On-line monitoring of intrinsic PEEP in ventilator-dependent patients

G. NUCCI,1 M. MERGONI,2 C. BRICCHI,2 G. POLESE,3 C. COBELL1,1 AND A. ROSSI4
1 Department of Electronics and Informatics, University of Padova, 35131 Padova; 2 Intensive Care Unit, Azienda Ospedaliera di Parma, 43100 Parma; 3 Center for Cystic Fibrosis, Azienda Ospedaliera di Verona, 37126 Verona; and 4 Pulmonary Division, Ospedali Riuniti di Bergamo, 24100 Bergamo, Italy

Received 21 January 2000; accepted in final form 5 April 2000

Nucci, G., M. Mergoni, C. Bricchi, G. Polese, C. Cobelli, and A. Rossi. On-line monitoring of intrinsic PEEP in ventilator-dependent patients. J Appl Physiol 89: 985–995, 2000.—Measurement of the intrinsic positive end-expiratory pressure (PEEPi) is important in planning the management of ventilated patients. Here, a new recursive least squares method for on-line monitoring of PEEP is proposed for mechanically ventilated patients. The procedure is based on the first-order model of respiratory mechanics applied to experimental measurements obtained from eight ventilator-dependent patients ventilated with four different ventilatory modes. The model PEEPi (PEEPi,mod) was recursively constructed on an inspiration-by-inspiration basis. The results were compared with two well-established techniques to assess PEEPi. End-expiratory occlusion to measure static PEEPi (PEEPi,st) and change in airway pressure preceding the onset of inspiratory airflow to measure dynamic PEEPi (PEEPi,dyn). PEEPi,mod was significantly correlated with both PEEPi,dyn (r = 0.77) and PEEPi,st (r = 0.90). PEEPi,mod (5.6 ± 3.4 cmH2O) was systematically > PEEPi,dyn and PEEPi,st (2.7 ± 1.9 and 8.1 ± 5.5 cmH2O, respectively), in all the models without external PEEP. Focusing on the five patients with chronic obstructive pulmonary disease, PEEPi,mod was significantly correlated with PEEPi,st (r = 0.71), whereas PEEPi,dyn (r = 0.22) was not. When PEEP was set 5 cmH2O above PEEPi,st, all the methods correctly estimated total PEEP, i.e., 11.8 ± 5.3, 12.5 ± 5.0, and 12.0 ± 4.7 cmH2O for PEEPi,mod, PEEPi,st, and PEEPi,dyn, respectively, and were highly correlated (0.97–0.99). We interpreted PEEPi,mod as the lower bound of PEEPi,st and concluded that our method is suitable for on-line monitoring of PEEPi in mechanically ventilated patients.

intrinsic positive end-expiratory pressure; mathematical model; on-line monitoring; respiratory mechanics; mechanical ventilation

MONITORING OF RESPIRATORY mechanics is important in mechanically ventilated patients to diagnose the disease underlying acute respiratory failure (ARF), to assess the status and progress of the disease, and to measure the effects of treatment such as drugs and application of positive end-expiratory pressure (PEEP) (27, 32). Abnormal respiratory mechanics is due not only to increased flow resistance and elastance but also to intrinsic PEEP (PEEPi) (26). The latter reflects the end-expiratory elastic recoil of the total respiratory system due to incomplete expiration and dynamic pulmonary hyperinflation. PEEPi is determined predominantly by the patient’s alterations in respiratory mechanics (increased compliance and resistance), but it is also influenced by ventilator settings, for example, a short expiratory time or a large tidal volume (26). An unrecognized PEEPi may cause 1) a misinterpretation of hemodynamic data, leading to erroneous evaluation of the patient’s volemic status; 2) an erroneous evaluation of respiratory mechanics (26); and 3) a severe patient-ventilatory asynchrony (27). Detection and measurement of PEEPi is paramount in ventilator-dependent patients, not only to prevent its adverse effects, but also to implement therapeutic strategies such as changes in the ventilator settings, aggressive administration of bronchodilators, and application of PEEP.

Whereas the assessment of PEEPi may present some problems in patients actively triggering the ventilator, this is relatively simple during controlled mechanical ventilation, when the respiratory muscles are relaxed, for example, by means of the end-expiratory occlusion technique (27). However, this technique requires either ventilators equipped with an end-expiratory occlusion button (26) or some additional equipment and skill that may not be routinely available in clinical settings (14). In addition, measurements obtained by the ventilator’s facilities require adequate correction (30), whereas the end-expiratory occlusion maneuver interferes with the ventilator settings and may not be suitable for continuous monitoring of PEEPi. In fact, continuous monitoring enables the early detection of changes in patient status, thus allowing a rapid therapeutic response as well as the evaluation of its effectiveness.

Mathematical models for on-line monitoring of respiratory mechanics during mechanical ventilation (3, 18)
offer an attractive tool to assess PEEP, continuously in the intensive care unit without interfering with the ventilator settings and also overcome some technical issues associated with the end-expiratory occlusion technique. However, only one group of investigators (12) has specifically addressed monitoring of PEEP, in ventilated acute respiratory distress syndrome patients in whom the levels of PEEP are, in general, relatively low.

The hypothesis of this study was that on-line monitoring of PEEP, in ventilator-dependent patients is possible when using a recursive least square approach. The purpose here is to present this new approach and to try to interpret our measurements by comparing them with the values of PEEP, obtained by means of two more commonly used techniques, i.e., 1) end-expiratory airway occlusion and 2) the change in airway pressure preceding the onset of inspiratory airflow (26, 27).

