Influence of F_{IO_2} on P_{aCO_2} During Noninvasive Ventilation in Patients With COPD

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BACKGROUND: The administration of a high F_{IO_2} to COPD patients breathing spontaneously may result in hypercapnia, due to reversal of preexisting regional hypoxic pulmonary vasoconstriction, resulting in a greater dead space. Arterial blood gas trends have not been reported in these patients. In a 31-bed medical ICU in a teaching hospital we prospectively investigated the response of 17 CO_2-retaining COPD patients, after acute respiratory crisis stabilization with noninvasive ventilation, to an F_{IO_2} of 1.0 for 40 min, after having been noninvasively ventilated with an F_{IO_2} of ≤ 0.50 for 40 min. RESULTS: The mean ± SD baseline findings were: P_{aO_2} 101.4 ± 21.7 mm Hg, P_{aCO_2} 52.6 ± 10.4 mm Hg, breathing frequency 17.8 ± 3.7 breaths/min, tidal volume 601 ± 8 mL, and Glasgow coma score of 14.8 ± 0.3. P_{aO_2} significantly increased ($P < .001$) when F_{IO_2} was increased to 1.0, but there was no significant change in P_{aCO_2}, breathing frequency, tidal volume, or Glasgow coma score. CONCLUSIONS: During noninvasive ventilation with an F_{IO_2} sufficient to maintain a normal P_{aO_2}, a further increase in F_{IO_2} did not increase P_{aCO_2} in our CO_2-retaining COPD patients. *Key words: noninvasive ventilation; obstructive lung disease; oxygen; P_{aCO_2}; P_{aO_2}; carbon dioxide; hypercapnia.* [Respir Care 2014;59(3):383–387. © 2014 Daedalus Enterprises]

Introduction

General principles guide the management of COPD patients presenting acutely to the ICU: treat precipitating factors (eg, infection); increase expiratory flow (eg, with β agonist); reduce pulmonary inflammation (eg, with corticosteroid); and manage gas exchange (eg, improve oxygenation).[1] However, the administration of high F_{IO_2} to these patients may result in hypercapnia.[2-6] The reasons for this effect have been debated for many years: some believe there is a reduction in respiratory drive from the carotid chemoreceptors, and others think a worsened ventilation-perfusion matching is the cause.[7]

Noninvasive ventilation (NIV) benefits patients with COPD, and it seems reasonable to expect that NIV would increase tidal volume (V_T) and improve CO_2 elimination, and thus reduce respiratory drive.[8] Published studies provide reasonable recommendations based on the effectiveness of NIV in COPD patients: reduction of treatment failure, lower mortality, fewer complications, and lower intubation rate, compared to conventional medical treatment.[9] In these patients 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 in

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The authors have disclosed no conflicts of interest.

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severe episodes of respiratory failure.[11] Crossley et al[12] concluded that CO_2-retaining COPD patients following a period of mechanical ventilation with P_{aO_2} in the normal range can safely receive supplemental oxygen without retaining CO_2 or a depression of respiratory drive. A new ventilation-perfusion relationship is established during ventilation to normoxia, and it is not altered by further increasing the F_{IO_2}. Nevertheless, the safety of oxygen supplementation during NIV in CO_2-retaining COPD patients is not clear.

In CO_2-retaining COPD patients recovering from acute respiratory crisis on NIV and an F_{IO_2} of ≤ 0.5, we studied the response of P_{aCO_2} to an F_{IO_2} of 1.0.

QUICK LOOK

Current knowledge

High F_{IO_2} in spontaneously breathing patients with COPD may result in hypercapnia, due to reversal of hypoxic pulmonary vasoconstriction, resulting in increased dead space.

What this paper contributes to our knowledge

During noninvasive ventilation with an F_{IO_2} sufficient to maintain a normal P_{aO_2}, further F_{IO_2} increases did not increase P_{aCO_2} in spontaneously breathing patients with known carbon dioxide retention.

