Primate Pleuroesophageal Tissue Barrier Frequency Response and Esophageal Pressure Waveform Bandwidth in Health and Acute Lung Injury

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Background: Dynamic intraesophageal pressure (Pes) is used to estimate intrapleural pressure (Ppl) to calculate lung compliance and resistance. This study investigated the nonhuman primate Ppl-Pes tissue barrier frequency response and the dynamic response requirements of Pes manometers.

Methods: In healthy monkeys and monkeys with acute lung injury undergoing ventilation, simultaneous Ppl and Pes were measured directly to determine the Ppl-Pes tissue barrier amplitude frequency response, using the swept-sine wave technique. The bandwidths of physiologic Pes waveforms acquired during conventional mechanical ventilation were calculated using digital low-pass signal filtering.

Results: The Ppl-Pes tissue barrier is amplitude-uniform within the bandwidth of conventional Pes waveforms in healthy and acute lung injury lungs, and does not significantly attenuate Ppl-Pes signal transmission between 1 and 40 Hz. At Pes frequencies higher than conventional clinical regions of interest the Ppl-Pes barrier resonates significantly, is pressure amplitude dependent at low-pressure offsets, and is significantly altered by acute lung injury.

Conclusions: In monkeys, the Ppl-Pes tissue barrier has a frequency response suitable for Ppl estimation during low-frequency mechanical ventilation, and Pes manometers should have a minimum uniform frequency response up to 8.5 Hz. However, the Ppl-Pes tissue barrier adversely affects the accurate estimation of dynamic Ppl at high frequencies, with varied airway pressure amplitudes and offsets, such as the Ppl encountered during high-frequency oscillatory ventilation. (Key words: Lung elastance; manometry; respiratory mechanics.)

DYNAMIC intraesophageal pressure (Pes) is measured to estimate intrapleural pressure (Ppl) for the calculation of dynamic transpulmonary pressure and lung compliance. The accurate representation of dynamic Ppl using Pes measurements depends on the amplitude and phase frequency response of the intrapleural to intraesophageal tissue barrier (Ppl-Pes tissue barrier). This response is important for the accurate construction of dynamic lung compliance loops and resistance calculations and for the potential measurement of Pes during high-frequency oscillatory ventilation. One study directly compared Pes and Ppl in healthy adult dogs, however, direct Ppl and Pes comparisons to determine the frequency response of the primate Ppl-Pes barrier have not been published.

Intraesophageal pressure manometers should have a uniform frequency response and linear phase shift over the dynamic Pes bandwidth. Frequency response characteristics of clinically used Pes manometers have been investigated but suggested minimum frequency response requirements for Pes manometers are based on dynamic airway pressure (Paw) waveform bandwidths. No data quantifying Pes bandwidth in primates have been published. Assumptions that Pes bandwidth is the same as Paw bandwidth may be invalid because Paw frequency components transmitted to Pes may be amplified or attenuated.
PLEUROESOPHAGEAL BARRIER FREQUENCY RESPONSE

We hypothesize that the Ppl-Pes tissue barrier has a uniform amplitude frequency response within the clinically relevant Pes waveform bandwidth, and is uniform, amplitude independent, and lung-condition independent at low and high frequencies. We aim to determine the frequency response of the primate Ppl-Pes tissue barrier using simultaneous Ppl and Pes measurements in healthy mechanically ventilated monkeys, and those with acute lung injury (ALI). Furthermore, we aim to quantify the dynamic response requirements of Pes manometers by determining Pes bandwidth before and after ALI.

