Estimating respiratory mechanics in the presence of flow limitation

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Bijaoui, Eve, Stephanie A. Tuck, John E. Remmers, and Jason H. T. Bates. Estimating respiratory mechanics in the presence of flow limitation. J. Appl. Physiol. 86(1): 418–426, 1999.—Dynamic collapse of the pulmonary airways, leading to flow limitation, is a significant event in a number of respiratory pathologies, including obstructive sleep apnea syndrome and chronic obstructive pulmonary disease. Quantitative evaluation of the mechanical status of the respiratory system in these conditions provides useful insights into airway caliber and tissue stiffness, which are hallmarks of such abnormalities. However, assessing respiratory mechanics in the presence of flow limitation is problematic because the single-compartment linear model on which most assessment methods are based is not valid over the entire breath. Indeed, even deciding which parts of a breath are flow limited from measurement of mouth flow and pleural pressure often proves to be difficult. In this study, we investigated the use of two approaches to assessing the overall mechanical properties of the respiratory system in the presence of inspiratory flow limitation. The first method is an adaptation of the classic Mead-Whittenberger method, and the second method is based on information-weighted histograms obtained from recursively estimated signals of respiratory resistance and elastance. We tested the methods on data simulated by using a computer model of the respiratory system and on data collected from obese sleeping pigs. We found that the information-weighted histograms provided the more robust overall estimates of respiratory mechanics.

respiratory resistance and elastance; recursive least squares; multiple linear regression; pressure-flow curve; resistive pressure; obese pigs; sleep apnea

The modern approach to assessing respiratory mechanics in patients or animals is to match measurements of pressure, flow, and volume made at the airway opening to the equation of a single-compartment linear model characterized by a resistance (R) and an elastance (E). This is done most efficiently on a computer by using multiple linear regression. However, this model assumes that both R and E are constant over the data record being analyzed, which, although satisfactory in many cases, breaks down completely in the presence of flow limitation because the effective flow resistance of the respiratory system changes markedly as flow limitation begins. Indeed, although flow is limited, one cannot even think of the system as having a resistance in the conventional sense because the flow is independent of the driving pressure. Consequently, the single-compartment linear model cannot be applied to an entire breath when flow limitation is present during some part of it. Nevertheless, clinical situations, such as ventilated patients with chronic obstructive pulmonary disease (6, 8), frequently present the need to assess respiratory mechanics during flow limitation.

In this study, we investigate two approaches for assessing respiratory mechanics in the presence of flow limitation. The first is based on the so-called Mead-Whittenberger (11) technique, in which E is estimated from the pressure change between the beginning and the end of inspiration. Subtracting the product of E and volume from pressure then yields the resistive pressure throughout the breath. The resistive pressure may be a very nonlinear function of flow when flow limitation occurs at some point in the breath. However, the Mead-Whittenberger method as traditionally implemented uses only two data points per breath to estimate E and so is particularly sensitive to noise. We have therefore developed a robust modification of the Mead-Whittenberger method that uses all the data within a breath to estimate E.

Our second approach to dealing with flow limitation is based on the recursive least squares (RLS) algorithm, which allows one to track changes in R and E with a very short memory. We suspected this might allow us to estimate R and E adequately during those parts of the breath that are not flow limited and possibly even detect the onset of flow limitation itself. The variations in the model parameter estimates over the breath can be represented by “information-weighted histograms” (10). The purpose of the present study was to evaluate both the modified Mead-Whittenberger and the RLS techniques for assessing respiratory mechanics during flow limitation in both simulated and experimental data.

METHODS

Modeling the Respiratory System

We modeled the lung, as shown in Fig. 1, as a single compartment connected to a single airway. The flow-resistive
pressure drop across the airway (Paw) obeys Rohrer's equation
\[ \text{Paw} = K_1 \dot{V} + K_2 \dot{V} \dot{V} \]
where \( K_1 \) and \( K_2 \) are constants, \( \dot{V} \) is ventilatory flow, and their values are listed in Table 1. The resistance of the airway (Raw) is thus \( K_1 + K_2 \dot{V} \).

The viscoelastic properties of the lung tissues are accounted for by a Kelvin body having parameters for static pulmonary elastance (Est,L), overall lung resistance (RL), and lung elastance (EL) (4, 7, 8). These parameters were assigned values found in normal subjects by Guerin et al. (8) and are listed in Table 1. The Kelvin body is connected between the two moving components of the compartment, as shown in Fig. 1.