Methods

This study was approved by the ethics committee of Hospital Moinhos de Vento, Porto Alegre, Brazil. All subjects or the subject's legal representative gave written informed consent.

Subjects

We studied 17 COPD subjects admitted to our 31-bed medical ICU in a primary care hospital, who required NIV during treatment of acute respiratory failure (ARF). We excluded patients who were uncooperative or needed intubation. The subjects were all chronic CO_2-retaining COPD patients, as defined by a resting P_{aCO_2} of ≥ 45 mm Hg, previous hospital stay due to ARF-related COPD, and 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). The subjects all received NIV (BiPAP Vision, Respironics, Murrysville, Pennsylvania) via oronasal mask (PerformaTrak, Respironics, Murrysville, Pennsylvania) for at least 24 hours, until stabilization of ARF.

Protocol

The high-F_{IO_2} measurements were conducted only after stabilization of ARF, and in our clinical judgment there was no risk of needing intubation. Before the high-F_{IO_2} measurements the noninvasive ventilator was calibrated with a gas flow analyzer (VT Plus-HF, Fluke Biomedical, Everett, Washington). Ventilator circuit leak was tested to calibrate the exhalation port (Whisper Swivel II, Respironics, Murrysville, Pennsylvania). The oronasal mask was positioned to permit a leak up to 20 L/min. The ventilator was set in the spontaneous/timed mode, with a PEEP of ≥ 5 cm H_2O and a peak inspiratory pressure of ≥ 10 cm H_2O, targeting and guarantying a V_T or ≥ 8 mL/kg. The F_{IO_2} was adjusted to maintain S_{pO_2} of $\geq 90\%$.

We recorded age, sex, weight, primary disease process, and predicted risk of death based on admission Acute Physiology and Chronic Health Evaluation II score. The subjects had received nothing by mouth for at least 4 hours before the high-F_{IO_2} measurements, were clinically stable, and remained on their usual treatment regimen. Baseline parameters for study purposes included V_T, breathing frequency, the means of all cycles during minute volume ($\dot{V}_E$) measurement, arterial blood gas values (ABL 520, Radiometer, Copenhagen, Denmark), and S_{pO_2} (66S, Hewlett Packard, Palo Alto, California).

The high-F_{IO_2} period involved only increasing the F_{IO_2} to 1.0: no other parameters were altered. Following 40 min at an F_{IO_2} of 1.0 we again measured V_T, breathing frequency, $\dot{V}_E$, arterial blood gases, S_{pO_2}, and Glasgow coma score. F_{IO_2} was then returned to its previous value. The subjects were not made aware of the F_{IO_2} changes.

Statistical Analysis

Continuous variables are expressed as mean ± SD. Differences between baseline and high-F_{IO_2} were analyzed with the paired *t* test, except for Glasgow coma score, which we analyzed with the Wilcoxon signed-rank test. All statistical analysis was performed by a statistician using statistics software (SPSS 16.0, SPSS, Chicago, Illinois). Statistical significance was set at $P < .05$.

Results

Among the 17 subjects, 9 were admitted due to pneumonia, and 8 were admitted due to COPD exacerbation (Table 1). No subjects were withdrawn after enrollment. Before the high-F_{IO_2} measurements all the subjects were on NIV and receiving an F_{IO_2} between 0.25 and 0.5.

The F_{IO_2} increase significantly increased the mean P_{aO_2}, from 101.4 ± 21.7 mm Hg to 290.5 ± 35.7 mm Hg

