Effect of PEEP on Regional Ventilation and Perfusion in the Mechanically Ventilated Preterm Lamb

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Improvement of gas exchange through closer matching of *regional* ventilation ($\dot{V}$) and lung perfusion ($\dot{Q}$) with the application of positive end-expiratory pressure (PEEP) was evaluated in vivo in six mechanically ventilated preterm lambs (107–126 days/145 days gestation). Changes in $\dot{V}$ and $\dot{Q}$ were determined from in vivo scintigraphic measurements in four lung regions with inhaled radioactive ^{81m}Kr, and infused ^{81m}Kr/dextrose and/or [^{99m}Tc]MAA as PEEP was applied at 2, 4, and 6 cm H_2O in each animal. Dynamic compliance varied between 0.02 and 0.40 ml/cm H_2O, which was consistent with surfactant deficiency. As PEEP was increased, the regional distribution of $\dot{Q}$ shifted from the rostral to the caudal lung regions ($p < 0.02$ to < 0.05), while that of $\dot{V}$ remained unchanged. Regional $\dot{V}/\dot{Q}$ matching improved together with a trend towards improvement of arterial blood gases as PEEP was increased from 2 to 4 cm H_2O. Pulmonary scintigraphy offers a noninvasive methodology for the quantitative assessment of regional $\dot{V}$ and $\dot{Q}$ matching in preterm lambs and may be clinically applicable to ventilated neonates.

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Pronounced unevenness in the distribution of pulmonary ventilation ($\dot{V}$) and perfusion ($\dot{Q}$) with resultant mismatching is found in the neonatal Respiratory Distress Syndrome (RDS) (*1*). Although the use of positive airway pressure has increased the survival of small neonates, the effects of this therapy on regional pulmonary $\dot{V}$ and $\dot{Q}$ are not well understood. Positive end-expiratory pressure (PEEP), an important determinant of the *regional* distributions of $\dot{V}$ and $\dot{Q}$, is used in mechanical ventilation of the neonate to prevent progressive alveolar atelectasis and further $\dot{V}$ and $\dot{Q}$ mismatching in RDS (*2,3*).

The distributions of $\dot{V}$ and $\dot{Q}$ have been studied using alveolar-arterial gradients of oxygen, carbon dioxide and nitrogen and alveolar-urinary nitrogen gradients in spontaneously breathing neonates (*4–8*) and intubated nonventilated premature neonates (*9*) as a function of continuous positive airway pressure (CPAP). While these are specific measures of $\dot{V}/\dot{Q}$ inequality, they measure the degree of distribution imbalance for the *total* lung, but provide no data on *regional* differences. Overall $\dot{V}/\dot{Q}$ relationships, including the magnitude of intrapulmonary shunts, have also been assessed as a function of PEEP in full-term lambs (*10*), dogs (*11*), and adults (*12,13*) using the multiple inert gas elimination technique (*14*). However, the in vivo *spatial* distributions of $\dot{V}$ and $\dot{Q}$ and their regional changes as a function of PEEP cannot be evaluated by these methods. Only radionuclide imaging of the lung and computer analysis offer a noninvasive methodology for the quantitative serial assessment of in vivo *regional* distributions of $\dot{V}$ and $\dot{Q}$ as a function of PEEP in adults (*15*), as well as infants (*1,16–18*). Such studies were carried out in preterm lambs with the maladaptive cardiopulmonary transition (RDS) similar to that exhibited by premature neonates (*19–21*), and developed in a joint North Short University Hospital (NSUH)-Brookhaven National Laboratory (BNL) program (*22*).

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The objective of this study was to determine whether an increase in PEEP will increase gas exchange efficiency in the mechanically ventilated preterm lamb (107–126 days/145 days gestation) by closer matching of *regional* $\dot{V}$ and $\dot{Q}$. Specifically, we: (a) evaluated the effects of PEEP at 2, 4, and 6 cm H_2O sequentially in random order on the in vivo regional distributions of $\dot{V}$ and $\dot{Q}$ in the same animal serving as its own control; and (b) compared $\dot{Q}$ measured with continuously intravenous infused krypton-81m (^{81m}Kr) in 5% dextrose with the standard procedure (*18*) of i.v. injected technetium-99m albumin macroaggregate ([^{99m}Tc]MAA).

MATERIALS AND METHODS

Animal Preparation

The experimental protocol used in these studies was reviewed and approved by the NSUH and BNL Institutional Animal Care and Use Committees. Six pregnant ewes were anesthetized using halothane for both induction and maintenance of general anesthesia. The fetal head and neck were exposed through a small uterotomy, and the carotid artery, external jugular vein, and trachea were cannulated via two 1.5-cm skin incisions. The carotid artery cannula was used to withdraw samples for analysis of arterial blood gases and pH, and to monitor blood pressure in lambs 4–6 (Table 1) with transducers (Gould Statham P23) and a Siemens monitor (Model 404). A shortened No. 4.5 endotracheal tube was secured to the trachea to prevent air leakage. This was verified by the absence of ^{81m}Kr gas tracer in the ambient air, since camera background did not increase.