The pressure across the Kelvin body (PKelvin) obeys the equation (7)
\[ P_{\text{Kelvin}}(t) + \frac{R_L}{E_L} \dot{P}_{\text{Kelvin}}(t) = E_{\text{st,}L} V(t) + R_L \left( 1 + \frac{E_{\text{st,}L}}{E_L} \right) V(t) \]
where \( P_{\text{Kelvin}} \) is the time derivative of \( P_{\text{Kelvin}} \) and \( V \) is volume. The pressure at the airway opening (Pao) (i.e., at the entrance to the airway) is then given by
\[ \text{Pao} = \text{Raw} \dot{V} + \dot{P}_{\text{Kelvin}} \]
and, therefore, the general motion equation of the model is
\[ E_L \dot{P}_{\text{ao}} + R_L \dot{P}_{\text{ao}}(t) = E_{\text{st,}L} V(t) + R_L E_{\text{st,}L} V(t) + [R_L (E_L + E_{\text{st,}L}) + E_L \text{Raw}] V(t) \]
\[ + R_L \text{Raw} \ddot{V}(t) + R_L \text{Raw} \dot{V}(t) \]

Table 1. Model parameter values

<table>
<thead>
<tr>
<th>Model/Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td></td>
</tr>
<tr>
<td>RL, cm H2O·s·l⁻¹</td>
<td>3.44</td>
</tr>
<tr>
<td>( \tau ), s</td>
<td>1.07</td>
</tr>
<tr>
<td>EL, cm H2O/l</td>
<td>3.21</td>
</tr>
<tr>
<td>Est,L, cm H2O/l</td>
<td>8.2</td>
</tr>
<tr>
<td>Airways</td>
<td></td>
</tr>
<tr>
<td>K₁, cm H2O·s⁻¹·l⁻¹</td>
<td>1.85</td>
</tr>
<tr>
<td>K₂, cm H2O·s⁻²·l⁻²</td>
<td>0.427</td>
</tr>
</tbody>
</table>

\( RL \), lung resistance; \( \tau \), a time constant equal to RL /lung elastance (EL); Est,L, static lung elastance; \( K_1 \) and \( K_2 \), Rohrer constants defining airway resistance according to Eq. 1.

Experimental Data

Three castrated male Vietnamese pot-bellied pigs were fed so that their body weight doubled in a few months (15). The pigs were 21, 24, and 20 mo of age and weighed 103, 104, and 118 kg, respectively. All protocols were approved by the Animal Care Committee at the University of Calgary. Sleep states were identified by using an electroencephalogram, electromyogram, and nose twitch as an indicator of phasic rapid-eye-movement sleep. The pleural pressure (Ppl) was also measured by placing a balloon in the pleural space. The animals were anesthetized and mechanically ventilated during the surgical procedures required to implant these devices.

The pigs breathed spontaneously through a face mask-pneumotachograph system to record V and Ppl and V signals were sampled at the rate of 100 Hz. We defined seven levels of IFL, going from "no flow limitation" to a threshold of 0.2 l/s.

Data Processing

RLS and information-weighted histograms. We fit our data to the equation of motion of the single-compartment linear model of the respiratory system. This equation is expressed in matrix notation as
\[ Y = XA \]
where
\[
\begin{bmatrix}
Y_1 \\
Y_2 \\
\vdots \\
Y_N 
\end{bmatrix} = 
\begin{bmatrix}
P_1 \\
P_2 \\
\vdots \\
P_N 
\end{bmatrix} 
\begin{bmatrix}
Y_1 \\
Y_2 \\
\vdots \\
Y_N 
\end{bmatrix} 
\]

Fig. 1. A 5-parameter model of the lung. Model consists of flow-dependent airway resistance (Raw; which contains 2 parameters through Eq. 1) together with a Kelvin body (characterized by 3 parameters: static pulmonary elastance (Est,L), overall lung resistance (RL), and lung elastance (EL)), accounting for viscoelasticity of lung tissue according to D'Angelo et al. (6). V_{Pao} volume of airway opening pressure.
is the vector of dependent variables, where \( N \) is the number of data points

\[
\mathbf{X} = \begin{bmatrix}
V_1 & V_1 & 1 \\
V_2 & V_2 & 1 \\
\vdots & \vdots & \vdots \\
V_N & V_N & 1
\end{bmatrix}
\]  

