Optimal Mean Airway Pressure during High-frequency Oscillation
Predicted by the Pressure-Volume Curve

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Background: A number of groups have recommended setting positive end-expiratory pressure during conventional mechanical ventilation in adults at 2 cm H2O above the lower corner pressure (PCL) of the inspiratory pressure–volume (P-V) curve of the respiratory system. No equivalent recommendations for the setting of the mean airway pressure (Paw) during high-frequency oscillation (HFO) exist. The authors questioned if the Paw resulting in the best oxygenation without hemodynamic compromise during HFO is related to the static P-V curve in a large animal model of acute respiratory distress syndrome.

Methods: Saline lung lavage was performed in seven sheep (28 ± 5 kg, mean ± SD) until the arterial oxygen partial pressure/fraction of inspired oxygen ratio decreased to 85 ± 27 mm Hg at a positive end-expiratory pressure of 5 cm H2O (initial injury). The PCL (20 ± 1 cm H2O) on the inflation limb and the point of maximum curvature change (PMC; 26 ± 1 cm H2O) on the deflation limb of the static P-V curve were determined. The sheep were subjected to four 1-h cycles of HFO at different levels of Paw (PCL + 2, + 6, + 10, + 14 cm H2O), applied in random order. Each cycle was preceded by a recruitment maneuver at a sustained Paw of 50 cm H2O for 60 s.

Results: High-frequency oscillation with a Paw of 6 cm H2O above PCL (PCL + 6) resulted in a significant improvement in oxygenation (P < 0.01 vs. initial injury). No further improvement in oxygenation was observed with higher Paw, but cardiac output decreased, pulmonary vascular resistance increased, and oxygen delivery decreased at a Paw greater than PCL + 6. The PMC on the deflation limb of the P-V curve was equal to the PCL + 6 (r = 0.77, P < 0.05).

Conclusion: In this model of acute respiratory distress syndrome, optimal Paw during HFO is equal to PCL + 6, which correlates with the PMC.

Conceptually, HFO provides an attractive alternative to conventional mechanical ventilation. By definition, HFO is provided with a lung protective strategy. As discussed by Froese, ventilating pressure during HFO should be kept above the lower corner pressure (PCL) and the peak alveolar pressure below the upper corner pressure (PUC) on the inflation limb of the pressure–volume (P-V) curve of the respiratory system. Consequently, the ventilator-induced lung injury associated with the shear stress of alveolar recruitment and derecruitment and alveolar overdistension can be avoided using these boundaries. During conventional ventilation, this approach has resulted in decreased pulmonary and systemic inflammatory mediator release and improved mortality when compared with ventilatory strategies that were not lung protective.

During HFO, the selection of initial settings are frequently based on those existing during conventional ventilation, by trial and error adjustment or by the clinical experience of the user. Oxygenation during HFO is primarily affected by mean airway pressure (Paw), with the initial setting determined by the Paw during conventional ventilation. We questioned if the Paw that resulted in the best oxygenation without hemodynamic insult could be predicted from the inflation limb of the P-V curve of the injured lung.

Materials and Methods

The following protocol was approved by the Subcommittee on Research Animal Care of the Massachusetts General Hospital. Animals were managed according to the Guiding Principles in the Care and Use of Animals of the National Institutes of Health.

