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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 H_2O above the lower corner pressure (P_{CL}) of the inspiratory pressure–volume (P-V) curve of the respiratory system. No equivalent recommendations for the setting of the mean airway pressure (P_{aw}) during high-frequency oscillation (HFO) exist. The authors questioned if the P_{aw} 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 mmHg at a positive end-expiratory pressure of 5 cm H_2O (initial injury). The P_{CL} (20 ± 1 cm H_2O) on the inflation limb and the point of maximum curvature change (PMC; 26 ± 1 cm H_2O) 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 P_{aw} (P_{CL} + 2, + 6, + 10, + 14 cm H_2O), applied in random order. Each cycle was preceded by a recruitment maneuver at a sustained P_{aw} of 50 cm H_2O for 60 s.**

Results: **High-frequency oscillation with a P_{aw} of 6 cm H_2O above P_{CL} (P_{CL} + 6) resulted in a significant improvement in oxygenation ($P < 0.01$ *vs.* initial injury). No further improvement in oxygenation was observed with higher P_{aw}, but cardiac output decreased, pulmonary vascular resistance increased, and oxygen delivery decreased at P_{aw} greater than P_{CL} + 6. The PMC on the deflation limb of the P-V curve was equal to the P_{CL} + 6 ($r = 0.77$, $P < 0.05$).**

Conclusion: **In this model of acute respiratory distress syndrome, optimal P_{aw} during HFO is equal to P_{CL} + 6, which correlates with the PMC.**

HIGH-FREQUENCY oscillation (HFO) has become the standard of care for the ventilatory management of the most critically ill neonates.[1–5] Recently, there has been increased interest in the use of HFO as a rescue therapy for both pediatric[6,7] and adult[8] patients with severe acute respiratory distress syndrome (ARDS).

Conceptually, HFO provides an attractive alternative to conventional mechanical ventilation. By definition, HFO is provided with a lung protective strategy.[9] As discussed by Froese,[9] ventilating pressure during HFO should be kept above the lower corner pressure (P_{CL}) and the peak alveolar pressure below the upper corner pressure (P_{CU}) 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[10] can be avoided using these boundaries. During conventional ventilation, this approach has resulted in decreased pulmonary and systemic inflammatory mediator release[11] and improved mortality[12] 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.[1–8] Oxygenation during HFO is primarily affected by mean airway pressure (P_{aw}),[13,14] with the initial setting determined by the P_{aw} during conventional ventilation.[6–8] We questioned if the P_{aw} 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.) 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-

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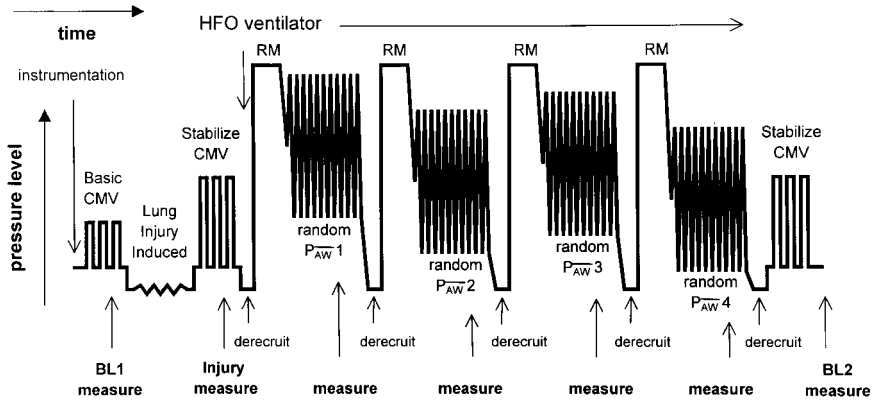

Fig. 1. Schematic providing details of the experimental protocol and the time line for each experiment. HFO = high-frequency oscillation; RM = recruitment maneuver; BL = baseline pressure measurements; CMV = conventional mechanical ventilation; P_{AW} = mean airway pressure.