(7)

is the matrix of independent variables, and

\[
\mathbf{A} = \begin{bmatrix}
R \\
E \\
K
\end{bmatrix}
\]  

is the parameter vector (bold symbols denote vectors and matrices). \( P_i, V_i, \) and \( V_i \) are the \( i \)th measurements of tracheal pressure, volume, and flow, respectively. \( V \) was obtained by a Simpson's rule integration of \( V_i \). The parameters \( R \) and \( E \) are referred to as resistance and elastance, respectively, of the system, and \( K \) is the value of pressure in the model when both flow and volume are equal to zero.

The conventional least squares estimate of \( \mathbf{A} \) (i.e., the estimate provided by fitting the model to all the data at once in the usual way) is given by

\[
\hat{\mathbf{A}} = [\mathbf{X}^T \mathbf{X}]^{-1} \mathbf{X}^T \mathbf{Y} = \mathbf{Q} \mathbf{X}^T \mathbf{Y}
\]  

(9)

where \( \mathbf{Q} \) is the so-called "information matrix" of the system and \( \mathbf{T} \) is the matrix transpose operator. The leading diagonal elements of \( \mathbf{Q} \) are proportional to the SDs of the estimates of the parameters. Thus, if these diagonal elements are large, the confidence regions about the corresponding parameter estimates are also large.

In contrast to conventional least squares, the RLS algorithm begins by assuming that all parameter values are zero and then proceeds to update the parameters each time a new data set arrives. In other words, the RLS algorithm performs conventional multiple linear regression on a finite data set, but it does so recursively so that a sequence of estimates is obtained for each parameter rather than just a single value for the entire data set. Thus, if \( \hat{\mathbf{A}}_k \) is the estimated parameter vector obtained from the first \( k \) measurements, then the estimated parameter vector obtained from the first \( k+1 \) measurements is given by

\[
\hat{\mathbf{A}}_{k+1} = \hat{\mathbf{A}}_k + \mathbf{Q}_{k+1} \mathbf{X}_{k+1} (y_{k+1} + \mathbf{X}_{k+1}^T \hat{\mathbf{A}}_k) / (\rho + \mathbf{X}_{k+1}^T \mathbf{Q}_{k+1} \mathbf{X}_{k+1})
\]  

(10)

where \( y_{k+1} \) is the most recent measurement of the dependent variable and

\[
\mathbf{Q}_{k+1} = \frac{1}{\rho} [\mathbf{Q}_k - \mathbf{Q}_k \mathbf{X}_{k+1} \mathbf{Q}_k / (\rho + \mathbf{X}_{k+1}^T \mathbf{Q}_{k+1} \mathbf{X}_{k+1})]
\]  

(11)

\( \rho \) is a constant (0 < \( \rho \) < 1) called the forgetting factor and is related to the time constant \( \tau_{mem} \) of the memory by the relation \( \tau_{mem} = -\delta t / \ln(\rho) \), where \( \delta t \) is the sampling interval. The RLS algorithm was initialized with \( \hat{\mathbf{A}}_0 = 0 \) and \( \mathbf{Q}_0 = 10^6 \mathbf{I} \) (\( \mathbf{I} \) is the identity matrix). For both simulated and experimental data, \( \tau_{mem} \) was 0.4 s, similar to previous studies (1, 3).

Figure 2 shows an example of a complete breath of \( V \) and \( P \) simulated by the model, together with the recursively estimated \( R \) and \( E \) both without IFL (Fig. 2A) and when the IFL threshold was 0.3 l/s (Fig. 2B). Even without IFL, there is some variation in both \( R \) and \( E \) throughout the breath (Fig. 2A) because of the flow dependence of \( \text{Raw} \) and the frequency dependence of the viscoelastic tissue mechanical properties. However, this variation is greatly accentuated in the presence of IFL (Fig. 2B). In particular, \( R \) begins to decrease and \( E \) begins to increase markedly as soon as IFL starts.
We calculated information-weighted histograms, as defined by Bates and Lauzon (3), from the recursively estimated R and E. This requires that the value of $\tau_{mem}$ be chosen appropriately. If $\tau_{mem}$ is too large, then there will be systematic deviations between the measured P signal and that predicted by the model because R and E will not be able to change their values fast enough to account for all the variation in the data. Conversely, if $\tau_{mem}$ is too small, then the model will predict not only the deterministic parts of P but also any noise it contains. Choosing $\tau_{mem}$ appropriately between the extremes allows the model to account for the deterministic variation in the data, but not the noise. This gives rise to R and E signals that generally exhibit considerable variations over a breath. These variations were represented in what we call information-weighted histograms. That is, rather than simply assigning each value in a parameter signal to its appropriate bin, as is usually done when constructing a histogram, we first scaled each point in the parameter signal by the inverse of its corresponding diagonal element in the information matrix ($Q$). In other words, we calculated histograms from the products of each parameter with the inverse of its variance.

