Quantifying Mechanical Heterogeneity in Canine Acute Lung Injury

Impact of Mean Airway Pressure

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Background: The heterogeneous pattern of acute lung injury (ALI) predisposes patients to ventilator-associated lung injury. Currently, there is no simple technique that can reliably quantify lung heterogeneity during the dynamic conditions of mechanical ventilation. Such a technique may be of use in optimizing mechanical ventilatory parameters such as rate, tidal volume, or positive end-expiratory pressure.

Methods: To determine the impact of heterogeneity on respiratory mechanics, the authors measured respiratory impedance ($Z_{rs}$), expressed as respiratory resistance ($R_{rs}$) and elastance ($E_{rs}$), in 11 anesthetized dogs from 0.078 to 8.9 Hz using broadband pressure and flow excitations under baseline conditions and after ALI produced by infusion of 0.08 ml/kg oleic acid into the right atrium. Data were obtained at mean airway pressures ($P_{aw}$) of 5, 10, 15, and 20 cm H$_2$O. The $Z_{rs}$ spectra were fit by various models of the respiratory system incorporating different distributions of parallel viscoelastic tissue properties.

Results: Under baseline conditions, both $R_{rs}$ and $E_{rs}$ exhibited dependence on oscillation frequency, reflecting viscoelastic behavior. The $E_{rs}$ demonstrated significant dependence on $P_{aw}$. After ALI, both the level and frequency dependence of $R_{rs}$ and $E_{rs}$ increased, as well as the apparent heterogeneity of tissue properties. Both $R_{rs}$ and $E_{rs}$ as well as heterogeneity decreased with increasing $P_{aw}$, approaching baseline levels at the highest levels of $P_{aw}$.

Conclusions: These data demonstrate that $Z_{rs}$ can provide specific information regarding the mechanical heterogeneity of injured lungs at different levels of $P_{aw}$. Moderate increases in $P_{aw}$ seem to be beneficial in ALI by reducing heterogeneity and recruiting lung units. These noninvasive measurements of lung heterogeneity may ultimately allow for the development of better ventilation protocols that optimize regional lung mechanics in patients with ALI.

ACUTE lung injury (ALI) is a complex pathologic process involving a heterogeneous interaction of mechanical and biochemical processes.¹ Although there are many etiologies for this syndrome, it is ultimately characterized by respiratory failure in the presence of airway closure and atelectasis, alveolar flooding, increased lung resistance, reduced lung compliance, and impairments in gas exchange.¹² The current mainstay of treatment is supportive therapy with tracheal intubation and mechanical ventilation.¹ Given the heterogeneous nature of this disease, positive-pressure ventilation may expose certain regions of the lung to further injury due to either an unequal distribution of inspired volume, resulting in high alveolar pressures and overdistention, or repetitive end-expiratory derecruitment and reopening.³¹ Because such ventilator-associated lung injury is the direct result of the heterogeneous nature of the injury, the ability to quantify mechanical heterogeneity may be useful in optimizing ventilatory parameters such as positive end-expiratory pressure (PEEP), tidal volume, or frequency.

The forced oscillation method to measure respiratory input impedance ($Z_{rs}$), the complex ratio of pressure to flow at the airway opening as a function of frequency, is gaining increasing acceptance as a valid method for assessing dynamic mechanical properties of the respiratory system.⁵ When measured over frequencies ranging from approximately 0.1 to 10.0 Hz, $Z_{rs}$ is a sensitive indicator of serial and parallel airway heterogeneity,⁶–⁸ provides insight into the locus of airway obstruction in asthma and chronic obstructive pulmonary disease,⁹,¹⁰ and may be useful in partitioning the mechanical properties of the lung tissues.¹¹

The goal of this study was to characterize the dynamic mechanical behavior of the respiratory system in a canine model of ALI. We used the frequency-dependent features of $Z_{rs}$, specifically respiratory resistance ($R_{rs}$) and elastance ($E_{rs}$), to assess the degree and severity of lung injury in dogs after administration of oleic acid. Particular emphasis was placed on quantifying mechanical heterogeneity before and after injury at different levels of mean airway pressure ($P_{aw}$). The motivation for this work arises from recent morphometric modeling studies that demonstrate a strong association between the heterogeneity of airway constriction and the frequency-dependent features of $R_{rs}$ and $E_{rs}$.⁶,⁸,¹²–¹⁴ Although the structure-function relation of the respiratory system is extremely complex, we reasoned that the heterogeneous changes in regional lung elastances occurring in ALI may affect $Z_{rs}$ in a specific and predictable manner. Furthermore, we hypothesized that as $P_{aw}$ increased and lung regions became more uniformly ex-
panded, there would be characteristic changes in $Z_{rs}$, reflecting the process of recruitment and possibly a reduction in lung heterogeneity.

The specific aims of this study were (1) to measure $Z_{rs}$ in mongrel dogs at baseline and after ALI induced with oleic acid; (2) to use an inverse distributed modeling approach to characterize $Z_{eq}$ in terms of different distributions of respiratory tissue heterogeneity; and (3) to investigate the impact of $\dot{P}_{(ao)}$ on $Z_{rs}$ and by extension, on mechanical heterogeneity.

