Respiratory mechanics during high-frequency oscillatory ventilation:

a physical model and preterm infant study

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1Division of Newborn Medicine, Baystate Medical Center, Springfield, Massachusetts; 2Division of Neonatology, Stony Brook University Medical Center, Stonybrook, New York; 3Equilibrated Bio Systems, Incorporated, Smithtown, New York; and 4Department of Internal Medicine, American University of Beirut, Beirut, Lebanon

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Singh R, Courtney SE, Weisner MD, Habib RH. Respiratory mechanics during high-frequency oscillatory ventilation: a physical model and preterm infant study. J Appl Physiol 112: 1105–1113, 2012. First published December 29, 2011; doi:10.1152/japplphysiol.01120.2011.—Accurate mechanics measurements during high-frequency oscillatory ventilation (HFOV) facilitate optimizing ventilator support settings. Yet, these are influenced substantially 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 vs. model-predicted mean intratracheal pressure [mPtr (meas)] vs. mPtr (pred), and 2) reproducible respiratory system resistance (Rrs) and compliance (Crs) may be derived from no-leak oscillatory Ptr and proximal flow. With the use of ETT test-lung models, proximal airway opening (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 (∆P), and inspiratory time (%tI)] and varying test-lung Crs. 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 nonphysiologic 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 (mPao), ∆P, %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 mPtr (meas) and mPtr (pred), and consequently, their oscillatory respiratory mechanics were evaluated. Infant resistance at the proximal ETT (RETT; resistance airway opening = RETT + Rrs; P < 0.001) and ETT inerance (P = 0.014) increased significantly with increasing ∆P (50%, 100%, and 150% baseline), whereas Rrs showed a modest, nonsignificant increase (P = 0.14), and Crs was essentially unchanged (P = 0.39). We conclude that verifying no-leak conditions is feasible with model-derived vs. distending mPtr (meas). This facilitated the reliable and accurate assessment of physiologic respiratory mechanical properties that can objectively guide ventilatory management of HFOV-treated preterm infants.

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 (CMV) 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 ([Pao] + mean airway pressure (mPaw)) (7, 23). The oscillatory tidal volume breath is defined by the pressure oscillation amplitude (∆P), inspiratory time (%tI), 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, 23–25).

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 ∆P settings on HFOV will overestimate the true delivered lung-distending pressure and ∆P as ETT leaks increase (10), and therefore, the derived respiratory mechanical properties [e.g., resistance (Rrs) and compliance (Crs) respiratory systems] under such conditions are of little physiologic value and will be dominated by the ETT mechanical properties (21).

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METHODS

Test-Lung Model Measurements

We adapted a 1-liter neonatal/pediatric test lung (SensorMedics, now CareFusion, San Diego, CA) and a cuffed ETT (3.0 mm ID; Hudson RCI/Sheridan-cuffed ETT; Teleflex Medical, Research Triangle Park, NC) to create a physical model representing the clinical situation (Fig. 1). This test lung containing copper wool was one-half filled with water to decrease its gas volume and hence, reduce its effective Crs (\(\Delta V = 0.36\) ml/cmH2O adiabatic gas equation) to more closely approximate preterm infant respiratory system Crs. 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, now Covidien Pharmaceuticals, Hazelwood, MO) was inserted so that the monitoring lumen was at the tip of the cuffed ETT (Fig. 1). This physical model was then ventilated using HFOV (SensorMedics Model 3100A, CareFusion), while the ETT cuff was slowly inflated using a programmable syringe pump (Baxter Model AS50, Baxter Healthcare, Deerfield, IL) until the leak was removed completely (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 Flow.osc. Paw was measured using pressure transducers (Validyne DP45-28, Validyne Engineering, Northridge, CA) at three points: the proximal ETT (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: Paw of 10, 15, and 20 cmH2O; \(\Delta P\) of 10, 20, and 30 cmH2O; oscillation frequency (Freq) of 5, 10, and 15 Hz; and \%tI of 33%, 40%, and 50%.

Estimated vs. Measured No-Leak mPtr During HFOV

We hypothesized that under conditions of no-to-negligible leak around the ETT, the mPtr, estimated based on HFOV settings and proximal ETT pressures, will closely approximate the true mPtr \([mPtr (meas)]\). 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, Covidien Pharmaceuticals). 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 (Fig. 1). Measurements were repeated for three different load conditions (impedance) at multiple combinations of HFOV settings, changing a single parameter at a time: Paw of 10, 20, and 30 cmH2O; \(\Delta P\) of 10, 20, and 30 cmH2O; Freq of 5, 10, and 15 Hz; and \%tI of 33%, 40%, and 50%. Load impedance was manipulated (increased) by decreasing the effective test-lung Crs (\(C_{TL}; \) high) by inserting 100...
(C_{TL} medium) and 200 (C_{TL} low) play marbles into the test lung to reduce its effective gas volume.