METHODS

This study was approved by the ethics committee of the institution, and informed consent was obtained from each patient or the next of kin. Eight patients admitted into the intensive care unit of the Ospedale Maggiore of Parma (Italy) who required mechanical ventilation because of respiratory failure of various etiologies were enrolled into this study. All patients were stable hemodynamically with a mean arterial pressure of 70 mmHg without inotropic drugs. None had chest wall abnormalities, hemothorax, pneumothorax, or high intracranial pressure. The patients’ characteristics and ventilator patterns at the time of the inclusion into the study are shown in Tables 1 and 2, respectively. All patients were mechanically ventilated with Dräger Evita II (Drägerwerk, Luebeck, Germany).

Measurements. Flow (V) was measured with a heated pneumotachograph (Fleisch no. 2, Lausanne, Switzerland) connected to a differential pressure transducer (Validyne MP 45. ±2 cmH2O, Validyne, Northridge, CA) that was inserted through cones between the Y piece of the circuit and the proximal tip of the endotracheal or tracheostomy tube. The pneumotachograph was calibrated with a supersyringe using the gas mixture in use and was linear over the experimental range of flow. The instrumental dead space was 120 ml. Volume (V) was obtained by numerical integration of the flow signal. Because of the inspiration-by-inspiration analysis performed (see Estimation algorithm), we reset the integration of airflow at the beginning of each breath. Pressure was measured at the airway opening between the pneumotachograph and the artificial airway. The side ports were connected through air-filled noncompliant catheters 50 cm long and 1.5 mm of internal diameter to two differential pressure transducers (Validyne MP 45 ±80 cmH2O). Calibration of the transducers was done with a water manometer. To reduce the effects of the compliance and resistance of the circuit on the mechanics measurements, a single length of standard noncompliant tubing (2 cm ID and 60 cm long) was used, and the humidifier was omitted from the inspiratory line. Special care was taken to avoid air leaks within the equipment and around the cuff of the tube. All signals were recorded on a personal computer (Macintosh II CI; Apple Computer, Cupertino, CA) via an analog-to-digital converter (MacLab Analog Digital Instrument, Castle Hill, Australia) at a sample rate of 100 Hz and were stored in diskettes for subsequent computer analysis. During the measurements, a physician not involved in the study was always present for patient care.

Procedure. The investigation was performed with the patient in the supine position, sedated with a continuous infusion of phentanyl (0.02 to 0.03 µg·kg⁻¹·min⁻¹) and diazepam (0.6 µg·kg⁻¹·min⁻¹) and paralyzed with vecuronium (0.1 mg/kg, followed by 0.05 mg/kg if necessary). Measurements were taken during four different ventilatory modalities applied in random order, each characterized by a distinct ventilatory pattern: pattern 1, volume-controlled ventilatory mode with an inspiratory flow of ~1 l/s and without PEEP (zero end-expiratory pressure, ZEEP); pattern 2, identical to pattern 1 except for the addition of an external PEEP equal to PEEP, on ZEEP increased by 5 cmH2O; pattern 3, volume-controlled ventilatory mode on ZEEP, with an inspiratory flow of ~0.5 l/s; and pattern 4, pressure-controlled ventilatory mode on ZEEP.

The tidal volume, respiratory frequency, and total inspiratory duration were constant in the four different ventilatory modalities (Table 3). With the Dräger Evita II ventilator, total inspiratory duration is the sum of the duration of inspiration and of the end-inspiratory pause.

A standard procedure was followed with the four ventilatory modalities: 2 min of ventilation, then three end-expiratory occlusions lasting 5–6 s, interspersed between at least 10 standard breathing cycles. The expiratory occlusion maneuvers were performed by clamping the rubber catheter mount inserted between the Y piece of the circuit and the tracheal tube.

Data analysis. For each ventilatory pattern the following parameters were determined: 1) static PEEP, (PEEP,static), i.e., the value of airway pressure recorded at the end of the expiratory occlusion maneuver as the mean value of airway pressure during the last 0.2 s of the occlusion period (Fig. 1); reported values are means of three measurements; 2) dynamic PEEP, (PEEP,dynam), i.e., the increase in airway pressure preceding the onset of inspiratory flow (Fig. 2); and 3) model-based, on-line estimates of PEEP, (PEEP,mod) that were obtained as described below.

Clearly, all three of these techniques to estimate PEEP, really provide the value of the total PEEP (PEEP), i.e., the cumulative effect of PEEP, external PEEP, and PEEP owing to the ventilator circuits and valves. However, if PEEP is not set by the ventilator, the value of the positive expiratory pressure due to the resistive properties of the expiratory line of the ventilator is small, and most of PEEP actually reflects PEEP, except in patients with values of PEEP, close to 1 cmH2O, in whom PEEP, might be due both to a slight

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>SAPS II</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83</td>
<td>F</td>
<td>COPD</td>
<td>45</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>F</td>
<td>Acute postoperative respiratory failure</td>
<td>53</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>M</td>
<td>Head injury with COPD</td>
<td>38</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>M</td>
<td>Cardiac arrest</td>
<td>65</td>
<td>D</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>M</td>
<td>Cerebral hemorrhage</td>
<td>37</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>73</td>
<td>F</td>
<td>COPD</td>
<td>49</td>
<td>S</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>F</td>
<td>COPD</td>
<td>84</td>
<td>D</td>
</tr>
<tr>
<td>8</td>
<td>51</td>
<td>F</td>
<td>COPD</td>
<td>41</td>
<td>S</td>
</tr>
</tbody>
</table>

F, female; M, male; COPD, chronic obstructive pulmonary disease; SAPS II, simplified acute physiologic score; S, survived; D, died.
end-expiratory recoil and to the resistive properties of the expiratory line. In fact, the PEEP, values due to the ventilator used in this study are in the range 0.5–0.8 cmH₂O (personal observation). In all circumstances, PEEP can be computed according to the formula PEEPᵣ = PEEPᵢ − PEEP (27). In this paper, we will term PEEPᵢ the values obtained under the ZEEP condition (settings 1, 3, and 4) and PEEPᵣ, the values obtained when PEEP was intentionally set by the ventilator, as was the case in setting 2. This terminology will apply to all three techniques.

