrease was from 131 ± 18 to 104 ± 25 torr ($P < .005$). Arterial diastolic pressures in 15 of 18 determinations decreased; in three determinations no change occurred. The average decrease was from 109 ± 28 to 72 ± 19 torr ($P < .001$).

$Ca\text{-}\bar{v}_{O_2}$ showed significant increases above control levels during the second, fourth, fifth, sixth, eighth, and tenth hours, but these increases did not appear to be progressive with time. Values for $Ca\text{-}\bar{v}_{O_2}$ were not determined during the brief periods of CMV at 25-torr PEEP. T_{PCWP} remained constant.

¶ In one animal Pa_{CO_2} rose to 69 torr during the ninth hour and to 77 torr during the twelfth hour of the study period.

TABLE 1. Cardiovascular Effects of High PEEP (Means ± SD)

	Control 0 PEEP	Hours of 20 Torr PEEP								Hours of 25 Torr PEEP			
		1	2	3	4	5	6	7	8	1 (9)	2 (10)	3 (11)*	4 (12)*
Cardiac output (l/min)	1.29 ± .41	1.12 ± .17	.99 ± .09	.96 ± .04	.93 ± .06	1.01 ± .11	.90 ± .19	1.12 ± .31	.93 ± .14	1.13 ± .47	1.06 ± .35	.99 ± .07	1.15 ± .20
$\overline{AP}$ (torr)	116 ± 15	107 ± 30	104 ± 24	110 ± 23	112 ± 18	118 ± 18	102 ± 17	106 ± 17	101 ± 7	103 ± 18	106 ± 17	103 ± 27	115 ± 23
$Ca\text{-}\bar{v}_{O_2}$ (vol)	4.28 ± .55	4.52 ± 1.15	5.77† ± 1.43	5.57 ± 1.41	6.52† ± 1.64	5.90† ± 1.22	6.10† ± .77	5.10 ± 1.15	6.60† ± 1.70	6.46 ± 2.22	7.26† ± 1.80	5.80 ± 1.65	5.90 ± 1.51
T_{PCWP} (torr)	8 ± 3	14 ± 8	11 ± 4	8 ± 3	7 ± 6	9 ± 7	11 ± 7	13 ± 8	8 ± 4	9 ± 6	7 ± 6	6 ± 7	4 ± 6
$\dot{V}_{O_2}$ (ml/min)	53.2 ± 10.0	50.4 ± 12.3	56.9 ± 9.2	57.0 ± 16.2	60.8 ± 16.3	62.4 ± 19.6	52.3 ± 2.0	54.4 ± 16.3	56.7 ± 9.6	63.3 ± 20.0	69.3 ± 26.1	59.6 ± 15.3	68.2 ± 21.0
$\dot{Q}_A/\dot{Q}_T$	.054 ± .038	.041 ± .033	.040 ± .030	.037 ± .028	.038 ± .027	.037 ± .026	.036 ± .026	.035 ± .026	.036 ± .024	.037 ± .025	.036 ± .025	.035 ± .024	.038 ± .025

* Four animals.
† $P < .025$ compared with control at 0 PEEP.
‡ $P < .05$ compared with control at 0 PEEP.

