number of measures can be taken to optimize the conditions of extubation, eg, steroid pretreatment, optimization of fluid balance, glucose control, and nutrition support. These patients could also be targeted for interventions such as aggressive bronchial hygiene protocols, early mobilization, and careful titration of analgesics.

The prediction of early versus late re-intubation includes different variables, suggesting that different characteristics contribute to failure and potentially via different pathways. Our prediction models suggest that residual hypoxemia on the prediction day, likely representative of underlying pulmonary disease or other comorbidities, can predispose patients to the risk of failed extubation also in a non-imminent period. In terms of accuracy of prediction, our models of early and late failure performed well. The fact that only 70% of the events were correctly classified indicates that there is unexplained residual variability. This unexplained variability could represent inherent variability, unmeasured variables, or new events not necessarily directly related to the reasons leading to the first intubation. To minimize the latter sources, we excluded re-intubations performed in conjunction with surgical procedures.

This study[1] represents an initial step in identifying areas of opportunity to improve and minimize the occurrence of re-intubation, an event that is associated with prolonged ventilation, longer ICU stay, and increased hospital costs.[2] We are currently working on a prospective cohort to better define the time course of failure. Analysis of time to failure will have to account for competing risk events such as censoring by tracheostomy or death.

Miriam M Treggiari MD PhD
Department of Anesthesiology and Pain Medicine
University of Washington
Seattle, Washington

N David Yanez PhD
Department of Biostatistics
University of Washington
Seattle, Washington

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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?

To the Editor:

I read with interest the original article entitled "Influence of F_{IO_2} on P_{aCO_2} During Noninvasive Ventilation in Patients with COPD," in which 17 subjects with stable COPD were evaluated after stabilization of acute respiratory failure.[1]

Of the 17 subjects, 8 had pneumonia, and 9 had COPD exacerbations. All subjects were chronic retainers of P_{aCO_2} at $>$ 45 mm Hg and were treated by noninvasive ventilation with $F_{IO_2} < 0.50$ and, after 40 min, $F_{IO_2} = 1$. The objective of the study was to monitor the changes in P_{aCO_2} and secondarily to observe changes in breathing frequency, tidal volume, minute volume, and Glasgow coma scale. The authors found no significant alteration in either P_{aCO_2} or the secondary outcomes assessed.[1]

My opinions regarding these findings and their applicability to clinical practice are as follows.

1. It has long been known[2] that hyperoxia may increase pulmonary dead space, which reverses hypoxemic pulmonary vasoconstriction in the existing regional lung. Consequent to this, hypoxemic pulmonary perfusion would increase in poorly ventilated areas of the lung because of increase in dead space and P_{aCO_2}. This effect would be more pronounced in patients with COPD and $P_{aO_2} < 60$ mm Hg. The authors reported basal P_{aO_2} values of 101.4 $\pm$ 21.7 mm Hg, with an average S_{pO_2} of 94.3 $\pm$ 2.2%.
2. The response time of exposure to high F_{IO_2} for 40 min might not be the same as that in longer time periods, and therefore, the authors' findings may not be relevant to clinical practice.

   For the patient with respiratory failure and hypoxemia, exposure to F_{IO_2} might be for longer than 40 min; instead, it could be for longer periods of 6–8 h. During such prolonged periods, a patient with moderate-to-severe COPD would require an increase in the minute volume to maintain a constant P_{aCO_2} with high exposure to F_{IO_2}. This might be beyond a patient's ventilatory capacity. Even with noninvasive ventilation, the patient may require adjustments in inspiratory pressure levels and noninvasive ventilation strategies that allow a preset tidal volume to be maintained.[3]
3. For these 17 subjects during the phase of stabilization, the authors provided no spirometric data, no plethysmographic data, and no other data to assess the degree of COPD severity.[4] In a patient with COPD, depending on the degree of lung hyperinflation and hypoxemia, the increase in F_{IO_2} could reverse the hypoxemic pulmonary vasoconstriction and alter ventilation/perfusion, causing an increase in dead space.

   In contrast, the response to changes in neurological status (encephalopathy) measured by the Glasgow coma scale during so short a period as 40 min might not be the same as that in long time periods at high F_{IO_2} because of the diffusing capacity for carbon monoxide in cerebrospinal fluid.[5,6]

The authors did not provide data on dead space measurement or previous pulmonary hypertension values, and hypercapnia could affect clinical measurements.

In their final analysis, the authors evaluated the changes in P_{aCO_2}, breathing frequency, minute volume, and tidal volume in a group of stable subjects undergoing noninvasive ventilation with an F_{IO_2} of 1 for a short time period. Their findings might not be comparable to findings obtained in subjects with different degrees of COPD exacerbation and exposed for prolonged periods to F_{IO_2}, for whom oxygen therapy has some impact on survival.

I suggest that the foregoing observations be taken into account when considering the use of high F_{IO_2} to improve oxygenation in hypercapnic patients.

Killen H Briones Claudett MD
Department of Respiratory-Intensive Care Medicine
Panamericana Clinic
Department of Respiratory Medicine-Intensive Care
Santa Maria Clinic
Pulmonology Department
Military Hospital
Guayaquil, Ecuador

The author has disclosed no conflicts of interest.

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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.

Romina N González
Gastón G Morel Vulliez
Centro del Parque
División Kinesiología Respiratoria
Buenos Aires, Argentina

Eduardo L De Vito MD PhD
Centro del Parque
División Kinesiología Respiratoria
and
Instituto de Investigaciones Médicas Alfredo Lanari
Universidad de Buenos Aires
Consejo Nacional de Investigaciones Científicas y Técnicas
Buenos Aires, Argentina

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