**Model of lung mechanics.** The model used in literature (3, 18) for on-line monitoring of respiratory mechanics is the first-order lumped viscoelastic model. It is described by

\[
P_{\text{aw}}(t) = R \cdot V(t) + E \cdot V(t) + P_o
\]

where Paw is the airway pressure, V is airflow, V is lung volume, R accounts for total inspiratory resistance, E accounts for respiratory system elastance, P₀ is the value of the total positive pressure at the end of expiration, and t is continuous time.

Although this model does not take into account relevant features of respiratory mechanics, such as higher order and nonlinear behavior (21, 29, 31), it has been shown to be the best candidate for real-time parameter estimation because the performance of recursive least square methods (RLS) deteriorates sharply with increasing model complexity (16). In this work we adopted the RLS approach, albeit modifying the estimation procedure because the goal was the assessment of PEEPᵢ.

**Estimation algorithm.** The RLS algorithm with an exponential weighting factor, λ, has been used to track changes in the mechanical properties of the respiratory system in real time (3, 18). To do so, one can express the measured samples of the Paw in discrete time form

\[
P(kT) = \Phi(kT) \cdot \phi(kT) + \epsilon(kT)
\]

where \(T\) is the sampling time, \(\Phi(kT) = [R(kT), E(kT), P_o(kT)]\)’ is the parameter vector, \(\phi(kT) = [V(kT), V(kT), 1]’\) is the data vector, and \(\epsilon(kT)\) is the error term representing both noise measurements and model prediction errors.

The RLS algorithm provides an updated parameter estimate at each new sampling time as

\[
\hat{\phi}(kT) = \hat{\phi}([kT]) + \Gamma(kT) \cdot (\epsilon(kT) - \phi(kT) \cdot \hat{\phi}(kT))
\]

where the current parameter estimate, \(\hat{\phi}(kT)\), is derived by correcting the previous estimate, \(\hat{\phi}([kT])\), with a term proportional to the a priori model prediction error, \(\epsilon(kT)\), times the gain of the algorithm \(\Gamma(kT)\). These quantities are adjusted recursively as

\[
\epsilon(kT) = P(kT) - \hat{\phi}([kT]) \cdot \phi(kT)
\]

\[
\Gamma(kT) = \frac{\lambda \cdot \phi(kT) \cdot \phi(kT)'}{1 + \lambda \cdot \phi(kT) \cdot \phi(kT)'}
\]

where \(\phi(kT)\) is a matrix proportional to the covariance of parameter estimates (20)

\[
\Omega(kT) = \text{Cov}[\hat{\phi}(kT)] = \delta(kT) \cdot \Pi(kT)
\]

with \(\delta(kT)\), the estimated noise variance, given by

\[
\delta(kT) = \lambda \cdot \epsilon(kT) \cdot [1 - \phi'(kT) \cdot \Pi(kT) \cdot \phi(kT)]
\]

\[
\lambda = \text{is the forgetting factor of the algorithm, which determines the memory of the estimation procedure, i.e., the effective length and weight of past data used to fit the model at each time point. The selection of an appropriate value for } \lambda (0 < \lambda \leq 1) \text{ is crucial: a value close to 1 reduces the sensitivity of parameter estimation to noise but produces a less prompt algorithm.}

We have followed the strategy proposed by Bates and Lauzon (6). The choice of \(\lambda\) is based on the randomness of the residuals between the model prediction and measurements.

**Table 3. Experimental ventilatory patterns**

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Vₑ, ml</th>
<th>V, l/s</th>
<th>f, breaths/min</th>
<th>Tₑ, s</th>
<th>Tₑ, s</th>
<th>Tₑ, s</th>
<th>Tₑ, s</th>
<th>PₑcmH₂O</th>
<th>PₑcmH₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern 1</td>
<td>656 ± 173</td>
<td>0.98 ± 0.1</td>
<td>11.0 ± 1.60</td>
<td>1.64 ± 0.27</td>
<td>0.74 ± 0.08</td>
<td>0.30 ± 0.05</td>
<td>63.8 ± 13.0</td>
<td>0.62 ± 2.0</td>
<td></td>
</tr>
<tr>
<td>Pattern 2</td>
<td>628 ± 134</td>
<td>1.00 ± 0.9</td>
<td>11.4 ± 1.77</td>
<td>1.64 ± 0.27</td>
<td>0.75 ± 0.07</td>
<td>0.30 ± 0.05</td>
<td>67.1 ± 7.56</td>
<td>9.89 ± 6.0</td>
<td></td>
</tr>
<tr>
<td>Pattern 3</td>
<td>644 ± 151</td>
<td>0.55 ± 0.1</td>
<td>11.1 ± 1.86</td>
<td>1.68 ± 0.38</td>
<td>1.24 ± 0.35</td>
<td>0.31 ± 0.07</td>
<td>62.5 ± 18.3</td>
<td>0.11 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>Pattern 4</td>
<td>665 ± 180</td>
<td>0.74 ± 0.2</td>
<td>10.8 ± 1.39</td>
<td>1.5 ± 0.39</td>
<td>1.46 ± 0.23</td>
<td>0.27 ± 0.07</td>
<td>25.5 ± 8.37</td>
<td>1.67 ± 3.5</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. Vₑ, tidal volume; V, inspiratory flow rate; Tₑ, inspiratory plus end-inspiratory pause time; Tₑ, inspiratory time; Tₑ, s, total inspiratory to respiratory time; Pₑ, maximal working pressure.
Because the first-order model (Eq. 1) is too simple to provide a good fit, i.e., random residuals, we chose the maximum value of $\lambda$ in accordance with uncorrelated residuals. This enables an unbiased estimation of the parameters but brings deterministic variations in the estimates that account for higher order and nonlinear behavior of respiratory mechanics. To overcome these limitations, an information-weighted histogram within the respiratory cycle is introduced first (4, 6), and then the mean and the standard deviation of the histogram are computed and updated at each new sample (5). To do so, a weighting function for each parameter estimate ($i = 1, 2, 3$) can be defined

