Background: The aim of our study was to assess the effect of periodic hyperinflations (sighs) during pressure support ventilation (PSV) on lung volume, gas exchange, and respiratory pattern in patients with early acute respiratory distress syndrome (ARDS).

Methods: Thirteen patients undergoing PSV were enrolled. The study comprised 3 steps: baseline 1, sigh, and baseline 2, of 1 h each. During baseline 1 and baseline 2, patients underwent PSV. Sighs were administered once per minute by adding to baseline PSV a 3- to 5-s continuous positive airway pressure (CPAP) period, set at a level 20% higher than the peak airway pressure of the PSV breaths or at least 35 cm H2O. Mean airway pressure was kept constant by reducing the positive end-expiratory pressure (PEEP) during the sigh period as required. At the end of each study period, arterial blood gas tensions, air flow and pressures traces, end-expiratory lung volume (EELV), compliance of respiratory system (Crs), and ventilatory parameters were recorded.

Results: Pao2 improved (P < 0.001) from baseline 1 (91.4 ± 27.4 mmHg) to sigh (133 ± 42.5 mmHg), without changes of Paco2. EELV increased (P < 0.01) from baseline 1 (1,242 ± 507 ml) to sigh (1,377 ± 484 ml). Crs improved (P < 0.01) from baseline 1 (40.2 ± 12.5 ml/cm H2O) to sigh (45.1 ± 15.3 ml/cm H2O). Tidal volume of pressure-supported breaths and the airway occlusion pressure (P0.1) decreased (P < 0.01) during the sigh period. There were no significant differences between baselines 1 and 2 for all parameters.

Conclusions: The addition of 1 sigh per minute during PSV in patients with early ARDS improved gas exchange and lung volume and decreased the respiratory drive.

CURRENT ventilatory approaches to the acute respiratory distress syndrome (ARDS) suggest the use of low tidal volumes (Vt)1 to limit alveolar distending pressure2,3 and relatively high positive end-expiratory pressure (PEEP)4 to prevent alveolar collapse and cyclic opening and closing.5 In a recent large multicenter trial, ventilation with Vt as low as 6 ml/kg of predicted body weight reduced mortality compared with traditional ventilation with larger Vt.1 Although it is effective in limiting injury associated with alveolar stretching,2,5 ventilation with low Vt may lead to progressive atelectasis and consequent hypoxia.6 Although the use of high PEEP levels may partially counteract this tendency and stabilize alveoli, minimize cyclic inspiratory opening, and prevent further lung collapse,7,8 atelectatic lung regions may persist. Lung recruitment maneuvers (RMs) such as sighs have been successfully used in patients during general anesthesia to restore the decreased respiratory system compliance (Crs) and arterial oxygenation commonly associated with use of low Vt.9 This result has led investigators to test the use of RMs in patients with ARDS during ventilation with low Vt and high PEEP, improving lung function10 and outcome.4 Cyclically delivered RMs have been effective in ARDS patients managed with continuous positive pressure ventilation (CPPV), to induce alveolar recruitment11 and allow the use of lower PEEP and mean airway pressure (Pawm), while preserving gas exchange and lung volumes.12 Recently, many clinicians and investigators underscored the potential role and benefits of maintaining spontaneous breathing by using modes of partial ventilatory support such as pressure support ventilation (PSV).

The ability of PSV to permit diaphragmatic activity13,14 and reduce the need for sedative drugs15 might be of benefit to patients with acute respiratory failure. In a recent study,16 PSV was utilized effectively in patients with acute lung injury, with no significant gas exchange differences in comparison with CPPV. In that study, PSV was more likely to fail in patients with a high minute ventilation (V̇E) and low Crs in agreement with previous studies that showed decreased efficacy of PSV in sicker patients.17,18 The beneficial effect of sighs during CPPV may possibly extend to modes of partial ventilatory support, such as PSV. Sighs may counteract the tendency of lung collapse associated with low Vt and thus improve gas exchange.
The aim of our study was to investigate the effects of sighs, administered at a frequency of one per minute, on gas exchange, lung volume, and respiratory pattern during PSV in patients with early ARDS.

Materials and Methods

Subjects
We enrolled 13 patients (table 1) who met the criteria for ARDS defined by the American-European Consensus Conference and had no history of chronic obstructive pulmonary disease. All patients were studied within 7 days after the diagnosis of ARDS. At the time of enrollment, all subjects were intubated and had an arterial catheter in place. The level of sedation, obtained with benzodiazepines, propofol, and fentanyl, allowed patient arousal and coordinated motor responses to verbal commands. Subjects were studied during clinical and hemodynamic stability in a supine or semirecumbent position. On the day of the study, patients were already ventilated with PSV set by the attending physician according to empirical criteria.