Materials and Methods

Animal Preparation and Measurements

Measurements were made in 11 mongrel dogs weighing between 7.6 and 20.0 kg. The protocol was approved by the Johns Hopkins Animal Care and Use Committee (Baltimore, Maryland) to ensure humane treatment of animals. Each dog was anesthetized with pentobarbital given intravenously (25 mg/kg at induction with 5 mg/kg hourly maintenance), relaxed with pancuronium, orally intubated with an 8.0-mm-ID endotracheal tube, and mechanically ventilated (initial rate 20 min$^{-1}$ and tidal volume 15 ml/kg, titrated to achieve an end-tidal level between 30 and 40 mmHg, and 5 cm H$_2$O PEEP). Oxygen saturation was continuously monitored with a pulse oximeter applied to the tongue. Femoral arterial and venous catheters were inserted via femoral cut-down, and a pulmonary artery catheter (7.5 French; Edwards Lifesciences LLC, Irvine, CA) was inserted through the femoral vein. Systemic arterial, pulmonary arterial, and central venous pressures were continuously monitored (Tram-Rac 4A; GE Marquette Medical Systems, Milwaukew, WI). Cardiac output was measured in triplicate using the thermodilution technique. Airway flow was measured with a pneumotachograph (Hans Rudolph 4700A; Kansas City, MO) coupled to a pressure transducer (Honeywell DC001NDC4 $\pm$ 1 in H$_2$O; Morristown, NJ). Tracheal pressure was measured with an additional pressure transducer (Honeywell DC020NDC4 $\pm$ 20 in H$_2$O) attached to a small polyethylene catheter placed through the endotracheal tube and allowed to extend approximately 2 cm into the trachea. An intravenous infusion of lactated Ringer’s (15 ml·kg$^{-1}$·h$^{-1}$) was given for maintenance fluid replacement.

Protocol

To measure $Z_{rs}$, each dog was disconnected from the conventional mechanical ventilator and connected to a custom-built servo-controlled pneumatic pressure oscillator. This device is based on a proportional solenoid valve (ASCO Posiflow model SD8202G4V; Florham Park, NJ) that adjusts flow in proportion to an applied voltage and is incorporated into a closed-loop arrangement that provides accurate control of $\dot{P}_{(ao)}$ during superimposed oscillations. To standardize volume history, a deep inflation to 30 cm H$_2$O was first performed, and then tracheal pressure was reduced to a specified $P_{(ao)}$. A discretized broadband pressure excitation signal with energy between 0.078 to 8.9 Hz was generated at a sampling rate of 40 Hz using a digital-to-analog converter (Data Translations DT-2811; Marlboro, MA). This digital signal consisted of nine sinusoids with equivalent amplitudes and random phases, with frequency components chosen to obey a nonsum nondifference criterion to minimize the impact of nonlinearities in computations of $Z_{rs}$. The digital signal was low-pass filtered at 10 Hz (Frequency Devices 858L8B-2; Haverhill, MA) and presented to the electronic control unit of the proportional solenoid. The net amplitude of the driving signal was adjusted to yield a delivered tidal volume of approximately 50 ml root mean square, as computed using trapezoidal integration of the sampled flow waveform. Corresponding tracheal pressure and flow signals were low-pass filtered at 10 Hz and sampled at 40 Hz by an analog-to-digital converter (Data Translations DT-2811) for subsequent processing. Between oscillatory pressure excitations, the dog was reconnected to the ventilator for a period of 4–5 min. The $Z_{rs}$ measurements were obtained at $\dot{P}_{(ao)}$ levels of 5, 10, 15, and 20 cm H$_2$O applied in random order.

Lung injury was then induced by infusing 0.08 ml/kg oleic acid (Sigma-Aldrich, Inc., St. Louis, MO) into the right atrial port of the pulmonary artery catheter over 20 min. After allowing 90–120 min for the injury to stabilize, clinical signs of severe pulmonary injury were evident, including bilateral crackles and wheezes, and oxygen saturation less than 91% with inspired oxygen fraction equal to 1.0. The $Z_{rs}$ measurements were then repeated as above. Dogs were killed with an intravenous overdose of pentobarbital (10–20 mg/kg) followed by rapid injection of 50 ml saturated solution of potassium chloride.

Signal Processing

Respiratory impedance $Z_{rs}$ and its coherence function $\gamma^2$ were determined using an overlap-average periodogram technique. Each $Z_{rs}$ spectrum was computed using a 25.6-s time window with 83% overlap. After neglecting the first 1,000 points in the data record (approximately 25 s) to minimize the influence of transient responses, between 12 and 20 overlapping windows were used to calculate $Z_{rs}$ for each animal. Total $R_{rs}$ was determined as the real part of $Z_{rs}$ only at those frequencies $f_k$ where input energy was placed: $R_{rs} (f_k) = \text{Re}(Z_{rs} (f_k))$. The effective $E_{rs}$ was calculated from the imaginary part: $E_{rs} (f_k) = -2\pi f_k \text{Im}(Z_{rs} (f_k))$. In no instance did we find that $\gamma^2$ was less than 0.95 at any $f_k$. 

