

# Specific compliance and gas exchange during high-frequency oscillatory ventilation

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**Objectives:** To evaluate the use of specific compliance (static compliance/functional residual capacity) to adjust mean airway pressure, resulting in optimal gas exchange during high-frequency oscillatory ventilation in a surfactant-deficient newborn piglet.

**Design:** Prospective controlled animal study.

**Setting:** Laboratory.

**Subjects:** Eight newborn piglets at 5 days of age.

**Background:** High-frequency oscillatory ventilation enables the use of relatively high mean airway pressures without the lung damage associated with conventional positive pressure ventilation. Mean airway pressures can be increased, resulting in static lung expansion that approaches total lung capacity with its negative impact on venous return. Therefore, knowledge of lung volume is important for safe patient management. A simple, noninvasive technique to enable the clinician to determine the optimal mean airway pressure likely would improve patient management.

**Interventions:** The lungs were lavaged after placement of central catheters and tracheostomy to lower respiratory system compliance and worsen ventilation perfusion matching. The animals were ventilated with high-frequency oscillatory ventilation at the same mean airway pressure as before lung lavage. Mean airway pressures then were increased in a step-wise fashion up to 30 cm H<sub>2</sub>O or until clinical deterioration occurred. All other ventilator variables, F<sub>IO<sub>2</sub></sub>, frequency, and pressure amplitude were constant throughout the experiment.

**Measurements and Main Results:** Before lavage and at each level of mean airway pressure after lung lavage, respiratory

system compliance and functional residual capacity were measured. Additionally, central arterial pressure, central venous pressure, heart rate, arterial blood gas, and pulse oximetric saturation were recorded. Lung lavage significantly lowered respiratory system compliance (static as well as specific compliance) and worsened ventilation perfusion matching as evidenced by an increase in Paco<sub>2</sub> and a decreased arterial to alveolar oxygen ratio. With increasing mean airway pressures, static/specific compliance improved and then peaked before declining, functional residual capacity increased, and blood gas improved until reaching the flat portion of the pressure-volume relationship of the lung. Optimal gas exchange as reflected by the highest arterial to alveolar oxygen ratio and lowest Paco<sub>2</sub> at constant ventilation was found at a mean airway pressure that maintained the functional residual capacity and static respiratory system compliance at the same level as the preinjury levels ("normalized" functional residual capacity and respiratory system compliance).

**Conclusions:** These results suggest that specific compliance measurement that incorporates static respiratory system compliance and functional residual capacity during high-frequency oscillatory ventilation can be used to adjust mean airway pressure and achieve "normalized" functional residual capacity, static compliance, and gas exchange. These measurements may provide a simple method to optimize lung volume in a surfactant-deficient patient during high-frequency oscillatory ventilation. (Crit Care Med 2002; 30:1523-1527)

**KEY WORDS:** high-frequency oscillatory ventilation; functional residual capacity; compliance; surfactant deficient

**H**igh-frequency oscillatory ventilation (HFOV) is used frequently in infants with respiratory distress syndrome as well as in other forms of respiratory failure. Without larger tidal breaths, HFOV allows the use of relatively high mean airway pressure (MAP) with-

out the lung volutrauma associated with the positive pressure breaths of conventional mechanical ventilation. Because MAP can be raised to levels that would bring lung expansion to near total lung capacity and result in decreased venous return (1) and increased epithelial permeability (2), assessment of lung volume is important for safe management of these patients. Too low a lung volume also has been associated with increased lung injury in both human and animal trials (3, 4). Targeting lung volume rather than gas exchange alone may improve survival in patients with acute hypoxic respiratory failure (5, 6). Currently, the usual method for assessing lung volume during HFOV is by chest radiograph.

If other noninvasive bedside techniques were available to assist the clinician in determining optimal MAP, patient care and outcome could improve.

Functional residual capacity (FRC) measures resting lung volume at the end of expiration and can be measured noninvasively at the bedside. In this study we examined the physiologic interaction between MAP, respiratory system compliance (static Crs), and FRC. In this study, FRC was defined as the lung volume at mean distending pressure during HFOV. The relationship of these variables to measures of gas exchange in surfactant-deficient newborn piglets during HFOV also was examined. We hypothesized that during HFOV, compliance would be

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greatest at a lung volume of "normalized" FRC or when FRC becomes within normal range. We expected to find low compliance in both underinflated lungs (because of atelectasis and the pressure costs of overcoming surface active forces) and overinflated lungs (because of decreased tissue elastance in distended parenchyma). We speculated that the pressure for "ideal" lung volume in a mechanical sense could be predicted. This ideal lung volume is defined as the point where the compliance of the respiratory system was greatest and where ventilation perfusion matching would be optimum. If the measurement of compliance during HFOV allowed clinicians to determine optimum lung volume and optimum gas exchange, a valuable tool would be added to the clinician's arsenal. The objective of this study was to evaluate use of specific compliance (static Crs/FRC) to adjust MAP and provide optimal gas exchange during HFOV in a surfactant-deficient newborn piglet.

