The efficacy of sighs in patients with COPD undergoing general anesthesia and controlled ventilation

CHUCK BIDDLE, CRNA, MS
Kansas City, Kansas
LARRY EPPS, CRNA, MS
Cookeville, Tennessee
RUTH HASSANEIN, PhD
Kansas City, Kansas

Fourteen patients with COPD underwent elective procedures below the umbilicus, all receiving a standard anesthetic. They were randomized to one of four groups differentiated by the presence or absence of sighing during mechanical ventilation. Patients who were sighed experienced both statistically and clinically significant improvement in their oxygenation efficiency as measured by the alveolar to arterial oxygen gradient.

The spontaneous sigh is an innate reflex consisting of a complicated interaction between peripheral chemoreceptors and vagally mediated input that augment inspiratory flow. Factors known to stimulate spontaneous sighing include decreases in lung compliance, noxious stimuli, histamine, cyanide and hypoxia. Sighs, which occur 9-10 times an hour in awake humans, appear to function physiologically by hyperinflating the lung, expanding atelectatic air spaces and keeping the work of breathing, pulmonary compliance and venous admixture within normal range.

There is evidence that periodic lung hyperinflations (sighs) prevent both decreases in pulmonary compliance and the closure of pulmonary units. Sighing minimizes the alveolar to arterial oxygen tension gradient [(A-a)DO₂], optimizing and stabilizing the partial pressure of arterial oxygen (PaO₂). High compliance and PaO₂ are goals pursued during anesthesia and surgery.

It has been proposed that the falling compliance which attends mechanical ventilation without sighing is attributable to atelectasis, a phenomenon found to be quantitatively measurable by determining (A-a)DO₂. There is a strong correlation between alveolar atelectasis during anesthesia and a widening (A-a)DO₂. Teleologically, one can surmise that the primary cause of lower PaO₂ values was atelectasis that developed in those patients not sighed.

Consensus is lacking regarding the efficacy of sighing mechanically ventilated patients undergoing anesthesia. Panday and Nunn failed to show a consistent change in arterial PaO₂ following sighs. However, upon close examination of this study, (A-a)DO₂ gradients actually were reduced in a manner that was statistically significant. Grim and Housley also failed to demonstrate the ability of sighing to reduce (A-a)DO₂ in patients undergoing surgery and general anesthesia. It is important to recognize that none of these studies involved patients with overt pulmonary pathophysiology.

To date, no study of the efficacy of the sigh has been done involving patients with documented chronic obstructive pulmonary disease (COPD) undergoing general anesthesia with controlled ventilation. Research into this patient population is needed because PaO₂ decrement in COPD patients may be deleterious to their clinical course, while the same decreases may be inconsequential in their healthier counterparts. In an earlier pilot study, we determined that sighs are not routinely administered to surgical patients. The above incongruities...
between the controversial efficacy of sighing and the observed lack of sighing by clinical practitioners, coupled with minimal recent clinical study of the sigh, prompted this investigation.

This study was undertaken to evaluate the efficacy of the sigh when utilized in surgical patients with COPD in terms of its ability to reduce or stabilize (A-a)DO_2. The effects of sighing surgical COPD patients can probably be extrapolated to COPD patients undergoing mechanical ventilation in the intensive care unit. The hypothesis of this study was that periodic sighing of COPD patients during anesthesia, paralysis and controlled ventilation would reduce or stabilize their (A-a)DO_2 gradient as compared to a control group that did not receive sighs.

**Methodology**

Following institutional approval and informed consent of all subjects, a prospective clinical trial was undertaken to test the hypothesis. Each subject was required to have a diagnosis of COPD based on the following criteria: forced expiratory volume in one second (FEV_1) less than 2 liters, FEV_1/FVC (forced vital capacity) less than 75% of predicted, forced expiratory flow at 25% and 75% of FVC (FEF_{25,75}) less than 75% of predicted, and a room air blood gas with PaO_2 less than 75 mmHg or a PCO_2 greater than 45 mmHg.

Additional criteria for inclusion were as follows: males 45-80 years of age, a surgical procedure below the umbilicus, less than 130% of ideal body weight, and free from congestive heart failure, neurologic, hepatic, renal and endocrine disease. Furthermore, no patients with bullous emphysema were included. These strictly defined criteria were required in order to control the number of confounding variables influencing the dependent variable, (A-a)DO_2 values.

