A difficult intubation poses one of the most challenging tasks for anesthesia professionals, representing 27% of all adverse respiratory events, 93% of which are unanticipated. Unanticipated difficult mask ventilation and intubation may result in serious complications. Safe airway management requires proper and thorough preoperative airway evaluation and a plan to secure the airway, with alternate plans available when the initial plan fails. Pediatric, obese, and obstetric patients undergoing general anesthesia with endotracheal intubation are considered to be at risk of rapid desaturation. As an adjunct to conventional preoxygenation techniques, continuous oxygen administration during the apneic period, termed apneic oxygenation, assists in the maintenance of oxygenation when tracheal intubation is attempted. Nine articles were selected for appraisal in this literature review: 6 randomized control trials, 2 prospective studies, and 1 retrospective study. Multiple apneic oxygenation techniques, including nasopharyngeal catheter, nasal prongs, endotracheal tube, intratracheal catheter, and high-flow transnasal humidified oxygen, demonstrated effectiveness at delaying the onset of hypoxemia during the apnea period. Prolonging the apneic window changes the nature of airway management in patients at high risk of desaturation and when an unanticipated difficult airway arises.

**Keywords:** Apneic oxygenation, avelilatory mass flow, difficult airway, high-flow nasal cannula, nasopharyngeal oxygen insufflation.

**M**aintenance of oxygenation during airway management is of utmost concern for anesthesia providers. Adverse respiratory events accounted for 17% of the most damaging events in the American Society of Anesthesiologists (ASA) closed-claims database from 1990 to 2007, and 31.8% of the claims in the American Association of Nurse Anesthetists (AANA) database from 2003 to 2012. Damaging events are defined as adverse outcomes that result in malpractice claims. Even with advances in respiratory monitoring technology and practice guidelines for managing the difficult airway, difficult airway management accounted for 27% of all adverse respiratory events in the ASA closed-claims database: 67% on induction and 12% on extubation.1,2

A preoperative evaluation of the patient’s airway history and physical examination of anatomical variables may be predictive of a difficult intubation. The ability to predict and prepare for management of a difficult airway may further reduce the adverse consequences encountered at the time of induction; these include but are not limited to neurologic injury, airway trauma, unnecessary surgical airway, and death. A cohort study conducted by Nørskov et al3 appraised 188,064 cases that were recorded in the Danish Anesthesia Database, evaluating the diagnostic accuracy in predicting the difficult intubation. There were 3,391 difficult intubations; among these, 93% were not predicted to be difficult (P < .05). The ASA recommendations for evaluation of the airway were employed, and the authors concluded there is no single predictor of a difficult intubation.3

In 2013, the Canadian Airway Focus Group4 updated its recommendations for management of the anticipated difficult airway. Included was the endorsement of continuous oxygen (O2) administration during the apneic period, termed apneic oxygenation (AO), when tracheal intubation is attempted.4 Research demonstrates that AO can safely prolong the duration of apnea without desaturation, maintaining an oxygen saturation measured by pulse oximetry (SpO2) at or above 90%.5-14 The Difficult Airway Society and the Obstetric Anaesthetists’ Association, located in the United Kingdom, released new guidelines for management of the unanticipated difficult airway and management of the difficult airway in obstetrics. Emphasis was placed on AO in patients who are considered at high risk of desaturation after the induction of anesthesia.15,16 More recently, an analysis was conducted on the Pediatric Difficult Intubation (PeDI) registry in the United States; hypoxemia was the most common complication related to tracheal intubation. Based on adult studies and anecdotal reports, PeDI investigators speculate that AO would delay the onset of hypoxemia in children and reduce the number of tracheal intubation attempts.17 Currently, the application of AO is not standard practice in the United States.

