Respiratory Mechanics During High Frequency Oscillatory Ventilation:  
*A Physical Model and Preterm Infant Study*

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**Running title:** Infant lung mechanics during HFOV

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Abstract

Accurate mechanics measurements during high frequency oscillatory ventilation (HFOV) facilitate optimizing ventilator support settings. Yet, these are substantially influenced by endotracheal tube (ETT) contributions which may dominate when leaks around uncuffed ETT are present. We hypothesized that 1) the effective removal of ETT leaks may be confirmed via direct comparison of measured versus model-predicted mean intra-tracheal pressure (mPtr); and 2) reproducible respiratory system resistance (Rrs) and compliance (Crs) may be derived from no-leak, oscillatory Ptr and proximal flow. Using ETT - test lung models, proximal (Pao) and distal (Ptr) pressures and flows were measured during slow cuff inflations until leaks are removed. These were repeated for combinations of HFOV settings [Frequency, mean-airway-pressure (Paw), oscillation amplitudes (ΔP) and inspiratory time (%tI)] and varying Test-Lung compliance. Results showed that leaks around the ETT will 1) systematically reduce the effective distending pressures and lung-delivered oscillatory volumes, and 2) derived mechanical properties are increasingly non-physiologic as leaks worsen. Mean pressures were systematically reduced along the ventilator circuit and ETT (Paw > Pao > Ptr) even for no leak conditions. ETT size-specific regression models were then derived for predicting mPtr based on: mean Pao, ΔPao, %tI and Frequency. Next, in 10 of 11 studied preterm infants (0.77±0.24 kg), no-to-minimal leak was confirmed based on excellent agreement between measured and model-predicted mPtr and, consequently, their oscillatory respiratory mechanics were evaluated. Infant resistance at the proximal ETT (Rao=R_{ETT}+Rrs; p<0.001) and ETT inertance (I_{ETT}; p=0.014) increased significantly with increasing oscillation amplitude (ΔP = 50%, 100% and 150% baseline) whereas Rrs showed a modest non-significant increase (p=0.14) and Crs was essentially unchanged (p=0.39). We conclude that verifying no-leak conditions is feasible by comparison of
model-derived versus measured mean distending Ptr. This facilitated the reliable and accurate assessment of physiologic respiratory mechanical properties that can objectively guide ventilatory management of HFOV-treated preterm infants.

**Key Words:** mechanical ventilation, endotracheal tube leak, tracheal pressure monitoring, very low birth weight
INTRODUCTION

High frequency oscillatory ventilation (HFOV) is used to provide mechanical ventilatory support to preterm infants in respiratory failure. Frequently, this is done after less invasive approaches or conventional mechanical ventilation modalities have failed. [2, 3] The best oxygenation and ventilation outcomes with HFOV are usually achieved when small amplitude, high frequency (5–15 Hz) mechanical breaths are delivered at optimal lung volume.[7] The infant’s functional lung volume is varied by the application of positive distending pressure at the airway opening (Paw; mean airway pressure).[7,23] The oscillatory tidal volume breath is defined by the pressure oscillation amplitude (ΔP), inspiratory time and frequency settings on the ventilator as well as by the mechanical properties of the underlying load [infant + endotracheal tube (ETT)]. This relationship also provides the basis to assess respiratory mechanics in infants treated with this ventilator from HFOV pressure-flow data. [7,11,23-5]

In theory, respiratory mechanics measurements, if readily available and accurate, provide the objective quantitative means to manage infants on HFOV. However, their use in neonates is compromised by the unpredictable errors introduced by the possible substantial and variable leaks around the uncuffed ETT which are used to decrease cuff-related risk of tracheal tissue necrosis. The Paw and ΔP settings on HFOV will overestimate the true delivered lung distending pressure and oscillation amplitudes as ETT leaks increase [10] and, therefore, the derived respiratory mechanical properties [e.g., resistance (Rrs) and Compliance (Crs)] under such conditions are of little physiologic value and will be dominated by the ETT mechanical properties.[21]

We hypothesized that during HFOV, the minimization or absence of leaks around the ETT may be confirmed objectively via direct comparison of the measured intra-tracheal
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distending pressure [$mPtr(meas)$] against the corresponding predicted distending pressure

[$mPtr(pred)$] computed from regression equations at the prevailing HFOV settings. We further

hypothesized that for confirmed zero or negligible leak conditions, physiologically relevant

oscillatory respiratory mechanical properties [resistance (Rrs) and compliance (Crs)] may be

derived from measurements of oscillatory tracheal pressure [$Ptr,osc$] and proximal airway

oscillatory flow [$Flow,osc$].