Method

Instrumentation

Twelve female Vervet monkeys (Cercopithecus aethiops, 3.9 ± 0.60 kg) were anesthetized (20 mg/kg ketamine induction and 10 mg·h⁻¹·kg⁻¹ ketamine, > 30 μg·h⁻¹·kg⁻¹ sufentanil [Janssen-Cilag, Johannesburg, South Africa], and 5 μg·h⁻¹·kg⁻¹ adrenaline maintenance continuous infusions), paralyzed (10 μg·h⁻¹·kg⁻¹ vecuronium [Omnimed, Johannesburg, South Africa], and intubated orally (cuffed 4.5 mm, Mallinkrodt, Athlone, Ireland), and mechanically ventilated in the supine position with warm humidified 100% O₂ (fraction of inspired oxygen [FIO₂] = 1.0) using a high-flow-rate pressure-cycle pressure-limit ventilator (model 105; Premecare, San Antonio, Texas). University Animal Ethics Clearance (96/113/2B) was obtained. The right femoral vein was cannulated for injection of oleic acid to produce ALI.

Intrapleural Pressure and Intraesophageal Pressure Catheter Design and Pressure Measurements

Intraesophageal pressure and Ppl catheters were adapted for dynamic pressure measurements by scaling the tips of size 7 French gauge transducer-tip catheters (Millar Mikro-tip SPC 470; Millar Instruments, Inc., Houston, Texas) into water-filled latex balloons 2 cm in length. The distal end of the Ppl transducer catheter was enclosed in a right-angled rigid perforated acrylic cylinder, around which the balloon was tied. The cylinder was fashioned with a distal pointed end, such that the catheter would act as an introducer during transthoracic positioning, and, once inserted, the water-filled balloon rested parallel to the chest wall inside the pleural space. A second catheter attached to the Ppl catheter was linked to an underwater chest drain for pneumothorax deflation. The water volumes of the Ppl and Pes catheter balloons were set to allow maximum balloon-catheter compliance. The frequency responses of the two catheters were amplitude-linear and -equivalent.

With the aid of a transcutaneous cut-down to pleura and dilating trocars, the Ppl catheter was inserted transthoracically in either a cranial or a caudal direction into the left or right sides of the chest (n = 3 of each side per group) at the level of the seventh intercostal space in the mid axillary line. The in vivo Pes catheter site was chosen according to the best “paralyzed airway occlusion test,” in which the airway is briefly occluded and abdominal pressure is applied to assess how faithfully ΔPes reproduces ΔPpl in an isovolumic chest of anesthetized paralyzed subjects.

Airway opening pressure was measured with a piezoresistive differential pressure transducer (Microswitch 170PC; Honeywell, Morristown, NJ) inserted to the proximal endotracheal tube perpendicular to the gas flow direction.

All pressure transducer signals were preamplified using the same apparatus (Hellige Servomed, Freiburg, Germany) and digitized at 500 Hz (Biopac MP100 and AcqKnowledge version 3.3.2; Biopac Systems Inc., Goleta, CA).

Intrapleural-Intraesophageal Pressure Tissue Barrier Frequency Response Determination

Intrapleural pressure waveforms were generated by applying sinusoidal Paw waveforms using the pneumatic driver unit of a high-frequency oscillatory ventilator (3100A; SensorMedics, Bilthoven, The Netherlands, and Manta Medical Systems, Johannesburg, South Africa). To generate sine-wave rather than square-wave Paw outputs, the square-wave frequency generator of the ventilator was bypassed, and the DC-coupled amplifier was controlled by a separate sine-wave generator (Dynamic Signal Analyser 3562A; Hewlett Packard, Palo Alto, CA).

Amplitude frequency responses of the Ppl-Pes tissue barrier were calculated by comparing the Ppl and Pes waveform signals generated between 1 Hz (taken as the DC response to which the responses were normalized) and 40 Hz. Swept-sine waves were applied at 0.98 Hz intervals with a 20-s integration time and a 90% integration threshold for each frequency interval (Dynamic Signal Analyser 3562A). The dynamic signal analyzer performs a high-resolution Fourier transform at each measured frequency and extracts amplitude and phase information from the acquired Ppl and Pes waveform signals only at the frequency of interest, thereby ignoring any harmonics created by distortion. In each subject,
10 swept-sine wave sequences (performed by disconnecting the standard ventilator and connecting the high-frequency oscillatory ventilator at 5-min intervals) were averaged at each of two mean Paw offsets: 1 cm H$_2$O and 10 cm H$_2$O above atmospheric pressure. These mean Paw pressure offsets were generated during the swept-sine measurements by injecting excess oxygen into the airway and allowing the excess to bleed off under water at the appropriate depth. Frequency response traces during which esophageal peristalsis occurred were rerecorded.

