A model of the spontaneously breathing patient: applications to intrinsic PEEP and work of breathing

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Schuessler, Thomas F., Stewart B. Gottfried, and Jason H. T. Bates. A model of the spontaneously breathing patient: applications to intrinsic PEEP and work of breathing. J. Appl. Physiol. 82(5): 1694–1703, 1997.—Intrinsic positive end-expiratory pressure (PEEPi) and inspiratory work of breathing (WI) are frequently encountered in patients with severe obstructive respiratory disease. We used a computer model of spontaneously breathing patients with chronic obstructive pulmonary disease to assess the sensitivity of measurement techniques for dynamic PEEPi (PEEPidyn) and WI to expiratory muscle activity (EMA) and cardiogenic oscillations (CGO) on esophageal pressure. Without EMA and CGO, both PEEPidyn and WI were accurately estimated (r = 0.999 and 0.95, respectively). Addition of moderate EMA caused PEEPidyn and WI to be systematically overestimated by 141 and 52%, respectively. Furthermore, CGO introduced large random errors, obliterating the correlation between the true and estimated values for both PEEPidyn (r = 0.29) and WI (r = 0.38). Thus the accurate estimation of PEEPidyn and WI requires steps to be taken to ameliorate the adverse effects of both EMA and CGO. Taking advantage of our simulations, we also investigated the relationship between PEEPidyn and static PEEPi (PEEPi_stat). The PEEPidyn/PEEPi_stat ratio decreased as stress adaptation in the lung was increased, suggesting that heterogeneity of expiratory flow limitation is responsible for the discrepancies between PEEPidyn and PEEPi_stat that have been reported in patients with severe airway obstruction.

positive end-expiratory pressure; computer simulation; respiratory mechanics; chronic obstructive pulmonary disease; dynamic hyperinflation; flow limitation

DYNAMIC HYPERINFLATION and intrinsic positive end-expiratory pressure (PEEPi) are frequently encountered in patients with severe airway obstruction, e.g., in chronic obstructive pulmonary disease (COPD). PEEPi represents a threshold load that needs to be overcome by the patient’s inspiratory muscles before inspiratory flow can be initiated during both spontaneous breathing and assisted modes of mechanical ventilation (9, 10, 22, 26, 35). The additional inspiratory work of breathing (WI) required to overcome this threshold load is thought to be a major contributing factor to the development of inspiratory muscle fatigue, particularly in the face of the inherently disadvantageous operating conditions of the inspiratory muscles during dynamic hyperinflation (28). Consequently, determining the presence and magnitude of both PEEPi (9, 27) and WI (4, 8, 32) is of great clinical importance for the management of critical care patients.

During spontaneous breathing or assisted mechanical ventilation, dynamic PEEPi (PEEPidyn) can be estimated from esophageal pressure (Pes) and volume traces as the deflection in Pes from its end-expiratory relaxation value (Pes0) before the onset of inspiratory flow (24). PEEPidyn is often considered a reasonable approximation of the value of PEEPi measured under static conditions (PEEPi_stat) (24, 26), although recent studies indicate that PEEPidyn can substantially underestimate PEEPi_stat in patients with significant time-constant inhomogeneities and/or tissue viscoelasticity (12, 17, 24). WI can also be estimated from Pes and volume traces as the integral of the inspiratory deflection in Pes from Pes0 over inspired volume, taking into account the work required to distend the chest wall (6, 18).

It would clearly be of great benefit to be able to automatically assess PEEPidyn and WI breath by breath with the use of computerized monitoring equipment. Unfortunately, although this is straightforward in principle, the breath-by-breath estimation of Pes0 is complicated in practice by cardiogenic oscillations (CGO) on Pes. Furthermore, any expiratory muscle activity that might be present at the end of a breath can potentially cause overestimation of Pes0 and, hence, corrupt measurements of PEEPidyn and WI. However, a quantitative analysis of the measurement errors requires knowledge of the true values of PEEPidyn and WI, which is essentially impossible in patients.

