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Maintenance of Oxygenation during Rapid Sequence Intubation in the Emergency Department

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Rapid sequence intubation (RSI) is the most common method of airway control in the emergency department (ED).[1,2] Administration of an anesthetic agent and a neuromuscular blocking agent (NMBA) optimizes conditions for tracheal intubation and is thought to minimize the risk of aspiration.[3-10] Evidence suggests that RSI improves first pass success and reduces complications in the critically ill.[11-14] However, RSI in the ED is not without its drawbacks.[15,16] The use of an NMBA results in the cessation of spontaneous ventilation, and consequently an interruption of continued alveolar oxygen delivery. A crucial step in maximizing the safety of RSI is preoxygenation, as this creates a large intrapulmonary oxygen reservoir which can be utilized during the period of apnea until mechanical ventilation can be initiated.[17-25] Even with preoxygenation, a significant number of patients undergoing RSI in the ED experience desaturation.[26,27] Most of the time, this is transient and is easily reversed with manual positive pressure ventilation. But occasionally desaturation becomes critical, and may result in life-threatening complications such as dysrhythmias, cardiovascular collapse, hypoxic brain injury or cardiac arrest.[28-30] Recently, apneic oxygenation has been promoted as an adjunct to RSI to prevent desaturation.[23] While the principle and technique of apneic oxygenation have been known for over half a century, the last few years have seen a great deal of research, interest and discussion regarding its role during RSI in the critically ill.[23,31-50] During apnea, the ongoing uptake of oxygen from the alveoli into the bloodstream creates a negative pressure gradient between the upper airway and the lungs. By providing a continual supply of oxygen to the upper airway, a reservoir of oxygen is maintained, and this oxygen can passively diffuse into the alveoli in the absence of any airflow.[31,32] Studies performed on elective surgical patients in the operating room have demonstrated that apneic oxygenation can significantly prolong the safe apnea time.[51-55] In this issue of *Academic Emergency Medicine*, Caputo and colleagues present the results of a randomized controlled trial of apneic oxygenation during RSI in the ED. In this study, 206 patients were randomized to undergo standard RSI or standard RSI with the addition of apneic oxygenation. The intervention group had oxygen supplied at ≥15 L/min via a standard nasal cannula (intra-nasally) and also via an end tidal CO_2 nasal cannula (infra-nasally), and thus received a minimum of 30 L/min during intubation. The authors sought to determine if the use of apneic

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oxygenation would result in a decrease in the prevalence of hypoxemia during the peri-intubation period. They found no difference in the incidence of moderate hypoxemia (SpO_2<90%) or severe hypoxemia (SpO_2<80%). There also was no difference in the mean lowest saturation (control group 93% vs. apneic oxygenation group 92%). At first glance, these results may seem surprising, but close analysis of the data reveals the reason why no benefit was seen: most of the patients in this trial were intubated very rapidly. The mean apnea time was 64 seconds in the control group and 58 seconds in the apneic oxygenation group. Over 90% of the patients were intubated in less than 100 seconds. We know from physiologic modeling experiments and human studies that with complete preoxygenation several minutes of safe apnea time can be expected in adults.[56-58] Since most of the patients in this study were intubated within a couple of minutes, the preoxygenation alone would likely have provided an adequate oxygen reservoir to prevent desaturation. Apneic oxygenation would only be beneficial in those patients who have exhausted their oxygen reserves, for example, patients who had prolonged laryngoscopies. This study illustrates the problem of studying apneic oxygenation in the critically ill- the necessity of rapid intubation and restoration of alveolar oxygen delivery precludes evaluation of the outcome measure of interest- an extended safe apnea time.

