Cardiopulmonary Effects of Positive Pressure Ventilation During Acute Lung Injury* 

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Study objectives: To assess the gas exchange and hemodynamic effects of pressure-limited ventilation (PLV) strategies in acute lung injury (ALI). We hypothesized that in ALI, the reduction of plateau airway pressure (Paw) would be associated with less alveolar overdistention and thus have better hemodynamic and gas exchange characteristics than larger tidal volume (Vt) ventilation.

Setting: Laboratory.
Design: Prospective time-controlled sequential animal study.
Measurements: Right atrial, pulmonary artery, left atrial, arterial, lateral pleural (Ppl), and pericardial (Ppc) pressures, Paw, ventricular stroke volume, mean expired CO₂, and arterial and mixed venous oxygen contents. Airway resistance and static lung compliance were also measured.

Interventions: Intermittent positive pressure ventilation (IPPV) given before (control) and after induction of ALI by oleic acid infusion (0.1 mL/kg). IPPV at FIO₂ of 1, Vt of 12 mL/kg, and frequency adjusted to maintain normocarbia. ALI PLV was given during ALI and defined as that Vt which gave a similar plateau Paw to that of control IPPV. High-frequency jet ventilation (HFJV) and ALI HFJV were also given and defined as frequency within 10% of heart rate and mean Paw similar to that during control IPPV.

Results: After ALI, static lung compliance, PaO₂, and pH decreased, whereas airway resistance and PaCO₂ increased. For a constant lung volume, Ppl and Ppc were not different between control and ALI. Both absolute dead space (Vd) and intrapulmonary shunt fraction increased after ALI, but absolute Vd was lower with ALI PLV and ALI HFJV when compared with ALI IPPV. Ventilation did not alter hemodynamics during ALI.

Conclusions: Changes in lung volume determine Ppc and Ppl. PLV strategies do not alter hemodynamics but result in less of an increase in Vd/Vt than would be predicted from the obligatory decrease in Vt.

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ALI=acute lung injury; HFJV=high-frequency jet ventilation; IPPV=intermittent positive pressure ventilation; Paw=airway pressure; PeCO₂=mean expired CO₂; PEEP=positive end-expiratory pressure; PLV=pressure-limited ventilation; Ppc=pericardial pressure; Ppl=pleural pressure; Qpa=pulmonary artery flow; Qs/Qt=intrapulmonary shunt fraction; Raw=airway resistance; SV=stroke volume; Vd=dead space; Vt=tidal volume

Key words: ARDS; dead space; dog model; heart-lung interaction; mechanical ventilation; pericardial pressure; pleural pressure

The ventilatory support of patients with acute lung injury (ALI) has evolved over recent years as our understanding of the distribution of lung injury and its interactions with positive-pressure ventilation has increased. The distribution of lung consolidation in patients with ALI is nonhomogeneous with aerated lung units displaying normal specific compliance. Thus, as airway pressure (Paw) increases, aerated lung units in patients with ALI expand to the same extent as would normal lungs for the same increase in Paw. Because the total amount of aerated and recruitable lung units available to be ventilated is reduced in patients with ALI, tidal volumes (Vts) that would otherwise be normal in non-ALI condition will overdistend smaller total aerated lung units in these patients. One manifestation of this regional overdistention will be an increase in end-inspiratory plateau Paw when otherwise normal Vts are given. Clinically, increased peak inspiratory Paw is commonly seen in ventilated patients with ALI and probably reflects regional alveolar overdistention.

Assuming that high plateau Paw occurs during mechanical ventilation of patients with ALI, several pathophysiologic effects may be seen. First, marked overdistention of lung units will decrease their regional blood flow because of increasing regional pulmonary vascular resistance, and, thus, dead space (Vd) venti-
lation will increase. Second, such regional increases in aerated lung pulmonary vascular resistance will divert blood flow to nonaerated consolidated or collapsed lung units, thereby increasing shunt blood flow. Third, to the extent that increases in local lung units compress the cardiac fossa, local intrathoracic pressure will rise, which may decrease venous return and thus cardiac output. Finally, repetitive overexpansion of aerated lung units will injure respiratory epithelial tight junctions, inducing capillary leaks, ALI, and even death.

