Effects of sedation on clinical, gasometric, and respiratory muscle parameters in critically ill chronic obstructive pulmonary disease patients
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Background Severe chronic obstructive pulmonary disease (COPD) exacerbation requiring mechanical ventilation is commonly encountered in the ICU. Sedation is necessary to facilitate mechanical ventilation. The effect of no-sedation strategy on different patient parameters on the ventilator has not yet been well studied. The aim of this study was to test the efficacy of no-sedation protocol in controlling COPD patient’s gasometric and clinical parameters during mechanical ventilation.

Patients and methods Patients with COPD who required mechanical ventilation were randomized to either: sedated with daily interruption (control group) (n=50) or nonsedated group (n=47). The change in the partial pressure of arterial CO\textsubscript{2} (PaCO\textsubscript{2}) was the primary outcome measure. Secondary outcome measures included: changes in pH, heart rate (HR), mean arterial blood pressure (MAP), respiratory rate, airway occlusion pressure (P0.1), and negative inspiratory force (NIF). Recordings for arterial blood gases, HR, MAP, and respiratory rate were performed as baseline at intubation, 1, 2, 12, 24, and 48 h after intubation. NIF and P0.1 were recorded 48 h after intubation.

Results No significant difference was found in baseline recordings of PaCO\textsubscript{2}, pH, HR, MAP, and respiratory rate between the sedated and nonsedated groups. Further recordings of PaCO\textsubscript{2} (P\textsubscript{1}=0.9, P\textsubscript{2}<0.001, P\textsubscript{3}<0.001, P\textsubscript{4}=0.87, P\textsubscript{5}<0.001), HR (P<0.001), and respiratory rate (P<0.001) were significantly higher in the nonsedated group. The rate of correction of pH from acidosis was faster among the sedated patients. MAP was significantly higher in nonsedated patients in recordings 2, 12, and 48 h after intubation (P\textsubscript{1}=0.9, P\textsubscript{2}<0.001, P\textsubscript{3}<0.001, P\textsubscript{4}=0.87, P\textsubscript{5}<0.001). No significant difference was found in NIF or P0.1 between the two groups (P=0.8 and 0.1, respectively).

Conclusion COPD patients managed by no-sedation strategy had higher PaCO\textsubscript{2}, HR, MAP, and respiratory rate. No-sedation had no significant effect on respiratory muscle function when compared with daily interruption of sedation. Egyt J Bronchol 2019 13:328–334 © 2019 Egyptian Journal of Bronchology


Keywords: chronic obstructive pulmonary disease, intensive care, mechanical ventilation, sedation

Introduction Chronic obstructive pulmonary disease (COPD) represents a major health problem worldwide. Its global prevalence is estimated to be 11.7\% [1], accounting for three million deaths annually [2]. Severe COPD exacerbations requiring mechanical ventilation represent a considerable percentage of ICU admissions [3,4]. Sedation is necessary to facilitate intubation, spend smooth stay on the ventilator, and avoid asynchrony. No-sedation has been suggested recently in randomized, controlled trials [5,6]. It was found that no-sedation protocol increased ventilator-free days and reduced ICU stay [5]. The effect of no-sedation strategy on patient blood gases, and clinical and respiratory muscle parameters is still unknown. Our aim was to test the effect of sedation on pH, partial pressure of arterial CO\textsubscript{2} (PaCO\textsubscript{2}), clinical and respiratory muscle parameters in mechanically ventilated COPD patients.

This study aimed to test the effectiveness and safety of no-sedation protocol in controlling COPD patients’ parameters on a ventilator.

Patients and methods This is a randomized, controlled trial conducted in the respiratory ICU. The study was approved by the local ethics committee. A written consent was taken from the patient or his legal representative for participation. If permission was given by the patient’s representative, information and consent was obtained from the patient after discharge from the ICU. It was registered at Clinicaltrials.gov under the number NCT03678532. COPD patients admitted to the respiratory ICU for mechanical ventilation were included. Exclusion criteria were: marked renal impairment (creatinine >2 mg/dl), liver cell failure (bilirubin >3 mg/dl), central nervous system disorders, age less than 18 years or more than 70 years and pregnancy.