Interestingly, the results of this study are similar to those found by another randomized controlled trial that was performed in the intensive care unit (ICU).[34] In this study of 150 patients, Semler and colleagues evaluated the impact of apneic oxygenation at 15 L/min via nasal cannula on patients undergoing emergency RSI in the ICU. They found that the use of apneic oxygenation had no effect on the mean lowest saturation during the peri-intubation period (90% in the control group vs. 92% in the apneic oxygenation group). It is notable however, that many of the patients in this trial had hypoxemic respiratory failure requiring non-invasive ventilation (NIV), suggesting that they had significantly reduced functional residual capacities (FRC). Previous work has demonstrated that patients with reduced FRC to body weight ratios have limited tolerance to apneic oxygenation.[59] Additionally, one third of the patients in the apneic oxygenation group received preoxygenation with a nonrebreather (NRB) mask at 15 L/min, a technique which has been shown to result in poor preoxygenation.[60-62] Inadequate preoxygenation may reduce the benefit of apneic oxygenation.[59]

These two randomized control trials contrast with some recent observational studies which have demonstrated a benefit with the use of apneic oxygenation during emergency intubation.[35-37] Wimalasena and colleagues incorporated apneic oxygenation into their aeromedical RSI protocol and found in a before-and-after study that the prevalence of desaturation to <93% decreased from 23% to 17%.[35] In the author's ED, the introduction of apneic oxygenation was found to be associated with an increase in first pass success without hypoxemia (82% vs. 69%).[36] In a subset of patients with intracranial hemorrhages, who were at great risk of harm from hypoxemia, apneic oxygenation was associated with a reduced prevalence of desaturation to <90% (7% vs. 29%), to <80% (4% vs. 18%) and to <70% (3% vs. 9%).[37] It's important to note however, that in these studies nasal oxygen administration was initiated during the preoxygenation phase, and thus part of the improvement seen may in fact be due to improved preoxygenation from a higher fraction of inspired oxygen (FiO_2) that the patients in the apneic oxygenation groups received.[58] Recent studies have demonstrated that the addition of nasal cannula to

NRB mask preoxygenation results in an improved fraction of expired oxygen (FeO_2), an indicator of the completeness of denitrogenation.[60,61]

Several meta-analyses of apneic oxygenation studies have been published in the last year and all have demonstrated a clinical benefit with the use of apneic oxygenation during emergency RSI.[42-46] Holyoak and colleagues performed a meta-analysis of 17 studies involving 2,422 patients in the ED, ICU or prehospital setting and found that there was a significant reduction in both the prevalence of mild desaturation to <90% (RR=0.65) and critical desaturation to <80% (RR=0.61).[45] When divided by indication for intubation, the effect became non-significant for patients intubated for respiratory failure, but remained significant for patients intubated for other indications. Additionally, seven studies in this meta-analysis showed a statistically significant improvement in first pass success (RR=1.06). Again, on subgroup analysis they found this effect became non-significant in patients intubated for respiratory failure, but remained significant for those intubated for other indications. Pavlov and colleagues performed a meta-analysis of eight studies involving 1,953 patients in the ED, ICU and prehospital setting and found that apneic oxygenation reduced the relative risk of clinically significant hypoxemia by 30%.[43] Oliveira J e Silva and colleagues performed a review of 14 ED/ICU studies on apneic oxygenation involving 2,023 patients.[46] A meta-analysis of eight of these found that apneic oxygenation was associated with decreased hypoxemia (SpO_2<93%), but not decreased severe (SpO_2<80%) or life-threatening (SpO_2<70%) hypoxemia. Several points regarding these meta-analyses are worth noting. One, is that these reviews used many of the same studies in their analyses, so it is not surprising that they all found similar benefits with apneic oxygenation. Second, the quality of studies included in the analyses was relatively low, thus there is a low to moderate level of certainly in the point estimates presented. Third, the meta-analyses included both low flow (≤15 L/min) and high flow (≥50 L/min) apneic oxygenation studies. While the literature on the efficacy of high flow apneic oxygenation is quite robust, that for low flow apneic oxygenation is less so. Inclusion of the high flow studies might have inflated the overall benefit of apneic oxygenation, particularly in regard to low flow apneic oxygenation. Physiologic modelling data indicates that the duration of safe apnea time is highly dependent on the ambient fraction of oxygen that the airway is exposed to.[63] Lastly, as pointed out by Wong and colleagues in their narrative review of apneic oxygenation, adverse events were not reported, and the studies were not adequately powered to detect them.[47]

