## Prediction of Early and Late Re-intubation: Is It a Crossed or Separate Line?

*To the Editor*:

We read with interest the article by Miu et al[1] on a very important issue regarding weaning from mechanical ventilation: the identification of predictors of re-intubation in subjects who have successfully completed a spontaneous breathing trial. We would like to comment on the selection of periods at risk for re-intubation used in this study. Two related aspects should be considered when selecting these periods for the prediction to be the most useful.

First, a prediction of risk for re-intubation assumes a near mechanistic relationship between the condition of the patient on the day of prediction and of extubation failure. How long does this relationship last? Does it include most patients at risk? Does it yield a sufficiently accurate prediction? Although more patients may require re-intubation within the first 24 h than in any subsequent day, the risk is likely to extend beyond this period. The authors indicate a median time to re-intubation of 22 h, but the results suggest that only 41% of all re-intubated patients (155 of 379) were re-intubated in the first 24 h. Time periods for risk of extubation failure of 48 and 72 h have been more commonly studied.[2-5] In contrast, after a number of days, unforeseen conditions can develop in critically ill patients and be responsible for a new respiratory failure.[3] Can an extubation failure 6 days after extubation be reasonably predicted? We suspect that, after a period of time post-extubation, the relationship between the condition on extubation day and extubation failure weakens, the associated risk decreases, and a prediction of high risk for late re-intubation becomes less accurate.

The second aspect to consider is the clinical implication of the prediction. A prediction of high risk for early re-intubation would allow the clinician either to delay extubation until the patient's condition further improves or to apply immediate, more intensive measures after extubation, as suggested by the authors, to minimize such risk. A prediction of high risk for late re-intubation would, however, have less clear implications. Options such as delaying extubation for several days, tracheostomy, and immediate extubation with prolonged intensive respiratory care could affect a sizable number of patients, and resources. Knowing the accuracy of this latter prediction would be very important to assist with these decisions.

The period at risk for early re-intubation of 24 h selected in this study may not include a substantial proportion of re-intubations related to the patient condition on the prediction day. Analyzing the frequency of distribution of time to re-intubation could be informative to select a more inclusive early period at risk. Depending on its accuracy, a prediction for a longer early period could enhance its clinical implication.

The alternative period at risk selected, any time after extubation, may include re-intubations not directly related to the patient condition on prediction day and may be heavily influenced by a majority of re-intubations in the first few days, including the first 24 h. Selecting mutually exclusive early and late periods at risk may better inform whether late re-intubations are predictable.

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## Prediction of Early and Late Re-intubation: Is It a Crossed or Separate Line?—Reply

*In Reply*:

We thank Drs Figueroa-Casas and Esquinas for their important comments regarding the prediction of early and late re-intubation.

We agree that there are multiple potential mechanisms and pathways leading to extubation failure. Our data suggest that there are several patient characteristics that predict the likelihood of requiring re-intubation. We also concur that these patient characteristics do not necessarily resolve and represent an ongoing risk of extubation failure.

In terms of defining early and late events, we chose 24 h because more than half of the patients would have failed extubation within this window. In addition, this time frame might have implications regarding the decision to transfer out of the ICU. If high-risk patients are immediately discharged postextubation, they may require rapid readmission to the ICU. It would make clinical sense to extend the ICU monitoring ~24 h after extubation; however, an increased risk of extubation failure beyond 24 h would be unlikely to justify a longer ICU stay. For patients with long-term failure, the ability to identify those at risk may not only allow targeting specific therapies but also potentially allow informed discussions on prognosis involving the decision to (re)intubate or perform a tracheostomy.

Prediction of extubation failure can be thought of as the prediction of mortality based on physiologic variables and chronic health evaluation noted on ICU admission, which are the basis of the Acute Physiology and Chronic Health Evaluation (APACHE) score calculation. When predicting mortality on ICU admission, it is not possible to account for all the events or subsequent complications that might occur during the ICU stay. Nonetheless, certain predisposing factors can be identified, and there is value in identifying high-risk patients, particularly if certain risk factors are potentially modifiable. For high-risk patients, for example, a

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.

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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.