Frequency response measurements were recorded at two mean Paw offsets (1 or 10 cm H$_2$O) before and 2.5 h after intervention (oleic acid (ALI group [ALIG], n = 6) or saline (control group [CTRL], n = 6 injection). These measurements were recorded at a low applied Ppl amplitude (low applied Ppl; ΔPpl waveform mean amplitudes were set to be ± 1.0 cm H$_2$O at 1 Hz, reducing to ± 0.5 cm H$_2$O at 40 Hz). At 7.5 h after intervention, the frequency response measurements were recorded at a mean Paw offset of 20 cm H$_2$O at low applied Ppl amplitude, and again at Paw offset of 10 cm H$_2$O, but at a larger applied Ppl amplitude (high Ppl amplitude; ΔPpl waveform mean amplitudes were set to be ± 4.7 cm H$_2$O at 1 Hz, reducing to ± 1.0 cm H$_2$O at 40 Hz).

**Intraesophageal Pressure Dynamic Waveform Bandwidth**

Intraesophageal pressure and Paw measurements were made in six subjects before (baseline, PesB, and PawB) and 5.5 h after (PesA and PawA) oleic acid injection in the ALI group (n = 6). Respiratory rate (RR) and maximum Paw (Paw pk) were adjusted to achieve an arterial carbon dioxide pressure (Paco$_2$) of 30-40 mmHg. In addition, Pes and Paw traces were acquired during extreme conditions by raising Paco$_2$ of 30-40 mmHg. In addition, Pes and Paw traces were acquired during extreme conditions by raising peak Paw 50% above the physiologically required peak Paw and simultaneously doubling the respiratory rate (elevated PesB and PawB, or elevated PesA and PawA).

Trains of 10 PesB and PesA waveform sequences, each containing 10 mechanical breaths, were selected and low-pass filtered using a Blackman (AcqKnowledge version 3.3.2; Biopac Systems Inc.) finite impulse response linear phase filter with minimal phase shift, for which the response was tailored to be near −1 dB at chosen low-pass cut-off frequencies. Twelve low-pass cut-off frequencies were selected that reduced the areas under the curve (%AUC) of the Pes continuous-power spectrum by predetermined proportions. Power spectra were determined by ensemble-averaging of the power spectra of 10 PesB and PesA breaths. The mean value was subtracted from each ensemble and the data was padded with zeros before fast Fourier transform (AcqKnowledge version 3.3.2; Biopac Systems). One hundred percent of Pes waveform power was assumed to be contained between 0 and 40 Hz.

The average Pes amplitude between Pes at onset of expiration to Pes at onset of inspiration for each of 10 mechanical breaths was determined manually for the original trains of unfiltered Pes waveforms and compared with those of the incrementally low-pass-filtered Pes waveforms. The maximum waveform amplitude error (% amplitude difference from original Pes waveform) averaged for 10 breaths was determined among the six subjects. The Pes bandwidth, up to which a Pes manometer should have a uniform amplitude frequency response to yield a 3% or less or 5% or less error when measuring the end-expiratory to end-inspiratory amplitude of physiologic or extreme-case Pes waveforms, was determined (Pes EI-EE bandwidth).

**Statistical Analysis**

Amplitude frequency responses in which the mean Pes-Ppl ratio deviated by more than 10% from 1.0, plus the 95% confidence interval value excluded 1.0 (both conditions met), were considered to significantly deviate from that of uniformity. Significant within-group (within the ALI or within the CTRL) progressive changes were detected using Friedman analysis of variance (repeated measures), followed by identification with the Wilcoxon signed rank test. The Mann-Whitney test was used to determine significant differences between the ALI and CTRL groups (Statistica; Statsoft, Tulsa, OK). Frequency response graphically displayed values are the mean ± SEM; all ventilation variables are the mean ± SD; and differences with P values < 0.05 are regarded as statistically significant.

