

## **Influence of inspired oxygen concentration on PaCO<sub>2</sub> during noninvasive ventilation in patients with chronic obstructive pulmonary disease**

**Running title:** oxygen therapy for COPD patients during NIV

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The authors have no commercial associations which impact on this work.

**Conflict of Interest**

The authors have disclosed no conflicts of interest.

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## ABSTRACT

*Background:* The administration of a high inspired oxygen concentration (FIO<sub>2</sub>) to chronic obstructive pulmonary disease (COPD) patients breathing spontaneously may result in hypercapnia; due to reversal of preexisting regional hypoxic pulmonary vasoconstriction resulting in a greater deadspace. In these patients, during noninvasive ventilation (NIV), the arterial gases behavior was not previously studied.

*Objectives:* To investigate the response of CO<sub>2</sub>-retaining COPD patients, after acute respiratory crisis stabilization using noninvasive ventilation (NIV), to a high inspired oxygen concentration (FIO<sub>2</sub> = 1.0) after having been noninvasively ventilated with FIO<sub>2</sub> ≤ 0.50 for a period of time.

*Design:* Experimental prospective study.

*Setting:* A 18-bed medical-ICU in a university teaching hospital.

*Patients:* CO<sub>2</sub>-retaining COPD patients recovering from acute respiratory failure using NIV.

*Interventions:* FIO<sub>2</sub> increased to 1.0.

*Measurements and Main Results:* Seventeen NIV-ventilated CO<sub>2</sub>-retaining COPD patients were studied both at their baseline FIO<sub>2</sub> (0.25 to 0.50), and following a 40-min period of exposure to an FIO<sub>2</sub> of 1.0. Mean (±SD) baseline findings were: PaO<sub>2</sub> of 101.4 ± 21.7mmHg, PaCO<sub>2</sub> of 52.6 ± 10.4mmHg, respiratory rate (RR) of 17.8 ± 3.7breaths/min, tidal volume (V<sub>T</sub>) of 601 ± 8mL, and Glasgow coma scale (GCS) of 14.8 ± 0.3. Statistical analysis using the paired Student's t-test showed that the PaO<sub>2</sub> (290.5 ± 35.7mmHg; p <0.001) increased significantly when the FIO<sub>2</sub> was increased to 1.0, but there was no significant change in PaCO<sub>2</sub> (51.5 ± 12.3mmHg), RR (17.5 ± 2.8breaths/min), V<sub>T</sub> (608 ± 8mL) and GCS (14.8 ± 0.3).

*Conclusion:* These results show that during noninvasive ventilation with an FIO<sub>2</sub> sufficient to maintain a normal PaO<sub>2</sub>, a further increase in FIO<sub>2</sub> does not result in an increased PaCO<sub>2</sub> in this group of CO<sub>2</sub>-retaining COPD patients.

## INTRODUCTION

General principles guide the management of chronic obstructive pulmonary disease (COPD) patients presenting acutely to the intensive care unit (ICU): treat precipitating factors (eg, infection); increase expiratory flow (eg, beta agonists use); reduce pulmonary inflammation (eg, corticosteroid use); and manage gas exchange (eg, improve oxygenation) [1]. However, the administration of high inspired oxygen concentration ( $FIO_2$ ) to these patients may result in hypercapnia [2-6]. The reasons for this effect have been debated for many years, with some advocating a reduction in respiratory drive from the carotid chemo receptors, and others citing a worsening ventilation-perfusion match as the cause [7].