Based on these considerations, increased interest has developed in minimizing lung overdistention in patients with ALI while maintaining adequate arterial oxygenation. Numerous novel ventilatory strategies have been developed to address this problem, all of which involve the use of a limited VT breath while maintaining mean Paw elevations. It is not clear, however, what effect pressure-limited ventilation (PLV) has on shunt, Vd, or cardiovascular performance during ALI.

Accordingly, we studied the hemodynamic and gas exchange effects of two different types of PLV as compared with fixed VT positive-pressure ventilation in an animal model of ALI. Different ventilatory strategies can be used to limit end-inspiratory Paw while maintaining mean Paw at a defined level. High-frequency jet ventilation (HFJV) accomplishes this by combining high inspiratory gas flow and frequency with small VT, whereas, low-frequency PLV accomplishes this by decreasing inspiratory flow rate and VT. It is not clear, however, if these two different strategies have similar hemodynamic and gas exchange effects, because both the degree of change of lung volume and intrathoracic pressure differ between these two forms of ventilation. Thus, we studied both HFJV and low-frequency PLV.

**Materials and Methods**

**Preparation**

After approval of our protocol by the Animal Care and Use Committee, seven male mongrel dogs weighing 18.3 to 25 kg (mean, 23.3 kg) were anesthetized with IV pentobarbital sodium (30 mL/kg). Their tracheas were intubated with auffed endotracheal tube (9-mm-inner diameter; Hi-Lo National Catheter; Argyle, NY) equipped with a 2.4-mm-inner diameter jet ventilation port (open 5 cm from the distal orifice) and an open port at the distal end for measuring Paw. The dogs were placed in the supine position during the entire experiment. Anesthesia was maintained with a continuous IV infusion of pentobarbital sodium at a rate of 4 mg·kg⁻¹·h⁻¹ supplemented by a bolus of 50 to 100 mg IV as needed. Ventilation during the surgical procedure was provided at a respiratory rate of 20 breaths/min, a VT of 10 mL/kg, and a forced inspired oxygen of 1.0 (Siemens Servo 900 B Ventilator; Siemens; Elema AB, Sweden). Arterial blood gas values were monitored periodically (ABL-30; Radiometer; Copenhagen). Corrections in the acid-base balance during the surgical procedure were made by administration of sodium bicarbonate IV to maintain a pH between 7.35 and 7.45, and by increasing the VT to 15 mL/kg and subsequently the respiratory rate as necessary to maintain a PaCO₂ between 35 and 40 mm Hg. A standard lead 2 ECG was used to monitor the heart rate. A calibrated infrared CO₂ detector (Capnometer 47210A; Hewlett Packard; Palo Alto, Calif) was connected to the endotracheal tube to monitor the end-expiratory CO₂ was used as an initial guide to adjust the respiratory rate.

A saline solution-filled polyethylene catheter with end and multiple side holes was placed in the descending aorta and in the right atrium via the peripheral cutdown sites to measure aortic and right atrial pressures, respectively. A 7.5F balloon-tipped flow-directed thermodilution catheter, with an injection port 15 cm from the distal end, was placed in the pulmonary artery to measure the pulmonary arterial pressure (Baxter-Edwards; Irvine, Calif). The blood temperature was monitored continuously via the thermistor of the pulmonary artery catheter, and temperature was maintained above 35°C using external heating pads. A midline sternotomy was performed, and the heart was suspended in a pericardial cradle. A saline solution-filled polyethylene catheter with end and multiple side holes was placed in the left atrium via its appendage to measure the left atrial pressure. A circumferential electromagnetic flow probe (Carolina Medical Electronics; King, NC) was placed snugly around the root of the pulmonary artery. In two dogs, because of anatomic limitations, the flow probe could not be placed around the pulmonary artery so it was placed around the aortic root. During steady state, mean aortic and pulmonary blood flow were assumed to be equal. The flow probe signal was linear to ±5% over the range of flow studied. Zero pulmonary artery or aortic flow was taken as the diastolic plateau of the flow signal. Absolute pulmonary artery flow (Qpa) was quantified in vivo during an apneic steady state by the thermodilution technique (Edwards 9520 cardiac output computer; American Edwards Laboratory; Santa Ana, Calif) using the average of three 5-mL iced-saline solution injections (each value had to be within 10% of each other to be accepted). Right or left ventricular stroke volume (SV) was derived by integration of the respective flow signals. Cardiac output was calculated as the product of SV and heart rate. A 10×1.5-cm thin-walled air-filled latex balloon attached to a polyethylene catheter with end and multiple side holes was placed over the left lateral aspect of the heart in the long axis direction and secured with stay sutures to measure the pericardial pressure (Ppc). The pericardium was then approximated with multiple sutures. A second identical air-filled balloon catheter was positioned on the right lateral mid chest wall in the long axis direction at the height of the atria and secured in place with stay sutures to measure the pleural pressure (Ppl). Chest tubes were placed bilaterally. The positions of all the catheters and balloons were confirmed by palpation before chest closure. The left atrial, pericardial, and pleural balloon catheters and the flow-probe cable were exteriorized. The sternum was approximated, and the fascia and skin were closed in three layers to ensure an airtight seal.