What are we to conclude from this plethora of interesting yet conflicting studies? Should we alter our current RSI practice and routinely use apneic oxygenation in the ED? Certainly, apneic oxygenation is a simple and low-cost intervention to institute in most EDs. The brief period of oxygen administration is unlikely to result in any harm to most patients, however, care should be taken in patients who can be adversely affected by the concomitant hypercarbia that develops with apnea, such as those with increased intracranial pressure, metabolic acidosis or pulmonary hypertension.[41,64-66] Also, it is important to note that rare cases of gastric rupture, pneumothorax and pneumomediastinum have been reported with nasopharyngeal oxygen administration, even at very low oxygen flow rates.[67-71] Apneic oxygenation can potentially be of benefit to patients undergoing emergency RSI, particularly those with difficult airways who have prolonged intubation attempts. Since many difficult airways are not able to be identified prospectively, it would be reasonable to provide apneic oxygenation to all patients undergoing RSI in the ED.[72] Certainly it should be used on any patient that is anticipated to have a potentially long laryngoscopy or is likely to have rapid desaturation due to reduced oxygen reserves. Use of a standard nasal cannula at 15 L/min is recommended for apneic oxygenation. End tidal CO_2 nasal cannula should not be used, as these devices don't deliver oxygen through the nasal prongs, but through a series of small holes in the tubing just below the nose. Moreover, they are only rated to deliver oxygen at ≤5 L/min. In patients that are deemed very high risk for desaturation, apneic oxygenation using a high flow nasal cannula (HFNC) system, such as Optiflow™ or Vapotherm™, is recommended, particularly if increasing $PaCO_2$ is a concern. [73-78] In the operating room, the Optiflow™ HFNC system at an oxygen flow of 70 L/min (THRIVE) has been demonstrated to produce prolonged safe apnea times, with the added benefit of minimizing increases in $PaCO_2$ by also providing a modicum of apneic ventilation.[73] Some data on the use of THRIVE in the critically ill requiring emergency intubation suggests that it can reduce desaturation events.[75,76] It should be emphasized that when apneic oxygenation is used as an adjunct during RSI, a patent airway must be maintained at all times to allow apneic diffusion of oxygen from the upper airway into the lungs. Additionally, it should be recognized that the benefit of apneic oxygenation will only be realized if it is preceded by good preoxygenation.[59]

While apneic oxygenation recently has come into vogue for emergency intubation, perhaps the issue that warrants greater consideration is the provision of proper preoxygenation in the critically ill.[22-25,42,79-83] Increased attention to this crucial step of RSI is likely to reduce the likelihood of desaturation in the critically ill and thus have the greatest impact on patient safety.[79,81,82] Much of the literature concerning preoxygenation is based upon elective intubations in the operating room using an anesthetic circuit and mask with a good seal. This is not practical for emergent intubations and thus alternative methods must be used. In some countries, flow dependent Mapleson breathing systems are available in the ED and have been shown to be very effective for preoxygenation.[84-88] In the United States, Mapleson circuits are not available, and the only manual resuscitators available for preoxygenation are flow independent self-inflating bags, also known as a bag-valve-masks (BVMs). Unfortunately, BVMs from different manufacturers vary considerably in their design, and thus deliver a widely variable FiO_2 in spontaneously breathing patients, ranging from 40% to 95%.[89-97] In particular, BVMs without a one-way valve on the expiratory port allow entrainment of large amounts of room air during spontaneous ventilation and thus deliver a greatly reduced FiO_2.[89] Also, BVMs that use corrugated tubing for the oxygen reservoir, as opposed to an inflatable plastic bag, have been found deliver a lower FiO_2.[94] Due to the lack of consistency in the ability of BVMs to deliver a high FiO_2, many emergency physicians instead use a NRB mask with a bag reservoir for preoxygenation. A common practice in the ED has been to preoxygenate using a NRB mask at 15 L/min. This flow is unlikely to meet the peak inspiratory flow of many patients in the ED and recent studies have in fact demonstrated the inadequacy of this method of preoxygenation.[60,61,98] Groombridge and colleagues have demonstrated that in healthy adults a NRB mask at 15 L/min only results in a mean FeO_2 of 52%, significantly less than the 80% that can be achieved with an anesthetic circuit or a BVM with a functional expiratory valve.[61] This is because many NRB masks are rigid and nonconforming to the face, and thus permit the entrainment of room air, which significantly reduces the FiO_2. Interestingly, a recent study by Driver and colleagues demonstrated that the leak from a NRB mask can be overcome by increasing the oxygen flow to the "flush rate".[62] In this study, using a NRB mask with an oxygen flow of 50 L/min resulted in a mean FeO_2 of 86% in healthy adults, which was significantly higher than the mean FeO_2 achieved with a NRB mask at 15 L/min (54%), and which was comparable to the mean FeO_2 that was achieved with a BVM at 15 L/min (77%).