We, therefore, decided to investigate the measurement errors in PEEPidyn and WI using a computer model in which the true values are known accurately and where confounding factors can be precisely controlled. In the present paper, we develop a comprehensive computer model of a spontaneously breathing COPD patient and use it to examine how CGO and expiratory muscle activity affect measurements of PEEPidyn and WI. Taking advantage of our simulation, we also further investigate the possible mechanisms responsible for the discrepancies observed between PEEPidyn and PEEPi_stat during severe airway obstruction (12, 17, 24).
METHODS

Overview. A nonlinear, viscoelastic model of the respiratory system was developed to simulate a spontaneously breathing subject (Fig. 1). Flow (V) determined the pressure drop across each passive compartment of the respiratory system. A predefined neural output signal was used to generate a volume- and flow-dependent muscular pressure (Pmus). The individual pressures were summed as illustrated in Fig. 1 to yield airway opening pressure (Pao). Pao was fed back into an active numerical controller that rapidly adjusted V to maintain Pao equal to atmospheric pressure. The patient was thus breathing spontaneously and without any ventilatory support. The mean and SD of each model parameter were chosen according to the literature (Table 1) to generate a population of 100 random hypothetical patients with severe COPD. This type of simulation is often referred to as a Monte Carlo simulation and is well suited for studying complex systems over a wide range of parameter values.

The model was implemented by using the Matlab 4.2/ Simulink 1.3 mathematical and simulation software package (The MathWorks, Natick, MA). It was solved using Matlab's fourth-order Runge-Kutta integration routine with a precision setting of $10^{-6}$. Sample traces of the simulated V, volume, and Pes signals are shown in Fig. 2.

Lung and chest wall. To model the nonlinear static volume-pressure (V-P) relationship of the lung, we employed an

![Diagram](http://jap.physiology.org/)

Fig. 1. Schematic representation of computer model used to simulate severe chronic obstructive pulmonary disease (COPD) patients during spontaneous breathing with dynamic hyperinflation and intrinsic positive end-expiratory pressure (PEEP). Pao, airway opening pressure; PA, alveolar pressure; Ppl, pleural pressure; Pes, esophageal pressure; Pmus, muscle pressure; CCP, cardiopulmonary coupling factor; CCE, cardioesophageal coupling factor; depend, dependence; mechan, mechanical. See text for further details.
Specific parameter values used in each simulated patient were drawn randomly from normal distributions having the means and SD values shown. A, B, K, parameters of lung (subscript L); R, resistance; t, time constant; subscripts ox, and aw, chest wall and airways, respectively; \( \gamma_{P0} \), empirical parameter occurring in Eq. 4; Pexp, expiratory peak pressure of the lung; C, cardiac output; CEE, cardioesophageal coupling factor; P, esophageal pressure; COPD, chronic obstructive pulmonary disease; FEV \(_1\), forced expiratory volume in 1 s; FVC, forced vital capacity; VT, tidal volume.

Airways. The pressure drop across the airways during inspiration was modeled using Rohrer’s equation (25)

\[
\Delta P_{ao} = K_{aw,1} V + K_{aw,2} V/V_0
\]

and previously reported values for \( K_{aw,1} \) and \( K_{aw,2} \) (where subscript aw is airways) were used (11). Unfortunately, this equation is not sufficient to describe the behavior of the airways during expiration in the presence of flow limitation. Whereas the mechanisms of expiratory flow limitation have been extensively investigated (14, 15), an empirical description of flow limitation in the lung as a whole has not been previously proposed. We, therefore, incorporated an empirical description into the model, such that the forced expired volume in 1 s (FEV \(_1\)), forced vital capacity (FVC), and PEEP, assumed values similar to those reported in the literature (2). An exponential function of flow with a hyperbolic volume dependence was employed to account for the pressure drop across the site of expiratory flow limitation. We then fit the resulting equation for the expiratory pressure drop across the airways

\[
\Delta P_{ao,exp} = K_{aw,1} V + K_{aw,2} V/V_0 + \alpha \left[ e^{\frac{V}{V_0} - W} - 1 \right]
\]

to the family of isovolume pressure-flow curves shown by Lambert (15), setting \( K_{aw,1} \) equal to Lambert’s airway resistance for very small flows. As illustrated in Fig. 3, Eq. 4 was able to reproduce the principal characteristics of the isovolume pressure-flow curves when constants \( K_{aw,2} \), \( \alpha \), \( \beta_0 \), and \( \gamma_0 \) equalled 0.34 cmH\(_2\)O·l\(^{-1}\)·s\(^{-2}\), 1.83·10\(^{-4}\) cmH\(_2\)O, 1.227 s/l, and 1.823, respectively, and the volume \( V_0 \) was set to total lung capacity (TLC). In our model, the expiratory flow limitation mechanism was placed in parallel with the block representing Rohrer’s equation (Fig. 1). A 100-ms time constant was assigned to the waterfall compartment to produce the supramaximal flow transients at the onset of expiration.

