Inverse ratio ventilation (IRV) is a ventilatory concept that has become widely used in patients with acute lung injury and ARDS. In IRV, the pressure of inspiration is less than the pressure of expiration, with the ratio of peak inspiratory to peak expiratory pressure (Ppeak/PEEP) often set between 0.5 and 0.7. This technique is designed to reduce the airway pressure during inspiration and thus decrease the work of breathing and the risk of ventilator-induced lung injury. In contrast, conventional ventilation (CVV) typically uses a positive end-expiratory pressure (PEEP) to maintain alveolar pressure and improve gas exchange. The use of IRV has been shown to improve gas exchange, reduce lung injury, and decrease the work of breathing in patients with acute lung injury. However, the optimal settings for IRV and CVV remain a subject of ongoing research.

Key words: ARDS; intrinsic PEEP; inverse ratio ventilation; lung clearance; PEEP; ventilation, artificial

Abbreviations: ARF = acute respiratory failure; FIO2 = fraction of inspired oxygen; I:E = inspiratory to expiratory ratio; Insp hold = end-inspiratory pressure; IRV = inverse ratio ventilation; NS = not significant; PCIRV = pressure-controlled inverse ratio ventilation; PEEP = positive end-expiratory pressure; 99mTc-DTPA = technetium 99m diethylene triamine penta-acetic acid; T1/2 = half-life time; VCV = volume-controlled ventilation ZEEP = zero PEEP
positive end-expiratory pressure (PEEP) has been judged inadequate.  

The observation that high peak airway pressures may cause lung injury of the high permeability type has been brought forward as an argument for the use of PCIRV.  

It has been argued that pressure control ventilation with decelerating inspiratory gas flow and increased inspiratory time may result in a more homogenous gas distribution with less risk of alveolar overdistention. Structural damage to the alveolo-capillary unit may in this way be reduced and the risk of lung injury by mechanical ventilation minimized. However, experimental evidence supporting this theory has not been presented.

Isotope techniques using inhaled aerosolized technetium-99m diethylene triamine penta-acetic acid (99mTc-DTPA) have been used to study the integrity and function of the alveolo-capillary unit in vivo. After deposition in peripheral airways, the tracer traverses the alveolo-capillary barrier that comprises the surfactant layer, the alveolar epithelium, the basement membrane, and the capillary endothelium. Tracer activity over the lungs is measured repeatedly. A lung clearance rate is determined and is usually expressed as the half-life time (T1/2) or fractional rate of loss (0.693/T1/2).

In a previous study comparing PCIRV and VCV with PEEP (VCV PEEP) at equal end-expiratory and end-inspiratory lung volumes in mechanically ventilated rabbits, 99mTc-DTPA lung clearance was found to be higher with PCIRV at an inspiratory to expiratory (I:E) ratio of 4:1 than with PEEP ventilation at an I:E ratio of 1:2. The present study has been carried out to compare the effects of VCV PEEP and PCIRV on 99mTc-DTPA lung clearance, lung mechanics, and gas exchange in oleic acid-induced lung injury in rabbits.

**Materials and Methods**

Twenty-four New Zealand white rabbits (mean body weight, 3.8±0.7 kg) (ESF; Norttälje, Sweden) were used in these experiments. The study was approved by the local animal ethics committee.

**Preparation**

We have previously described the animal model used in this study. Following an IM injection of Hypnorm (fentanyl citrate, 0.315 mg/mL, and fluanisone, 10 mg/mL), 0.15 mL/kg, the animal was weighed and catheters were inserted in the right and left auricular veins. A catheter was placed in the left auricular artery and used for blood gas sampling and BP measurements. Anesthesia was induced by IV injection of diazepam, 0.6 mg/kg, and the trachea was intubated with a cuffed endotracheal tube (3.0 mm internal diameter; Sheridan Catheter Corp; Argyle, NY). Correct tube positioning was checked by capnography. The animal was connected to a ventilator (Siemens 300 Servoventila-

**Hemodynamics, Lung Function, and Gas Exchange**

Systemic artery pressure was recorded (Patient Data Monitor 565A; Bene, Kone; Finland) using pressure transducers (Transpac; Abbott Critical Care Systems; Sligo, Ireland). The pressure registration system was calibrated against a water column and checked according to standard procedures.