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Modeling Analysis

To interpret the $Z_{rs}$ spectra and quantify parallel tissue heterogeneity, we modified the distributed modeling approach of Suki and coworkers.\textsuperscript{19–22} We modeled the respiratory system as a parallel arrangement of branches with equivalent linear resistive ($R$) and inertial ($I$) elements, with each branch subtended by a unique viscoelastic constant-phase tissue element (fig. 1).\textsuperscript{23} These branches do not represent distinct anatomical structures, but rather discrete functional compartments that uniquely contribute to the overall mechanical properties of the respiratory system. The $R$ element is a frequency-independent parameter reflecting both airway resistance as well as the purely Newtonian component of chest wall resistance.\textsuperscript{24} The $I$ element accounts primarily for the inertia of gas in the central airways with a small contribution from the mass of the parenchymal tissues and chest wall. The viscoelastic tissue elements are characterized by identical hysteresivity parameters ($\eta$), which account for the dynamic pressure–volume hysteresis of the respiratory tissues (i.e., tissue resistance), but unique elastance parameters ($H_1, H_2, \ldots, H_N$) that vary from branch to branch according to a probabilistic manner. The exponent $\alpha$ depends on $\eta$: $\alpha = (\frac{\gamma}{\eta})\tan^{-1}(\frac{\alpha_H}{\omega});$ angular frequency; and $j$: unit imaginary number (i.e., $\sqrt{-1}$).

 five independent parameters ($R$, $I$, $\eta$, $H_{min}$, and $H_{max}$), which were estimated using a nonlinear gradient technique that minimized the sum of squared differences between actual $Z_{rs}$ spectrum and the corresponding model prediction (Matlab version 7.0; The Mathworks, Natick, MA). If the gradient search algorithm converged to a unique solution for two or more model distributions, the most appropriate distribution for a given $Z_{rs}$ spectrum was established using the corrected Akaike Information Criterion ($\text{AIC}_C$).\textsuperscript{26,27} For the model with the lowest $\text{AIC}_C$ score, we determined its relative likelihood of being the best model among the other candidates using the technique of Akaike weights.\textsuperscript{28} Based on the mean and SD of this selected distribution function, we computed an effective tissue elastance ($\mu_H$) and heterogeneity index ($\sigma_H$) for each $Z_{rs}$.

Statistical Analysis

To assess the impact of $P_{aO_2}$ and injury on the overall levels of impedance, we computed the average magnitude of $Z_{rs}$ across all frequencies:

$$\left|Z_{av}\right| = \frac{1}{K} \sum_{k=1}^{K} \sqrt{(\text{Re}\{Z_{rs}(f_k)\})^2 + (\text{Im}\{Z_{rs}(f_k)\})^2},$$

where $K$ is the total number of frequencies in the pressure excitation signal. A one-way analysis of variance (ANOVA) of the four $P_{aO_2}$ levels (5, 10, 15, and 20 cm H$_2$O) was used to compare values of $R_{rs}$ and $E_{rs}$ at each $f_k$; $Z_{rs}$, the five model parameters from the most appropriate distribution function, as well as $\mu_H$ and $\sigma_H$ before and after injury (SAS version 8.2; SAS Institute Inc., Cary, NC). If significance was obtained with ANOVA, post hoc analysis was performed using the least significant difference criterion. At each $P_{aO_2}$, preinjury and postinjury
Table 1. Gas Exchange and Hemodynamic Data for the 11 Dogs at Baseline and after ALI

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>$133 \pm 25$</td>
<td>$108 \pm 20^*$</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>$3.02 \pm 0.83$</td>
<td>$1.72 \pm 0.63^§$</td>
</tr>
<tr>
<td>MSAP, mmHg</td>
<td>$111 \pm 16$</td>
<td>$100 \pm 20$</td>
</tr>
<tr>
<td>MPAP, mmHg</td>
<td>$17 \pm 4$</td>
<td>$23 \pm 7^†$</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>$20 \pm 3$</td>
<td>$19 \pm 3$</td>
</tr>
<tr>
<td>VT, ml</td>
<td>$236 \pm 53$</td>
<td>$268 \pm 69^†$</td>
</tr>
<tr>
<td>PaCO2, mmHg</td>
<td>$7.34 \pm 0.06$</td>
<td>$7.26 \pm 0.07$</td>
</tr>
<tr>
<td>pH</td>
<td>$38.6 \pm 6.6$</td>
<td>$42.1 \pm 6.2$</td>
</tr>
<tr>
<td>PAO2/FIO2, mmHg</td>
<td>$528 \pm 77$</td>
<td>$261 \pm 125^§$</td>
</tr>
<tr>
<td>Qs/QT</td>
<td>$0.14 \pm 0.09$</td>
<td>$0.32 \pm 0.12^†$</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>$9.4 \pm 1.3$</td>
<td>$10.5 \pm 1.5^*$</td>
</tr>
</tbody>
</table>

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$, § $P < 0.0001$ vs. baseline.

