HETEROGENEOUS AIRWAY VERSUS TISSUE MECHANICS AND THEIR RELATION TO GAS EXCHANGE FUNCTION DURING MECHANICAL VENTILATION

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Abstract

We have advanced a commercially available ventilator (NPB840, Puritan Bennett/Tyco Healthcare, Pleasanton, CA) ventilator to deliver an Enhanced Ventilation Waveform (EVW). This EVW delivers a broadband waveform that contains discrete frequencies blended to provide a tidal breath, followed by passive exhalation. The EVW allows breath-by-breath estimates of frequency dependence of lung and total respiratory resistance (R) and elastance (E) from 0.2 to 8Hz. We hypothesized that the EVW approach could provide continuous ventilation simultaneously with an advanced evaluation of mechanical heterogeneities under heterogeneous airway and tissue disease conditions. We applied the EVW in 5 sheep before and after a bronchial challenge and an oleic acid (OA) acute lung injury model. In all sheep, the EVW maintained gas exchange during and after bronchoconstriction, as well as during OA injury. Data revealed a range of disease conditions from mild to severe with heterogeneities and airway closures. Correlations were found between the arterial partial pressure of oxygen ($P_aO_2$) and the levels and frequency-dependent features of R and E that are indicative of mechanical heterogeneity and tissue disease. Lumped parameter models provided additional insight on heterogeneous airway and tissue disease. In summary, information obtained from EVW analysis can provide enhanced guidance on the efficiency of ventilator settings and on patient status during mechanical ventilation.

Key Terms: ARDS, sheep, dynamic lung mechanics, PEEP
INTRODUCTION

There is an increasing body of evidence that airway (i.e. asthma) and tissue diseases (i.e. acute respiratory distress syndrome or ARDS and emphysema) affect the lung in a heterogeneous fashion. Heterogeneous disease conditions can create ventilation-perfusion mismatch, increased work of breathing, and require higher pressures for spontaneous ventilation. Eventually deterioration of gas exchange occurs which may result in artificial mechanical ventilation. During mechanical ventilation, positive end-expiratory pressure (PEEP) levels are typically titrated against the patient’s static pressure-volume curve in an effort to maximize alveolar recruitment while minimizing ventilator induced lung injury. However, the act of ventilation is dynamic, not static and the mechanical load against which a ventilator must act depends upon the patient’s dynamic respiratory resistance (R) and elastance (E).

Several techniques exist to assess R and E during mechanical ventilation at a single frequency. It is now known that with heterogeneous lung properties, R and E become highly frequency dependent for frequencies surrounding typical ventilation rates. Moreover, the frequency dependence from 0.2 to 8 Hz reflects not only the viscoelastic nature of parenchymal tissue but also the magnitude and distribution of airway and tissue disease (i.e. distribution of time constants throughout the airway tree). Recent studies have invoked anatomic, morphometrically consistent lung models to predict the impact of heterogeneous lung diseases and the results (Figure 1) are consistent with data taken under similar conditions. Such data may permit inference of abnormal ventilation distribution. In principle, this information could even aid in determining ventilator settings that reduce the heterogeneity so as to minimize the likelihood of lung injury.

In a previous study, our group reported a broadband enhanced ventilator waveform (EVW) approach that can provide reliable estimates of R and E for 0.2 to 8 Hz while delivering a normal tidal volume (VT) during mechanical ventilation. In principal, this form of ventilation could replace conventional ventilation (CV) while simultaneously providing a breath-by-breath account of frequency-dependent features of R and E (and thus indices of the heterogeneity of lung disease). We hypothesized that the EVW approach could provide continuous mechanical
ventilation simultaneously with an advanced evaluation of mechanical heterogeneities under heterogeneous airway and tissue disease conditions. The EVW was applied during the progression of two intubated sheep models of lung disease: carbachol, which primarily affects the airways, and oleic acid (OA) injury, which is more of a tissue level injury. Specifically, carbochol increases overall airway resistance by direct bronchoconstriction and OA induces widespread pulmonary edema by increasing capillary permeability, which results in an overall change in tissue mechanics as estimated at the airway opening. Sheep were chosen since their lung size is comparable to human lungs. After confirming that the EVW could sustain ventilation, we evaluated how frequency dependent parameters derived from EVW data correlated with gas exchange function of the lung. We also applied mathematical models to examine the contributions of airway and tissue heterogeneities to deterioration in gas exchange.

**METHODS**

Dynamic lung and respiratory system mechanics and arterial blood gases (ABGs) were measured in 5 sheep before and after a carbachol treatment to induce bronchoconstriction and before and after an OA treatment to induce a state similar to ARDS. In all experiments, the sheep were connected to either a conventional ventilator or our modified ventilator which delivered the EVW. Measurements were taken at baseline and throughout the progression of the disease state. We first evaluated the impact of transient bronchoconstriction created via inhalation of carbachol on the ventilation capabilities and the frequency dependence tracking ability of the EVW. The sheep were allowed several weeks to fully recover, and then we repeated the assessment of the EVW during simulated ARDS created with OA. The premise of evaluating the EVW in these two distinct diseases was to assess and contrast the usefulness of the EVW during conditions of acute airway and tissue heterogeneity.

**Animal Preparation:**

The protocol was approved by the Institutional Animal Care and Use Committee at Tufts University School of Veterinary Medicine. We studied 5 female sheep (mean weight, 48.8 ± 4.2
kg). Measurements were performed while the sheep were under anesthesia, induced with 7 mg/kg of intravenous ketamine (Ketaset, Fort Dodge Pharmaceuticals, Fort Dodge, Iowa) and 0.25 mg/kg of diazepam (Valium, Roche Pharmaceuticals, Nutley, New Jersey)\(^5\). Intravenous access was obtained via an external jugular vein catheter. Anesthesia was maintained with continuous intravenous drip of propofol (Propoflo, Abbott Labs, Columbus, OH) at the rate of 50mg/kg/min. A standard 10-mm ID endotracheal tube was inserted orotracheally under fiberoptic guidance and secured in place. A 7 cm latex esophageal balloon containing ~0.5ml of air connected to a polyethylene catheter was introduced to the level of the mid-thorax, and the desired position verified by observing maximal trans-pulmonary pressure (\(P_{\text{tp}}\)) shifts. Heart rate and hemoglobin saturation were continuously monitored using a pulse oximeter (BIOX3740 Pulse Oximeter, Ohmeda, Louisville, CO). ABGs were obtained from a carotid artery loop inserted 3-5 weeks prior to experiments. The arterial blood gas levels and percent hemoglobin saturation were analyzed using a calibrated blood gas analyzer (IRMA SL Blood Analysis System, Diametrics Medical, St. Paul, MN).