Following preoperative placement of radial artery catheters, subjects were randomly assigned to one of four groups. Group I (four patients) received no sighs and served as the control group. Group II (three patients) was sighed continuously throughout the surgical procedure. Group III (three patients) was sighed for the first two and one-half hours of the operation, then not sighed for the remainder of the procedure. Group IV (four patients) was sighed for 90 minutes and then not sighed for 90 minutes alternatively throughout the surgical procedure. Groups II and IV were thus subjected to both control and experimental conditions (crossover design).

While three independent experimental groups (II, III, IV) complicated the methodological approach, we felt that testing the relationship between the independent variable (sighing) and the dependent variable ((A-a)DO_2) in a variety of clinical scenarios would serve to maximally quantify that relationship. Crossover design is known for providing statistical power to data in which a small population is studied.\(^\text{14}\)

All subjects received an anesthetic induction of thiopental (4 mg/kg), vecuronium (0.1 mg/kg to facilitate endotracheal intubation and surgical relaxation), and isoflurane (0.5 to 1.0% inspired concentration). Anesthetic maintenance employed sufentanil (1\(\ \mu\)g/kg/hour) and isoflurane (0.5 to 1.0%) in 100% oxygen.

Ventilation was controlled mechanically at a volume of 100 cc/kg/minute (tidal volume adjusted at 9-15 cc/kg to maintain normocapnia measured continuously by end-tidal capnometry) and 5 cm H_2O pressure of positive end-respiratory pressure (PEEP). Cardiac output was indirectly assessed throughout the procedure by observing heart rate, blood pressure, urinary output, skin color, body temperature and pulse oximeter derived hemoglobin saturation. Direct measurement of cardiac output was not ethically feasible in this study.

Ten minutes after insertion of the endotracheal tube, a baseline arterial blood gas (ABG) was drawn on each patient; ABGs were subsequently measured every 30 minutes. After the first baseline ABG, the experimental groups (II, III, IV) received three consecutive sighs every 10 minutes (in the pattern required by each group's protocol), each sufficient to generate 40 cm H_2O pressure and held constant for five seconds. This manner of sighing was selected because of its previous and accepted experimental use as well as its facility in providing a safe and reproducible maneuver in each patient.\(^\text{14}\) (A-a)DO_2 was then calculated for each intraoperative PaO_2 as follows:

\[
(A-a)DO_2 \text{ equation}\]

The partial pressure of oxygen in the alveolus (PaO_2) is equal to the partial pressure of the oxygen inspired (PPO_2) minus the partial pressure of arterial carbon dioxide (PaCO_2):

\[
\text{PaO}_2 = \text{PPO}_2 - \text{PaCO}_2
\]

In this study, since 100% oxygen with 100% humidity was delivered to the subjects, the relative humidity must be considered and incorporated into the above equation. The equation was modified as follows:

\[
\text{PaO}_2 = \text{PPO}_2 - (\text{PaCO}_2 + \text{H}_2\text{O vapor})
\]
Using barometric pressure as 760 mmHg and the partial pressure of water vapor as 47 mmHg, the equation was further developed as follows:

$$PAO_2 = 760\text{ mmHg} - (\text{PaCO}_2 + 47\text{ mmHg})$$

By ascertaining the PaCO₂ value from blood gas measurements, the partial pressure of the alveolar oxygen can then be calculated. Once obtained, the PAO₂ value is placed into the following formula to determine the alveolar to arterial oxygen gradient, commonly called the (A-a)DO₂:

$$PAO_2 - \text{PaO}_2 = \text{DO}_2$$

Statistical analysis was accomplished using ANCOVA (baseline oxygen gradient was the covariate), with $p<0.05$ considered significant. Additionally, correlational analysis was performed to test the ability of preoperative characteritics to predict (A-a)DO₂ intraoperatively.

**Results**

The demographics of the patient population are detailed in Table I. Correlational analysis of preoperative characteristics demonstrated significance ($p<0.05$) only for the variables of age ($r = +0.8$) and room air PaO₂ ($r = -0.82$). Smoking history demonstrated a moderate correlation ($r = +0.55$) that was not considered statistically significant ($p = 0.06$). The FEV₁ and FEV₁/FVC both had poor correlations that were not clinically significant ($r = +0.36$ and $-0.35$; $p = 0.2$ and 0.24, respectively) as demonstrated in Table II.

