PREOXYGENATION, REOXYGENATION, AND DELAYED SEQUENCE INTUBATION IN THE EMERGENCY DEPARTMENT

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Abstract—Background: The goal of preoxygenation is to provide us with a safe buffer of time before desaturation during Emergency Department intubation. For many intubations, the application of an oxygen mask is sufficient to provide us with ample time to safely intubate our patients. However, some patients are unable to achieve adequate saturations by conventional means and are at high risk for immediate desaturation during apnea and laryngoscopy. For these patients, more advanced methods to achieve preoxygenation and prevent desaturation are vital. Discussion: We will review the physiology of hypoxemia and the means to correct it before intubation. Next, we will discuss apneic oxygenation as a means to blunt desaturation and the optimal way to reoxygenate a patient if desaturation does occur. Last, we will discuss the new concept of delayed sequence intubation, a technique to be used when the discomfort and delirium of hypoxia and hypercapnia prevents patient tolerance of conventional preoxygenation. Conclusions: These new concepts in preoxygenation and reoxygenation may allow safer airway management of the high-risk patient.

INTRODUCTION

Conventional preoxygenation techniques provide safe intubation conditions for a majority of emergency airways. However, in a subset of patients, these techniques will lead to inadequate preoxygenation and fail to prevent desaturation. To safely intubate this group, an understanding of the physiology of oxygenation is essential to allow for optimal intubating conditions. This knowledge can then be applied at the bedside in the care of high-risk patients. The goal of this work is to translate the tenets of physiology and the most recent literature to allow the safest possible intubation of critically ill patients.

DISCUSSION

The Pathophysiology of Hypoxemia

To understand oxygenation, it is essential to understand the causes of hypoxemia. These causes are inadequate alveolar oxygenation (low environmental oxygen pressure or alveolar hypoventilation), diffusion abnormalities, dead space (high ventilation, low perfusion [V/Q] mismatch), low V/Q mismatch, shunt, and low venous blood saturation. In the Emergency Department (ED) patient placed on ≥ 0.4 fraction-inspired oxygen (fiO₂), all of these problems have inconsequential effects on oxygenation except shunt and low venous blood saturation. See Figure 1 for an explanation of these two phenomena.

An anatomical shunt is a direct connection between the arterial and venous blood flow, for example, a
septal defect in the heart. When we speak about shunt as the cause of hypoxemia, we are rarely referring to anatomical shunts. Physiologic shunt is the major cause of poor oxygenation in ill ED patients already on supplemental oxygen. A physiologic shunt is caused by areas of alveoli that are blocked from conducting oxygen, but still have intact blood vessels surrounding them. This perfusion without any ventilation leads to a direct mixing of deoxygenated venous blood into the arterial blood. Causes of shunt include pneumonia, atelectasis, pulmonary edema, mucus plugging, and adult respiratory distress syndrome. No matter how high the \(\text{FiO}_2\), these areas will never have an improved oxygenation because inhaled gas never reaches the blood. The only way to improve oxygenation in these areas of the lungs is to fix the shunt.

Low venous oxygen saturation is also an important cause of hypoxemia in the ED. Venous blood is never fully desaturated when it reaches the lungs. In normal patients, the hemoglobin reaching the lungs has a saturation of \(\sim 65\%\), therefore, only a small amount of exposure to oxygen can rapidly bring the saturation to 100%. In shock states, the venous blood will arrive at the lungs with lower saturations due to greater tissue extraction. This venous blood will require more exposure to oxygen to reach a saturation of 100%; in injured lungs this may not occur. This problem becomes much more deleterious when combined with physiologic shunt. In this combination, the already abnormally low saturation venous blood mixes directly into the arterial supply.

This should impel the practitioner to always consider the circulatory system when evaluating the patient’s respiratory status. If the patient about to be intubated is in shock, attempts to improve and prevent the reduction of cardiac output become methods to improve oxygenation. Tailoring sedative medications to the patient’s cardiac status and blood volume is critical (1,2). If time allows, these patients will also benefit from aggressive preintubation normalization of preload, afterload, and inotropy (3,4).