The chest tubes were connected to continuous suction at ~15 cm H₂O and a positive end-expiratory pressure (PEEP) of 5 cm H₂O was added to ensure lung reexpansion. As previously described and validated, in situ pressure-volume curves were then generated for each balloon, and the volume of air left in the balloon was always lower than the in situ stressed volume of the system. The chest tubes were transiently occluded to assess any potential effects of suction applied on the drainage system on Ppc and Ppl. No effects of chest tube clamping were observed. All pressures were referenced to the midthorax. The vascular catheters were connected to low-displacement transducers (Gould Statham P-50; Gould Inc; Cleveland), and the air-filled Ppal, pericardial, and pleural catheters were connected to high-sensitivity transducers (Bell and Howell 4327F; Gould Inc). Airway, aortic, left and right atrial, Ppl, Ppc, pulmonary artery pressure, and Qpa were continuously recorded on an eight-channel strip-chart recorder (Gould Inc), digitized on line (Advantage A to D; Menlo Park, Calif), and stored on disk for subsequent analysis.
Protocol

After stabilization for 30 min, defined as hemodynamic stability in the absence of bleeding, arrhythmias, or ongoing metabolic acidosis, the protocol was begun (usually 1 h after the completion of surgery). Mechanical ventilation was provided using a constant inspiratory flow pattern by a positive-pressure ventilator (Siemens 900 B) during intermittent positive pressure ventilation (IPPV) runs and by a jet ventilator (Acutronic MK500; Medical Systems; Basel, Switzerland) during the HFJV runs. During HFJV, a one-way valve (exhalation only) was placed at the end of the endotracheal tube to prevent entrainment of room air, which allowed us to deliver an exact amount of gas per HFJV inspiration as previously described by our laboratory.14 HFJV was delivered asynchronously, but at a frequency within 10% of the heart rate to minimize cardiovascular instability.

The protocol consisted of observing the effects of various types of positive-pressure ventilation during control and ALI conditions. Hemodynamic variables were averaged over the entire ventilatory cycle and a minimum of three breaths was used to derive mean pressures and SV. Muscle paralysis (vecuronium bromide, 0.01 mg/kg IV) was induced at the beginning of each condition to abolish spontaneous movement. The control condition consisted of four sequential ventilatory stages: (1) IPPV (IPPV 1); (2) HFJV; (3) a second episode of IPPV (IPPV 2) to serve as a time control; and (4) apnea used as a baseline minimal heart-lung interaction. The ALI condition consisted of the same ventilatory stages as the control plus an additional PLV stage consisting of an IPPV-like run in which the Paw was adjusted downward until the plateau Paw was similar to the IPPV plateau Paw during the control. These five ALI stages are referred to in the text as ALI IPPV 1, ALI PLV, ALI HFJV, ALI IPPV 2, and ALI apnea. IPPV was defined as a frequency of 20 breaths/min, the inspiratory/expiratory (I/E) ratio was 1/3, and the Paw was adjusted for a PaCO₂ between 35 and 45 mm Hg, with an average Vt of 12 mL/kg. The plateau Paw was defined using the flow interrupter technique at end-inspiration. Mean Paw was also recorded during IPPV 1 and was used to define HFJV ventilator settings because estimates of plateau Paw during HFJV are difficult to determine. During HFJV, the ventilatory rate was fixed within 10% of the heart rate, the I/E ratio was 1/4, and the driving pressure of the HFJV air flow was adjusted to match the mean Paw as during IPPV 1. Ventilatory settings during IPPV 1 and 2 were identical. By using these three ventilatory modes, we could compare the effects of plateau Paw (IPPV vs PLV), lung volume (IPPV vs PLV vs HFJV), and mean Paw (IPPV vs PLV and HFJV) on gas exchange and hemodynamics.