Noninvasive ventilation (NIV) has a number of potentially beneficial effects in COPD. It seems reasonable to expect that it would increase tidal volume ( $V_T$ ), improve  $CO_2$  elimination, and hence reduce respiratory drive [8]. Published data provide a reasonable series of recommendations based on the relative effectiveness of NIV in COPD patients: reduction of treatment failure, lower mortality, fewer complications, and lower intubation rate comparing with conventional medical treatment [9]. In these patients, the  $CO_2$  elimination is increased but overall ventilation-perfusion mismatch is not changed during NIV [10]. A more important effect is the unloading of the respiratory muscles, which are often close to fatigue conditions in severe episodes of respiratory failure [11]. Crossley et al [12] conclude that  $CO_2$ -retaining COPD patients following a period of mechanical ventilation with  $PaO_2$  in the normal range can safely receive oxygen supplementation without retaining  $CO_2$  or a depression of respiratory drive occurring. A new ventilation/perfusion relationship is established during ventilation to normoxia and it is not altered by further increasing the  $FIO_2$ . Nevertheless, the safety of oxygen supplementation during NIV use in  $CO_2$ -retaining COPD patients is not clear yet.

Our objective was to study the response of  $PaCO_2$  in retaining COPD patients to a high  $FIO_2$  (of 1.0) recovering from acute respiratory crisis using NIV, after having been noninvasively ventilated with  $FIO_2 \leq 0.5$  for a period of time.

## MATERIALS AND METHODS

## Subjects

Following hospital ethics committee approval and after obtaining informed consent, we studied 17 COPD subjects admitted to a 31-bed medical-ICU in a primary care hospital who required NIV during treatment of acute respiratory failure (ARF). The subjects were all chronic CO<sub>2</sub>-retaining COPD patients, as defined by a resting PaCO<sub>2</sub> of  $\geq 45$  mmHg, previous hospital stay due to ARF-related COPD with history of narcosis related to oxygen delivery. The diagnosis of COPD was based on history, physical examination, chest radiograph, and previous pulmonary function tests (if available). These subjects had all received a period of ventilatory support with bilevel pressure ventilator (BiPAP Vision; Respironics) delivered by a full face mask (Performa Trak; Respironics) during at least 24 hours, until stabilization of ARF.

## Protocol

The study was conducted only after stabilization of ARF, and clinical judgment of no risk of intubation. Before start the experiment, the noninvasive ventilator was calibrated using specific equipment (VT Plus-HF Gas flow analyzer, Fluke Biomedical, USA). Leakage of ventilatory circuit was tested to calibrate the exhalation port (Whisper Swivel II, Respironics). The full face mask was positioned to permit a leak up to 20L/min. Bilevel pressure ventilators were set in the spontaneous/timed mode, with a positive end-expiratory pressure (PEEP)  $\geq 5$  cm H<sub>2</sub>O, and peak inspiratory pressure (PIP)  $\geq 10$  cmH<sub>2</sub>O, targeting and guarantying a tidal volume ( $V_T$ )  $\geq 8$  mL/kg. The FIO<sub>2</sub> was adjusted to maintain SpO<sub>2</sub>  $\geq 90\%$ . Subjects were excluded if they or their family refused to give consent, if they were uncooperative, needed of intubation or requiring MV.

Demographic and background information included age, gender, weight, primary disease process, and predicted risk of death based on admission Acute Physiology and Chronic Health Evaluation (APACHE) II score. The subjects were given nothing by mouth for at least 4 hours before the study, were clinically stable, and remained on their usual treatment regimen. Baseline parameters for study purposes included  $V_T$ , and respiratory rate (RR), means of all cycles during minute volume ( $V_E$ ) measurement, and arterial blood gases (ABG). Arterial blood gases were measured on a

blood gas analyzer (ABL 520 Radiometer – Copenhagen, Denmark). SpO<sub>2</sub> was measured using a pulse oximeter (66S, Hewlett Packard, Waltham, MA).

The study involved increasing the baseline FIO<sub>2</sub> up to 100% oxygen. No other parameters were altered. Following 40 minutes at an FIO<sub>2</sub> of 1.0, the V<sub>T</sub>, RR, V<sub>E</sub>, ABG, and SaO<sub>2</sub> were again recorded, as well changes in mental status (evaluating Glasgow coma score [GCS]). The subjects were then returned to their baseline FIO<sub>2</sub>. They were not aware of any changes to their FIO<sub>2</sub> being made.