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Ninety-seven critically ill COPD patients undergoing mechanical ventilation admitted to the respiratory ICU were included in the present study. History, clinical examination, and chest radiography were done for all patients. Spirometry was performed if possible after discharge from the ICU. The patient to nurse ratio is 2:1. Eligible patients were expected to need mechanical ventilation for more than 24 h.

The patients were randomly allocated to two groups (sedated and nonsedated groups). Midazolam was used for sedation in both groups. Richmond agitation and sedation score (RASS) [7] was used to monitor the sedation or agitation level. The control group received sedation with daily interruption. After intubation, the patients received intravenous infusion of midazolam, gradually increasing dose till RASS reached −4 or −5 [infusion rate at 1–2 mg/h; to be increased in increments of 1–2 mg/h until adequate sedation is achieved (RASS>−3)]. Infusion stopped at 7:00

Table 1 Demographic data and patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sedation group (N=50)</th>
<th>No-sedation group (N=47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>41 (82)</td>
<td>33 (70)</td>
<td>0.17</td>
</tr>
<tr>
<td>Female</td>
<td>9 (18)</td>
<td>14 (30)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.5±8</td>
<td>62.4±9</td>
<td>0.08</td>
</tr>
<tr>
<td>Smoking status [n (%)]</td>
<td></td>
<td></td>
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<tr>
<td>Nonsmokers</td>
<td>10 (20)</td>
<td>14 (29.8)</td>
<td>0.15</td>
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<tr>
<td>Current smokers</td>
<td>18 (36)</td>
<td>21 (44.7)</td>
<td></td>
</tr>
<tr>
<td>Exsmokers</td>
<td>22 (44)</td>
<td>12 (25.5)</td>
<td></td>
</tr>
<tr>
<td>Indication for MV [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO2 narcosis</td>
<td>32 (64)</td>
<td>30 (63.8)</td>
<td>0.27</td>
</tr>
<tr>
<td>Severe respiratory</td>
<td>10 (20)</td>
<td>7 (14.9)</td>
<td></td>
</tr>
<tr>
<td>distress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiorespiratory</td>
<td>6 (12)</td>
<td>3 (6.4)</td>
<td></td>
</tr>
<tr>
<td>arrest</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other indications</td>
<td>2 (4)</td>
<td>7 (14.9)</td>
<td></td>
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<tr>
<td>APACHE-II score</td>
<td>18.7±0.3</td>
<td>19.6±3.8</td>
<td>0.2</td>
</tr>
</tbody>
</table>

P value less than 0.05 is considered statistically significant.

Figure 1

Effect of sedation on CO2. Data are expressed as means±SD. Group A: sedation group, group B: no-sedation group. P value less than 0.05 is considered statistically significant. CO2_0=baseline PaCO2 at intubation, CO2_1 is PaCO2 1 h after intubation, CO2_2 is PaCO2 2 h after intubation, CO2_3 is PaCO2 12 h after intubation, CO2_4 is PaCO2 24 h after intubation, CO2_5 is PaCO2 48 h after intubation. PaCO2, partial pressure of arterial CO2.
AM. If the patient was awake, there was no need for resuming infusion. If there were signs of discomfort, infusion returned at half of the previous dose, targeting conscious sedation (RASS 0, −3). Signs of discomfort included: agitation (RASS ≥1), increased respiratory rate of more than 35 breaths/min, decreased SpO₂ of less than 90%, increase in heart rate (HR) of more than 140 beats/min (or a change of 20% in either direction), systolic blood pressure of more than 180 mmHg, increased anxiety, and diaphoresis.

Intervention group was managed by the protocol of no-sedation. Patients received bolus doses of midazolam only when needed (1–5 mg), after a trial to control agitation by correcting the underlying cause if present. If the patient needed more than three bolus doses, intravenous infusion of midazolam was started by the daily interruption strategy as in the control group. Crossover was not allowed between groups. Analysis was done by the principle of intention-to-treat. Ventilator settings were adjusted according to the required local ventilatory strategy for COPD patients.