Table 1. Subject Characteristics at Study Admission

Subject Number	Sex	Age y	Weigh kg	Cause of Acute Respiratory Failure	APACHE II Score	F_{IO_2} During NIV
1	Male	65	82	Pneumonia	18	0.40
2	Male	62	80	Exacerbation of COPD	15	0.40
3	Female	72	65	Pneumonia	21	0.45
4	Male	64	72	Pneumonia	23	0.50
5	Male	70	69	Exacerbation of COPD	18	0.25
6	Female	69	55	Exacerbation of COPD	15	0.30
7	Female	68	52	Pneumonia	17	0.40
8	Female	61	68	Pneumonia	19	0.45
9	Male	75	92	Pneumonia	22	0.45
10	Male	63	86	Exacerbation of COPD	24	0.30
11	Female	62	69	Exacerbation of COPD	18	0.28
12	Male	59	75	Exacerbation of COPD	19	0.45
13	Female	71	72	Exacerbation of COPD	18	0.40
14	Male	69	67	Pneumonia	17	0.35
15	Male	64	77	Exacerbation of COPD	22	0.40
16	Male	80	79	Exacerbation of COPD	21	0.35
17	Female	71	85	Pneumonia	16	0.50

APACHE II = Acute Physiology and Chronic Health Evaluation II
NIV = noninvasive ventilation

Table 2. Respiratory Data Before and After F_{IO_2} of 1.0

	On Baseline F_{IO_2}	On F_{IO_2} 1.0	*P*
Tidal volume, mL	601 ± 8	608 ± 8	.10
Breathing frequency, breaths/min	17.8 ± 3.7	17.5 ± 2.8	.66
Minute volume, L/min	10.7 ± 2.4	10.7 ± 2.6	.96
pH	7.36 ± 0.06	7.35 ± 0.05	.32
P_{aCO_2}, mm Hg	52.5 ± 10.4	51.5 ± 12.3	.38
P_{aO_2}, mm Hg	101.4 ± 21.7	290.5 ± 35.7	< .001
S_{pO_2}, %	94.3 ± 2.2	98.8 ± 0.8	< .001
Glasgow coma score	14.8 ± 0.3	14.8 ± 0.3	> .99

Values are mean ± SD.

($P < .001$) and the mean S_{pO_2}, from 94.3 ± 2.2% to 98.8 ± 0.8% ($P < .001$). There were no significant changes in any of the other measurements (Table 2). The mean baseline P_{aCO_2} was 52.5 ± 10.4 mm Hg, and the mean high-F_{IO_2} was 51.5 ± 12.3 mm Hg. We think that a P_{aCO_2} increase of 5 mm Hg is the minimum clinically important change. The standard deviation of the difference between the P_{aCO_2} recordings at the 2 different F_{IO_2} levels was 4 mm Hg. For a paired sample of 17 patients, this study has a power of 99%.

Discussion

Our results support the hypothesis that increasing the F_{IO_2} in CO_2-retaining COPD subjects on NIV does not cause any clinically important change in CO_2 retention.

A COPD exacerbation is defined as worsening dyspnea, cough, and/or sputum production.[13] Expiratory air-flow obstruction is worsened, the work of breathing increases, and mucus production or mucociliary clearance, or both, are altered. Spirometry shows worsened expiratory air-flow obstruction, and arterial blood gas analysis usually shows an additional decrease in P_{aO_2}, which leads to pulmonary arterial vasoconstriction and pulmonary hypertension.[14]

Supplemental oxygen is the most useful treatment in COPD-induced hypercapnic ARF, and oxygen is administered to all hypoxemic COPD patients during exacerbation. Oxygen decreases anaerobic metabolism and lactic acid production; improves brain function; decrease arrhythmias, ischemia, and pulmonary hypertension; improves right-heart function; decreases the release of antidiuretic hormone; increases the kidneys' ability to clear free water; decreases the formation of extravascular lung water (ie, pulmonary edema); improves survival; and decreases red blood cell mass and hematocrit.[14,15]

The P_{aCO_2} 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 in CO_2 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 arte-

rial blood gas analyses, with central nervous system or cardiovascular side effects. Carbon dioxide narcosis may occur with excessive F_{IO_2}, but is much less likely with low-flow, controlled oxygen therapy.[14]

Other authors have studied the behavior of P_{aCO_2} during increases of F_{IO_2} in spontaneously breathing[19-23] and mechanically ventilated COPD patients,[12] but P_{aCO_2} behavior during NIV has not previously been investigated. Sassoon et al,[19] in 17 stable COPD patients found that when the mean F_{IO_2} was increased to 0.94 the mean P_{aCO_2} increased significantly, by 4.4 mm Hg, primarily due to a 4% increase in dead space. They concluded that hyperoxia-induced hypercapnia is primarily due to impairment of gas exchange rather than to depression of ventilation.

