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 (ΔP), and inspiratory time (%tI)] and varying test-lung Csrs. 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), ΔP, %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 inertance (P = 0.014) increased significantly with increasing ΔP (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 by comparison of 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 (ΔP), 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 is 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 ΔP 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).

We hypothesized that during HFOV, the minimization or absence of leaks around the ETT may be confirmed objectively via direct comparison of the measured mean intratracheal 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 (Rrs and Crs) may be derived from measurements of oscillatory tracheal pressure (Ptr,osc) and proximal airway oscillatory flow (Flow,osc).

Accordingly, this study aimed to 1) develop, with the use of a series of physical model investigations, an objective and practical method to confirm ETT leak removal in HFOV-supported infants and 2) use no-leak Ptr,osc data in combination with Flow,osc/volume data, measured at the proximal ETT, to derive reliable respiratory mechanics parameters—free of ETT effects—which may be used to guide ventilatory management of very low birth weight (VLBW) infants supported with HFOV.

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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 ($\frac{-0.36 \text{ ml/cmH}_2\text{O adiabatic gas equation}}{}$) 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 ($C_{TT};$ high) by inserting 100

Fig. 1. Top: test-lung physical model set-up. HFOV, high-frequency oscillatory ventilator; Ptach, pneumotachograph; Pao, proximal airway opening pressure measurement port; Ptr, tracheal pressure measurement ports. Bottom: frequency response of the Ptr through the endotracheal tube (ETT) monitoring lumen (Ptr1) vs. directly (Ptr2).
measurements were preceded with a 5-min stabilization period at the
setting). The order of the latter two
while only varying
the three studied
data acquisition system (Biopac Systems, Goleta, CA) at a sampling
pressure of oxygen and carbon dioxide measurements (TCM4, Radi-
pulse oximeter, Masimo, Irvine, CA), and transcutaneous partial
SensorMedics, CareFusion), pulse rate, oxygen saturation (Radical
frequency of 1 Hz (test lung) and 2 Hz (infants),
ponents and spontaneous breathing in infants)- and high (oscillatory-
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 ± 0.24 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)
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 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 (Mallinkrodt 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 = 5)],
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 tracings (Respiband Plus and Respitrace,
SensorMedics, CareFusion), pulse rate, oxygen saturation (Radical
pulse oximeter, Masimo, Irvine, CA), and transcutaneous partial
pressure of oxygen and carbon dioxide measurements (TCM4, Radi-
diometry 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 com-
ponents 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 pro-
cessed 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 property either at
the airway opening [resistance (Rao), inertance, compliance; includes
ETT contributions] or at the level of the trachea (%tI, Ps, Crs; no ETT
contributions) by applying an RIC (Rs (R), cmH2O·s·l−1; Is (I),
cmH2O·s·l−1; Crs (C), mL/cmH2O) multiple linear regression model to
the measured oscillatory Pao(t) and Ptr(t), respectively

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

where \( P_0 \) is a constant reflecting static pressure, \( \text{dFlow}(t)/dt \) (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 approx-
imates Ptr2, 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 airway flow, 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 Ptr-Volume loops showed the
profil effects of ETT leaks on the pressure-volume data. As
expected, the derived mechanical properties differed substan-
tially 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 (Cyl.; 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 ∆P (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% ∆P: 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

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 (∆P; ∆Pao) = 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 ΔP on which they were based (100%, 150%, and 50% of the set ΔP; 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 ΔP settings, are summarized in Table 3. Fig. 6 illustrates selected effects of increasing HFOV ΔP on estimated respiratory mechanical properties. Specifically, with increasing ΔP (or oscillatory tidal volumes), both Rao at the proximal ETT (P < 0.001) and ETT inerance (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 ΔP.

Dampening of the ΔP at the distal relative to proximal ETT tended to be slightly greater with increasing ΔP, or the mPtr and ΔP (ΔPtr)/ΔPao (%) ratio tended to decrease (P = 0.088; Table 3). This ratio seemed to be associated with infant Crs, irrespective of the set ΔP (50% − 150% baseline). Specifically, relatively higher tracheal pressure oscillations, ΔPtr/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-

