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The author has disclosed no conflicts of interest.

DOI: 10.4187/respcare.03354

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Influence of F_{IO_2} on P_{aCO_2} in COPD Patients With Chronic CO_2 Retention

To the Editor:

We have read with interest the original article entitled "Influence of F_{IO_2} on P_{aCO_2} During Noninvasive Ventilation in Patients with COPD."[1] In this article, the authors prospectively evaluated 17 CO_2-retaining COPD subjects recovering from acute respiratory crisis on noninvasive ventilation (NIV) with F_{IO_2} of ≤ 0.5, and they studied the response of P_{aCO_2} to an F_{IO_2} of 1.0. The authors found that during NIV with an "F_{IO_2} sufficient to maintain a normal P_{aO_2}," a further increase in F_{IO_2} did not result in an increased P_{aCO_2}.

The accentuation of hypercapnia when oxygen is administered to hypercapnic COPD patients is a concern due to increased CO_2 retention and respiratory acidosis. NIV seems to be a more effective treatment for carbon dioxide retention in these patients.[2]

We feel the need to make some remarks on this study. Table 2 shows that before an increase in F_{IO_2} to 1.0, the P_{aO_2} values were 101.4 ± 21.7 mm Hg and after increased significantly to 290.5 ± 35.7 mm Hg (S_{pO_2} $94.3 \pm 2.2\%$ and $98.8 \pm 0.8\%$, respectively). Both P_{aO_2} and S_{pO_2} were significantly elevated compared with the usual values for COPD patients with chronic CO_2 retention. In fact, we could say that a P_{aO_2} of 100–120 mm Hg (21.7 is the upper SD) may well be the result of indiscriminate oxygen therapy. With those high P_{aO_2} values, the mechanisms for the increase in P_{aCO_2} may have been generated as well, and further increases in P_{aO_2} could not have had any additional effect on P_{aCO_2}. We wonder what the P_{aCO_2} would be with breathing ambient air, under baseline conditions. It is in this situation when the previously described increase in P_{aCO_2} is expected. Hypercapnia becomes dangerous somewhere in the range of 80–120 mm Hg.[3]

The mechanisms of CO_2 retention in patients with COPD have been described.[4-7] These mechanisms do not have the same relevance in every CO_2-retaining patient with COPD. First, the traditional theory that oxygen administration to CO_2-retaining patients causes loss of hypoxic drive, resulting in hypoventilation and ventilatory failure, is a myth. This mechanism does not suffice to justify the 20% increase in P_{aCO_2}, and it may be canceled due to the concomitant decrease in CO_2 production.[3] In the subjects studied by Savi et al,[1] the use of NIV could prevent such a mechanism from occurring.

Deoxygenated hemoglobin binds CO_2 with greater affinity than oxygenated hemoglobin. Hence, oxygen induces a rightward shift in the CO_2 dissociation curve, which is called the Haldane effect, and is very important in canceling severe hypoxia (up to 25% increased P_{aCO_2}), but it is negligible in the absence of the Haldane effect (~5% increased P_{aCO_2}).

An underventilated lung usually has low oxygen content, which leads to localized vasoconstriction, limiting blood flow to that lung. The main mechanism of CO_2 retention occurs because supplemental oxygen abolishes localized vasoconstriction, limiting blood flow at a low ventilation/perfusion ratio.

The administered oxygen flow is not important, but the P_{aCO_2} (and, indirectly, the P_{aO_2}) achieved is. Because the mechanisms described are of different relevancy in individual subjects, it might have been important to provide the blood gas report with the target S_{pO_2} of 88–92% (regardless of F_{IO_2}) and to observe changes with increasing F_{IO_2}.

The results of the article are supportive of the authors' hypothesis that increasing the F_{IO_2} in CO_2-retaining subjects with COPD on NIV does not cause clinically important changes in CO_2 retention.[1] This is relevant new information. We think these considerations should be taken into account when analyzing these results.

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The authors have disclosed no conflicts of interest.

DOI: 10.4187/respcare.03499

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Influence of F_{IO_2} on P_{aCO_2} During Noninvasive Ventilation in Patients with COPD: What Will Be Constant Over Time?—Reply

Influence of F_{IO_2} on P_{aCO_2} in COPD Patients With Chronic CO_2 Retention—Reply

In Reply:

We thank you for your elegant and insightful commentaries on our article.