Flow limitation is more pronounced in COPD patients. In our model, FEV \(_1\), FVC, and PEEP, assumed appropriate

Table 1. Means and SD values of parameter values used to simulate a population of 100 COPD patients

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Source/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>( A_L )</td>
<td>7.41</td>
<td>1.18</td>
<td>Pare´ et al. (21), group III</td>
</tr>
<tr>
<td></td>
<td>( B_L/A_L )</td>
<td>1.02</td>
<td>0.44</td>
<td>Pare´ et al. (21), group III</td>
</tr>
<tr>
<td></td>
<td>( K_L )</td>
<td>0.249</td>
<td>0.079</td>
<td>Pare´ et al. (21), group III</td>
</tr>
<tr>
<td></td>
<td>( R_{2,L} )</td>
<td>8.75</td>
<td>1.21</td>
<td>Guerin et al. (11)</td>
</tr>
<tr>
<td></td>
<td>( k_{L} )</td>
<td>1.4</td>
<td>0.19</td>
<td>Guerin et al. (11)</td>
</tr>
<tr>
<td>Chest wall</td>
<td>( A_{cw} )</td>
<td>1.36</td>
<td>0.2</td>
<td>Fit to Smith and Loring (34)</td>
</tr>
<tr>
<td></td>
<td>( B_{cw}/A_{cw} )</td>
<td>1.699</td>
<td>0.3</td>
<td>Fit to Smith and Loring (34)</td>
</tr>
<tr>
<td></td>
<td>( K_{cw} )</td>
<td>0.05</td>
<td>0.01</td>
<td>Fit to Smith and Loring (34)</td>
</tr>
<tr>
<td></td>
<td>( R_{2,cw} )</td>
<td>3.25</td>
<td>0.6</td>
<td>Guerin et al. (11)</td>
</tr>
<tr>
<td></td>
<td>( k_{cw} )</td>
<td>2.49</td>
<td>0.48</td>
<td>Guerin et al. (11)</td>
</tr>
<tr>
<td>Airways</td>
<td>( K_{aw,1} )</td>
<td>5.03</td>
<td>0.45</td>
<td>Guerin et al. (11)</td>
</tr>
<tr>
<td></td>
<td>( K_{aw,2} )</td>
<td>2.69</td>
<td>0.63</td>
<td>Guerin et al. (11)</td>
</tr>
<tr>
<td></td>
<td>( \gamma_{P0} )</td>
<td>3</td>
<td>0.25</td>
<td>To produce typical FEV (_1) and FVC</td>
</tr>
<tr>
<td>Neural output</td>
<td>Breath rate</td>
<td>21.1</td>
<td>5.9</td>
<td>Appendini et al. (2)</td>
</tr>
<tr>
<td></td>
<td>Duty cycle</td>
<td>0.41</td>
<td>0.04</td>
<td>Appendini et al. (2)</td>
</tr>
<tr>
<td></td>
<td>Rate of increase</td>
<td>5</td>
<td>2</td>
<td>To match VT from (2)</td>
</tr>
<tr>
<td>Noise</td>
<td>Heart rate</td>
<td>100</td>
<td>20</td>
<td>Empirical</td>
</tr>
<tr>
<td></td>
<td>CCP</td>
<td>0.5</td>
<td>0.2</td>
<td>Empirical</td>
</tr>
<tr>
<td></td>
<td>CEE</td>
<td>3</td>
<td>1</td>
<td>Empirical</td>
</tr>
<tr>
<td></td>
<td>Pes</td>
<td>3</td>
<td>2</td>
<td>Empirical</td>
</tr>
</tbody>
</table>

The static V-P curve of the chest wall was modeled by an analogous equation

\[
V = A_{cw} + B_{cw} e^{K_{cw} P_{cw}}
\]

where \( P_{cw} \) is the static elastic recoil pressure of the chest wall. This equation was fit to previously reported data for the elastic recoil of the rib cage and the passive diaphragm in normal supine subjects (34) to determine \( A_{cw}, B_{cw}, \) and \( K_{cw} \) (\( V = 1.36 + 2.31 \cdot e^{0.05 - P}, P^2 = 0.94 \)). We did not modify these parameters for the COPD patients, since available evidence suggests that the chest wall V-P relationship is not altered in COPD (11).

Stress adaptation of both the lung and the chest wall was modeled by assigning a Maxwell body in parallel to their respective static elastances (Fig. 1). The parameter values for the Maxwell bodies’ resistances \( (R_{2,L}, R_{2,cw}) \) and time constants \( (k_{L}, k_{cw}) \) were chosen according to recently reported data for severe COPD patients (11) (see Table 1).