Anesthesia and Instrumentation

Eight fasted Dorset sheep (28 ± 5 kg) were orotracheally intubated (Hi-Lo Jet Tracheal Tube, 9.0-mm ID; Mallinckrodt Laboratories Ltd., Athlone, Ireland) during halothane mask anesthesia. To ensure gastric drainage, a nasogastric tube (151-14, 14-French; Mallinckrodt Laboratories Ltd., Athlone, Ireland) was also inserted. The external jugular vein was then cannulated, and an 8-French sheath introducer (Avanti+, Cordis, Miami, FL) was inserted using the Seldinger technique. After line placement, the anesthetic was switched to total intravenous anesthesia with a loading dose of 10 mg/kg pentobarbital, 3 mg/kg ketamine, and 0.1 mg/kg pancuronium followed by contin-
continuous infusion of 10 mg · kg⁻¹ · h⁻¹ pentobarbital, 0.5 mg · kg⁻¹ · h⁻¹ ketamine, and 0.1 mg · kg⁻¹ · h⁻¹ pancuronium. After establishing intravenous anesthesia, surgical cannulation of the femoral artery was performed, and a pulmonary artery catheter (Model 131HF7; Baxter Healthcare Corp., Irvine, CA) was inserted via the 8-French sheath introducer. Maintenance of intravascular volume was achieved by infusion of lactated Ringer solution (20 ml · kg⁻¹ · h⁻¹). A heating blanket was used to maintain core temperature of 39°C. Basic ventilator settings (NPB 7200ae ventilator; Nellcor-Puritan-Bennett, Carlsbad, CA) were volume control ventilation; FIO₂, 1.0; positive end-expiratory pressure (PEEP) of 5 cm H₂O. The respiratory rate was adjusted to achieve normoventilation (arterial carbon dioxide partial pressure = 35–45 mmHg) at baseline.

**Experimental Protocol**

After a stabilization period of 60 min, baseline measurements, including pulmonary gas exchange, hemodynamics, and a static inflation and deflation P-V curve of the respiratory system were obtained. Severe lung injury was then produced by bilateral lung lavage with 30-ml/kg instillations of isotonic saline warmed to 39°C, repeated every 15 min until the arterial oxygen partial pressure decreased to less than 120 mmHg and remained stable (±10%) for 60 min at an FIO₂ of 1.0 and PEEP of 5 cm H₂O. After establishment of lung injury, another set of measurements (injury) was obtained, and a static P-V curve was measured to identify the PCL and PCU on the inflation limb as well as the point of maximum curvature (PMC) on the deflation limb. The sheep were then ventilated with HFO. Settings of the oscillator (3100B; SensorMedics, Yorba Linda, CA) were as follows: FIO₂, 1.0; bias flow, 30 l/min; oscillatory frequency, 8 Hz; and inspiratory to expiratory ratio, 1:1. The pressure amplitude (ΔP) was adjusted to achieve an arterial carbon dioxide partial pressure of 35–50 mmHg. The sheep were provided four 1-h cycles of HFO. Hourly measurement of arterial and mixed venous blood gases and hemodynamics were made at Paw, Pcl, 2, Pcl, + 2, Pcl, + 4, Pcl, + 10, and Pcl, + 14 cm H₂O, applied in random order. Each cycle was preceded by a recruitment maneuver with a sustained Paw of 50 cm H₂O for 60 s while maintaining HFO. Between cycles, the lung was derecruited by a standardized 30-s ventilator disconnection with airway suctioning. After the four random applications of Paw, the animals were placed back on standard volume control as previously described for 30 min, after which baseline P-V curve, gas exchange, and hemodynamic measurements were made (fig. 1). On completion of the study, all animals were killed by a bolus dose of pentobarbital and potassium chloride.

**Measurements**

**Hemodynamics.** Systemic arterial pressure, pulmonary artery pressure, and central venous pressure were monitored using pressure transducers (Model 1280C; Hewlett Packard, Waltham, MA) with the zero level at mid-thorax in the supine position. Pulmonary artery wedge pressure and central venous pressure were measured at end expiration. Cardiac output was measured in triplicate by thermodilution technique (Cardiac Output Computer 9520A; American Edwards Laboratory, Irvine, CA).

**Gas Exchange.** Paired arterial and mixed venous blood samples were drawn and analyzed at each measurement point (Model 238; Ciba Corning Diagnostics Corp., Norwood, MA). Hemoglobin content and oxygen saturation were also measured (Model 282; Instrumentation Laboratory, Lexington, MA). The venous admixture (Qs/Qt) was calculated using the standard equation:

\[
\frac{Qs}{Qt} = \frac{(C_{CO_2} - Ca_{O_2})}{(C_{CO_2} - Cv_{O_2})}
\]

and the oxygenation index was calculated using the following formula:

\[
OI = \frac{(FIO_2 \times Paw \times 100)}{Pao_2}
\]

**Pulmonary Mechanics.** Airway pressures proximal and distal to the endotracheal tube were monitored with precision pressure transducers (Model 45-32-871±100;
All signals were amplified (Model 8805C, Hewlett Packard) and recorded at a sampling rate of 300 Hz per channel with an analog–digital conversion system (Windaq/200 v1.36; Dataq Instruments, Hartfield, PA). All devices were calibrated at the beginning of the experiment.