At the beginning and end of control and ALI conditions, static inflation compliance curves were generated in 100-mL increments up to 500 mL above the resting lung volume using a 1-L supersyringe. Airway resistance (Raw) was estimated at end-inspiratory lung volume using an end-inspiratory hold maneuver, wherein the ratio of the immediate decline in airway pressure at end-inspiration to inspiratory gas flow reflected Raw at the end-inspiratory lung volume. This maneuver also allowed for the measurement of plateau Paw defined as Paw at 6 s of end-inspiratory hold. Thirty-second expired gas was collected during each mechanical ventilation step of the protocol in a 15-L polyester film (Mylar) plastic bag, which was then assayed for mean expired CO₂ (PeCO₂). The expired volume was also measured during HFJV runs to calculate true Vt. Paired mixed venous and arterial O₂ contents were also measured using a co-oximeter adjusted for dog blood (Co-oximeter IL-282, Instrumentation Laboratories; Lexington, Mass). The ratio of Vd to Vr was estimated by the following formula:

\[ \text{Vd/Vr} = \frac{(\text{PaCO}_2 - \text{CaCO}_2)}{\text{PaCO}_2 - \text{CvCO}_2} \]

where \( \text{PaCO}_2 \), \( \text{CaCO}_2 \), and \( \text{CvCO}_2 \) were the O₂ content of the pulmonary capillary, systemic arterial, and mixed venous blood, respectively, and assuming a fully saturated end-capillary blood sample and a plasma oxygen solubility of 0.003 mL O₂ per mm Hg of PaO₂.

ALI was induced by injection of oleic acid (0.1 mL/kg) in the right atrium over 5 min after the solution was vigorously agitated (Vortex; Fisher Scientific Industries; Bohemia, NY) for 30 s in 20 mL of 0.9% sodium chloride. The ALI stages of the protocol began approximately 90 min after induction of ALI and after hemodynamic stabilization, as previously suggested.18,19 During ALI IPPV, the respiratory rate usually had to be increased in an attempt to maintain normocapnia. Measures for each stage were made only after measures of PeCO₂ were stable for over 5 min and frequency was held constant across the condition. During ALI HFJV, the same settings as during the control stage of HFJV were used. Measurements taken during IPPV 2 and ALI IPPV 2 served as time controls for their respective conditions. Hemodynamic measurements were performed after stabilization (usually after 5 min) at each ventilatory step for control and ALI conditions. Hemodynamic variables were averaged over the ventilatory cycle taking approximately ten beats. After induction of ALI, hypoxemia occasionally was severe enough to require supplemental PEEP to maintain a minimal level of arterial oxygenation (\( \text{PaO}_2 > 50 \text{ mm Hg} \)) during the stabilization period and the intervals between the ventilatory stages. All measurements were taken after the application of supplemental PEEP was discontinued and hemodynamic stabilization was achieved, usually in 1 or 2 min. Gas exchange measures were not made during apneic steps of the protocol. In live dogs, frothy pulmonary edema occurred during the ALI condition requiring intermittent suctioning of the endotracheal tube and PEEP in between the protocol steps. The entire control and ALI sequences took approximately 20 min and 30 min, respectively, to complete. An infusion of dextran (60 g/L) was given IV during the control condition at 2 to 4 mL · kg⁻¹ · h⁻¹ and during the ALI condition at 10 mL · kg⁻¹ · h⁻¹ to maintain a constant apneic transmural left arterial pressure (defined as left arterial pressure minus Ppc).

Statistical Analysis

Analysis was performed on group data by ventilatory stages and experimental conditions using a two-way analysis of variance for repeated measures. Post hoc analysis was done using the Scheffe test. Paired comparisons between control and ALI conditions for compliance curves and Raw were done by a two-tailed t-test. Since PaO₂ values among conditions were not distributed normally, we compared these values between conditions by a nonparametric Wilcoxon signed rank test. A p value < 0.05 was considered significant. All data are shown as mean±SD.