The lamb was delivered through the uterotomy, manually ventilated via Ambu bag with an F_iO_2 of 85–100% and paralyzed with i.v. pancuronium bromide (0.1 mg/kg). The lamb was instrumented with ECG leads and a rectal temperature probe. An esophageal balloon catheter was inserted per os into the lower third of the esophagus, as determined by measuring the length of the tubing against the lamb's chest and from subsequent pressure-time tracings with minimized cardiac artifacts. The 4-ml rubber balloon was filled with 1 ml air, so that measurement of esophageal pressure was independent of the balloon's compliance. The animal was then placed supine in a specially built constant-volume plethysmograph-incubator (Fig. 1) for imaging. A heated (40°C) water jacket loosely enclosed the lamb's chest to maintain constant body, as well as plethysmograph, temperatures. Air leakage was prevented by the use of O-ring seals for all connections and instrument leads. No invasive procedures were performed on the lamb after delivery.

The animal was ventilated with a pressure-cycled respirator (Bear Cub 2001) at a PEEP of 2 cm H_2O with respirator settings adjusted to provide a square wave ventilation pattern. Peak inspiratory pressure (PIP) (32–45 cm H_2O), inspiratory: expiratory time (1:1.5), respirator rate (60/min), FiO_2 (85–100%), and respirator gas flow rate (12 L/min) were held constant throughout each study. $\dot{V}$ and $\dot{Q}$ were studied at PEEPs of 2, 4, and 6 cm H_2O in random order. Heart rate was measured with a neonatal monitor (Siemens 404) using subcutaneous gold disc electrodes (Grass type E5GH). Measurements were made after the cardiopulmonary status was stable for at least 10 min.

Air flow and tidal volume (V_T), and transpulmonary pressure were measured with a specially built pneumotachometer and a differential pressure transducer (Gould Statham PM6), respectively, and recorded (Gould Model 2400) at each PEEP. The pneumotachometer output was 113 ml/min per mm chart deflection, and was linear from 50–1250 ml/min. The instruments were calibrated against an air rotameter for flow, a syringe for volume, and a water manometer for pressure. Minimum values of 50 ml/min, 0.3 ml, and 0.1 cm H_2O could be measured. Dynamic lung compliance (C_L) was calculated using the method Mead and Whittenberger (*23*) from the decreasing volume and pressure tracings as the ventilator PIP was gradually reduced. The corresponding differences of pressure and volume from end-inspiration to end-expiration were determined from the no-flow points and plotted. Compliance was then calculated from the slope of the straight part of the volume-pressure curve. The total elapsed time from delivery to conclusion of the experimental procedures was <5 hr. The lamb was euthanized by an overdose of pentobarbital anesthesia at the termination of the studies.

Radionuclide Imaging of Regional Ventilation and Perfusion

Regional $\dot{Q}$ ($\dot{Q}_r$) was measured with infused ^{81m}Kr/5% dextrose from a rubidium-81/krypton-81 (^{81}Rb/^{81m}Kr) generator (Medi-Physics or Brookhaven National Laboratory [BLIP]) and/or [^{99m}Tc]MAA, while regional $\dot{V}$ ($\dot{V}_r$) was measured with ^{81m}Kr gas from the same 10–15 mCi generator. The regional Kr-81m count rate for normal adult respiratory rates is determined largely by inflow of fresh ^{81m}Kr, i.e., regional *ventilation*. Excellent count density images are obtained using ^{81m}Kr. The theoretical basis for quantitating the ^{81m}Kr count distributions in terms of absolute $\dot{V}$ and $\dot{Q}$ or the lung ventilatory washout rate, $\dot{V}/V$ or $\dot{V}/V'$, where V and V′ are the lung volumes of inhaled and infused ^{81m}Kr, respectively, has been extensively discussed (*17,24–26*).

The relationship between the ^{81m}Kr count rate in the lung and ventilation is fairly linear at low ventilatory washout (1.5–2.0 l/min-l) and becomes curved at higher ventilatory washout as the ventilatory washout process overrides radioactive decay. This is the case with neonates and preterm lambs with high minute ventilation and, therefore, high $\dot{V}/V$ or $\dot{V}/V'$, resulting in equilibration beetween inspired or infused and alveolar concentrations of ^{81m}Kr. Steady-state regional count rates will then reflect merely regional lung *volume*. The method we used to correct for the high $\dot{V}/V$ is described in Data Analysis.

A large field-of-view scintillation camera (Picker Digital Dynama Camera or Ohio Nuclear Series 110) with a parallel hole, 280-keV, medium-resolution collimator, was utilized to obtain posterior lung images. Technetium-99m MAA ($t_{1/2}$ = 6.0 h, 140 keV photopeak) was injected through the jugular venous catheter at each PEEP in successive doses of 1.5, 3.0, and 4.5 mCi, and >100,000 counts were acquired in each image, even after the values from each prior injection were subtracted. Since the animal was paralyzed and not moved during the study, it is unlikely that there were errors in subtracting prior [^{99m}Tc]MAA counts. Krypton-81m ($t_{1/2}$ = 13 sec, 190-keV photopeak) was either eluted with 5% dextrose solution (pH ∼7) and infused continuously at 5 ml/min through the jugular venous catheter, or eluted with 30 ml/