uous 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 at a respiratory rate of 15 breaths/min, tidal volume of 12 ml/kg, inspiratory to expiratory ratio of 1:2 with an inspiratory plateau time of 0.7 s , fraction of inspired oxygen (F_{IO_2}) of 1.0, and positive end-expiratory pressure (PEEP) of 5 cm H_2O. 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 F_{IO_2} of 1.0 and PEEP of 5 cm H_2O. After establishment of lung injury, another set of measurements (injury) was obtained, and a static P-V curve was measured to identify the P_{CL} and P_{CU} 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: F_{IO_2}, 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 P_{aw} P_{CL} + 2, P_{CL} + 6, P_{CL} + 10, and P_{CL} + 14 cm H_2O, applied in random order. Each cycle was preceded by a recruitment maneuver with a sustained P_{aw} of 50 cm H_2O 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 P_{aw}, the animals were placed back on standard volume control as previously described for 30 min, after which baseline 2 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 ($\dot{Q}s/\dot{Q}t$) was calculated using the standard equation:

$$Qs/Qt = (Cc_{O_2} - Ca_{O_2}) \div (Cc_{O_2} - Cv_{O_2}) \quad (1)$$

and the oxygenation index was calculated using the following formula:

$$OI = (F_{IO_2} \times P_{aw} \times 100) \div Pa_{O_2} \quad (2)$$

Pulmonary Mechanics. Airway pressures proximal and distal to the endotracheal tube were monitored with precision pressure transducers (Model 45-32-871±100;

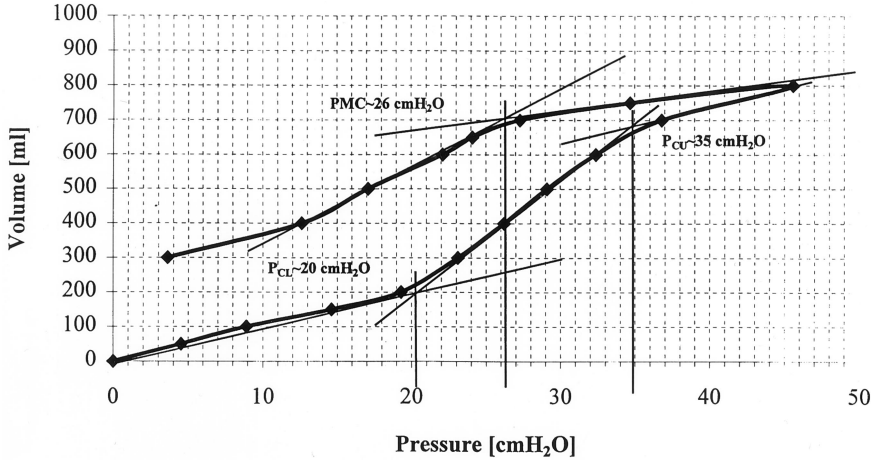

Fig. 2. Representative static pressure volume curve of the total respiratory system in a lung injured sheep, depicting the graphical determination of lower corner pressure (P_{CL}), upper corner pressure (P_{CU}), and point of maximal curvature (PMC).

Validyne, Northridge, CA). 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 H_2O 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 P_{CL} 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 P_{CU}. The PMC was identified as the point of intersection between the slopes of the initial flat and subsequently steep portions of the deflation limb of the P-V curve (fig. 2). P_{CL}, P_{CU}, 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. P_{CL}, P_{CU}, 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 P_{CL} 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/F_{IO_2} (P/F) ratio decreased ($P < 0.01$; fig. 3), $\dot{Q}s/\dot{Q}t$ increased ($P <$

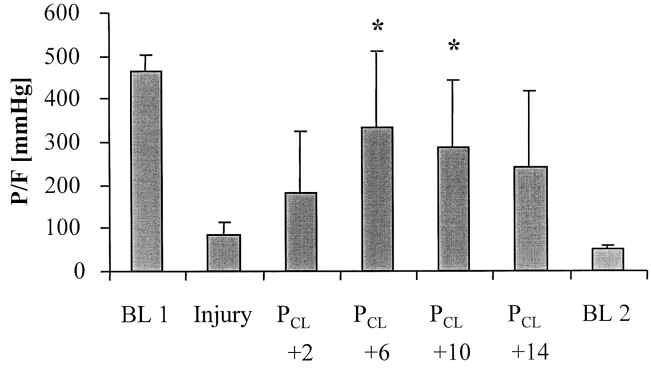

Fig. 3. Arterial oxygen partial pressure/F_{IO_2} (P/F) ratio at baseline 1 (BL 1), injury, four settings for mean airway pressure during high-frequency oscillation (P_{CL} + 2, + 6, + 10, and + 14) and at baseline 2 (BL 2). Mean and SD. *$P < 0.05$ *versus* injury.