Table I

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Range</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63</td>
<td>45-79</td>
<td>11.7</td>
</tr>
<tr>
<td>FEV₁ (liters)</td>
<td>1.94</td>
<td>1.36-3.3</td>
<td>0.5</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>65</td>
<td>48-76</td>
<td>8.8</td>
</tr>
<tr>
<td>Smoking history (pack years)</td>
<td>48</td>
<td>15-100</td>
<td>29.7</td>
</tr>
<tr>
<td>Exercise tolerance (flights of stairs)</td>
<td>1.25</td>
<td>1-2</td>
<td>0.45</td>
</tr>
<tr>
<td>Room air PaO₂ (mmHg)</td>
<td>69.7</td>
<td>58-88</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Table II

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Poor correlation</th>
<th>Moderate correlation</th>
<th>Strong correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>0.36</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>-0.35</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Smoking history</td>
<td>-</td>
<td>0.55</td>
<td>-</td>
</tr>
<tr>
<td>Exercise tolerance</td>
<td>-0.389</td>
<td>-</td>
<td>0.8</td>
</tr>
<tr>
<td>Age</td>
<td>-</td>
<td>-</td>
<td>-0.8</td>
</tr>
<tr>
<td>Room air PaO₂</td>
<td>-</td>
<td>-</td>
<td>-0.8</td>
</tr>
</tbody>
</table>

Table III

<table>
<thead>
<tr>
<th>Patients who were sighed</th>
<th>Patients who were not sighed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in (A-a)DO₂</td>
<td></td>
</tr>
<tr>
<td>+16.72</td>
<td>-19.73</td>
</tr>
</tbody>
</table>

Table III illustrates the percentage change of the mean (A-a)DO₂ relative to the first baseline value in each patient. A positive value indicates that (A-a)DO₂ improved from the baseline, whereas a negative percentage denotes that (A-a)DO₂ deteriorated. In those patients not sighed, the (A-a)DO₂ widened on the average -19.73% from the baseline values. In the patients who were sighed, the gradient was reduced an average of 16.72% from the baseline. Patients numbered 8-14 are listed as both treatment and control as they received sighs and no sighs in a crossover fashion. A significant ($p<0.05$) improvement in (A-a)DO₂ was observed in all patients who were sighed compared to those not sighed.

The four patients in Group I, who were not sighed, showed a generalized widening of (A-a)DO₂ with the passage of time (Figure 1). Group II patients (all three sighed) had serial (A-a)DO₂ values that were reduced compared to the baseline value. These values also had a tendency to decay with time, as (A-a)DO₂ values moved closer to but did...
not exceed the baseline value. Patient #7 experienced a widening of his gradient, yet with time his $(A-a)DO_2$ returned to baseline (Figure 2).

Group III was a crossover group in which all patients received sighs for two and one-half hours followed by a similar period of no sighs. Dramatic differences between sighed and non-sighed values were observed in this group (see Figure 3); sighing...
reduced the gradient and the absence of sighing widened the gradient. Group IV was subjected to a crossover pattern of alternating sighs and no sighs at 90-minute intervals. This scenario demonstrated the virtually instantaneous effect that sighing had on (A-a)DO₂. This was exemplified by a "roller coaster" effect in the observed data that paralleled the sighing pattern (see Figure 4).

**Discussion**

There are several causes of wide (A-a)DO₂, or shunt, which may involve any of the following factors:

1. Hypoventilation, leading to a rise in PACO₂ and subsequent fall in PaO₂. This was not a factor in this study since constant mechanical ventilation with normocapnia was maintained.

2. Diffusion problems: Hypoxemia due to diffusion impairment is readily overcome by oxygen administration. This was not a problem as 100% oxygen was used.

3. Maldistribution effects (increased scatter of ventilation/perfusion inequalities). Again, by using 100% oxygen this factor was rendered insignificant.

4. Fall in cardiac output at a constant rate of a metabolic oxygen consumption can produce hypoxemia. We assumed this played a minor role in this study, as narcotic anesthesia, with its inherent hemodynamic stability, was utilized. There was no observed clinical evidence of significant alterations in cardiac output. The inhalant anesthetic, isoflurane, minimally decreases cardiac output in the concentrations employed in this study.