Accordingly, this study aimed a) to develop, using a series of physical model

investigations, an objective and practical method to confirm ETT leak removal in HFOV-
supported infants and b) to use no-leak oscillatory $Ptr$ data in combination with oscillatory

flow/volume data measured at the proximal ETT to derive reliable respiratory mechanics

parameters - free of ETT effects - that may be used to guide ventilatory management of very low

birth weight (VLBW) infants supported with HFOV.
METHODS

**Test Lung Model Measurements.** We adapted a 1L neonatal/pediatric test lung (SensorMedics, Yorba Linda, CA) and a cuffed ETT (3.0 mm internal diameter, Hudson RCI/Sheridan cuffed ETT; Teleflex Medical, Research Triangle Park, NC)) to create a physical model representing the clinical situation [Figure 1-Top]. This test lung containing copper wool was half–filled with water to decrease its gas volume and, hence, reduce its effective compliance (~ 0.36 mL/cmH₂O - adiabatic gas equation) to more closely approximate preterm infant respiratory system compliance. The ETT was inserted (cuff down, maximal leak conditions) in tubing to simulate the trachea - ETT interface. As a neonatal ETT with both a cuff and a monitoring lumen was not available, the tip of a second same size ETT (uncuffed, with monitoring lumen; Mallinckrodt, Inc; St. Louis, MO) was inserted so that the monitoring lumen was at the tip of the cuffed ETT [Figure 1 – Top]. This physical model was then ventilated using HFOV (SensorMedics Model 3100A CareFusion, Inc., Yorba Linda, CA) while the ETT cuff was slowly inflated using a programmable syringe pump (Baxter, Model AS50, Baxter Healthcare Corporation, Deerfield, IL) until the leak was completely removed (slow cuff inflation over 3-5 min). Airway flow was measured using a pneumotachograph (series 8411A, Hans Rudolph, Kansas City, MO) placed between the ventilator and the ETT.[4] A second pneumotachograph placed distally between the test lung and the simulated trachea recorded flow independent of leak. Ventilator-delivered volumes were computed using trapezoidal integration of the oscillatory flow. Airway pressures were measured using pressure transducers (Validyne DP45-28, Northridge, CA ) at three points: the proximal ETT (airway opening pressure, Pao); the model trachea using the pressure monitoring port of the ETT (Ptr1); and a direct measure immediately distal to the ETT (Ptr2). Slow cuff inflation measurements in this model were repeated at multiple combinations of
HFOV settings changing a single parameter at a time: mean airway pressures of 10, 15 and 20 cmH₂O (Paw); oscillation amplitudes of 10, 20 and 30 cmH₂O (ΔP); oscillation frequency of 5, 10 and 15 Hz; and inspiratory times (%tᵢ) of 33%, 40% and 50%.

Estimated vs. Measured No-leak Mean Tracheal Pressure during HFOV. We hypothesized that, under conditions of no-to-negligible leak around the ETT, the mean Ptr estimated based on HFOV settings and proximal ETT pressures will closely approximate the true (measured) mean Ptr. We performed a series of bench model measurements using the same uncuffed 2.5 and 3.0 mm ETT with Ptr measurement lumen that was used in the infants (Mallinckrodt, Inc; St. Louis, MO). Here, the test-lung was connected to each ETT assuring that there are no leaks at the ETT - test lung interface and connected to the ventilator [Figure 1]. Measurements were repeated for three different load conditions (impedance), at multiple combinations of HFOV settings changing a single parameter at a time: mean airway pressures of 10, 20 and 30 cmH₂O (Paw); oscillation amplitudes of 10, 20 and 30 cmH₂O (ΔP); oscillation frequency of 5, 10 and 15 Hz; and inspiratory times (%tᵢ) of 33%, 40% and 50%. Load impedance was manipulated (increased) by decreasing the effective test lung compliance (Cₜ₇; High) by inserting 100 (Cₜ₇; Medium) and 200 (Cₜ₇; Low) play marbles into the test lung to reduce its effective gas volume.

For a given ETT, the mean Ptr data were pooled with the Pao (mean and amplitude) and the corresponding HFOV settings and load conditions to derive mathematical prediction models (multiple linear regression) for estimating mean Ptr [mPtr (pred)] for any given combination of HFOV settings. These models were then applied to infant measurements to objectively ascertain no-leak conditions by calculating the mPtr (pred) in each case and comparing it to the actual mean Ptr measured through the ETT tracheal pressure port. A Bland-Altman analysis [1,15] was
used to ascertain the bias and limits of agreements comparing the mPtr (pred) and mPtr (meas) based on which one may accept or reject the assumption of no-leak condition.

**Frequency Response of Endotracheal Tube Distal Pressure Monitoring Lumen.** In order to employ the ETT with monitoring lumen in the infants (see Infant Data, below), it was necessary to determine the frequency response of the ETT pressure monitoring lumen (Ptr1) by direct comparison to the tracheal pressure (Ptr2) amplitudes at multiple frequencies between 5 and 15 Hz.[Figure 1, bottom]. Ptr1 and Ptr2 were processed via a narrow band-pass (HFOV frequency ±25%) filter. The power spectra were then calculated to derive thePtr1/Ptr2 amplitude ratio at the oscillation frequency. This frequency response characterization was repeated under conditions of no leak, intermediate leak and large leak around the ETT.