Stress adaptation can be interpreted to reflect time-constant inhomogeneities within the lung, viscoelastic tissue properties, or a combination of the two, since both phenomena have been shown to have identical mathematical representations (33). A variety of other models have been proposed to describe tissue viscoelasticity (36). However, they all behave essentially identically to the Kelvin body over the frequency range involved in our study, and there are no published parameter values corresponding to COPD patients for these other models.
values for COPD patients and flow limitation during tidal breathing was achieved (Fig. 4) when ε was raised to \( T_{\tau_0} = 3 \). In this case, the average simulated patient was described by FEV1 = 0.81 liter, FVC = 2.36 liters, FEV1/FVC = 34%, PEEPstat = 4.8 cmH2O, and PEEPidyn = 4.5 cmH2O. In contrast, flow limitation during tidal breathing could not be achieved when β was raised while ε was maintained equal to \( T_\tau \).

Patient effort. The central neural output to the respiratory musculature (Pneur, in pressure units) is modulated by a variety of factors, such as the physiological needs of the body, as well as psychological and voluntary factors that are beyond the scope of our model. For this study, we assumed inspiratory and expiratory Pneur to be piecewise linear as shown in Fig. 5. Breathing frequency and duty cycle were chosen according to the data of Appendix et al. (2) for spontaneously breathing patients with severe COPD in acute respiratory failure. Inspiratory Pneur was assumed to increase at a constant rate up to an end-inspiratory plateau of 200 ms. The rate of increase of Pneur was chosen such that when all other model parameters were set to their population means (Table 1), a tidal volume (VT) of 330 ml was achieved (2). At the beginning of expiration, the inspiratory activity decreased linearly to zero by 200 ms. Subsequently, expiratory Pneur increased linearly to an end-expiratory plateau of 200 ms. The expiratory peak value of Pneur (Pexp) was set to 4 \pm 2 cmH2O, which approximately averages the values reported in the recent literature (2, 16, 20). Expiratory Pneur linearly returned to zero over the last 200 ms of each tidal breath.

To reproduce the length-tension relationship that has been reported for the diaphragm (31), we employed a biexponential volume dependence for inspiratory Pmus/Pneur, as shown in Fig. 6 (solid line). The volume dependence of Pmus during maximal inspiration and expiration has been shown to be approximately inverse (1). In the absence of a more detailed description, we used a mirrored version of the biexponential function to implement the volume dependence of Pmus/Pneur during expiration (Fig. 6, dashed line). For both inspiration and expiration, Pmus/Pneur was scaled to unity at FRC.

We implemented the flow dependence of the inspiratory Pmus/Pneur according to the model of Younes and Riddle (39) (see Fig. 1). Because flow dependence of the expiratory musculature has not been quantitatively described in the literature, this feature was omitted from our model. Both the inspiratory and expiratory muscles were assigned a neural
response time constant of 60 ms and a mechanical response time constant of 100 ms (39).

For each simulation, six identical neural outputs as described above were concatenated to generate six tidal breaths. A forced expiratory maneuver was appended to these breaths as shown in Fig. 5. To simulate truly maximal effort during this maneuver, the peak values of Pneur were set to 100 cmH2O for inspiration and to 200 cmH2O for expiration, and the Pneur waveform was altered such that these plateau values were reached more rapidly than in the tidal breaths, namely within 500 ms. The total inspiratory time was doubled during the forced breath, and the total expiratory time was fixed at 8 s.

CGO. A waveform for the CGO was generated by passing a train of impulses representing the basic heartbeat through a linear low-pass filter with a cutoff frequency of 100 Hz and a resonance at 10 Hz. This filter was adjusted such that at the average heart rate, the mean value of the CGO pressure (P'CGO) equaled zero. The effect of the beating heart on pleural pressure was modeled by multiplying P'CGO with a cardiolungal coupling factor (CCP) and adding the result to pleural pressure (Fig. 1). However, strong CGO on Pes, concurrent with mild CGO on V and Pao, as often observed under true physiological conditions, could only be achieved after a second cardioesophageal coupling factor (CCE) was introduced between P'CGO and Pes (Fig. 1). Both the heart rate and the values for CCP and CCE were randomized as shown in Table 1.