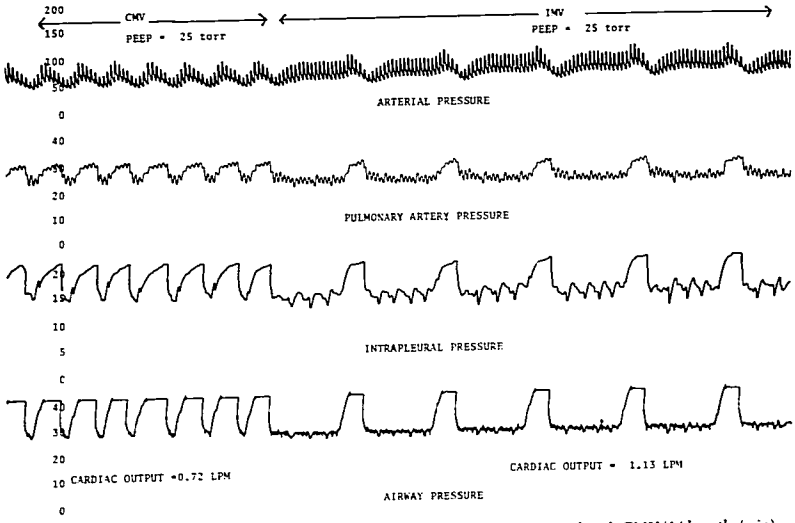

FIG. 1. Arterial blood pressure and cardiac output are significantly decreased with CMV (14 breaths/min) compared with IMV (6 breaths/min) at 25 torr PEEP. Intrapleural pressure is less during IMV because of fewer mechanical inspiratory peaks and the decrease in baseline pressure that occurs with each spontaneous inspiration. Hence, cardiac output and blood pressure are augmented. During IMV the monkey's spontaneous breathing rate is 18 breaths/min. Heart rate is unchanged during both CMV and IMV. Thus, the decrease in cardiac output with CMV is a result of a decrease in stroke volume. (Total time of recording = 1½ minutes.)

RESPIRATORY FUNCTION (TABLE 1)

No change in $\dot{Q}_A/\dot{Q}_T$ was found and $\dot{V}_{O_2}$ remained constant throughout the study. There was no pneumothorax, but subcutaneous emphysema occurred in all five animals.

ACID–BASE (TABLE 2)

Non-respiratory (metabolic) acidosis did not occur, as evidenced by stability of HCO_3^- and *in-vivo* base excess. Pa_{CO_2} occasionally increased significantly, accompanied by mild to moderate decreases in pH_a.

RENAL FUNCTION (FIGURE 2)

Urinary output averaged 162 ± 61 ml/hour. In two monkeys the urine was initially blood-tinged but cleared rapidly as the study progressed.

FLUID AND BLOOD ADMINISTRATION (FIGURE 2)

Averages of 123 ± 55 ml blood, 54 ± 14 g salt-poor albumin, and 30 ml/kg/hour lactated Ringer's solution were administered during the control and during the 12-hour study periods.

PATHOLOGIC CHANGES

Grossly and microscopically, the lungs, liver, spleen, and kidneys were normal except for some areas of microscopically visible pulmonary interstitial emphysema and interstitial pulmonary edema in all animals and passive congestion of the liver of one.

Discussion

The potentially deleterious effects of PEEP, recognized for many years, include decreases

in venous return, cardiac output, and oxygen transport.[10,11] Alterations in cardiac performance, as well as the possibility of pulmonary barotrauma, have led to recommendations that PEEP not be employed in excess of 15 cm H_2O. However, with this arbitrary limitation, some patients with particularly severe respiratory failure may be treated inadequately.[5]

Many investigators have reported that the depressant cardiovascular effects of PEEP are minimized when normal intravascular volume is maintained. Qvist *et al.*[12] showed that no circulatory adaptive response occurred to return reduced transmural cardiac filling pressures, cardiac indexes, and stroke indexes to control levels in normal dogs subjected to CMV and 12 cm H_2O PEEP. However, following autologous whole-blood transfusion (25 ml/kg), cardiac index returned to normal. In the present study we demonstrated a similar finding at levels of PEEP two and three times that which they employed.

However, we also found that even significant volume expansion did not totally offset the effects of high PEEP and CMV, and only with IMV was cardiovascular stability maintained. The difference between the two modes of ventilation is that the mean intrathoracic pressure with IMV is reduced compared with that with CMV at any level of PEEP, for two reasons: 1) there are fewer inspiratory peaks during any given period; 2) the mean intrathoracic pressure decreases to below baseline each time a spontaneous inspiratory effort occurs, thereby augmenting venous return (fig. 1). These findings also have been confirmed in a series of patients undergoing surgical intensive care, by direct measurement of intrathoracic pressure and cardiac output.**

We questioned whether elevations of Pa_{CO_2} contributed to cardiovascular stability at high PEEP. Such an occurrence was deemed unlikely, since significant elevations of Pa_{CO_2} occurred in only four of the 12 hours studied (table 2). Furthermore, during two of these intervals (hours 9 and 12), the mean was increased because of a marked increase of Pa_{CO_2} in the fifth animal.