Results

Model Characteristics

The model was stable throughout the control and
the ALI conditions. Besides the arterial pH, which demonstrated a moderate metabolic acidosis during ALI IPPV 2 compared with ALI IPPV 1 (7.23±0.12 and 7.35±0.07, respectively; p<0.03), comparisons of time control between IPPV 1 and IPPV 2 and between ALI IPPV 1 and ALI IPPV 2 demonstrated no difference in any measured variable between pair time-controlled steps of the protocol. Thus, only the initial IPPV sequences were used for subsequent comparisons. Oleic acid-induced ALI was characterized by a significant decrease in PaO$_2$ and pH, and an increase in PaCO$_2$ for all stages (Table 1). Furthermore, static total thoracic compliance decreased from 62±15 to 32±8 mL/cm H$_2$O (p<0.01) and Raw increased compared with the control (7.1±1.4 to 18.6±8.6 cm H$_2$O/min; p<0.01). Transpulmonary pressure, which was defined as Paw-Ppl, also increased for a given change in lung volume after ALI (p<0.0001) with every inflation step (Fig 1, top). However, Ppl and Ppc increased by similar amounts during both the control and ALI conditions for similar increases in lung volume (Fig 1, center and bottom, respectively), although the increase in Ppc was proportionally less than the increase in Ppl (p<0.05).

**Ventilation Characteristics**

When V$_t$ was maintained similar to control IPPV during ALI (ALI IPPV), both plateau and mean Paw increased (by 25 and 57% respectively; Table 1); when plateau Paw was maintained constant (ALI PLV), both mean Paw and V$_t$ decreased. ALI HFJV had a lower V$_t$ than either IPPV or ALI IPPV and a lower mean Paw than ALI IPPV. During HFJV, the gas flow

<table>
<thead>
<tr>
<th>Stage</th>
<th>V$_t$, mL</th>
<th>Frequency, Beat/min</th>
<th>Plateau Paw, mm Hg</th>
<th>Mean Paw, mm Hg</th>
<th>PaO$_2$, mm Hg</th>
<th>PaCO$_2$, mm Hg</th>
<th>pH</th>
<th>Vd/Vt, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPPV</td>
<td>288±20</td>
<td>21±0</td>
<td>7.4±0.9</td>
<td>2.8±0.3</td>
<td>542±43</td>
<td>36±3</td>
<td>7.38±0.03</td>
<td>19±7</td>
</tr>
<tr>
<td>HFJV</td>
<td>138±33$^i$</td>
<td>125±19$^i$</td>
<td>...</td>
<td>2.1±0.6$^i$</td>
<td>559±64</td>
<td>35±5</td>
<td>7.39±0.06</td>
<td>69±9$^i$</td>
</tr>
<tr>
<td>ALI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALI IPPV</td>
<td>285±20</td>
<td>24±4</td>
<td>9.9±1.1$^i$</td>
<td>4.4±1.1$^i$</td>
<td>60±24$^i$</td>
<td>42±3$^i$</td>
<td>7.35±0.06</td>
<td>52±9$^i$</td>
</tr>
<tr>
<td>ALI PLV</td>
<td>184±52$^i$</td>
<td>36±6$^i$</td>
<td>...</td>
<td>3.4±0.7$^i$</td>
<td>45±6$^i$</td>
<td>53±8$^i$</td>
<td>7.22±0.06</td>
<td>55±9$^i$</td>
</tr>
<tr>
<td>ALI HFJV</td>
<td>147±60$^i$</td>
<td>125±19$^i$</td>
<td>...</td>
<td>3.2±1.0$^i$</td>
<td>35±11$^i$</td>
<td>44±8$^i$</td>
<td>7.29±0.06</td>
<td>73±10$^i$</td>
</tr>
</tbody>
</table>

*Data=mean±SD; for abbreviations see text.
$^i$p<0.01 vs non-HFJV ventilatory modes.
$^p$p<0.02 ALI vs IPPV.
$^*p$p<0.05 ALI IPPV vs ALI PLV.