Arterial blood gas sampling was done as a baseline measure at intubation, 1, 2, 12, 24, and 48 h after intubation. Recording of clinical monitoring parameters [HR, mean arterial blood pressure (MAP), and respiratory rate] was done at the same intervals. Affection of respiratory muscles was assessed by measurement of the negative inspiratory force (NIF) and airway occlusion pressure (P₀.₁), 48 h after intubation. NIF is defined as maximum pressure that can be generated against an occluded airway [8]. NIF was measured three times and the most negative result was recorded. P₀.₁ is defined as the inspiratory depression of airway pressure, achieved after 100 ms of occlusion [8]. P₀.₁ was measured five times over a period of 60–90 s and the average of the five measurements was calculated and recorded [9].

Outcome measures
Primary outcome measure was determined by changes in PaCO₂. Secondary outcome measures included: changes in pH, HR, MAP, respiratory rate, NIF, and P₀.₁.

![Figure 2](image_url)

Effect of sedation on pH. Data are expressed as mean±SD. Group A: sedation group, group B: no-sedation group. P value less than 0.05 is considered statistically significant. pH₀ = baseline pH at intubation, pH₁ is pH 1 h after intubation, pH₂ is pH 2 h after intubation, pH₃ is pH 12 h after intubation, pH₄ is pH 24 h after intubation, and pH₅ is pH 48 h after intubation.
**Statistical analysis**
Data analysis was done using SPSS for Windows statistical package, version 19.0 (IBM Corp., Armonk, NY). Data were analyzed by intention to treat. The $P$ value was considered significant if less than or equal to 0.05.

**Results**
Table 1 demonstrates that there was no significant difference between both groups as regards demographic data and patient characteristics.

Regarding the arterial blood gases, sedated patients had lower $\text{PaCO}_2$ levels than those managed by the no-sedation protocol. Rate of correction of pH was faster in sedated patients as well (Figs 1 and 2, respectively).

As regards clinical parameters, sedated patients had significantly lower HR than nonsedated patients as evident from Fig. 3. Regarding the MAP, most MAP readings were significantly lower among the sedated group, in comparison to the nonsedated group (Fig. 4). Also, respiratory rate was significantly lower in the sedated group (Fig. 5). As regards respiratory muscle determinants, no significant difference was found in NIF or P0.1 between the two groups (Table 2).

**Discussion**
The current study focused on testing the effect of sedation on controlling patient parameters on the ventilator. COPD patients were randomly assigned to either: sedation with daily interruption or no-sedation. In the present study it was found that $\text{PaCO}_2$ readings were significantly lower in sedated patients. Rate of correction of pH from respiratory acidosis to normal range was faster in patients who received sedation. As regards clinical parameters, patients who received sedation had significantly lower HR, MAP, and respiratory rate.

It is clear that sedation strategy worldwide is moving toward minimizing sedation in critically ill patients.

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**Figure 3**

![HR Graph](image_url)

Effect of sedation on HR. HR: heart rate. Data are expressed as means±SD. Group A: sedation group. Group B: no-sedation group. $P$ value less than 0.05 is considered statistically significant. $HR_0$=baseline heart rate at intubation, $HR_1$=heart rate 1 h after intubation, $HR_2$=heart rate 2 h after intubation, $HR_3$=heart rate 12 h after intubation, $HR_4$=heart rate 24 h after intubation, and $HR_5$=heart rate 48 h after intubation.
No-sedation has been proposed recently by Strøm et al. [5]. They found that no-sedation protocol increased ventilator-free days and reduced ICU stay. However, it increased the incidence of delirium, and this refers to the fact that patient comfort during mechanical ventilation without sedation is questionable.