Figure 3 gives the information-weighted histograms of R and E for a complete breath without IFL (Fig. 3A) and when the IFL threshold was 0.3 l/s (Fig. 3B). The information-weighted histograms without IFL are reasonably narrow, reflecting the modest variability of R and E seen in Fig. 2A. By contrast, the histograms obtained with IFL are wide and multimodal, reflecting the large degree of parameter variability seen in Fig. 2B.

**Modified Mead-Whittenberger method.** The original Mead-Whittenberger method assumes a constant E between two points of zero flow to obtain elastic pressure. At each of these two points the term RV in Eq. 4 becomes zero, so that $E = \frac{\Delta P}{\Delta V}$, where $\Delta P$ and $\Delta V$ are the differences in pressure and volume between the two points. Consequently, E is determined by only two points in the entire breathing cycle and is therefore very susceptible to errors in the measurement of P or V at these points. In particular, P tends to change very rapidly at the end of inspiration, so the accurate identification of the zero-flow point here can be problematic.

We thus decided to modify the Mead-Whittenberger method as follows. We assumed that the resistive pressure, Pres, is a single-valued, although nonlinear, function of V. This means that Pres plotted against V over the breath should define a single curve with no looping. That is

$$\int_{cycle} \text{Pres} \, d\dot{V} = 0$$

where

$$\text{Pres} = P - EV - K = RV$$

This leads to

$$\int_{cycle} P \, d\dot{V} - \int_{cycle} K \, d\dot{V} - E \int_{cycle} V \, d\dot{V} = 0$$

so that

$$E = \frac{\int_{cycle} P \, d\dot{V} - \int_{cycle} K \, d\dot{V}}{\int_{cycle} V \, d\dot{V}}$$

The constant K was estimated from the plateau in P at the end of expiration and then used in Eq. 13 along with E from Eq. 15 to yield Pres over the cycle. Dividing Pres by V then

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Fig. 3. Information-weighted histograms for R and E without flow limitation (A) and with an IFL threshold of 0.3 l/s (B).
gave R over the breathing cycle. A mean value for R was estimated as the slope obtained from a linear regression analysis between Pres and V˙ for each breath.

Figure 4A shows Pres obtained by using the modified Mead-Whittenberger method both with and without IFL. Even without IFL, Pres plotted against V describes a loop because the model has two mechanical degrees of freedom. In the presence of IFL (solid line), the Pres-V˙ curve becomes very nonlinear during inspiration due to inspiratory V ˙ being clipped above the IFL threshold. Figure 4B shows the time course of R during inspiration (R i) obtained by using the modified Mead-Whittenberger method, without (dotted line) and with (solid line) IFL. Without IFL, R i is reasonably stable throughout inspiration. However, with the onset of IFL (at ~0.4 s), R i starts to increase significantly due to the increase in Pres while V is constant.

RESULTS

We compared the estimates of R provided by the information-weighted histograms and the modified Mead-Whittenberger techniques as a function of the IFL threshold. Figure 5 shows the mean ± SD value of R provided by the information-weighted histograms and the mean value of R from modified Mead-Whittenberger method. Also shown in Fig. 5 are the mean ± SD values of the actual RLS estimates themselves. For both RLS and modified Mead-Whittenberger methods, mean R increases rapidly with decreasing IFL threshold. The mean of the information-weighted histograms for R is the least sensitive to IFL, even though its SD increases markedly.