Static P-V curves of the respiratory system were obtained with a calibrated 2-l syringe (Model S2000; Hamilton, Reno, NV) using the method described by Harris et al.15 Stepwise inflations in increments of 50 ml up to a total volume of 200 ml followed by steps of 100 ml until the plateau airway pressure reached 45 cm H2O were performed while recording the corresponding airway pressure. On completion of the inspiratory limb, the syringe was disconnected and the sheep briefly ventilated. The syringe was then reconnected, the lungs were slowly inflated to the same volume reached at the end of the inspiratory limb, and then stepwise deflation was performed in four decrements of 50 ml, followed by steps of 100 ml, which established the deflation limb of the P-V curve. Volumes were adjusted to reflect body temperature pressure saturated conditions. The PCL was determined as the point of intersection between the slopes of the initial flat and subsequently steep and linear portions of the inflation limb of the P-V curve. The point of intersection between the slopes of the steep, linear, and final flat portions of the inflation limb identified the PCU. The PMC was identified as the point of intersection between the slopes of the steep, linear, and final flat portions of the inflation limb of the P-V curve (fig. 2). PCL, PCU, and PMC were all determined by the manual application of tangents to the corresponding slopes of the P-V curve. Analysis was performed by the same trained investigator blinded to the outcome of the analysis. PCL, PCU, and PMC were clearly determined in all animals studied. To ensure a consistent lung volume history, three consecutive sighs with a tidal volume of 24 ml/kg, using the sigh function of the PB 7200, were applied before the P-V curve measurement.

Statistical Analysis

Experimental data are expressed as mean ± SD. One-way analysis of variance for repeated measures was used to compare data. Post hoc analysis was performed with the Scheffé test. The Pearson correlation coefficient was used to determine the relation between PCL and PMC. A statistics software package (Statistica v5.1; StatSoft Inc., Tulsa, OK) was used, and a P value of 0.05 was considered statistically significant.

Results

Data from seven of the eight sheep investigated were analyzed. One sheep died during establishment of lung injury because of intractable hypoxemia. Seven sheep (28 ± 5 kg) completed the 4-h protocol. No sheep died during the study period.

Lung Injury

The average number of lung lavages needed to establish lung injury was 3 ± 1. After establishment of lung injury, the arterial oxygen partial pressure/FIO2 (P/F) ratio decreased (P < 0.01; fig. 3), Qs/Qt increased (P <
Table 1. Lung Mechanics and Optimal Mean Airway Pressure in Each Animal Studied

<table>
<thead>
<tr>
<th>Animal</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCL (cm H₂O)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>21</td>
<td>19</td>
<td>19</td>
<td>20</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>PCL (cm H₂O)</td>
<td>36</td>
<td>36</td>
<td>38</td>
<td>38</td>
<td>40</td>
<td>41</td>
<td>42</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>PMC (cm H₂O)</td>
<td>25</td>
<td>26</td>
<td>27</td>
<td>27</td>
<td>25</td>
<td>25</td>
<td>26</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>PawOPT (cm H₂O)</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>27</td>
<td>25</td>
<td>25</td>
<td>26</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>V @ PCL (ml)</td>
<td>200</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>500</td>
<td>280</td>
<td>360</td>
<td>320</td>
<td>109</td>
</tr>
<tr>
<td>V @ PCU (ml)</td>
<td>550</td>
<td>680</td>
<td>1,000</td>
<td>940</td>
<td>1,400</td>
<td>800</td>
<td>1,100</td>
<td>924</td>
<td>282</td>
</tr>
<tr>
<td>V @ PMC (ml)</td>
<td>570</td>
<td>680</td>
<td>1,100</td>
<td>920</td>
<td>1,350</td>
<td>760</td>
<td>1,000</td>
<td>911</td>
<td>267</td>
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</table>

All volumes measured at body temperature pressure saturated.