Simulation Protocol

To test the sensitivity of measurement techniques for PEEP, and WI, we performed 100 randomized patient simulations in four configurations: a, with neither expiratory effort nor CGO (CCE, CCP, and Pexp = 0; control); b, with Pexp as shown in Table 1 and no CGO; c, with no expiratory effort and CCE and CCP, as shown in Table 1; and d, with both expiratory effort and CGO, i.e., with all parameters as shown in Table 1. Finally, to investigate whether increased time constant inhomogeneities altered the ratio of PEEP, to PEEP, as previously suggested (12, 17), the control experiment was repeated, with the model parameters altered such that the effects of stress adaptation in the lung were amplified, i.e., simulating a more heterogeneous and/or viscoelastic lung (e). This was achieved by multiplying R2,1 by a factor of five, i.e., setting its mean value to 43.75 cmH2O·l⁻¹·s⁻¹.

To accelerate convergence of the simulation toward a stable breathing pattern, an estimate of the expected dynamic hyperinflation was employed as the initial lung volume for each patient simulation. The change in end-expiratory lung volume between breaths 4 and 5 averaged 1.2% of the dynamic hyperinflation volume at the end of breath 5, indicating that steady-state breathing had essentially been achieved and dynamic hyperinflation was completely developed.

Data Analysis

At the end of breath 5, the true PEEP was evaluated as the total static recoil pressure. The true PEEP was evaluated as the sum of the static recoil pressures and the pressures across the Maxwell bodies of lung and chest wall at the onset of the sixth inspiratory effort. Vr was the volume inspired in breath 6, and minute ventilation was computed by multiplying Vr by the patient’s breathing frequency. In the same breath, the true WI was computed by integrating Pmus over the inspired volume and dividing the result by Vr. FEV1 and FVC were obtained from the forced expiratory maneuver as illustrated in Fig. 2.

Over the period in which expiratory flow was present, the derivative of Pes (dPes/dt) was evaluated. The baseline value of Pes at end expiration (Pes,bsln) was identified automatically at the point closest to the end of expiratory flow at which dPes/dt did not exceed its minimum by >5% of its range over that expiratory period. The threshold for the detection of Pes,bsln was thus not fixed but depended on the Pes waveform during the breath under consideration. The measured dynamic PEEP (PEEP,meas) was obtained from the deflection

Fig. 5. Time course of expiratory (A) and inspiratory (B) neural output (Pneur) with all neural output parameters adjusted to their population means (see text for details) for 1 tidal breath (left) and a deep inflation/forced expiration maneuver (right). Pneur is expressed in units of driving pressure it generates at functional residual capacity under isovolume conditions. Pexp, expiratory peak value of Pneur.

Fig. 6. Volume dependence of inspiratory (solid line) and expiratory (dashed line) muscles used in model simulation. See text for details. VC, vital capacity.
from \( P_{es,bln} \) to the value of \( P_{es} \) at the onset of inspiratory flow in breath 6 (Fig. 2). When the value identified at the onset of inspiratory flow exceeded \( P_{es,bln} \), which occasionally occurred in the presence of CGO, \( P_{EPPim} \) was set to zero. A measurement of \( W_{i} \) (Wmeas) was evaluated as the integral of the difference between \( P_{es,bln} \) and \( P_{es} \) over inspired volume, plus the work done to distend the chest wall, divided by \( V_{t} \). A constant linear chest wall elastance of 5 \( \text{cmH}_2\text{O/l} \) was used to calculate the work done to distend the chest wall.

### RESULTS

The ventilation parameters that resulted from simulating 100 patients as described above for all five configurations (Table 2) were in agreement with the ones reported in the literature for COPD patients (2, 11, 24). \( V_{t} \) and minute ventilation were mildly affected by expiratory muscle activity during the tidal breathing nor CGO noticeably altered \( FEV_1 \) and \( FVC \). However, when the time-constant inhomogeneities were increased (configuration e), all four quantities were reduced (Table 2).

Figure 7 shows \( P_{EPPim} \) with respect to \( P_{EPPid} \) for configurations shown in Fig. 7, A-D. Without expiratory effort and CGO (Fig. 7A), \( P_{EPPim} \) reproduced \( P_{EPPid} \) with a good degree of accuracy (\( y = 0.96x - 0.03, r = 0.999 \)). In the presence of expiratory effort (Fig. 7B), \( P_{EPPim} \) systematically underestimated \( P_{EPPid} \) (\( y = 1.08x + 4.79, r = 0.85 \)). As anticipated, the measurement error (\( P_{EPPim} - P_{EPPid} \)) was closely correlated with \( P_{exp} \) (Fig. 8A) (\( y = 1.13x + 0.008, r = 0.98 \)). In Fig. 7C, CGO introduced a random error in \( P_{EPPim} \), which effectively obliterated the correlation between \( P_{EPPim} \) and \( P_{EPPid} (r = 0.29) \). The mean error was 0.51 \( \text{cmH}_2\text{O} \), which is 12.5% of the mean \( P_{EPPid} (4.1 \text{cmH}_2\text{O}) \), whereas the SD of the error was 3.54 \( \text{cmH}_2\text{O} \). With both expiratory effort and CGO (Fig. 7D), the scatter in \( P_{EPPim} \) was even more pronounced (\( r = 0.18 \)). It should be noted that data points representing a small number of simulated patients who were able to expire below their equilibrium volumes when their expiratory muscles were active were excluded from Fig. 7, B and D, since they did not develop dynamic hyperinflation and \( P_{EPP} \), under those conditions.