$$w_i(kT) = \frac{\hat{\delta}_i(kT)}{\hat{\alpha}_i(kT)}$$

and the mean $[\hat{\mu}(kT)]$ and parameter variability $[\hat{\Delta}(kT)]$ in a respiratory cycle can be constructed.

The above strategy has been successfully applied in tracking resistance and elastance variations in postoperative ARF patients with flow limitation. The algorithm starts the estimation procedure when the airway pressure switches from expiration (decreasing) to inspiration (increasing) and stops when the lung volume ends its increasing portion (before the begin of end-inspiratory pause that causes air redistribution and/or tissue stress-relaxation that the model used is not able to explain).

Inspiration-by-inspiration estimation is then performed by using the following formulas

$$\hat{\delta}_i(h) = \sum_{j=(k-n+1)T}^{kT} \hat{\delta}_i(j) \cdot w_i(j)$$

$$\hat{\alpha}_i(h) = \sum_{j=(k-n+1)T}^{kT} w_i(j)$$

where $n$ is the number of samples in the inspiration and $h$ ($h = 1, 2, \ldots$) is the current breathing cycle.

We used cycle-by-cycle analysis instead of updating $\mu_i$ and $\Delta_i$ at each new sample because we have not made any a priori assumption about the length and constancy of inspiratory cycle.

Statistical analysis. Statistical analysis was performed on the measured and estimated PEEP, by use of Student’s $t$-test for paired data. Linear regression analysis was made by using the least square method. Bland-Altman plots were constructed after regression analysis (10).

RESULTS

For each ventilatory modality, 2 min of respiratory signal measurements were analyzed by the proposed algorithm. Figure 3A shows a representative $V(t)$, $P_{aw}(t)$, and $P_{aw}(t)$ trace for one of the subjects in our database in the ZEEP ventilatory pattern 1. The recursive procedure identified, breath by breath, the portion of inspiratory data on which to perform real-time PEEP estimation (Fig. 3B). This allowed us to obtain the time course of PEEP estimates. The tracking algorithm was tuned according to the criteria previously

Fig. 1. Measurement of static intrinsic positive end-expiratory pressure (PEEPi,stat) by the end-expiratory occlusion maneuver in patient 7 with ventilatory pattern 1. The arrow in B indicates the value of PEEPi,stat.

Fig. 2. A: airway pressure ($P_{aw}$) vs. flow diagram in patient 3 with ventilatory pattern 1. Twenty-two consecutive ventilatory cycles are superimposed. Inspiration is rightward. Note that the start of inspiration precedes the zero flow (dotted line). The target portion (dashed box) is magnified in B. Dynamic PEEP ($PEEP_{i,dy}n$) is measured as the difference between the value of $P_{aw}$ at zero flow and end-expiratory pressure. The small end-expiratory pressure reflects the resistive pressure due to the end-expiratory flow and is included in the value of PEEPi,dy.
described, leading to a choice of \( \lambda = 0.95 \) that is a weighted data window of \( \pm 0.2 \) s. Figure 3B also depicts the on-line estimates during the inspiratory cycle provided by the method \((\pm SD)\). The estimated PEEP \(_i\) exhibits a modest increase during inspiration. Parameter SDs are relatively low except for the end-inspiratory data, in which the effect of transient phenomena and/or higher order behavior of the respiratory system are more marked and lead to a spike in PEEP \(_i\) estimates. The initial decrease of PEEP, during the initial portion of inspiration is probably due to this spike and to the memory effect of the algorithm (see Estimation algorithm).

Figure 4 shows the time course of the estimated PEEP \(_i\) \([\mu_{PEEP}(t) \pm \Delta_{PEEP}(t)]\) for the same subject during 2 min of ventilation with ventilatory pattern 1. The interval \( \pm \Delta_{PEEP}(t) \) is the real-time measure of parameter variation during inspiration. The breath-by-breath estimates, as well as parameter variability, are very stable, and this enables us to evaluate the algorithm performance and to test the reliability of the estimates using the mean of the on-line estimates during all the measurement intervals. In this way, we were able to compare the individual and mean values of PEEP \(_i\) derived from PEEP \(_{i,mod}\), PEEP \(_{i,st}\), and PEEP \(_{i,dyn}\) for the three ZEEP patterns (patterns 1, 3, and 4). Data are shown in Table 4. At any given ventilatory modality, the mean values of PEEP \(_i\) obtained with the same technique were not significantly different \((P > 0.21)\). By contrast, the values of PEEP \(_i\) obtained with the three techniques were very different, regardless of the given ventilator setting (Table 4). It can be noted that PEEP \(_{i,dyn}\) \(2.7 \pm 1.9 \) cmH\(_2\)O and PEEP \(_{i,st}\) \(8.1 \pm 5.5 \) cmH\(_2\)O provided the lowest and highest values, respectively. The pooled mean PEEP \(_{i,mod}\) \(5.6 \pm 3.4 \) cmH\(_2\)O was significantly lower than PEEP \(_{i,st}\) and greater than PEEP \(_{i,dyn}\). However, Fig. 5 shows that the values of PEEP \(_i\) obtained from the three techniques were significantly correlated. PEEP \(_{i,dyn}\) measurements were significantly correlated with PEEP \(_{i,st}\) \((r = 0.65, P < 0.001)\), although linear regression anal-

Fig. 3. A: representative record of ventilatory flow, Paw, and volume (by numerical integration of flow) in patient 3 with ventilatory pattern 1. B: inspiratory portion of data as identified by the estimation algorithm in a breathing cycle for patient 3 with ventilatory pattern 1 (first 3 panels). The last panel illustrates the time course of estimated PEEP \(_i\) (thick line) \(\pm SD\) (thin line) obtained from the records shown.