Airway pressures and gas volumes were recorded by transducers in the ventilator through a personal computer monitoring system. Static end-inspiratory (insp hold) and end-expiratory pressures were measured at the end of a 2-s hold maneuver. End-tidal CO2 concentration was analyzed by capnometry (Engström Eliza CO2 Analyzer; Engström AB; Solna, Sweden). Arterial blood samples were analyzed for PaO2, PaCO2, pH, and hemoglobin, and oxygen saturation was determined by spectrophotometry (ABL 520; Radiometer; Copenhagen, Denmark). All equipment was intermittently checked and calibrated according to the manufacturers’ instructions.

**Lung Clearance**

99mTc-DTPA was prepared from a commercial kit (Soclo DTPA; Sorin Biomedica; Saluggia, Italy) using 99mTc-sodium pertechnetate (Amersham International; Amersham, UK). Labeling yield before and after ultrasonic nebulization was assessed chromatographically. 99mTc-DTPA was delivered by an ultrasonic nebulizer placed in the inspiratory circuit. The mass median diameter of the nebulized particles was 3.5 μm measured with a laser light scattering technique (Malvern MasterSizer X, Ver 1.2a; Malvern Instruments Ltd; Malvern, UK). Nebulization was carried out for 3 min until a total count rate over the lungs of 3,000 counts per second was obtained corresponding to a total delivered dose of approximately 34 MBq. Radioactivity was measured in the anterior view using a gamma camera (Xi-Camera 400 AT; General Electric; Milwaukee) with a low energy general purpose collimator for 40 min in successive 1-min (group B animals treated with oleic acid 6 h before lung clearance measurement) or 15-s frames (group A animals that received oleic acid during clearance measurement). A logarithmic plot of activity vs time was obtained from a region of interest corresponding to both lungs. Correction was made for physical decay and background subtracted. Monoexponential equations were fitted to the curves by the least squares method and the clearance rate was expressed as T1/2. In the animals given oleic acid during clearance measurements, three T1/2 values (15 min preceding oleic acid injection, 5 min after oleic acid, and 15 to 20 min after oleic acid) were computed.

**Statistics**

Results are presented as mean±SD. The Mann-Whitney U test was used for group comparisons, and p values of ≤0.05 were considered indicative of statistical significance.

**Experimental Protocol**

In accordance with our previous study on lung clearance, the experimental protocol was designed to detect (1) the influence of...
the ventilatory pattern (PCIRV or VCV PEEP) of 6 h on the subsequent development of lung injury ("test of the priming period") and (2) the influence of the ventilatory pattern (as above) during 6 h of ventilation in the presence of lung damage (Fig 1).

Baseline measurements of BP, airway pressures, and gas exchange were performed during volume-controlled zero PEEP ventilation at an I:E ratio of 1:2 in all 24 animals. In 12 animals (group B), lung injury was induced by IV injection of oleic acid (0.15 mL/kg).15 The remaining 12 animals in group A did not receive oleic acid at this time. The ventilator was then switched to VCV using an I:E ratio of 1:2 and an externally applied PEEP of 5 cm H2O (VCV PEEP) in 12 animals (6 treated with oleic acid and 6 untreated) or to PCIRV at an I:E ratio of 80% in 12 animals (6 treated with oleic acid and 6 untreated). Static end-expiratory pressure was checked and if <5 H2O, an external PEEP of 1 to 2 cm H2O was applied to reach a static end-expiratory pressure of 5 cm H2O. The animals were mechanically ventilated with VCV PEEP or PCIRV for 6 h. Airway pressures, BP, and gas exchange were measured after 1 h in the untreated animals and after 6 h in the oleic acid-treated group. At 6 h, lung clearance was measured for a period of 15 min. The previously untreated animals were then given oleic acid IV (0.15 mL/kg) while lung clearance was measured continuously for another 25 min. Measurements of airway pressures and gas exchange were then repeated. At the end of the experiment, each animal was killed by IV injection of potassium chloride. Tidal volumes (7 mL/kg) and ventilator frequency (40/min) were kept constant throughout the study. At the start of every experiment, a fraction of inspired oxygen (FIO2) of 0.4 was used. This value had to be increased to avoid life-threatening hypoxemia after induction of lung injury in some but not all of the animals. We have therefore chosen to report oxygenation as the PaO2/FIO2 ratio.