TABLE 1
Lamb Characteristics and Measured Cardiopulmonary Function

Animal*	Gestation Age (days)	PIP cm H_2O	PEEP cm H_2O	V_T ml	C_L ml/cm H_2O	HR (bpm)	BP sys/dias mmHg	pH	$PaCO_2$ mmHg	PaO_2 mmHg
1	123	45	2	15.1	0.38	144	—	7.14	69	47
			4	12.5	0.32	169	—	—	—	—
			6	10.7	0.29	167	—	—	—	—
2	107	45	2	11.1	0.29	240	—	7.18	41	36
			4	—	—	243	—	7.33	38	57
			6	—	—	230	—	7.24	74	42
3	124	45	2	2.6	0.07	170	—	7.34	55	78
			4	2.0	0.06	171	—	7.29	50	74
			6	1.6	0.05	147	—	7.25	60	74
4	123	45	2	1.3	0.03	182	52/35	7.20	49	46
			4	0.9	0.02	218	57/42	7.05	94	41
			6	0.8	0.02	198	66/48	6.94	124	40
5	126	40	2	14.0	0.38	220	73/54	7.35	40	39
			4	13.4	0.32	187	64/51	7.37	37	68
			6	14.0	0.28	136	68/50	7.40	35	49
6	126	32	2	8.2	0.40	248	78/65	7.35	38	35
			4	7.9	0.37	240	81/63	7.35	38	50
			6	5.1	0.29	175	59/47	7.26	49	45

* All animals were mechanically ventilated at 60 breaths/min, inspiratory: expiratory time of 1:1.5 and respirator gas flow rate of 12 l/min.

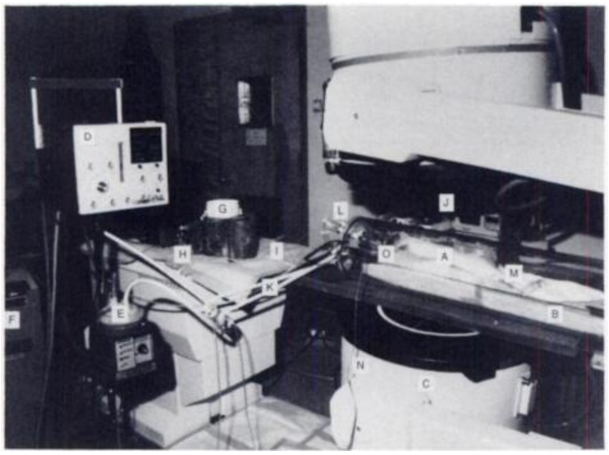

FIGURE 1
Mechanically ventilated lamb (A) in body plethysmograph (B) during imaging with scintillation camera (C). The experimental equipment includes the ventilator (D), humidifier (E), and air compressor (F); lead-shielded ^{81m}Kr generator (G) with air blower (H) and gas line to lamb (I); infusion pumps (J); ventilator hose (K); arterial and venous catheters (L); rectal temperature probe (M); and esophageal balloon catheter (N); and endotracheal tube (0).

min air and introduced into a tube parallel to the axis of the endotracheal tube to mix with ambient respirator air. Data were acquired for 60 sec, the first 30 sec at steady state for ~100,000 count images, followed by measurement of the activity decrease in 1-sec increments, after the flow of ^{81m}Kr was abruptly terminated (*22*). $\dot{Q}$ was measured with infused ^{81m}Kr only once at each PEEP in order to minimize the volume added to the lamb's circulation. $\dot{V}$ was measured five times, and a mean value calculated for each PEEP.

Data Analysis

The quantitated images of the radionuclides for each lamb were analyzed with a computer (Digital Equipment Corp., PDP 11/34) and displayed in a 64 × 64 matrix with a gray scale. The contours of the lung fields were determined automatically by setting all pixels below a 20% threshold to zero. However, within the lung fields all values were included. Each lung image was then divided horizontally into two regions of equal length. The regions were defined as in Figure 2. Relative percentages of the total $\dot{V}(\dot{V}_t)$ and $\dot{Q}$ $(\dot{Q}_t)$ were calculated from the steady-state counts of ^{81m}Kr for each region, $\dot{V}_r/\dot{V}_t$ and $\dot{Q}_r/\dot{Q}_t$, respectively. $\dot{Q}_r/\dot{Q}_t$ was also determined from the [^{99m}Tc]MAA activity. We used the approach of Ciofetta et al. (*17*), who quantitated $\dot{V}$ as well as $\dot{Q}$ with ^{81m}Kr in infants. $\dot{V}$ and $\dot{Q}$ were corrected by multiplying the regional and total ^{81m}Kr steady-state counts by the respective exponential rates of ^{81m}Kr activity decline - $\dot{V}/V$ or $\dot{V}/V'$ plus λ. The ^{81m}Kr removal rate was measured from the slope of the activity-time curve, consisting of 10–15 points, after abruptly terminating the inhalation or infusion of ^{81m}Kr. The final activity values of the steady-state plateau and the exponential part of the curve were selected as the first and last points of the washout curve. Cross-talk from even 9 mCi of [^{99m}Tc]MAA in the ^{81m}Kr energy window was <15% of the total activity. The washout data were corrected for this background before the slope of the curve was determined. When the ^{81m}Kr infusion was discontinued, radioactivity in the heart continued to be evolved into the alveoli. The onset of lung clearance of ^{81m}Kr was therefore delayed by several seconds, but clearance was otherwise not affected. The ratio of $\dot{V}_r/\dot{V}_t$ to $\dot{Q}_r/\dot{Q}_t$ was used to determine the regional $\dot{V}/\dot{Q}$ ratios. In this approach, regional $\dot{V}/\dot{Q}$ values were normalized to a value of 1.0 for the overall lung, which may be slightly higher than the true value. Thus the $\dot{V}/\dot{Q}$ obtained in this study is not identical with the $\dot{V}/\dot{Q}$ used in respiratory physiology, since the actual value depends on the ratio of total alveolar ventilation to cardiac output, whose magnitudes were not measured. Nevertheless, it quantitatively describes the regional adjustments of $\dot{V}$ and $\dot{Q}$.