Protocol
The protocol was approved by the institutional ethics committee, and informed consent was obtained from the patient’s next of kin. The investigation was conducted according to the Helsinki Declaration. After enrollment, all patients were connected to an Evita-4 ventilator (Dräger, Lübeck, Germany), set in PSV with fraction of inspired oxygen (FiO₂), inspiratory pressure, and PEEP levels previously selected by the attending physician. The time of inspiratory pressure rise was set at 0.2 s, and TiS obtained by design during Sigh (fig. 1). The Pawm on oxygenation, Pawm (averaged over a 1-min period) was always kept constant by adjusting the PEEP level.

Gas Exchange and Hemodynamics
We determined all measurements at the end of each study period. We collected arterial blood samples to measure \( P_{aO_2} \), \( P_{aCO_2} \), pH, and hemoglobin concentration and saturation (HbO₂) (ABL 350; Radiometer, Copenhagen, Denmark). Blood pressures were measured with pressure transducers zeroed at the mid-axillary line. During Sigh, all hemodynamic parameters were measured between two sighs.
Respiratory Mechanics

Airway pressure and flow were measured with a CP100 Pulmonary Monitor (Bicore Monitoring Systems, Irvine, CA), through a disposable flowmeter (Variflex flow transducer; Bear Medical Systems, Bilthoven, The Netherlands) inserted between the Y-piece of the ventilator circuit and the proximal end of the endotracheal tube. The analog output of the pulmonary monitor was connected to a personal computer and processed via an analog-to-digital converter (Colligo, Elekton, Italy) at a sample rate of 100 Hz. A 5-min-long sample was recorded at the end of each study period and stored for subsequent computer analysis. After the first 3 min of recording, we performed a minimum of three end-expiratory and three end-inspiratory airway occlusions, by pressing for at least 3 s the appropriate button on the ventilator panel. During Sigh, the occlusion maneuvers were performed between two sighs. The airway pressure drop in the first 100 ms of an occluded inspiration (P0.1) was measured as an index of the neuromuscular drive.21 We performed the end-expiratory occlusion first, to avoid interference with the measurement of P0.1. Data were then analyzed with dedicated software (Computo; Elekton, Agliano Terme, Italy). Tidal volume was obtained by integration of the flow signal.

From the analysis of traces with nonoccluded breaths we obtained (1) respiratory rate, by counting the number of breaths in 1 min; (2) inspiratory time (TIPSV) and expiratory time (TEPSV) and inspiratory to expiratory time ratio (I:E PSV) by averaging at least 10 PSV breaths; (3) mean tidal volume in 1 min (VT,mean); (4) VE, calculated as VT,mean/respiratory rate; (5) Pawm, measured as the average of the Pawm signal during a 60 s period; and (6) VT of PSV breaths (VT,PSV), determined by averaging at least 10 breaths. From sigh breaths we determined (1) tidal volume (VT,S); (2) inspiratory time (TIS); (3) inspiratory plateau pressure (PlatS), corresponding to the higher BIPAP level applied to perform sighs; (4) and fraction of minute ventilation supplied by the sigh breaths (VE,S), calculated as VT,S/VE.

From the analysis of occluded breaths we computed (1) end-inspiratory elastic recoil pressure (Pel,rsi), measured as the plateau airway pressure (Paw) at relaxation of respiratory muscles, identified by visual inspection during an inspiratory occlusion; (2) end-expiratory elastic recoil pressure (Pel,rse) measured as the plateau Paw at relaxation of the respiratory muscles, identified by visual inspection during an end-expiratory occlusion (all the occlusions that did not reach an identifiable relaxation were discarded); and (3) P0.1, measured during the end-expiratory pause as the deflection in Paw in the first 100 ms after the start of patient inspiratory effort. We discarded by inspection the initial 5 ms to avoid uncertainties in recognizing the actual start of the inspiratory effort; the Paw drop in the following 100 ms was taken as the P0.1 value.22 We computed the Crs as Crs = VT,PSV/Pel,rsi − Pel,rse).