### Table 1—Ventilatory Effects of Positive-Pressure Ventilation*

*Figure 1. Effects of static lung inflation on the following: top: transpulmonary pressure (Paw-Ppl); center: Ppc; and bottom: Ppe for both control (closed circles) and ALI (open diamonds). Data are presented as mean±SD. Asterisk denotes differences between control and ALI (p<0.001).
(driving pressure) had to be decreased to prevent hypopacnia, which resulted in a significant decrease in mean Paw compared with IPPV. PaO₂ was constant during the different modes of ventilation within the separate control and ALI conditions with the exception of ALI HFJV during which it was reduced (Table 1). The PaO₂ did not change between the two ALI IPPV runs (60±24 to 48±8 mm Hg; p=0.17, paired t test; p=0.1, Wilcoxon signed rank test). After the induction of ALI and despite increasing respiratory frequency from 21 to 36 breaths/min, PaCO₂ increased by 17% during ALI IPPV (p<0.001, ALI vs control). During ALI PLV, PaCO₂ was higher by 30% than during ALI IPPV and ALI HFJV (p<0.05, respectively). These acute increases in PaCO₂ fully account for the decreases in pH. Despite increasing respiratory frequency and Raw during ALI conditions, we observed no increase in end-expiratory pleural pressure during any ventilatory mode. Compared with IPPV, both ALI IPPV and ALI PLV had doubled Vd/Vt (Table 1). Calculated physiologic Vd decreased significantly during ALI PLV as compared with ALI IPPV (p<0.05) (Fig 2). The increase in Vd/Vt was 174 and 189% for ALI IPPV and ALI PLV, respectively, when compared with IPPV. These changes in Vd/Vt were associated with a 17 and 47% increase in PaCO₂, respectively. Although Vd/Vt was greater during control HFJV as compared with IPPV, it did not change during ALI, although PaCO₂ did increase 27% above control HFJV value.

**Hemodynamic Characteristics**

ALI was associated with a lower aortic pressure and a higher transmural pulmonary artery pressure (pulmonary artery minus Ppc or right ventricular ejection pressure) than the control (Table 2). No differences were seen in SV, heart rate, right atrial pressure, or transmural left atrial pressure (left atrial pressure minus Ppc, or left ventricular filling pressure) across different conditions or modes of ventilation. Interestingly, hemodynamic values during ventilatory modes were not dissimilar to apneic values. The induction of ALI was associated with an increase in Qs/Qt. There were no differences, however, in Qs/Qt across ventilatory

### Table 2—Hemodynamic Effects of Positive-Pressure Ventilation*

<table>
<thead>
<tr>
<th>Stage</th>
<th>SV, mL</th>
<th>HR, Beats/min</th>
<th>CO, L/min</th>
<th>Pa, mm Hg</th>
<th>Platm, mm Hg</th>
<th>Ppmax, mm Hg</th>
<th>Qs/Qt, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>IPPV</td>
<td>14.5±3.2</td>
<td>128±30</td>
<td>1.9±0.5</td>
<td>144±32</td>
<td>7.7±3.7</td>
<td>14.8±3.6</td>
</tr>
<tr>
<td></td>
<td>HFJV</td>
<td>13.3±2.1</td>
<td>123±28</td>
<td>1.6±0.5</td>
<td>140±29</td>
<td>6.5±2.8</td>
<td>13.8±3.7</td>
</tr>
<tr>
<td></td>
<td>Apnea</td>
<td>13.2±3.0</td>
<td>125±27</td>
<td>1.6±0.5</td>
<td>137±30</td>
<td>8.6±5.0</td>
<td>15.9±3.5</td>
</tr>
<tr>
<td>ALI</td>
<td>ALI Vt</td>
<td>13.8±3.1</td>
<td>129±22</td>
<td>1.8±0.5</td>
<td>105±33</td>
<td>5.4±3.4</td>
<td>16.4±2.7</td>
</tr>
<tr>
<td></td>
<td>ALI Paw</td>
<td>13.7±3.7</td>
<td>121±17</td>
<td>1.7±0.5</td>
<td>102±34</td>
<td>6.1±4.1</td>
<td>16.6±2.7</td>
</tr>
<tr>
<td></td>
<td>ALI HFJV</td>
<td>17.3±5.1</td>
<td>129±20</td>
<td>2.2±0.8</td>
<td>121±43</td>
<td>6.3±3.3</td>
<td>19.3±5.1</td>
</tr>
<tr>
<td></td>
<td>ALI apnea</td>
<td>16.0±4.7</td>
<td>131±17</td>
<td>2.1±0.6</td>
<td>115±27</td>
<td>6.2±2.0</td>
<td>17.9±3.3</td>
</tr>
</tbody>
</table>

*Data=mean±SD; HR=heart rate; CO=cardiac output; Pa=mean arterial pressure; Platm=left atrial pressure relative to pericardial pressure; Ppmax=pulmonary artery pressure relative to pericardial pressure.

1p<0.02 ALI vs control.
modes in either control or ALI conditions.

