0090-3493/82/1301-0034$02.00/0
CRITICAL CARE MEDICINE
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Vol. 13, No. 1
Printed in U.S.A.

Mean airway pressure vs. positive end-expiratory pressure during mechanical ventilation

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To investigate the effects of both positive end-expiratory pressure (PEEP) and mean airway pressure ($\overline{Paw}$) on gas exchange, we used lung lavage to induce severe respiratory insufficiency in six lambs. The animals were then mechanically ventilated at constant tidal volume, respiratory rate, and inspired O_2 fraction. PEEP levels were varied −5, +5 and +10 cm H_2O around the pressure (Pflex) corresponding to a major change in slope of the inspiratory limb of the respiratory volume-pressure curve. In each animal the effects of the three PEEP levels were studied at two $\overline{Paw}$ levels, differing by 5 cm H_2O.

Increasing $\overline{Paw}$ significantly improved Pa_{O_2} and reduced venous admixture. A 5-cm H_2O PEEP increase from +5 to +10 did not affect oxygenation; however, oxygenation was significantly better when PEEP was greater than Pflex. Both Pa_{CO_2} and anatomic dead space were higher at higher PEEP, and decreased with increasing $\overline{Paw}$. Hence, $\overline{Paw}$ was a major determinant of oxygenation, although a PEEP greater than Pflex appeared necessary to optimize oxygenation at a constant $\overline{Paw}$.

Mean airway pressure ($\overline{Paw}$) rather than positive end-expiratory pressure (PEEP) has been advocated as the major determinant of gas exchange during mechanical ventilation.[1] However, few data are available to establish the relative importance of $\overline{Paw}$ and PEEP; a major difficulty arises from the fact that in most PEEP studies, changes in PEEP cause parallel changes in $\overline{Paw}$. Moreover, the relationship between PEEP and gas exchange is often strikingly alinear, owing to the presence of a critical PEEP level corresponding to step changes in oxygenation.[2,3] This has been related to the sudden opening of previously collapsed lung units at an inflection-point pressure (Pflex). Pflex is the point at which there is a major change in the slope of the inflation limb of the respiratory system's volume-pressure (VP) curve.[2] Hence, the same change in PEEP may have very different effects on different regions of the VP curve.

This study investigated the independent effects of PEEP and $\overline{Paw}$ on gas exchange in six lambs with severe respiratory insufficiency corresponding to a clearly biphasic VP curve.

MATERIALS AND METHODS

Experimental Procedure

Six lambs weighing an average of 23 ± 4.8 (SD) kg underwent general anesthesia (50% oxygen-nitrous oxide, halothane) and muscle relaxation. A cuffed tracheostomy tube, an iv line, and carotid artery and 5-Fr thermodilution pulmonary artery catheters were positioned in sequence. The lambs were then mechanically ventilated in prone position, while anesthesia was maintained by a thiopental infusion. Pancuronium was given as needed in hourly boluses. All animals received a continuous 10-ml/kg·h infusion of glucosaline solution.

Severe respiratory insufficiency was induced by repeated lung lavage (modified from Lachmann[4]), each time using two 1-L doses of 38°C isotonic saline under a pressure not exceeding 50 cm H_2O. The lavages were done at 10-min intervals until Pa_{O_2} had decreased below 60 torr at an inspired O_2 fraction (FI_{O_2}) of 0.4 and a PEEP of 10 cm H_2O. Tidal volume (VT) was individually adjusted to maintain Pa_{CO_2} between 35 and 45 torr at a respiratory rate of 20 breath/min.

A VP curve was obtained immediately after placing the animal prone, and again at 90 min after completion of the last lung lavage. Pflex was determined by inspection (Fig. 1). Three PEEP levels were then selected at −5, +5, +10 cm H_2O relative to Pflex for each lamb. The effects of the three PEEP levels were studied at two $\overline{Paw}$ levels differing by 5 cm H_2O. Hence, each animal received six treatments (Table 1). To minimize the possible bias in the treatment sequence, treatments were allocated in a Latin square, so that all treatments and all animals were represented at each experimental time.[5]

$\overline{Paw}$ was set by varying the inspiratory/expiratory time (I/E) ratio, and PEEP was adjusted by means of a water valve. For very high I/E ratios, the measured PEEP was sometimes higher than the level set by the

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This study was supported, in part, by MPI 79/80 cat 12, cap 01, Fondo E and by CNR grant 80.00313.86.