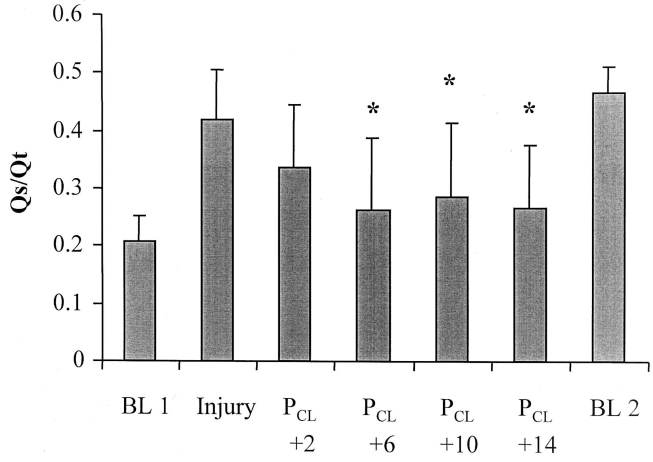

Fig. 4. Venous admixture ($\dot{Q}s/\dot{Q}t$) at baseline 1 (BL 1), injury, four settings for mean airway pressure during high-frequency oscillation (P_{CL} + 2, + 6, + 10, and + 14) and at baseline 2 (BL 2). Mean and SD. *P < 0.05 *versus* injury.

0.01; fig. 4), and plateau airway pressure increased from 19 ± 2 cm H_2O to 27 ± 3 cm H_2O ($P < 0.05$). The P-V relation identified a P_{CL} and PMC at 20 ± 1 cm H_2O and 26 ± 1 cm H_2O, respectively, and a P_{CU} at 38 ± 2 cm H_2O (table 1). There were no differences in any of these values at baseline 2: P_{CL} = 20 ± 2 cm H_2O, PMC = 27 ± 2 cm H_2O, and P_{CU} = 39 ± 2 cm H_2O.

Pulmonary Gas Exchange

Baseline and postinjury (injury) blood gases, oxygenation index, and venous admixture ($\dot{Q}s/\dot{Q}t$) during conventional mechanical ventilation (PEEP = 5 cm H_2O, F_{IO_2} = 1.0) are listed in table 2 and figures 3 and 4. In all animals, ventilation and acid base balance were normal after injury, but the P/F ratio decreased to 85 ± 27 mmHg. With the application of HFO, normocapnia and acid base balance could be maintained with pressure amplitudes of 50–70 cm H_2O. The P/F ratio increased to a maximum at a P_{aw} level of P_{CL} + 6 (26 ± 1 cmH_2O) ($P < 0.05$ *vs.* injury). Increasing P_{aw} to levels of P_{CL} + 10 (30 ± 1 cm H_2O) or P_{CL} + 14 (34 ± 1 cm H_2O) did not further significantly improve the P/F ratio. At P_{CL} + 14, the P/F ratio lost significance *versus* injury. On returning to baseline ventilation after 4 h of HFO (baseline 2), the P/F ratio decreased equivalent to that of injury. The calculated $\dot{Q}s/\dot{Q}t$ showed significant improvement at P_{CL} + 6, P_{CL} + 10 and P_{CL} + 14 *versus* injury (fig. 3). The oxygenation index increased at injury but was not significantly altered from injury during any P_{aw}. However, oxygenation index tended to be lower than injury at P_{CL} + 6.

Hemodynamics and Oxygen Delivery

Heart rate, mean arterial pressure, and oxygen consumption did not change significantly throughout the experiment (table 3). At all P_{aw} levels, the mean pulmonary arterial pressure and pulmonary capillary wedge pressure were significantly elevated *versus* injury ($P < 0.05$), but no differences were observed among settings. Central venous pressure *versus* injury was increased at P_{CL} + 6, P_{CL} + 10, and P_{CL} + 14 ($P < 0.05$; table 3). Stroke volume decreased at P_{CL} + 10 *versus* injury and P_{CL} + 2, and at P_{CL} + 14 *versus* injury, P_{CL} + 2 and P_{CL} + 6 ($P < 0.05$; table 3). Systemic vascular resistance increased at P_{CL} + 14 *versus* P_{CL} + 2 and P_{CL} + 6 ($P < 0.05$; table 3). At P_{CL} + 2 and P_{CL} + 6, cardiac output did not change *versus* injury; however, at P_{CL} + 10 and P_{CL} + 14, cardiac output was significantly lower than at injury, P_{CL} + 2 and P_{CL} + 6 ($P < 0.05$; fig. 5). Pulmonary vascular resistance at injury, P_{CL} + 2, and P_{CL} + 6 was significantly lower than at P_{CL} + 10 and P_{CL} + 14 ($P < 0.05$; fig. 6). The calculated arterial oxygen delivery at P_{CL} + 10 was significantly decreased *versus* injury, P_{CL} + 2, and P_{CL} + 6. At P_{CL} + 14, arterial oxygen delivery was significantly lower than at all preceding settings ($P < 0.05$; fig. 7).