**Results**

**Hemodynamic and Gas Exchange Data**

Baseline and postinjury hemodynamic and gas exchange data during conventional mechanical ventilation are shown in table 1. After lung injury, we observed significant decreases in heart rate, cardiac output, and the arterial partial pressure of oxygen/fraction of inspired oxygen ratio and significant increases in mean pulmonary arterial pressure, shunt fraction, and hemoglobin concentration.

**Impedance Data**

Figure 3 shows examples of $R_{rs}$ and $E_{rs}$ spectra in two representative dogs measured at baseline and after lung injury at $P_{ao}$ levels of 5, 10, 15, and 20 cm H$_2$O. Also shown are the corresponding fits to the data from the model of figure 1 using the most appropriate distribution function $P(H)$ based on the minimum AIC$_C$ score. For dog A, which exhibited a relatively minor response to oleic acid based on the degree of changes in $Z_{rs}$, a model comprising a linear distribution of tissue elastances was sufficient to describe the $Z_{rs}$ spectra at nearly all $P_{ao}$ values. Dog B was considered a more severe responder to oleic acid, with baseline $Z_{rs}$ at most values of $P_{ao}$, best described by a linear distribution of elastances but postinjury $Z_{rs}$ better characterized by a uniform distribution. For both dogs, baseline levels of $E_{rs}$ increased with increasing $P_{ao}$, regardless of frequency.

Figure 4 shows a summary of the $R_{rs}$ and $E_{rs}$ spectra for all 11 dogs at baseline and after ALI at the four levels of $P_{ao}$. At baseline, $R_{rs}$ demonstrated a frequency-dependent decrease throughout the bandwidth under excitation for all values of $P_{ao}$. The $E_{rs}$ demonstrated a slight positive frequency dependence up to approximately 2 Hz, beyond which it demonstrated a frequency-dependent decrease and often became negative at the highest frequencies. This high frequency decrease results from the effect of gas inertia in the central airways on the
respiratory system reactance, from which the $E_{rs}$ spectrum is computed. At baseline, the $E_{rs}$ at 20 cm H$_2$O was significantly higher over the 0.07- to 4.02-Hz range compared with 5, 10, and 15 cm H$_2$O. After lung injury, both $R_{rs}$ and $E_{rs}$ exhibited increases in their respective mean levels and dependence on frequency compared with baseline for all values of $P_{ao}$. Significant increases in $R_{rs}$ and $E_{rs}$ after ALI were observed using paired $t$ tests at each $f_k$ as shown in figure 4. After ALI, $R_{rs}$ at 5 cm H$_2$O $P_{ao}$ was significantly higher compared with 10, 15, and 20 cm H$_2$O $P_{ao}$ at all frequencies, although the $E_{rs}$ at 5 cm H$_2$O was higher only for frequencies between 0.20 and 2.31 Hz.

The impact of injury and $P_{ao}$ on $Z_{rs}$ is shown in figure 5. At baseline, $|Z_{rs}|$ at 20 cm H$_2$O was significantly higher compared with 5, 10, and 15 cm H$_2$O. After lung injury, significant increases in $|Z_{rs}|$ were observed at all values of $P_{ao}$, and $|Z_{rs}|$ was significantly increased at $P_{ao} = 5$ cm H$_2$O compared with all other values of $P_{ao}$.

**Model Analysis**

Figure 6 shows a summary of the most appropriate distribution functions as selected according to AICC score for all 11 dogs at each $P_{ao}$ at baseline and after lung injury. At baseline, the $Z_{rs}$ for most dogs was best described by a linear distribution of tissue elastances. After lung injury, there was an increase in the number of dogs for which $Z_{rs}$ was best described by a uniform distribution of tissue elastances, although the majority of dogs were still best characterized by a linear distribution. A summary of the Akaike weights for the selected model
After injury, the number of dogs requiring a model with a uniform distribution of tissue elastances increased for 5, 10, and 20 cm H₂O. The heterogeneous nature of ALI is characterized by mechanically disparate lung regions, including collapsed

distributions is shown in Table 2, along with the number of dogs for which two or more model distributions converged for a particular $Z_\alpha$ data set using the nonlinear gradient search algorithm. Under baseline conditions, the likelihoods that the selected distribution generated the data when compared to the alternate candidate distributions ranged from 85.4 to 90.5% as averaged at each $P_ao$. After lung injury, the likelihoods decreased at all values of $P_ao$, with mean values ranging from 60.2 to 77.8%. No clear trend of Akaike weight on $P_ao$ was observed. Although at least one distribution function converged for every $Z_\alpha$ data set examined, the number of dogs for which two or more distribution functions converged decreased after lung injury.

