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REVIEW ARTICLE/BRIEF REVIEW

The effectiveness of apneic oxygenation during tracheal intubation in various clinical settings: a narrative review

Efficacité de l'oxygénation apnéique pendant l'intubation trachéale dans divers contextes cliniques: un compte rendu narratif

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Abstract

Purpose *During the process of tracheal intubation, patients are apneic or hypoventilating and are at risk of becoming hypoxemic. This risk is especially high in patients with acute or chronic respiratory failure and accompanying compromised respiratory reserve. To address this concern, apneic oxygenation can be administered during tracheal intubation to aid in maintaining arterial oxygen saturation. The objective of this narrative review is to examine the utilization of apneic oxygenation within the operating room, intensive care unit (ICU), emergency department, and pre-hospital settings and to determine its efficacy compared with controls.*

Source *For this narrative review, we obtained pertinent articles using MEDLINE® (1946 to April 2016), EMBASE™ (1974 to April 2016), Google Scholar, and manual searches. Apneic oxygenation was administered using various techniques, including the use of nasal prongs, nasopharyngeal or endotracheal catheters, or laryngoscopes.*

Principal findings *First, all 12 operating room studies showed that apneic oxygenation significantly prolonged the duration to, and incidence of, desaturation. Second, two of the five ICU studies showed a significantly smaller decline in oxygen saturation with apneic oxygenation, with three studies showing no statistically significant difference vs controls. Lastly, two emergency department or pre-hospital studies showed that the use of apneic oxygenation resulted in a significantly lower incidence of desaturation and smaller declines in oxygen saturation.*

Conclusion *Sixteen of the 19 studies showed that apneic oxygenation prolongs safe apneic time and reduces the incidence of arterial oxygen desaturation. Overall, studies in this review show that apneic oxygenation prolongs the time to oxygen desaturation during tracheal intubation. Nevertheless, the majority of the studies were small in size, and they neither measured nor were adequately powered to detect adverse respiratory events or other serious rare complications. Prolonged apneic oxygenation (with its consequent hypercarbia) can have risks and should be avoided in patients with conditions such as increased intracranial pressure, metabolic acidosis, hyperkalemia, and pulmonary hypertension.*

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Résumé

Objectif *Pendant le processus d'intubation trachéale, les patients sont en état d'apnée ou d'hypoventilation et courent le risque de devenir hypoxémiques. Ce risque est particulièrement élevé chez les patients atteints d'insuffisance respiratoire aiguë ou chronique souvent accompagnée d'une réserve respiratoire compromise. Afin de traiter ce problème, une oxygénation apnéique peut être*

mise en œuvre pendant l'intubation trachéale afin d'aider à maintenir la saturation artérielle en oxygène. L'objectif de ce compte rendu narratif était d'examiner l'utilisation de l'oxygénation apnéique en salle d'opération, à l'unité de soins intensifs (USI), à l'urgence, et dans des contextes pré-hospitaliers ainsi que de déterminer l'efficacité de cette approche par rapport à des témoins.

Source Pour ce compte rendu narratif, nous avons obtenu les articles pertinents dans les bases de données MEDLINE® (1946 à avril 2016), EMBASE™ (1974 à avril 2016), Google Scholar et par des recherches manuelles. L'oxygénation apnéique était administrée à l'aide de diverses techniques, notamment l'utilisation de pinces nasales, de sondes nasopharyngées ou endotrachéales, ou de laryngoscopes.

Constatations principales Premièrement, les 12 études traitant du contexte de la salle d'opération ont toutes démontré que l'oxygénation apnéique prolongeait significativement la durée jusqu'à et l'incidence de désaturation. Deuxièmement, deux des cinq études à l'USI ont montré un déclin significativement réduit de la saturation en oxygène avec l'application d'une oxygénation apnéique, et trois études n'ont montré aucune différence significative d'un point de vue statistique par rapport aux témoins. Enfin, deux études réalisées à l'urgence ou dans un contexte pré-hospitalier ont montré que l'utilisation de l'oxygénation apnéique entraînait une incidence significativement réduite de désaturation et des déclins moindres de la saturation en oxygène.