Although we did not attempt to maintain Pa_{CO_2} and pH_a within normal ranges in

TABLE 2. Acid–Base Effects of High Level PEEP (Means ± SD)

	Control 0 PEEP	Hours of 20 Torr PEEP								Hours of 25 Torr PEEP			
		1	2	3	4	5	6	7	8	1 (9)	2 (10)	3 (11)*	4 (12)*
Pa_{CO_2} (torr)	41.3 ± 4.0	49.0 ± 8.2	44.7 ± 2.4	48.8‖ ± 3.0	43.3 ± 7.9	48.6 ± 7.3	47.9 ± 3.0	47.4 ± 4.7	44.3 ± 7.7	57.5‖ ± 10.7	54.1‖ ± 8.1	47.7 ± 6.5	57.5‖ ± 13.3
Arterial *p*H	7.38 ± .05	7.29 ± .08	7.30‖ ± .02	7.30‖ ± .02	7.31 ± .09	7.29‖ ± .07	7.28‖ ± .01	7.31 ± .06	7.29‖ ± .03	7.21§ ± .01	7.23‖ ± .09	7.30 ± .07	7.23 ± .11
HCO_3^- (mEq/l)	23.7 ± 1.3	22.6 ± 3.0	21.2 ± 1.5	23.1 ± 1.0	22.4 ± 4.6	22.6 ± 2.0	21.5 ± 1.6	23.5 ± 1.4	20.6 ± 3.9	21.9 ± 4.0	22.3 ± 6.2	23.5 ± 6.5	22.9 ± 3.0
In-vivo base excess (mEq/l)	−.3 ± 1.8	−2.6 ± 2.6	−3.1 ± 1.3	−2.0 ± 1.3	−3.7 ± 2.6	−2.3 ± 2.2	−3.2 ± 1.2	−1.6 ± 2.1	−3.9 ± 2.5	−4.6 ± 3.7	−3.0 ± 5.6	−1.5 ± 6.2	−3.2 ± 3.5

* Four animals.
‖ $P < .025$ compared with control at 0 PEEP.
‡ $P < .05$ compared with control at 0 PEEP.
§ $P < .005$ compared with control at 0 PEEP.

** Downs, J.B., personal communication.

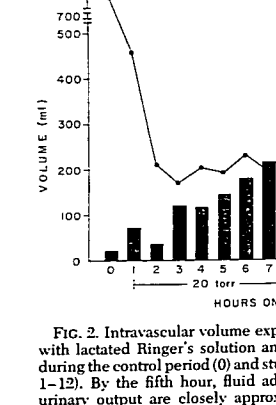

FIG. 2. Intravascular volume expansion (ml/hour) with lactated Ringer's solution and urinary output during the control period (0) and study period (hours 1–12). By the fifth hour, fluid administration and urinary output are closely approximated (average values for all five animals).

the monkeys, this was not the case in our patients. In patients treated with high PEEP, Pa_{CO_2} has been kept normal by adjustment of the IMV rate.[5] Even though Pa_{CO_2} did not increase in the patients, the cardiovascular stability was comparable to that of the animals in this study.[5]

Of further interest is the documentation that urinary output can be maintained even at very high PEEP so long as adequate blood replacement and fluid and electrolyte therapy are provided. The volumes of replacement and maintenance fluids required in this study (fig. 2) were considerably greater than those which we have given to our patients with acute respiratory failure treated with IMV and comparable levels of PEEP. This observation may be related to a greater proportion of the pressure's being transmitted to the intrathoracic great vessels through normal lungs rather than through badly diseased, poorly compliant ones. Fluid requirements of patients with respiratory failure and multiple organ system dysfunction must be determined individually by serial measurements of cardiopulmonary and renal function.[5] No nomogram or rule-of-thumb can predict the type or amount of replacement necessary under such conditions.

The frequently increased values of $Ca\text{-}\bar{v}_{O_2}$ suggest decreased tissue perfusion. Although localized areas of hypoperfusion may have been present, $\dot{V}_{O_2}$ remained constant, and significant non-respiratory acidosis did not occur. The normal appearance of the visceral organs and the high rate of production of urine suggest that perfusion was adequate. Which of these factors best reflects peripheral distribution of blood flow cannot be determined on the basis of our data.

The modest elevation of Pa_{CO_2} to above control levels and the concomitant depression of pH_a are consistent with an increase in deadspace or a decrease in alveolar ventilation. We did not measure the CO_2 in expired gas, and thus cannot differentiate between the two possibilities.