Pediatric, obese, and obstetric patients undergoing general anesthesia are considered at high risk of rapid desaturation. Increased O2 consumption and reduced...
functional residual capacity (FRC) hastens the development of hypoxemia in the obstetric and obese populations.\textsuperscript{16,18,19} Compared with adults, pediatric patients desaturate more quickly because they have a higher metabolic rate and greater O\textsubscript{2} consumption.\textsuperscript{12,17} Multiple attempts with direct laryngoscopy increase the risk of pharyngeal and laryngeal trauma. Subsequently, the resulting trauma may increase the difficulty of successful face-mask ventilation and successful intubation via repeated laryngoscopy.

As evidenced by clinical research, AO provides acceptable O\textsubscript{2} saturations. Frumin et al\textsuperscript{9} and Cook et al\textsuperscript{12} suggest saturations greater than 95\% for 45 minutes in the nonobese adult patient and 10 minutes in the pediatric patient, respectively. Extending the safe apnea period, which is defined as the time between the onset of apnea and when the Sp\textsubscript{O\textsubscript{2}} concentration reaches 90\% or less, increases the margin of safety with tracheal intubation.\textsuperscript{19} This may alleviate a high-stress start-stop scenario during laryngoscopy and help avoid a “cannot intubate, cannot ventilate” scenario.\textsuperscript{6} Conventional preoxygenation techniques may not be adequate in providing a safe apnea period in all populations. This literature review evaluates a proposed alternative, which is the use of AO as an adjunct to traditional preoxygenation techniques.\textsuperscript{4,18}

**Physiology of Apneic Oxygenation**

Ensuring adequate oxygenation and ventilation is the primary objective of airway management; thus, before the induction of anesthesia, patients are preoxygenated with 100\% O\textsubscript{2} via face mask. Preoxygenation denitrogenates the lungs, creating an alveolar O\textsubscript{2} reservoir, which helps reduce the frequency and severity of desaturation. In a nonobese adult patient without pulmonary disease, conventional preoxygenation techniques provide 4 to 8 minutes of safe apnea.\textsuperscript{19} Metabolic O\textsubscript{2} consumption and carbon dioxide (CO\textsubscript{2}) production of the adult human body weighing approximately 70 kg is approximately 250 mL/min and 200 mL/min, respectively. Following denitrogenation of the FRC, O\textsubscript{2} diffuses from the alveolus into the bloodstream at a rate of about 250 mL/min.\textsuperscript{19,20} During apnea, CO\textsubscript{2} production remains unchanged; however, the elimination of CO\textsubscript{2} is almost completely halted and diffuses into the alveolar space at a rate of approximately 10 mL/min. The pressure difference results in a net gas flow of 240 mL/min from the alveoli into the blood, generating a negative pressure gradient. Negative pressure that is created from the diffusion of O\textsubscript{2} causes entrainment of ambient gases into the lungs and describes the physiological phenomenon of a-v-ventilatory mass flow (AVMF). Normally, room air gases (79\% nitrogen and 21\% O\textsubscript{2}) are entrained into the lungs, and as nitrogen accumulates, desaturation occurs. Provided that a patent air passage exists from the lungs to the pharynx, the insufflation of O\textsubscript{2} into the pharynx extends the reservoir, allowing AVMF of O\textsubscript{2} (Figure 1).\textsuperscript{20} The clinical use of this procedure, regarded as AO, allows for persistent oxygenation without ventilations.

**Carbon Dioxide Physiology During Apneic Oxygenation**

The human body produces approximately 200 mL of CO\textsubscript{2} every minute. Carbon dioxide is highly soluble and elimination is dependent on alveolar ventilation. Holmdahl\textsuperscript{20} estimated that during AO, 90\% of the CO\textsubscript{2} produced stays in circulation and is distributed throughout the body, whereas only 10\% enters the alveoli, resulting in an uncompensated respiratory acidosis. Five studies\textsuperscript{5,6,8,12,14} evaluated the rate of rise in CO\textsubscript{2}, and none of the studies reported uncontrolled cardiovascular complications or other complications suggestive of CO\textsubscript{2} toxicity: seizures, arrhythmias, and cardiovascular collapse. Studies\textsuperscript{5,6,8,14} in adult patients reported average increases in CO\textsubscript{2} ranging from 1.12 mm Hg/min to 2.4 mm Hg/min. In 2 studies,\textsuperscript{6,8} several patients underwent procedures and were apneic for 45 minutes and 65 minutes; the highest CO\textsubscript{2} measurements recorded were 89 mm Hg and 112 mm Hg, respectively. All studies reported results after ventilation was resumed, and patients fully recovered without experiencing any complications.

