The most common adverse event encountered during the intubation of critically ill patients is oxygen desaturation, which is often a harbinger of serious complications such as cardiovascular collapse, anoxic brain injury, and death. It is imperative to attenuate this risk by optimizing pre-oxygenation prior to intubation. This paper explores the physiology and challenges related to preoxygenation and maintenance of oxygenation during intubation in these high-risk patients.

The purpose of preoxygenation is to maintain hemoglobin saturation despite ongoing oxygen consumption during apnea. This is accomplished in principle by denitrogenating the alveoli so that the functional residual capacity (FRC) serves as an oxygen reservoir, the efficacy of which can be evaluated by the fraction of expired O$_2$ (FeO$_2$) (Fig. 1).

The FeO$_2$ achieved using several methods of denitrogenation has been studied in healthy volunteers and elective surgical patients. Masks that create a tight seal provide the most effective denitrogenation with mean single-breath FeO$_2$ around 80% after 3 min, compared to a non-rebreather mask (NRB), which achieves an FeO$_2$ of 52% [1, 2]. Interestingly, adding a nasal cannula only improved the FeO$_2$ in the presence of a mask leak [1, 2]. Maximum exhalation prior to denitrogenation, or taking eight deep breaths in 60 s can accelerate the denitrogenation process [3, 4].

Preoxygenation with high O$_2$ concentrations in the absence of positive end-expiratory pressure (PEEP) increases the risk of atelectasis due to alveolar denitrogenation. High-flow nasal oxygen during the apneic period, termed apneic oxygenation (ApOx), can augment the efficacy of preoxygenation and theoretically prolongs the time to desaturation by continuously replenishing the oxygen consumed from the FRC. Additionally, high-flow nasal oxygen creates a flow-dependent positive pharyngeal pressure, which prevents the atelectasis associated with denitrogenation [5].

While in healthy individuals preoxygenation and denitrogenation may be synonymous, in critically ill patients preoxygenation must involve more than denitrogenation. First, increased oxygen consumption leads to faster hemoglobin desaturation and reduces the safe apnea time. Second, as the alveolar-arterial [A-a] gradient increases, the oxygen reservoir stored in the FRC is less efficient at saturating hemoglobin. Thus, as the A-a gradient increases, preoxygenation involves addressing arterial oxygen content and delivery rather than denitrogenation alone. This is particularly evident in patients with acute respiratory distress syndrome (ARDS), where extensive alveolar filling results in a functionally smaller area of lung available for gas exchange. The high shunt fraction limits the ability to continuously saturate hemoglobin despite maximal denitrogenation, reflected clinically as a high FeO$_2$, appropriate oxygen saturation (SpO$_2$), and a partial pressure of arterial O$_2$ (PaO$_2$) near the upper inflection of the oxygen–hemoglobin dissociation curve. While the PaO$_2$ does not significantly contribute to O$_2$ content, it is an indication of the efficiency of the alveolar–capillary interface, and thus time to desaturation. In this case the FeO$_2$ and SpO$_2$ could both be high, with a PaO$_2$ indicating the time to desaturation will be short as the reservoir of oxygen in the lungs is effectively inaccessible.

In these patients, 4 min of denitrogenation with a bag-valve mask (BVM) to an FeO$_2$ of 87% has been shown
to result in poor overall preoxygenation with only minimal PaO₂ change [6]. Doubling the time to 8 min resulted in no significant improvement in preoxygenation, with only 22 % achieving a PaO₂ greater than 100 mmHg and 24 % worsening their PaO₂ [7]. In a study in patients with hypoxemic respiratory failure comparing a non-rebreathing BVM for 3 min to non-invasive positive pressure ventilation (NIPPV) with 5 cmH₂O of PEEP, NIPPV achieved a higher mean PaO₂ (Fig. 1) [8]. The improved PaO₂ reflects a decreased shunt fraction from alveolar recruitment thus improving the alveolar–capillary interface.

The addition of ApOx in emergency department patients has been shown to increase first-pass success without hypoxemia, presumably by increasing the duration of the first attempt without desaturation [9]. In ICU patients with hypoxemia, data have been more variable. Denitrogenation with 60 L/min by high-flow nasal cannula (HFNC) with the cannula left in place for ApOx was compared to an NRB mask at 15 L/min and a higher median lowest saturation was found with HFNC [10]. However, a second randomized study found no difference with the same comparison (NRB at 15 L/min or HFNC at...
recommendations:

On the basis of the available data, we offer the following recommendations. Yet these are the most commonly reported outcomes.

Interpretation of preoxygenation data in critically ill patients is difficult for multiple reasons. First, performing the intubation precludes evaluating the physiologic endpoint, time to desaturation. Second, the surrogate outcome of desaturation during intubation does not have a standard definition. Additionally, there are no data to indicate what saturation can be tolerated by the brain and cardiovascular system during intubation, and for what duration. Third, in patients with a high A-a gradient, neither FeO2 nor SpO2 indicates the duration of safe apnea, yet these are the most commonly reported outcomes. On the basis of the available data, we offer the following recommendations:

1. “Preoxygenation” should be defined as the initiation of denitrogenation to the initiation of mechanical ventilation and thus includes the apneic period.

2. Denitrogenation should begin with maximum exhalation followed by high-flow oxygen administration with a tight-fitting mask for at least 3 min. In the presence of a mask leak, a nasal cannula should be added.

3. In patients with a high A-a gradient, preoxygenation with NIPPV should be performed for at least 3 min for alveolar recruitment. Promising pilot data suggest that HFNC may be useful as well [14].

4. ApOx efficacy depends on denitrogenation adequacy, the A-a gradient, and the degree of shunt. ApOx performed with an HFNC capable of 40–60 L/min may be effective and, if not available, a nasal cannula at greater than 15 L/min could be added after adequate denitrogenation. NIPPV by nasal mask can provide similar flows and the addition of positive pressure when the mouth is closed.

All airway managers intubating the critically ill should be intimately familiar with these concepts and understand their application to optimize oxygenation before and during intubation to maximize the safety of the procedure.

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Compliance with ethical standards

Conflicts of interest

None for all authors.

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