5. Alteration in pulmonary venous blood admixture to arterial blood oxygen (shunt or widened (A-a)DO₂); two primary causes of this are general anesthesia and COPD. The contribution to shunt caused by general anesthesia alone could not be controlled. However, other factors that would amplify the shunt such as obesity, abdominal surgery, and retractors encroaching upon the lung were controlled by excluding them from the study.

The other cause of altered pulmonary venous admixture and most vital to this study is COPD. These pulmonary diseases include asthma, bronchitis, and emphysema. Common characteristics include a resistance to the flow of gases in the terminal bronchioles and destruction of alveolar walls. This destructive process leads to ventilation/perfusion inequalities and widened (A-a)DO₂. The setting of COPD was the primary focus of this study. The influence of other variables was mitigated by controlling as many factors as possible through the establishment of rigid prestudy inclusion criteria.

Preoperative spirometric studies (FEV₁ and FEV₁/FVC) were found to be poor predictors of intraoperative (A-a)DO₂. This was surprising, as many clinicians view these tests as sensitive indicators of (A-a)DO₂. Although high risk patients can be identified by these tests, patients with a moderate degree of risk are more difficult to assess. The poor correlation suggests that these tests, when considered alone, are of minimal value in predicting intraoperative (A-a)DO₂.

Smoking history showed a moderate correlation with (A-a)DO₂ values. This was expected, since the incidence of COPD is increased as the lifetime cigarette consumption extends beyond eight pack years. As smoking history increases, closing volume increases until it encroaches upon the lungs' expiratory reserve volume. Smokers breathing at normal tidal volumes experience pulmonary atelectasis and shunt, resulting in a widened (A-a)DO₂.

Age showed a strong correlation in predicting a widened (A-a)DO₂. As one ages, there is a decrease in gas exchange efficiency and a widening of (A-a)DO₂. The major contributors to this decline are reduced membrane surface area, increased membrane thickness, reduced membrane permeability and reduced capillary blood volume.

Room air PaO₂ values also showed a strong correlation in predicting the (A-a)DO₂. Many authorities believe that an isolated PaO₂ is a poor indicator of pulmonary morbidity. However, the present data suggest that if a gradient is wide on room air, then the (A-a)DO₂ will be large on 100% oxygen.

In the human COPD model studied here, sighing resulted in a significant improvement in (A-a)DO₂ compared to a non-sighed control group. Sighed patients reduced their oxygen gradients by an average of 16.72% as compared to those who were not sighed, whose gradients widened an average of 19.73%. Even small increases in the gradient in the face of an already large venous admixture may represent an intolerable burden. Thus, the importance of sighing COPD patients to prevent increases in their (A-a)DO₂ values is evident.

This study can be criticized for several different reasons. First, the sample was small; this deficiency was compensated for in several different ways. For example, entry criteria were rigid and subjects represented a highly homogenous group free from the influence of extraneous variables. Additionally, both the research design and analytical techniques were carefully selected prior to data collection; these techniques (crossover design and ANCOVA with repeat measures) are acknowledged techniques used to compensate for small sample size.
Another criticism might be that baseline (A-a)DO₂ values varied among subjects. This would have been impossible to "standardize" in a clinical investigation and the intent of this investigation was to ascertain the general effect of sighing on existing (A-a)DO₂, rather than judge a specific effect upon a given oxygen gradient. Another major criticism might be that the authors utilized (A-a)DO₂ as their barometer of sighing efficacy. However, given the enormous body of literature in favor of the (A-a)DO₂ as a measurement tool, the authors believe the study is both theoretically and clinically sound.

The authors found that sighing patients with COPD resulted in a significant improvement in (A-a)DO₂ when compared to a non-sighed control group. Even small increases in (A-a)DO₂ may be intolerable in patients with an already high gradient, while moderate increases in (A-a)DO₂ may be inconsequential in their healthy counterparts. Sighing, through mechanisms detailed above, appears to offer clinicians an effective and safe technique to optimize oxygenation in anesthetized patients. The authors recommend its routine use in patients with COPD unless its use its contraindicated (e.g., bullos emphysema), and believe that all surgical patients, even those who are without pulmonary pathophysiology, should be sighed routinely during anesthesia.

REFERENCES