A summary of the estimated model parameters is shown in figure 7. The $R$ parameter, reflecting both airway resistance and the Newtonian component of chest wall resistance, demonstrated no significant dependence on $P_ao$ during baseline or ALI conditions. Although $R$ demonstrated considerable intersubject variability after lung injury, there was no significant difference between preinjury and postinjury $R$ at any $P_ao$. The $I$ parameter, reflecting the total inertia of the respiratory system, exhibited no significant dependence on $P_ao$ at baseline. After lung injury, $I$ significantly increased compared with baseline at all $P_ao$ values. ANOVA demonstrated a significant dependence of postinjury estimates of $I$ on $P_ao$, with its value at 5 cm H₂O significantly higher compared with 15 and 20 cm H₂O. Baseline values of the hysteresivity parameter $\eta$ were within the range reported by previous studies and significantly increased after lung injury at all $P_ao$ levels. Neither the $H_{min}$ nor the $H_{max}$ parameters demonstrated any dependence on $P_ao$ at baseline. ANOVA demonstrated a significant dependence of $H_{max}$ on $P_ao$ after lung injury, with its value at 5 cm H₂O significantly higher than that at 10, 15, or 20 cm H₂O. After injury, $H_{min}$ increased significantly only at 20 cm H₂O, whereas $H_{max}$ increased significantly at 5, 10, and 15 cm H₂O.

Figure 8 shows the impact of $P_ao$ and injury on the derived effective tissue elastance ($\mu_H$) and heterogeneity index ($\sigma_H$). At baseline, ANOVA demonstrated no significant dependence of either $\mu_H$ or $\sigma_H$ on $P_ao$. After ALI, $\mu_H$ significantly increased at all $P_ao$ levels, whereas $\sigma_H$ increased only at 5 and 10 cm H₂O. Both $\mu_H$ and $\sigma_H$ demonstrated dependence on $P_ao$ after ALI, with postinjury values at 5 cm H₂O significantly increased compared with 10, 15, and 20 cm H₂O. The $\sigma_H$ was significantly increased compared with baseline at 5 and 10 cm H₂O.

**Discussion**

The heterogeneous nature of ALI is characterized by mechanically disparate lung regions, including collapsed

Table 2. Summary of Akaike Weights for Model Distributions with Lowest AIC<sub>C</sub> Score

<table>
<thead>
<tr>
<th>$\bar{P}_ao$ (cm H₂O)</th>
<th>Baseline</th>
<th>Post Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>86.0 ± 15.4% (58.2–99.6%)</td>
<td>60.2 ± 0.09% (52.3–69.2%)</td>
</tr>
<tr>
<td>10</td>
<td>90.5 ± 16.0% (55.3–99.9%)</td>
<td>71.4 ± 21.3% (50.0–98.4%)</td>
</tr>
<tr>
<td>15</td>
<td>90.0 ± 18.1% (50.0–99.9%)</td>
<td>77.8 ± 26.2% (39.6–99.9%)</td>
</tr>
<tr>
<td>20</td>
<td>85.4 ± 20.4% (50.5–99.9%)</td>
<td>71.7 ± 23.9% (42.7–99.6%)</td>
</tr>
<tr>
<td>n</td>
<td>11</td>
<td>8</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD of percent likelihood that the selected model generated the respiratory impedance ($Z_\alpha$) data at each condition and mean airway pressure ($\bar{P}_ao$). Parentheses denote the range of likelihoods at each condition and $\bar{P}_ao$, and $n$ represents the number of dogs for which two or more model distributions converged to a unique solution using the nonlinear gradient search algorithm.

AIC<sub>C</sub> = corrected Akaike Information Criterion.
nonventilated regions, injured but recruitable regions, normally ventilated regions, and overdistended regions prone to inflation injury. Recently, an “open-lung approach” to ventilation in these patients has been advocated, using PEEP to recruit collapsed lung units and improve oxygenation and low tidal volumes to minimize the risk of overdistention injury. However, optimal PEEP and tidal volume for injured lungs are difficult to determine. Although PEEP may improve compliance in some regions of the lung by recruiting alveoli, it may simultaneously decrease compliance in other regions by overstretching units.

In the past, quasi-static pressure–volume curves were thought to provide insight into the “safe” ranges over which lung recruitment and overdistention injuries occur and therefore have been proposed for use in optimizing the mechanical stresses placed on the lungs during positive-pressure ventilation and more recently during high-frequency ventilation. However, as static measurements constructed under periods of zero flow, these curves provide no information regarding the dynamic regional mechanics in the lung or insight into the nature and distribution of lung injury during mechanical ventilation. Simple dynamic measure indices of lung mechanics, such as resistance and elastance measured at a single breathing frequency, can provide some insight into gross pathophysiology of the entire respiratory system but can be misleading if used to interpret regional mechanics of the lungs in the complex pathophysiology of ALI or to optimize ventilation strategy under varying conditions of frequency, tidal volume, or PEEP. More recently, Ranieri et al. characterized the concavity of the airway pressure–time curve during constant flow inflation with a power law expression to infer the balance between intratidal recruitment and overdistention occurring on a whole lung scale. Although this simple “stress index” may have some predictive value for the development of ventilator-associated lung injury, it does not quantify regional mechanical heterogeneity, which may be a more sensitive indicator. Multibreath inert gas washouts have also been used to detect the presence of heterogeneity and follow trends during the development of ALI, but these approaches do not
directly quantify heterogeneity or changes in the mechanical properties of the respiratory tissues. Finally, other investigators have used high resolution computed tomography to assess heterogeneity in ALI, although such a technique is not amenable to bedside implementation. Given the paucity of techniques available to assess heterogeneity in ALI, the ability to optimize the delicate balance of recruitment, oxygenation, and overdistention in this syndrome remains a challenge.