**Infant Data.** We collected data in 11 VLBW preterm infants [4/6 male/female, 25.5±1.4 weeks (gestation), 0.77±0.24 kg (weight) and 4.4±7.4 days (age)] who were supported with HFOV for respiratory distress syndrome. These infants were part of an ongoing trial assessing respiratory inductance plethysmography (RIP) to monitor changes in lung volume during HFOV. The trial was approved by the Baystate Medical Center and North Shore Long Island Jewish Health System IRBs; parental consent was obtained. Infants in this study were intubated with an uncuffed ETT (2.5 or 3.0 mm, inner diameter) with tracheal pressure monitoring access located at the end of the ETT (Mallinckrodt ETT, Nellcor, Pleasanton, CA). Measurements always followed a feeding to facilitate study completion. The ETT leak was minimized by use of appropriate ETT size, varying head position, and gentle pressure on the trachea when necessary. We measured Pao, Ptr and airway flow at the infants’ clinically set mean airway pressure (range
8–14 cmH\textsubscript{2}O, inspiratory time (\%\textsubscript{t\textsubscript{i}} = 33\%) and frequency [10 Hz (n=4), 12 Hz (n=2), and 15 Hz (n=5)] while only varying pressure oscillations amplitudes [\Delta P] at 100\%, 50\% and 150\% of baseline or clinical setting]. The order of the latter two \Delta P settings was randomized. All measurements were preceded with a 5 minute stabilization period at the 100\% \Delta P setting followed by 2 minute measurement periods at each of the three studied \Delta P settings. Continuous monitoring of flow, Pao, Ptr, rib cage (RC) and abdominal (ABD) RIP tracings (Respiband Plus and Respitrace, SensorMedics, Corp, Yorba Linda, CA), pulse rate, oxygen saturation (SaO\textsubscript{2}, Radical pulse oximeter, Masimo Corp, Irvine, CA), transcutaneous partial pressure of oxygen (TcPO\textsubscript{2}) and carbon dioxide (TcPCO\textsubscript{2}) measurements (TCM4, Radiometer, Inc., Westlake, OH) were recorded on the computerized data acquisition system (BioPac Systems, Inc., Goleta, CA) at a sampling rate of 1000 Hz per channel.

**Signal Processing and Analysis.** A low pass digital filter [cutoff frequency of 1 Hz (test-lung) and 2 Hz (infants), -92 dB Blackman, BioPac Systems] was used to separate the low-(includes static components and spontaneous breathing in infants) and high-frequency (oscillatory) components for all measured pressure, flow and RIP signals. For mechanics analysis, pressure and flow data were processed by applying a narrow bandpass filter (\pm 25\%) around the set HFOV frequency [e.g., for freq = 10 Hz, bandpass cutoffs of 7.5 and 12.5 Hz were used]. Pressure volume loops for the various leak conditions in the test lung and the varying \Delta P settings in the infants were constructed from the intratracheal and airway opening oscillatory pressures (Ptr and Pao respectively) together with the corresponding oscillatory volume (time-integrated flow) data. These data were also analyzed to estimate the mechanical properties either at the airway opening (Rao, Iao, Cao; includes ETT contributions) or at the level of the trachea (Rrs, Irs, Crs; no ETT contributions) by applying an RIC [Resistance (R; cmH\textsubscript{2}O.s.mL\textsuperscript{-1}),
compliance (C; mL.cmH$_2$O$^{-1}$) and inertance (I; cmH$_2$O.s$^2$.m$^{-1}$)] multiple linear regression model
to the measured oscillatory $P_{ao}(t)$ and $P_{tr}(t)$, respectively:

\[ P_{\text{model}}(t) = R \times \text{Flow}(t) + \frac{\text{Volume}(t)}{C} + I \times \frac{\text{dFlow}(t)}{\text{dt}} + P_0 \quad (1) \]

Where, $P_0$ is a constant reflecting static pressure, $\frac{\text{dFlow}(t)}{\text{dt}}$ (mL/s$^2$) is the time
derivative of Flow, and Volume is time-integrated flow in mL.
RESULTS

Test Lung Model

Figure 1 (bottom) shows the derived frequency response for the ETT-lumen (Ptr1) compared to direct tracheal pressure measurements (Ptr2). These data indicated that, for the range of HFOV frequencies typically used in infants, Ptr1 closely approximates Ptr2 provided that the leaks around the ETT are relatively small.

Figure 2 (left) illustrates an example representative data set, where the ETT leak is gradually reduced by slow cuff inflation, showing the corresponding effects on airway flow, volume, airway opening pressure (Pao) and tracheal pressure (Ptr) measurements in the physical model at the specified HFOV settings. These data span the entire range of leak magnitudes starting from maximal leak with substantial differences in both mean and oscillatory pressures at the proximal versus distal ETT and ending in fully inflated cuff or no leak conditions. The resulting changes in Ptr and Pao as a function of time of cuff inflation (or decreasing leak) show that mean Ptr will approximate, but not equal, the mean Pao even when the leaks are completely removed. [Figure 2 (right, top)] These results were qualitatively similar for all the combinations of HFOV settings (Frequency, %tI, Paw and ΔPao), load impedance and ETT sizes. For large leak ETT - trachea size mismatch, the reduction in the difference between the mean distending pressure at the proximal versus distal ETT are largely a result of leak effects with a smaller contribution from other sources (e.g., ventilator settings, ETT characteristics). When the mismatch is minimized or completely removed, the residual difference between mean Pao and mean Ptr will be exclusively explained by ventilator and ETT factors.
The derived Pao-Volume and Ptr-Volume loops showed the profound effects of ETT leaks on the pressure-volume data. As expected, the derived mechanical properties differed substantially for the various leak magnitudes [Figure 2 (right, middle/bottom)]. Table 1.

Figure 3 illustrates, when no leaks are present at the distal ETT, the decrease in the delivered mean distending pressure at the distal (mean Ptr) versus proximal (mean Pao) ETT as a function of increasing HFOV oscillation amplitudes (ΔPao). This drop in mean pressure also depends on the applied HFOV settings such as: the oscillation frequency [Freq; Figure 3-A], the set mean airway pressure Paw [Figure 3-B], and the inspiratory time [%tI; Figure 3-C]. This drop in mean pressure, however, was unaffected by changes in load impedance or compliance [C_TL; Figure 3-D]. Table 2 shows the predictive models for mean tracheal pressure using 2.5 mm or 3.0 mm ID tracheal tubes derived using multiple linear regression at high, medium and low in vitro model lung compliance.