One of the limitations of using no-sedation protocol is that it may increase patient suffering on the ventilator. Pain and stress during mechanical ventilation result in anxiety and increased catecholamine release [10], which in turn result in rise in HR, blood pressure, and respiratory rate. This may adversely affect patient clinical parameters during mechanical ventilation. Increased patient suffering without sedation may result in increased incidence of delirium as evident in the Strøm et al. [5] study. Sedation by benzodiazepines has the advantage of retrograde amnesia [11]. This benefits mechanically ventilated patients to forget their stressful experience on the ventilator. A US National Survey conducted by Guttormson et al. [12] demonstrated that most nurses consider mechanical ventilation to be stressful and that sedation is required to ensure patient comfort.

A post-hoc analysis was conducted by Strøm et al. [13] based on their previous study [5]. A total of 103 patients were included in their retrospective review. They found no statistically significant difference in MAP. The results of the current study disagree with Strøm and his colleague’s trial in that a significant modest increase in most MAP readings was found in nonsedated patients. The concept of patient comfort may be not well achieved in nonsedated patients, which can explain this slightly higher MAP, which may be clinically insignificant.

The results of the present study agreed with that conducted by Nortvedt and colleagues who explored the ethical issues regarding managing patients with no-sedation protocol. They stated that no-sedation might increase patient suffering during mechanical ventilation [14].
Bassuoni and colleagues studied 230 patients in a surgical ICU, comparing no-sedation versus daily interruption of sedation. They observed increased respiratory rate in nonsedated patients, which agrees with the current study. They found that no-sedation protocol was associated with higher double triggering and increased patient’s effort during triggering [15], but they found that patients managed by no-sedation strategy had significantly lower PaCO₂ levels. This form of ventilator asynchrony can explain the higher CO₂ in nonsedated patients in the present study. This suggests that patient comfort is not achieved in patients managed with no-sedation protocol. In contrast to the present study, they found that patients managed by no-sedation strategy had significantly lower PaCO₂ levels. This controversy in this item can be explained by the difference in the study design. While the present study included only COPD patients, Bassuoni and colleagues excluded those with COPD.

Kress and colleagues agree with the current study. They compared periods of sedative interruption and periods of infusion regarding clinical and hemodynamic parameters. They found that HR, MAP, and respiratory rate were significantly higher during the interruption [16]. This agreed with the present study findings, where significantly higher HR, MAP, and respiratory rate in nonsedated patients were observed. They also found a marked increase in the levels of epinephrine, norepinephrine, and dopamine relative to the baseline levels in patients who were not receiving exogenous vasoactive drug infusions. The present study and that of Kress and his colleagues suggested that less sedation may adversely affect patient hemodynamics,

Table 2 Effect of sedation on respiratory muscle determinants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sedation group</th>
<th>No-sedation group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIF (cmH₂O)</td>
<td>3.5±1.1</td>
<td>3.4±1.4</td>
<td>0.8</td>
</tr>
<tr>
<td>P0.1 (cmH₂O)</td>
<td>−27.5±5.5</td>
<td>−24.57±11.6</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. NIF, negative inspiratory force; P0.1, airway occlusion pressure. P value less than 0.05 is considered statistically significant.
due to increased suffering. These results raise questions about the safety of no-sedation in critically ill patients and emphasize on the importance of achieving patient comfort.

Regarding the respiratory muscle function, no significant difference was found in the present study in NIF or P0.1 between the two groups. This suggested that respiratory muscle function is not affected by sedation. Further research is needed to elucidate the effect of sedation on respiratory muscles.

The value of the current study is that it was done on a special type of medical patients suffering from respiratory failure. It was focused on one disease affecting one system (the respiratory system), and on patient comfort during mechanical ventilation, which is important to ensure sound stay on the ventilator and to avoid long-term psychological sequelae.

A multicenter trial with more number of patients is needed to validate the present results.

Further research is needed to test the safety of no-sedation strategy in critically ill patients. Further research is required to determine the optimum sedation protocol that should be used in patients with respiratory failure, especially those with COPD.

Conclusion
No-sedation strategy is associated with significantly higher PaCO2, HR, MAP, and respiratory rate in COPD mechanically ventilated patients. No significant difference was found in respiratory muscle function. Minimizing sedation may not affect the overall patient outcome but may have adverse effects on patient comfort on the ventilator.

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Conflicts of interest
There are no conflicts of interest.

References