**Results**

**Intrapleural–Intraesophageal Tissue Barrier Frequency Response**

Mean Pes-Ppl area under the curve ratios were more than 0.90 in all groups for the anesthetized monkey Pes manometer occlusion tests (table 1). Figure 1 depicts the swept-sine amplitude frequency response at baseline in
Table 1. Anesthetized Monkey Occlusion Test Ratios

<table>
<thead>
<tr>
<th>Paw Offset</th>
<th>Pes/Ppl</th>
<th>Paw/Ppl</th>
<th>Baseline AUC (n = 12)</th>
<th>CTRL (n = 6)</th>
<th>ALIG (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 cm H₂O</td>
<td>0.94 ± 0.067</td>
<td>0.90 ± 0.126</td>
<td>0.90 ± 0.061</td>
<td>0.95 ± 0.092</td>
<td>0.90 ± 0.082</td>
</tr>
<tr>
<td>10 cm H₂O</td>
<td>0.90 ± 0.080</td>
<td>0.90 ± 0.148</td>
<td>0.97 ± 0.163</td>
<td>0.96 ± 0.099</td>
<td>0.92 ± 0.077</td>
</tr>
</tbody>
</table>

AUC = area under the curve, ratio of two pressure waveform AUC values; Paw offset = airway pressure offset during occlusion test; Pes/Ppl = AUC ratio of esophageal to pleural pressure during occlusion test; Paw/Ppl = AUC ratio of airway to pleural pressure during occlusion test; CTRL = control group receiving saline; ALIG = acute lung injury group receiving oleic acid.

the combined (n = 12) ALIG and CTRL subjects (Paw offset = 1 cm H₂O and 10 cm H₂O). The Ppl-Pes tissue barrier amplitude frequency response was uniform from 1 to 40 Hz when Paw offset was 10 cm H₂O. However, the 95% confidence interval lower limit of the response was greater than unity and the mean response was greater than 1.10 at frequencies more than 14.7 Hz when Paw offset was 1 cm H₂O. From 20.5-40 Hz, the amplitude frequency response when Paw offset was 1 cm H₂O was significantly greater than when Paw offset was 10 cm H₂O (fig. 1).

After control saline injection the CTRL (n = 6) amplitude frequency response was uniform between 1 and 40 Hz (similar to CTFU baseline at Paw offset of 10 cm H₂O from fig. 1) and, at Paw offset of 1 cm H₂O, the response was significantly resonant, from 13.7 to 15.7 Hz and from 26.4 to 32.2 Hz (before lung injury, it was uniform from 1 to 40 Hz, baseline, fig. 1). Within the ALIG, the amplitude response was significantly different between Paw offset of 1 cm H₂O versus Paw offset of 10 cm H₂O, from 3.0 to 5.9 Hz and 8.9 to 14.7 Hz and at 30.3 Hz (fig. 2).

At Paw offset of 20 cm H₂O, the CTRL amplitude response was uniform, from 1 to 40 Hz (similar to CTRL baseline at Paw offset of 10 cm H₂O from fig. 1 and to CTRL after saline injection at Paw offset of 10 cm H₂O), whereas the ALIG amplitude response continued to deviate from uniformity between 4.0 and 5.0 Hz and 30.3 and 36.1 Hz (resembling the ALIG amplitude response at

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Fig. 1. Baseline intrapleural pressure (Ppl)-intraesophageal pressure (Pes) tissue barrier amplitude frequency responses at low and high mean airway pressure offsets. Hz = swept-sine frequency in cycles/s; Paw = airway opening pressure; Pes-Ppl = amplitude gain of esophageal pressure over intrapleural pressure. *P < 0.05 and **P < 0.01; amplitude gain significantly different for Paw offset of 10 cm H₂O versus 1 cm H₂O; +amplitude response deviates significantly from uniformity (see criteria in Methods).