Fig. 4. The thick line shows the time course of model PEEP \(_i\) (PEEP \(_{i,mod}\)) estimated on 22 consecutive ventilatory cycles on an inspiration-by-inspiration basis. The thin lines illustrate \(\pm 1\) parameter variability within each inspiratory cycle. The model estimates are quite stable, and dispersion within the inspiratory cycle is limited. Data are from patient 3 ventilated with pattern 1.
ysis gave a slope $m = 0.23$ (significantly different from 1, $P < 0.001$) and an intercept $q = 0.86$ cmH$_2$O (not significantly different from 0). PEEP$_{i,mod}$ exhibited a higher correlation with PEEP$_{i,st}$ ($r = 0.90$, $P < 0.001$); the slope of the regression equation was $m = 0.560$ (significantly different from 1, $P < 0.001$), whereas $q = 1.05$ cmH$_2$O (not significantly different from 0). Comparison between PEEP$_{i,dyn}$ and model estimates also gave a significant correlation ($r = 0.768$, $P < 0.001$), and linear extrapolation yielded $m = 1.359$ (not significantly different from 1) and $q = 1.908$ cmH$_2$O (significantly different from 0, $P < 0.05$). The findings of the correlation analysis are better evidenced in the Bland-Altman diagrams (Fig. 5), in which it is clear that PEEP$_{i,mod}$ is systematically lower than PEEP$_{i,st}$ and systematically higher than PEEP$_{i,dyn}$. Consequently, the model estimates are in better agreement with PEEP$_{i,st}$ than with PEEP$_{i,dyn}$ (having notably lower 95% confidence limits), particularly in patients with PEEP$_i > 5$ cmH$_2$O.

Table 5 shows that, when PEEP was set by the ventilator (ventilator setting 2) at a value 5 cmH$_2$O greater than PEEP$_{i,st}$ on ZEEP, the values of PEEP$_t$ were essentially identical, without any significant difference. This is confirmed by Fig. 6, in which it can be seen that data points lie virtually on the identity lines with slopes not significantly different from 1 and intercepts not significantly different from 0, the correlation coefficients ranging from 0.97 to 0.99 ($P < 0.001$). The Bland-Altman analysis does not show any appreciable discrepancy; the data were well under the 95% limit of agreement, and the small underestimation ($-0.5$ cmH$_2$O) is not statistically significant (Fig. 6).

Finally, we compared the performance of the two methods suitable for a breath-by-breath PEEP$_i$ estimation in chronic obstructive pulmonary disease (COPD) patients ventilated at ZEEP, i.e., the condition with the highest PEEP$_i$, by taking the values of PEEP$_{i,st}$ as a reference. As illustrated in Fig. 7, cycle-by-cycle measurements of both PEEP$_{i,dyn}$ and PEEP$_{i,mod}$ were always lower than occlusion PEEP$_i$. However, whereas values of PEEP$_{i,dyn}$ were not significantly correlated to PEEP$_{i,st}$ ($r = 0.225$), PEEP$_{i,mod}$ exhibited a strong correlation with PEEP$_{i,st}$ ($r = 0.707$, $P < 0.01$), linear regression giving a slope ($m = 0.707$) not significantly different from 1 and an intercept ($-1.571$ cmH$_2$O) not significantly different from 0.

Table 4. Individual and mean values of PEEP$_t$ from model estimates, end-expiratory occlusion and Paw at zero flow on the three ZEEP ventilatory patterns

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>PEEP$_{i,mod}$</th>
<th>PEEP$_{i,st}$</th>
<th>PEEP$_{i,dyn}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pattern 1</td>
<td>Pattern 3</td>
<td>Pattern 4</td>
<td>Pattern 1</td>
</tr>
<tr>
<td>1</td>
<td>COPD</td>
<td>6.93</td>
<td>5.10</td>
<td>4.85</td>
</tr>
<tr>
<td>2</td>
<td>ARF</td>
<td>2.50</td>
<td>2.30</td>
<td>2.80</td>
</tr>
<tr>
<td>3</td>
<td>COPD</td>
<td>10.33</td>
<td>9.20</td>
<td>8.30</td>
</tr>
<tr>
<td>4</td>
<td>ARF</td>
<td>0.32</td>
<td>1.78</td>
<td>2.45</td>
</tr>
<tr>
<td>5</td>
<td>ARF</td>
<td>1.94</td>
<td>2.16</td>
<td>2.72</td>
</tr>
<tr>
<td>6</td>
<td>COPD</td>
<td>11.71</td>
<td>12.53</td>
<td>8.93</td>
</tr>
<tr>
<td>7</td>
<td>COPD</td>
<td>8.29</td>
<td>6.77</td>
<td>5.45</td>
</tr>
<tr>
<td>8</td>
<td>COPD</td>
<td>4.84</td>
<td>6.25</td>
<td>6.21</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>5.86 ± 4.14</td>
<td>5.76 ± 3.78</td>
<td>5.21 ± 2.51</td>
</tr>
</tbody>
</table>