**Heterogeneity and Respiratory Impedance**

In 1956, Otis et al. were the first to demonstrate how parallel time constant heterogeneity in the lung can cause frequency dependence in $Z_{rs}$ and $E_{rs}$. Since then, other groups have shown that the mechanical impedance spectrum of the lungs or total respiratory system can be a sensitive indicator of mechanical heterogeneity.

Using a computer-generated (but anatomically accurate) airway tree, Lutchen et al demonstrated that two distinct pathophysiologic mechanisms can be uniquely identified from $Z_{rs}$: (1) parallel time constant heterogeneity, which results in enhanced frequency dependence of $R_{rs}$ and $E_{rs}$ predominately below 2 Hz; and (2) random airway closure and derecruitment of lung units, which results in less lung tissue in communication with the airway opening and hence an increase in the levels of $R_{rs}$ and $E_{rs}$ throughout the entire bandwidth of interest. Both of these mechanisms can substantially increase $R_{rs}$ and $E_{rs}$ near breathing frequencies, exclusive of large increases in either overall airway resistance or actual tissue elasticity.

Our $Z_{rs}$ data are surprisingly similar to those data reported in many of these earlier modeling studies. At baseline, both $R_{rs}$ and $E_{rs}$ are dependent on frequency, which has been attributed primarily to the viscoelastic properties of the parenchymal tissues and chest wall in the healthy respiratory system, although some baseline mechanical heterogeneity may also contribute to frequency dependence. Under control conditions, we observed significant increases in $E_{rs}$ and $|\tilde{Z}_{rs}|$ with increasing $P_{at}$, which may result from overstretching and plastoelastic phenomena. After lung injury, we observed significant increases in $|\tilde{Z}_{rs}|$ and both the levels and frequency dependence of $R_{rs}$ and $E_{rs}$ at all values of $P_{at}$, indicating widespread mechanical heterogeneity and loss of alveolar units in communication with the airway opening as edema fluid fills air spaces. In contrast to baseline conditions, $E_{rs}$ and $|\tilde{Z}_{rs}|$ both decreased with increasing $P_{at}$ after ALI, consistent with the notion that moderate increases in $P_{at}$ are beneficial by reducing heterogeneity and recruiting lung units.

**Model Analysis**

To further quantify mechanical heterogeneity from our $Z_{rs}$ data, we relied on the distributed modeling approach initially developed by Suki and coworkers to describe the mechanical properties of the lungs during bronchoconstriction. More recently, this group proposed a similar analysis to describe the heterogeneity of tissue elastances in mouse model of emphysema, which predicts frequency dependence in both $R_{rs}$ and $E_{rs}$. They used only a hyperbolic distribution of tissue elastances to characterize $Z_{rs}$, whereas our data suggest that other tissue distribution functions may in fact be more appropriate to describe the dynamic behavior of the respiratory system after lung injury in dogs. In normal lungs, the AICC predicts that the linear distribution of tissue elastances was most appropriate for describing $Z_{rs}$ in most dogs regardless of $P_{at}$. After lung injury, there was an increase in the number of dogs for which $Z_{rs}$ was best characterized by a uniform distribution of tissue elastances. Nonetheless, most dogs were still best described by a linear distribution of elastances.

Although the model distribution with the lowest AICC score was most likely to have generated the data, it is important to understand that the AICC does not provide information regarding how well a particular distribution outperforms the other candidate distributions or the relative likelihood that this distribution generated the data. We determined this information using the technique of Akaike weights. For the majority of dogs, the likelihood that the selected distribution generated the data were unequivocal ($I > 95$%), although for a few dogs, the distinction between distributions was not as clear, particularly after lung injury (table 2).

Surprisingly, our $R$ parameter demonstrated no significant dependence on $P_{at}$. Although the value of $R$ is composed of both airway resistance and Newtonian chest wall resistance, both may be influenced by thoracic volume to different extents. This may mask any detectable relation between $R$ and $P_{at}$. The $I$ parameter, which in the healthy respiratory system primarily reflects the inertia of gas in the central airways, was significantly increased after ALI. This may result from a net increase in the oscillating mass of lung tissue due to the accumulation of edema fluid in the air spaces.