**Standard ED Preoxygenation**

The standard recommended technique for ED preoxygenation is tidal volume breathing of oxygen from a high \(\text{FiO}_2\) source for at least 3 min or eight vital capacity breaths (5). When possible, a maximal exhalation preceding the tidal volume breathing improves preoxygenation (6,7). The non-rebreather mask (NRB), though the routine oxygen source, provides only 65–80\% of \(\text{FiO}_2\) (8). In a healthy non-obese adult patient, these standard techniques have been shown to provide a buffer as long as 8 min before the saturation drops below the critical 90% threshold (9). In the ill patient with injured lungs, abnormally small body habitus, or upregulated metabolism, this time is significantly shortened (9). In some cases it is impossible to obtain a saturation \(> 90\%\) before the
intubation attempt, regardless of the duration of standard preoxygenation.

A patient with a saturation < 95% on a nasal cannula set to 6 L/min of oxygen is exhibiting at least some degree of shunting, as this setting will provide \( \sim 0.4 \text{fiO}_2 \) (8). If the saturation is < 95% on a NRB, the patient is exhibiting signs of moderate to severe shunting. These latter patients are at risk for a precipitous and dramatic decline in oxygen saturation during the intubation procedure.

We have seen many situations in which a patient preintubation is saturating < 90% even with a NRB; the providers become frustrated, abandon further attempts at preoxygenation, and proceed to the immediate intubation of the patient to improve the saturation. However, if the patient is saturating < 90% before rapid sequence intubation (RSI), they may have an immediate and profound desaturation almost immediately after the RSI drugs are administered. Figure 2 shows the oxygen-hemoglobin dissociation (saturation) curve. The patient in this circumstance is already on the steep portion of this curve and will shortly be at critically low pressures of oxygen.

This abandonment of preoxygenation and rush to premature intubation may be predicated on the fallacy that saturation declines in a linear fashion over time. The shape of the curve in Figure 2 demonstrates that the time to go from 100% to 90% is dramatically longer than the time it takes to go from 90% to injuriously low levels of oxygen pressure resulting in dysrhythmia, seizure, and cardiac arrest.

In this circumstance of low saturation before RSI, many airway experts recommend preoxygenation with a bag-valve-mask device (BVM). When the BVM is manufactured with an appropriate exhalation port and a tight mask seal is obtained, it can deliver > 0.9 fiO2 both when the patient spontaneously breathes and with assisted ventilations (10). However, this increase from a fiO2 of \( \sim 0.7 \) (NRB) to \( \sim 0.9 \) (BVM) will do nothing to ameliorate shunt and little to correct low V/Q mismatched alveoli. In addition, it requires a practitioner to maintain an ideal mask seal during the stressful moments of preparing for RSI. If the mask seal is inadequate, room air will be entrained.

**Preoxygenation in High-risk Patients**

Non-invasive ventilation (NIV) has become a mainstay in the management of respiratory emergencies in most EDs. NIV is also the optimal technique for preoxygenation of high-risk patients. With a properly fitted, full-face NIV mask, fiO2 of \( \sim 1.0 \) is assured, and because these masks strap around the patient’s head, no practitioner is needed to maintain the mask seal. With a setting of continuous positive airway pressure (CPAP) at 0 cm H2O, this NIV set-up will simply provide a source of nearly 100% oxygen. With increased CPAP settings, shunt can actually be treated and the patient’s oxygenation significantly improved (11–15).

Starting with a CPAP setting of 5 and titrating up to a maximum of 15 cm H2O, 100% saturation can be achieved in patients in whom NRB or BVM preoxygenation did not result in adequate saturations. This strategy requires the NIV machine or, preferably, a standard ventilator standing by in the ED. Unless the ED is consistently staffed with an in-department respiratory therapist, it is also necessary for the clinicians to know how to immediately set up and apply NIV to themselves.

In EDs where neither a ventilator nor a NIV machine is available, the patient can be preoxygenated by spontaneously breathing through a BVM with a positive end-expiratory pressure (PEEP) valve attached. This is suboptimal, as a provider must hold the mask tightly over the patient’s face and even a slight break in the mask seal eliminates the PEEP. PEEP valves will be discussed in more detail below.