**Infant Data**

Since load impedance did not alter mean Ptr prediction[Figure 3, Table 2], we used the All-Data equations in Table 2 on infant measurements, at each HFOV setting and ETT size combination, to derive mPtr (pred) values and compared them to the corresponding mPtr (meas) values. The no-leak measured mPao was always greater than the corresponding measured mPtr at the distal ETT. [Figure 4-Top] Yet, the model-predicted mean pressure mPtr(pred) closely approximated the directly measured Ptr in 10 of 11 infants [4 male, 25.6±1.5 weeks (gestation), 0.76±0.24 kg (weight) and 2.3±2.9 days (postnatal age)] and for all oscillation amplitudes. [Figure 4-middle] Their absolute mean Ptr difference (predicted - measured) varied between -0.40 and +0.38 cmH2O (%Difference: -5.4% - 3.1%), while one infant showed poor mean
pressure agreement [e.g. (for 100% ΔP): mean Pao (meas) = 11.7; mPtr (pred) = 11.3 and mPtr
(meas) = 7.4; all in cmH2O]. Results of the Bland Altman analysis excluding this one infant
showed nearly zero bias (-0.02 cmH2O) and relatively narrow limits of agreement [lower/Upper:
-0.40/0.36 cmH2O] over the range of applied mean pressures in our infants[Figure 4 - Bottom].
Based on these results, if the measured Ptr is more than 5% to 10% lower than the mPtr (pred) it
may be considered as being outside the accepted limits and significant residual ETT leaks may
be assumed.

Figure 5-left shows Pao, Ptr, flow, tidal volume and RIP data collected in a representative
premature infant (male, 872 grams, 25.5 wks gestation, postnatal age = 1 day). The pressure-
volume plots corresponding to Pao and Ptr were of similar characteristics irrespective of the
oscillation amplitudes they were based on [100%, 150% and 50% of the set ΔP; Figure 5-Right].
The corresponding derived mechanical properties using an RIC model for this infant are shown
in Figure 5 legend, while the averaged results from all 10 infants, including ventilatory and
respiratory mechanics parameters at all three ΔP settings, are summarized in Table 3. Figure 6
illustrates selected effects of increasing HFOV pressure oscillation amplitudes on estimated
respiratory mechanical properties. Specifically, with increasing ΔP (or oscillatory tidal volumes),
both airway opening resistance at the proximal ETT (Rao; p<0.001) and ETT inertance (IETT;
p=0.014) were increased significantly. Alternatively, we observed a modest and non-significant
rise in Rrs (p=0.14) and an essentially unchanged Crs (p=0.39) with increasing ΔP.

Dampening of the oscillation amplitudes at the distal relative to proximal ETT tended to
be slightly greater with increasing ΔP, or ΔPtr/ΔPao (%) ratio tended to decrease (p=0.088).
[Table 3] This ratio seemed to be associated with infant compliance (Crs) irrespective of the set
ΔP (50% - 150% baseline). Specifically, relatively higher tracheal pressure oscillations,
∆Ptr/∆Pao (%), were observed in infants with low compliance values (Crs). [Figure 7].
DISCUSSION

Accurate and reliable estimation of respiratory mechanical properties in mechanically ventilated VLBW infants remains a formidable challenge including technical (equipment) limitations, lack of controlled measurements, and the fragility of this patient population. Advancements in conventional mechanical ventilation (CMV), including flow/volume measurements, have provided clinicians with the ability to monitor changes in pulmonary compliance at the bedside and to adjust ventilator parameters accordingly. Our infant study population was representative of infants requiring HFOV primarily for surfactant deficient respiratory distress syndrome. For HFOV, bedside pulmonary mechanics assessment has not yet been developed as is the case for CMV. Yet, as previously suggested [8,9,11,17,22-25], determining lung mechanics properties during HFOV can be of significant value in optimizing HFOV settings in individual subjects. [11,12,17] Even more problematic is the near universal practice of using uncuffed ETT in the young pediatric population. [6,14,16] Air leaks around the uncuffed ETT, depending on their magnitude, may render meaningless all mechanics assessments based on proximal airway measurements [10], in addition to possibly hindering the delivery of consistent optimal HFOV support. Schumann et al. [20] point out the difficulty in modeling an air leak and, as is customary, evaluated its effects on mechanics estimates during HFOV using a no-leak model.

