Effects of sedation on clinical, gasometric, and respiratory muscle parameters in critically ill chronic obstructive pulmonary disease patients

Atef F. Alkarn[a], Mohamed F. Abdelghany[a], Mohammad G.A. Khalaf[a], Emad Z. Kamel[b], Wafaa A.H. Gadalla[a]

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_2 ($PaCO_2$) 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 $PaCO_2$, pH, HR, MAP, and respiratory rate between the sedated and nonsedated groups. Further recordings of $PaCO_2$ (P_1, P_2, P_3, and P_4$<$0.001, P_5=0.005), HR ($P<0.001$), and respiratory rate ($P<0.001$) were significantly higher in the nonsedated group. The rate of correction of pH from acidosis was faster among the sedated patients. MAP was significantly higher in nonsedated patients in recordings 2, 12, and 48 h after intubation (P_1=0.9, P_2$<$0.001, P_3$<$0.001, P_4=0.87, P_5$<$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 $PaCO_2$, HR, MAP, and respiratory rate. No-sedation had no significant effect on respiratory muscle function when compared with daily interruption of sedation.
Egypt J Bronchol 2019 13:328–334

Egyptian Journal of Bronchology 2019 13:328–334

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

Departments of, [a]Chest Diseases, [b]Anesthesia and Critical Care, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Mohammad G.A. Khalaf, MD (Lecturer) Chest Diseases, Department of Chest Diseases, Assiut University Hospital, Assiut 71515, Egypt. Tel: +20 882 413 709; Fax: +20 882 333 327; e-mail: dr.mga2011@au.edu.eg

Received 12 October 2018 **Accepted** 3 February 2019

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_2 ($PaCO_2$), 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.

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.

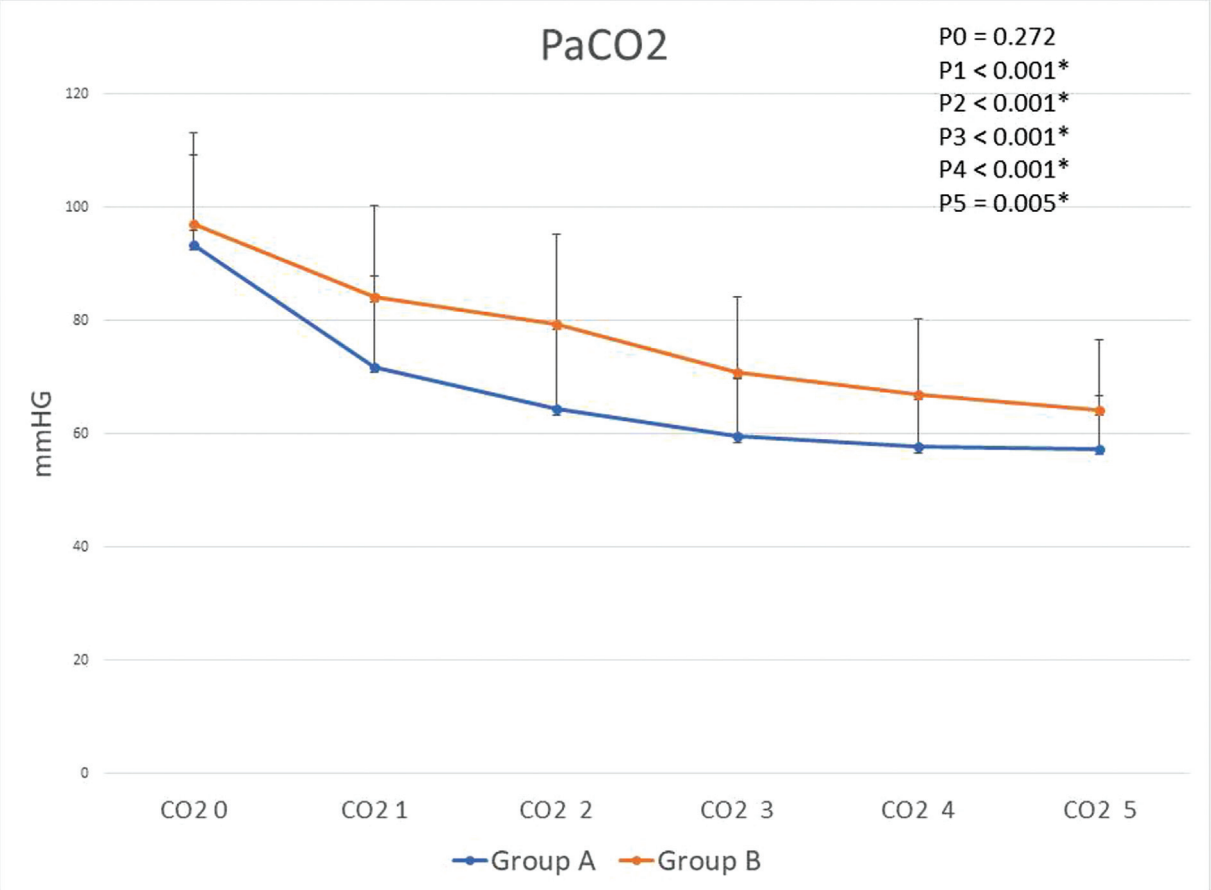
The patients were randomly allocated to two groups (sedated and nonsedated groups). Midazolam was used for sedation in both groups. Richmond agitation and sedation score (RASS) [7] was used to monitor the sedation or agitation level. The control group received sedation with daily interruption. After 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