For a given ETT, the mPtr 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 mPtr (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 with the actual mPtr (meas) 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 ETT Distal Pressure-Monitoring Lumen

To use 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 with the tracheal pressure (Ptr2) amplitudes at multiple frequencies between 5 and 15 Hz (Fig. 1). Ptr1 and Ptr2 were processed via a narrow band-pass (HFOV frequency ±25%) filter. The power spectra were then calculated to derive the Ptr1/Pt2 amplitude ratio at the Freq. 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 [four/six male/female, 25.5 ± 1.4 wk (gestation), 0.77 ± 0.02 kg (weight), and 4.4 ± 7.4 days (age)], who were supported with HFOV for respiratory distress syndrome (RDS). These infants were part of an ongoing trial assessing respiratory inductance plethysmography (RIP) in neonates with RDS at the Baystate Medical Center and North Shore Long Island Jewish Health System Institutional Review Boards; parental consent was obtained. Infants in this study were intubated with an uncuffed ETT (2.5 or 3.0 mm, ID) with tracheal-pressure-monitoring access located at the end of the ETT (Mallinckrodt ETT, Covidien-Nellcor, Boulder, CO). 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 mPaw (range 8–14 cmH2O), %tI (33%), and frequency [10 Hz (n = 4)], 12 Hz (n = 2), and 15 Hz (n = 3)], while only varying ΔP (100%, 50%, and 150% of baseline or clinical setting). The order of the latter two ΔP settings was randomized. All measurements were preceded with a 5-min stabilization period at the 100% ΔP setting, followed by 2-min measurement periods at each of the three studied ΔP settings. Continuous monitoring of flow, Pao, Ptr, rib cage, and abdominal RIP traces (Respiramed Plus and Respiratrace, SensorMedics, CareFusion), pulse rate, oxygen saturation (Radical pulse oximeter, Masimo, Irvine, CA), and transcutaneous partial pressure of oxygen and carbon dioxide measurements (TCM4, Radiometer America, Westlake, OH) was recorded on the computerized data acquisition system (Biopac Systems, Goleta, CA) at a sampling rate of 1,000 Hz/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 (oscillatory)-frequency components for all measured pressure, flow, and RIP signals. For mechanics analysis, pressure and flow data were processed by applying a narrow band-pass filter (±25%) around the set HFOV frequency (e.g., for freq = 10 Hz, band-pass 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 ΔP settings in the infants were constructed from the Ptr and Pao, respectively, together with the corresponding oscillatory volume (time-integrated flow) data. These data were also analyzed to estimate the mechanical properties at the airway opening [resistance (Rao), inertance, compliance; includes ETT contributions] or at the level of the trachea (Rxs, Ixs, Crs; no ETT contributions) by applying an RIC (Rxs (R), cmH2O-s-1”; Ixs (I), cmH2O-s2-1”, Crs (C), mL/cmH2O) multiple linear regression model to the measured oscillatory Pao(t) and Ptt(t), respectively

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

where P0 is a constant reflecting static pressure, dFlow(t)/dt (ml/s2) is the time derivative of Flow (l/s), and Volume (ml) is derived as time-integrated flow.

RESULTS

Test-Lung Model

Figure 1 shows the derived frequency response for the ETT–lumen (Ptr1) compared with direct tracheal pressure measurements (Ptr2). These data indicated that for the range of HFOV frequencies typically used in infants, Ptr1 closely approximates Ptt2, provided that the leaks around the ETT are relatively small.

Figure 2 illustrates an example-representative data set, where the ETT leak is reduced gradually by slow cuff inflation, showing the corresponding effects on airflow, volume, Pao, and 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 vs. 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 mPtr will approximate, but not equal, the mean Pao (mPao), even when the leaks are removed completely (Fig. 2). These results were qualitatively similar for all of the combinations of HFOV settings [frequency, %tI, Paw, and mPao and ΔP (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 vs. distal ETT is 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 removed completely, the residual difference between mPao and mPtr will be explained exclusively by ventilator and ETT factors.