Figure 6 gives an example of the Ppl and V signals over a single breathing cycle obtained from one of the pigs studied, both awake without IFL (Fig. 6A) and asleep with IFL (Fig. 6B). IFL was defined as being present if V reached a plateau for more than the latter half of the breath. The experimental data with IFL differ in some important ways from the simulated data shown above (Fig. 2B), particularly with regard to V. Specifically, expiratory V can be divided into three parts, indicated as i, ii, and iii in Fig. 6B. In part i, V is only slightly negative and relatively stable. This changes suddenly to a steep increase in slope in part ii. Finally, V levels off again in part iii. The corresponding Ppl signal shown in Fig. 6B is essentially flat throughout expiration, indicating that the various features seen in V are not due to respiratory muscle activity and therefore presumably reflect time variations in expiratory flow resistance.

Figure 7 shows examples of information-weighted histograms for R and E obtained from the three pigs studied. Figure 7A shows histograms without IFL, whereas Fig. 7, B-D, shows histograms with IFL. A number of consecutive breaths were analyzed under each condition, and the means and SDs of the histogram means and SDs are given in Table 2. All histograms were wide and multimodal, although the widths of the histograms (SD in Table 2) were greater for most of the IFL cases.

Figure 8 shows a plot of Pres vs. V for the same data as Fig. 7. Each curve describes a “figure-eight” loop, similar to the data in Fig. 4. Mean values of R and E and their SDs obtained from multiple breaths analyzed in all pigs with the modified Mead-Whittenberger method are given in Table 2.
DISCUSSION

Flow limitation is an important feature of chronic airway obstruction (8). In subjects with obstructive sleep apnea syndrome, IFL often anticipates the appearance of an apnea or a respiratory-event-related arousal (9, 12, 13). Flow limitation exists, by definition, when flow and respiratory efforts are dissociated, which implies that the respiratory system ceases to have a resistance in the conventional sense. Consequently, if flow limitation occurs at some point within a breath, then the usual mechanical parameters R and E can no longer be assessed in a meaningful way for that breath in its entirety. Of course, those parts of the breath that do not involve flow limitation may be used to estimate values for R and E in the usual way, although the challenge then becomes to determine where in the breath flow limitation occurs, or at least to analyze the data in such a way that the flow-limited portions do not exert undue influence on the results. We chose to examine the case where flow limitation occurs at some point during inspiration because this was thought to be an important respiratory event occurring in our obese pigs with sleep-disordered breathing (15).

We investigated two approaches to the problem of assessing respiratory mechanics in the presence of flow limitation. One of these approaches was based on the classic method suggested by Mead and Whittenberger (11), which is generally invoked under the assumption that the respiratory system can be adequately represented as a single, uniformly ventilated compartment with an R and E that remain constant throughout the breathing cycle (i.e., Eq. 13). As a general tool for assessing respiratory R and E, the Mead-Whittenberger method has been superseded in recent years by the use of multiple linear regression for reasons of speed and robustness. However, whereas the assumption of constant R and E is binding for the multiple linear regression approach when applied to an entire breath, the Mead-Whittenberger method is only strictly limited by an assumption of constant E. The Pres curve that it returns, after subtraction of the product of E and volume from P, may take on any nonlinear shape as a function of V, so that Pres divided by V may be similarly nonlinear. This means that the Mead-Whittenberger method should be applicable to the flow-limited situation, provided that E remains constant throughout the breath and can be accurately estimated.

The problem with the Mead-Whittenberger method, from a practical point of view, is that it uses only two data points, those at the beginning and end of inspiration, when V is zero, to estimate E. This means that E is very sensitive to noise in the data. Even more problematic, it may be difficult to accurately determine P at points of zero because P may be changing rapidly at these points (particularly in the transition from inspiration to expiration). Errors in the determination of E then lead to errors in Pres and R. We therefore modified the method in a manner that uses all the P and V data over the breath to determine E. The modification is based on the assumptions that E remain constant throughout the breath and that Pres be a single-valued function of V. Neither of these assumptions is particularly good. For example, E is expected to vary throughout the breath due to the nonlinear and multicompart-
mental nature of respiratory system mechanics. Also, Pres is expected to depend on both lung volume and lung-volume history, and indeed the effects of this are clearly visible in the looping of both the simulated data (Fig. 4) and the data from the pigs (Fig. 8). The potential utility of the modified Mead-Whittenberger method is demonstrated in Fig. 4, which shows the vertical segment of Pres vs. V where IFL occurred in the simulated data. Although no such clear vertical spike is seen in the real data (Fig. 8), all three pigs show a nearly vertical segment of Pres at the end of inspiration, which presumably reflects IFL.