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Figure 2. Intrapleural pressure (Ppl)–intrathoracic pressure (Pes) tissue barrier amplitude frequency responses at low and high mean airway pressure offsets after acute lung injury (ALI; ALI group). Hz = swept-sine frequency in cycles/s; Paw = airway opening pressure; Pes-Ppl = amplitude gain of esophageal pressure over intrapleural pressure. *P < 0.05; amplitude gain significantly different for Paw offset of 10 cm H$_2$O versus 1 cm H$_2$O; +amplitude response deviates significantly from uniformity (see criteria in Methods).

Paw offset of 10 cm H$_2$O from fig. 2, which deviated from uniformity after ALI.

At Paw offset of 10 cm H$_2$O, but with high Ppl amplitude, CTRL was uniform between 1 and 40 Hz (similar to the baseline fig. 1 and postsaline CTRL responses at Paw offset of 10 cm H$_2$O with low Ppl amplitude), whereas the ALIG significantly deviated from uniformity between 23.5 and 31.3 Hz (similar to the ALIG response at Paw offset of 10 cm H$_2$O with low Ppl amplitude from fig. 2). Minimum to maximum phase differences were small: $-11$ to $+26^\circ$ among all frequencies and lung conditions tested.

Intrathoracic Pressure Waveform EI-EE Bandwidth

The physiologic Paw and Pes waveforms, as measured before (physiologic PawB and PesB) and after lung injury (physiologic PawA and PesA) used for Pes EI-EE bandwidth determination are characterized in table 2. The effect of low-pass filtering of physiologic PesB waveforms is shown in figure 3. Incrementally, low-pass filtering between the third and fourth (1.2 Hz) and the second and third (0.8 Hz) harmonic frequencies leads to errors in the end-inspiratory to end-expiratory waveform amplitudes.

The mean (n = 6 subjects) frequencies at which power in the Pes waves is 78–90% of total power are shown in figure 4. On average, among all the lung conditions, up to 90% and 78% of Pes waveform power is found to be less than 8.0 and 3.4 Hz, respectively.

Figure 5 shows the maximum Pes waveform error produced by low-pass filtering of Pes of healthy lungs (fig. 5A) and lungs with ALI (fig. 5B). With increasing attenuation of Pes energy, the waveform error increases. The maximum waveform error showed a trend toward being larger for elevated PesA waveforms than for physiologic PesB waveforms. The maximum waveform errors were larger for PesA waveforms (after ALI) than for PesB waveforms (at baseline; fig. 5B, physiologic PesA vs. fig. 5A, physiologic PesB).

Among Pes for all subjects, the highest cut-off frequencies (largest waveform EI-EE bandwidth) that yielded a more than 5% waveform error was 1.9, 3.4, 4.6, and 8.5 Hz for the physiologic PesB, elevated PesB, physiologic PesA, and elevated PesA waveforms, respectively. Corre-

Table 2. Physiologic Ventilation Characteristics for Pes EI-EE Bandwidth Determination

<table>
<thead>
<tr>
<th></th>
<th>Before ALI</th>
<th>5.5 hr after ALI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PawB</td>
<td>PesB</td>
</tr>
<tr>
<td>RR</td>
<td>19 ± 4.9</td>
<td>33 ± 10.7</td>
</tr>
<tr>
<td>Paw pk</td>
<td>12 ± 0.9</td>
<td>7 ± 2.4</td>
</tr>
<tr>
<td>PEEP</td>
<td>3 ± 1.0</td>
<td>1 ± 1.9</td>
</tr>
<tr>
<td>Paw M</td>
<td>6 ± 0.8</td>
<td>3 ± 2.2</td>
</tr>
</tbody>
</table>

Values are those necessary for $PaCO_2$ of 30–40 mmHg.
ALI = oleic acid–induced acute lung injury; Paw pk, M = peak and mean proximal airway pressure in cm H$_2$O; PawB, PawA = physiologic mean proximal airway pressure at baseline and in ALI; PEEP = positive end-expiratory pressure; PesB, PesA = physiologic mean intrathoracic pressure at baseline and in ALI; RR = respiratory rate.
Fig. 3. Illustration of low-pass filtering effect on intraesophageal pressure (Pes) waveforms. Overdamped Pes acquisitions result in gradual erosion of Pes waveform shape. Paw = original proximal airway pressure waveform; Pes = original and two filtered (low-pass cut-off frequencies, 1.8 and 0.8 Hz, respectively) intraesophageal physiologic pressure waveforms at baseline.