## MATERIAL AND METHODS

Eight term newborn Yorkshire piglets were used in this study. They were chosen because of our experience with this species and because of their similarities with preterm newborn infants with respect to size, cardiopulmonary function, and pulmonary mechanics. The animals ranged in weight from 2000 to 3000 g (mean 2288 g), and were all healthy at the time of the study. Eastern Virginia Medical School's Institutional Review Board and Animal Care Committee approved our experimental protocol.

The piglets were anesthetized by using ketamine, 30 mg/kg intramuscularly. The carotid artery and the internal jugular vein were cannulated to facilitate pressure measurements. Continuous infusion of 2–7 mg·kg<sup>-1</sup>·hr<sup>-1</sup> ketamine provided sedation. In some cases, additional bolus doses of ketamine were administered. The central venous catheter was maintained by using a 5% dextrose/water infusion at a rate of 75 mL·kg<sup>-1</sup>·day<sup>-1</sup>. An uncuffed endotracheal tube (4.0, NCC Division Mallinckrodt, St. Louis, MO) was placed by tracheotomy and tied with umbilical tape to secure the tube and eliminate airleak. Arterial pressure and central venous pressure waveforms were monitored continuously (SpaceLabs 90303B, Redmond, WA), as was arterial saturation, by using pulse oximetry (Nellcor, Seattle, WA). Arterial blood gas (Corning 288, Medfield, MA) was obtained in four animals after ventilator changes. Pulmonary function was measured by using a computerized (SensorMedics 2600, Yorba Linda, CA) pulmonary function cart. The SensorMed-

ics 2600 measures static respiratory system compliance and resistance with a single occlusion passive respiratory technique as described by LeSuef et al. (7). The methodology and the performance of this system have been described and validated previously (8), and the system has been used frequently to measure respiratory mechanics in ventilated newborn infants (9–12). The functional residual capacity measurement on the SensorMedics 2600 is based on the constant-flow nitrogen washout method as described by Gerhardt et al. (13). This technique also has been validated in ventilated infants and children (14, 15).

HFOV was provided by using a 3100A high-frequency oscillatory ventilator (SensorMedics, Yorba Linda, CA). This device uses an electromagnetically driven piston/diaphragm to generate active inspiratory and expiratory phases of respiration. The 3100A has independent settings for MAP (3–45 cm H<sub>2</sub>O) and wave amplitude (0–95 cm H<sub>2</sub>O), monitored at the airway opening, as well as adjustments for percentage of inspiratory time (30% to 50%) and frequency (3–15 Hz). The piglets' temperatures were servo-regulated in an infant transport incubator (Healthdyne TI-11, Marietta, GA). The animals were stabilized at MAP of 6, amplitude of 13 cm H<sub>2</sub>O, frequency of 10 Hz, and inspiratory time of 33%. Once animals were stabilized, baseline compliance and functional residual capacity were measured. Baseline blood gases, serum electrolytes, ionized calcium, hemoglobin, hematocrit, and serum glucose also were measured. These measurements were repeated during the experiment to assess subject stability. In preliminary experiments (data not included), pulmonary function tests were performed at 15, 30, 45, and 60 mins after changes in MAP with constant pressure amplitude, frequency, and FIO<sub>2</sub>. The results of this experience demonstrated that stable values were uniformly achieved by 15 mins. Therefore, all pulmonary function test measurements after changes in MAP in this study were made at 15 mins.

The piglets then were removed from the ventilator and their lungs were repeatedly lavaged (three to five times) with 15 mL/kg warm (37°C) normal saline while the animal was rotated gently from side to side, as described by Lachmann (16) until lung compliance decreased by ≥50% from baseline values. After another period of stabilization, the piglets were placed on HFOV at a MAP of 6 cm H<sub>2</sub>O, the same as before lung lavage. MAP then was increased in a stepwise fashion until a MAP of 30 cm H<sub>2</sub>O was reached or clinical deterioration occurred. All other ventilator variables, FIO<sub>2</sub>, frequency, inspiratory time, and pressure amplitude remained constant throughout the experiment. The testing procedures were repeated at each MAP.