The pig data also showed some features not present in the simulated data. Specifically, in Fig. 6 the representative breath shown has been divided into three phases in expiration. In phase i expiratory flow is small and relatively constant. One possibility for this observation is that these pigs were flow limited early in expiration as well as inspiration because correlation between IFL and expiratory flow limitation has been previously reported (14). However, we think it most likely that the changes in expiratory resistance reflect actively regulated expiratory braking, probably by the larynx, whereby the obese animal regulates lung volume during expiration (2). The rapidly increasing expiratory flow in phase ii then presumably results from the sudden reopening of the upper airway. Finally, at the end of expiration, flow again becomes limited and so levels off in phase iii. Furthermore, although we have not identified phases of expiration for the non-IFL pig (Fig. 6), it seems that glottic braking is also occurring here because V at the start of expiration is much less than later on. These factors all contribute to the substantial degree of looping seen in the Ppl-V curves for all animals seen in Fig. 8.

The second method we investigated was based on the RLS method of fitting the single-compartment linear model to respiratory data. Although this approach is, in principle, bound by the same assumptions as conventional multiple linear regression, its recursive nature means that the model is effectively being fit to only a small segment of data at any one time (the data length being determined by the memory time constant of the RLS algorithm). Our initial hope was that this might allow us to identify the point at which IFL began, as a sudden change in the estimated values of R and E. Unfortunately, the issue is not completely clear in practice. Although it is certainly true that IFL did produce significant changes in R and E (Fig. 2B), R and E still varied somewhat without any IFL (Fig. 2A). This occurred because the single-compartment linear model does not describe a nonlinear, multicompartment respiratory system perfectly, so

![Fig. 7. Information-weighted histograms for R and E from awake pig 1 (A) and from NREM sleeping pigs 1-3 (B-D). Data in A were non-flow limited, whereas data in B-D were flow limited.](image-url)

Table 2. Results of analysis of consecutive breaths in 1 non-flow-limited pig (pig 1, awake) and 3 flow-limited pigs (pigs 1-3, NREM)

<table>
<thead>
<tr>
<th>Pig</th>
<th>E (MMW), cmH₂O/l</th>
<th>R (MMW), cmH₂O·s⁻¹</th>
<th>Mean E (IWH), cmH₂O/l</th>
<th>SD E (IWH), cmH₂O/l</th>
<th>Mean R (IWH), cmH₂O·s⁻¹</th>
<th>SD R (IWH), cmH₂O·s⁻¹</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pig 1 awake</td>
<td>11.85 (5.61)</td>
<td>38.29 (4.26)</td>
<td>4.07 (1.02)</td>
<td>16.10 (5.61)</td>
<td>38.34 (1.37)</td>
<td>13.74 (1.32)</td>
<td>4</td>
</tr>
<tr>
<td>Pig 1 NREM</td>
<td>18.84 (1.15)</td>
<td>50.83 (6.56)</td>
<td>14.69 (2.18)</td>
<td>23.55 (3.73)</td>
<td>50.26 (6.53)</td>
<td>19.45 (4.72)</td>
<td>14</td>
</tr>
<tr>
<td>Pig 2 NREM</td>
<td>39.86 (0.56)</td>
<td>44.87 (2.27)</td>
<td>22.73 (3.76)</td>
<td>37.55 (3.07)</td>
<td>44.02 (1.45)</td>
<td>17.71 (1.49)</td>
<td>13</td>
</tr>
<tr>
<td>Pig 3 NREM</td>
<td>38.10 (1.43)</td>
<td>27.75 (1.69)</td>
<td>22.44 (5.64)</td>
<td>24.52 (2.05)</td>
<td>27.89 (1.98)</td>
<td>11.09 (1.20)</td>
<td>14</td>
</tr>
</tbody>
</table>

n, No. of breaths. NREM, non-rapid eye movement; E, elastance; R, resistance; MMW, modified Mead-Whittenberger; IWH, information-weighted histograms; SD, standard deviation. Mean IWH parameter values are means of histogram means. SD IWH values are SDs of histogram means. SDs of all quantities are in parentheses.
that variations in the best-fit values of $R$ and $E$ throughout a breath are expected even in the normal lung. Thus the detection of flow limitation from changes in recursively estimated $R$ and $E$ values becomes a question of degree, and it is not clear how to decide a priori how much variation should be taken as an indication of flow limitation.