Figure 3 shows the maximal Ppl and Ppc changes (delta) between peak-inspiratory and end-expiratory nadir values. We found no significant changes in delta Ppl or delta Ppc between IPPV and ALI IPPV. Delta Ppl and delta Ppc were smaller during ALI PLV than control IPPV and ALI IPPV. The delta Ppl and Ppc data were quantitatively similar to predicted changes from static compliance data (Fig 1). A delta pressure, defined as the maximum range of pressure changes over time measured at the nadir of the insufflation curve for Ppl and Ppc was also analyzed during the HFJV runs as peak minus trough pressure values. Although significantly different delta Ppl and Ppc values were seen in the control and ALI conditions, unlike in all other ventilatory models, delta Ppc was greater than delta Ppl during HFJV runs (p<0.05).

Inspection of the lungs of all animals at necropsy revealed diffuse patchy areas of hemorrhagic consolidation, which tended to be greatest in dependent regions and in the lower lobes. One animal had primary upper-lobe, lingula, and right middle-lobe consolidation. All animals had clearly defined regions of aerated lung units that expanded easily with slight increases in airway pressure. A small quantity of watery bloodtinged pleural effusion was present in all animals and the tracheas were filled with pink to red frothy fluid.

**Discussion**

This study demonstrates that positive-pressure ventilation has differential effects on gas exchange and hemodynamics, such that selective changes in either may occur with changes in ventilatory pattern. Over the range of airway pressures analyzed, PLV strategies had similar effects to volume-controlled IPPV on hemodynamics and shunt in this canine model of ALI. This was true even though the Vt delivered with PLV was almost half that of volume-controlled ventilation. Interestingly, following the induction of ALI PLV was associated with a lower physiologic Vd, thus minimizing the potential alveolar hypoventilation-induced hypercarbica that would be predicted to occur. Indeed, for a 35% decrease in Vt, we measured only a 5% increase in Vd/Vt (Table 1). Furthermore, the primary determinant of increases in both lateral chest Ppl and Ppc during positive pressure ventilation is the Vt, and neither the compliance nor resistance characteristics of the lungs alter this relationship. Finally, ventilation during ALI was not associated with increased end-expiratory Ppl, suggesting that dynamic hyperinflation was not a component of our model.

A decrease in lung compliance has been shown to decrease the transmission of Paw to the pleural space,20-22 potentially minimizing the effect of increased airway pressure on right atrial pressure, and subsequently on the pressure gradient for venous return. These findings have been challenged by O'Quin et al23 who measured juxtacardiac Ppl and found that the fractional change of Ppl vs airway pressure was only slightly decreased after ALI in a canine model. Furthermore, Potkin et al24 and Viquerat et al25 showed, in patients with ARDS, that the stepwise reduction in cardiac chamber size with increasing PEEP was associated with a decrease in cardiac output. Similarly, Scharf and Ingram26 measured Ppl during incremental increases in PEEP before and after induction of ALI in a canine model and found that decreases in cardiac output occurred independently of lung compliance, but were dependent on Ppl. Finally, Venus et al27 studying an ALI model in swine, demonstrated that the transmission of the Paw to the pleural space was reduced by ALI, whereas, with a constant Vr, the changes in Ppl were unaltered by changes in lung compliance. These conclusions are in accordance with our present study. Neither Cabrera et al28 analyzing the effects of changes in airway pressure on Ppc in an ALI dog model, nor Pinsky and Guimond,19 examining the effect of ALI on the transmission of PEEP to the pleural and pericardial spaces, examined the effects of lung volume itself on Ppc. This study allowed us to unify these previous studies and to explain the apparent discrepancies. The primary determinant of change in Ppl and Ppc during positive-pressure breathing is the amount of lung inflation. If Vr is not held constant throughout the course of an entire experiment, then apparent decreases in transmission of Paw may incorrectly be assumed to be due to decreased lung compliance related to the ALI condition when, in fact, decreased Vr alone was responsible for this effect.

We attribute the apparently higher compliance of Ppc as opposed to Ppl, reflected by a significantly lower amplitude change in Ppc compared with Ppl during HFJV conditions (Fig 3), to the effect of lung inflation on the heart. According to this model,19 increasing lung volume would compress the heart limiting its size, such that the associated increase in intrathoracic pressure would impede venous return, resulting in a decrease in the right ventricular volume and a smaller increase in Ppc. This is consistent with the hypothesis that when lung volume changes are rapid enough, as with HFJV, mechanical heart-lung interactions are accentuated because insufficient time is allowed for the blood to leave the heart when compared with “conventional” positive pressure breathing. In support of this hypothesis, we saw that the swings in Ppc during ventilation increased as frequency increased while Ppl swings were unaltered.