**EVW Delivery and Data Acquisition Systems:**

In conjunction with Puritan Bennett/Tyco Healthcare, an experimental ventilator platform (NPB840, Puritan Bennett/Tyco Healthcare, Pleasanton, CA) was programmed to deliver an EVW ventilation pattern. The EVW waveform has been described previously\(^{19}\). Briefly, the ventilation pattern is similar to a conventional ventilator waveform in that it delivers typical tidal \(V_T\) and allows for passive expiration. The unique aspect of the inspiratory waveform is that it is the sum of distinct sinusoids ranging from 0.2 to 8Hz. The energy at each frequency of the waveform was weighted such that the lowest frequency component had the most energy so as to provide a tidal breath. Figure 2 depicts an example of the flow and pressure waveforms associated with the EVW as compared to that of CV. The sheep were connected to either an adult volume-cycled conventional ventilator (Bear I, Bear Medical Systems, Inc, Riverside, CA) or the updated EVW delivery system. Ventilation settings such as \(V_T\) and I:E ratio were the same regardless of mode of ventilation. These two ventilators were connected to an angled stopcock allowing leak free
switching between modalities. The airway opening flow, $V_{ao}$, was measured with a pneumotachograph (Model 4700, Hans Rudolph, Kansas City, MO) connected to a pressure transducer (Model LCVR, 0-2cm H$_2$O, Celesco, Chatsworth, CA). Airway opening pressure, $P_{ao}$, was measured with a differential pressure transducer (Model LCVR, 0-50 cm H$_2$O, Celesco, Chatsworth, CA). Transpulmonary pressure, $P_{tp}$ ($P_{ao}-P_{es}$ where $P_{es}$ is esophageal pressure), was also measured with a differential pressure transducer (Model LCVR, 0-50 cm H$_2$O, Celesco, Chatsworth, CA). All signals were low pass filtered at 10 Hz (4 Pole Butterworth, Frequency Devices, Haverhill, MA) and sampled at 50 Hz (DT-2811 A/D board, Data Translations, Marlboro, MA).

**Bronchoconstriction Protocol:**

The EVW was applied to the sheep before and after experimental bronchoconstriction. The ventilation settings for both CV and EVW were as follows: $f=15$ breaths/min, $I:E=1:3$, $V_T=500$ ml ($\approx$10 ml/kg), 100% oxygen, and PEEP=0 cmH$_2$O. After anesthesia and intubation, the sheep were stabilized on CV for 30 min. The EVW was then applied for 30 min at baseline and mechanics and ABGs were measured throughout this period. After the baseline measurements, doubling concentrations of nebulized carbachol (starting with 2mg/ml and up to 16 mg/ml) were delivered for 2 min each. Although the dose was the same in each sheep, there was no effort made to standardize the response levels since our aim was to create varying degrees of bronchoconstriction in order to evaluate EVW ventilation under a variety of disease conditions. ABG and EVW data taken at 5, 15, and 30 min. Albuterol aerosol (900 mcg) was then administered by an in-line delivery device (AeroVent, Trudell Medical International, London, Ont) and EVW measurements were repeated after 10 min.

**Oleic Acid Injury Protocol:**

After a recovery period of 4-6 weeks, the EVW was applied in the same five sheep before and during OA treatment. After stabilization on CV, ABG and EVW measurements were collected at baseline. The ventilation settings were the same as for the bronchoconstriction protocol with
the exception that PEEP was set to 5 cmH₂O. While being ventilated with the EVW, OA (0.1 ml/kg) emulsified in blood was administered by intravenous injection (slowly for 3-min) in three equal portions, every 10 min for a 30 min period¹⁴,³². This was directly followed by an injection of Hetastarch (6%, 500ml). For the remainder of the experiment, Lactated Ringers Injection (Baxter Healthcare Corporation, Deerfield, IL) was delivered at a rate of 8 ml/kg/hr to maintain volume status. The OA treatment was allowed to progress over a period of 30 min directly following the last injection of OA or until the animal’s $P_{aO_2}$ dropped below 200 mmHg. If the target of $P_{aO_2}/FIO_2<200$ was not reached, additional doses of OA were administered. ABG and EVW measurements were collected before each dose of OA and every 15 min thereafter. Once the target disease state was reached, the sheep were ventilated on CV for 15 min or EVW for 15 min in a randomized order. Directly following each 15 min ventilation period, ABG and EVW measurements were taken. At the end of the experiment, animals were sacrificed using an IV dose of 120mg/kg of pentobarbital solution (Beuthanasia-D, Schering-Plough Animal Health, Union, NJ).

**Data Processing:**

The EVW data were processed according to a previously described method by Kaczka et al¹⁹. Briefly, inspiratory segments of pressure and flow files were first isolated and the resulting $\dot{V}_{ao}$ and $P_{tp}$ (or $P_{ao}$) quantities were fit to a trigonometric series by employing a linear regression technique. The $P_{tp}$ data allowed for estimates of lung impedance ($Z_L$) while the $P_{ao}$ data allowed for estimates of respiratory system impedance ($Z_{rs}$). With the EVW, each inspiration is initiated when expiratory airflow has ceased. Therefore, the measured inspiratory flow and pressure segments following each expiration period consist of both transient and steady state components. Since the lowest frequency component in the EVW waveform completes only a half cycle of oscillation during a given inspiration, distortion in the estimate of $R$ and $E$ at this frequency is likely when the technique of Kaczka is applied. Hence, we modified the analysis as follows: The inspiratory segments of the EVW were first low-pass filtered digitally using a 3rd order Butterworth
filter with a cutoff frequency of 0.35 Hz to isolate the lowest frequency component (0.2 Hz) present in the waveform. We then fit the data for each inspiration to the following:

\[ P = R \cdot \dot{V}_{ao} + E \cdot \int \dot{V}_{ao} \, dt + P_o \]  

(1)

where \( P_o \) represents the pressure at which volume and flow are zero. The resulting average \( R \) and \( E \) estimates for each impedance measurement substituted for the lowest frequency \( R \) and \( E \) estimates.

**Data Analysis:**

One set of impedance data consisted of both lung and respiratory system \( R \) and \( E \) at five distinct frequencies (0.1953, 0.4883, 1.8555, 3.6133, and 8.1054 Hz). For each of the 5 sheep and in each of the two lung disease treatments, we obtained such impedance data as well as an ABG measurement at the time points specified previously. The impact of bronchoconstriction and alveolar collapse/flooding on mechanics, and gas exchange function, were analyzed via feature and model analyses of the impedance data. The structure-function correlates of the features were based on published anatomically consistent computational models\(^1, 9, 22, 43\). Specifically, both the absolute difference between \( R \) at 0.2 Hz and \( R \) at 8 Hz and the difference between \( E \) at 2Hz and \( E \) at 0.2Hz are indices of frequency dependence of \( R \) and \( E \), and thus reflect the heterogeneity of disease. It is important to note that other mechanisms such as tissue viscoelasticity and airway wall shunting can contribute to both of these absolute differences; however, we assume that the preponderance of the increase in frequency dependence is due to disease heterogeneity. As complete airway closure, extreme airway narrowing, or alveolar collapse/flooding occur, there will be an increase in the low frequency \( E \) since less lung is communicating with the airway opening. An increase in this \( E \) can also be attributed to increases in overall tissue stiffness. In summary, \( E \) at 0.2 Hz is as an index representing the combined effects of “effective” airway closure at this ventilation frequency, derecruitment, and tissue stiffness. Widespread peripheral airway constriction can cause flow to shunt into the stiffer central airway walls which creates a corresponding increase in \( E \) at 8 Hz\(^10\). Thus, the value of \( E \) at 8Hz is an index of airway wall shunting. Finally, tissue resistance decreases to 0 at
approximately 5Hz due to the viscoelastic nature of lung tissue \(^{20, 26, 34}\) so that \(R\) at 8 Hz is an index of airway resistance. All five indices were correlated with blood oxygen levels using both first and second order linear models. The above analyses were done for \(Z_{rs}\) (no esophageal balloon) and \(Z_L\) (requiring a balloon). We extended our analysis to included \(Z_{rs}\) to evaluate conditions more applicable in clinical settings where placement of an esophageal balloon during mechanical ventilation may not be an option. Also, we compared CV and EVW ventilation at baseline and after OA injury by comparing \(P_aO_2\) levels after the ventilation periods described previously. \(V_T\) and all other ventilation settings were matched during the CV and EVW ventilation periods. Our intent was to insure that the EVW's gas exchange matched those of a conventional waveform.