However, even though it may be difficult to identify the onset of flow limitation, the RLS method does enable us to deal with the situation where the single-compartment linear model gives a poor fit to the data from an entire breath. Specifically, by allowing $R$ and $E$ to vary over the breath, rather than requiring they achieve a single representative value, we can gain some measure of the departure of the mechanical behavior of the respiratory system from that of a single compartment. The obvious way to represent the variation in a signal, such as $R$ or $E$ in Fig. 2, is to construct a histogram of the values, thereby representing the relative frequencies of appearance of each value over the data record. Unfortunately, this does not always produce physiologically sensible results because the recursively estimated parameter values may be negative at some points during the breathing cycle. Bates and Lauzon (3) found, however, that those portions of the data that produced such meaningless values invariably contained very little information, as reflected in the corresponding diagonal values of the information matrix (these diagonal values are proportional to the estimated variances of the estimated parameters). This led to the notion of the information-weighted histogram proposed by Bates and Lauzon (3) and used subsequently by Avanzolini et al. (1). Here, the variations in $R$ and $E$ are represented in a histogram, but the contribution of each value to the histogram is weighted by the inverse of the corresponding diagonal element of the information matrix. The result is a histogram largely dominated by only those parameter values that are strongly determined by the data, and hence the physiologically meaningless values tend to be almost completely suppressed.

The modest widths of the information-weighted histograms from the simulated data without IFL (Fig. 3A) are due to the modest degree of parameter variation over the breathing cycle (Fig. 2A). In contrast, the histograms from the IFL simulated data (Fig. 3B) are much wider, in keeping with the greater degree of variation in $R$ and $E$ (Fig. 2B). The histograms from the pig data (Fig. 7) are wider still, and significant portions of the $E$ histograms are negative, even in the non-flow-limited example, despite the information weighting. The greater proportion of negative values in the histograms for $E$, as opposed to those for $R$ (Fig. 7), could reflect an influence of inertance because some parts of the signals recorded from the pigs changed rapidly (Fig. 6).

To summarize the large amount of detail in the histograms, we characterized them in terms of their means and SDs. These are plotted for $R$ estimated from the simulated data as a function of IFL threshold in Fig. 5 and show that, as the fraction of inspiration that is flow limited increases (i.e., as the IFL threshold decreases), the SDs of the histograms also increase. This is to be expected because IFL produces an in-

![Fig. 8. Pres vs. $\dot{V}$ curves for awake pig 1 (A) and from NREM sleeping pigs 1-3 (B-D). Data in A were non-flow limited, whereas data in B-D were flow limited.](image-url)
creased variation in $R$ throughout the breath. The mean value of $R$ also increases with the severity of IFL, in agreement with the findings of Hudgel et al. (9) and Condos et al. (5), who also found that mean $R$ increased with the level of IFL. However, the increase we found in mean $R$ from the information-weighted histogram is not as much as the increases in mean $R$ calculated by either the modified Mead-Whittenberger method or the mean of the recursively estimated $R$ signal (Fig. 5). This suggests that the information-weighted histograms may be the more robust means for arriving at an estimate of respiratory resistance in the presence of IFL. The information-weighted histograms were also quite reproducible from one breath to the next. Table 2 shows that both the means and SDs of the histograms obtained from each animal studied had relatively small SDs. Indeed, the SDs of the histogram means were of similar magnitudes to the SDs of the corresponding parameter values obtained by the modified Mead-Whittenberger method (Table 2).

To summarize, we have investigated the use of two methods for assessing respiratory mechanics in the presence of IFL, the modified Mead-Whittenberger method and the RLS method with information-weighted histograms. Both methods clearly show that the effective $R$ of the respiratory system varies significantly over the breath cycle in the presence of IFL and that this variation increases as the IFL threshold decreases (i.e., as the fraction of inspiration in which flow is limited increases). Our results from simulated data suggest that the information-weighted histograms may be the more robust means for obtaining an effective overall value for $R$ in the presence of IFL, even though the concept of resistance during IFL is somewhat dubious. The widths of the information-weighted histograms may also serve as an index of mechanical pathology. That is, a certain variability in $R$ and $E$ is expected throughout the breath, even from a normal lung, but when the respiratory system becomes abnormal and exhibits flow limitation during tidal ventilation, this variability is greatly increased.

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REFERENCES