**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>2.5 mm (ID)</td>
<td>mPtr (pred) = -0.91 + 1.02 × mPao - 0.13 × ΔPao + 0.023 × %tI + 0.025 × Frequency</td>
</tr>
<tr>
<td>All data:</td>
<td>mPtr (pred) = -1.01 + 1.01 × mPao - 0.064 × ΔPao + 0.002 × %tI + 0.025 × Frequency</td>
</tr>
<tr>
<td>High Crs:</td>
<td>mPtr (pred) = -1.26 + 1.01 × mPao - 0.064 × ΔPao + 0.024 × %tI + 0.023 × Frequency</td>
</tr>
<tr>
<td>Medium Crs:</td>
<td>mPtr (pred) = -1.13 + 1.01 × mPao - 0.065 × ΔPao + 0.021 × %tI + 0.026 × Frequency</td>
</tr>
<tr>
<td>Low Crs:</td>
<td>mPtr (pred) = -1.25 + 1.01 × mPao - 0.069 × ΔPao + 0.025 × %tI + 0.024 × Frequency</td>
</tr>
<tr>
<td>3.0 mm (ID)</td>
<td>mPtr (pred) = -0.92 + 1.01 × mPao - 0.069 × ΔPao + 0.017 × %tI + 0.015 × Frequency</td>
</tr>
<tr>
<td>All data:</td>
<td>mPtr (pred) = -1.01 + 1.01 × mPao - 0.071 × ΔPao + 0.018 × %tI + 0.021 × Frequency</td>
</tr>
<tr>
<td>High Crs:</td>
<td>mPtr (pred) = -0.92 + 1.01 × mPao - 0.069 × ΔPao + 0.017 × %tI + 0.019 × Frequency</td>
</tr>
<tr>
<td>Medium Crs:</td>
<td>mPtr (pred) = -0.92 + 1.01 × mPao - 0.069 × ΔPao + 0.017 × %tI + 0.0061 × Frequency</td>
</tr>
<tr>
<td>Low Crs:</td>
<td>mPtr (pred) = -0.82 + 1.01 × 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).
including 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 mPao may be predicted accurately from the proximal Pao values, adjusted based on the applied HFOV settings (Table 2), closely approximates the mPao (meas) 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 misestimation of the true (or no-leak conditions) test-lung oscillatory mechanical properties. When
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)</th>
<th>100% ΔP (2)</th>
<th>150% ΔP (3)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HFOV parameters</strong></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 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>
</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>
</tr>
<tr>
<td>ΔPtr, cmH2O</td>
<td>4.85 ± 1.62</td>
<td>7.67 ± 2.76</td>
<td>11.14 ± 5.11</td>
<td>&lt;0.001 All</td>
</tr>
<tr>
<td>ΔP/o (cmH2O)</td>
<td>0.58 ± 0.17</td>
<td>0.55 ± 0.16</td>
<td>0.52 ± 0.16</td>
<td>0.088</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>
</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 1v3</td>
</tr>
<tr>
<td>P–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>
</tr>
<tr>
<td>P–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>
</tr>
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**Mechanical properties**

| Rrs, cmH2O · s · l | 65.5 ± 34.0 | 75 ± 30.4 | 89.2 ± 39.2 | <0.001 All |
| Rs, cmH2O · s · l | 1.09 ± 2.84 | 0.70 ± 1.63 | −0.88 ± 3.11 | 0.91 |
| Cs, cmH2O · s · l | 15.9 ± 12.8 | 18.4 ± 11.6 | 22.9 ± 16.0 | 0.14 |
| Rrs, cmH2O · s · l | 0.36 ± 0.18 | 0.34 ± 0.14 | 0.37 ± 0.18 | 0.39 |
| RErr, cmH2O · s · l | 50.5 ± 26.0 | 57.1 ± 23.7 | 66.3 ± 36.6 | <0.001 1v3, 2v3 |
| RErr, cmH2O · s · l | 0.34 ± 0.10 | 0.36 ± 0.18 | 0.44 ± 0.20 | 0.014 1v3, 2v3 |

ΔPtr = Ptr and ΔP; Rrs = resistance respiratory system; RErr = resistance at the proximal ETT; Irs = inertance at the proximal ETT. 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 \( \Delta P \) 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 overdentention 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 Rrs, as reported previously (18, 21, 22).

The increase in Rao with increasing \( \Delta P \) derives, in large part, from the flow dependence of the tracheal tube Rrs. This, in turn, is a factor in determining the drop in the mean distending pressure, as well as in the \( \Delta P \) 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 \( \text{OPR} \) 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 Crs increases (Fig. 7), and hence, changes in OPR may provide a practical and rather readily available (no computations needed) insight to changes in lung Crs 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

![Fig. 6. Effect of increasing HFOV \( \Delta P \) on estimated preterm infant respiratory mechanical properties. A: Rao and Rrs; B: Crs and ETT inertance (IETT; see Table 3 and RESULTS for details).](image)

![Fig. 7. Respiratory system Crs plotted vs. relative mPtr and \( \Delta P \) (\( \Delta P_{\text{ptr}}/\Delta P_{\text{Pao}} \)) in preterm infants at all 3 \( \Delta P \) settings (50%, 100%, and 150% baseline). Lines represent sigmoidal model fit (solid) and 95% confidence interval (dashed) of all Crs–\( \Delta P_{\text{ptr}}/\Delta P_{\text{Pao}} \) data combined (see model equation in graph panel).](image)
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 Pr,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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