Compared with adults, CO\textsubscript{2} levels increase faster in pediatric patients because they have a higher metabolic rate. A study in pediatric patients reported that during the first minute of apnea the mean increase in PaCO\textsubscript{2} was 12.2 mm Hg, followed by 4.2 mm Hg/min over the next 4 minutes.\textsuperscript{12} Frumin et al\textsuperscript{9} suggests that hypercarbia produced by apnea periods of even 30 minutes may be tolerable in an anesthetized nonobese adult patient, with complete recovery. However, it is important for the
clinician to understand that AO provides little relevant clearance of CO\textsubscript{2} and progresses to eventual respiratory acidosis, which may be severe.

**History and Review of the Literature**

Apneic oxygenation has been explored for more than a century.\textsuperscript{6,8,9,18} Although the physiological nomenclature of AO has changed several times, the physiological phenomenon remains unchanged.\textsuperscript{6,18} Holmdahl\textsuperscript{20} first described the concept of apneic diffusion oxygenation in humans in 1956. The technique was used to prevent desaturation during bronchoscopies while allowing the endoscopist to work without the need for ventilations.\textsuperscript{20} Most recently, AO has been studied and used clinically to prevent desaturation during panendoscopies, otolaryngeal procedures, brain death testing, and laryngoscopy.\textsuperscript{6,8,18} In 2011, Weingart and Levitan\textsuperscript{18} recommended Nasal Oxygen During Efforts Securing A Tube (NO DESAT), which describes the use of AO in efforts to prevent desaturation during emergency airway management. Their recommendations consist of using a nasal cannula to deliver O\textsubscript{2} at 15 L/min during the apneic period.\textsuperscript{18} The Canadian Airway Focus Group\textsuperscript{4} and the Difficult Airway Society\textsuperscript{15} have evaluated recommendations for and the empirical evidence of AO, suggesting its use in patients who are considered at high risk of desaturation. Additionally, the recommendations have been adopted by the Obstetric Anaesthetists’ Association\textsuperscript{16} and employed in guidelines for management of the difficult and failed tracheal intubation in obstetrics.

An electronic database search was conducted using The Cochrane Library, Cumulative Index to Nursing & Allied Health Literature, PubMed, Springer Link, Google Scholar, and Wolters Kluwer. The search also included the following professional organizations’ websites: ASA, AANA, and Difficult Airway Society. The following search terms were used alone and in combination: *apneic oxygenation, difficult airway, a ventilatory mass flow, nasopharyngeal oxygen insufflation, and high flow nasal cannula*. Evidence sources were also examined to determine if they evaluated the use of AO. Results of the search are displayed in Figure 2.

- **Apneic Oxygenation in Adults.** The empirical evidence of AO has been studied using several different techniques, which all support prolonging the period of safe apnea by extending the time to desaturation. Techniques examined include insufflation of O\textsubscript{2} using a nasopharyngeal catheter, nasal prongs, intratracheal catheter, and high-flow transnasal humidified O\textsubscript{2}.\textsuperscript{5-14} The sample demographics, preoxygenation techniques, AO intervention and comparator, and associated findings are summarized in the Table.