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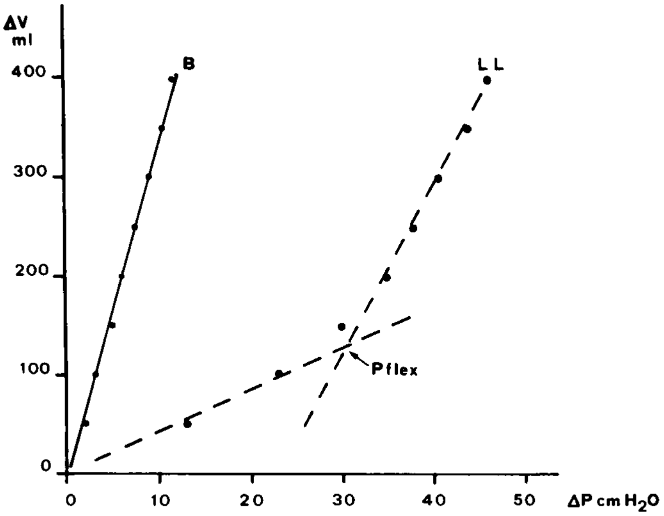

FIG. 1. VP curves of a representative lamb. B: basal measurement; LL: 90 min after lung lavage. Note that in B the VP curve is linear, while it curves upward in LL. *Dotted lines* indicate the graphic method to detect Pflex.

water valve. In these cases the water column was reduced to reach the desired PEEP level.

Mean V_T was held at 19 ± 4.4 ml/kg, within 20 ml of the V_T 90 min after lung lavage. F_{IO_2} and respiratory rate were kept at 0.4 and 20 breath/min, respectively, throughout the entire study.

After each 30-min treatment period the following variables were measured: cardiac output; central venous, pulmonary, arterial, and airway pressures; expired gas; V_T and arterial and pulmonary blood gases.

Instrumentation and Methods

A Siemens Servo Ventilator C (Elema Shonander, Sweden) was used. V_T was recorded from the digital display of the ventilator. This value was not adjusted for the 0.5-ml/cm H_2O compression volume and breathing circuit expansion.

Arterial, pulmonary, central venous, and airway pressures were measured by transducers, recorded and averaged.

Expired gases were analyzed for CO_2. End-tidal samples were obtained from a side-port near the tracheostomy tube. Mixed expired gases were sampled by connecting the expiratory port of the ventilator to a mixing chamber (a 9-m long, 38-mm ID spiral copper tube).

Anatomic dead space was computed according to the formula: $V_D/V_T = (F_{ETCO_2} - F_{ECO_2}) / (F_{ETCO_2})$, where F_{ETCO_2} and F_{ECO_2} are the fractional CO_2 concentrations in the end-tidal and mixed expired gases, respectively.

Blood gases and pH were measured by a blood gas analyzer. Total hemoglobin, oxygenated hemoglobin, and carboxyhemoglobin (HbCO) were measured for arterial and mixed venous samples using an oximeter.

Pulmonary venous admixture ($\dot{Q}sp/\dot{Q}t$) was computed according to the Bergreen equation: $(Cc'-Ca)/(Cc'-C\bar{v})$, where Cc', Ca and $C\bar{v}$ are capillary, arterial and mixed venous blood oxygen contents, respectively. Because the computed alveolar P_{O_2} was always greater than 150 torr, the end-capillary oxygen saturation was taken as 100%, minus the measured HbCO percentage for arterial blood.

Sulphur hexafluoride (SF_6) retention[6] was used to measure the true right-to-left shunt ($\dot{Q}s/\dot{Q}t_{SF_6}$), i.e., the fraction of cardiac output perfusing lung compartments having near-zero ventilation/perfusion ratios. An SF_6-equilibrated solution was continuously infused through a peripheral vein at a rate of 100 ml/h; the ratio of arterial to mixed venous concentrations of SF_6 (retention) was obtained by gas chromatography after nitrogen extraction from blood withdrawn into gas-tight syringes.

Cardiac output was measured by thermodilution using a cardiac output computer.

The VP curve (inspiratory limb) was obtained by manually plotting the airway pressures resulting from the step-by-step inflation, using 50-ml increments of air injected from a 100-ml syringe.

Statistical Analysis

Data were treated by the analysis of variance method as a 2 × 3 factorial experiment. The use of the Latin square allowed the effects of time (e.g., deterioration of the animal preparation) to be distinguished from the effects of treatment.