Aubier et al[20] treated 20 COPD patients in ARF with oxygen at 5 L/min for 30 min, and measured arterial blood gases before and at the end of oxygen administration. They found only a small rise in P_{aCO_2} (from 61 mm Hg to 68 mm Hg), despite a large rise in P_{aO_2}. Although P_{aCO_2} rose in all the subjects, and $\dot{V}_E$ fell slightly (14%), there was no correlation between the rise in P_{aCO_2} and the fall in ventilation, which suggests that the rise is not predominantly the result of a decrease in ventilation.

In another study,[21] the same group studied the effects of 100% oxygen on $\dot{V}_E$ and arterial blood gases in COPD patients in ARF, and concluded that, despite removal of the hypoxic stimulus, the activity of the respiratory muscles maintained the $\dot{V}_E$ at nearly the same value as that while breathing room air. Again, there was no correlation between P_{aCO_2} and $\dot{V}_E$. These data led those authors to conclude that, during ARF, although there is an initial decrease in ventilation resulting from loss of hypoxic drive, the rise in P_{aCO_2} following correction of hypoxia is not primarily caused by decreased ventilation.

In our patients the NIV guaranteed V_T and did not permit changes in $\dot{V}_E$ (10.7 ± 2.4 L/min vs 10.7 ± 2.6 L/min, $P = .96$). In agreement, Hanson et al[24] and Dick et al[25] concluded that changes in physiologic dead space are sufficient to account for the hypercapnia.

Scano et al[22] studied stable COPD patients and found that respiratory drive in response to CO_2 is similar in hypercapnic COPD patients 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 ratio in patients with a COPD exacerbation. They found that in patients in whom P_{aCO_2} rises in response to 100% oxygen, ventilation decreases and alveolar dead space increases. In our study the only significant changes during high F_{IO_2} were increased P_{aO_2} and S_{pO_2}. There was no evidence of depression of respiratory drive due to high F_{IO_2}, since Glasgow coma score, V_T, breathing frequency, pH, P_{aCO_2}, and $\dot{V}_E$ were unchanged.

In patients who remained hypoxemic and/or in respiratory distress despite standard medical therapy (including oxygen), NIV has successfully supported gas exchange and prevented intubation. By counterbalancing intrinsic PEEP with applied PEEP, and by augmenting V_T, NIV reduces the work of breathing and averts the circle leading to ARF.[27] NIV improves vital signs, gas exchange, and dyspnea; may obviate intubation; reduces morbidity and mortality; and shortens hospital stay in patients with moderate to severe COPD exacerbation.[9,11] A recent meta-analysis[28] found that, compared with standard therapy, NIV reduced the need for intubation by 65% (95% CI 0.26–0.47%), decreased in-hospital mortality by 55% (95% CI 0.30–0.66%), and shortened hospitalization by 1.9 days (95% CI 0.0–3.9). Thus, NIV is considered the ventilation mode of choice in hypercapnic patients with exacerbations of COPD.

Our study strengths include that it was a bedside clinical study, and the sample size calculation. Since the ventilator measurements were from a digital readout and blood gas results printed from a machine, we feel there was little chance of bias on the part of the data collectors. Our study limitations were that dead space was not measured, the sample size was small, the study was not randomized, but, since it was a physiologic study, we supposed that randomization was not needed.

Conclusions

During NIV with an F_{IO_2} sufficient to maintain a normal P_{aO_2}, a further increase in F_{IO_2} does not result in an increased P_{aCO_2} in CO_2-retaining COPD patients, since no changes occur in $\dot{V}_E$.

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