Animal = individual animal studied; PCL = lower corner pressure; PCU = upper corner pressure; PMC = point of maximal compliance change on the deflation limb of the P-V curve; PawOPT = optimal mean airway pressure for oxygenation during high-frequency oscillatory ventilation; V @ PCL = lung volume above functional residual capacity at PCL; V @ PCU = lung volume above functional residual capacity at PCU; V @ PMC = lung volume above functional residual capacity at PMC.

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Lung Volume above Functional Residual Capacity

The lung volume above functional residual capacity (FRC) at PCL was 320 ± 109 ml, at PCL it was 924 ± 282 ml, and at PMC it was 911 ± 267 ml. There was a significant correlation between the lung volume above FRC at PCU and at PMC (r = 0.98, P < 0.05; table 1).

Discussion

The major findings of this study can be summarized as follows: (1) a Paw equal to the PCL + 6 optimized oxygenation without adversely affecting hemodynamics; (2) a Paw of PCL + 2 yielded suboptimal oxygenation; (3) Paw higher than PCL + 6 did not further improve oxygenation but significantly impaired hemodynamics; and (4) the PCL + 6 was essentially equal to the PMC of the deflation limb of the P-V curve with this degree of lung injury.

Mean Airway Pressure

During HFO, Paw is the primary variable affecting oxygenation and is set independent of other variables on the oscillator. Because distal airway pressure changes during HFO are minimal, the Paw during HFO can be viewed in a manner similar to that observed with PEEP in conventional ventilation.

During conventional ventilation, a PEEP equal to the PCL + 2 has been shown to be effective in minimizing lung injury and pulmonary and systemic mediator activation and has been attributed to improving mortality. We have shown that a higher Paw was needed in HFO to optimize oxygenation. The reason for this difference may be the presence of tidal recruitment during conventional ventilation and the lack of tidal recruitment during HFO. The small tidal volumes during HFO may be unable to replenish the lung volume lost to reabsorption atelectasis because of V/Q mismatch or alveolar instability that conventional ventilation can, and thus the need for a higher Paw compared with PEEP to optimize oxygenation.

The Pressure–Volume Curve

As noted in figure 1, a distinct change in the slope of the P-V curve (PCL) occurs during the initial inspiratory phase. This had previously been thought to represent the area of the curve when lung recruitment occurred. However, as illustrated by Hickling, the PCL may simply represent the airway pressure where recruitment of collapsed lung units begins, with recruitment continuing

<table>
<thead>
<tr>
<th>Table 2. Gas Exchange Data</th>
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<tr>
<td></td>
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<tr>
<td>pH</td>
</tr>
<tr>
<td>PacO₂ (torr)</td>
</tr>
<tr>
<td>BEa (mM)</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
</tr>
<tr>
<td>O₂</td>
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All values are mean ± SD, Scheffé post hoc test: * P < 0.05 versus PCL + 6.

BL = baseline; PCL = lower corner pressure; HR = heart rate; MAP = mean arterial pressure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; SV = stroke volume; SVR = systemic vascular resistance; VO₂ = oxygen consumption.

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throughout inflation until the P CU is established. The change in slope at the P CU may represent the airway pressure causing overdistension or, as proposed by Hickling, may simply represent the airway pressure where recruitment during inflation decreases or stops.

On the deflation limb of the P-V curve, the PMC identifies the airway pressure below which lung volume rapidly decreases. As shown in our example, the lung volume at PMC is approximately 85–90% of the total volume delivered during the P-V curve measurement and approximates the lung volume at P CU.

**Optimal Oxygenation**

If Hickling is correct regarding the significance of the P-V curve during HFO, oxygenation should improve at P aw above P CL. This is exactly what we found. It is also reasonable to expect that optimal oxygenation during HFO would occur at a P aw equivalent to the PMC. As lung volume at PMC is approximately equal to the lung volume at P CU (fig. 1 and table 1) or a volume reflective of maximal lung recruitment, P aw above PMC would not be expected to further improve oxygenation, since additional lung volume is not recruited beyond P CL and the maintenance of P aw or lung volume above this level may simply reflect an overdistending P aw or lung volume. The extent of the lung injury did not improve over time. As noted in table 2 and figures 2 and 3, there were no differences among the data obtained at injury and second baseline. However, we would caution direct extrapolation of our data to patients because ARDS in patients is not a surfactant deficiency problem. Multiple causes account for the development of ARDS, and we have not shown that a similar response would occur in patients.