Leaks around the ETT may significantly affect the delivered pressures and volumes to the lungs.[10] Such decreases in mean pressure and oscillatory pressure amplitude resulting from a large leak contribute to ineffective ventilatory support. This loss in delivered mean distending pressure intra-tracheally is distinct from the static (mean) pressure loss along the airways due to
their physical properties as has been reported in both physical models [18,21] as well as in preterm lambs.[19] Though most conventional ventilators now monitor percent leak and may have leak compensation, this is not true for HFOV. Availability of such leak estimates is useful when managing ventilation delivery even if their effects on respiratory mechanics assessments remain an incompletely understood issue with either mode of ventilation - conventional or oscillatory. Approaches to dealing with the above-described ETT leak effects are needed if lung mechanics during HFOV are to prove useful for a) optimizing ventilator settings, b) tracking the regression or progression of the underlying respiratory disease, and c) to determine the effects and efficacy of treatments (such as surfactant) on mechanics of breathing. Until now, an objective and practical method to confirm ETT leak removal in infants - and during HFOV - has not been described. In this study, we showed that when no leaks are present, the mean Ptr may be accurately predicted from the pressure at the proximal ETT (mean Pao) adjusted to the specific HFOV settings (Frequency, ΔP, and inspiratory time) as described in the mathematical model (Equation 1). [Figure 4] Therefore, a simple comparison of the predicted mean Ptr to the directly measured mean Ptr provides an objective indicator of the presence and extent of airway leaks at the distal ETT. Specifically, if the mean Ptr predicted from the corresponding proximal Pao values adjusted based on the applied HFOV settings [Table 2] closely approximates the measured mean Ptr to within a few percent, then a negligible or no leak state may be reasonably assumed.

Our analysis also illustrated [see Table 1] how leaks - which are an accepted aspect of neonatal ventilatory support – may substantially hinder our ability to accurately and reliably assess respiratory system mechanical properties (Rrs, Crs). We showed that with larger
leak magnitudes, mechanical properties estimated using tracheal pressure measurements will lead to systematically greater mis-estimation of the true (or no-leak conditions) test-lung oscillatory mechanical properties. When airway opening pressures are used for such calculations, the mechanical properties of the tracheal tube will increasingly dominate the estimated overall (equal to ETT + test-lung) mechanical properties as the magnitude of the leak worsens. [Table 1]

Moreover, for large leak, the mean Pao and oscillation amplitudes (ΔPao) at the proximal ETT are substantially greater than the corresponding pressures at the distal end (mean Ptr and ΔPtr). [Figure 2] Indeed, both the actual (delivered) mean Pao and mean Ptr, at the proximal and distal ETT respectively, will grossly underestimate the targeted mean airway pressure as set on the ventilator by the physician. [Figure 2] In addition to its unwanted effects on ventilation efficacy and mechanics assessment accuracy, this scenario represents an often neglected yet considerable risk of serious injury to the ventilated infant in case of a sudden and substantial decrease in the magnitude of leak around the ETT. When substantial leaks are present, physicians will likely use very high Paw and ΔP settings to overcome these leaks and provide sufficient ventilation. If such leaks are suddenly removed (or decreased considerably) such as due to secretion build-up or spontaneous neck repositioning, then dangerously high mean pressures and amplitudes may result and could cause lung tissue damage (barotrauma) and possibly overdistention and/or air leak.

In contrast, we showed that when leaks are minimal or completely removed such as we were able to achieve in the studied preterm infants, it is possible to get valuable insight about the underlying lung mechanics during HFOV support [Figure 6, Table 3], and also avoid the potential for inadvertent excessively high pressures. In VLBW preterm infants on HFOV, it was noteworthy that an inertance element was needed to properly model oscillatory Pao data but not
This indicates that 1) VLBW preterm infant sub-ETT or respiratory system (airway and lung/chest wall tissue) inertance effects remain negligible at 10-15 Hz, 2) the inertance element needed to properly model Pao data reflects primarily the mass properties of the gas within the ETT consistent with previously reported data in intubated infants by Dorkin and colleagues [5], and 3) the ETT contributes significantly to Rao estimates that includes the ETT resistance as previously reported.[18,21,22]

The increase in Rao with increasing oscillation amplitudes derives, in large part, from the flow dependence of the tracheal tube resistance. This, in turn, is a factor in determining the drop in the mean distending pressure as well as in the oscillatory amplitudes at the distal end of the tracheal tube.[8,9,18,24] Both of these flow-related ETT-effects will vary with tube size [21,22], and could also differ in magnitude depending on the ventilation modality; e.g., conventional versus HFOV. During HFOV, the relative tracheal to proximal airway oscillatory pressure ratio [OPR or equivalently the ΔPtr/ΔPao (%)], will also reflect the relative impedance distribution of the non-physiologic ETT versus the physiologic load or the respiratory system.[8,9,24] In particular, the OPR will decrease as Crs increases [Figure 7], and hence changes in OPR may provide a practical and rather readily available (no computations needed) insight to changes in lung compliance of treated infants. This potentially represents a simple and objective indicator of progression/regression of disease or of efficacy of treatments (e.g., pre and post surfactant). Lastly, the OPR is also a measure of carinal pressure amplitude which has been proposed as a critical determinant of barotrauma during HFOV.[24]
**Technical Considerations and Study Limitations**

The data we present provide a basis on which to develop practical approaches to dealing with optimizing HFOV support in the challenging preterm infant population. However, some significant technical considerations remain before oscillatory mechanics in HFOV treated infants are available in a manner similar to that available in infants treated with modern conventional mechanical ventilators. For example, we used an in-line pneumotachograph to measure airway flow between the oscillator and the ETT with potential implications of the added in-series resistance on delivered tidal volume amplitudes.[4] Other approaches to measure air flow with reduced resistance should be attempted and validated. In some infants, we encountered intermittent loss of the Ptr signal due to occlusion of the pressure monitoring port of the ETT by tracheal secretions or fluid accumulation. To minimize the possibility of such secretions on Ptr measurements, we routinely cleared the lumen of the ETT distal pressure port used to measure Ptr by introducing a small volume of air prior to each data collection sequence. Respiratory mechanics measurements in such a fragile patient population must be conducted between therapies and feeding and, hence, may be affected by possible artifacts. In our study, this concern was minimized by studying only stable infants and always after a scheduled feeding.