Corresponding values for a waveform error of more than 3% were 2.1, 4.9, 6.0, and 8.5 Hz.

Discussion

Intruleural-Intraesophageal Pressure Tissue Barrier Frequency Responses

Concerns pertaining to Pes measurements are raised through findings such as the lung volume dependency and Paw dependency of Pes changes in infants and adults, and the frequency dependency and Paw dependency of lung compliance values in healthy adult monkeys. The mechanical properties of the esophageal wall and surrounding structures are a potential cause of signal alteration when estimating dynamic Ppl from Pcs.

Our Ppl and Pes catheters are comparable to clinically used Pes air-balloon catheters but have a lower volume-displacement coefficient, are amplitude independent, and have a wider dynamic range suitable for assessing the Ppl-Pes tissue barrier at high frequencies. Using direct, simultaneous Ppl and Pes measurements, we have demonstrated that the amplitude frequency response of the Ppl-Pes tissue barrier is uniform within the EI-EE.

Fig. 4. Frequency value of power spectrum of intraesophageal pressure (Pes) as a function of Pes waveform energy content, assuming 100% of waveform energy content lies between 0 and 40 Hz. AUC = % energy above 0 Hz remaining under the power spectrum curve relative to that between 0 and 40 Hz (100%); Hz = average frequency recorded for the particular area under the curve value. PesB, PesA = mean intraesophageal pressure waveforms at baseline and after acute lung injury, at physiological (PaCO2 of 30-40 mmHg) or artificially elevated airway pressures.
bandwidth (up to 8.5 Hz) of physiologicPes waveforms measured in anesthetized mechanically ventilated primates and with healthy lungs and ALI. The barrier does not significantly attenuate Ppl-Pes signal transmission between 1 and 40 Hz. However, at higher frequencies in this range, the Ppl-Pes frequency response resonates significantly, is amplitude dependent, and is significantly altered in the presence of lung disease.

Studies that used direct Ppl measurements, but with markedly differing methodologies among the studies, have shown that the Ppl-Pes amplitude frequency response in dogs did not deviate by more than 10% from unity between 2 and 20 Hz, and no amplitude dependency was observed by varying the mean Paw offset. In rabbits there was slight attenuation of Pes measured at discrete frequencies of 30, 40, and 50 Hz.

Alterations in the Ppl-Pes tissue barrier frequency response seen after induction of ALI could be caused by changing lung conditions in ALI that affect Ppl-Pes transmission or by reduced amplitudes in the Ppl waveforms during the ALI swept-sine runs, if the system is nonlinear. In the current study, Ppl amplitude power spectra were similar before and after ALI; therefore, the alterations in the Ppl-Pes tissue barrier frequency response seen after induction of ALI probably are related to respiratory system ALI changes. Changes in the Ppl-Pes barrier could result from partial or complete isolation of the Ppl or Pes catheters. This is also unlikely because we inserted the Ppl catheter among subjects into both the left or the right sides of the chest, in caudal or cranial directions, and the Ppl, Pes, and Paw occlusion test results before and after ALI were similar (table 1). The generation of negative pressures in the airways during oscillation, which occurred when mean Paw offset was 1 cm H$_2$O, may have altered the Ppl-Pes tissue barrier frequency responses. Inaccuracy of Pes measurements has been attributed to chest wall distortion producing uneven pleural pressure distribution. However, this is an unlikely contributing factor because the Ppl-Pes tissue barrier frequency responses at low frequencies did not depend on mean Paw (and thus on negative Paw) in our animals (fig. 1).