Conclusion Seize des 19 études ont montré que l'oxygénation apnéique prolonge le temps d'apnée sécuritaire et réduit l'incidence de désaturation artérielle en oxygène. Globalement, les études examinées dans ce compte rendu montrent que l'oxygénation apnéique prolonge le temps jusqu'à la désaturation en oxygène pendant l'intubation trachéale. Toutefois, la majorité de ces études étaient de petite taille et ne mesuraient pas ou ne possédaient pas la puissance nécessaire pour déceler les complications respiratoires et autres complications graves rares. Une oxygénation apnéique prolongée (avec son hypercarbie conséquente) peut comporter des risques et devrait être évitée chez les patients présentant certaines conditions, notamment une pression intracrânienne élevée, une acidose métabolique, une hyperkaliémie ou une hypertension pulmonaire.

Patients with acute respiratory failure or chronic conditions affecting respiratory reserve are at risk of developing hypoxemia, especially during attempts at tracheal intubation. Acute respiratory failure involves conditions such as congestive cardiac failure, exacerbation of chronic obstructive pulmonary disease, and respiratory infection. Chronic conditions compromising respiratory reserve include illnesses such as morbid obesity, chronic obstructive pulmonary disease, and pulmonary fibrosis. During the process of tracheal intubation with an apneic patient, there is a high probability that at-risk patients may become hypoxemic. Apneic oxygenation has been shown to improve arterial oxygen saturation and prolong the duration of safe apneic periods.

The purpose of this review is to examine the literature on the effectiveness of apneic oxygenation in patients undergoing tracheal intubation or airway manipulation in various settings, including the operating room, intensive care unit (ICU), emergency department, and pre-hospital settings.

Physiological mechanism of apneic oxygenation

During regular breathing in an adult, approximately 250 $mL \cdot min^{-1}$ of oxygen flows from the alveoli into the bloodstream, and 250 $mL \cdot min^{-1}$ of carbon dioxide returns from the bloodstream to the alveoli. When a patient is apneic, approximately 250 $mL \cdot min^{-1}$ of oxygen flows from the alveoli into the bloodstream, while only 8-20 $mL \cdot min^{-1}$ of carbon dioxide returns from the bloodstream to the alveoli. The remaining carbon dioxide produced is buffered in the bloodstream and tissues[1,2] (Fig. 1). The difference between the volume of oxygen leaving and carbon dioxide entering creates a negative pressure in the alveoli.[1,2] Supplemental oxygen provides an oxygen-rich mixture in the pharynx compared to when no supplemental oxygen is used. As a result of the negative pressure generated, there is a mass movement of gases from the pharynx into the alveoli, provided that the upper airway is patent.[1] This process of apneic oxygenation may improve arterial oxygen saturation, prolong the safe apneic period for tracheal intubation, and reduce multiple attempts at laryngoscopy, thereby averting consequent risks of airway or dental trauma.[3]