In a separate experimental series, five animals were used to establish if the time receiving mechanical ventilation affected the tracer elimination pattern during and after oleic acid in PCIRV. These five animals were anesthetized and started on mechanical ventilation. Within 30 min of intubation, the animals received tracer inhalation under the conditions described above. Following completion of nebulization, ventilation was switched to PCIRV and clearance measurement was begun. After 15 min, oleic acid in a dose of 0.15 mL/kg was given IV. The clearance measurement was continued for 25 min.

**RESULTS**

**Gas Exchange, Lung Mechanics, and Hemodynamics**

**Prior to Induction of Lung Injury:** Baseline measurements of lung mechanics, BP, heart rate, and gas exchange during VCV PEEP were equal in both groups (Table 1). After 1 h of ventilation with either conventional or inverse ratio in group A, mean airway pressure was 8±1 cm H2O with VCV PEEP and 12±4 cm H2O with PCIRV (p<0.05). There were no differences in peak airway pressure, static end-inspiratory pressure, systemic BP, or blood gas values (Table 2).

**After Induction of Lung Injury:** Results 6 h after induction of lung injury in group B are shown in Table 3. Mean airway pressure was 17±2 cm H2O with PCIRV and 10±2 cm H2O with VCV PEEP (p<0.005). PaO2/FIO2 was lower in the PCIRV-treated animals (17 kPa) than in the animals ventilated with VCV PEEP (43 kPa, p<0.01). Systemic BP was lower with PCIRV than with VCV PEEP (64 vs 74 mm Hg, p<0.05).

Table 4 shows results from the animals in group A that had been ventilated for 6 h prior to IV injection of oleic acid. Measurements were performed 40 min after induction of lung injury. Mean airway pressure was higher and peak airway pressure was lower with PCIRV (12±2 and 14±2 cm H2O) in comparison to

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21759/ on 06/25/2017)

**Figure 1.** Experimental protocol. ZEEP = zero PEEP.
VCV PEEP (9±2 and 19±4 cm H2O, p<0.05). PaO2/FiO2 was 24 kPa with PCIRV and 44 kPa with VCV PEEP (p<0.05).

**99mTc-DTPA Clearance**

Distribution of tracer was uniform in all animals prior to induction of lung injury. With development of pulmonary edema, areas of activity were observed in the lower trachea or larger bronchi of some of the animals. These areas were shielded during clearance measurements.

**Before Induction of Lung Injury:** Results of lung clearance measurements prior to induction of lung injury in group A are shown in Figure 2. The PCIRV-treated animals had a mean lung clearance expressed as T½ of 21±8 min. With VCV PEEP, mean T½ was 126±59 min (p<0.005).

**During Induction of Lung Injury:** IV injection of oleic acid in group A resulted in a sudden increase in clearance rate from 126±59 min to 13±9 min (p<0.001) (Fig 2) during VCV PEEP ventilation. This was followed by a slower elimination phase (T½, 38±17 min). During ventilation with PCIRV, oleic acid injection did not result in any significant change in clearance rate although the clearance pattern was observed to change from single-compartment to multicompartment type elimination. In the five animals studied during PCIRV immediately following start of mechanical ventilation, the clearance pattern before, during, and after oleic acid administration was similar to that observed in the animals that had been mechanically ventilated for 6 h prior to oleic acid injection.

**Six Hours After Induction of Lung Injury:** The animals ventilated with PCIRV had a mean T½ of 25±9 min 6 h after IV oleic acid injection, which was not significantly different from the clearance before lung injury. In the VCV PEEP group, T½ was 36±16 min (not significant [NS] in comparison to PCIRV after lung injury, p<0.001 in comparison to VCV PEEP before lung injury).