Lung Volume

To assess the effects of sighs on lung volumes, we measured the end-expiratory lung volume (EELV), which represents the total gas volume at end expiration when PEEP is applied. A 5-cm clampable tube was inserted...
between the endotracheal tube and the Y-piece of the ventilator. Immediately after an end-expiratory occlusion maneuver, performed as described above, we clamped the endotracheal tube. We then disconnected the patient from the ventilator and measured the lung volume by a simplified closed-circuit helium dilution technique. Measurements were performed in duplicate. During Sigh, the EELV was measured one or two breaths immediately before a new sigh.

**Statistical Analysis**

Values are expressed as mean ± SD. We used one-way analysis of variance for repeated measurements to compare the three study steps. Individual comparisons were performed with use of paired t tests, with application of the Bonferroni correction for multiple comparisons. We specifically planned to compare Sigh with Base 1 and Base 2 with Base 1. For all the tests used, P < 0.05 was considered significant.

**Results**

Relevant characteristics of the patients at the time of enrollment are shown in table 1. The main study results are shown in table 2. Time elapsed from the diagnosis of ARDS was 3.7 ± 1.8 days. Hemodynamic parameters did not show any significant change throughout the study.

**Sigh Profile**

Platₜ was 38 ± 3.2 cm H₂O, corresponding to a Vₜₜ of 1,148 ± 301 ml; Tiₜ was 3.6 ± 0.7 s.

**Gas Exchange**

The introduction of one sigh per minute was associated with an increase in PAO₂ (41.6 ± 33.9 mmHg [29.8 ± 16.2%]; P < 0.001; fig. 2A). By contrast, PaCO₂, HbO₂, and pH did not show any significant change throughout the study.

**Lung Volume and Respiratory Mechanics**

PEEP was significantly lower during Sigh with respect to Base 1 (average decrease, 1.1 ± 0.7 cm H₂O). Vₚ did not show any significant difference among the three steps. EELV increased significantly from Base 1 to Sigh (average increase, 136 ± 140 ml [12.3 ± 10.8%]; range, −82−592 ml; P < 0.01; fig. 2B) and returned to baseline value after discontinuation of the sigh. Tiₚ increased significantly during Sigh with respect to Base 1 (4.9 ± 4.9 ml × cm H₂O⁻¹ [10.4 ± 9.4%]; P < 0.01), whereas Tiₚ Base 2 was not significantly different from Crs Base 1 (fig. 2C).

**Discussion**

The main result of this study was that the addition of one sigh per minute during PSV in patients with early ARDS improved arterial oxygenation and likely promoted alveolar recruitment.

**Table 2. Gas Exchange, Hemodynamics, and Ventilatory Parameters**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline 1</th>
<th>Sigh</th>
<th>Baseline 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAO₂ (mmHg)</td>
<td>91.4 ± 27.4</td>
<td>133 ± 42.5†</td>
<td>93.3 ± 21.6</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>45.8 ± 7.6</td>
<td>47.3 ± 10.7</td>
<td>47.9 ± 10.3</td>
</tr>
<tr>
<td>HbO₂ (%)</td>
<td>94.9 ± 2.4</td>
<td>96.4 ± 2.2‡</td>
<td>94.9 ± 3.1</td>
</tr>
<tr>
<td>pH</td>
<td>7.43 ± 0.05</td>
<td>7.43 ± 0.05</td>
<td>7.43 ± 0.06</td>
</tr>
<tr>
<td>HR (b·m⁻¹)</td>
<td>89 ± 17</td>
<td>90 ± 16</td>
<td>91 ± 18</td>
</tr>
<tr>
<td>PaAs (mmHg)</td>
<td>143 ± 19</td>
<td>148 ± 29</td>
<td>143 ± 43</td>
</tr>
<tr>
<td>PaD (mmHg)</td>
<td>65 ± 12</td>
<td>63 ± 14</td>
<td>64 ± 8</td>
</tr>
<tr>
<td>Vₚ (L·min⁻¹)</td>
<td>9.2 ± 2.5</td>
<td>9.9 ± 2.8</td>
<td>9.5 ± 2.3</td>
</tr>
<tr>
<td>Pawₚₕ (cm H₂O)</td>
<td>14.9 ± 4.7</td>
<td>14.9 ± 4.9</td>
<td>14.9 ± 4.4</td>
</tr>
<tr>
<td>PEEP (cm H₂O)</td>
<td>11 ± 3</td>
<td>10 ± 4‡</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>EELV (ml)</td>
<td>1242 ± 507</td>
<td>1378 ± 484‡</td>
<td>1260 ± 547</td>
</tr>
<tr>
<td>Crs (ml·cm H₂O⁻¹)</td>
<td>40 ± 12</td>
<td>45 ± 15‡</td>
<td>38 ± 13</td>
</tr>
<tr>
<td>VT,PSV (ml)</td>
<td>418 ± 57</td>
<td>370 ± 81‡</td>
<td>405 ± 61</td>
</tr>
<tr>
<td>Tᵢₚₜ (s)</td>
<td>0.8 ± 0.2</td>
<td>0.7 ± 0.2‡</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td>VTₚₘₚ (ml)</td>
<td>1148 ± 301</td>
<td>1148 ± 301</td>
<td>—</td>
</tr>
<tr>
<td>Tiₚₜ (s)</td>
<td>3.6 ± 0.7</td>
<td>3.6 ± 0.7</td>
<td>—</td>
</tr>
<tr>
<td>%Vₑₑₑₛ</td>
<td>11.2 ± 3</td>
<td>11.2 ± 3</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD; † Sigh vs. Baseline 1, P < 0.001; ‡ Sigh vs. Baseline 1, P < 0.01. PAO₂ = arterial tension of oxygen; PaCO₂ = arterial tension of carbon dioxide; HbO₂ = oxygenated hemoglobin (percent); HR = heart rate; PaAs = systolic arterial pressure; PaD = diastolic arterial pressure; Vₚ = minute ventilation; Pawₚₕ = mean airway pressure; PEEP = positive end expiratory pressure; EELV = end expiratory lung volume; Crs = compliance of respiratory system; VT,PSV = tidal volume of pressure support ventilation; Ti,PSV = inspiratory time of pressure support ventilation; I:EPSV = inspiratory to expiratory ratio; RR = respiratory rate; Platₜ = higher PEEP level during BIPAP breath; VTₚₘₚ = tidal volume of sigh; Tiₚₘₚ = inspiratory time of sigh; %Vₑₑₑₛ = fraction of minute ventilation supplied by the sigh breath.