To gain further insight into the physiological mechanisms responsible for the changes in lung mechanics and gas exchange, a second level of analysis invoked lumped parameter models. Three models were considered: the constant phase model \(^{11}\), a distributed airway resistance model \(^{40}\) with constant phase tissue properties, and a recently published distributed tissue elastance model with constant phase tissue properties \(^{15}\).

The constant phase tissue impedance model assumes homogeneous airways, with resistance \(R_{aw}\) and inertance \(I_{aw}\) leading to homogeneous viscoelastic tissues characterized with tissue elastance (H) and damping (G) coefficients \(^{11}\). Here,

\[
Z = Z_{aw} + Z_{ui}
\]

(2)

where

\[
Z_{aw} = R_{aw} + j\omega_n I_{aw}
\]

(3)

and

\[
Z_{ui} = \frac{G - jH}{\omega_n^2}
\]

(4)

with

\[
\alpha = \frac{2}{\pi} \arctan \left( \frac{H}{G} \right)
\]

(5)

where \(\omega_n\) represents the normalized circular frequency with the normalization factor \(\omega_o = 1\) rad/sec \((\omega_n = \omega/\omega_o)\) and j is the imaginary unit \(^{15}\). The hysteresivity \((\eta)\), a material property of tissue, is defined as follows:
In this model, there are four parameters to estimate from the impedance spectra: \( R_{aw} \), \( I_{aw} \), \( G \) and \( H \).

Two variations of the constant phase model have recently been published. In 1997, Suki et al. published a variation of the constant phase model, allowing for airway heterogeneity via a distributed airway resistance model (see Appendix). We used this model to fit the carbochol provocation data since we assumed mechanical heterogeneity in this treatment condition occurred primarily in the airways. This model assumes a hyperbolically decreasing probability distribution of \( R_{aw} \) of \( p(R_{aw}) \) from \( R_{min} \) to \( R_{max} \) throughout the airway tree. Implicit in this model is that every airway pathway leads to an identical constant phase tissue compartment. In this model, there are five parameters to estimate from the impedance spectra: \( R_{min} \), \( R_{max} \), \( I_{aw} \), \( G \), and \( H \). This distribution ensures that the probability of a higher \( R_{aw} \) occurring is less than that of a lower \( R_{aw} \) and the spread of \( R_{aw} \) is quantified via the standard deviation (SD) of \( p(R_{aw}) \) (see Appendix). With heterogeneous airway constriction, one would expect an increase in \( R_{min} \) and \( R_{max} \) in a manner in which SD increases as well. A second variation of the model is more applicable to ARDS. This disease involves heterogeneity at the level of the tissue via flooding and collapse. To account for this, Ito et al. recently developed a variation of the distributed airway resistance model \(^{15}\). Here, the tissue compartment is constant phase, but the model assumes a hyperbolically decreasing probability distribution of \( H \) of \( p(H) \) from \( H_{min} \) to \( H_{max} \) throughout the airway tree with identical airway and hysteretic properties in each pathway (see Appendix). This model was fit to the OA protocol data. In this model, there are five parameters to estimate from the impedance spectra: \( H_{min} \), \( H_{max} \), \( \eta \), \( R_{aw} \), and \( I_{aw} \). Similar to the distributed airway resistance model, with heterogeneous tissue disease, one would expect the SD of \( p(H) \) to increase from baseline. Both distributed parameter models add only one additional parameter. In all cases, the ten data points (5 real and 5 imaginary) taken from the measured \( Z_L \) were fit to the appropriate model impedance \( Z \) by using a nonlinear gradient search technique to minimize the following objective function:

\[
\eta = \frac{G}{H}
\]
\[ \Phi = \sum_{i=1}^{n} \left[ (\text{Re}\{Z_L(k)\} - \text{Re}\{Z(k)\})^2 + (\text{Im}\{Z_L(k)\} - \text{Im}\{Z(k)\})^2 \right] \]  

where \( k \) represents the \( k^{th} \) frequency component of the impedance.

**Statistical Analysis:**

All data are presented in terms of mean ± SD. Blood gas data were analyzed by one-way analysis of variance (ANOVA) for repeated measures with one factor repetition (SigmaStat, San Rafael, CA). Comparisons of model parameters between the different stages of each disease were analyzed by two-way ANOVA for repeated measures (SigmaStat, San Rafael, CA). Differences between treatments were considered statistically significant at \( p<0.05 \) unless otherwise noted. Student-Newman-Keuls analysis was used for all pairwise multiple comparisons. An \( F \) test was used to compare alternative lumped parameter model structures and linear regression models \(^\text{30}\). In the multiple linear regression analysis, both backward and forward stepwise linear regression techniques were used to obtain independent variables from a list of candidate variables (SigmaStat, San Rafael, CA).

**RESULTS**

*Comparison of EVW Ventilation to CV:*

Table I shows that there was no statistically significant difference between \( P_a\text{O}_2 \) or \( P_a\text{CO}_2 \) before and after 30 min of CV versus EVW ventilation at baseline or after OA injury. The type of ventilation did not alter the blood gas levels even after lung injury.

*Bronchoconstriction Results:*

The sheep responded with varying degrees of constriction after the administration of carbachol. Figure 3 shows the blood gas responses (for baseline, 5 min and 15 min post carbachol) and lung mechanical responses (for baseline, 15 min post carbachol, and albuterol) for a mild and a severe responder to the bronchial challenge. Respiratory R and E responses
were similar in shape but slightly increased from lung R and E values at all frequencies due to the addition of the chest wall impedance. One of the sheep did not respond to the carbachol treatment and the other two sheep’s mechanical and blood gas response were moderate and fell between these two example responders (data not shown). With increased constriction, R and E are more elevated at all frequencies. The elevated E at lowest frequency is indicative of airway closures and this combined with increases in frequency dependence of both R and E from 0-4Hz is indicative of the heterogeneity of constriction. The severe responder shows evidence of substantial airway closure (elevated E at 0.2 Hz) and heterogeneous constriction (more frequency dependence). Accordingly, PaO$_2$ levels are extremely depressed and PaCO$_2$ levels are extremely elevated. In the severe case, albuterol did not completely alleviate the elevations in R and E. Interestingly, all cases reach a plateau E at 4Hz.

We fit both the constant phase model and distributed airway resistance model to impedance data taken at baseline, 5 min post carbachol, and 15 min post carbachol. The distributed airway resistance model lowered the model fit percent error in all cases. While the reduction in model fit error was larger as the frequency dependence of R and E increased, often it did not reach statistical significance. Table II shows the mean constant phase model parameters (G, H, R$_{aw}$) and the derived parameter $\eta$ for baseline, 5 min post, and 15 min post. All parameters increased substantially and significantly from baseline at 5 min post challenge and remained near these levels at 15 min post challenge. The increase in G was disproportionately higher than that of H so that $\eta$ also increased from baseline. The distributed airway resistance model, in principal, can absorb airway heterogeneities that would normally work to increase G. Figure 4 shows distributed airway resistance model parameters $R_{min}$ and $R_{max}$, as well as derived parameters $\eta$ and SD of p($R_{aw}$). At both 5 min and 15 min post treatment, the values of $\eta$ from distributed airway resistance model decreased from that estimated with the constant phase model. Additionally, there was an increase in $R_{min}$, $R_{max}$, and the SD of p($R_{aw}$) from baseline at 5 min and 15 min post carbachol.