The progressive decrease in the average dynamic elastance parameter $e_{\text{al}}$ with increasing $P_{at}$ in injured animals is consistent with lung recruitment and previous reports of changes in the static lung elastance as a consequence of alveolar flooding and airway closure. Therefore, it is unlikely that changes in $e_{\text{al}}$ reflect alterations in the actual elastic properties of the parenchymal tissues or chest wall. Baseline values of our heterogeneity index $\sigma_{I\text{al}}$ demonstrated a decreasing trend with $P_{at}$ up to 15 cm H$_2$O but increased slightly at 20 cm H$_2$O, although this did not achieve statistical significance. Although this is consistent with lung recruitment and decreases in mechanical heterogeneity, higher levels of $P_{at}$ may result in overdistention occurring in a somewhat heterogeneous manner. After lung injury, $\sigma_{I\text{al}}$ increased.
significantly compared with baseline at 5 and 10 cm H$_2$O, implying an increase in mechanical heterogeneity. In addition, ANOVA demonstrated a significant dependence of σ$_{ij}$ on $\bar{P}_{ao}$ after ALI, with its highest value at 5 cm H$_2$O. Further increases in $\bar{P}_{ao}$ seem to reduce σ$_{ij}$, also consistent with lung recruitment.

We observed significant increases in our hysteresivity parameter $\eta$ after ALI. Hysteresivity has been proposed by Fredberg and Stamenovic$^{29}$ as an index to describe the hysteretic pressure-volume relation of the lung tissues and can be thought of as a ratio of energy dissipation to energy storage during cyclic changes in lung volume. It has long been held that $\eta$ is relatively constant across lung volume, breathing frequency, and tidal volume.$^{29}$ However, these assumptions have been called into question in recent studies,$^{47,49}$ especially in animal models of ALI.$^{50,51}$ A key assumption of our modeling analysis is that $\eta$ is constant throughout the respiratory tissues regardless of disease condition.$^{20,29}$ Our observed increases in $\eta$ after ALI may reflect actual changes in the coupling of energy dissipation and storage in the respiratory tissues.$^{29}$ Hysteresivity is known to be influenced by several factors, including surface forces of the air-tissue interface, Coulomb friction between collagen and elastin fibers, and cross-bridge cycling in airway smooth muscle or other contractile elements in the lung parenchyma, any of which may be influenced by ALI. Moreover, there may be additional airway or tissue heterogeneity that is not appropriately described by our distribution functions, resulting in modeling error with an artifactualy high estimate of $\eta$.$^{9,11,41}$

**Limitations**

Despite the apparent utility of our approach to quantify mechanical heterogeneity in the respiratory system, these techniques rely on a few key assumptions that must be considered when using them to quantify regional mechanics. First, for mathematical convenience and simplicity, we evaluated only three simple tissue distribution functions to describe respiratory system heterogeneity as assessed at the airway opening. Although it seems that the $Z_{rs}$ of most dogs is best described by a linear distribution of tissue elastances, we cannot be certain how accurately these functions describe actual tissue variability. Such information is probably more accurately obtained using functional computed tomography to quantify specific elastances.$^{39}$ Future studies may incorporate similar modeling approaches with imaging data to obtain more accurate tissue distribution functions for describing $Z_{rs}$. Therefore, although the current accuracy of our heterogeneity estimates may be somewhat biased because of modeling error, σ$_{ij}$ may still be a useful marker to assess the degree of heterogeneity in the lungs.

In addition, our modeling approach assumes that tissue heterogeneity is randomly distributed throughout the lungs and, as such, does not provide specific anatomic information on regional mechanics. Tissue heterogeneity in ALI may be distributed in a more deterministic manner, depending on the etiology of the injury, orientation in the gravitational field, local pulmonary blood flow, or proximity to the pleura or other organs. Whether such additional anatomical information would be useful in optimizing ventilatory parameters is unknown.

Finally, we recognize that our modeling analysis accounts only for tissue heterogeneity. Airway heterogeneity may also contribute to the enhanced frequency dependence in $R_{rs}$ and $E_{rs}$,$^{6,12,19,21,41}$ although the degree to which it does so in ALI is not clear. A previous study by Barnas et al.$^{44}$ using alveolar capsules in dogs demonstrated that increases in the frequency dependence of lung resistance and elastance after oleic acid-induced pulmonary edema were due primarily to changes in parenchymal tissue mechanics, implying that changes in airway resistance are not significant in the oleic acid model of lung injury. Similarly, our model analysis demonstrated no significant differences between preinjury and postinjury $R$. Therefore, we believe it is unlikely that airway heterogeneity contributed significantly to the frequency dependence we observed in $R_{rs}$ and $E_{rs}$ after ALI.

**Summary**

In summary, these data demonstrate that $Z_{rs}$ can provide specific information about the mechanical heterogeneity of the lungs and the impact of $\bar{P}_{ao}$. After lung injury, both the level and frequency dependence of $R_{rs}$ and $E_{rs}$ increase compared with baseline, indicating the presence of widespread mechanical heterogeneity. These differences seem to be reduced by increases in $\bar{P}_{ao}$, consistent with the recruitment of lung units and minimization of the impact of heterogeneity on dynamic respiratory mechanics. Model analysis of $Z_{rs}$ demonstrate that both effective tissue elastance and mechanical heterogeneity increase after ALI and decrease with increasing $\bar{P}_{ao}$. These noninvasive approaches may be useful in identifying optimal PEEP levels and tidal volume during conventional mechanical ventilation and possibly allow for the development of ventilation protocols to optimize regional lung mechanics in patients with ALI. Future research should be directed toward the development of more accurate tissue distribution functions to quantify the heterogeneity of injured lungs, which will be essential in the validation of this technique as a clinical diagnostic tool.