PEEP$_t$, total PEEP; Paw, airway pressure; ZEEP, zero end-expiratory pressure; PEEP$_{i,mod}$, model intrinsic PEEP; PEEP$_{i,st}$, static intrinsic PEEP; PEEP$_{i,dyn}$, dynamic intrinsic PEEP; ARF, acute respiratory failure.
DISCUSSION

Since the recognition of Auto-PEEP, almost 20 years ago (23), clinicians in critical care settings have become increasingly conscious that PEEP is a fundamental physiological parameter to be measured in ventilator-dependent patients and that it is important to have a simple technique that is reliable for measurement and even monitoring in the clinical environment (17). In this study, we have presented a new approach for on-line monitoring of PEEPi based on the simple first-order model of respiratory mechanics and an RLS estimation approach. We then critically evaluated our measurements by comparing them with two well-established experimental techniques, i.e., end-expiratory occlusion and change in airway pressure preceding the onset of inspiratory airflow (26). As mentioned previously, we are well aware that our model estimates, as well as the other two techniques for measuring PEEPi, i.e., the zero-flow technique for PEEPi,dyn and the end-expiratory occlusion technique for PEEPi, provide values of total PEEP (PEEPT). The latter is determined by PEEPi, reflecting the end-expiratory elastic recoil pressure of the respiratory system and any positive pressure either set intentionally by the ventilator or due to the resistance of the ventilator expiratory circuits, tubing, and valves. However, it is a reasonable assumption that without PEEP intentionally set, PEEPT essentially reflects PEEPi. In fact, in patients with expiratory flow limitation, such as COPD patients (5 out of 8 in this study), external positive pressure lower than PEEPi does not alter the value of PEEPi and does not add to it (27). Under these circumstances, the values of PEEPi and PEEPT are essentially identical. By contrast, in patients without expiratory flow limitation, external positive pressure may affect the value of PEEPi, and hence the term PEEPT may also be more correct in the ZEEP condition. In our three patients with ARF without COPD, the values of PEEPi (or PEEPT on ZEEP) were small and <3 cmH2O in all cases. On one hand, it cannot be excluded that a slight PEEPi was detectable in these patients, because it has been shown that PEEPi can also be present in

Table 5. Individual and mean values of PEEPT from model estimates, end-expiratory occlusion and Paw at zero flow on the high PEEP ventilatory pattern.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>PEEPi,mod</th>
<th>Pattern 2</th>
<th>PEEPi,oc</th>
<th>Pattern 2</th>
<th>PEEPi,dyn</th>
<th>Pattern 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>COPD</td>
<td>10.87</td>
<td>11.87</td>
<td>10.80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>ARF</td>
<td>7.03</td>
<td>8.31</td>
<td>7.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>COPD</td>
<td>18.00</td>
<td>18.11</td>
<td>18.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>ARF</td>
<td>5.13</td>
<td>6.37</td>
<td>6.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>ARF</td>
<td>5.85</td>
<td>6.04</td>
<td>6.74</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>COPD</td>
<td>17.80</td>
<td>16.95</td>
<td>14.76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>COPD</td>
<td>14.57</td>
<td>15.63</td>
<td>14.97</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>COPD</td>
<td>15.29</td>
<td>16.73</td>
<td>16.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>11.82 ± 5.32</td>
<td>12.50 ± 5.02</td>
<td>12.04 ± 4.65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 6. Identity plots (A) and Bland-Altman plots (B) comparing values of PEEPi obtained at the high PEEP ventilatory pattern with the 3 methods. In A, dashed lines are the identity lines, and solid lines are computed according to regression analysis. In B, the dashed lines represent the ±2-SD interval.

Fig. 7. Identity plots (A) and Bland-Altman plots (B) comparing PEEPi obtained in the COPD patients ventilated with the ZEEP patterns. In A, dashed lines are the identity lines, and solid lines are computed according to regression analysis. In B, the dashed lines represent the ±2-SD interval.
MONITORING INTRINSIC PEEP

patients without COPD (11). On the other hand, part of PEEP
i could be due to the low resistive pressure at end-expiration as a result of the expiratory ventilator
circuits, as shown by comparing Tables 3 and 4. How-
ever, it could be argued that values of PEEP i or PEEP i < 3 cmH2O might not be of significant clinical
relevance in ventilator-dependent patients. By con-
trast, with PEEP set by the ventilator, all three tech-
niques provide values of PEEP i that, as shown in Table
5, were very similar. Under these circumstances,
PEEP i may be computed according to the simple equa-
tion PEEP i = PEEP t – PEEP (27).

A number of studies (3–7, 9, 16, 18, 19) involving the
RLS technique have recently been designed to track
changes in respiratory system resistance and elastance
in real time. However, no study addressed the issue of
monitoring PEEP i using a mathematical model of lung
mechanics together with recursive parameter estimation
techniques. The only previous publication that
presented a method suitable to estimate PEEP i (12) on
a breath-by-breath basis and without the need of a flow
interruption maneuver was based on the off-line least
square fit of the first-order model (Eq. 1). In addition,
that method (12) was tested only in mechanically vent-
itated patients with acute respiratory distress syn-
drome and with high levels of PEEP (11 ± 2 cmH2O).
In this paper, we present a new algorithm for continu-
ous, on-line monitoring of PEEP i in ventilator-depen-
dent patients, but we also include patients with COPD
in our analysis, namely, the patients with the highest
levels of PEEP i, and in whom PEEP i may have the
worst adverse effects (26).