**Oleic Acid Injury Results:**
Figure 5 shows the ABG and the lung mechanical response (for baseline, initial and final doses of OA) results for two of the five sheep: a mild and severe responder. Again, respiratory $R$ and $E$ responses were similar in shape but slightly increased at all frequencies. The other three sheep’s mechanical and blood gas responses were moderate and fell between these two responders (data not shown). The $E$ at 0.2 Hz became elevated with treatment, indicative of airway closure and/or alveolar collapse, and this is consistent with the drop in $P_{aO_2}$ and rise in $P_{aCO_2}$. In general, for any one sheep, as the disease progresses from initial to final dose corresponding increases in both the $R$ and $E$ occur at all frequencies as well as in their frequency dependence. Indeed, the blood gas levels deteriorate with the disease progression as well. Again, the $E$ values plateau at 4Hz.

For each sheep, we fit both the constant phase model and distributed tissue elastance model to impedance data taken at baseline, initial dose OA, and final dose OA. The distributed tissue elastance model lowered the model fit percent error in all cases; however, the reduction in error did not always reach statistical significance. The constant phase model parameters ($G$, $H$, $R_{aw}$) and the derived parameter $\eta$ for baseline, after initial dose of OA, and after final dose of OA are summarized in Table III. Both $G$ and $H$ increased significantly after the initial dose of OA and more so after the final dose. The increases were not proportional and, hence, $\eta$ increased from its baseline value. While the $R_{aw}$ trend is to increase after OA, the increase was not statistically significant suggesting that the preponderance of the OA response resides at the level of the tissue in the lung periphery. Figure 6 shows the distributed tissue elastance model parameters $H_{min}$, $H_{max}$, $\eta$, as well as the SD of $p(H)$ as calculated by Ito et al. $^{15}$ The model parameters $H_{min}$, $H_{max}$, and $\eta$ all showed a statistically significant increase from baseline while $R_{aw}$ and $I_{aw}$ did not. Interestingly, the $\eta$ parameter estimates are actually higher when using the distributed tissue elastance model as compared to the value obtained when using the constant phase model.

**Relating Dynamic Mechanical Function and Gas Exchange:**

$P_{aO_2}$ vs. **Impedance Features:** The combination of bronchoconstriction and OA injury data provided a range of constriction/disease conditions thus allowing for the correlation of $P_{aO_2}$
and mechanics data over a wide range. Both first and second order linear models were fit to $P_aO_2$ levels and the five features were extracted from $Z_{rs}$ or $Z_L$ data for both disease types, as well as the combined data. In most cases, the F test showed the second order model to be superior to the first order model. Table IV shows the correlation coefficients for all cases. The cases for which the first order model sufficiently described the data are indicated. Figure 7 shows examples of the regression data between $P_aO_2$ levels and four of these indices.

**$P_aO_2$ vs. Model Parameters:** The parameters obtained from the model fitting were also correlated with $P_aO_2$ using a multiple linear regression technique. We analyzed the carbachol and OA data sets separately. Beginning with the parameters taken from the constant phase model, a forward and backward stepwise regression was performed to evaluate which of these independent variables contribute to the multiple linear regression prediction of $P_aO_2$ levels in each of the diseases. For the carbachol data set, the following parameters were found to contribute statistically to the prediction of $P_aO_2$: $G$ ($p<0.001$), $R_{aw}$ ($p=0.007$), and $I_{aw}$ ($p=0.018$). The resulting equation was

$$P_aO_2 = 513.3 - (7.8 \times G) - (29.8 \times R_{aw}) + (4666 \times I_{aw})$$

with an $r^2$ value of 0.864. In contrast, for the OA data set, the single parameter that was found to contribute statistically to the prediction of $P_aO_2$ was $H$ ($p<0.001$). The resulting equation was

$$P_aO_2 = 729.6 - (7.7 \times H)$$

with an $r^2$ value of 0.611.

The same analysis was done for both data sets using the parameters from the distributed models. For the carbachol data set, we performed stepwise regression on the parameters of the distributed airway resistance model. It was found that $G$ and $R_{max}$ are the contributing independent parameters and the resulting equation was

$$P_aO_2 = 593.6 - (12 \times G) - (2.7 \times R_{max})$$

with an $r^2$ value of 0.865. For the OA data set, the same regression analysis showed that $H_{min}$ and $H_{max}$ of the distributed tissue elastance model were the parameters contributing statistically to the prediction of $P_aO_2$. The resulting equation was


\[ P_aO_2 = 743.3 - (9.9 \times H_{\text{min}}) - (0.86 \times H_{\text{max}}) \]  

(11)

with an \( r^2 \) value of 0.550.

**DISCUSSION**

The premise of this study was that during mechanical ventilation the frequency dependence of \( R \) and \( E \) should reflect a variety of mechanisms sensitive to disease level and distribution. Conventional ventilation cannot be used to track frequency dependence while, in principle, the EVW can. We showed that the EVW is a viable continuous ventilation method with potential to simultaneously provide new information regarding the mean level and heterogeneity of lung disease. The degree of heterogeneity directly reflects the mechanical requirements of breathing and potential ventilation-perfusion (V/Q) mismatches. Hence, application of the EVW in clinical settings can provide enhanced diagnostic information, which in turn could aid in setting mechanical ventilation parameters. To our knowledge the EVW method is the first one capable of breath-to-breath tracking of the frequency dependence of \( R \) and \( E \) during mechanical ventilation and without imposing an external forcing not associated with the ventilation flow. Also, these data allow for lumped parameter modeling by delivering normal \( V_T \) with passive exhalation with a waveform that minimizes the nonlinear effects\(^\text{19}\). The models provide additional insight on airway versus tissue changes during disease.

**Comparison with Other Techniques:**

The EVW has been applied in the past on intubated and anesthetized COPD patients for approximately 40-50s in order to measure inspiratory impedance\(^\text{17}\). The current study demonstrates that the EVW can be used to obtain \( Z \) estimates over extended time periods. Specifically, the EVW and CV methods compared statistically similar in terms of their effects on \( P_aO_2 \) and \( P_aCO_2 \) during baseline and OA conditions and the EVW method was used for approximately 4-5 hours during the development of lung injury in the OA protocol. During EVW ventilation \( P_aCO_2 \) levels were high in both disease cases (Figure 3 and Figure 5). However, no
attempt was made to adjust the ventilation settings to account for this hypercapnia and, although high, EVW and CV resulted in statistically similar $P_a CO_2$ levels (Table I).

Other approaches have been reported to estimate the frequency dependence of $R$ and $E$ during mechanical ventilation. A few studies attempted spectral analysis with standard ventilation waveforms such as a step or ramp $^3, ^{16, 25}$. But these standard waveforms have poor signal-to-noise ratios at harmonics above the ventilation frequency, and cannot avoid nonlinear distortion $^{25}$. Navajas and Farre used small-amplitude forced oscillations generated by loudspeakers $^7, ^{29}$. However, disconnection from mechanical ventilation is required in this technique.

We used a modified EVW analysis technique to estimate $R$ and $E$ at the lowest frequency of the waveform. Kaczka et al. did not require such an approach and relied on windowing to avoid distortion due to transients $^{19}$. The apparent noisy estimation of the first frequency point that we observed may have been a function of differences in the EVW delivery system used (i.e., our EVW may not have been as pure regarding the non-sum-non-difference frequency content). Nevertheless, while our adjusted analysis requires more computation, we feel it is likely to be more robust in estimating the low frequency $R$ and $E$ estimates. Also, due to the low pass filtering involved in this analysis, its applicability requires that flow limitation is not present. Flow limited patients exhibit differences in inspiratory and expiratory lung mechanics and filtering the data may result in smearing of the spectral energy between inspiration and expiration. We did not see any evidence of flow-limitation in our flow and pressure waveforms for any of our conditions.