RESULTS

The average volume of saline used for lung lavage was 13 ± 5.2 L. The VP curve 90 min after completion

TABLE 1. Ventilatory settings (mean ± SD)

	Low $\overline{\text{Paw}}$			High $\overline{\text{Paw}}$		
PEEP relative to Pflex ($cm\ H_2O$)	−5	+5	+10	−5	+5	+10
$\overline{\text{Paw}}$ ($cm\ H_2O$)	40 ± 6.3	39 ± 5.1	40 ± 5.2	45 ± 4.7	44 ± 4.5	45 ± 4.6
PEEP ($cm\ H_2O$)	19 ± 5.1	29 ± 5.1	34 ± 5.1	19 ± 5.3	29 ± 5.1	34 ± 5.0
Peak airway pressure ($cm\ H_2O$)	66 ± 8.8	76 ± 10.2	81 ± 11.7	65 ± 11.4	78 ± 12.2	79 ± 6.8
I/E ratio	2.86 ± 1.12	0.47 ± 0.03	0.18 ± 0.06	3.65 ± 0.59	1.28 ± 0.71	0.55 ± 0.11

TABLE 2. Gas exchange (mean ± SD)

	Low $\overline{Paw}$			High $\overline{Paw}$		
PEEP relative to Pflex (cm H_2O)	−5	+5	+10	−5	+5	+10
PaO_2 (torr)	49 ± 14	72 ± 20	91 ± 37	89 ± 36	120 ± 58	131 ± 56
$\dot{Q}sp/\dot{Q}t$ (%)	53 ± 26	30 ± 18	26 ± 16	25 ± 17	18 ± 21	15 ± 17
$\dot{Q}s/\dot{Q}tSF_6$ (%)	39 ± 17	23 ± 45	18 ± 15	19 ± 13	13 ± 18	9 ± 13
$PaCO_2$ (torr)	35 ± 7	37 ± 8	45 ± 9	29 ± 2	30 ± 3	33 ± 4
V_D/V_T (%)	56 ± 18	65 ± 5	71 ± 6	58 ± 6	64 ± 5	67 ± 4

Comparison	F-values for the comparison				
	PaO_2	$PaCO_2$	$\dot{Q}sp/\dot{Q}t$	$\dot{Q}s/\dot{Q}tSF_6$	V_D/V_T
I: PEEP > Pflex vs PEEP < Pflex	17.7[a]	9.62[a]	13.4[a]	15.7[a]	10.3[a]
II: PEEP +5 vs. PEEP +10	2.41	9.86[a]			8.69[a]
III: Low $\overline{Paw}$ vs. High $\overline{Paw}$	29.5[a]	32.8[a]	14.9[a]	17.4[a]	5.10[b]
IV: Interaction I × III			3.18	2.5	
V: Interaction II × III		2.46			3.90

[a] $p < .01$.
[b] $p < .05$.

TABLE 3. Hemodynamics (mean ± SD)

	Low $\overline{Paw}$			High $\overline{Paw}$		
PEEP relative to Pflex (cm H_2O)	−5	+5	+10	−5	+5	+10
Cardiac output (L/min)	3.68 ± 1.56	3.43 ± 1.59	3.94 ± 2.39	3.53 ± 1.38	2.62 ± 0.56	2.76 ± 1.14
CVP (mm Hg)	13.2 ± 9.5	12.8 ± 10.3	14.3 ± 10.6	10.0 ± 7.9	12.3 ± 6.1	18.3 ± 7.0
PAP (mm Hg)	41 ± 11	39 ± 10	38 ± 10	39 ± 9	41 ± 9	43 ± 6
SAP (mm Hg)	78 ± 35	72 ± 26	75 ± 33	72 ± 39	75 ± 36	64 ± 19

Comparison	F-values for the comparison			
	Cardiac output	CVP	PAP	SAP
I: PEEP > Pflex vs. PEEP < Pflex	2.54	19.3[a]		
II: PEEP + 5 vs. PEEP + 10		24.6[a]		
III: Low $\overline{Paw}$ vs. High $\overline{Paw}$	6.52[b]		2.37	
IV: Interaction I × III		14.1[a]	4.74[b]	
V: Interaction II × III		8.84[a]		

[a] $p < .01$.
[b] $p < .05$.

of lavage was biphasic (Fig. 1) in all animals. The average Pflex was 23.5 ± 4.9 cm H_2O.

The selected PEEP and $\overline{Paw}$ values as well as the I/E ratios and peak airway pressures used are reported in Table 1. PEEP values lower than Pflex were considered as controls.

Tables 2 and 3 show the mean values for variables measured after each treatment, and the statistical comparisons between treatments.