Various techniques for applying apneic oxygenation

Numerous techniques in the administration of apneic oxygenation have been described (Fig. 2). One such technique is the use of nasal prongs (nasal cannula). A flexible tube with two short protruding prongs is connected to an oxygen source at one end and placed directly under the patient's nose at the other end. The standard prongs,
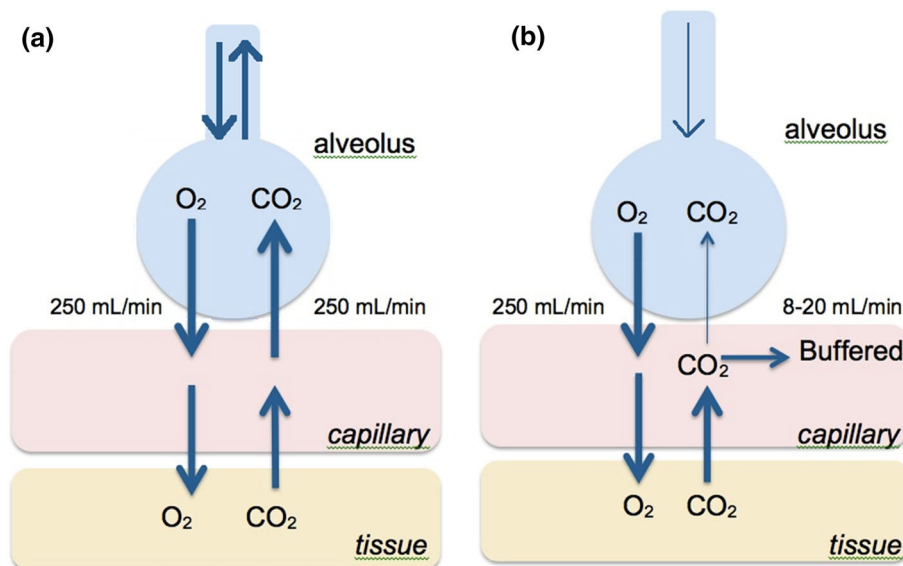
Fig. 1 Gas exchange during regular breathing and apnea. (a) During regular breathing, O_2 moves at a rate of 250 mL·min^{-1} from the alveoli into the capillaries and into the tissues. Approximately an equal amount of CO_2 leaves the tissues and moves into the capillaries and into the alveoli. The volume of gases entering alveoli during inspiration and the volume of gases leaving alveoli during expiration are roughly equal (double arrows in bronchus). (b) During apnea, O_2 moves at a rate of 250 mL·min^{-1} from the alveoli into the capillaries

and into the tissues. However, a small amount of CO_2 is buffered in the tissues, while a larger amount is buffered in the bloodstream, leaving only 8-20 mL·min^{-1} to move into the alveoli. The difference in the volume of oxygen leaving and carbon dioxide entering creates a small negative pressure in the alveoli, thereby resulting in a movement of gases from the pharynx into the alveoli (arrow in bronchus towards alveolus)
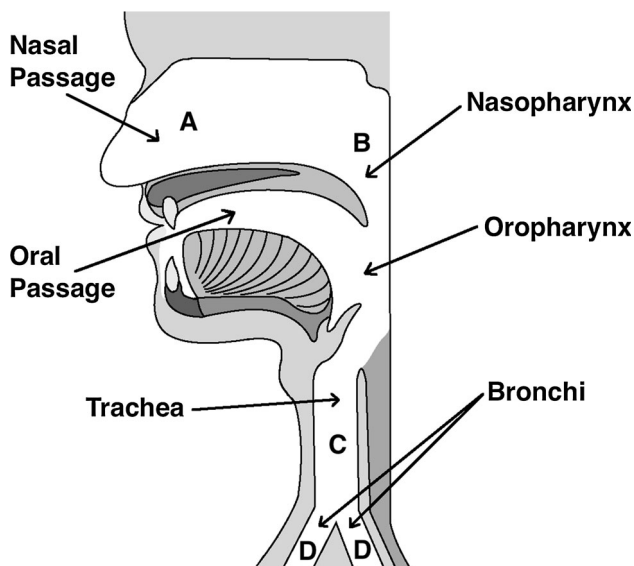

Fig. 2 Schematic diagram showing the four possible locations of the tip of the cannula or catheter in the upper airway (A) just inside the nares; (B) nasopharynx; (C) trachea, and (D) main stem bronchi

measuring approximately half the diameter of the nares, are inserted at the entry of the nostrils. A second technique is the use of a nasopharyngeal catheter, which is inserted into the nostril and advanced into the nasopharynx with its distal end lying above the vocal cords. The distance from

the nares to the tragus of the ear is often measured and used as an estimate for the depth of catheter insertion.[4] A third technique is nasal or oral insertion of a catheter supplying oxygen and passage of the catheter past the vocal cords and into the trachea. A fourth technique is placing bilateral endobronchial catheters in the right and left main stem bronchi to provide apneic oxygenation. Lastly, a laryngoscope can be used whereby oxygen can be delivered through a channel on one side of the laryngoscope blade.