*Insights into Lung Function during Bronchoconstriction and OA injury:*

With worsening bronchoconstriction or OA injury (Figure 3 and Figure 5), we found increased $R$ and $E$ at the breathing frequency and increased frequency dependence of both coupled with further depression of $P_a O_2$ levels. With both interventions these changes reflected increased heterogeneity of disease and closures of airways and/or lung units. In the case of carbachol, the data showed substantial elevations in overall $R_{aw}$, but much less so for the OA
injury. Upon more rigorous evaluation of impedance features (and model analysis, see below) other distinctive aspects of these interventions emerge.

It is of interest to note that one of our sheep did not respond to the carbachol intervention, which may have been a function of our choice of anesthetics. Both propofol and ketamine have been shown to mitigate the severity of bronchoconstriction⁴. Although this may have attenuated the overall degree of bronchoconstriction, it most likely did not affect the pattern or heterogeneity of the constriction.

Another interesting finding is that the E spectra in the sheep seems to plateau in both of the disease cases. Model analysis has shown that $E_L$ will likely plateau at a value slightly below the value of airway wall elastance as frequency approaches affinity. The frequency at which this plateau occurs is a function of the relationship between airway wall elastance and the peripheral downstream impedance in the lung. In our range of measurements (0.2 to 8Hz) we have not seen such a plateau in human subjects under various disease conditions¹², ²⁴, however, this plateau seems to be a common occurrence in disease models in the sheep (i.e. carbachol, oleic acid, saline lavage). This suggests a morphometry and/or structure of the sheep lung that is distinct from the human lung. Also, this plateau may reflect a greater degree of airway wall shunting in the sheep lung than is commonly observed in asthma¹², ²⁴ or late-stage emphysema¹⁷ human subjects.

The constant phase tissue model is often used to distill out airway from lung periphery and tissue changes. Our results showed that carbachol provocation, which primarily acts to constrict airways, resulted in significant increase in $R_{aw}$ and H at 5 min post carbachol. We would expect increases in H for two main reasons: 1) less overall lung participating during the ventilation cycle, and/or 2) an increase in the stiffness of the tissue. Most likely, a large amount of lung tissue is not being ventilated at 5 min due to severe airway constriction resulting in airway closures (increase in both $R_{aw}$ and H). Similar phenomenon has been reported by various investigators in a variety of animal models of bronchoconstriction²¹, ³³, ³⁹, ⁴⁰. As the carbachol response degrades at 15 min (slight decrease in $R_{aw}$ and H from 5 min to 15 min post), more lung
is likely being ventilated. In this carbachol case, η was statistically elevated at 15 min. It has been previously reported that estimates of G, and thus η, can be artifactually amplified in the present of heterogeneous airway constriction\(^{23}\). Thus, part of the increase in η at 15 min is likely an artifact of the heterogeneity of airway constriction. In principal, the distributed airway model will allow for the heterogeneity to impact \(R_{aw}\) rather than G. Indeed, in all of the cases, G and η decrease when using the distributed model compared to the estimates obtained from the constant phase model. Unfortunately, formal statistical analysis did not necessitate using the more complex model although we attribute this to the relatively low number of impedance points being modeled in the F-test (n=10). It is important to note that even after accounting for this increase, η still appears to be elevated when compared to baseline. Thus perhaps some of the increase in η is real and reflective of an increased cross-bridge cycling and energy dissipation in the smooth muscle\(^{18}\).

When applying the constant phase model to the OA data both G and H significantly increased from baseline after the initial dose of oleic acid and continued to increase after the final dose (Table III). Oleic acid induces pulmonary edema and subsequent surfactant deactivation that facilitates widespread atelectasis. The overall effect in the lung is that portions of the lung (due to edema and/or collapse) are no longer participating in ventilation. Thus, after injury, the tidal breath is distributed to a smaller portion of the lung resulting in an increase in estimated G and H. However, we found that η also increases substantially. Recall we found that with the distributed tissue elastance model, there was an increase in the SD of \(\rho(H)\) after injury (Figure 6) consistent with a heterogeneous increase in lung tissue stiffness. Thus, one possibility is, as in bronchoconstriction, the heterogeneity created an artifactual increase in η. However, with the distributed tissue model we also found that η increased, not decreased from that estimated with the constant phase model. Perhaps, then, the post-OA increase in η is more fundamentally at the tissue level and not just due to an artifact of the heterogeneity. It is known that η for a solution of polymers is higher (~0.4-0.5) than that of healthy parenchymal tissue (~0.1-0.2), therefore, it is possible that the fluid filling of the lung occurring with OA injury is also responsible for increases
in $\eta$. Finally, it may also be that the increase in $\eta$ is merely an artifact of using the distributed tissue elastance model in which $\eta$ is forced to be a parameter. Regardless, information reflective of the distribution of elastance throughout the lung would not have been available from a single frequency and/or static measurement.

Of course in the case of OA injury impedance data, the choice of models is again subject to debate. It is interesting to note in one of the most severe responding sheep, the F test confirmed that the distributed tissue elastance model was superior. Hence, while the constant phase model is likely sufficient for healthy and moderately diseased conditions, during more severe cases of constriction and disease, the distributed parameter models more accurately distinguish the disease conditions.

**Relating Dynamic Lung Mechanics to Gas Exchange:**

In principal, the heterogeneity of lung disease should modulate the disease’s functional, and hence clinical, severity. Few studies have examined the correlation between mechanical heterogeneity (as measured by increased frequency dependence of $R$ and $E$) and abnormalities in gas exchange (as measured by blood gases). A recent study, by Wetter et al., found no correlation between the frequency dependence of $R_{rs}$ and measured levels of $P_{a}O_{2}$. However, they measured the frequency dependence of $R$ as the absolute difference of $R_{rs}$ at 5 and 25 Hz and the effects of heterogeneous distribution of lung disease are most evident in the range 0-2 Hz. Our data (Figure 7, Table IV) indicated high correlations (whether it be lung or respiratory) between $P_{a}O_{2}$ and indices of heterogeneity and/or loss of aerated lung volume. This is expected since both of these indices reflect a decreased amount of the lung participating in the tidal breath (due to presence of very long time constants and due to airway closures).

These correlations suggest that mechanical conditions can be identified for which gas exchange function is depressed. While there are many factors that affect gas exchange function during disease aside from heterogeneity, our goal was to examine the correlation between novel mechanical indices of heterogeneity and $P_{a}O_{2}$ levels in two disease states characterized by heterogeneity. Specifically, with regards to ARDS, we do not intend to suggest that $P_{a}O_{2}$ should
be used as outcome variable or that a normal $P_aO_2$ necessarily reflects a non-diseased lung. For example, $P_aCO_2$ is also an important variable to consider when assessing gas exchange function. Although correlations between our mechanical indices and this variable were not as strong, there was a trend of increasing $P_aCO_2$ levels with increasing heterogeneity and derecruitment as assessed with the mechanical indices.