**Oxygenation during the Apneic Period**

In standard RSI, the oxygen mask is left on the patient’s face until the time of intubation. However, nothing is done to maintain a patent connection between the mouth and the glottis. As the sedative and paralytic drugs take effect, the tongue and the posterior pharyngeal tissues can occlude the passageway of oxygen to the glottis.
Although this seems irrelevant as the patient is no longer breathing, it ignores the benefits of apneic oxygenation.

**Apneic Oxygenation**

In an experiment by Frumin et al., patients were preoxygenated, intubated, paralyzed, and placed on an anesthesia machine that provided 1.0 \( \text{FiO}_2 \) and no ventilations \((16)\). These patients were maintained in this apneic state for between 18 and 55 min. None of these patients desaturated below 98%, despite being paralyzed and receiving no breaths. Although their CO\(_2\) levels rose, their oxygenation was maintained due to apneic oxygenation. Oxygen was absorbed from the patients’ alveoli by pulmonary blood flow; this established a gradient for the continued pull of oxygen from the endotracheal tube and anesthesia circuit. In another study, Teller et al. showed that pharyngeal insufflation with oxygen significantly extended the time to desaturation during apnea \((17)\).

Numerous studies on apneic oxygenation during brain death testing confirm that even without any respiratory effort, oxygen saturation can be maintained \((18–20)\).

If a continuous path of oxygen is maintained from the pharynx to the glottis during the apneic period of RSI, the patient will continue to oxygenate. This has led us to perform a jaw thrust in all high-risk patients during their apneic period. In some cases, we also place nasopharyngeal airways to augment the passage of oxygen. These techniques, combined with high-flow O\(_2\) from a NRB mask, NIV mask, or the facemask of a BVM, will allow continued apneic oxygenation.

Another problem during the apneic period is absorption atelectasis due to alveoli filled with near 100% oxygen. The nitrogen in normally ventilated alveoli serves to maintain their patency. When we preoxygenate with high \( \text{FiO}_2 \), our goal is to completely wash out this nitrogen. This can lead to alveolar collapse as the oxygen is taken up by pulmonary blood; further shunt is the result \((21)\). The use of NIV ventilation with CPAP can maintain these alveoli in an open state during the apneic period. When NIV is combined with a jaw thrust and patent oro/nasopharyngeal passage of air, the potential benefits of apneic oxygenation can be fully realized.

**REOXYGENATION**

If the first pass at intubation fails and the patient’s oxygen saturation drops below 90–95%, reoxygenation is required before any further intubation attempts. The standard method for reoxygenation is to ventilate the patient with a BVM apparatus attached to high-flow O\(_2\). Skilled practitioners will also place an oropharyngeal airway and, if there is any difficulty, nasopharyngeal airways as well. Even in skilled hands, this method can be problematic; when performed by a novice, it can be deadly.

Every BVM breath during reoxygenation potentially puts the patient at risk for gastric insufflation and aspiration. Ideally, the patient would receive the minimum number of ventilations to achieve reoxygenation and these breaths would be delivered in a slow, gentle manner to avoid overcoming the lower esophageal sphincter opening pressure of \( \sim 20–25\ \text{cm H}_2\text{O} \) \((22)\). However, studies show the difficulty of maintaining these goals during the stressful environment of an emergency resuscitation \((23,24)\).

In addition to changes in time perception when stressed, another possible explanation for this is a misunderstanding of the effects of increased ventilations on oxygen saturation. Ventilating the patient at increased respiratory rates will not raise the oxygen saturation any faster than at a controlled rate. In Figure 3, the effects of alveolar ventilation on oxygenation can be appreciated. At a \( \text{FiO}_2 \) of 0.5, only \( \sim 500\ \text{mL/min} \) of ventilation must reach the alveoli to generate a high PaO\(_2\). At a \( \text{FiO}_2 \) of 1.0, even less alveolar ventilation must occur to yield a PaO\(_2 \) > 500 mm Hg. Even assuming a high fraction of dead space in a patient undergoing resuscitation, this means that to achieve reoxygenation with the buffer of a high PaO\(_2\), only 3–4 breaths/min are needed. Given this information, the rate of 10 breaths/min recommended by most resuscitation guidelines seems reasonable and safe, offering at least double the required number of breaths. Ten slow (1.5–2 s per breath), low tidal volume breaths