**Recruitment Maneuver**

Ventilation at a lung volume equal to that at PMC (on the deflation limb of the P-V curve) was insured by using a recruitment maneuver before the random setting of each P aw. As noted in figure 1, the lung volume maintained above FRC at any specific P aw is dependent on whether the P aw is set by going up the inflation limb of the P-V curve or down the deflation limb. In figure 1, a P aw of 26 cm H2O established on the inflation limb resulted in a lung volume of 400 ml above FRC, whereas when the same P aw is established on the deflation limb, lung volume above FRC is 680 ml.

The use of a recruitment maneuver for the purpose of opening the lung and insuring ventilation on the defla-
tion limb of the P-V curve during HFO was first proposed by Kolton et al. They and other investigators set the $P_{aw}$ at 25–30 cm H$_2$O for 10–15 s. We used a $P_{aw}$ of 50 cm H$_2$O for 60 s as a recruitment maneuver. This pressure exceeded $P_{Cl}$ in all animals and insured that a pressure sufficient to open recruitable lung was applied. Because we were using a large animal model (30-kg sheep) compared with the small animals (premature monkeys or 2.5–4.0-kg rabbits) used by other investigators, and because in our pilot data we could not recruit the lung with lower pressures, higher pressures were used. However, in this study and others using this particular lung injury model, recruitment maneuvers at similar pressures could be applied without the development of barotrauma. The use of high-pressure recruitment maneuvers during ARDS has been proposed by numerous groups. Peak alveolar pressures of 40 cm H$_2$O held for 15 s were required by Rothen et al. to recruit healthy lungs after 20 min of general anesthesia. Sjöstrand et al. required peak airway pressure of 55 cm H$_2$O maintained for 5–10 min to recruit lung in a porcine model of ARDS. Fujino et al. found that maximal recruitment required 60 cm H$_2$O peak airway pressure applied for 2 min in a sheep saline lavage ARDS model. In patients with ARDS, Gattinoni et al. reported the need for 46 cm H$_2$O peak airway pressure to recruit collapsed lung, while Amato et al. applied 35–40 cm H$_2$O continuous positive airway pressure for 30–40 s, and Lapinsky et al. applied 40 cm H$_2$O for 20 s to recruit collapsed lung in ARDS patients. None of these studies reported barotrauma or a sustained hemodynamic compromise resulting from the recruitment maneuver.

**Limitations**

The major limitation of this study is that it was performed on a saline lavage injury animal model of ARDS and not in patients. ARDS in patients is rarely, if ever, solely a result of surfactant deficiency. Multiple causes are responsible for primary pulmonary and extrapulmonary ARDS. As a result, the response of the ARDS lung may be very different from that of the saline lavage injured lung. In addition, the P-V curve findings in our model were very consistent across animals; as a result, we cannot conclude that these findings would have been observed if the level of lung injury resulted in markedly different P-V curve results. The steps in $P_{aw}$ evaluated ($P_{Cl}$ + 2, + 6, + 10 and + 14) were large (4 cm H$_2$O), and as a result it is impossible to know if a $P_{aw}$ equal to $P_{Cl}$ + 4 or + 8 would have resulted in better gas exchange than $P_{Cl}$ + 6. This potential clearly affects the strength of the implications of the correlation between $P_{Cl}$ + 6 and PMC. Finally, this was a short-term random application of different $P_{aw}$ values, which prevented us from evaluating the effects of this approach on ventilator-induced lung injury. Consequently, care must be exercised in the extrapolation of these data to humans or other animal models. In addition, the short time frames for which each $P_{aw}$ was applied and the use of each animal as its own control prevented identification of any long-term effects of each $P_{aw}$.

In conclusion, in this saline lavage injury model of ARDS, the optimal $P_{aw}$ during HFO is equal to $P_{Cl}$ + 6, which in this model correlated with the PMC on the deflation limb of the P-V curve. Increases in $P_{aw}$ above $P_{Cl}$ + 6 did not further improve oxygenation but did result in hemodynamic compromise.

**References**