	Sedation group (*N*=50)	No-sedation group (*N*=47)	*P* value
Sex [*n* (%)]			
Male	41 (82)	33 (70)	0.17
Female	9 (18)	14 (30)	
Age (years)	63.5±8	62.4±9	0.08
Smoking status [*n* (%)]			
Nonsmokers	10 (20)	14 (29.8)	0.15
Current smokers	18 (36)	21 (44.7)	
Exsmokers	22 (44)	12 (25.5)	
Indication for MV [*n* (%)]			
CO_2 narcosis	32 (64)	30 (63.8)	0.27
Severe respiratory distress	10 (20)	7 (14.9)	
Cardiorespiratory arrest	6 (12)	3 (6.4)	
Other indications	2 (4)	7 (14.9)	
APACHE-II score (mean±SD)	18.7±0.3	19.6±3.8	0.2

P value less than 0.05 is considered statistically significant.

Figure 1



Effect of sedation on CO_2. 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. CO_2_0=baseline $PaCO_2$ at intubation, CO_2_1 is $PaCO_2$ 1 h after intubation, CO_2_2 is $PaCO_2$ 2 h after intubation, CO_2_3 is $PaCO_2$ 12 h after intubation, CO_2_4 is $PaCO_2$ 24 h after intubation, CO_2_5 is $PaCO_2$ 48 h after intubation. $PaCO_2$, partial pressure of arterial CO_2.

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 SpO_2 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.