Optimal Mean Airway Pressure and Pulmonary Mechanics

The P_{aw} that resulted in the maximum oxygenation without hemodynamic compromise (P_{CL} + 6, 26.0 ± 1 cm H_2O) was approximately equal to the PMC on the expiratory limb of the P-V curve (26.0 ± 1 cm H_2O; r = 0.77, $P < 0.05$; table 1).

Table 1. Lung Mechanics and Optimal Mean Airway Pressure in Each Animal Studied

Animal	1	2	3	4	5	6	7	Mean	SD
P_{CL} (cm H_2O)	20	20	20	21	19	19	20	20	1
P_{CU} (cm H_2O)	36	36	38	38	40	41	42	39	2
PMC (cm H_2O)	25	26	27	27	25	25	26	26	1
P_{awOPT} (cm H_2O)	26	26	26	27	25	25	26	26	1
V @ P_{CL} (ml)	200	200	300	400	500	280	360	320	109
V @ P_{CU} (ml)	550	680	1,000	940	1,400	800	1,100	924	282
V @ PMC (ml)	570	680	1,100	920	1,350	760	1,000	911	267

All volumes measured at body temperature pressure saturated.

Animal = individual animal studied; P_{CL} = lower corner pressure, P_{CU} = upper corner pressure on the inflation limb of the P-V curve; PMC = point of maximal compliance change on the deflation limb of the P-V curve; P_{awOPT} = optimal mean airway pressure for oxygenation during high-frequency oscillatory ventilation; V @ P_{CL} = lung volume above functional residual capacity at P_{CL}; V @ P_{CU} = lung volume above functional residual capacity at P_{CU}; V @ PMC = lung volume above functional residual capacity at PMC.

Table 2. Gas Exchange Data

	BL 1	Injury	P_{CL} + 2	P_{CL} + 6	P_{CL} + 10	P_{CL} + 14	BL 2
pH_a	7.38 ± 0.04	7.35 ± 0.04	7.32 ± 0.04	7.32 ± 0.06	7.31 ± 0.07	7.31 ± 0.06	7.30 ± 0.04
$Paco_2$ (torr)	41 ± 5	40 ± 2	44 ± 4	44 ± 5	45 ± 6	46 ± 7	47 ± 5
BE_a (mM)	−0.3 ± 0.9	−2.3 ± 2.8	−2.4 ± 2.5	−2.3 ± 2.4	−2.7 ± 2.4	−2.9 ± 2.7	−3.4 ± 2.5
Svo_2 (%)	88.2 ± 4.6	70.9 ± 13.5	72.8 ± 7.3	80.9 ± 6.5	75.4 ± 10.0	67.0 ± 17.5	60.0 ± 8.8*
OI	1.8 ± 0.2	14.3 ± 6.0	20.0 ± 12.5	11.8 ± 10.2	17.0 ± 15.4	27.3 ± 26.3	23.1 ± 4.5

All values are mean ± SD. Scheffé *post hoc* test: * $P < 0.05$ *versus* P_{CL} + 6.

BL = baseline; P_{CL} = lower corner pressure; pH_a = arterial pH; $Paco_2$ = arterial carbon dioxide tension; BE_a = arterial base excess; Svo_2 = mixed venous oxygen saturation; OI = oxygenation index.

Lung Volume above Functional Residual Capacity

The lung volume above functional residual capacity (FRC) at P_{CL} was 320 ± 109 ml, at P_{CU} 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 P_{CU} 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 P_{aw} equal to the P_{CL} + 6 optimized oxygenation without adversely affecting hemodynamics; (2) a P_{aw} of P_{CL} + 2 yielded suboptimal oxygenation; (3) P_{aw} higher than P_{CL} + 6 did not further improve oxygenation but significantly impaired hemodynamics; and (4) the P_{CL} + 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, P_{aw} 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 P_{aw} during HFO can be viewed in a manner similar to the PEEP level in conventional ventilation. The pressure amplitude of the oscillations (ΔP) are attenuated by the endotracheal tube and the conducting airways.[8] According to Fort *et al.*,[8] the SensorMedics 3100B high-frequency oscillator generates a pressure amplitude across a 8.0-mm endotracheal tube at a frequency of 5 Hz that is approximately 15% of the pressure amplitude measured proximal to the tube. As frequency increases, a greater percentage of the pressure amplitude is dissipated across the endotracheal tube. As a result, tidal recruitment as seen in conventional ventilation becomes negligible in HFO.[9] Therefore, the P_{aw} during HFO that results in optimal oxygenation should be predictable from the P-V curve in a manner similar to that observed with PEEP in conventional ventilation.