We wondered whether there would be a more explicit relationship between loss of lung units participating in ventilation and degradation of $P_aO_2$ levels. To examine this further, we recast the data of Figure 8A and Figure 8B in terms of percent of non-ventilated lung. Specifically, let us assume that all of the increase in $E_L$ at 0.2 Hz reflects dropouts of ventilation units. In the case of carbachol, this would be due to stimulated airway constriction to the point of closure. In the case of OA, it would be caused by derecruitment of alveoli due to pulmonary edema or collapse. Considering the lung as a set of parallel gas exchanging units, we can derive the following relationship to reflect percent of the lung that has been derecruited and is non-ventilated at this frequency (i.e. not participating in gas exchange):

$$
\% \text{ Non-Ventilated Lung} = \left(1 - \frac{E_{baseline}(0.2\text{Hz})}{E(0.2\text{Hz})}\right) \times 100
$$

If all parallel units are open at baseline, $E$ at 0.2 Hz will equal $E_{baseline}$ at 0.2 Hz and 0% of the lung has been derecruited. When all lung units are de-recruited, $E(0.2\text{Hz}) \gg E_{baseline}(0.2\text{Hz})$ such that $1 - \frac{E_{baseline}(0.2\text{Hz})}{E(0.2\text{Hz})} \approx 1$. When displayed in this manner, the data suggests that on the order of 40-50% of the parallel alveoli can become derecruited before blood gases are affected, after which point blood gases degrade rapidly. Such behavior likely reflects V/Q mismatch leading to intrapulmonary shunting and is consistent with the $O_2$ dissociation curve. It is believed that V/Q matching occurs in the lung when there is a distribution of non-ventilated and poorly ventilated regions through certain physiological mechanisms. These mechanisms include the decrease in blood flow or perfusion to these non-ventilated and poorly ventilated regions by the
increase of vascular resistance and the increase in ventilation to the well-perfused regions by the
decrease in airway resistance. The qualitative behavior of this curve is consistent with the idea
that once a certain number of parallel gas exchanging lung units drop out, V/Q matching can no
longer compensate through the mechanisms stated above, and there will be a rapid degradation
in $P_aO_2$.

In reality, the amount of lung units that need to drop out before a rapid degradation in
blood gases occurs is a combination of ventilation dropouts and V/Q matching and it is not
necessarily 50%. Also, the above analysis assumes all of the increase in $E$ at 0.2Hz is due to
derecruitment and airway closures when in reality there is probably a contribution from other
mechanisms such as increases in tissue stiffness. Nevertheless, the qualitative behavior
connoted in Figure 8 have important clinical implications. Specifically, by tracking a patient’s
dynamic mechanics from some baseline condition, one can identify mechanical conditions for
which gas exchange, while currently normal, are at risk of becoming rapidly degraded unless
effective recruitment maneuvers are performed.

With regards to the modeling analysis and multiple linear regression, the constant phase
model suggests that during broncho-provocation the model parameters that are most sensitive to
heterogeneous airway phenomena ($R_{aw}$ and $G$) are the only ones that were needed to describe
$P_aO_2$ degradation (eq. 8). In contrast, OA creates lung injury primarily by affecting the tissues in
the lung periphery and correspondingly the constant phase tissue-based parameter $H$ was
statistically the only parameter needed to describe $P_aO_2$ degradation (eq. 9). It is important to
note that, in terms of data, heterogeneity appears to be a significant phenomena in both disease
cases. The corresponding changes in the shape of $R$ and $E$ compared to baseline is consistent
with previously published data and model predictions. In principle, a more refined probing of
heterogeneity of airway and tissue properties can be achieved via distributed airway or tissue
models but lack of statistical significance precludes judgment at this time. Consequently, the
results of the multiple linear regressions should be viewed with caution since the parameter
estimates of the distributed models are not sufficiently unique.
**Potential Applications to Ventilation Strategies:**

There has recently been much debate surrounding optimal ventilator strategies that will maximize gas exchange while minimizing ventilator induced lung injury. Due to the patchy or highly heterogeneous nature of ARDS, volume delivered during mechanical ventilation tends to enter the less diseased areas. There have been a variety of researchers who have shown this through techniques such as CT, in vivo microscopy, and mathematical modeling. Thus, the static PV curve can be looked at as an average of many individual PV curves throughout the lung. For this reason, many researchers argue that ventilation strategies cannot be based on such a basic measure of lung mechanics. Additionally, many studies have reported the absence of a lower inflection point in the static PV curve and have attributed this to the heterogeneous nature of the lung disease. Moreover, ventilation is a dynamic and cyclic process. Very recently, there have been studies supporting the use of a more dynamic view of lung mechanics in setting PEEP. Overall, new methods to guide selecting an optimum PEEP are necessary. These new methods should aim at quantifying dynamic lung mechanics and the heterogeneity of the disease state.

We believe that the EVW has the potential to greatly aid in assessing lung disease heterogeneity during ARDS. In conjunction with the lumped parameter modeling techniques outlined in this paper, it may be possible to quantify degrees of recruitment/decruitment as well as potential overdistension from the frequency information obtained from the EVW (through assessment of $H_{\text{min}}$ and $H_{\text{max}}$ values and the implied elastance distribution). Moreover, the EVW acts as a typical ventilation waveform with a frequency and $V_T$ that can be adjusted and can be applied at various levels of PEEP. Hence, it may be possible to use the EVW to assess the effect PEEP has on homogenizing time constants in the lung (due to recruitment).

**Summary:**

Our data show that when the EVW is applied over an extended time period (>hours) ventilation is maintained as well as a conventional ventilator waveform by maintaining comparable levels of normoxia and eucapnia during baseline and ARDS type conditions. In
addition to the maintenance of ventilation, we have shown that it is possible to continuously track a particular disease state at the level of dynamic mechanical function, which in turn can be correlated back to gas exchange function. Heterogeneity and airway closures/flooding appear to be excellent predictors of and consistent with degradation in gas exchange function. Also, the application of relevant lumped parameter models to the data obtained from the EVW provides insight into relative changes in the lung periphery and/or tissue properties.
ACKNOWLEDGMENTS

This work was supported by the National Science Foundation BES-0114538 and NIH HL-62269-02. The EVW technique is protected by U.S. Patent No. 091535135 and a licensing agreement exists between Boston University and Puritan Bennett/Tyco Healthcare. Additionally, Puritan Bennett/Tyco Healthcare provided the prototype NPB840 used in the experiments.
# NOMENCLATURE

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG</td>
<td>Arterial Blood Gas</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>CV</td>
<td>Conventional ventilation</td>
</tr>
<tr>
<td>E</td>
<td>Elastance</td>
</tr>
<tr>
<td>EVW</td>
<td>Enhanced Ventilator Waveform</td>
</tr>
<tr>
<td>f</td>
<td>Frequency</td>
</tr>
<tr>
<td>FIO2</td>
<td>Fraction of Inspired Oxygen</td>
</tr>
<tr>
<td>G</td>
<td>Tissue Damping</td>
</tr>
<tr>
<td>H</td>
<td>Tissue Elastance</td>
</tr>
<tr>
<td>H_{max}</td>
<td>Maximum tissue elastance in distributed tissue elastance model</td>
</tr>
<tr>
<td>H_{min}</td>
<td>Minimum tissue elastance in distributed tissue elastance model</td>
</tr>
<tr>
<td>I_{aw}</td>
<td>Airway Inertance</td>
</tr>
<tr>
<td>j</td>
<td>Imaginary unit</td>
</tr>
<tr>
<td>k</td>
<td>Frequency Index</td>
</tr>
<tr>
<td>I:E</td>
<td>Inspiratory to Expiratory</td>
</tr>
<tr>
<td>OA</td>
<td>Oleic Acid</td>
</tr>
<tr>
<td>P_{ao}</td>
<td>Airway opening pressure</td>
</tr>
<tr>
<td>P_{a}O_{2}</td>
<td>Arterial partial pressure of oxygen</td>
</tr>
<tr>
<td>P_{a}CO_{2}</td>
<td>Arterial partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive End Expiratory Pressure</td>
</tr>
<tr>
<td>P_{es}</td>
<td>Esophageal pressure</td>
</tr>
<tr>
<td>p(H)</td>
<td>Probability distribution of tissue elastance</td>
</tr>
<tr>
<td>P_{o}</td>
<td>Pressure at which volume and flow equal 0</td>
</tr>
<tr>
<td>p(R_{aw})</td>
<td>Probability distribution of airway resistance</td>
</tr>
<tr>
<td>P_{ip}</td>
<td>Transpulmonary pressure</td>
</tr>
<tr>
<td>R</td>
<td>Resistance</td>
</tr>
<tr>
<td>R_{aw}</td>
<td>Airway Resistance</td>
</tr>
<tr>
<td>R_{max}</td>
<td>Maximum airway resistance in distributed airway resistance model</td>
</tr>
<tr>
<td>R_{min}</td>
<td>Minimum airway resistance in distributed airway resistance model</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>V_{ao}</td>
<td>Airway opening flow</td>
</tr>
<tr>
<td>V_{T}</td>
<td>Tidal volume</td>
</tr>
<tr>
<td>V/Q</td>
<td>Ventilation-Perfusion</td>
</tr>
<tr>
<td>Z_{aw}</td>
<td>Airway Impedance</td>
</tr>
<tr>
<td>Z_{ti}</td>
<td>Tissue Impedance</td>
</tr>
<tr>
<td>Z_{L}</td>
<td>Lung impedance</td>
</tr>
<tr>
<td>Z_{rs}</td>
<td>Respiratory system impedance</td>
</tr>
<tr>
<td>\alpha</td>
<td>Angular Frequency Exponent</td>
</tr>
<tr>
<td>\eta</td>
<td>Hysteresivity</td>
</tr>
<tr>
<td>\omega_n</td>
<td>Normalized Angular Frequency</td>
</tr>
<tr>
<td>\omega</td>
<td>Angular Frequency</td>
</tr>
<tr>
<td>\omega_o</td>
<td>Normalization Factor for Angular Frequency</td>
</tr>
</tbody>
</table>
APPENDIX