Wmeas is plotted with respect to \( W_i \) in Fig. 9 for configurations a-d. Under control conditions (Fig. 9A), Wmeas slightly underestimated the true \( W_i \) (\( y = 0.99x - 0.04, r = 0.97 \)), although the average relative error remained smaller than 5%. In the presence of expiratory effort (Fig. 9B), Wmeas systematically overestimated \( W_i \) (\( y = 1.36x + 0.15, r = 0.81 \)). As above for \( P_{EPPid} \), the measurement error of \( W_i \) (Wmeas – \( W_i \)) was closely correlated with \( P_{exp} \) (Fig. 8B) (\( y = 0.11x - 0.015, r = 0.91 \)). When CGO were present, the correlation between Wmeas and \( W_i \) was lost (Fig. 9C, \( r = 0.38 \), and the difference between Wmeas and \( W_i \) amounted to \(-0.018 \pm 0.29 (SD) \)) / \( l \), compared with a mean \( W_i \) of 0.92 / \( l \). The scatter became even greater when both expiratory effort and CGO were present (\( r = 0.27 \)).

The relationship between \( P_{EPPi,s} \) and \( P_{EPPi,d} \) was plotted under control conditions (configuration a, Fig. 10). At higher levels of \( P_{EPP} \), the data points were scattered about the line of identity, whereas \( P_{EPPi,d} \) increased underestimating \( P_{EPPi,s} \) as \( P_{EPPi,s} \) decreased. In contrast, \( P_{EPPi,d} \) underestim-

### Table 2. Means and SD values of physiological variables obtained from a population of 100 simulated-COPD patients

<table>
<thead>
<tr>
<th>Configuration</th>
<th>( V_t ), liter</th>
<th>( V_{e} ), l/min</th>
<th>( FEV_1 ), liter</th>
<th>( FVC ), liters</th>
<th>( FEV_1/FVC ), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a: Control</td>
<td>0.34 ± 0.19</td>
<td>6.8 ± 3.1</td>
<td>0.82 ± 0.31</td>
<td>2.34 ± 0.55</td>
<td>33.8 ± 6.0</td>
</tr>
<tr>
<td>b: Expiratory effort only</td>
<td>0.37 ± 0.22</td>
<td>7.4 ± 3.7</td>
<td>0.81 ± 0.31</td>
<td>2.34 ± 0.55</td>
<td>33.7 ± 6.0</td>
</tr>
<tr>
<td>c: Cardiogenic oscillations only</td>
<td>0.34 ± 0.19</td>
<td>6.8 ± 3.1</td>
<td>0.81 ± 0.31</td>
<td>2.34 ± 0.55</td>
<td>33.8 ± 6.0</td>
</tr>
<tr>
<td>d: Expiratory effort and cardiogenic oscillations</td>
<td>0.37 ± 0.22</td>
<td>7.4 ± 3.7</td>
<td>0.81 ± 0.31</td>
<td>2.34 ± 0.55</td>
<td>33.7 ± 6.0</td>
</tr>
<tr>
<td>e: Increased inhomogeneities</td>
<td>0.24 ± 0.11</td>
<td>4.8 ± 1.7</td>
<td>0.61 ± 0.28</td>
<td>1.94 ± 0.54</td>
<td>30.5 ± 6.2</td>
</tr>
</tbody>
</table>

Values are means ± SD. \( V_{e} \), minute ventilation.

![Fig. 7. Identity plots relating measured and true dynamic intrinsic PEEP (PEEPi) in 4 different configurations. A: no expiratory effort or cardiogenic oscillations; B: expiratory effort alone; C: cardiogenic oscillations alone; and D: both expiratory effort and cardiogenic oscillations. Dashed lines are lines of identity.](http://jap.physiology.org/Downloadedfrom)
mated $\text{PEEP}_{\text{stat}}$ in a larger number of cases and to a greater extent when the time-constant inhomogeneities were increased (configuration $\text{e}$, $\text{f}$ in Fig. 10). Both data sets displayed in Fig. 10 are without expiratory effort and CGO.