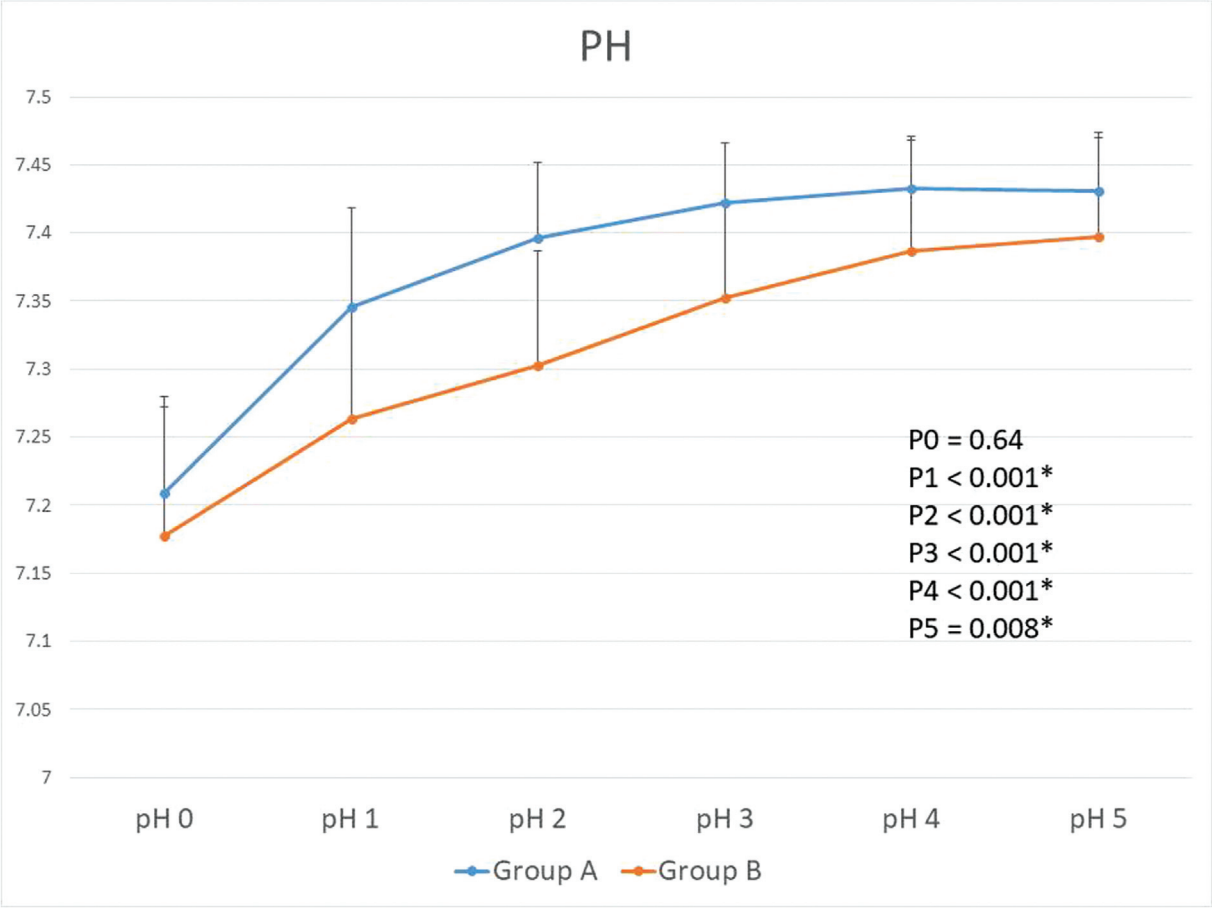
Intervention group was managed by the protocol of no-sedation. Patients received bolus doses of midazolam only when needed (1–5 mg), after a trial to control agitation by correcting the underlying cause if present. If the patient needed more than three bolus doses, intravenous infusion of midazolam was started by the daily interruption strategy as in the control group. Crossover was not allowed between groups. Analysis was done by the principle of intension-to-treat. Ventilator settings were adjusted according to the required local ventilatory strategy for C OPD 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 $PaCO_2$. Secondary outcome measures included: changes in pH, HR, MAP, respiratory rate, NIF, and P0.1.

Figure 2



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. pH_0=baseline pH at intubation, pH_1 is pH 1 h after intubation, pH_2 is pH 2 h after intubation, pH_3 is pH 12 h after intubation, pH_4 is pH 24 h after intubation, and pH_5 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 $PaCO_2$ 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