All statistical analyses were performed by using SAS/STAT software (SAS Institute, Cary, NC). For descriptive purposes, mean and sd are provided. To describe changes during HFOV with increasing airway pressure, we calculated the percentage change from baseline value. Compared with the prelavage baseline, we analyzed to what extent pulmonary function tests and blood gas characteristics changed after lavage in the course of HFOV with different levels of MAP. A value that was not statistically different from the baseline (Student's *t*-test) indicated that pulmonary function tests and blood gas characteristics were similar to the prelavage level. Multivariate analysis of variance procedures were used to investigate changes in the response after lavage for heart rate, blood pressure, and central venous pressure.

## RESULTS

Mean baseline FRC was 18.46 ± 4.94 mL/kg on HFOV (Table 1). After lung lavage, at a MAP of 6 cm H<sub>2</sub>O, FRC decreased 26.9% to 13.87 ± 4.39 mL/kg. Increasing MAP on HFOV to 10 cm H<sub>2</sub>O returned the FRC back to 18.28 ± 5.82 mL/kg. Figure 1 demonstrates the relationship of FRC to MAP throughout the ramped MAPs on HFOV. The linear relationship can be defined by FRC/kg = 1.38 × airway pressure + 6 (*r* = .923).

Baseline static compliance was 0.83 ± 0.30 mL·cm H<sub>2</sub>O<sup>-1</sup>·kg<sup>-1</sup> on HFOV (Table 1) and decreased to 0.35 ± 0.17 mL·cm H<sub>2</sub>O<sup>-1</sup>·kg<sup>-1</sup> after lavage. A MAP of 10 cm H<sub>2</sub>O returned the static compliance to the prelavage value of 0.86 ± 0.26 mL·cm H<sub>2</sub>O<sup>-1</sup>·kg<sup>-1</sup>. With increasing MAP, static compliance reached a plateau and decreased beyond a MAP of 15 cm H<sub>2</sub>O (Figure 1). Intersubject coefficient of variation was between 0.10 and 0.43 for both FRC/kg (mean, 0.248; SEM, 0.015) and Crs/kg (mean, 0.33; SEM, 0.025). Intrasubject variance in plateau pressures during occlusion was mean coefficient of variation = 5.24 ± 3.2%, and variance in FRC was mean coefficient of variation = 3.1 ± 2.4%. Specific compliance, static Crs normalized by the measured FRC, showed a more precipitous decrease from baseline to postlavage (44 to 23.8 mL·cm H<sub>2</sub>O<sup>-1</sup>·L<sup>-1</sup>); specific compliance peaked at a MAP of 13 cm H<sub>2</sub>O and then decreased sharply above 15 cm H<sub>2</sub>O, as seen in Figure 2.

Changes in pH, PaCO<sub>2</sub>, and arterial to alveolar (a/A) oxygen ratio are presented in Figure 2. Oxygen saturation was nearly 100% throughout the experiments. There appeared to be an inverse relationship

Table 1. Postlavage changes with increasing mean airway pressure

	Postlavage							
	Baseline 6 cm H <sub>2</sub> O	% Change 6 cm H <sub>2</sub> O	% Change 10 cm H <sub>2</sub> O	% Change 13 cm H <sub>2</sub> O n = 4	% Change 15 cm H <sub>2</sub> O	% Change 20 cm H <sub>2</sub> O	% Change 25 cm H <sub>2</sub> O	
Static compliance, Crs/kg	0.83 (0.30)	-59.2 (9.4) <sup>a</sup>	8.29 (20.5)	47.1 (51.3)	60.9 (36.2) <sup>a</sup>	62.1 (47.2) <sup>a</sup>	59.76 (77.2)	
Functional residual capacity, FRC/kg	18.46 (4.94)	-26.9 (9.8) <sup>a</sup>	-3.03 (9.3)	12.3 (11.8)	41.6 (23.8) <sup>a</sup>	90.4 (35.7) <sup>a</sup>	119.4 (31.7) <sup>a</sup>	
Specific compliance, Crs/FRC	45.15 (10.48)	-42.1 (14.4) <sup>a</sup>	13.7 (41.7)	31.9 (50.4)	17.4 (37.0)	-14.2 (35.2)	-27.9 (42.1)	
Paco <sub>2</sub> , torr n = 4	35.75 (7.41)	15.4 (23.7)	-8.54 (30.9)	9.59 (40.52)	33.4 (48.0)	67.6 (29.0) <sup>a</sup>	102 (50.8) <sup>a</sup>	
a/AO <sub>2</sub> ratio n = 4	0.56 (0.17)	-60.7 (2.9) <sup>a</sup>	0.03 (27.0)	-12.5 (32.2)	-10.3 (28.9)	-15.0 (30.0)	-18.5 (20.5)	
pH n = 4	7.44 (0.06)	-2.1 (1.2) <sup>a</sup>	0.2 (1.1)	-0.64 (1.4)	-1.78 (1.3)	-2.92 (0.6) <sup>a</sup>	-4.0 (0.9) <sup>a</sup>	