**DISCUSSION**

In the present study, we have employed a computational model of the spontaneously breathing patient to quantitatively analyze measurement errors in $\text{PEEP}_{\text{dyn}}$ and $\text{WI}$. Computer simulations are particularly well suited for this kind of analysis, because they provide access to variables that are impossible to measure in patients and because the simulated experimental conditions can be manipulated at will. This allows the effects of various factors to be evaluated independently of all others. Also, computer simulations allow an essentially unlimited number of subjects to be studied and under conditions that would be unacceptable to real patients. Indeed, with the growing awareness of the ethical issues involved in human and animal experimentation, we may expect computer simulations to play an increasingly important role in future biomedical research.

To generate our population of simulated patients, all model parameters were randomized simultaneously by using the means and SDs shown in Table 1. Provided that the number of simulated subjects substantially exceeds the number of parameters in the model, this so-called Monte Carlo simulation yields a wide range of parameter combinations so that the resulting patient population covers most of the physiological parameter space. Therefore, the Monte Carlo simulation is well suited for the study of systems with a large number of parameters.

The results of any computer simulation study are always open to question in that the underlying model will never completely reproduce human physiology. The model structure and parameters used for this study were taken from the recent literature wherever possible, although some aspects of our model required extrapolation of published data (such as the formula used for expiratory flow limitation, Eq. 4). However, the simulated pressure and flow waveforms and the values of FEV$_1$, FVC, and $\text{PEEP}_{\text{stat}}$ that we obtained were consistent with clinical observations in patients. In any case, much of our study was concerned with measurement errors in $\text{PEEP}_{\text{dyn}}$ and $\text{WI}$. Even if the mechanism...
that determined these quantities in our simulation was not entirely realistic, a robust algorithm should still have estimated them correctly. Finally, our scheme for identifying \( P_{es,bsln} \) was based on the derivative of \( P_{es} \). This approach works well in a computer simulation where random measurement noise is absent but is likely to perform less well in a practical measurement situation where numerical differentiation amplifies measurement noise and necessitates further signal processing that may introduce additional errors to \( P_{es,bsln} \). In this sense, the data presented in Figs. 7–9 are a best-case scenario, whereas poorer performance would be expected in a true measurement situation.

Our simulations demonstrate the extent to which automated breath-by-breath measurements of both \( P_{EEP_{dyn}} \) and \( WI \) are susceptible to errors due to expiratory muscle activity and CGO. In the absence of expiratory effort and CGO, both \( P_{EEP_{dyn}} \) (Fig. 7A) and \( WI \) (Fig. 9A) were well estimated. The slight systematic error in \( P_{EEP_{meas}} \) (Fig. 7A) was presumably due to small changes in the pressure drop across the stress adaptation compartments that occurred during the time required to evaluate \( P_{EEP_{meas}} \). The random error in \( P_{EEP_{meas}} \) was negligible. \( WI \) exhibited a slight systematic error with a small degree of random scatter (Fig. 9A). Comparing these results to estimates of \( WI \) obtained using each patient’s individual chest wall mechanics, we established that most of the error in \( W_{meas} \) under control conditions was due to the assumption of a fixed chest wall elastance of 5 cmH\(_2\)O/l. This strategy is motivated by the fact that chest wall elastance is not easily obtained in actively breathing patients and, as a result, a normal predicted value is commonly used (3, 5, 23). A fixed chest wall elastance of 5 cmH\(_2\)O/l has also been employed in the \( WI \) algorithm of a commercially available pulmonary monitoring device (CP-100, Bicore, Irvine, CA). In any case, our results indicate that the errors introduced by assuming a fixed chest wall elastance for all patients are minor.

With the introduction of expiratory effort, we obtained significant errors in both \( P_{EEP_{meas}} \) (Fig. 7B) and \( W_{meas} \) (Fig. 9B). The measurement errors for both quantities correlated linearly with \( P_{exp} \) (Fig. 8), indicating that the measurement errors are predominantly determined by the expiratory muscle activity and do not depend on the level of dynamic hyperinflation itself. Several investigators have suggested using changes in gastric pressure to estimate the magnitude of the expiratory muscle pressure, which may then be employed to correct \( P_{EEP_{meas}} \) (2, 16). Although the pressure generated by the expiratory muscles of the rib cage may not be completely reflected in gastric pressure (7, 20), this method is certain to be better than no correction at all. Presumably, gastric pressure could also be used to make a corresponding correction in \( W_{meas} \), but to the best of our knowledge this has not yet been investigated. Unfortunately, we were unable to investigate the use of gastric pressure in our model because of the lack of published data showing quantitatively how the abdominal wall and contents contribute to respiratory mechanics.