The real question is, what is the best approach to preoxygenation in the ED? In patients with inadequate spontaneous ventilation, the decision is straightforward- they require manually assisted ventilations with a BVM. Fortunately, the reduced FiO_2 seen with some BVMs during spontaneous ventilation is not an issue when manual positive pressure ventilation is provided by squeezing the bag. The decision on the appropriate preoxygenation method in patients with adequate spontaneous ventilation is more complicated. In cooperative patients, the use a BVM with a functional expiratory valve is a good option for preoxygenation if a tight face mask seal can be achieved. Great care must be taken to maintain a good mask seal, as even a small leak can result in poor preoxygenation due to entrainment of room air.[99-103] Unfortunately, small leaks can be difficult to appreciate, especially without monitoring end tidal O_2 or end tidal CO_2.[103] In patients who are uncooperative, or in whom an adequate mask seal cannot be maintained, a NRB mask at flush rate is an acceptable alternative, if the actual flush rate is known, and is ≥50 L/min. It should be recognized that the flow achieved from wall oxygen at flush rate can vary considerably from institution to institution. Recent reports from Australia found that flush rate preoxygenation with a NRB mask only resulted in an oxygen flow of 19 L/min and only marginally improved FeO_2.[104,105] Ideally, wall oxygen flow meters that are calibrated to 15 L/min should be replaced with ones that are calibrated up to 70 L/min so the exact flow can be controlled during preoxygenation. Also, the use of NRB masks that have two functioning expiratory valves are preferred for preoxygenation to minimize entrainment of room air and maximize the FiO_2.

Whenever preoxygenation is performed it should be done with patients in the head-up position, as this increases the FRC and thus the volume of oxygen stores that can be achieved with preoxygenation.[106,107] Multiple studies on patients in the operating room have demonstrated that the head-up position results in improved preoxygenation and increases the safe apnea time.[108-111] Interestingly, a recent randomized controlled trial in critically ill patients in the ICU found that preoxygenation in the head-up position resulted in no improvement in oxygenation compared to the supine position.[112] The majority of the patients in this trial, however, had respiratory failure, many with shunt physiology, and this many have limited the benefits of upright preoxygenation. Based upon all data currently available, it would seem prudent to preoxygenate critically ill patients in the ED in the upright position when feasible. While three minutes of tidal volume breathing is recommended for preoxygenation, it should be appreciated that this many not be sufficient in some patients.[19-21,24,99,103,113,114]