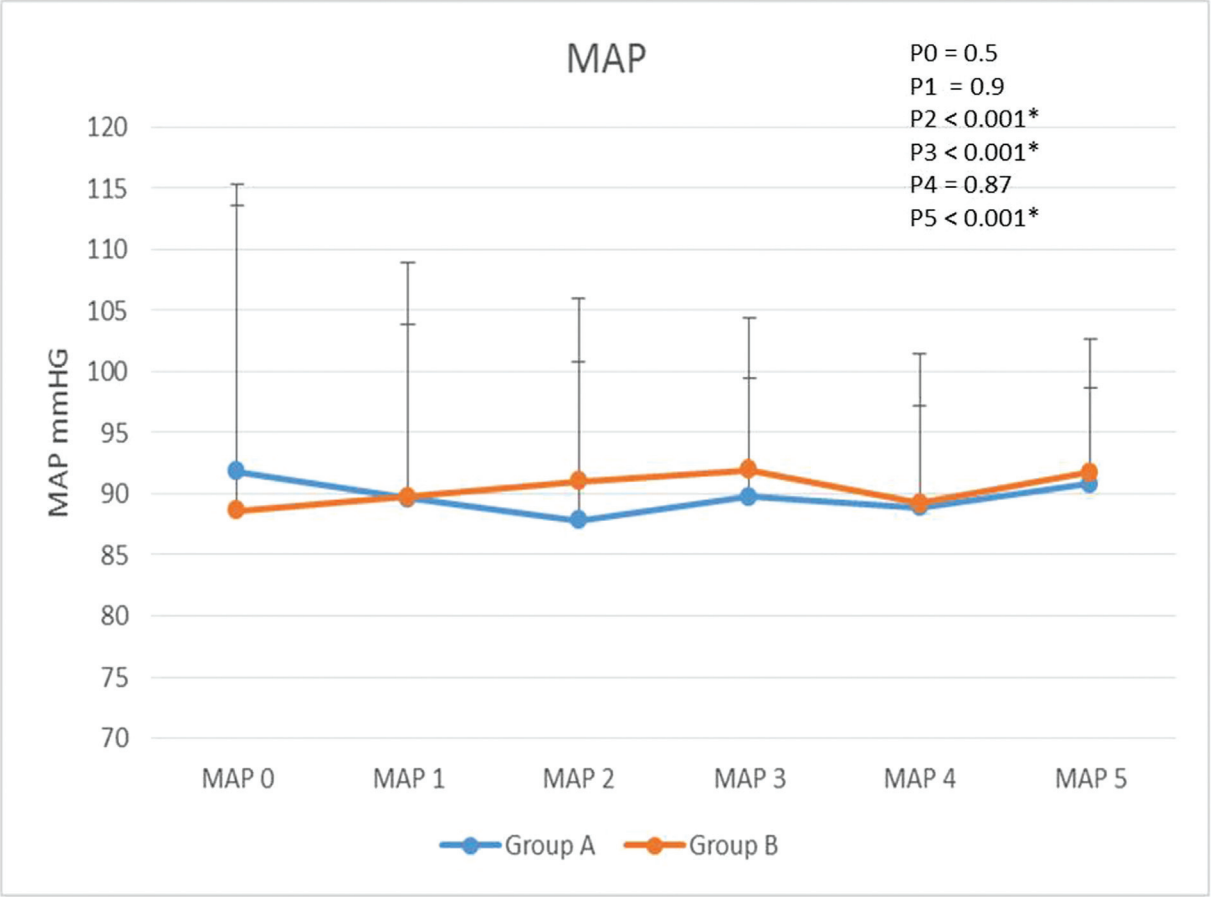
The current study focused on testing the effect of sedation on controlling patient parameters on the ventilator. COPD patients were randomly assigned to either: sedation with daily interruption or no-sedation. In the present study it was found that $PaCO_2$ readings were significantly lower in sedated 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.

Figure 3

Effect of sedation on HR. HR: heart rate. 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. 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.

Figure 4



Effect of sedation on MAP. MAP, mean arterial blood pressure. Group A=sedation group, group B=no-sedation group. Data are expressed as mean±SD. *P* value less than 0.05 is considered statistically significant. MAP_0=baseline MAP at intubation, MAP_1=MAP 1 h after intubation, MAP_2=MAP 2 h after intubation, MAP_3=MAP 12 h after intubation, MAP_4=MAP 24 h after intubation, and MAP_5=MAP 48 h after intubation.