	Postlavage							
	Baseline 6 cm H <sub>2</sub> O	Post-lavage 6 cm H <sub>2</sub> O	% Change 10 cm H <sub>2</sub> O	% Change 13 cm H <sub>2</sub> O n = 4	% Change 15 cm H <sub>2</sub> O	% Change 20 cm H <sub>2</sub> O	% Change 25 cm H <sub>2</sub> O	F <sup>b</sup> (p)
Heart rate, min <sup>-1</sup>	220.9 (54.3)	195.6 (34.2)	0.6 (17.5)	6.6 (24.4)	-5.6 (13.0)	0.5 (17.1)	7.1 (18.4)	2.66 (.18)
Blood pressure, mm Hg	90 (12.9)	71.9 (11.3)	-4.1 (8.5)	8.3 (11.1)	3.8 (7.9)	7.2 (8.6)	5.1 (15.3)	2.98 (.20)
Central venous pressure, mm Hg	4 (1.29)	3.86 (1.2)	26.0 (41.5)	42.5 (43.5)	57.2 (67.3)	87.9 (85.0) <sup>c</sup>	124.3 (116.0) <sup>c</sup>	33.7 (.029) <sup>c</sup>

<sup>a</sup>p ≤ .05 paired t-test; <sup>b</sup>Multivariate analysis of variance-based responses derived at 10, 15, 20, and 25 cm H<sub>2</sub>O; <sup>c</sup>p ≤ .05.

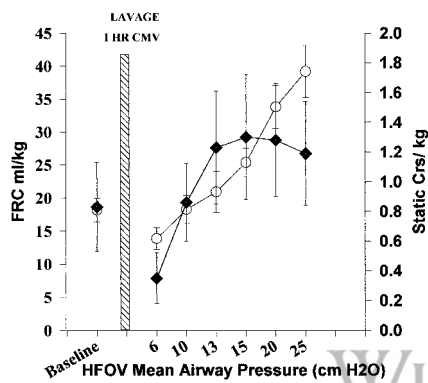


Figure 1. Effect of varying mean airway pressure on static respiratory system compliance (Crs)/kg (mean ± SEM) and functional residual capacity (FRC)/kg (mean ± SEM) at baseline and after lung lavage during high-frequency oscillatory ventilation (HFOV). CMV, conventional mechanical ventilation.

between Paco<sub>2</sub> and specific compliance. Paco<sub>2</sub> was lowest at a MAP of 10 cm H<sub>2</sub>O and increased significantly after 15 cm H<sub>2</sub>O. The pH had an inverse response, being highest at 10 cm H<sub>2</sub>O and falling to near 7.10 at the highest levels of MAP. The a/A oxygen ratio, as an index of oxygenation, was also highest at the 10 cm H<sub>2</sub>O level.

Although mean arterial blood pressure and heart rate decreased after lung lavage, there was no significant change with increasing MAP until airway pressures exceeded 25 cm H<sub>2</sub>O (Table 1). At ≥25 cm H<sub>2</sub>O, most of the animals became hemodynamically unstable and experienced significant decreases in specific

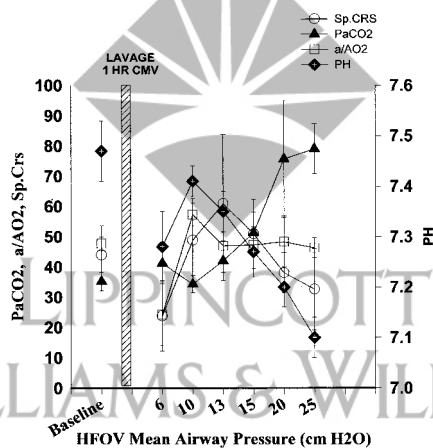


Figure 2. Effect of increasing mean airway pressure on specific compliance (Sp,Crs), pH, Paco<sub>2</sub>, and arterial to alveolar oxygen (a/AO<sub>2</sub>) ratio as mean ± SEM at baseline and after lung lavage. CMV, conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation.