Gas Exchange (Table 2)

PaO_2 as well as $\dot{Q}sp/\dot{Q}t$ and $\dot{Q}s/\dot{Q}tSF_6$ were significantly better when PEEP was greater than Pflex; in contrast, no significant effect could be shown when a 5-cm H_2O increase in PEEP was applied in a range higher than Pflex.

Increasing $\overline{Paw}$ significantly improved PaO_2, $\dot{Q}sp/\dot{Q}t$, and $\dot{Q}s/\dot{Q}tSF_6$, regardless of the PEEP level.

For all PEEP increments, $PaCO_2$ increased irrespective of Pflex. By contrast, increasing $\overline{Paw}$ caused a decrease in $PaCO_2$. The behavior of V_D/V_T mirrored these results.

Hemodynamics (Table 3)

Cardiac output decreased significantly with time, from an initial average of 4.43 ± 1.42 L/min, to 2.24 ± 0.84 L/min at the end of the experiment ($F = 7.81$, $p < .01$). However, while cardiac output was significantly reduced by the $\overline{Paw}$ increase, it was not significantly affected by changes in PEEP.

PEEP increased CVP, particularly at higher $\overline{Paw}$ (interaction I × III and II × III, comparisons IV and V, Table 3). There were no significant changes in either mean pulmonary pressure (PAP) or mean systemic artery pressure (SAP). However, there was a significant negative interaction (comparison IV, Table 3) for PAP; hence, increasing PEEP above Pflex decreased PAP at low $\overline{Paw}$, while it had an opposite effect at higher $\overline{Paw}$.

DISCUSSION

The results obtained in neonates by Ciszek et al.[7] and in adults by Gallagher and Banner[1] and Marcolin et al.[8] tend to restrict the importance of PEEP as a determinant of gas exchange: when different PEEP levels were compared at constant $\overline{Paw}$ by changing the I/E ratio, there were no concomitant changes in oxygenation. In both these adult studies, PEEP levels were presumably higher than Pflex. We also found that PEEP, when applied in a range higher than Pflex, had no significant effects on oxygenation. However, our data indicate a very significant difference in oxygenation when PEEP lower than Pflex is compared to PEEP higher than Pflex. These results, in conjunction with previous work,[1,8] are consistent with the concept of a minimal effective PEEP.[2]

The minimal effective PEEP places the tidal ventilation in a pressure range always higher than the pressure (Pflex) corresponding to significant end-expiratory alveolar collapse. PEEP, when clinically applied at variable $\overline{Paw}$ values, can affect oxygenation through direct action on end-expiratory volume, or through secondary changes in $\overline{Paw}$. The relative importance of each mechanism appears to depend on the characteristics of the individual VP curve at the pressure range considered. Using a similar lung lavage model, Kolton et al.[9] conclude that constant airway pressure throughout the ventilatory cycle (as with high-frequency oscillation) is preferable to the phasic pressure pattern associated with continuous positive-pressure ventilation. Our study suggests that for a given $\overline{Paw}$, the deleterious effects of airway pressure reduction during expiration disappear at PEEP levels higher than Pflex.

CO_2 Exchange

The decreasing V_D/V_T and Pa_{CO_2} concomitant to the $\overline{Paw}$ increase confirm the results of Boros[10] and Ciszek et al.[7] in neonates: it is possible that prolonging the inspiratory time improves the distribution of ventilation between lung units having different time constants.[11] However, the risk of gas trapping might contraindicate the use of high I/E ratios in patients with high airway resistance.[12]

Literature on the effects of PEEP on V_D/V_T and Pa_{CO_2} is conflicting.[13] Our data show that when PEEP is increased at constant V_T and $\overline{Paw}$, dead space and Pa_{CO_2} always increase.

Hemodynamics

The decrease in cardiac output induced by the 5-cm H_2O $\overline{Paw}$ increment stresses the importance of $\overline{Paw}$ as a composite reflection of all pressures transmitted to the airways. Despite the relative instability of hemodynamic variables and the lack of pleural pressure data, PEEP was shown to have different effects at different $\overline{Paw}$ values, especially on PAP. The mechanism of these apparently discordant results requires further investigation. However, it is conceivable that lung volume, with which both airway pressures and pulmonary vascular resistances are alinearly related, could be important in determining the observed effects.

ACKNOWLEDGMENTS

We thank Prof. G. Aguggini, Director, Istituto di Fisiologia Veterinaria, for expert advice and continuous support; and SIEMENS, Italy, for providing the ventilator used in this study.

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