Apneic oxygenation necessitates a patent airway to allow for the delivery and entrainment of O\textsubscript{2} from the pharynx to the lungs. Placement of a nasopharyngeal catheter effectively delivers O\textsubscript{2} to the pharynx, providing an extension of the O\textsubscript{2} reservoir during apnea. Nasopharyngeal oxygenation is achieved by placing an O\textsubscript{2} catheter in the naris to the depth of the nasopharynx. Catheter depth is determined by measuring from the base of the nose to the tragus.\textsuperscript{21} Four studies\textsuperscript{5,7,10,14} examined the efficacy of AO using a nasopharyngeal catheter and

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**Figure 2. Flowchart of Literature Search**

Abbreviations: AO, apneic oxygenation; RCT, randomized control trial.
<table>
<thead>
<tr>
<th>Evidence source</th>
<th>Sample/evidence level</th>
<th>Preoxygenation technique</th>
<th>Intervention/comparator</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Teller et al,10 1988 | • N = 12  
• RCT  
• ASA 1 or 2  
• Scheduled to undergo general anesthesia | 3 min of normal tidal breathing of 100% O₂ via face mask | NC placed, insufflated O₂ at 3 L/min vs no O₂ in control group | • AO group tolerated 10 min of apnea and maintained SpO₂ ≥ 98%  
• Control group desaturated to SpO₂ of 92%, with mean apnea time of 6.8 min |
| Taha et al,5 2006 | • N = 30  
• RCT  
• ASA 1 or 2  
• Mean subject height of 165.5 cm and weight of 66.5 kg  
• Elective procedure undergoing general anesthesia | 4 deep breaths in 30 seconds of 100% O₂ via face mask | NC placed, insufflated O₂ at 5 L/min vs no O₂ in control group | • AO group tolerated 6 min of apnea  
• Control group desaturated to SpO₂ of 95% and had mean apnea time of 3.65 min |
| Jain et al,14 2009 | • N = 40  
• RCT  
• ASA 1 or 2  
• Mean subject weight: 50.7 kg  
• Elective procedure undergoing general anesthesia | 4 deep breaths in 30 seconds of 100% O₂ via face mask | NC placed, insufflated O₂ at 5 L/min vs no O₂ in control group | • AO group tolerated 6 min of apnea, maintaining SpO₂ > 96%  
• Control group desaturated to SpO₂ of 95%, and mean apnea time was 4.04 min |
| Baraka et al,7 2007 | • N = 34  
• RCT  
• ASA 1 or 2  
• Morbidly obese patients: mean BMI of 42 kg/m²  
• Undergoing gastric bypass surgery | 3 min of normal tidal breathing of 100% O₂ via face mask | NC placed, insufflated O₂ at 5 L/min vs no O₂ in control group | • AO group: 16 of 17 patients maintained SpO₂ of 100% and tolerated 4 min of apnea  
• Control group desaturated to SpO₂ < 95%, and mean apnea time was 145 s |
| Ramachandran et al,11 2010 | • N = 30  
• RCT  
• ASA 1 or 2  
• Obese patients: mean BMI of 31 kg/m²  
• Elective procedure undergoing general anesthesia | 8 VC breaths or normal tidal breathing of 100% O₂ via face mask until ET O₂ of 90% | Nasal prongs placed, insufflated O₂ at 5 L/min vs no O₂ in control group | • AO group: 53% of patients maintained SpO₂ ≥ 95%, and mean apnea time was 5.29 min  
• Control group: 1 patient maintained SpO₂ ≥ 95%, and mean apnea time was 3.49 min  
• Mean SpO₂ significantly higher in AO group, 94.3 ± 4.4% vs 87.7 ± 9.3% in control group |
| Achar et al,13 2014 | • N = 56  
• RCT  
• ASA 1 or 2  
• Mean BMI: 23 kg/m²  
• Elective procedure undergoing general anesthesia | Deep breathing of 100% O₂ via face mask until ETO₂ of 90% | Insufflated O₂ at 5 L/min via NC or nasal prongs | • NC group: all patients tolerated 10 min of apnea without desaturation  
• Nasal prong group: 9 patients desaturated to SpO₂ < 95% |
| Rudolf & Hohenhorst,8 2013 | • N = 47  
• Retrospective study  
• ASA 2 or 3  
• Range of subject weight of 44-156 kg and mean height of 171.5 cm  
• Undergoing panendoscopy | 3 min of normal tidal breathing of 100% O₂ via face mask, desired ET O₂ of 90% | Insufflated O₂ at 0.5 L/min via intratracheal catheter | • Apnea was maintained throughout procedure for 44 of 47 patients, and mean apnea time was 24.7 min  
• Maximum apnea time of 45 min and minimum apnea time of 1 min |