**Distributed Airway Resistance Model** \(^40\). This model assumes a hyperbolically decreasing \(p(R_{aw})\) from \(R_{min}\) to \(R_{max}\) throughout the airway tree. The tissue compartment is constant phase, given by equation 4, and is assumed to remain homogeneous throughout the airway tree. \(Z\) is given by

\[
Z = \frac{Z_a}{K + \ln \left( \frac{R_{min} + Z_a}{R_{max} + Z_a} \right)} \tag{13}
\]

where

\[
K = \ln \left( \frac{R_{max}}{R_{min}} \right) \tag{14}
\]

and

\[
Z_a = Z_{ti} + j \omega_n I_{aw} \tag{15}
\]

The mean and SD of \(p(R_{aw})\) are as follows:

\[
R_{mean} = \frac{R_{max} - R_{min}}{K} \tag{16}
\]

\[
\text{SD of } p(R_{aw}) = \sqrt{\frac{(R_{max} - R_{min})^2}{2K} - \frac{(R_{max} - R_{min})^2}{K^2}} \tag{17}
\]

**Distributed tissue elastance Model** \(^15\). This model assumes a hyperbolically decreasing \(p(H)\) from \(H_{min}\) to \(H_{max}\). The model also assumes homogeneous airway and hysteretic properties throughout the airway tree. Reformulating \(Z_{tiss}\) (equation 4) in terms of \(H\) and \(\eta\) (equation 6), we obtain

\[
Z_{ti} = \frac{(n - j)H}{\omega^a} \tag{18}
\]

Therefore, due to the distribution of \(H\), it follows that \(Z_{tiss}\) will range in from \(Z_{min}\) to \(Z_{max}\) which are given by:

\[
Z_{ti-min} = \frac{(n - j)H_{min}}{\omega^a} \tag{19}
\]
\[ Z_{n_{\text{max}}} = \frac{(n - j)H_{\text{max}}}{\omega^\alpha} \]  

(20)

Combining these distributed tissue properties with a constant \( Z_{aw} \) (equation 2), we obtain

\[ Z = \frac{Z_{aw}}{F + \ln \left( \frac{Z_{n_{\text{min}}} + Z_{aw}}{Z_{n_{\text{max}}} + Z_{aw}} \right)} \]  

(21)

where

\[ F = \ln \left( \frac{H_{\text{max}}}{H_{\text{min}}} \right) \]  

(22)

The mean and SD of \( p(H) \) are as follows:

\[ H_{\text{mean}} = \frac{H_{\text{max}} - H_{\text{min}}}{F} \]  

(23)

\[ \text{SD of } p(H) = \sqrt{\frac{\left( H_{\text{max}}^2 - H_{\text{min}}^2 \right)}{2F} - \frac{\left( H_{\text{max}} - H_{\text{min}} \right)^2}{F^2}} \]  

(24)
REFERENCES


7. Farre, R., M. Ferrer, M. Rotger and D. Navajas. Servocontrolled generator to measure respiratory impedance from 0.25 to 26 Hz in ventilated patients at different PEEP levels. *Eur Respir J.* 8: 1222-1227, 1995.


**TABLES**

Table I. Blood oxygen values after CV and EVW ventilation taken at baseline and post OA injury.

<table>
<thead>
<tr>
<th>Property</th>
<th>Baseline-CV</th>
<th>Baseline-EVW</th>
<th>OA Injury-CV</th>
<th>OA Injury-EVW</th>
</tr>
</thead>
<tbody>
<tr>
<td>(P_aO_2), mm Hg</td>
<td>612.3 ± 40.8</td>
<td>576.1 ± 67.1</td>
<td>184.65 ± 83.41 *</td>
<td>181.6 ± 100.6 *</td>
</tr>
<tr>
<td>(P_aCO_2), mm Hg</td>
<td>45.2 ± 3.5</td>
<td>41.8 ± 4.1</td>
<td>83.3 ± 32.9</td>
<td>71 ± 9.7</td>
</tr>
</tbody>
</table>

*Definition of abbreviations:* CV = conventional ventilation; EVW = enhanced ventilation waveform; OA = oleic acid. Values represent means ± standard deviation, * p<0.05 compared to baseline value, n=5.
Table II. Constant Phase Model Parameters from carbochol protocol.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>5 min post</th>
<th>15 min post</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{aw}$</td>
<td>0.14 ± 0.06</td>
<td>3.55 ± 2.56*</td>
<td>3.1 ± 2.47*</td>
</tr>
<tr>
<td>$I_{aw}$</td>
<td>0.020 ± 0.0035</td>
<td>0.0039 ± 0.0067*</td>
<td>0.005 ± 0.0087</td>
</tr>
<tr>
<td>G</td>
<td>1.86 ± 1.2</td>
<td>20.29 ± 20.15</td>
<td>22.24 ± 19.53</td>
</tr>
<tr>
<td>H</td>
<td>10.21 ± 4.62</td>
<td>50.93 ± 26.64*</td>
<td>41.92 ± 18.9*</td>
</tr>
<tr>
<td>h</td>
<td>0.121 ± 0.075</td>
<td>0.334 ± 0.224</td>
<td>0.461 ±0.226*</td>
</tr>
</tbody>
</table>

Values represent mean ± standard deviation.
* p<0.05 compared to baseline.
Table III. Constant Phase Model Parameters from oleic acid protocol.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>initial dose</th>
<th>final dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{aw}$</td>
<td>$0.45 \pm 0.12$</td>
<td>$1.53 \pm 1.27$</td>
<td>$0.63 \pm 0.84$</td>
</tr>
<tr>
<td>$I_{aw}$</td>
<td>$0.019 \pm 0.0023$</td>
<td>$0.0039 \pm 0.0066$</td>
<td>$0.0058 \pm 0.0066^*$</td>
</tr>
<tr>
<td>$G$</td>
<td>$2.06 \pm 0.57$</td>
<td>$9.29 \pm 4.2^*$</td>
<td>$19.71 \pm 7.65^*$</td>
</tr>
<tr>
<td>$H$</td>
<td>$16.63 \pm 2.33$</td>
<td>$39.87 \pm 11.04^*$</td>
<td>$64.94 \pm 14.87^*$</td>
</tr>
<tr>
<td>$h$</td>
<td>$0.127 \pm 0.045$</td>
<td>$0.232 \pm 0.149^*$</td>
<td>$0.318 \pm 0.149^*$</td>
</tr>
</tbody>
</table>

Values represent mean ± standard deviation.
* $p<0.05$ compared to baseline.  $p<0.05$ compared to initial dose.
Table IV. Correlation coefficients for various mechanical indices and arterial blood oxygen levels.