### Statistical analysis

All data were expressed as mean ± standard deviation (SD) for continuous variables. Differences between the baseline and FIO<sub>2</sub> of 1.0 were analyzed with the use of paired *t*-test, except for GCS that was analyzed with Wilcoxon signed rank test. All statistical analysis was performed by a statistician using the commercially available software (SPSS 16.0, SPSS, Chicago, Illinois). Statistical significance was set at *p* < 0.05.

## RESULTS

Of the 17 subjects admitted to the medical-ICU in the study, nine were due to pneumonia, and eight were admitted for exacerbations of COPD. No subjects had to be withdrawn from the study. At the commencement of the study, all subjects were ventilating with NIV, and receiving an FIO<sub>2</sub> of 0.25 to 0.5. The demographic data, APACHE II score, and baseline FIO<sub>2</sub> during NIV are shown in Table 1.

In these 17 CO<sub>2</sub>-retaining COPD subjects, an increase in FIO<sub>2</sub> from baseline to 1.0 caused a statistically significant increase in the subject's PaO<sub>2</sub> (101.4 ± 21.7mmHg vs. 290.5 ± 35.7mmHg; *p* <0.001) and in SpO<sub>2</sub> (94.3 ± 2.8% vs. 98.8 ± 0.8%; *p* <0.001). There was no significant difference in any of the other parameters measured (V<sub>T</sub>, RR, V<sub>E</sub>, pH, or PaCO<sub>2</sub>) or GCS at the two FIO<sub>2</sub> levels (Table 2).

The baseline PaCO<sub>2</sub> of 52.6 ±10.4mmHg was unchanged (51.5 ±12.3mmHg) at an FIO<sub>2</sub> of 1.0. We considered that an increase in PaCO<sub>2</sub> of 5 mmHg would indicate a

clinically significant degree of CO<sub>2</sub> retention when the FIO<sub>2</sub> was increased from baseline to 1.0. The SD of the difference between the PaCO<sub>2</sub> recordings at the two different FIO<sub>2</sub> levels was 4mmHg. For a paired sample of 17 patients, this study has a power of 99%.

## DISCUSSION

Our results support the hypothesis that increase in the FIO<sub>2</sub> in CO<sub>2</sub>-retaining COPD subjects ventilated with NIV do not cause any clinically significant degree of CO<sub>2</sub> retention.

A COPD-acute exacerbation is defined as a patient with a sustained worsening of dyspnea, cough or sputum production [13]. Expiratory airflow obstruction is worsened, the work of breathing (WOB) increases, and mucus production or mucociliary clearance, or both, are altered. Spirometry shows worsened expiratory airflow obstruction, whereas ABG usually demonstrate an additional decrease in the PaO<sub>2</sub> that leads to pulmonary arterial vasoconstriction and pulmonary hypertension [14].

Administration of controlled oxygen therapy is the single most useful treatment in COPD-induced hypercapnic ARF, and supplemental oxygen therapy should be administered to all hypoxemic patients who present with an acute exacerbation. The use of supplemental oxygen leads to (a) a decrease in anaerobic metabolism and lactic acid production; (b) an improvement in brain function; (c) a decrease in cardiac arrhythmias and ischemia; (d) a decrease in pulmonary hypertension; (e) an improvement in right-sided heart function with improvement in right-sided heart failure; (f) a decrease in the release of antidiuretic hormone and an increase in the kidneys' ability to clear free water; (g) a decrease in the formation of extravascular lung water (i.e., pulmonary edema); (h) an improvement in survival; and (i) a decrease in red blood cell mass and hematocrit [14, 15].

The PaCO<sub>2</sub> commonly rises somewhat when a patient with COPD receives supplemental oxygen [16], but carbon dioxide narcosis due to oxygen therapy is uncommon, and patients should not be kept hypoxemic for fear that oxygen therapy

could aggravate carbon dioxide retention [17]. The increase of CO<sub>2</sub> is probably due to a change in dead space or shift of the hemoglobin-oxygen binding curve rather than decreased respiratory drive [18]. This expected rise should not be specifically treated unless it is excessive, resulting in a trend toward acute respiratory acidosis on serial ABG determinations, with central nervous system or cardiovascular side effects. Carbon dioxide narcosis may occur with excessive oxygen therapy but is much less likely with low-flow-controlled oxygen therapy [14].