Our results indicate that the algorithm provides
stable and repeatable PEEP i measurements during the
2 min of controlled mechanical ventilation (see Fig. 4)
in all 32 traces analyzed. The adequacy of our model
estimates is also supported by two other consider-
atations. First, PEEP i,mod did not exhibit any different
behavior from PEEP i,dyn and PEEP i,st when the inspi-
ryatory flow rate or profile was modified: there was
no significant difference in the values of PEEP i pro-
vided by the same method at any given ventilatory
pattern. Second, values of PEEP i,mod were always cor-
related with PEEP i obtained by means of other tech-
niques, in particular PEEP i,st, which represents a more
reliable value than PEEP i,dyn. However, the three
methods to measure PEEP i yielded different results,
although correlated.

The simplest way to validate our measurements
would have been the comparison with a gold standard.
This has been done, for example, when different tech-
niques to measure PEEP i,st have been proposed (33).
However, this kind of comparison was not possible to
validate our model because the estimated value of PEEP i
was obtained under dynamic conditions, i.e.,
during the ventilatory cycle, and from the analysis of
almost the whole mechanical inflation. By contrast,
PEEP i,st and PEEP i,dyn are obtained respectively during
end-expiratory airway occlusion, i.e., a static ma-
nuver, and from a single point (zero flow) at the
beginning of the inspiration. Literature consistently
shows that PEEP i,dyn is systematically and signifi-
cantly lower than PEEP i,st during spontaneous breath-
ing (24) as well as during assisted (1, 33) and controlled
(22) mechanical ventilation. Whereas the physiological
meaning of PEEP i,st is acceptably clear, PEEP i,dyn is a
matter of more debate (2). PEEP i,st represents the
average end-expiratory elastic recoil of the total respi-
atory system at the lung volume at which the airway
occlusion occurs. In fact, during the 3–5 s of airway
occlusion, both stress adaptation phenomena occur,
and lung units with different regional time constants,
and hence different PEEP i can equalize (pendelluft).
The achieved equilibration between regional alveolar
and airway pressure is indicated by the plateau in
airway pressure (26). By contrast, PEEP i,dyn repre-
sents the lowest regional PEEP i that has to be coun-
terbalanced by the positive pressure of the ventilator to
start inspiratory flow (26). The difference between
PEEP i,dyn and PEEP i,st during controlled mechanical
ventilation can be very great, PEEP i,dyn amounting
only to 25–30% of PEEP i,st (22). In our patients, the
PEEP i,dyn–PEEP i,st ratio averaged 30%. This result
concerns with the fact that 63% of our patients (5 out of
8) were COPD patients, who are well known to have a
large degree of lung inhomogeneity (11) that substan-
tially affects the PEEP i,dyn–PEEP i,st ratio by decreasing
it (22). It should be said that a recent experimen-
tal study, in mechanically ventilated anesthetized
rabbits, found that PEEP i,dyn could be greater than
PEEP i,st (13). However, some technical issues suggest
that this finding should be treated with caution and
requires further confirmation (2).

Our PEEP i,mod estimates were smaller than PEEP i,st,
although the values from the two methods were sig-
ificantly correlated in all instances (Figs. 5–7). This
might not be surprising in line with the results ob-
tained by the other authors who showed that PEEP i
measured under dynamic conditions, i.e., before a suf-
cient equilibration time between regional alveolar
and airway opening pressure had elapsed, is consis-
tently smaller than PEEP i,st. Our PEEP i,mod is con-
structed from time-variant estimation of P0 in the
first-order model during inspiration, i.e., under dy-
namic conditions. However, our PEEP i,mod was system-
atically greater than PEEP i,dyn measured from the
positive value of airway pressure at the point of zero
flow, i.e., when inspiration starts, although the two
values were correlated. Our interpretation of the dif-
ference between PEEP i,dyn and PEEP i,mod is as follows.
The positive airway pressure at the point of zero flow,
i.e., PEEP i,dyn according to common terminology, re-
forces the negative pressure needed to start inspira-
tion, which is the pressure that counterbalances the
lowest PEEP i. In fact, as soon as the lowest regional
value of PEEP i is counterbalanced, mechanical lung
inflation begins. From that point on, the inspiratory
flow continues, and lung regions with higher values of
PEEP i can be recruited to inspiration by the increasing
positive pressure. This progressive recruitment of
alveolar regions with higher PEEP i cannot be appreci-
ated because inspiration had already started. However, if inspiratory flow is delivered by a preset constant profile, the endowment of a constant flow indicates that all lung units are filling at the same rate even in the presence of lung heterogeneity and hence that most of the regional PEEP has been counterbalanced (8). It has been shown that inspiratory flow becomes constant after a variable time from the beginning of inspiration (25). With constant pressure ventilation (pattern 4), the flow profile exhibits an initial rapid rise and a subsequent slow decay (25). The lung units with a fast time constant receive the initial rapid flow, whereas the units with a longer time constant fill later with the slower flow. Clearly, the fast time constant units are those with the lowest PEEP, and airway pressure at zero flow reflects the lowest regional PEEP. Therefore, with both constant and decelerating flow, PEEP_{i,dyn} reflects the minimum PEEP. By contrast, the PEEP_{i,mod} cycle-by-cycle estimates are obtained as the weighted mean of the time course of intrinsic PEEP during inspiration. Hence, the value of PEEP_{i,mod} is affected not only by the initial lowest PEEP but also by the subsequent higher values of PEEP in the lung units with a longer time constant, which are recruited either by the increasing airway pressure or by the decreasing flow rate with the progress of inspiration.