<table>
<thead>
<tr>
<th></th>
<th>Treatment Type</th>
<th>Lung</th>
<th>OA</th>
<th>Combined</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n=28</td>
<td>n=26</td>
<td>n=54</td>
</tr>
<tr>
<td>E at 0.2Hz</td>
<td>0.78</td>
<td>0.80</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>R at 0.2Hz - R at 8Hz</td>
<td>0.86</td>
<td>0.60</td>
<td>0.68*</td>
<td></td>
</tr>
<tr>
<td>E at 8Hz</td>
<td>0.88</td>
<td>0.68</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>R at 8Hz</td>
<td>0.84</td>
<td>0.34</td>
<td>0.47*</td>
<td></td>
</tr>
<tr>
<td>E at 2Hz - E at 0.2Hz</td>
<td>0.67</td>
<td>0.86</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=28</td>
<td>n=21</td>
<td>n=49</td>
</tr>
<tr>
<td>E at 0.2Hz</td>
<td>0.81</td>
<td>0.75</td>
<td>0.75*</td>
<td></td>
</tr>
<tr>
<td>R at 0.2Hz - R at 8Hz</td>
<td>0.87</td>
<td>0.50</td>
<td>0.66*</td>
<td></td>
</tr>
<tr>
<td>E at 8Hz</td>
<td>0.90</td>
<td>0.64</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>R at 8Hz</td>
<td>0.84</td>
<td>0.32</td>
<td>0.50*</td>
<td></td>
</tr>
<tr>
<td>E at 2Hz - E at 0.2Hz</td>
<td>0.74</td>
<td>0.83</td>
<td>0.75</td>
<td></td>
</tr>
</tbody>
</table>

Values represent $r^2$ value for the linear regression between mechanical index (extracted from either lung or respiratory system impedance) and arterial blood oxygen levels. *First order linear model used. Second order linear model was used in all other cases. OA, Oleic Acid.
FIGURE LEGENDS

1. Schematic example of lung impedance for a baseline lung (black, solid), heterogeneous airway disease (light gray, dashed), and heterogeneous tissue disease (dark gray, dashed-dotted). Simulations derived from anatomically consistent 3D computational model of the sheep lung.

2. Depiction of example (A) EVW and (B) CV flow patterns and (C) EVW and (D) CV pressure patterns. Note that while the pressure patterns for both waveforms are similar, there is increased high frequency content in the EVW.

3. Bronchoconstriction mechanics and ABG results for a mild responder (left) and a severe responder (right). The top panels display ABGs. The middle and the bottom panels display the R and E spectra, respectively. R and E data corresponding to baseline, 15 min response, and albuterol is shown, while ABG data corresponding to baseline, 5 min, and 15 min response is shown.

4. Model parameters (A) $R_{\text{min}}$ and (B) $R_{\text{max}}$, and derived parameters (C) SD of $p(R_{aw})$ and (D) $\eta$ estimated using the distributed airway resistance model fit to carbachol data for baseline, 5 min, 15 min response. Individual points for each sheep as well as mean and SD are shown. * $p<0.05$ compared to baseline.

5. OA Injury mechanics and ABG results for a mild responder (left) and a severe responder (right). The top panels display arterial blood gas measurements, which were taken periodically. The middle and the bottom panels display the R and E spectra, respectively. Data corresponding to baseline, initial, and final OA dose response is shown.

6. Model parameters (A) $H_{\text{min}}$, (B) $H_{\text{max}}$, and derived parameters (C) SD of $p(H)$, (D) $\eta$ estimated using the distributed tissue elastance model fit to OA injury data for baseline, initial dose, and final
dose. Individual points for each sheep as well as mean and SD are shown. * p<0.05 compared to baseline, $p<0.05$ compared to initial dose.

7. Correlations between arterial $P_aO_2$ levels and an (A) $E_{lung}$ at 0.2Hz, (B) $R_{lung}$ at 0.2Hz - $R_{lung}$ at 8Hz, (C) $E_{lung}$ at 8Hz, and (D) $R_{lung}$ at 8Hz. Data from the bronchoconstriction protocol (dark gray) and from the OA injury (light gray) is shown. Solid black line indicates the regression for the combined data with the n and R-value shown in the legend. No regression line is shown in F due to the low $R^2$ value. An F test was used to determine whether the first or second order linear models were more appropriate and the resulting model is shown.

8. Percent baseline $P_aO_2$ vs % of Non-Ventilated Lung as defined in Equation 12 calculated from $E_{lung}$ at 0.2 Hz. A Gompertz 3-parameter model was fit to the data for visual effect.
FIGURES

Figure 1, C.L. Bellardine

A

B
Figure 2, C.L. Bellardine

EVW

CV

Pressure (cmH₂O)

Flow (L/s)
Figure 3, C.L. Bellardine

MILD
Sheep #1

SEVERE
Sheep #4

**PaO₂ (mmHg) vs. PaCO₂ (mmHg)**

- **Baseline**
- **5 min post**
- **15 min post**

**Resistance (cmH₂O/L/s)**

- **Baseline**
- **15 min post**
- **Albuterol**

**Elastance (cmH₂O/L)**

- **Baseline**
- **15 min post**

**Frequency (Hz)**

- **0**
- **2**
- **4**
- **6**
- **8**

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- **PaO₂**
- **PaCO₂**

- **Baseline**
- **5 min post**
- **15 min post**

**Sheep #1**

**Sheep #4**
Figure 4, C.L. Bellardine

[Graphs showing data points and error bars for different measurements over baseline, 5 min post, and 15 min post conditions.]
Figure 5, C.L. Bellardine

MILD
Sheep #5

SEVERE
Sheep #2

PaO₂ (mmHg)
PaCO₂ (mmHg) \times 10

Resistance (cmH₂O/L/s)

Elastance (cmH₂O/L)

Frequency (Hz)
Figure 6, C.L. Bellardine

A

- Hmin (cmH2O/L/s)
- Baseline, Initial Dose, Final Dose

B

- Hmax (cmH2O/L/s)
- Baseline, Initial Dose, Final Dose

C

- SD of p(H)
- Baseline, Initial Dose, Final Dose

D

- \eta
- Baseline, Initial Dose, Final Dose
Figure 7, C.L. Bellardine

A. $E_{\text{lung}}$ at 0.2Hz (cmH$_2$O/L)
B. $R_{\text{lung}}$ at 0.2Hz - $R_{\text{lung}}$ at 8Hz (cmH$_2$O/L/s)
C. $E_{\text{lung}}$ at 8Hz (cmH$_2$O/L)
D. $R_{\text{lung}}$ at 8Hz (cmH$_2$O/L/s)
Figure 8, C.L. Bellardine

![Graph showing the relationship between % Baseline PaO2 and % Non-ventilated Lung. The graph includes data points for Carbochol and Oleic Acid, with a trend line indicating a decrease in PaO2 as the % Non-ventilated Lung increases. The data is calculated using $E_{\text{lung}}$ at 0.2 Hz.]