The derived Pao-Volume and Ptt-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 (Fig. 2 and 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 (mPtr) vs. proximal (mPao) ETT as a function of increasing HFOV ΔP (ΔPao). This drop in mean pressure also depends on the applied HFOV settings, such as the Freq (Fig. 3A), the set mPaw (Fig. 3B), and the %tI (Fig. 3C). This drop in mean pressure, however, was unaffected by changes in load impedance or Crs (C_{TL}; Fig. 3D). Table 2 shows the mPtr (pred) models 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 Crs.

Infant Data

Since load impedance did not alter mPtr (pred) (Fig. 3 and 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 with the corresponding mPtr (meas) values. The no-leak mPao (meas) was always greater than the corresponding mPtr (meas) at the distal ETT (Fig. 4). Yet, the mPtr (pred) closely approximated the Ptr (meas) in 10 of 11 infants [four male, 25.6 ± 1.5 wk (gestation), 0.76 ± 0.24 kg (weight), and 2.3 ± 2.9 days (postnatal age)] and for all ΔP (Fig. 4). Their absolute mPtr difference (predicted – measured) varied between 0.40 and +0.38 cmH2O (%Difference: −5.4% – 3.1%), whereas one infant showed poor mean pressure agreement [e.g., for 100% ΔP: mPao (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 ΔP.

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 (maximal)</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>

Resistance airway opening (Rao) and tracheal (Rtr; cmH2O · s · l⁻¹); inertance airway opening (Iao) and tracheal (Itr; cmH2O · s² · l⁻¹); compliance airway opening (Cao) and tracheal (Ctr; ml/cmH2O · R-I-C). R² = square of the correlation coefficient between measured and model-estimated pressures. All parameter estimates were statistically significant (P < 0.01). High-frequency oscillatory ventilation (HFOV) settings: Frequency = 10 Hz; airway pressure = 10 cmH2O; Pao and oscillation amplitude (ΔP; ΔPao) = 8 cmH2O; inspiratory time (%ti) = 33%. Endotracheal tube (ETT) used was a 3.0-mm ID cuffed tube (see METHODS).
mean pressures in our infants (Fig. 4). Based on these results, if the PTr (meas) is more than 5–10% lower than the mPTr (pred), it may be considered as being outside of the accepted limits, and significant residual ETT leaks may be assumed.

Figure 5 shows PAO, PTr, flow, tidal volume, and RIP data collected in a representative premature infant (male, 872 g, 25.5 wk gestation, postnatal age = 1 day). The pressure-volume plots corresponding to PAO and PTr were of similar characteristics, irrespective of the ∆P on which they were based (100%, 150%, and 50% of the set ∆P; Fig. 5). The corresponding derived mechanical properties using an RIC model for this infant are shown in the Fig. 5 legend, whereas the averaged results from all 10 infants, including ventilatory and respiratory mechanics parameters at all three ∆P settings, are summarized in Table 3. Fig. 6 illustrates selected effects of increasing HFOV ∆P on estimated respiratory mechanical properties. Specifically, with increasing ∆P (or oscillatory tidal volumes), both RAO at the proximal ETT (P < 0.001) and ETT ineritance (P = 0.014) were increased significantly. Alternatively, we observed a modest and nonsignificant rise in Rrs (P = 0.14) and an essentially unchanged Crs (P = 0.39) with increasing ∆P.

Dampening of the ∆P at the distal relative to proximal ETT tended to be slightly greater with increasing ∆P, or the mPTr and ∆P (ΔPTr/ΔPAO (%)) ratio tended to decrease (P = 0.088; Table 3). This ratio seemed to be associated with infant Crs, irrespective of the set ∆P (50% – 150% baseline). Specifically, relatively higher tracheal pressure oscillations, ∆PTr/ΔPAO (%), were observed in infants with low Crs values (Fig. 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 (12, 13, 20). Advancements in CMV, in-