Our interpretation of this physiological meaning of PEEP_{i,mod} is supported by three findings in this work. First, PEEP_{i,mod} is always significantly correlated with PEEP_{i,st}, the latter being the best gold standard available because of its safe physiological interpretation, even in conditions in which PEEP_{i,dyn} loses the significant correlation (Fig. 7). Second, the coefficients of correlation between PEEP_{i,mod} and PEEP_{i,st} are always greater than between PEEP_{i,dyn} and PEEP_{i,st}. This is in line with the fact that PEEP_{i,dyn} comes from a single point, whereas both PEEP_{i,mod} and PEEP_{i,st} are influenced by values of PEEP from different lung units. The algorithm is likely to estimate the PEEP_{i,st} lower bound. Finally, when PEEP is abolished by PEEP set 5 cmH_2O above PEEP, all the techniques provide virtually identical results (Table 5 and Fig. 6) for PEEP. A reasonable explanation of the excellent agreement among all the techniques to measure PEEP, can be found in the more homogeneous lungs when PEEP is replaced by PEEP. In fact, whereas in the nonhomogeneous lungs the fast time constant units can start filling while the long time constant units are still emptying, in the more homogeneous lungs, most if not all the lung units can start filling almost simultaneously. In the most homogeneous condition, all the lung units can start filling from their elastic equilibrium point. This can be the case when external PEEP has abolished PEEP. Under these circumstances, the differences between any PEEP_{i,dyn} and PEEP_{i,st} disappears. This interpretation is supported by some results obtained by Rossi and colleagues (28), who showed that ventilation-perfusion mismatching diminishes and PaO_2 and PaCO_2 improve when PEEP replaces PEEP, suggesting more homogeneous lungs. As shown in Fig. 6, in our patients, when PEEP was set by the ventilator at a value greater than PEEP, no difference was detectable among PEEP, measured by means of different techniques. The agreement shown in Fig. 6 further supports the validity of our on-line method to estimate PEEP and PEEP_i.

The estimate obtained with our model gave us a better approximation of PEEP_{i,st} than that given by the other methods not requiring any maneuver or additional equipment and explained the differences found between our method and the standard measurement of PEEP_{i,dyn}, which does not adequately describe the heterogeneity of alveolar pressure distributions.

To be thorough, we have also applied to our ZEEP-COPD data the other possible methods proposed in Refs. 5 and 12 for performing continuous monitoring of PEEP. However, as specified by the authors in Ref. 5, the term P_0 of Eq. 1 represents essentially the value of Paw when both V and V are 0 (i.e., PEEP). This is confirmed by comparing the real-time estimates obtained by this method with the end-expiratory occlusion measurements: we found a poor correlation with PEEP_{i,st} [r = 0.12, P = nonsignificant (NS)]. Repeating the same procedure, we have compared the results of Eberhard and coworkers’ (12) method with PEEP_{i,st}. Here, the mathematical method fails if the database is restricted to the case of COPD patients ventilated at ZEEP. In fact, in this case, the correlation with PEEP_{i,st} is lost (r = 0.44, P = NS).

Finally, we would like to point out that our on-line method to estimate PEEP provides a value obtained from the whole mechanical breath analysis whereas the so-called PEEP_{i,dyn} comes from only one point of airway pressure at zero flow. Because, at the beginning of the breath, the rise in airway pressure is very fast and steep, the single-point PEEP_{i,dyn} is likely to be less accurate than our weighted value from the whole breath. Furthermore, the end-expiratory airway occlusion technique not only requires a slight intervention in the ventilator setting from the caregiver but also needs either additional equipment if the patient is ventilated with ventilators without the end-expiratory occlusion facility (14) or adequate correction if the facilities available in the ventilator are used (15, 30). Therefore, our on-line estimation of PEEP provides some technical advantages over the other available techniques for monitoring PEEP, in ventilator-dependent patients. Moreover, although PEEP_{i,st} remains a reliable parameter, there is an important reason why PEEP_{i,mod} should be obtained: PEEP_{i,st} is a static parameter that provides the lung recoil pressure at a given volume when all the stress adaptation transients have dissipated. This does not represent the situation regarding the pressures inside the lung at the end of a normal dynamic breath.

In summary, in this study we have adopted a recursive least square algorithm combined with the classical first-order model of respiratory mechanics and continuous measurement of airflow and airway pressure to quantify PEEP_i in real time. The method constructs,
from the recursive estimation of $P_0$ during inspiration (see Eq. 1), a weighted mean and standard deviation of dynamic intrinsic PEEP. This value is updated on a cycle-by-cycle basis to give real-time monitoring of this important clinical index in ventilator-dependent patients with ARF of different etiologies, including COPD. The latter is the condition in which the highest values of PEEP are commonly found. Our method is limited to patients without any respiratory activity during controlled mechanical ventilation. Furthermore, it must be stressed that our on-line estimate of PEEP, is really an estimate of $PEEP_t$, i.e., the total positive pressure at the end of the expiration. Without PEEP set by the ventilator, PEEP, essentially reflects $PEEP_i$, i.e., the end-expiratory elastic recoil. When PEEP was set by the ventilator, PEEP, could be computed by subtracting the set value of PEEP from the estimated $PEEP_t$, and this can also be done automatically in the algorithm. The value of PEEP, estimated by our on-line model more closely reflects a true $PEEP_{i,dyn}$ than the conventional one-point measurement of $PEEP_{i,dyn}$ at zero flow, because it is influenced by almost all the values of PEEP occurring during mechanical lung inflation.

Although limited to controlled mechanical ventilation, our method for monitoring $PEEP_i$ ($PEEP_i,0$) on-line may provide the possibility for useful clinical applications. This can be determined by additional studies.

We thank the Intensive Care Unit nursing staff of the Azienda Ospedaliera di Parma for kind cooperation. We are grateful to Dr. Lorenzo Appendini for helpful discussion in the interpretation of the data. We are also grateful to the reviewers of this manuscript for valuable comments.

The work of G. Nucci and C. Cobelli was supported in part by the Bioingegneria del Sistema Respiratorio grant from the Ministero della Università e della Ricerca Scientifica e Tecnologica, Roma, Italy.

REFERENCES