**Respiratory Pattern**

During Sigh, there was a significant decrease of VTₚₘₚ (P < 0.01; fig. 3A), Tiₚₘₚ (P < 0.01; fig. 3B), and Pa₀.₁ (P < 0.01; fig. 3C). All three parameters returned to baseline after discontinuation of sighs, and no significant differences were found between Base 1 and Base 2. There was no significant change in I:EPSV during the three study periods.

**Effect of Ventilatory Strategy on Gas Exchange and Lung Volume**

The use of sigh with Platₜ higher than 35 cm H₂O improved arterial oxygenation in all studied patients, in spite of a slightly lower PEEP and similar Pawₚₕ (table 2). This positive effect on gas exchange was associated with...
an increase in EELV and Crs, suggesting that sighs possibly promoted alveolar recruitment. These results are in agreement with the reported beneficial effect of various types of RMs that have been applied in fully ventilated and paralyzed patients. These RMs included the administration of a sustained inflation lasting several seconds,\textsuperscript{10,24} a cyclical higher inflation pressure,\textsuperscript{11} and a cyclical higher PEEP.\textsuperscript{12}

We computed Crs by applying the airway occlusion technique during PSV breaths, recognizing the presence of muscle relaxation by visual inspection. In spite of the many possible limitations of this method, we showed in a previous study\textsuperscript{25} that during PSV the airway pressure plateau during inspiratory occlusion is a reliable measurement of the relaxed elastic recoil pressure of the respiratory system in patients with acute lung injury or ARDS.

The average $\text{Plat}_S$ used in our study was 38 cm H$_2$O. Using higher inflation pressure during a sigh might have resulted in more effective recruitment and further improvement in arterial oxygenation but also in increased risk of barotrauma. The $\text{Plat}_S$ values that we used are similar to the inflation pressures that have been effective in improving gas exchange in other studies in which sighs were cyclically delivered.\textsuperscript{11,12} Moreover, in spontaneously breathing patients, inspiratory pressure levels may also be limited by subjective tolerability and stimulation of the cough reflex.

The modality used in our study to administer sigh differs in some ways from other studies in which cyclically delivered sighs successfully improved gas exchange.\textsuperscript{11,12} First, it was our goal to preserve spontaneous respiratory activity. During CPPV in paralyzed patients, gas distribution in the lung is determined mainly by regional

Fig. 2. Changes in arterial tension of oxygen ($\text{PaO}_2$) (A), end-expiratory lung volume (EELV) (B), and compliance of respiratory system (Crs) (C) during baseline 1 (BASE1), sigh (SIGH), and baseline 2 (BASE2). Solid lines represent changes in each patient between different steps. Solid horizontal bars represent the mean values, and open vertical columns indicate SD ($\dagger$SIGH versus BASE1, $P < 0.001$; *SIGH versus BASE1, $P < 0.01$).