![Figure 3. Alveolar ventilation vs. alveolar oxygenation. When breathing room air, approximately 3 L must reach the alveoli to maintain a PaO\(_2 \) > 100 mm Hg. If the \( \text{FiO}_2 \) is increased to 0.5, only 1 L/min is needed to generate a PaO\(_2 \) > 500 mm Hg. If the \( \text{FiO}_2 \) is increased beyond 0.5, even less alveolar ventilation is needed.](image-url)
per minute would seem the optimum rate for reoxygenation. Yet, when the patient has desaturated, we often witness rates as high as 60–120 breaths/min.

Beyond ensuring the proper rate and timing of ventilations, ideal mask seal is also imperative or the ventilations will not reach the alveoli. During our training, we are still taught how to correctly hold the mask of the BVM with one hand, but this is an inferior method that often does not achieve an adequate seal. Two providers are needed for reliably effective BVM ventilation: one to hold the mask with two hands and a second person to squeeze the bag.

Standard BVMs cannot provide PEEP, which, as we have previously discussed, is the only effective means to treat shunt during emergent intubation. In patients who required CPAP for preoxygenation, to attempt to reoxygenate with zero PEEP is illogical and often unsuccessful. PEEP valves are available that fit on the exhalation port of most BVM devices. These strain valves allow the generation of some PEEP by occluding the exhalation port to a selectable extent, but the PEEP disappears with continued gas absorption or with any loss of mask seal. Despite these disadvantages, when no other options exist, PEEP valves can have dramatic effects on reoxygenation.

There is, however, another commonly available solution to the problems of BVM reoxygenation: the standard ED mechanical ventilator as a reoxygenation device. This same ventilator can be used for the non-invasive preoxygenation as mentioned above and therefore it is advantageous to have at the bedside a standard ventilator rather than a non-invasive ventilation machine for the intubation of a high-risk patient.

The ventilator provides guaranteed slow, low tidal volume breaths. PEEP can be added and titrated to the patient’s requirements. A single provider can hold the two-hand mask seal while the ventilator delivers the respirations, freeing up a practitioner. Ventilator settings for reoxygenation are shown in Figure 4. Two studies have compared handheld ventilators to BVMs for non-intubated ventilations; these studies have shown the handheld ventilator to be safe and that it may be associated with fewer complications (25,26). The improved valve structure and more precise settings of a standard rather than handheld ventilator make it even more desirable. For this strategy to be successful, the clinicians must be able to set up the

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**Non-Invasive Ventilation (NIV) as a Preoxygenation Technique**

Get NIV machine or preferably a ventilator
Place properly fitted NIV Mask
If mask not available and intubation is imminent, use the mask from a BVM and hold a two hand mask seal
If using a ventilator, set the mode to CPAP mode
Set FiO₂ to 100%
Set PEEP/CPAP to 5 cm H₂O
Titrate up to 15 cm H₂O if necessary
After patient achieves saturation >95%, allow them to continue to breathe to flush out nitrogen, 3 minutes is ideal
Push RSI medications leaving the mask in place
Remove mask after paralytic has fully taken effect

**Ventilator as a better BVM**

Place oropharyngeal airway
Start respirations with a standard BVM hooked to 15 lpm wall O₂ at a rate of 10-12 breaths per minute
Turn on ventilator
Place in AC Volume mode
Set Tidal Volume to 550 ml
Set Flow Rate to 30 lpm (this delivers the breath over 1 second)
Set FiO₂ to 100%
Set Respiratory Rate to 12 bpm
Set PEEP to 5-15 cm H₂O depending on patient’s condition
Leave standard BVM mask on the patient’s face, remove bag, and attach ventilator circuit to the mask
Continue respirations until saturation >95%

**Delayed Sequence Intubation (DSI)**

Administer Ketamine 1 mg/kg as slow IV push
When patient has become disassociated, place on non-rebreather mask or NIV (as above)
Once the patient has reached a saturation of > 95%, allow them to continue to breathe for ~3 minutes
Administer a paralytic agent
Leave the mask in place until the paralytic has fully taken effect
Remove mask and intubate

Figure 4. The steps of non-invasive ventilation for preoxygenation, using the ventilator for reoxygenation, and delayed sequence intubation (DSI).
ventilator themselves without having to wait for a therapist to be paged down to the ED.