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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 (ID)</th>
<th>Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mm (ID)</td>
<td>mPTr (pred) = −1.01 + 1.013 × mPAO − 0.064 × ΔPAO + 0.023 × %tI + 0.025 × Frequency</td>
</tr>
<tr>
<td>All data:</td>
<td></td>
</tr>
<tr>
<td>High Crs:</td>
<td>mPTr (pred) = −1.26 + 1.013 × mPAO − 0.064 × ΔPAO + 0.024 × %tI + 0.023 × Frequency</td>
</tr>
<tr>
<td>Medium Crs:</td>
<td>mPTr (pred) = −1.13 + 1.013 × mPAO − 0.065 × ΔPAO + 0.021 × %tI + 0.026 × Frequency</td>
</tr>
<tr>
<td>Low Crs:</td>
<td>mPTr (pred) = −1.25 + 1.013 × mPAO − 0.069 × ΔPAO + 0.025 × %tI + 0.024 × Frequency</td>
</tr>
<tr>
<td>3.0 mm (ID)</td>
<td>mPTr (pred) = −0.92 + 1.013 × mPAO − 0.069 × ΔPAO + 0.017 × %tI + 0.015 × Frequency</td>
</tr>
<tr>
<td>All data:</td>
<td></td>
</tr>
<tr>
<td>High Crs:</td>
<td>mPTr (pred) = −1.01 + 1.014 × mPAO − 0.071 × ΔPAO + 0.018 × %tI + 0.021 × Frequency</td>
</tr>
<tr>
<td>Medium Crs:</td>
<td>mPTr (pred) = −0.92 + 1.013 × mPAO − 0.069 × ΔPAO + 0.017 × %tI + 0.019 × Frequency</td>
</tr>
<tr>
<td>Low Crs:</td>
<td>mPTr (pred) = −0.82 + 1.012 × mPAO − 0.066 × ΔPAO + 0.017 × %tI + 0.0061 × Frequency</td>
</tr>
</tbody>
</table>

*Crs = test-lung compliance respiratory system (Crs); mPTr (pred) = model-predicted mean PTr; mPAO = mean PAO. *All models fit the data extremely well, with R² > 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 Fig. 4).
cluding flow/volume measurements, have provided clinicians with the ability to monitor changes in pulmonary Crs at the bedside and to adjust ventilator parameters accordingly. Our infant study population was representative of infants requiring HFOV, primarily for surfactant-deficient RDS. For HFOV, bedside pulmonary mechanics assessment has not yet been developed, as is the case for CMV. Yet, as previously suggested (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. (21) 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 intratracheally 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).

Although 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 1) optimizing ventilator settings, 2) tracking the regression or progression of the underlying respiratory disease, and 3) determining 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 mPtr may be predicted accurately from the proximal Pao values, adjusted based on the applied HFOV settings (Table 2), as described in the mathematical model (Eq. 1; see Fig. 4).

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 misestimation of the true (or no-leak conditions) test-lung oscillatory mechanical properties.

![Fig. 4. A: comparison of measured (meas) mPao at proximal ETT vs. mPtr at the distal ETT in 10 infants at all 3 ∆P settings (symbols). Bar graph inset shows the same ∆P comparisons summarized across infants [50% ∆P (white); 100% ∆P (gray); 150% ∆P (black)]. VLBW, very low birth weight. B: the corresponding comparisons for model predicted (Ptr,p) vs. Ptr (meas) (Ptr). C: Bland-Altman (1) plot to show the agreement between mPtr (meas) and predicted (pred) vs. the reference method (15), with lines showing average error (solid; bias = −0.02 cmH2O) and upper (0.36 cmH2O) and lower (−0.40 cmH2O) limits of agreement (dashed), defined as the error mean (mn) ± 1.96 × SD.]
Pao 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 ΔPao at the proximal ETT is substantially greater than the corresponding pressures at the distal end (mPtr and ΔPtr; Fig. 2). Indeed, both the actual (delivered) mPao and mPtr at the proximal and distal ETT, respectively, will grossly underestimate the targeted mPaw, as set on the ventilator by the physician (Fig. 2). In addition to its unwanted effects on ventilation efficacy and mechanics assessment accuracy, this scenario represents an often-neglected yet considerable risk of

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>Overall Significance</th>
<th>Pairwise Significance</th>
</tr>
</thead>
<tbody>
<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 All</td>
<td>&lt;0.001 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 All</td>
<td>&lt;0.001 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 All</td>
<td>&lt;0.001 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>0.088</td>
<td>0.02</td>
</tr>
<tr>
<td>ΔPao/ΔPtr (%)</td>
<td>0.58 ± 0.17</td>
<td>0.55 ± 0.16</td>
<td>0.52 ± 0.16</td>
<td>&lt;0.001 1v3, 2v3</td>
<td>&lt;0.001 1v3, 2v3</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>0.002 1v3</td>
</tr>
<tr>
<td>Pao (mean), cmH2O</td>
<td>8.67 ± 2.38</td>
<td>8.30 ± 2.33</td>
<td>7.80 ± 2.37</td>
<td>&lt;0.001 1v3, 2v3</td>
<td></td>
</tr>
<tr>
<td>ΔPtr–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 1v3, 2v3</td>
<td></td>
</tr>
<tr>
<td>ΔPtr–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 1v3, 2v3</td>
<td></td>
</tr>
</tbody>
</table>

ΔP = Ptr and ΔP; Rrs = resistance respiratory system; Rrs = resistance respiratory system; Rrs = resistance respiratory system; Irs = inertance respiratory system; Irs = inertance respiratory system. Infants: 4/6 male/female, 25.6 ± 1.5 wk (gestation), 0.76 ± 0.24 kg (weight), and 2.3 ± 2.9 days (postnatal age). All were intubated with a 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%.