When we controlled the airway pressure by decreasing the Vr after induction of ALI (ALI PLV) (Table 2), we did not find any beneficial hemodynamic effects of PLV compared with volume-limited positive-pressure ventilation in the range of airway pressures explored in
our canine model. PLV was associated with smaller pleural and pericardial excursions during ventilation, however, and cardiac output tended to improve at the extremes of low VT ventilation (jet ventilation). It is not clear if these changes would have resulted in hemodynamic differences if the intravascular volume status had not been well maintained. We vigorously resuscitated these animals during ALI to keep left-side filling pressures constant. This approach was occasionally associated with marked pulmonary edema formation. If resuscitative efforts had been more restrained, we may speculate that decreased mean Ppl induced by PLV might have been associated with a higher venous return.

The observation that the physiologic V̇d is moderately affected by changes in VT has already been described and is attributed to a decrease in the anatomic V̇d in normal lungs. When nonhomogeneous lung injury conditions prevail, however, as in our model, decreasing VT is also likely to allow a better matching of ventilation and perfusion secondary to decreased overinflation. Because overdistention is a potential cause of further lung injury, limiting the airway pressure during mechanical ventilation is a logical ventilatory strategy. The obligatory reduction in VT usually induces alveolar hypoventilation and has given rise to the term permissive hypercapnia to denote the inevitable increase in arterial PCO₂. The goal of ventilatory therapy in patients with ALI is to maximize gas exchange while minimizing the detrimental effects of positive-pressure breaths on the lungs. Our results suggest that PLV compared with large VT positive-pressure breaths may be better tolerated than previously thought. The improved ventilatory efficiency due to the decreases in physiologic V̇d ventilation is also associated with lower inspiratory-increase in Ppl. Thus, pressure-limited ventilation strategies may not worsen hemodynamics or gas exchange.

Limitations of the Study

Our model of ALI follows oleic acid infusion with microembolism of lipids and diffuse endothelial injury. This may alter lung perfusion by mechanisms not associated with changes in alveolar pressure. Endothelial injury models, however, reflect the more common sepsis-type lung injury seen clinically in patients with ALI. Moreover, IV oleic acid induced an ALI in our canine model with a nonhomogeneous distribution of the lesions, decreased lung compliance, pulmonary ventilation-perfusion mismatch, and systemic vasodilation, mimicking many of the pathophysiologic events occurring in patients with ALI. Furthermore, even if mean airway pressure did not increase to the levels usually seen during human ALI, the lesions were severe enough to produced a 50% decrease in static lung compliance, making the findings of our model relevant.

Another potential limitation of our study was that we varied minute ventilation during our ALI conditions to keep PaCO₂ as close to control values as possible. This resulted in a greater frequency of ventilation during PLV than during conventional ventilation. Despite this maneuver, we measured a significant increase in PaCO₂ during ALI conditions. If CO₂ flux was not in equilibrium, then calculated Vd/VT could be inaccurate. We continuously monitored end-tidal CO₂, however, and took measurements only after baseline shifts had disappeared. Thus, although we may not have adequate data to calculate CO₂ excretion, the assumptions made in the calculation of Vd/VT by the Bohr equation are still valid.

Our study did not use PEEP, which is used in patients to maintain adequate PaO₂, because we wanted to analyze the direct effects of changing the ventilatory parameters on hemodynamics and gas exchange. Clearly, increased levels of PEEP would distend further aerated alveoli and, if anything, would have exaggerated the differences in physiologic V̇d between pressure-limited and volume-limited ventilation. A final limitation of our study was that extreme hypoxemia and marked decrease in airway compliance were produced by the oleic acid injection. This, however, resulted in only minor changes in the mean airway pressure. The absence of beneficial effects of pressure-controlled ventilation on hemodynamics may be related to the relatively small decrease in plateau airway pressure achieved.

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REFERENCES

140:659-67
25 Viquerat CE, Righetti A, Suter PM. Biventricular volumes and function in patients with adult respiratory distress syndrome ventilated with PEEP. Chest 1983; 83:509-14

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