**DISCUSSION**

The most striking findings of the present study were that in the presence of oleic acid-induced lung injury, pulmonary epithelial clearance (using DTPA) was similar in the PCIRV and VCV PEEP-ventilated animals but oxygenation was less efficient with

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**Table 1—Baseline Measurements Using Volume-Controlled Ventilation Without PEEP (VCV PEEP) at an I:E Ratio of 1:2**

<table>
<thead>
<tr>
<th></th>
<th>VCV PEEP (n=12)</th>
<th>PCIRV (n=12)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.36±0.02</td>
<td>7.37±0.05</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO2, kPa</td>
<td>5.4±1.3</td>
<td>5.4±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>PaO2/FiO2, kPa</td>
<td>57±13</td>
<td>53±13</td>
<td>NS</td>
</tr>
<tr>
<td>Peak Paw, cm H2O</td>
<td>11±2</td>
<td>12±2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Paw, cm H2O</td>
<td>2.6±0.5</td>
<td>3±1</td>
<td>NS</td>
</tr>
<tr>
<td>Insp hold, cm H2O</td>
<td>8±2</td>
<td>9±2</td>
<td>NS</td>
</tr>
<tr>
<td>SAPM, mm Hg</td>
<td>80±19</td>
<td>75±10</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Paw=airway pressure; SAPM=mean systemic artery pressure.

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**Table 2—Blood Gas Values, Airway Pressures, and Systemic BP After 1 h of Ventilation With VCV PEEP and PCIRV in the Group A Animals Not Given Oleic Acid**

<table>
<thead>
<tr>
<th></th>
<th>VCV PEEP, 1 h (n=6)</th>
<th>PCIRV, 1 h (n=6)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.52±0.05</td>
<td>7.42±0.12</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO2, kPa</td>
<td>4.0±1.2</td>
<td>3.8±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>PaO2/FiO2, kPa</td>
<td>65±10</td>
<td>63±9</td>
<td>NS</td>
</tr>
<tr>
<td>Peak Paw, cm H2O</td>
<td>17±3</td>
<td>15±5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Paw, cm H2O</td>
<td>8±1</td>
<td>12±4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Insp hold, cm H2O</td>
<td>13±2</td>
<td>15±2</td>
<td>NS</td>
</tr>
<tr>
<td>SAPM, mm Hg</td>
<td>64±12</td>
<td>60±6</td>
<td>NS</td>
</tr>
</tbody>
</table>

*See Table 1 footnote for explanation of abbreviations.

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**Table 3—Blood Gas Values, Airway Pressures, and Systemic BP After 6 h of Ventilation With VCV PEEP and PCIRV in the Group B Oleic Acid-Treated Group of Animals**

<table>
<thead>
<tr>
<th></th>
<th>VCV PEEP, 6 h (n=6)</th>
<th>PCIRV, 6 h (n=6)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.38±0.07</td>
<td>7.32±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO2, kPa</td>
<td>5.2±0.9</td>
<td>6.0±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>PaO2/FiO2, kPa</td>
<td>43±8</td>
<td>17±5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peak Paw, cm H2O</td>
<td>22±3</td>
<td>21±3</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Paw, cm H2O</td>
<td>10±2</td>
<td>17±2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Insp hold, cm H2O</td>
<td>17±2</td>
<td>19±3</td>
<td>NS</td>
</tr>
<tr>
<td>SAPM, mm Hg</td>
<td>74±7</td>
<td>64±7</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*See Table 1 footnote for explanation of abbreviations.

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**Table 4—Blood Gas Values and Airway Pressures After 6 h of Ventilation With VCV PEEP and PCIRV and Subsequent Administration of Oleic Acid in Group A**

<table>
<thead>
<tr>
<th></th>
<th>VCV PEEP, 1 h (n=6)</th>
<th>PCIRV, 1 h (n=6)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.42±0.07</td>
<td>7.44±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO2, kPa</td>
<td>5.4±1.4</td>
<td>4.6±1.3</td>
<td>NS</td>
</tr>
<tr>
<td>PaO2/FiO2, kPa</td>
<td>44±15</td>
<td>24±10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Peak Paw, cm H2O</td>
<td>19±4</td>
<td>14±2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean Paw, cm H2O</td>
<td>9±2</td>
<td>12±2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Insp hold, cm H2O</td>
<td>14±3</td>
<td>13±4</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Measurement results obtained 40 min after oleic acid injection. See Table 1 footnote for explanation of abbreviations.