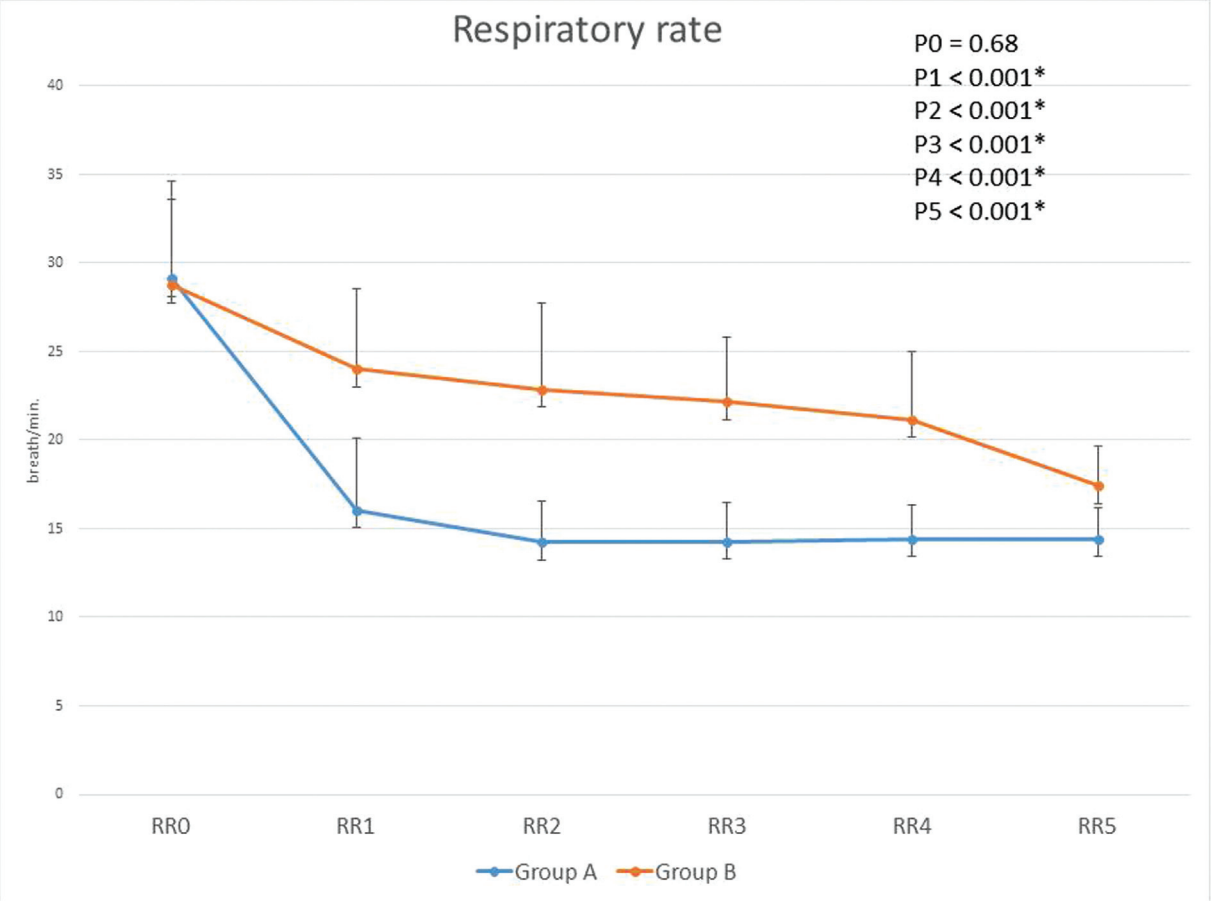
No-sedation has been proposed recently by Strøm *et al.* [5]. They found that no-sedation protocol increased ventilator-free days and reduced ICU stay. However, it increased the incidence of delirium, and this refers to the fact that patient comfort during mechanical ventilation without sedation is questionable.