Fig. 5. Top left: representative infant (respiratory distress syndrome, male, 872 g, 25.5 wk gestation, age = 1 day) Pao, Ptr, Flow, VT, and respiratory inductance plethysmography (RIP; chest-wall tidal excursions) data during HFOV under no-leak conditions at all 3 oscillation (Osc) amplitude settings [100%, 150%, and 50% of baseline ΔP (12 cmH2O)]. RC, rib cage; ABD, abdominal. Top right: pressure-volume plots using both Pao and Ptr data. The derived mechanical properties in this infant are summarized in the table (bottom). Note, an iner- tance element [respiratory system (IrS)] was not needed to fit Ptr data. Units: VT in mL; resistance [airway opening (Rao) and respiratory system (Rrs)] in cmH2O·s·l; compliance [airway opening (Cao) and Crs] in mL/cmH2O; inertance [airway opening (Iao) and Irs] in cmH2O·s·l. R2, square of the correlation coefficient between measured and model-estimated pressures.

ΔPtr = Ptr and ΔP; Rrs = resistance respiratory system; Irs = inertance respiratory system; Irs = inertance respiratory system. Infants: 4/6 male/female, 25.6 ± 1.5 wk (gestation), 0.76 ± 0.24 kg (weight), and 2.3 ± 2.9 days (postnatal age). All were intubated with a 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%.
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 P settings to overcome these leaks and provide sufficient ventilation. If such leaks are removed suddenly (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 overdilation and/or air leak.

In contrast, we showed that when leaks are minimal or completely removed, such as what 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 (Fig. 6 and 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 Ptr. 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, which include the ETT Rs, as reported previously (18, 21, 22).

The increase in Rao with increasing ΔP derives, in large part, from the flow dependence of the tracheal tube Rs. This, in turn, is a factor in determining the drop in the mean distending pressure, as well as in the ΔP at the distal end of the tracheal tube (18, 23a, 23b, 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 vs. 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 nonphysiologic ETT vs. the physiologic load or the respiratory system (23a, 23b, 24). In particular, the OPR will decrease as Rs increases (Fig. 7), and hence, changes in OPR may provide a practical and rather readily available (no computations needed) insight to changes in lung Rs 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 postsurfactant). 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 Rrs on delivered tidal volume amplitudes (4). Other approaches to measure air flow with reduced Rrs should be attempted and validated. In some infants, we encountered intermittent loss of the Ptr signal due to occlusion of the...

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Fig. 6. Effect of increasing HFOV ΔP on estimated preterm infant respiratory mechanical properties. A: Rao and Rs; B: Rs and ETT inertance (IETT; see Table 3 and RESULTS for details).

Fig. 7. Respiratory system Rs plotted vs. relative mPtr and ΔP (ΔPtr/ΔPao (%)) in preterm infants at all 3 ΔP settings (50%, 100%, and 150% baseline). Lines represent sigmoidal model fit (solid) and 95% confidence interval (dashed) of all Rs–ΔPtr/ΔPao (%) data combined (see model equation in graph panel).

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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, which 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, which were lower than are often required in sicker infants with poor lung Crs. 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 mPtr estimation facilitate efforts to minimize leaks around ETT during oscillatory ventilation. This, in turn, allows for more consistent HFOV support, and the simultaneous availability of measured Ptr,osc and Flow,osc—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.

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AUTHOR CONTRIBUTIONS
Author contributions: R.S., S.E.C., and R.H.H. conception and design of research; R.S. and S.E.C. performed experiments; M.D.W. and R.H.H. analyzed data; S.E.C., M.D.W., and R.H.H. interpreted results of experiments; R.H.H. prepared figures; R.S., S.E.C., M.D.W., and R.H.H. drafted manuscript; S.E.C., M.D.W., and R.H.H. edited and revised manuscript; R.S., S.E.C., M.D.W., and R.H.H. approved final version of manuscript.

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