Our study has some limitations that may limit the overall generalizability of the findings. Our study did not investigate all ETT sizes and types and derive corresponding mathematical models for estimating distal ETT mean pressures for each. This study was not intended to exhaustively consider all possible scenarios and ETT sizes and provide a universal solution applicable to all possible tracheal tubes. Yet, it is possible to do so for any ETT using a similar approach to ours. In keeping with the exploratory, technique-development nature of our investigations, we studied relatively well and stable preterm infants as the extensive
measurement protocol was inappropriate for clinically unstable babies. Consequently, we used oscillatory amplitudes and mean pressures that were lower than are often required in sicker infants with poor lung compliance. Ethical considerations limited the extent to which amplitude and mean pressure could be varied in the studied group.

In conclusion, we found that tracheal pressure measurement along with model-based mean Ptr estimation, facilitates efforts to minimize leaks around endotracheal tubes during oscillatory ventilation. This in turn allows for more consistent HFOV support. and the simultaneous availability of measured oscillatory Ptr and flows - under minimal or no leak conditions - provides reliable and accurate assessment of the physiologic respiratory mechanical properties. We recommend further study to determine a threshold for clinical application of these findings. Care providers may thereby objectively optimize ventilator settings to specific infant mechanics as well as to track the progression and regression of the disease process or the efficacy of treatments such as surfactant delivery.
GRANT:

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CONFLICT OF INTEREST STATEMENT:

The authors do not have any conflict of interest disclosures to make. The manuscript is not under consideration for publication elsewhere.

AUTHOR CONTRIBUTIONS:

R Singh - conception, design, data acquisition, and writing the article
SE Courtney - conception, design, data acquisition, interpretation, writing and revision
MD Weisner - analysis, interpretation, writing and revision
RH Habib – conception, design, writing and revision, lead role in analysis and interpretation
REFERENCES


Figure Legends

Figure 1. **Top:** Test-lung physical model set-up. HFOV, high frequency oscillatory ventilator; Ptach, pneumotachograph; Pao, proximal airway pressure measurement port; Ptr, tracheal pressure measurement ports. **Bottom:** Frequency response of the tracheal pressure measurement through the ETT monitoring lumen (Ptr1) versus directly (Ptr2).

Figure 2. **Left:** Representative effects of slow cuff inflation on airway flow, volume, airway opening pressure (Pao) and tracheal pressure (Ptr) measurements done in a Test-Lung intubated with an endotracheal tube (3.0 mm ID) at mean airway pressure (Paw) of 10 cmH₂O, frequency of 10 Hz and oscillation amplitude of 10 cmH₂O. Data spans the entire range of leak magnitudes; i.e., from maximal leak (#1) to no leak (#5). **Right:** Changes in mean Ptr and mean Pao as a function of time during a slow cuff inflation between a point of maximal leak (time = 0) and end point of No Leak (top); Pao-Volume (middle) and Ptr-Volume (bottom) loops corresponding to multiple (#1 through #5) leak magnitudes.

Figure 3. Percent drop in the delivered mean airway pressure between the proximal (Pao) and distal (Ptr) ends shown for a 3.0 mm (ID) endotracheal tube for low, intermediate and large oscillation amplitudes (ΔPao; cmH₂O) as other HFOV settings/conditions were varied. **Top (Left):** oscillation frequency (Freq; Hz); **Top (Right):** mean airway pressure (Paw; cmH₂O); **Bottom (Left):** inspiratory time (%tI) and **Bottom (Right):** Load or Test Lung compliance (C_{TL}).
Figure 4. **Top:** Comparison of measured mean Pao at proximal ETT versus mean Ptr at the distal ETT in 10 infants at all three ΔP settings (symbols). Bar graph insert shows the same ΔP comparisons summarized across infants [50% ΔP (white); 100% ΔP (gray); 150% ΔP (black)]. **Middle:** The corresponding comparisons for model predicted (Ptr,p) versus measured (Ptr). **Bottom:** Bland Altman [1] plot to show the agreement between measured and predicted mean Ptr versus the reference method [15] with lines showing average error (solid; bias = -0.02 cmH2O) and upper and lower limits of agreement (dashed; LL/UL= -0.40/0.36 cmH2O) defined as the error mean ±1.96×standard deviation.

Figure 5. **Left:** Representative infant (RDS, male, 872 grams, 25.5 wks gestation, age = 1 day) Pao, Ptr, Flow, tidal volume (VT) and respiratory inductance plethysmography (RIP; chest wall tidal excursions) data during HFOV under no leak conditions at all three oscillation amplitude settings [100%, 150% and 50% of baseline ΔP (12 cmH2O)]. **Right:** Pressure - volume plots using both Pao (top) and Ptr (bottom) data. The derived mechanical properties in this infant are summarized in below Table. Note, an inertance element (Irs) was not needed to fit Ptr data.