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Appendix

The model-predicted impedance ($\tilde{Z}_{rs}$) of the network of figure 1 can be defined as the reciprocal of the sum of admittances of each branch:

$$\tilde{Z}_{rs}(\omega) = \left( \sum_{r=1}^{N} \frac{1}{R + j\omega \alpha \tan^{-1}\left( \frac{\eta - jH_{rs}}{\omega^2} \right)} \right)^{-1}$$

(1)

with

$$\alpha = \frac{2 \tan^{-1}(1 / \eta)}{\pi}$$

(2)

and where $j$ is the unit imaginary number, $\omega$ is the angular frequency, and $N$ is the number of branches in the network. Alternatively, if we assume that the variation in tissue elastance between branches varies in a probabilistic manner, we can approximate $\tilde{Z}_{rs}$ as

$$\tilde{Z}_{rs}(\omega) = \left( \sum_{m} \frac{P_m(H_m)}{R + j\omega \alpha \tan^{-1}\left( \frac{\eta - jH_m}{\omega^2} \right)} \right)^{-1}$$

(3)

where $P_m$ represents a histogram function of bin width $\Delta H$, $H_m$ denotes the center value of elastances stored in bin $m$, and $M$ is the total number of bins in the distribution. In the limit as the number of branches tends toward infinity and $\Delta H$ approaches zero, we obtain an expression for $\tilde{Z}_{rs}$ that depends on a continuous probability density function $P(H)$ integrated over the upper and lower bounds $H_{min}$ and $H_{max}$:

$$\tilde{Z}_{rs}(\omega) = \left( \int_{H_{min}}^{H_{max}} \frac{P(H)}{R + j\omega \alpha \tan^{-1}\left( \frac{\eta - jH}{\omega^2} \right)} dH \right)^{-1}$$

(4)

Regardless of the form of $P(H)$, we can define an effective mean tissue elastance, $\mu_{eff}$, which provides a rough estimate of the overall elastance of the respiratory tissues:

$$\mu_{eff} = \int_{H_{min}}^{H_{max}} H P(H) dH$$

(5)

To quantify the heterogeneity of the respiratory tissues, we relied on the SD $\sigma_H$ of $P(H)$:

$$\sigma_H = \sqrt{\int_{H_{min}}^{H_{max}} (H - \mu_{eff})^2 P(H) dH}$$

(6)

To obtain simple, closed-form expressions for equation 4, we defined a probability density function $P(H)$ a priori to be of the form

$$P(H) = \begin{cases} \frac{L}{H^2} & H_{min} \leq H \leq H_{max} \\ 0 & \text{otherwise} \end{cases}$$

(7)

where $L$ is a constant which depends on $H_{min}$ and $H_{max}$ as well as the function $P(H)$. We assume $\lambda = -1, 0, 1$, which define models corresponding to linear, uniform, and hyperbolic distributions of tissue elastances, respectively (fig. 3). An expression for $L$ can be obtained by assuming that the area under the probability density function $P(H)$ is equal to 1:

$$L = \frac{1}{\int_{H_{min}}^{H_{max}} H^2 P(H) dH}$$

(8)

Thus, using equation 7 with $\lambda = -1$ to solve for equations 4, 5, and 6, we obtain for the linear distribution,

$$\tilde{Z}_{rs}(\omega) = \left( \frac{H_{max}^2 - H_{min}^2}{2\omega^2} \right) \left( \frac{(\eta - j)}{R + j\omega \alpha \tan^{-1}\left( \frac{\eta - jH_{max}}{\omega^2} \right)} \right)$$

(9)

and with $\lambda = 0$ for the uniform distribution

$$\tilde{Z}_{rs}(\omega) = \left( \frac{H_{max}^2 - H_{min}^2}{2\omega^2} \right) \left( \frac{(\eta - j)}{R + j\omega \alpha \tan^{-1}\left( \frac{\eta - jH_{max}}{\omega^2} \right)} \right)$$

(10)

and finally with $\lambda = 1$ for the hyperbolic distribution,

$$\tilde{Z}_{rs}(\omega) = \left( \frac{H_{max}^2 - H_{min}^2}{2\omega^2} \right) \left( \frac{(\eta - j)}{R + j\omega \alpha \tan^{-1}\left( \frac{\eta - jH_{max}}{\omega^2} \right)} \right)$$

(11)

(12)

(13)

(14)
Note that for equations 9, 12, and 15, we define the natural logarithm of any arbitrary complex number $z = x + jy$ as:

$$
\ln(z) = \ln|z| + j \arg(z) = \ln(\sqrt{x^2 + y^2}) + j \tan^{-1}\left(\frac{y}{x}\right)
$$