The ventilatory washout analysis is ideally suited to elucidate lung regions with mismatched $\dot{V}$ and $\dot{Q}$, i.e., low $\dot{V}/\dot{Q}$. Krypton-81m activity will accumulate in regions with good perfusion and a slow ventilatory washout following continuous infusion. At the same time, these regions will not be seen during ^{81m}Kr inhalation because their ventilation is reduced. Krypton-81m activity will accumulate during inhalation only in regions with good ventilation and ventilatory washout. The steady-state count rate, as well as ^{81m}Kr removal rates, are therefore weighted by the better ventilated lung units during continuous inhalation and by the perfused, but poorly ventilated, lung units during continuous infusion. Intraregional $\dot{V}/\dot{Q}$ inequalities may thus also be detected by determining the clearance ratio (CR), the ratio of infused-to-inhaled ^{81m}Kr ventilatory washouts. The computer-determined slopes of the ^{81m}Kr removal rates for inhaled and infused ^{81m}Kr were used to calculate the values of regional $\dot{V}/V$ and $\dot{V}/V'$, respectively, and CR.

Statistical Analysis

Rates of ^{81m}Kr ventilatory washout plus decay were obtained from least-squares fits of the activity-time data, calculated by linear regression analysis. Their statistical significance was determined by applying Student's t-test. Values of the

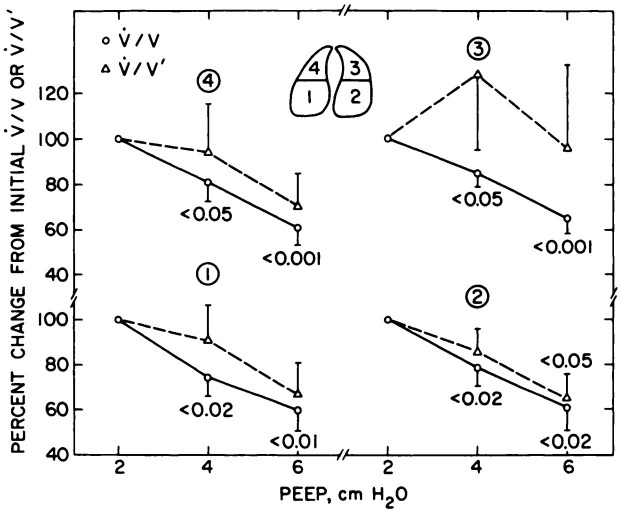

FIGURE 2
Percent change from the initial ventilatory washout—($\dot{V}/V$) of inhaled ^{81m}Kr (n = 6) and ($\dot{V}/V'$) infused ^{81m}Kr (n = 4) - plotted against PEEP for each lung region (1 and 4 in left lung; 2 and 3 in right lung). Statistically significant changes are shown. Values represent mean ± s.e.

mean ± s.e. of five ^{81m}Kr inhalation studies were used to determine the steady-state distributions of $\dot{V}$ and $\dot{V}/V$ for each level of PEEP and the inter-animal relationships with PEEP. Statistical significance of the changes with PEEP was determined by applying Student's paired t-test. A p value <0.05 was considered to be statistically significant.

RESULTS

Two preterm lambs (125 days/145 days gestation) were ventilated and monitored for ~5 hr after delivery and instrumentation to document their stability. Three sequential measurements of regional $\dot{V}$ and $\dot{Q}$, pulmonary function, and arterial blood gases were obtained 90 min apart at a constant PEEP of 2 cm H_2O. Heart rate varied between 128 and 210/min, and mean arterial pressure varied between 40 and 60 mmHg. The pH varied between 7.15 and 7.35 and inversely as a function of $PaCO_2$ (34–55 mmHg); however, the $PaCO_2$ did not increase with post-delivery time. PaO_2 (30–52 mmHg) did not vary either as a function of time. C_L varied between 0.26 and 0.34 ml/cm H_2O. V_T varied between 5.8 and 7.6 ml, measured between PIP and PEEP of 2 cm H_2O. Little change was found in regional $\dot{V}$ and $\dot{Q}$, measured with ^{81m}Kr and [^{99m}Tc]MAA, respectively.