Previously, authors studied the behavior of PaCO<sub>2</sub> during increases of FIO<sub>2</sub> in COPD-patients ventilating spontaneously [19-23] and supported by MV [12], but PaCO<sub>2</sub> behavior during NIV had not yet been investigated. Sassoon et al. [19] in 17 stable-COPD patients demonstrated that when the mean FIO<sub>2</sub> was increased to 0.94, the PaCO<sub>2</sub> increased significantly by 4.4 mmHg. This increase in PCO<sub>2</sub> was found to be primarily due to an increase in deadspace of 4%. They conclude that hyperoxic-induced hypercapnia is primarily due to impairment in gas exchange rather than to depression of ventilation. Aubier et al. [20] treated 20 patients with COPD and ARF with oxygen 5 L/min for 30 min. ABG were measured before and at the end of administration. They found only a small rise in PaCO<sub>2</sub> (61 to 68 mmHg) despite a large rise in PaO<sub>2</sub>. Although PaCO<sub>2</sub> rose in all patients and V<sub>E</sub> fell slightly (14%) there was no correlation between the rise in PaCO<sub>2</sub> and the fall in ventilation suggesting that the rise is not predominantly the result of the decreased of ventilation. In another study [21], the same group studied the effects of 100% oxygen on V<sub>E</sub> and arterial blood gases in COPD patients during acute respiratory failure, and concluded that despite removal of the hypoxic stimulus, the activity of the respiratory muscles maintained the VE at nearly the same value as that while breathing room air. Again, there was no correlation between PaCO<sub>2</sub> and V<sub>E</sub>. These data led the authors to conclude that, during acute respiratory failure, although there is an initial decrease in ventilation resulting from loss of hypoxic drive, the rise in PaCO<sub>2</sub> following correction of hypoxia is not primarily caused by decreased ventilation. In our patients, the NIV use guaranteed V<sub>T</sub> and do not permitted changes in V<sub>E</sub> (10.7 ± 2.4 vs. 10.7 ± 2.6; p = 0.96). In agreement, Hanson et al. [24] and Dick et al. [25] concluded that changes in physiologic deadspace are sufficient to account for the hypercapnia. Scano et al. [22] studied patients in a stable phase and demonstrated that respiratory drive in response to CO<sub>2</sub> is similar in hypercapnic patients with COPD to that in normal volunteers, although less than in normocapnic COPD



patients. Robinson et al. [26] used the multiple inert gas elimination technique to measure ventilation, cardiac output, and the distribution of ventilation-perfusion ratios in patients during an acute exacerbation of COPD. They showed that in patients in whom CO<sub>2</sub> tension rises in response to breathing 100% oxygen, ventilation decreases and alveolar deadspace increases. During the period of our study, there was no significant effect on any respiratory parameter when the FIO<sub>2</sub> was increased from baseline to 1.0 except for an increase in PaO<sub>2</sub> and SaO<sub>2</sub>. There was no evidence of depression of respiratory drive due to the increased FIO<sub>2</sub>, since the mental (GCS) and ventilatory parameters of (V<sub>T</sub>, RR, pH, PaCO<sub>2</sub> and V<sub>E</sub>) were unchanged.