continues on page 326
Patel & Nouraei, 2015  
- N = 25  
- Prospective study  
- ASA 1-4  
- BMI range: 18.52 kg/m²  
- Documented or suspected difficult airways  
- Undergoing general anesthesia for hypopharyngeal or laryngotraheal surgery  
Delivered transnasal humidified O₂ at 70 L/min for 10 min before induction  
Continued delivery of O₂ at 70 L/min until definitive airway was established  
- All patients maintained SpO₂ > 90%, mean apnea time was 17 min, and apnea times ranged from 5 to 65 min

Cook et al, 1998  
- N = 26  
- Prospective study  
- ASA 1 or 2  
- Pediatric patients: age range of 1 mo to 11 y  
- Subjects’ weight range: 3.7-48.6 kg  
- Undergoing cardiac catheterization

Table. Matrix of Randomized Controlled Trials and Observational Studies Reviewed

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study Design</th>
<th>Patient Selection</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel &amp; Nouraei, 2015</td>
<td>25</td>
<td>Prospective</td>
<td>General anesthesia</td>
<td>SpO₂ ≥ 90%, mean apnea time was 17 min, and apnea times ranged from 5 to 65 min</td>
</tr>
<tr>
<td>Cook et al, 1998</td>
<td>26</td>
<td>Prospective</td>
<td>Pediatric patients</td>
<td>Mean PaO₂ started at 561 mm Hg and decreased to 366 mm Hg after 5 min of apnea</td>
</tr>
</tbody>
</table>

Abbreviations: ABG, arterial blood-gas analysis; AO, apneic oxygenation; BMI, body mass index; ETCO₂, end-tidal carbon dioxide; ET₀₂, end-tidal oxygen concentration; NC, nasopharyngeal catheter; O₂, oxygen; PaO₂, arterial partial pressure of oxygen; RCT, randomized controlled trial; SpO₂, oxyhemoglobin saturation; VC, vital capacity.
occurred first. No patients in the nasopharyngeal catheter group desaturated compared with 32% in the nasal prongs group \((P = .001)\). These studies suggest that AO is better achieved with a nasopharyngeal catheter rather than nasal prongs. Insufflation of \(O_2\) via nasopharyngeal catheter distributes \(O_2\) close to the trachea, thus circumventing potential problems associated with nasal prongs when airway patency is not maintained. Ramachandran and colleagues\(^\text{11}^\) suggested that \(O_2\) flows above 5 L/min may enhance nasal patency, improving the delivery of \(O_2\) to the pharynx. Additional proposals for maintaining a patent airway consist of performing a jaw thrust for the duration of the procedure, inserting a nasal trumpet when using nasal prongs, and aligning the horizontal plane of the patient’s external auditory meatus and sternal notch.\(^7,13,18^\

Rudlof and Hohenhorst\(^8^\) investigated the clinical efficacy of AO in adult patients undergoing panendoscopy. Following induction, direct laryngoscopy was performed, an 8-French catheter was placed in the trachea, and \(O_2\) was insufflated at 0.5 L/min. Among the 47 patients included in the study, 44 tolerated the procedure, maintaining a mean \(SpO_2\) concentration of 98%, a mean apnea time of 24.7 minutes, and a maximum apnea time of 45 minutes.\(^8^\