compliance and pH whereas Paco<sub>2</sub> increased. Central venous pressures increased linearly from 4.0 to 7.5 mm Hg as MAP increased from 6 to 25 cm H<sub>2</sub>O. Limited data from the only animal stable enough at 30 cm H<sub>2</sub>O for measurements are not included.

## DISCUSSION

The low variability among animals in measurements of compliance and FRC was striking and supports the reproducibility of the model. This was reflected not only by similar compliance, normal-

ized for body weight after lavage, but by an intersubject coefficient of variation of between 0.10 and 0.43 for both FRC/kg and Crs/kg. Because the SensorMedics 2600, in manual operation, occludes the airway for compliance measurements and switches for FRC measurements at unspecified points in the oscillator cycle, we anticipated that intrasubject variability might be increased in these measurements because of the variability in the lung volume at this point in the ventilatory cycle. Gerstmann et al. (17) reported on the attenuation of the oscillatory pressure wave from the airway opening to the alveoli by using alveolar capsules in an animal model. They found that the pressure swing at the airway opening diminished to approximately one-tenth its value at the alveolar level. Based on our amplitude of 13 cm H<sub>2</sub>O, we expected the maximum variance in alveolar pressure at any MAP would be ≤1.3 cm H<sub>2</sub>O. This finding was demonstrated by the low intrasubject variance in plateau pressures during occlusion as well as the low variance in FRC when we initiated tests at unspecified airway pressures.

The linear relationship found between MAP and FRC has been demonstrated in previous studies for both spontaneously breathing and mechanically ventilated subjects (18–20). The baseline FRC measurements were within the normal expected range for newborn piglets based on both published and unpublished data (21 and personal communication). The decrease

in FRC after lavage appeared as expected attributable to the reduction in surfactant and alveolar instability, both of which decrease compliance, resulting in the loss of lung volume.

Compliance changes with loss of surfactant have been well documented in both animal and human data, so that the decreases in both compliance and specific compliance also were expected (9, 10, 22). With a stepwise increase in MAP, compliance increased, reached a plateau, and then decreased as the lung reached the top, flat portion of the pressure-volume curve. The low compliance in the underinflated lungs has been related to the atelectasis and the pressure costs of overcoming surface forces of reexpansion. Bond and Froese (23) found that critical opening pressure in lavaged animals was around 10 cm H<sub>2</sub>O. Similarly, the low compliance in the overinflated lungs attributable to decreased tissue elastance in distended parenchyma as the lung reaches near total lung capacity was expected. The plateau of static compliance between 13 and 15 cm H<sub>2</sub>O coincides with the linear portion of the pressure-volume curve.

The blood gas results as reflected by a/A oxygen ratio and Paco<sub>2</sub> show that the best gas exchange occurred at around 10 cm H<sub>2</sub>O MAP. At this level, there was the highest a/A oxygen ratio and lowest Paco<sub>2</sub>. At this MAP, ventilation/perfusion matching appears to be optimized. Schindler and Seear (24) demonstrated that high-frequency oscillation effectively decouples oxygenation from carbon dioxide removal in the lavaged animal model and that CO<sub>2</sub> removal is a function of amplitude times frequency and is independent of MAP. With the settings of frequency and amplitude unchanged, the lowered Paco<sub>2</sub> at any specific MAP would suggest that there is optimized matching for CO<sub>2</sub> flux from the blood. Although the system's deadspace, approximately 1.8 mL, potentially could cause a small increase in Paco<sub>2</sub> during the time required to make measurements, during our experiments this did not appear to be a significant problem.

Suter et al. (25), in their work on optimal positive end-expiratory pressure (PEEP), also demonstrated that the PEEP at which compliance was highest was the level at which oxygen delivery was greatest as defined by oxygen content times cardiac output. They defined this pressure as the "best PEEP" and reasoned that in patients with a markedly de-

creased FRC, there was indeed an optimal level of positive pressure that produced the greatest cardiopulmonary benefit. They suggested that this optimal level was when tidal ventilation was situated on the steepest part of the patient's pressure-volume curve. The other index reported in that study was the deadspace to tidal volume ratio, which was low at the point of optimal oxygen transport. The explanation for this relationship was that as atelectatic alveoli were rerecruited, improvements in ventilation to these perfused (previously shunted) units added to the overall gas exchange and decreased deadspace to tidal volume ratio. At higher levels of PEEP, the overdistension of these alveoli decreased perfusion as a result of the high intra-alveolar pressure that forced blood from the capillary bed and the decrease in cardiac output.