DEFER SEQUENCE INTUBATION

In some circumstances, the patients who most desperately require preoxygenation impede its provision. Hypoxia and hypercapnia can lead to delirium, causing these patients to rip off their non-rebreather or NIV masks. This delirium, combined with the oxygen desaturation on the monitor, often leads to precipitous attempts at intubation without adequate preoxygenation. Thanks to the availability of novel pharmacologic agents, another pathway exists to manage these patients.

Standard RSI consists of the simultaneous administration of a sedative and a paralytic agent and the provision of no ventilations until after endotracheal intubation (27). This sequence can be broken to allow for adequate preoxygenation without risking gastric insufflation or aspiration; we call this method “deferred sequence intubation” (DSI). DSI consists of the administration of specific sedative agents, which do not blunt spontaneous ventilations or airway reflexes; followed by a period of preoxygenation before the administration of a paralytic agent.

Another way to think about DSI is as a procedural sedation, the procedure in this case being effective preoxygenation. After the completion of this procedure, the patient can be paralyzed and intubated. Just like in a procedural sedation, we want the patient to be comfortable, but still spontaneously breathing and protecting their airway.

The ideal agent for this use is ketamine. This medication will not blunt patient respirations or airway reflexes and provides a dissociative state, allowing the application of a NRB or, preferably, NIV (28). A dose of 1–1.5 mg/kg by slow intravenous push will produce a calmed patient within ~45 s. Preoxygenation can then proceed in a safe controlled fashion. After a saturation of 100% is achieved, the patient is allowed to breathe the high fio2 oxygen for an additional 2–3 min to achieve adequate denitrogenation of the alveoli. A paralytic is then administered and after the 45–60 s apneic period, the patient can be intubated.

In patients with high blood pressure or tachycardia, the sympathomimetic effects of ketamine may be undesirable. These effects can be ameliorated with small doses of benzodiazepine and labetalol (28). In a slowly growing number of EDs, a preferable sedation agent is available for hypertensive or tachycardic patients. Dexmedetomidine is an alpha-2 agonist, which provides sedation with no blunting of respiratory drive or airway reflexes (29). It also will slightly lower heart rate and blood pressure (29). Acceptable conditions can be obtained with a bolus of 1 µg/kg over 10 min; if continued sedation is necessary, a drip can be started at 0.5 µg/kg/h (30–33). In many U.S. hospitals, this agent has not yet moved from the operating room and intensive care unit to the ED, mainly due to cost.

Another advantage of DSI is that frequently, after the sedative agent is administered and the patient is placed on non-invasive ventilation, the respiratory parameters improve so dramatically that intubation can be avoided. We then allow the sedative to wear off and reassess the patient’s mental status and work of breathing. If we deem that intubation is still necessary at this point, we can proceed with standard RSI as the patient has already been appropriately preoxygenated.

A video demonstrating the above concepts is available online at: http://blog.emcrit.org/misc/preox/.

CONCLUSION

Conventional preoxygenation techniques provide safe intubation conditions for a majority of emergency airways. However, in a subset of high-risk patients, these techniques will lead to inadequate preoxygenation and fail to prevent desaturation. To safely intubate this group, meticulous attention must be paid to optimizing preoxygenation, preventing deoxygenation and, if necessary, providing reoxygenation in a controlled manner. Future research is needed to delineate optimal timing, dosing, and methods to achieve these goals.

New techniques such as NIV as a preoxygenation technique, the ventilator as a better BVM, and breaking the sequence of RSI using the concepts of delayed sequence intubation may make the peri-intubation period safer.

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