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PCIRV. The data also confirm our previous observation\textsuperscript{14} that in the absence of oleic acid-induced lung injury, clearance was greater with PCIRV. These findings will be discussed in the following paragraphs.

**Gas Exchange and Hemodynamics**

As has been shown in previous reports, application of PEEP and PCIRV results in improved oxygenation in comparison to conventional ratio, zero
PEEP mechanical ventilation. It is generally believed that PCIRV results in equal or better levels of blood oxygenation than ventilation with VCV PEEP. Indeed, improved gas exchange is an important rationale for IRV in patients with severe acute respiratory failure (ARF) although clear-cut experimental evidence from controlled studies is lacking. The lung injury model employed in our study resulted in decreased blood oxygenation with PCIRV in comparison to VCV PEEP despite equal levels of end-expiratory pressure and equal tidal volumes. We did not measure functional residual capacity, but previous work has shown functional residual capacity to be equal at equal end-expiratory pressure levels. A difference could be demonstrated after 6 h of mechanical ventilation (Table 3) but also as early as 40 min after injection of oleic acid preceded by 6 h of ventilation with PCIRV and VCV PEEP, respectively (Table 4). These observations in a limited number of animals must be interpreted with caution. The observed difference in oxygenation may reflect variations in the effect of oleic acid injection in the two ventilatory modes. High levels of mean lung volume and mean airway pressure as in PCIRV, either before or after IV injections of oleic acid, may lead to a more severe lung injury than ventilation with VCV PEEP in the same conditions.

Alternatively, the explanation for the oxygenation differences may be sought in the observation made by Stewart et al. that elevation of mean airway pressure by external PEEP is more efficient than IRV in improving oxygenation. Also, in 1971, Cheney and Burnham showed that continuous positive pressure ventilation was more effective than IRV in improving oxygenation and decreasing venous admixture in oleic acid-induced pulmonary edema in dogs, despite equal levels of mean airway pressure. In a rabbit oleic acid lung injury model, Tyler and Cheney demonstrated essentially the same thing. Another possible contributing factor is presented in a recent model study by Kacmarek and coworkers in which equal levels of auto-PEEP and externally applied PEEP were compared with respect to distribution of local lung unit end-expiratory pressure and volume. A less homogenous distribution of pressure and volume was observed with auto-PEEP than with applied PEEP. The greatest end-expiratory lung volume and end-expiratory pressure occurred in slow lung units. Such lung units may receive less blood flow. Auto-PEEP, for example created by PCIRV, may thus lead to larger ventilation-to-perfusion inequalities than applied PEEP and result in poorer oxygenation. This explanation was also brought forward by Brandolese et al. In their study of 10

patients with ARF, PCIRV resulted in lower PaO2 in comparison to VCV PEEP at equal levels of end-expiratory pressure.

Finally, the difference in oxygenation may be caused by a reduced cardiac output leading to a lower mixed venous oxygen saturation in the PCIRV group. In this study, BF was lower in PCIRV than in VCV PEEP after 6 h of ventilation in group B (Table 3) and this observation confirms earlier reports in which PCIRV and VCV PEEP are compared.

The relative importance of the mechanisms discussed in the preceding paragraphs should be clarified in future experimental work.

**99mTc-DTPA Lung Clearance**

A detailed discussion of methodologic aspects in connection with 99mTc-DTPA lung clearance can be found in a previous article. It is a well-accepted method in detecting changes in alveolo-capillary permeability. Briefly, the amount and distribution of inhaled agents is dependent on particle size, endotracheal tube, as well as on ventilator-determined factors such as flow rate and flow waveform. Particles with a mean mass aerodynamic diameter of <0.5 µm are largely exhaled, whereas particles >2 µm are deposited in the trachea, larger bronchi, and bronchioles. Particles in the range of 0.5 to 2 µm penetrate to the alveoli and are deposited there by gravitational sedimentation. In our experimental setup, 30% of the delivered particles were between 0.5 and 2 µm and could be expected to deposit in small airways and alveoli. Ventilator settings during aerosol delivery were the same in both groups. Unequal deposition of tracer is therefore unlikely to explain the obtained results.