The characteristics of the six lambs and the measured values of cardiopulmonary function and arterial blood gases are shown in Table 1 as functions of PEEP at 2, 4, and 6 cm H_2O. C_L varied between 0.02 and 0.40 ml/cm H_2O, which was consistent with pulmonary surfactant deficiency in these preterm lambs. C_L decreased with increasing PEEP. While the lungs of the gestationally more mature animals were more compliant than those of the less mature ones, considerable inter-animal variability was found. C_L for the two 123-day lambs, for example, varied by more than an order of magnitude. Although lamb 2 was considerably less mature (107/145 days) than the others, its compliance, as well as arterial blood gases, were close to those of the most mature animals studied (126/145 days). The 126-day animals required a lower PIP than the less mature ones in order to attain arterial blood without hypercarbia at a PEEP of 2 cm H_2O. V_T decreased with increasing PEEP as PIP was held constant. As PEEP was increased from 2 to 4 cm H_2O, the trends were for $PaCO_2$ to decrease and PaO_2 to increase slightly, and for $PaCO_2$ to increase and PaO_2 to decrease at 6 cm H_2O. Although the animals were ventilated with an enriched oxygen mixture (F_iO_2 85–100%), arterial oxygenation reflected a widened alveolar-arterial oxygen gradient.

TABLE 2
Regional Ventilatory Washout of Inhaled ^{81m}Kr

Animal	PEEP, cm H_2O	$\dot{V}/V$ min^{-1} Region 1	Region 2	Region 3	Region 4
1	2	5.9	6.6	4.9	7.5
	4	5.1	5.8	4.8	6.0
	6	3.5	3.7	3.3	3.6
2	2	5.5	6.4	3.9	3.9
	4	7.0	7.5	3.1	5.2
	6	5.4	7.6	3.0	5.2
3	2	7.8	8.0	6.7	7.3
	4	7.6	7.6	5.9	7.3
	6	4.7	4.6	4.3	5.1
4	2	6.3	6.2	6.0	6.8
	4	2.9	3.0	3.6	3.8
	6	1.7	1.9	2.6	2.5
5	2	16.5	14.4	13.0	14.7
	4	11.5	11.9	12.3	10.1
	6	8.5	9.0	10.6	9.6
6	2	8.4	9.8	12.0	8.7
	4	6.5	8.1	10.7	8.6
	6	5.5	6.1	6.5	7.4

Values of $\dot{V}/V$ for inhaled ^{81m}Kr (Table 2) and $\dot{V}/V'$ for infused Kr-81m (Table 3) generally decreased with increasing PEEP in most regions, the latter decreasing at considerably lower rates. Mean values of $\dot{V}/V$ for all regions at 4 and 6 cm H_2O were 14 and 30% lower, respectively, than at 2 cm H_2O PEEP, which was significant (Fig. 2). Similarly, the overall trends of $\dot{V}/V'$ showed mean decreases at 4 and 6 cm H_2O of 10 and 25%, respectively, below those at 2 cm H_2O PEEP. Even with this small number of lambs, the changes of $\dot{V}/V'$ in Region 2 were significant, while those in Regions 1 and 4 just missed attaining statistical significance (p = 0.056–0.076).

No significant change if $\dot{V}_r/\dot{V}_t$ with PEEP was found in any lung region (Fig. 3). On the other hand, the trend was for the redistribution of $\dot{Q}_r/\dot{Q}_t$ from the rostral to the caudal lung regions as PEEP was increased from 2 to 4 cm H_2O. The trends in Regions 1 and 3 were statistically significant, while the attainment of significance was just missed in Regions 2 and 4 (p = 0.063–0.089). Additional redistribution of $\dot{Q}_r/\dot{Q}_t$ occurred in Regions 1 and 3 as PEEP was increased to 6 cm H_2O. However, the trends were reversed in Regions 2 and 4.

TABLE 3
Regional Ventilatory Washout of Infused ^{81m}Kr

Animal	PEEP, cm H_2O	$\dot{V}/V'$, min^{-1} Region 1	Region 2	Region 3	Region 4
3	2	3.2	3.2	1.9	1.9
	4	3.9	3.7	2.9	2.6
	6	3.1	2.9	1.7	1.8
4	2	3.0	2.8	3.8	3.8
	4	1.6	1.9	2.5	1.8
	6	1.2	1.0	1.2	1.2
5	2	10.8	5.7	4.2	6.7
	4	9.3	4.6	8.8	4.8
	6	4.8	3.6	8.3	4.6
6	2	5.8	7.4	5.9	5.1
	4	5.9	5.9	4.8	6.0
	6	5.0	5.2	3.9	4.3

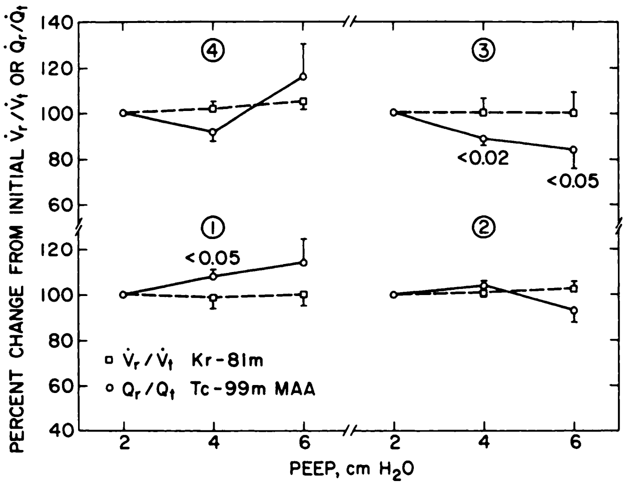

FIGURE 3
Percent change from the initial ^{81m}Kr ventilation ($\dot{V}_r/\dot{V}_t$) (n = 6) and [^{99m}Tc]MAA perfusion ($\dot{Q}r/\dot{Q}_t$) (n = 5) plotted against PEEP for each lung region. Statistically significant changes are shown. Values represent mean ± s.e.