When Paw pressure offsets were switched from 1 to 10 cm H$_2$O, the Ppl-Pes tissue barrier frequency response changed, in both the CTRL and ALIG, although the 1- or 10-cm H$_2$O Paw offsets at which the Ppl-Pes gain occurred is different in the ALIG vs. the CTRL. Such a change is not seen when the Paw pressure offsets were switched from 10 to 20 cm H$_2$O. In addition, increasing applied Ppl amplitude at a Paw offset of 10 cm H$_2$O did not significantly change the Ppl-Pes responses within the ALIG or the CTRL. To avoid the risk of Paw negative pressure trauma, we did not test the effect of a high Ppl amplitude when the Paw offset was 1 cm H$_2$O. The amplitude dependency lies at lower Paw pressures (1-10 cm H$_2$O). These findings suggest that, in conditions in
which peak end-expiratory pressure or mean Paw are higher (such as occur during high-frequency oscillatory ventilation modes), it may be possible to correct the Pes waveform output using an esophageal transfer function to compensate for the Ppl-Pes tissue barrier gain (found during ALI at 10 and 20 cm H₂O Paw offsets) because the Ppl-Pes frequency response exhibited a linear amplitude gain based on the 10- and 20-cm H₂O Paw offsets.

**Intraesophageal Pressure Waveform EI-EE Bandwidth**

The bandwidth of pressure waveforms is influenced by the type of transform used for frequency content analysis, characteristics of the chosen filters, and the criteria for waveform error. We based Pes waveform error on the Pes amplitude difference between end-inspiration and end-expiration because these are commonly used points of reference for lung compliance calculations in clinical settings. Using peak amplitude, or end-inspiratory to end-expiratory amplitude, based on the first points of zero gas flow, as opposed to the method we chose, reduces the calculated Pes waveform error and, thus, plays down the potential distorting effect on dynamic lung compliance loops. Our Pes EI-EE bandwidths represent the maximum likely bandwidths of a range of Pes waveforms encountered in healthy monkeys undergoing ventilation and monkeys with ALI.

The larger maximum EI-EE bandwidths noted in the supraphysiologic (elevated) PesB and PesA waveforms, compared with the physiologic PesB and PesA waveforms, probably are caused by increased energy content found at higher frequencies in some of the elevated Pes waveforms. The larger Pes EI-EE bandwidths noted after ALI (PesA) compared with healthy baseline lungs (PesB) may be caused by increased energy content at higher frequencies in some of the PesA waveforms because of the higher Paw values necessary for ALI (table 2), or because of the ALI condition itself altering the Ppl-Pes transmission of waveform frequency components. The latter is unlikely because the frequency response of the Ppl-Pes tissue barrier was uniform up to the determined EI-EE bandwidths before and after ALI.

**Conclusion**

Direct simultaneous Ppl and Pes measurement reveals that the Ppl-Pes tissue barrier has a uniform amplitude frequency response within the EI-EE bandwidth of conventional Pes waveforms in healthy lungs and ALI and does not significantly attenuate Ppl-Pes signal transmission between 1 and 40 Hz. At Pes frequencies higher than conventional clinical regions of interest, the Ppl-Pes barrier resonates significantly, is pressure amplitude dependent at low pressure offsets, and is significantly altered by ALI.

Allowing for 5% or less of Pes waveform error, the maximum Pes EI-EE bandwidths during conventional ventilation are 1.9 Hz and 3.4 Hz for physiologic and extreme-case waveforms in healthy lungs, and 4.6 Hz and 8.5 Hz during ALI. For a 3% or less waveform error, the maximum Pes EI-EE bandwidth is 8.5 Hz.

In Vervet monkeys, the Ppl-Pes tissue barrier has a frequency response suitable for Ppl estimation during low-frequency mechanical ventilation, and Pes manometers should have a uniform frequency response up to 8.5 Hz. However, the Ppl-Pes tissue barrier adversely affects the accurate estimation of dynamic Ppl at high frequencies, with varied airway pressure amplitudes and offsets, such as the Ppl encountered during high-frequency oscillatory ventilation. These findings may facilitate the improvement of the accuracy of primate pulmonary function studies in high-frequency respiratory mechanics.

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**References**