During conventional ventilation, a PEEP equal to the P_{CL} + 2 has been shown to be effective in minimizing lung injury[10] and pulmonary[11] and systemic mediator activation[11] and has been attributed to improving mortality.[12] We have shown that a higher P_{aw} was needed in HFO to optimize oxygenation. The reason for this difference may be the presence of tidal recruitment during conventional ventilation[16] and the lack of tidal recruitment during HFO.[9] The small tidal volumes during HFO may be unable to replenish the lung volume lost to reabsorption atelectasis because of $\dot{V}/\dot{Q}$ mismatch or alveolar instability that conventional ventilation can, and thus the need for a higher P_{aw} 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 (P_{CL}) 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,[16] the P_{CL} may simply represent the airway pressure where recruitment of collapsed lung units begins, with recruitment continuing

Table 3. Systemic and Pulmonary Hemodynamics

	BL 1	Injury	P_{CL} + 2	P_{CL} + 6	P_{CL} + 10	P_{CL} + 14	BL 2
HR (min^{-1})	128 ± 16	143 ± 14	149 ± 29	152 ± 19	144 ± 15	137 ± 10	156 ± 21
MAP (mmHg)	111 ± 4	111 ± 10	102 ± 8	103 ± 13	97 ± 15	96 ± 16	101 ± 13
PAP (mmHg)	16 ± 3	16 ± 2	21 ± 3*	23 ± 5*	24 ± 5*	25 ± 4*	20 ± 4
PCWP (mmHg)	9 ± 3	6 ± 2	10 ± 3*	11 ± 3*	12 ± 3*	13 ± 3*	9 ± 4
CVP (mmHg)	6 ± 2	6 ± 3	8 ± 2	10 ± 3*	10 ± 3*	11 ± 2*†	7 ± 2
SV (ml)	28 ± 3	25 ± 2	24 ± 3	24 ± 5	18 ± 2*†	17 ± 2*†‡	27 ± 6
SVR ($dyn \cdot s \cdot cm^{-5}$)	2,410 ± 108	2,409 ± 184	2,152 ± 171	2,171 ± 235	2,742 ± 249	3,040 ± 212†‡	1,926 ± 201
Vo_2 (ml/min)	89 ± 20	94 ± 30	111 ± 37	101 ± 28	82 ± 27	85 ± 27	91 ± 25

All values are mean ± SD. Scheffé *post hoc* test: * $P < 0.05$ *versus* Injury, † $P < 0.05$ *versus* P_{CL} + 2, ‡ $P < 0.05$ *versus* P_{CL} + 6.

BL = baseline; P_{CL} = 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; Vo_2 = oxygen consumption.

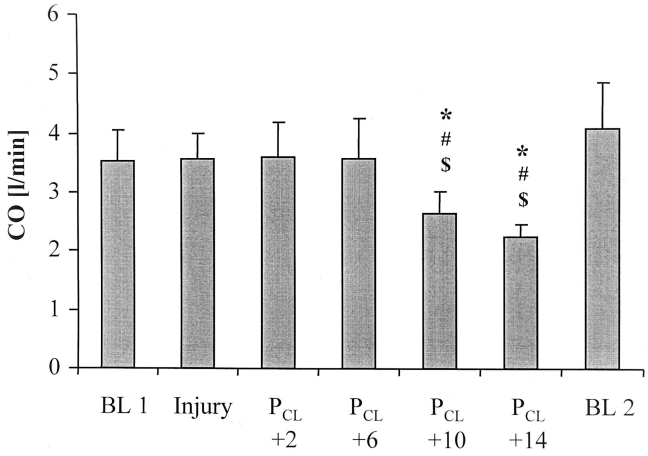

Fig. 5. Cardiac output (CO) at baseline 1 (BL 1), injury, four settings for mean airway pressure during high-frequency oscillation (P_{CL} + 2, + 6, + 10, and + 14) and at baseline 2 (BL 2). Mean and SD. **P* < 0.05 *versus* injury, #*P* < 0.05 *versus* P_{CL} + 2, $*P* < 0.05 *versus* P_{CL} + 6.