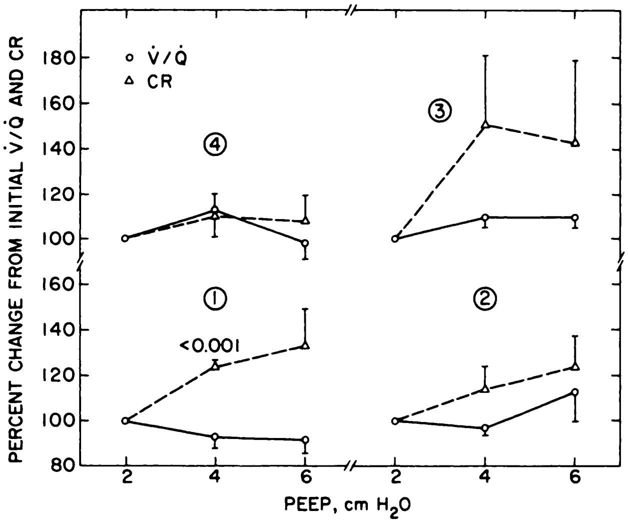

FIGURE 4
Percent change from the initial $\dot{V}/\dot{Q}$ (inhaled ^{81m}Kr/[^{99m}Tc] MAA) (n = 5) and CR ($\dot{V}$/V'infused ^{81m}Kr/$\dot{V}$/V inhaled ^{81m}Kr) (N = 4) plotted against PEEP for each lung region. Statistically significant change is shown. Values represent mean ± s.e.

Although there was greater dispersion of the infused ^{81m}Kr data, especially in Region 3, they were not statistically different from those obtained with [^{99m}Tc]MAA.

Regional $\dot{V}/\dot{Q}$ varied between 0.58 and 1.65 (Table 4). Mean overall lung values for all lambs increased from 1.03 to 1.08 as PEEP was increased to 4 cm H_2O. An analysis by lung regions showed that the apparent redistribution of $\dot{Q}_r$ (Fig. 3) from the rostral to caudal regions, as PEEP was increased from 2 to 4 cm H_2O, while $\dot{V}_r/\dot{V}_t$ remained constant, effected a change in regional $\dot{V}/\dot{Q}$ (Fig. 4), which, however, did not reach statistical significance. The mean $\dot{V}/\dot{Q}$ of 0.95 in the caudal regions at a PEEP of 2 cm H_2O decreased to 0.92 at a PEEP of 4 cm H_2O, and then increased again 1.01 at a PEEP of 6 cm H_2O. The mean rostral $\dot{V}/\dot{Q}$ of 1.11 at a PEEP of 2 cm H_2O increased to 1.24 at a PEEP of 4 cm H_2O, and then decreased to 1.10 at a PEEP of 6 cm H_2O. Although there was greater dispersion of the infused ^{81m}Kr data, especially in Region 3, they were not statistically different from those obtained with [^{99m}Tc]MAA.

Regional CR varied between 0.26 and 0.91 (Table 5). Mean overall lung values for all lambs increased from 0.49 to 0.59 as PEEP was increased to 4 cm H_2O, and then remained at this value at a PEEP of 6 cm H_2O. Analysis by lung region, however, showed that mean CR in the caudal regions at PEEPs of 4 and 6 cm H_2O increased by 19 and 29%, respectively, above the mean value of 0.53 at a PEEP of 2 cm H_2O. Similarly, the mean rostral CR at PEEPs of 4 and 6 cm H_2O increased by 31% and 26%, respectively, above the mean value of 0.45 at a PEEP of 2 cm H_2O. The

TABLE 4
Regional $\dot{V}/\dot{Q}$*

Animal	PEEP, cm H_2O	Region 1	Region 2	Region 3	Region 4
2	2	1.05	1.18	0.95	0.99
	4	1.10	1.20	0.93	1.11
	6	0.81	1.59	1.00	1.09
3	2	1.10	1.08	0.80	0.98
	4	1.19	0.93	0.79	1.16
	6	1.14	0.91	0.91	1.05
4	2	0.71	0.93	1.43	1.21
	4	0.58	0.92	1.65	1.46
	6	—	—	—	—
5	2	0.93	0.86	1.11	1.34
	4	0.86	0.89	1.32	1.18
	6	0.79	0.85	1.37	1.37
6	2	0.83	0.87	1.35	0.90
	4	0.65	0.83	1.62	1.14
	6	0.83	1.15	1.34	0.64

* V measured with ^{81m}Kr; $\dot{Q}$ measured with [^{99m}Tc]MAA.

TABLE 5
Regional Clearance Ratio

Animal	PEEP, cm H_2O	Region 1	Region 2	Region 3	Region 4
3	2	0.41	0.40	0.28	0.26
	4	0.51	0.49	0.50	0.35
	6	0.66	0.64	0.38	0.36
4	2	0.48	0.46	0.63	0.56
	4	0.55	0.63	0.69	0.48
	6	0.72	0.55	0.45	0.50
5	2	0.65	0.39	0.32	0.46
	4	0.81	0.39	0.71	0.48
	6	0.57	0.40	0.78	0.48
6	2	0.69	0.76	0.49	0.58
	4	0.90	0.73	0.45	0.69
	6	0.91	0.85	0.60	0.58

improvement of regional CR with increasing PEEP is shown in Fig. 4. The change in Region 1 from a PEEP of 2 to 4 cm H_2O was statistically significant.