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].

Figure 5



Effect of sedation on respiratory rate. Group A=sedation group, group B=no-sedation group. Data are expressed as mean±SD. *P* value less than 0.05 is considered statistically significant. RR0=baseline respiratory rate at intubation, RR1=respiratory rate 1 h after intubation, RR2=respiratory rate 2 h after intubation, RR3=respiratory rate 12 h after intubation, RR4=respiratory rate 24 h after intubation, and RR5=respiratory rate 48 h after intubation.

Table 2 Effect of sedation on respiratory muscle determinants

	Sedation group	No-sedation group	*P* value
NIF (cmH_2O)	3.5±1.1	3.4±1.4	0.8
P0.1 (cmH_2O)	–27.5±5.5	–24.57±11.6	0.1

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.

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 $PaCO_2$ levels. This form of ventilator asynchrony can explain the higher CO_2 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 $PaCO_2$ 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,

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 $PaCO_2$, 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.

Acknowledgements

The authors acknowledge the nursing staff of the respiratory ICU for their efforts in patients' care and for supporting their research.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflcits of interest.

References

1 Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, *et al.* Global and regional estimates of COPD prevalence: systematic review and meta-analysis. *J Glob Health* 2015; **5**:020415.?

2 Abubakar II, Tillmann T, Banerjee A. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **385**:117–171.

3 Liao KM, Chen YC, Cheng KC, Wang JJ, Ho CH. Trends in intensive care unit admissions of COPD patients from 2003 to 2013 in Taiwan. *Int J Chron Obstruct Pulmon Dis* 2018; **13**:2007.

4 Schmidt M, Demoule A, Deslandes-Boutmy E, Chaize M, De Miranda S, Bèle N, *et al.* Intensive care unit admission in chronic obstructive pulmonary disease: patient information and the physician's decision-making process. *Crit Care* 2014; **18**:R115.

5 Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet* 2010; **375**:475.

6 Laerkner E, Strøm T, Toft P. No-sedation during mechanical ventilation: impact on patient's consciousness, nursing workload and costs. *Nurs Crit Care* 2016; **21**:28–35.

7 Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'neal PV, Keane KA, *et al.* The Richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; **166**:1338–1344.

8 Conti G, Antonelli M, Arzano S, Gasparetto A. Equipment review: measurement of occlusion pressures in critically ill patients. *Crit Care* 1997; **1**:89.

9 Metwally A, Hussein K, El-Abdeen AZ, Hamed A, Ez-Eldeen A. The impact of pulmonary functions on outcome of intubated patients with chronic obstructive pulmonary disease. *Egypt J Bronchol* 2015; **9**:125.

10 Hughes CG, McGrane S, Pandharipande PP. Sedation in the intensive care setting. *Clin Pharmacol* 2012; **4**:53.

11 Beracochea D. Anterograde and retrograde effects of benzodiazepines on memory. *Sci World J* 2006; **6**:1460–1465.

12 Guttormson JL, Chlan L, Weinert C, Savik K. Factors influencing nurse sedation practices with mechanically ventilated patients: a US national survey. *Intensive Crit Care Nurs* 2010; **26**:44–50.

13 Strøm T, Johansen RR, Prahl JO, Toft P. Sedation and renal impairment in critically ill patients: a post hoc analysis of a randomized trial. *Crit Care* 2011; **15**:R119.

14 Nortvedt P, Kvarstein G, Jønland I. Sedation of patients in intensive care medicine and nursing: ethical issues. *Nurs Ethics* 2005; **12**:522–536.

15 Bassuoni AS, Elgebaly AS, Eldabaa AA, Elhafz AA. Patient-ventilator asynchrony during daily interruption of sedation versus no sedation protocol. *Anesth Essays Res* 2012; **6**: 151.

16 Kress JP, Vinayak AG, Levitt J, Schweickert WD, Gehlbach BK, Zimmerman F, *et al.* Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. *Crit Care Med* 2007; **35**:365–371.