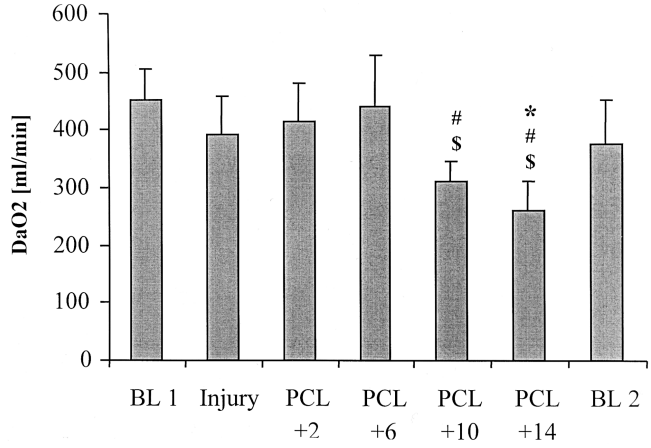

Fig. 7. Oxygen delivery (Dao_2) at baseline 1 (BL 1), injury, four settings for mean airway pressure during high-frequency oscillation (P_{CL} + 2, + 6, + 10, and + 14) and at baseline 2 (BL 2). Mean and SD. **P* < 0.05 *versus* injury, #*P* < 0.05 *versus* P_{CL} + 2, $P < 0.05 *versus* P_{CL} + 6.

throughout inflation until the P_{CU} is established. The change in slope at the P_{CU} may represent the airway pressure causing overdistension[17] or, as proposed by Hickling, may simply represent the airway pressure where recruitment during inflation decreases or stops.[16] 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[16] 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,[16] P_{aw} above PMC would not be expected to further improve oxygenation, since additional lung volume is not recruited beyond P_{CU} 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 difference 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.

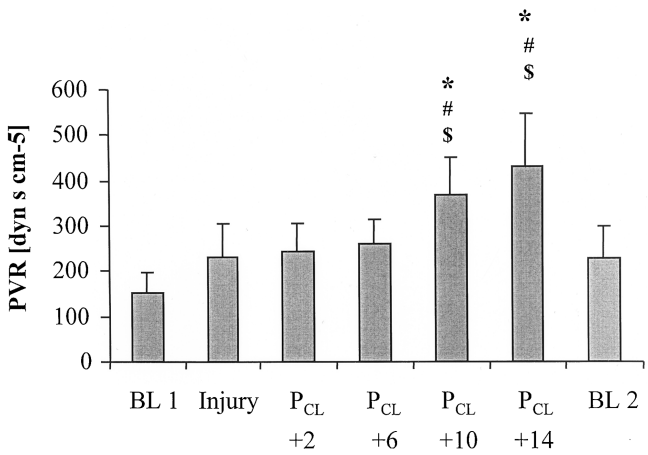

Fig. 6. Pulmonary vascular resistance (PVR) at baseline 1 (BL 1), injury, four settings for mean airway pressure during high-frequency oscillation (P_{CL} + 2, + 6, + 10, and + 14) and at baseline 2 (BL 2). Mean and SD. **P* < 0.05 *versus* injury, #*P* < 0.05 *versus* P_{CL} + 2, $*P* < 0.05 *versus* P_{CL} + 6.

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 H_2O 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.*[18] They and other investigators[14,19,20] set the P_{aw} at 25–30 cm H_2O for 10–15 s. We used a P_{aw} of 50 cm H_2O for 60 s as a recruitment maneuver. This pressure exceeded P_{CU} 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[20] or 2.5–4.0-kg rabbits[14,18,19]) 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[21] 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.[12,21–24] Peak alveolar pressures of 40 cm H_2O held for 15 s were required by Rothen *et al.*[22] to recruit healthy lungs after 20 min of general anesthesia. Sjöstrand *et al.*[23] required peak airway pressure of 55 cm H_2O maintained for 5–10 min to recruit lung in a porcine model of ARDS. Fujino *et al.*[21] found that maximal recruitment required 60 cm H_2O peak airway pressure applied for 2 min in a sheep saline lavage ARDS model. In patients with ARDS, Gattinoni *et al.*[24] reported the need for 46 cm H_2O peak airway pressure to recruit collapsed lung, while Amato *et al.*[12] applied 35–40 cm H_2O continuous positive airway pressure for 30–40 s, and Lapinsky *et al.*[25] applied 40 cm H_2O 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_2O), 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.

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