Our results are consistent with these findings, because our index of oxygenation, the a/A oxygen ratio, was also highest at the beginning of the compliance plateau. With stable cardiovascular measurements at this pressure level, it could be suggested that this also coincided with optimal oxygen transport. Although measurement techniques for deadspace to tidal volume ratio during HFOV have not been developed, the significant nadir in Paco<sub>2</sub> at this same level would suggest that for a constant ventilation (amplitude and frequency), a decrease in Paco<sub>2</sub> must be related to a functional decrease in deadspace to tidal volume ratio. The increase in Paco<sub>2</sub> and decrease of a/A oxygen ratio as MAP continued to increase beyond the "optimal MAP" suggest a worsening of ventilation/perfusion matching as the vascular bed was compressed.

The hemodynamic effects of increasing MAP during conventional mechanical ventilation have been well documented and may be secondary to a reduction in cardiac output that results from decreased venous return produced by increased intrathoracic pressure and subsequent decrease in right ventricular preload (26). The hemodynamic effects also may be secondary to an increase in right ventricular afterload evidenced by an increased pulmonary vascular resistance, and they may cause reflex neuronal (27) or humoral suppression of cardiac output (28). Work performed in animals ventilated with conventional mechanical ventilation and HFOV has shown a linear relationship between increased MAP and decreased cardiac output when

**T**hese measurements may provide a simple method to optimize lung volume in a surfactant-deficient patient during high-frequency oscillatory ventilation.

respiratory compliance is normal. However, when compliance is decreased, this relationship shifts and manifests only when higher airway pressures are applied (29, 30). Cardiac output and venous return are inextricably interdependent, and therefore, except for small transient disparities, the heart is unable to pump any more blood than is delivered to it through the venous system. The elevations in MAP would be expected to increase intrathoracic pressure and reduce preload by diminished venous return (31). In our study, central venous pressure increased linearly with increased MAP whereas heart rate did not change significantly as has been shown previously (30); however, we did not measure cardiac output. Decreased cardiac output has been attributed to reduction in stroke volume with increasing MAP. However, the occurrence of cardiac depression during HFOV is not a common clinical problem in infants with RDS (32).

Considering the previous work done on PEEP in respiratory failure, the finding that the "optimal MAP" occurred at a normal FRC has not been previously reported. Although the goal of PEEP therapy is to increase FRC to improve oxygenation, the question remains as to what is the optimal FRC. It seems that although normal FRC is determined by the balancing of mechanical forces of the respiratory system, it also coincides with optimal gas exchange. A limitation of our study is that we did not evaluate correlation between chest radiograph and FRC. However, from our study one can speculate a reduced need for frequent chest radiographs to assess optimum lung volume by using pulmonary lung function measurements to optimize MAP during HFOV.

## CONCLUSIONS

We found a linear relationship between MAP and FRC. Specific compliance (static Crs/FRC) normalized (i.e., reached prelavaged values) at a MAP of 10 cm H<sub>2</sub>O. A MAP of 10 cm H<sub>2</sub>O was associated with the highest a/A oxygen ratio, highest pH, and lowest PaCO<sub>2</sub>. Increases in MAP above 15 cm H<sub>2</sub>O significantly decreased compliance as the lung reached the flat portion of the recorded static pressure-volume curve. Heart rate and mean arterial blood pressures did not change significantly with increasing MAP until MAPs exceeded 25 cm H<sub>2</sub>O.

Based on the relationships between MAP, compliance, functional residual capacity, and indexes of ventilation/perfusion matching, we conclude that increasing MAP to achieve normal FRC or until the compliance or specific compliance (if FRC measurements are available) reaches a plateau (or peaks) is a simple method of optimizing lung volume in surfactant-deficient subjects. The additional safety considerations of avoiding overdistension from excessive MAP and its associated deleterious effect on cardiovascular function and increased alveolar permeability speak for the value of this measurement. The simplicity of the pulmonary mechanics measurement may make it a useful clinical tool for managing infants on HFOV.

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