Fig. 3. Changes in respiratory pattern of pressure support ventilation, during baseline 1 (BASE1), sigh (SIGH), and baseline 2 (BASE2): $V_{T,\text{PSV}}$ = mean tidal volume during pressure support ventilation (A); $T_{I,\text{PSV}}$ = inspiratory time of pressure support breaths (B); and $P_{0.1}$ = airway occlusion pressure (C). Solid lines represent changes in each patient between different steps. Solid horizontal bars represent the mean values, and open vertical columns indicate SD (*SIGH versus BASE1, $P < 0.01$).
compliance. In supine position, anterior (nondependent) regions of the lung are the most compliant, and ventilation in the posterior (dependent) regions may be compromised, leading to progressive atelectasis. It has been shown that preserving spontaneous ventilatory effort may improve gas exchange, possibly by enhancing ventilation of the dependent parts of the lung and preventing atelectasis.14,26

Second, in our study, sighs were pressure-controlled rather than volume-controlled. During pressure control ventilation, inspiratory flow stops when alveolar pressure reaches the set inspiratory pressure. If alveolar recruitment takes place, more gas is delivered to maintain plateau pressure, facilitating the filling and stabilization of newly opened alveoli.27

Third, regardless of the ventilatory mode, sigh pressure was maintained for a relatively long time, possibly favoring the filling of recruited alveoli also by gas redistribution.

Finally, compared to the study of Pelosi et al.,11 who used three consecutive sighs per minute, and the study of Foti et al.,12 who increased the PEEP for two consecutive breaths every 30 s, in our study a single sigh per minute proved beneficial. Identifying the lowest effective sigh rate is of primary importance because of the known drawbacks on lung parenchyma due to high distending volumes or pressures. However, Davies et al.28 showed that sighs delivered at a rate of two breaths every 10 min were of no benefit during PSV, despite the use of inflation pressures comparable with those of our study. The role of frequency on sigh effectiveness remains to be formally explored.

It is worth noting that Crs was slightly higher in our patients than in those studied by Pelosi et al.,11 suggesting the possibility of safe use of PSV in this patient population.

The observed effect of sighs on the P0.1 may also be explained in part by the changes in EELV,31 which may directly affect the P0.1 measurement. However, we did not find any significant correlation between the effect of sigh on P0.1 and that on EELV.

Clinical Implications

Partial ventilatory techniques prevent paralysis and reduce the use of sedative drugs. Our goal was to learn whether by adding sigh it was possible to extend the indication for the use of partial ventilatory techniques to patients with early ARDS. In a recent study, acute lung injury was successfully managed with PSV in 38 of 48 patients,11 suggesting the possibility of safe use of PSV in the early phases of ARDS. PSV was more likely to fail for patients with high ventilatory needs and low Crs. By decreasing the respiratory drive, as in this study, sigh may increase the efficacy of PSV in this patient population.

Moreover, the achievement of a better Crs and alveolar recruitment may play a relevant role in increasing the success rate of PSV in ARDS patients. The response to PSV is also directly affected by pulmonary edema17 and hypoxia.18 The increase in arterial oxygenation associated with the introduction of the sigh may increase PSV efficacy in this patient population.

It is worth considering that we selected patients in the earlier phase of acute respiratory failure, when alveolar collapse and dependent atelectasis, mainly related to increased lung weight and superimposed pressure, have shown good recruitability.5 The same results may not be achieved in patients with late-stage ARDS. In addition, sighs may have a less pronounced effect in patients who are recovering from the acute phase of respiratory failure,29 where a fibroproliferative process has started and alveolar collapse is driven by an increased pulmonary elastance. Early addition of sighs may have the function of opening previously collapsed lung and preventing lung collapse associated with low VT ventilation.

Our goal was to investigate the acute short-term physiologic effects of sigh administration. Indeed, no conclusion could be drawn about the outcomes for the patients. A different study design will be necessary to investigate the long-term effects of this approach.

In conclusion, the addition of one sigh per minute, delivered as pressure-controlled breath to PSV in ARDS patients, improves oxygenation and lung mechanics. These findings suggest a possible role for clinical evaluation of periodic recruitment maneuvers during assisted breathing.

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