DISCUSSION

Although PEEP had been shown previously to affect $\dot{V}$ and $\dot{Q}$ in the neonate, this study focuses on the in vivo *regional* distributions of $\dot{V}$, $\dot{Q}$, and $\dot{V}/\dot{Q}$ as functions of PEEP in a preterm lamb model of RDS. Earlier studies of neonates and newborn animals (*6–10*) employed methodologies in which the distributions of $\dot{V}$, $\dot{Q}$, and $\dot{V}/\dot{Q}$ were analyzed in the total lung, rather than regions within the lung. Pulmonary scintigraphy is the standard Nuclear Medicine methodology used in pulmonary diagnostics. It is noninvasive and facilitates the quantitative assessment of *regional* distributions of $\dot{V}$ and $\dot{Q}$ in the lungs of premature neonates that cannot be obtained by other methods (*27*). In principle, this procedure provides the possibility of obtaining quantitative information from all lung areas, which is especially important when studying *diffuse* lung disease, such as RDS. It is only limited by the resolution of the camera and the radioactivity levels, counts/unit area, attainable in the lung. The high level of radioactivity attained depends upon the specific activity of the ^{81m}Kr generator, since the V_T and functional residual capacity of the neonate or preterm lamb are very small (*28*).

V_T decreased with increasing PEEP as a result of a decrease in the difference between PIP and PEEP. Even though regional $\dot{V}/V$ generally decreased in most regions, the distribution of $\dot{V}_r/\dot{V}_t$ did not change with increasing PEEP. The additional lung volume was thus relatively evenly distributed throughout the lungs, so that regional C_L presumably decreased with increasing PEEP proportionately in all lung regions.

The effect of halothane, transferred across the placenta, on extrauterine neonatal respiratory physiology, has not been studied in lambs. However, hypoxic pulmonary vasoconstriction was not prevented in 1-3-day-old lambs ventilated with halothane (*29*). During halothane anesthesia of pregnant ewes, fetal oxygenation and acid-base status was found to remain stable (*30*). Therefore, a redistribution of $\dot{Q}$ would not be expected in the lamb on the basis of halothane anesthesia to the pregnant ewe. Similarly, the lamb's $\dot{V}_r/\dot{V}_t$ should not be affected by halothane anesthesia to the ewe, since it does not inspire halothane.

$\dot{Q}_r/\dot{Q}_t$ appeared to be redistributed from the rostral to the caudal lung regions as PEEP was increased to 4 cm H_2O, even though $\dot{V}_r/\dot{V}_t$ remained unchanged, resulting in only a relatively small $\dot{V}/\dot{Q}$ decrease, ~5%, at the caudal regions. Since anatomically most of the lamb's lung volume, as well as ~$2/3\dot{V}_t$, was in the caudal region, we suggest that more alveoli had been recruited in this region during the increase in PEEP from 2 to 4 cm H_2O. The apparent concomitant redistribution of blood flow caudally provided blood to the greatest number of newly recruited alveoli. As a result, there was a trend towards improved gas exchange. Increasing PEEP to 6 cm H_2O reversed this trend. This pressure may have caused blood to be shunted from previously recruited or more distended alveolar units. Since their walls were more compliant, the adjacent capillaries could have been squeezed with a decrease in capillary blood flow (*11*). Alternatively, this additional increase in PEEP may have increased extra-pulmonary right-to-left shunting at the level of the foramen ovale or ductus arteriosus (*31*).

$\dot{V}/V'$ for infused ^{81m}Kr decreased less than $\dot{V}/V$ for inhaled ^{81m}Kr with increasing PEEP, resulting in an increase of CR. Regional $\dot{V}$ and $\dot{Q}$ matching improved together with a trend towards improved gas exchange as PEEP was increased from 2 to 4 cm H_2O, but there was little change or even worsening with an additional increase in PEEP above 4 cm H_2O. CR appears to be a very sensitive indicator of intraregional mismatching of $\dot{V}$ and $\dot{Q}$. This is in agreement with the studies of Ciofetta et al. (*17*) and Koch et al. (*1*).

Values of C_L for our preterm lambs and their decrease with increased PEEP above 3 cm H_2O were comparable to those obtained to Shaffer et al. (*21,28*). Lambs of <126 days gestation probably had a greater degree of surfactant deficiency, as reflected in the greater PIP required to prevent hypercarbia at a PEEP of 2 cm H_2O. Since the lambs' compliances were considerably less than even for premature neonates with RDS, it was much harder to inflate their lungs to obtain a stable preparation. Thus, even a small PaO_2 increase would be significant and is indicative of the benefit of increased PEEP. Since we found a trend towards improved PaO_2 as PEEP was increased to 4 cm H_2O, the lambs appeared to respond in a manner similar to that of mechanically ventilated patients with adult respiratory distress syndrome (ARDS) (*13*). These patients' PaO_2 increased primarily because of the opening of closed airways and alveoli, and a reduction in blood flow to intrapulmonary shunts or low $\dot{V}/\dot{Q}$ regions.