While the above preoxygenation techniques will be satisfactory in most patients requiring intubation in the ED, patients with a significant right-to-left intrapulmonary shunt from air space disease will not be able to be adequately preoxygenated without positive end expiratory pressure (PEEP).[24,25,48] These patients require alveolar recruitment and thus should be preoxygenated with a BVM using a PEEP valve or with NIV. Studies in the ICU have demonstrated a clear benefit of NIV in patients with hypoxemic respiratory failure, with better preoxygenation achieved and a reduced prevalence of desaturation.[79,115] A recent study also has demonstrated that the combination of both NIV and HFNC was effective in reducing the severity of desaturation in profoundly hypoxemic patients.[116] If a patient cannot tolerate NIV, the use of HFNC at ≥50 L/min is an acceptable alternative, as data suggests that excellent preoxygenation can be achieved with this technique in patients with mild to moderate hypoxemia.[74,75,77] In a hypoxemic patient who cannot tolerate preoxygenation efforts, consideration can be given to using a delayed sequence intubation (DSI) technique.[117] This involves the administration of a dissociative dose of ketamine to allow the patient to tolerate preoxygenation. It should be borne in mind that some patients can be susceptible to apnea even from small doses of ketamine.[118] Thus, once a DSI is initiated and ketamine is administered, one must be prepared to immediately assume airway control.

It is important to recognize that many patients with physiologically difficult airways have a greatly reduced tolerance for apnea, and thus consideration should be given to performing a modified RSI with the provision of gentle manual ventilation (<20 cm H_2O).[5,119-121] Inexpensive disposable in-line manometers are available for BVMs and their use is recommended to avoid excessive manual ventilation pressures, which can increase the risk of gastric insufflation and regurgitation.[122-125] Alternatively, avoiding RSI altogether and performing an awake intubation is sometimes the most prudent course of action in the severely hypoxemic patient.[126-129] It is worth noting that HFNC is a tool that can also be used during awake intubations to prevent desaturation.[128,130]

While adherence to the principles of good preoxygenation in the ED is important, the reality is that the attainment of maximal intrapulmonary oxygen stores can never be ascertained without an objective indicator of alveolar oxygen content.[99,103] In the operating room, this is easily accomplished as anesthetic machines have built in gas analyzers which display end tidal O_2. In the ED, such equipment is not available. However, the recent introduction of a compact portable gas analyzer, the Masimo ISA OR+™ multigas analyzer, now makes measurement of FeO_2 feasible in the ED. Using sidestream gas analysis, this unit displays a capnogram, as well as a numeric readout of both FiO_2 and FeO_2. This provides vital information regarding the adequacy of ventilation, oxygen delivery and denitrogenation. Though measuring FeO_2 has some limitations, and must be interpreted with caution, it can be an invaluable tool in assessing the adequacy of the denitrogenation process.[21,25,131,132] We have used it in our ED for the past year and have found it very useful in helping to detect instances of inadequate preoxygenation. It has allowed operators to optimize preoxygenation by making adjustments to their technique, such as improving the face mask seal, increasing the oxygen flow or extending the duration of preoxygenation. Use of technology such as this may help to improve the safety of intubation in the ED by allowing improved preoxygenation, and thus potentially reducing desaturation events and the sequelae associated with them. It's important to note that measurement of FeO_2 requires a closed system, and thus can only be done when preoxygenating with a technique that utilizes a tight-fitting mask. Accurate FeO_2 measurements can be obtained when using a BVM with a good face mask seal or NIV if the unit has a separate expiratory limb. FeO_2 measurement is not possible with open preoxygenation methods such as NRB masks or HFNC systems.

Emergent tracheal intubation is one of the most critical, yet risky procedures an emergency physician can perform. Desaturation during RSI in the ED is common, and when severe, can result in life-threatening complications. The risk of desaturation can be substantially reduced with meticulous attention to preoxygenation, using the most appropriate method for the given clinical circumstances.

Portable oxygen analyzers are now available and may be helpful in maximizing preoxygenation before emergent intubation. Apneic oxygenation is a simple intervention that may help reduce the risk of desaturation, but it will not rescue poor preoxygenation. An emphasis on the maintenance of oxygenation during RSI in the ED is necessary to improve the safety of this life-saving procedure.

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