<table>
<thead>
<tr>
<th>ΔP</th>
<th>VT</th>
<th>Rao</th>
<th>Cao</th>
<th>Iao</th>
<th>R²</th>
<th>Rrs</th>
<th>Crs</th>
<th>Irs</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>1.04</td>
<td>67.3</td>
<td>0.221</td>
<td>0.233</td>
<td>0.990</td>
<td>13.1</td>
<td>0.194</td>
<td>N/A</td>
<td>0.994</td>
</tr>
<tr>
<td>100%</td>
<td>1.93</td>
<td>78.4</td>
<td>0.25</td>
<td>0.209</td>
<td>0.988</td>
<td>16.4</td>
<td>0.202</td>
<td>N/A</td>
<td>0.988</td>
</tr>
<tr>
<td>150%</td>
<td>2.67</td>
<td>84.2</td>
<td>0.269</td>
<td>0.214</td>
<td>0.973</td>
<td>18.8</td>
<td>0.208</td>
<td>N/A</td>
<td>0.981</td>
</tr>
</tbody>
</table>

Units: Tidal volume (VT) in mL, Resistance (Rao and Rrs) in cmH2O.s.L⁻¹; Compliance (Cao, Crs) in mL.cmH2O⁻¹; Inertance (Iao, Irs) in cmH2O.s².L⁻¹

Figure 6. Effect of increasing HFOV pressure oscillation amplitudes on estimated preterm infant respiratory mechanical properties: **Top:** airway opening (Rao) and respiratory system (Rrs)
resistance; *Bottom*: respiratory system compliance (Crs) and endotracheal tube inertance ($I_{ETT}$). (see Table 3 and results section for details).

**Figure 7.** Respiratory system compliance (Crs) plotted versus relative tracheal to airway opening pressure oscillation amplitudes, $\Delta P_{tr}/\Delta P_{ao}$ (%), in preterm infants at all three oscillation amplitude settings ($\Delta P$: 50%, 100% and 150% baseline). Lines represent sigmoidal model fit (solid) and 95% confidence interval (dashed) of all Crs - $\Delta P_{tr}/\Delta P_{ao}$ (%) data combined (see model equation in graph panel).
Table 1: Effects of ETT leak on oscillatory (10 Hz) mechanical properties derived from R-I-C model applied to airway opening (Pao) and tracheal (Ptr) pressure measurements.

<table>
<thead>
<tr>
<th>Leak</th>
<th>Pao-derived (ETT + Test Lung)</th>
<th>Ptr-derived (Test Lung Only)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rao</td>
<td>Cao</td>
</tr>
<tr>
<td>#1 (max)</td>
<td>36.8</td>
<td>3.2E+07</td>
</tr>
<tr>
<td>#2</td>
<td>41.5</td>
<td>6.4E+05</td>
</tr>
<tr>
<td>#3</td>
<td>40.6</td>
<td>0.860</td>
</tr>
<tr>
<td>#4</td>
<td>31.7</td>
<td>0.470</td>
</tr>
<tr>
<td>#5 (No leak)</td>
<td>27.6</td>
<td>0.619</td>
</tr>
</tbody>
</table>

Units: Rao and Rtr [cmH₂O.s.L⁻¹]; Cao and Ctr [ml.cmH₂O⁻¹]; Iao and Itr [cmH₂O.s².L⁻¹].

R² = square of the correlation coefficient between measured and model estimated pressures. All parameter estimates were statistically significant (P<0.01).

HFOV settings: Frequency = 10 Hz; Paw = 10 cmH₂O; ∆Pao = 8 cmH₂O; %tI = 33%.

ETT used was 3.0 mm ID cuffed tube (see Methods).
Table 2. Multiple Linear Regression models for predicting mean tracheal pressure in terms of measurements at the airway opening and ventilator settings.

<table>
<thead>
<tr>
<th>ETT Size</th>
<th>Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2.5 mm (ID)</strong></td>
<td></td>
</tr>
<tr>
<td>All Data:</td>
<td>$m_{Ptr} \ (pred) = -1.01 + 1.013 \times m_{Pao} - 0.064 \times \Delta P_{ao} + 0.023 \times % t_{I} + 0.025 \times \text{Frequency}$</td>
</tr>
<tr>
<td>High $C_{TL}$:</td>
<td>$m_{Ptr} \ (pred) = -1.26 + 1.013 \times m_{Pao} - 0.061 \times \Delta P_{ao} + 0.024 \times % t_{I} + 0.023 \times \text{Frequency}$</td>
</tr>
<tr>
<td>Medium $C_{TL}$:</td>
<td>$m_{Ptr} \ (pred) = -1.13 + 1.013 \times m_{Pao} - 0.065 \times \Delta P_{ao} + 0.021 \times % t_{I} + 0.026 \times \text{Frequency}$</td>
</tr>
<tr>
<td>Low $C_{TL}$:</td>
<td>$m_{Ptr} \ (pred) = -1.25 + 1.013 \times m_{Pao} - 0.069 \times \Delta P_{ao} + 0.025 \times % t_{I} + 0.024 \times \text{Frequency}$</td>
</tr>
<tr>
<td><strong>3.0 mm (ID)</strong></td>
<td></td>
</tr>
<tr>
<td>All Data:</td>
<td>$m_{Ptr} = -0.92 + 1.013 \times m_{Pao} - 0.069 \times \Delta P_{ao} + 0.017 \times % t_{I} + 0.015 \times \text{Frequency}$</td>
</tr>
<tr>
<td>High $C_{TL}$:</td>
<td>$m_{Ptr} \ (pred) = -1.01 + 1.014 \times m_{Pao} - 0.071 \times \Delta P_{ao} + 0.018 \times % t_{I} + 0.021 \times \text{Frequency}$</td>
</tr>
<tr>
<td>Medium $C_{TL}$:</td>
<td>$m_{Ptr} \ (pred) = -0.92 + 1.013 \times m_{Pao} - 0.069 \times \Delta P_{ao} + 0.017 \times % t_{I} + 0.019 \times \text{Frequency}$</td>
</tr>
<tr>
<td>Low $C_{TL}$:</td>
<td>$m_{Ptr} \ (pred) = -0.82 + 1.012 \times m_{Pao} - 0.066 \times \Delta P_{ao} + 0.017 \times % t_{I} + 0.0061 \times \text{Frequency}$</td>
</tr>
</tbody>
</table>