In cases still hypoxemic or still distressing respiratory despite standard medical therapy (including oxygen), NIV has been successfully used to support gas exchange and prevent intubation in these patients. By counterbalancing intrinsic PEEP with extrinsic PEEP, and by augmenting V<sub>T</sub> with intermittent positive-pressure ventilation, NIV reduces the WOB and averts the circle leading to ARF [27]. NIV improves vital signs, gas exchange, and dyspnea scores; reduces the rates of intubation, morbidity, and mortality; and shortens hospital length of stay in patients with moderate to severe exacerbations of COPD [9, 11]. Recent meta-analysis [28] compared with standard therapy, NIV reduced the risk of intubation by 65% (95% CI, 0.26 to 0.47), in-hospital mortality by 55% (95% CI, 0.30 to 0.66), and the length of hospitalization by 1.9 days (95% CI, 0.0 to 3.9). Thus, NIV is considered the ventilatory mode of choice in hypercapnic patients with acute exacerbations of COPD.

Our study strength: (a) bedside clinical study (b) sample size calculation. Since the ventilator parameters were from a digital readout and blood gas results printed from a machine, we feel there was little chance for bias on the part of the data collectors. Our study limitations: (a) deadspace was not measured; (b) small sample; (c) not randomized. Since it is a security study, we supposed that randomization was not need.

We conclude that during noninvasive ventilation with an FIO<sub>2</sub> sufficient to maintain a normal PaO<sub>2</sub>, a further increase in FIO<sub>2</sub> does not result in an increased PaCO<sub>2</sub> in the group of CO<sub>2</sub>-retaining COPD patients since that no changes occur in minute volume.

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Table 1. Patient characteristics upon study admission

N. Patient	Gender	Age, yr	Weigh, Kg	Acute respiratory failure cause	APACHE II score	FIO <sub>2</sub>
1	M	65	82	Pneumonia	18	0.40
2	M	62	80	Exacerbations of COPD	15	0.40
3	F	72	65	Pneumonia	21	0.45
4	M	64	72	Pneumonia	23	0.50
5	M	70	69	Exacerbations of COPD	18	0.25
6	F	69	55	Exacerbations of COPD	15	0.30
7	F	68	52	Pneumonia	17	0.40
8	F	61	68	Pneumonia	19	0.45
9	M	75	92	Pneumonia	22	0.45
10	M	63	86	Exacerbations of COPD	24	0.30
11	F	62	69	Exacerbations of COPD	18	0.28
12	M	59	75	Exacerbations of COPD	19	0.45
13	F	71	72	Exacerbations of COPD	18	0.40
14	M	69	67	Pneumonia	17	0.35
15	M	64	77	Exacerbations of COPD	22	0.40
16	M	80	79	Exacerbations of COPD	21	0.35
17	F	71	85	Pneumonia	16	0.50

*Abbreviations:* M = male; F = female; COPD = chronic obstructive pulmonary disease; APACHE II = Acute Physiology and Chronic Health Evaluation II score; FIO<sub>2</sub> = inspired oxygen concentration during noninvasive ventilation

Table 2. Respiratory parameters before and after exposure to an increased FIO<sub>2</sub> (mean ± SD)

Variable	Baseline FIO <sub>2</sub>	FIO <sub>2</sub> of 1.0	<i>p</i> Value
V <sub>T</sub> , mL	601 ± 8	608 ± 8	0.10
RR, breaths/min	17.8 ± 3.7	17.5 ± 2.8	0.66
V <sub>E</sub> , L/min	10.7 ± 2.4	10.7 ± 2.6	0.96
pH	7.36 ± 0.06	7.35 ± 0.05	0.32
PaCO <sub>2</sub> , mmHg	52.5 ± 10.4	51.5 ± 12.3	0.38
PaO <sub>2</sub> , mmHg	101.4 ± 21.7	290.5 ± 35.7	< 0.001
SaO <sub>2</sub> , %	94.3 ± 2.2	98.8 ± 0.8	< 0.001
GCS	14.8 ± 0.3	14.8 ± 0.3	1.00

*Abbreviations:* V<sub>T</sub> = tidal volume; RR = respiratory rate; V<sub>E</sub> = minute volume; SaO<sub>2</sub> = oximeter oxygen saturation; GCS = Glasgow coma score; FIO<sub>2</sub> = inspired oxygen concentration during noninvasive ventilation