Since pneumothorax did not occur, these findings are consistent with previous observations that in patients ventilated with IMV and high PEEP the incidence of pneumothorax is not increased over that reported for CMV and conventional PEEP (15 cm H_2O or less).[5,13] Our data show that the presence of subcutaneous emphysema and pulmonary interstitial emphysema does not necessarily predispose to pneumothorax. Presumably, subcutaneous emphysema occurs following rupture of overdistended alveoli into underlying perivascular sheaths, retrograde dissection of air along the sheaths to the mediastinum, and finally passage by fascial plains into the soft tissues of the neck, face and chest.[14] Thus, there is a large fascial reservoir into which air may enter and, in so doing, perhaps reduce the potential development of pneumothorax.

Not all patients require high PEEP in the treatment of acute respiratory failure. However, under conditions of continuous surveillance, with careful monitoring and close attention to intravascular volume expansion and cardiovascular function, it appears that IMV and high PEEP can be employed safely when the occasion demands and conventional therapy has failed.

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References

1. Ashbaugh DG, Petty TL, Bigelow DB, et al: Continuous positive pressure-breathing (CPPB) in adult respiratory distress syndrome. J Thorac Cardiovasc Surg 57:31–41, 1969
2. Kumar A, Falke KJ, Geffin B, et al: Continuous

positive-pressure ventilation in acute respiratory failure. N Engl J Med 283:1430–1436, 1970
3. Ashbaugh DG, Petty TL: Positive end-expiratory pressure: Physiology, indications and contraindications. J Thorac Cardiovasc Surg 65:165–170, 1973
4. Downs JB, Klein EF, Modell JH: The effect of incremental PEEP on Pa_{O_2} in patients with respiratory failure. Anesth Analg (Cleve) 52:210–215, 1973
5. Kirby RR, Downs JB, Civetta JM, et al: High level positive end expiratory pressure (PEEP) in acute respiratory insufficiency. Chest 67: 156–163, 1975
6. Downs JB, Klein EF, Desautels DA, et al: Intermittent mandatory ventilation: A new approach to weaning patients from mechanical ventilators. Chest 64:331–335, 1973
7. Desautels DA, Bartlett JL: Methods of administering intermittent mandatory ventilation (IMV). Resp Care 19:187–191, 1974
8. Forrester JS, Ganz W, Diamond G, et al: Thermodilution cardiac output determination with a single flow-directed catheter. Am Heart J 83:306–311, 1972
9. Ruiz BC, Tucker WK, Kirby RR: A program for calculation of intrapulmonary shunts, blood–gas and acid–base values with a programmable calculator. ANESTHESIOLOGY 42:88–95, 1975
10. Cournand A, Motley HL, Werko S, et al: Physiologic studies on the effects of intermittent positive-pressure breathing on cardiac output in man. Am J Physiol 152:162–174, 1948
11. Sugarman JH, Rogers RM, Miller LD: Positive end-expiratory pressure (PEEP): Indications and physiologic considerations. Chest 62: 86S–94S, 1972
12. Qvist J, Pontoppidan H, Wilson RS, et al: Hemodynamic responses to mechanical ventilation with PEEP: The effect of hypervolemia. ANESTHESIOLOGY 42:45–55, 1975
13. Kumar A, Pontoppidan H, Falke KJ, et al: Pulmonary barotrauma during mechanical ventilation. Crit Care Med 1:181–186, 1973
14. Macklin MT, Macklin CC: Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: An interpretation of the clinical literature in light of laboratory experiment. Medicine 23:281–358, 1944

Pulmonary Physiology

PHENTOLAMINE AND ASTHMA Drugs acting upon the autonomic nervous system may affect bronchial tone. Thus, administration of propranolol to the asthmatic patient may precipitate significant bronchospasm. The authors describe the treatment of a 45-year-old woman with severe exercise-induced asthma. Therapy was accomplished with the alpha-adrenergic blocking drug, phentolamine. Prior treatment with xanthines, prednisone, and ephedrine were of no assistance. Use of Bronkosol produced improvement of pulmonary function but was accompanied by nausea and vomiting. Inhalation of epinephrine or isoproternol produced initial bronchodilation followed by severe bronchospasm. The authors used a double-blind protocol producing blockade of exercise-induced bronchospasm with either the acute inhalation of phentolamine or long-term oral therapy. The authors conclude that the therapeutic response resulted from both alpha-adrendergic blockade and the direct effect upon bronchial smooth muscle. (*Gross GN, Souhrada JS, Farr RS: The long term treatment of an asthmatic patient using phentolamine. Chest 66:397–401, 1974.*)