In rabbits ventilated with pressure control at a respiratory rate of 40 breaths/min and with an inspiratory time of 33% and a PEEP of 2 cm H2O, Nilsson and Wollmer found T½ values of 75 to 94 min. The clearance rate increases during deep slow ventilation relative to shallow rapid ventilation, even if mean airway pressure is kept constant. In a previous study carried out by us in mechanically ventilated rabbits, 99mTc-DTPA lung clearance curves were monoexponential with both PCIRV and VCV PEEP. Mean lung clearance expressed as T½ was 16±9 min with PCIRV and 107±74 min with VCV PEEP (p<0.001). Morphologic examination revealed no differences between the groups and no evidence of significant lung injury after a treatment period of 6 h.

Increased clearance has been reported in experimental lung injury, such as tracheal instillation of hydrochloric acid, IV injection of oleic acid, and alveolar lavage. In these models, there is a
correlation between morphologic findings and an increase in lung clearance. Also, in clinical conditions causing a high-permeability lung injury (ARDS), there is a coupling between morphologically evident lung injury and clearance rate.11,31 However, we are not aware of any published data correlating increased lung clearance with histopathologic evidence of ventilator-induced lung damage. Therefore, a functional rather than a histopathologic difference may explain the findings cited above. These observations imply that PCIRV causes an alteration in lung epithelial function in comparison to VCV PEEP. This functional difference is most likely caused by the large time-weighted lung volume produced by pressure control in combination with a prolonged inspiration. The mechanism behind volume-induced clearance rate increase is unclear. Alveolar distention may result in an increased area for diffusion of the tracer and to an increased epithelial permeability due to stretching of tight junction regions. Surfactant changes may also be caused by alveolar distention and comprise a relative thinning of the surfactant layer or alterations in the functional integrity of the alveolar surfactant layer. In animal experiments, surfactant dysfunction induced by administration of detergent or by BAL increases the clearance rate.26,28-30 Oleic acid-induced lung injury in rabbits results in a multicompartment type of clearance curve with a marked increase in clearance rate (TV/2, 8.8 min) within 30 s of IV oleic acid injection followed by a slower elimination phase within a few minutes.30 This has been interpreted as reflecting the existence of at least two epithelial compartments: one with severe high-permeability damage and one with less damaged epithelium and lower clearance rate.11 A similar multicompartment clearance curve has been demonstrated in patients suffering from high-permeability pulmonary edema as in neonatal respiratory distress syndrome and ARDS.11,31 Interestingly, in cardiogenic high-pressure pulmonary edema, lung clearance is normal.31-33 It has been suggested that 99mTc-DTPA lung clearance may reflect not only increased epithelial permeability, but also capillary endothelial leakage.34 In our present study, oleic acid injection during VCV PEEP ventilation resulted in the multicompartment type of clearance curve described above. With PCIRV, the clearance rate did not show any dramatic change after oleic acid irrespective of the time receiving mechanical ventilation preceding induction of lung injury. It is tempting to infer that PCIRV in contrast to VCV results in a maximal permeability increase for the tracer. If that is the case, induction of a high-permeability type of lung injury with oleic acid could not be expected to increase the clearance rate further. After 6 h of ventilation, it was not possible to demonstrate any clearance difference between PCIRV and VCV PEEP. These findings attest to the conclusion that PCIRV leads to an increased pulmonary permeability already in the healthy lung.

Recently, controlled clinical studies in patients with ARF have been unable to demonstrate positive effects of PCIRV in comparison to conventional ventilation when end-expiratory pressure is held constant.18,35 Our experimental data support these findings.

**Conclusion**

The clearance results imply that PCIRV causes an alteration in lung epithelial or membrane function in comparison to VCV PEEP. This functional difference is most likely caused by the large time-weighted lung volume produced by pressure control in combination with a prolonged inspiration. Induction of high-permeability lung injury with oleic acid eliminates the difference between PCIRV and VCV PEEP. It remains to be established whether these findings are relevant with regard to ventilator-associated structural lung injury in man. The observation that oxygenation with PCIRV was worse than with VCV PEEP must be interpreted with caution in this animal study but may be coupled to the permeability changes observed with PCIRV.

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