Physiologically, patients with COPD are classified as dry lung, contrasting with subjects with ARDS and pneumonia, who are classified as wet lung. This classification is used because COPD patients present similar behavior with respect to shunt, hypoxic vascular response, alveolar ventilation/perfusion ($\dot{V}_A/\dot{Q}$) distribution, and response to 100% oxygen.[1] Patients with COPD exacerbation, whether requiring ventilatory support or not, exhibit low amounts of shunt (usually $< 10\%$), suggesting that the efficiency of collateral ventilation is very high or that complete airway obstruction does not occur functionally except in a few airways that are completely occluded by bronchial secretions.[1] In addition, these patients have an increased hypoxic vascular response. Finally, COPD causes severe $\dot{V}_A/\dot{Q}$ mismatching and nonuniform patterns (four different patterns) of $\dot{V}_A/\dot{Q}$ distribution. The distribution of both $\dot{V}_A$ and pulmonary blood flow, namely $\dot{V}_A/\dot{Q}$ mismatching, remains the most important cause of arterial hypoxemia, with or without hypercapnia, in both stable COPD and with COPD exacerbation.[2] The mechanisms that may contribute to CO_2 retention include a decrease in hypoxic ventilatory response consequent to the administration of oxygen, an increase in dead space consequent to release of hypoxic vasoconstriction and thus worsening of $\dot{V}_A/\dot{Q}$ relationships, and the Haldane effect (for any given amount of CO_2 bound to hemoglobin, P_{aCO_2} is considerably higher in the presence of high vs low S_{pO_2}).[3]

Dr Briones Claudett's main question concerns the clinical applicability of our findings in the short follow-up time of subjects after setting the F_{IO_2} to 1.0. Hyperoxia increases pulmonary dead space. However, using the multiple inert-gas elimination technique (breathing air and then 100% oxygen through a nose mask) in 22 subjects with COPD exacerbation, Robinson et al[4] also showed a decrease in $\dot{V}_A$ (expiratory minute volume of 9 ± 2 L/min vs 7.2 ± 1.6 L/min, $P < .05$) and an increase in low $\dot{V}_A/\dot{Q}$ units. They concluded that the major mechanism differentiating CO_2-retaining patients from CO_2-nonretaining patients is depression of ventilation rather than redistribution of blood flow caused by release of hypoxic vasoconstriction and that an increase in alveolar dead space could be secondary and not the cause of hypercapnia. However, we agree with González, Vulliez, and De Vito that our subjects may have received indiscriminate oxygen therapy at baseline (pre-100% F_{IO_2}). The high basal P_{aO_2} values (101.4 ± 21.7 mm Hg) in our subjects could have abolished the effect of hypoxemic pulmonary vasoconstriction reflex with a consequent increase in $\dot{V}_A/\dot{Q}$ mismatching. However, we believe that this increases the likelihood of retaining CO_2, which did not occur in our subjects.

Dr Briones Claudett questions the short follow-up of subjects in our study. Santos et al[5] evaluated the pulmonary gas exchange response to oxygen breathing in 8 subjects with acute lung injury and 4 subjects with COPD, and did not demonstrate changes in P_{aCO_2} (39 ± 6 mm Hg vs 44 ± 8 mm Hg, $P =$ not significant) after 60 min of 100% F_{IO_2}. The methodology used by these authors was replicated in our study because it intentionally alters the F_{IO_2} with the objective assessment of respiratory and hemodynamic parameters. Unlike the previously cited article,[4] Briones Claudett et al[6,7] performed two elegant studies with subjects with COPD and hypercapnic encephalopathy and did not change the supply of oxygen during the study period. Rather, they evaluated the respiratory response (P_{aCO_2}) of the different ventilatory strategies and different ventilatory pressures. Diaz et al[8] also evaluated the effect of noninvasive ventilation (NIV) on pulmonary gas exchange during COPD exacerbation for only 30 min.

In response to González, Vulliez, and De Vito, Diaz et al[8] reported that improvement in respiratory blood gases during NIV was essentially due to higher $\dot{V}_A$ and not to improvement in $\dot{V}_A/\dot{Q}$ relationships and that the increase in alveolar-arterial oxygen difference was explained by the increase in respiratory exchange ratio due to an increased clearance of body stores of CO_2 during NIV. In conclusion, we agree that the traditional theory that oxygen administration to CO_2-retaining patients causes loss of hypoxic drive, resulting in hypoventilation and ventilatory failure, is a myth, particularly during NIV.[9]

We agree with Dr Briones Claudett's criticism of the lack of spirometric data from our subjects, and we believe this is a flaw in our study.

In conclusion, our study had the clear objective of evaluating the safety of brief increases in F_{IO_2} (during respiratory therapy procedures and during O_2 saturation decreases secondary to maladjustments or interface leaks) in CO_2-retaining subjects with COPD and undergoing NIV.[10] No other clinical objective exists in sustained increases in F_{IO_2}, except temporarily, because in cases of persistent refractory hypoxemia, endotracheal intubation and mechanical ventilation are mandatory.

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The authors have disclosed no conflicts of interest.

DOI: 10.4187/respcare.03481

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