Although pulmonary blood flow was not measured during our study, cardiac output may have decreased or extra-pulmonary right-to-left shunting may have increased, in response to increases in PEEP. While Dantzker et al. (*12*) and Ralph et al. (*13*) have documented decreases in cardiac output with increasing PEEP in patients with ARDS, the latter group found that reduction in cardiac output was not the major mechanism of PEEP-induced changes. These points must still be clarified for the preterm lamb model, since significant pathophysiological differences exist between RDS in neonates and adults (*21*). Mirro et al. (*32*), for example, found no change in cardiac output with mean airway pressures up to 15 cm H_2O in newborn piglets, whose lung compliance was artifically decreased by saline lavage. However, Egan and Hessler (*31*) found increased extra-pulmonary right-to-left shunting as PEEP was increased to 15 cm H_2O in immature goats.

We studied the distribution and matching of $\dot{V}$ and $\dot{Q}$ in four lung regions. Since surfactant production and release into alveoli is nonuniform in RDS (*33*), and compliance varies as a function of surfactant sufficiency, both compliant and noncompliant alveolar units must therefore have been present in each lung region. Thus, we believe that measurements in smaller lung regions could have improved the $\dot{V}/\dot{Q}$ analysis, but normal and abnormal lung units would still overlap within any counting field, no matter how small.

Krypton-81m is an optimal tracer for conducting serial ventilation studies with a relatively low patient radiation dose [0.016 rad/100,000 counts for neonates (*18*), and requires no patient cooperation (*16*). Several groups have quantitated the in vivo regional distribution of $\dot{V}$ and $\dot{Q}$ in infants using inhaled and infused xenon-133 (*1*) and $^{81\mathrm{m}}$Kr (*17*), and inhaled $^{81\mathrm{m}}$Kr and i.v. injected [$^{99\mathrm{m}}$Tc]MAA (*16*). However, they did not measure the distribution of $\dot{V}$ and $\dot{Q}$ in RDS as a function of PEEP. Limited scintigraphic studies in infants recovering from RDS have indicated that mismatching of $\dot{V}$ and $\dot{Q}$ is more pronounced than in healthy neonates (*1*).

The standard method to measure $\dot{Q}$ uses i.v. injected [$^{99\mathrm{m}}$Tc]MAA (*18*). Infused $^{81\mathrm{m}}$Kr in 5% dextrose is clinically more suitable for use with neonates, who are at risk for increased right-to-left shunting across the patent foramen ovale and ductus arteriosus as PEEP is increased (*31*). Shunting of [$^{99\mathrm{m}}$Tc]MAA from the pulmonary to the systemic circulation may cause systemic capillary obstruction with resultant malperfusion. Although sterile $^{81\mathrm{m}}$Kr is not available for intravenous use, the clinical applicability of $\dot{V}$ and $\dot{Q}$ studies in the cardiopulmonary management of ventilated neonates with RDS would be optimized by using both inhaled and infused $^{81\mathrm{m}}$Kr in the neonatal ICU. On the other hand, corrections must be applied with the use of $^{81\mathrm{m}}$Kr, especially neonates, as discussed in Methods.

Ciofetta et al. (*34*) found that the distribution of continuously infused $^{81\mathrm{m}}$Kr in uniformly ventilated lungs is similar to that of i.v. injected [$^{99\mathrm{m}}$Tc]MAA, and pulmonary vascular defects showed up equally well with both. However, variations in the distribution of ventilation interfered with the infused $^{81\mathrm{m}}$Kr when portraying the topography of blood flow accurately. In addition, $\dot{V}/V'$ from infused $^{81\mathrm{m}}$Kr may cause over- or underestimation of $\dot{Q}_r$. Nevertheless, we obtained similar results when using infused $^{81\mathrm{m}}$Kr and [$^{99\mathrm{m}}$Tc]MAA, except for the greater dispersion with $^{81\mathrm{m}}$Kr in Region 3. This dispersion was presumably due to superposition of the right upper lung and heart. As a result, it was difficult to distinguish the $^{81\mathrm{m}}$Kr activity present in each organ. This apparent increase in $^{81\mathrm{m}}$Kr activity could also result from a decreased cardiac ejection fraction (*35*), with an overestimation of $\dot{Q}$ in the right upper lung. Ciofetta et al. (*17*) studied infants with infused $^{81\mathrm{m}}$Kr, but did not discuss this problem, which may be exaggerated in lambs due to differences in the cardiopulmonary anatomy.

SUMMARY

We were able to measure in vivo changes in regional $\dot{V}$ and $\dot{Q}$ in preterm lambs with surfactant deficiency as PEEP was varied. The distribution of $\dot{V}_r/\dot{V}_t$ remained unchanged, while $\dot{Q}_r/\dot{Q}_t$ was redistributed from the rostral to the caudal lung regions. $\dot{V}/\dot{Q}$ matching improved together with a trend towards improved gas exchange as PEEP was increased from 2 to 4 cm H_2O, with little benefit from a further increase to 6 cm H_2O. Furthermore, the clinical suitability of $\dot{V}$ and $\dot{Q}$ studies in the cardiopulmonary management of ventilated neonates with RDS would be optimized by using both inhaled and infused $^{81\mathrm{m}}$Kr.

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