Patel and Nouraei\(^6^\) researched the use of transnasal high-flow humidified \(O_2\) in patients with a difficult airway. Patients were preoxygenated using the Optiflow nasal cannula (Fisher & Paykel Healthcare Ltd), which provided \(O_2\) at a rate of 70 L/min for 10 minutes. After induction, the nasal cannula (Optiflow) continued to deliver \(O_2\) until a definitive airway was achieved. All patients maintained their \(SpO_2\) concentrations above 90%, and apnea times ranged from 5 to 65 minutes, with a mean apnea time of 17 minutes.\(^6^\) Although high-flow nasal cannulas are not readily available in the operating suite, this device was effective at prolonging the apnea time without desaturation in patients with a difficult airway and reduced FRC. Both this study and the one by Rudlof and Hohenhorst demonstrated that AO was able to prolong the apneic period, up to 45 minutes\(^8^\) and 65 minutes,\(^6^\) signifying it may provide crucial laryngoscopy time during a rapid-sequence intubation or when an unanticipated difficult airway arises.

The empirical evidence supports the efficacy of AO in delaying desaturation and prolonging the safe apnea period in adults. Another technique for providing AO is with a dual-use laryngoscope blade. The Miller Port American Profile Conventional Blade (SunMed LLC) has an internal lumen built inside the blade and allows for the noninvasive insufflation of \(O_2\) when laryngoscopy is performed (Figure 3). The Naso-Flo nasopharyngeal airway (Medis Medical Co Ltd) is another alternative, which features an \(O_2\) port and allows for \(O_2\) delivery directly to the pharynx (Figure 4).

The Canadian Airway Focus Group, Difficult Airway Society, and Obstetric Anaesthetists’ Association recommend the application of AO in high-risk patients. Considering that 93% of difficult intubations are unanticipated, AO should be considered in all patients undergoing general anesthesia. Prolonging the safe apnea period changes the nature of managing an airway in patients at high risk of rapid desaturation or when an unanticipated difficult airway arises.

**Apneic Oxygenation in Children.** Cook et al\(^\text{12}^\) examined changes in blood-gas tensions during AO in 26 pediatric patients aged from 1 month to 11 years, 5 of whom were infants. In all patients, the trachea was intubated, and \(O_2\) was delivered via T-piece at a rate of 1 L/min. Serial arterial blood-gas samples were taken every minute during apnea, over the course of 5 minutes. The starting mean \(PaO_2\) was 561 mm Hg and decreased to 366 mm Hg after 5 minutes of apnea \((P < .05)\). During the first minute of apnea, the mean decrease in \(PaO_2\) was 105 mm Hg, followed by a decrease of 31 mm Hg/min over the next 4 minutes \((P < .05)\). Investigators suggested that AO can safely delay desaturation for 5 minutes, with an upper limit of at least 10 minutes.\(^\text{12}^\)

The PeDI investigation group emphasized the concern of hypoxemia during management of the pedi-
atric airway.\(^7\) Considering that pediatric patients have a smaller apneic period for establishing a definitive airway, anesthesia providers should incorporate AO into their airway management plan. Minimal data are available to compare the safe limits of AO in children. A search of ClinicalTrials.gov,\(^2\) a database with public and private clinical studies involving human participants around the world, revealed 8 active or recently completed clinical studies on AO, and 3 are focused on the efficacy of AO in the pediatric population. As research evolves in the area of AO, these techniques provide a potentially lifesaving tool to be used by anesthesia professionals when critical time is needed to establish a definitive airway.

**Strengths and Limitations.** Strengths of the literature review demonstrate that multiple AO techniques are clinically available, and all are shown to be more effective at prolonging the safe apneic period compared with pre-oxygenation alone. Limitations of this literature appraisal include small samples and patient populations with a relatively low risk, classified as ASA class 1 or 2. Further investigations should incorporate large-scale multicenter trials concentrating on patient populations prone to rapid desaturation.

Although there are currently no available consensus guidelines for the clinical use of AO, clinicians should consider the potential patient safety applications of the technique. Given the vital nature of ensuring oxygenation and ventilation in rendering safe patient care, AO, although often underconsidered, may provide a potentially valuable clinical technique in selected patient scenarios.

**REFERENCES**


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The authors have declared they have no financial relationships with any commercial interest related to the content of this activity. The authors did not discuss off-label use within the article.

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