We also found that CGO produced large errors in both \( P_{EEP_{meas}} \) and \( W_{meas} \) (Fig. 7C and Fig. 9C). These errors can be reduced by averaging estimates from many breaths, provided that the CGO are not entrained with the breathing cycle. We computed the number of breaths required to reduce the SD of \( P_{EEP_{meas}} - P_{EEP_{dyn}} \) to <5% of the mean \( P_{EEP_{dyn}} \) with 95% confidence (13) and found that over 1,145 breaths would be required. An analogous computation showed that a similar level of confidence would be obtained for \( WI \) by averaging over 152 breaths. In our opinion, these numbers of breaths are too long to allow either \( P_{EEP_{dyn}} \) or \( WI \) to be accurately estimated in anything close to real time. On the other hand, single-breath estimates of both quantities are far too noisy to be useful. Furthermore, standard filtering techniques are not capable of reducing the confounding effects of CGO because the frequency spectra of respiratory and cardiac pressure waveforms overlap too much. Obviously, more sophisticated processing of \( P_{es} \), such as the recently described adaptive filter technique of Schuessler et al. (30), is required to ameliorate the effects of CGO. We note that almost no attention has been given to this matter in previous reports (2, 3, 16, 20, 24), yet it is clearly crucial to the successful estimation of both \( P_{EEP_{dyn}} \) and \( WI \) in particular when these quantities are to be evaluated automatically on a breath-by-breath basis. Not surprisingly, the errors were even greater when both expiratory muscle activity and CGO were present (Fig. 7D and Fig. 9D).

Under the control condition (configuration a, ○ in Fig. 10), i.e., in absence of expiratory effort and CGO and with \( R_{2L} \) as given in Table 1, we were not able to reproduce the significant differences that have been observed between \( P_{EEP_{stat}} \) and \( P_{EEP_{dyn}} \) in the setting of severe airway obstruction (12, 17, 24), especially when \( P_{EEP_{stat}} \) was large. We think this is because central airway flow limitation was the main determinant of expiratory flow in our simulations, which would have reduced the magnitude of the end-expiratory pressure in the stress adaptation compartment. In other words, expiratory flow was slowed in the central airways to an extent that much of the energy stored in viscoelastic tissues and in local pressure differences due to peripheral time-constant inhomogeneities could dissipate before end expiration. We were able to simulate differences between \( P_{EEP_{dyn}} \) and \( P_{EEP_{stat}} \). Similar to those reported in patients only after the degree of stress adaptation in the lung compartment had been increased fivefold (configuration e, ● in Fig. 10) over that reported for COPD patients during inspiration (11). This suggests that COPD patients exhibit more stress adaptation during expiration than during inspiration. Presumably, the only way this can happen is if these patients were inhomogeneously flow limited during expiration so that their lungs expired like a parallel arrangement of flow-limited compartments emptying at relatively different rates. Inhomogeneous emptying during flow limitation has been described previously in dogs (19, 37, 38). Because the degree of inhomogeneity in flow limitation is likely to vary considerably from
patient to patient, the relationship between PEEP$_{\text{dyn}}$ and PEEP$_{\text{stat}}$ is, in general, extremely difficult to predict in any particular individual. This may account for the wide range of PEEP$_{\text{dyn}}$/PEEP$_{\text{stat}}$ ratios reported in the literature (12, 17, 24, 26).

In summary, we have developed a comprehensive computational model of the spontaneously breathing patient. Presumably, in view of its general nature, our model could have a multitude of uses, including the analysis of physiological questions, as an aid in ventilator design, and as a teaching tool. In the present study, we employed the model to examine the extent to which automated breath-by-breath measurement techniques for PEEP$_{\text{dyn}}$ and WI are susceptible to errors due to expiratory muscle activity and CGO. Our data demonstrate that both quantities are highly sensitive both to the presence of expiratory muscle activity at end expiration and to CGO on the Pes trace. In general, some means of correction for these phenomena are necessary if PEEP$_{\text{dyn}}$ and WI are to be measured accurately on-line. Furthermore, our data suggest that discrepancies between PEEP$_{\text{stat}}$ and PEEP$_{\text{dyn}}$ are caused by the heterogeneity of expiratory flow limitation throughout the lung.

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