key: $m_{Ptr}$ = mean tracheal pressure; $m_{Pao}$ = mean airway opening pressure; $\Delta P_{ao}$ = airway opening pressure oscillation amplitude; $\% t_{I}$ and Frequency = HFOV inspiratory time (%) and Frequency setting.

* All models fit the data extremely well with $R^2 > 0.998$ in all cases, and all predictor variables were highly significant ($P<0.001$). Models were generally similar irrespective of load compliance (impedance) and the All-Data models were used in the infant predictions (see Figure 4).
Table 3. Summarized results from 10 preterm infants ventilated with HFOV at multiple oscillation pressure amplitudes.

<table>
<thead>
<tr>
<th>Variable/Parameter</th>
<th>50% ΔP (1) Mean±SD</th>
<th>100% ΔP (2) Mean±SD</th>
<th>150% ΔP (3) Mean±SD</th>
<th>Significance overall</th>
<th>pairwise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HFOV parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tidal Volume (Vₜ); mL</td>
<td>1.57±0.80</td>
<td>2.61±1.48</td>
<td>3.57±2.22</td>
<td>&lt;0.001</td>
<td>All</td>
</tr>
<tr>
<td>Vₜ/wt; mL/kg</td>
<td>2.04±0.78</td>
<td>3.29±1.34</td>
<td>4.41±1.89</td>
<td>&lt;0.001</td>
<td>All</td>
</tr>
<tr>
<td>ΔPao; cmH₂O</td>
<td>7.59±1.86</td>
<td>14.12±5.64</td>
<td>21.2±8.91</td>
<td>&lt;0.001</td>
<td>All</td>
</tr>
<tr>
<td>ΔPtr; cmH₂O</td>
<td>4.58±1.62</td>
<td>7.67±2.76</td>
<td>11.14±5.11</td>
<td>&lt;0.001</td>
<td>All</td>
</tr>
<tr>
<td>ΔPtr/ΔPao (%)</td>
<td>0.58±0.17</td>
<td>0.55±0.16</td>
<td>0.52±0.16</td>
<td>0.088</td>
<td></td>
</tr>
<tr>
<td>Pao (mean); cmH₂O</td>
<td>9.04±2.45</td>
<td>8.95±2.45</td>
<td>8.87±2.49</td>
<td>0.237</td>
<td></td>
</tr>
<tr>
<td>Ptr (mean); cmH₂O</td>
<td>8.67±2.38</td>
<td>8.30±2.33</td>
<td>7.80±2.37</td>
<td>0.002</td>
<td>1v3</td>
</tr>
<tr>
<td>Ptr-Pao (mean); cmH₂O</td>
<td>-0.37±0.12</td>
<td>-0.65±0.28</td>
<td>-1.07±0.48</td>
<td>&lt;0.001</td>
<td>1v3, 2v3</td>
</tr>
<tr>
<td>Ptr-Pao (mean); %</td>
<td>-4.1±1.1</td>
<td>-7.3±2.5</td>
<td>-12.3±4.9</td>
<td>&lt;0.001</td>
<td>1v3, 2v3</td>
</tr>
<tr>
<td><strong>Mechanical Properties</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rao; cmH₂O.s/L</td>
<td>65.5±34.0</td>
<td>75±30.4</td>
<td>89.2±39.2</td>
<td>&lt;0.001</td>
<td>All</td>
</tr>
<tr>
<td>Cao; mL/cmH₂O</td>
<td>1.09±2.84</td>
<td>0.70±1.63</td>
<td>-0.88±3.11</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Rrs; cmH₂O.s/L</td>
<td>15.9±12.8</td>
<td>18.4±11.6</td>
<td>22.9±16.0</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Crs; mL/cmH₂O</td>
<td>0.36±0.18</td>
<td>0.34±0.14</td>
<td>0.37±0.18</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>RₑTT; cmH₂O.s/L</td>
<td>50.5±26.0</td>
<td>57.1±23.7</td>
<td>66.3±36.6</td>
<td>&lt;0.001</td>
<td>1v2, 1v3</td>
</tr>
<tr>
<td>IₑTT; cmH₂O.s²/mL</td>
<td>0.34±0.10</td>
<td>0.36±0.18</td>
<td>0.44±0.20</td>
<td>0.014</td>
<td>1v3, 2v3</td>
</tr>
</tbody>
</table>

Infants: 4/6 male/Female, 25.6±1.5 weeks (gestation), 0.76±0.24 kg (weight) and 2.3±2.9 days (postnatal age). All were intubated with 2.5 or 3.0 mm ID uncuffed tube and ventilated with oscillation frequencies between 10 and 15 Hz and identical %tI of 33.3%.
\[
\text{Crs} = \frac{0.54}{1 + e^{-\left[\frac{\Delta P_{\text{Tr}}}{\Delta P_{\text{ao}}} (\%) - 71.4 \right] / (-11.3)}}
\]