Transnasal humidified high-flow oxygen

Optiflow[TM] (Fisher & Paykel Healthcare Limited, Laval, QC, Canada) is a recently developed oxygen therapy device that is capable of delivering oxygen via a nasal cannula at higher humidity over a broad range of concentrations and flows (Fig. 3). As a high-flow nasal cannula (HFNC) device, it consists of several main components: a breathing circuit, an oxygen humidification system, contoured nasal prongs, and a head strap (Fig. 4). Optiflow delivers oxygen at a temperature and humidity that matches the environment of healthy adult lungs, which results in improved tolerance by awake patients.[5,6] Optiflow can deliver the prescribed oxygen concentration at various flow rates (0-70 L·min^{-1})
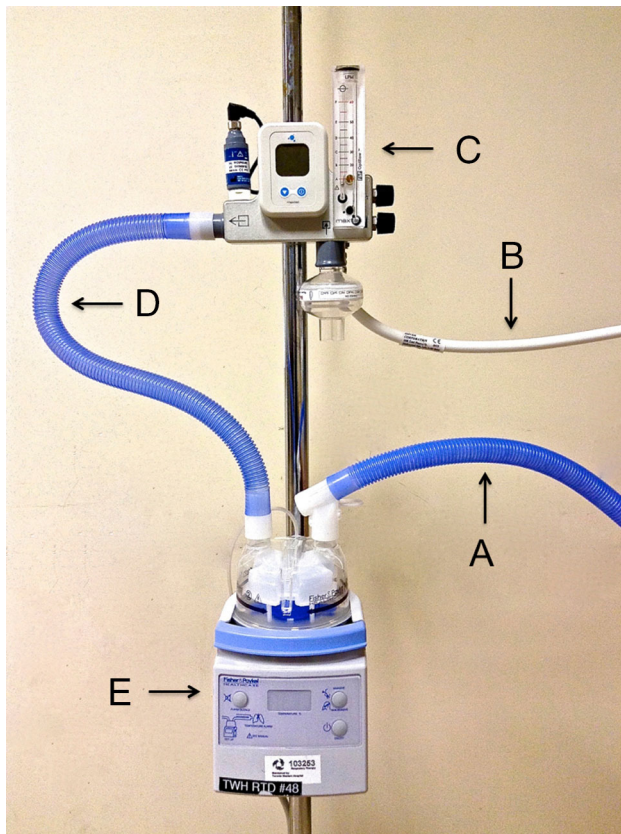
Fig. 3 High-flow nasal cannula system: Optiflow^{TM}. (A) Oxygen is supplied through a high-pressure tube connected to a wall oxygen source. (B) Oxygen and entrained room air enter the blender, mixing the two to achieve the desired FiO$_2$ and flow rate. (C) The oxygen mixture flows from the blender to the humidifier. (D) The oxygen mixture is humidified to the desired temperature and humidity level. (E) The humidified oxygen mixture flows from the humidifier to the nasal prongs

Fig. 4 Optiflow^{TM} Nasal Prongs

and elevate the mean airway pressure proportional to the oxygen flow rate.[5,7-11]

Search strategy for articles cited in this review

MEDLINE$^{®}$ (1946 to April 2016), EMBASE^{TM} (1974 to April 2016), Google Scholar, and manual searches were used to find relevant articles. The following keywords were used in the search: "apneic (or apnoeic) oxygenation", "ICU", "emergency", "artificial respiration", and "intermittent positive-pressure ventilation". We included abstracts published in the last three years and full articles with relevance to apneic oxygenation in patients at risk of hypoxemia.

Apneic oxygenation for tracheal intubation in various clinical settings

The use of apneic oxygenation in the operating room (Table 1)

Twelve prospective studies, eight of which are randomized-controlled trials, examined the use of apneic oxygenation in the operating room. Baraka et al.[12] studied morbidly obese patients undergoing endotracheal intubation under anesthesia and muscle paralysis in the operating room. Thirty-four patients were randomized to receive either supplemental nasopharyngeal oxygenation (apneic oxygenation group) at a rate of 5 L·min^{-1} or no supplemental oxygenation (control group). Time to SpO$_2$ < 95% was significantly prolonged in the apneic oxygenation group *vs* the control group [SpO$_2$ = 100% at 4 min in 16/17 patients *vs* SpO$_2$ < 95% in a mean (SD) time of 145 (27) sec, respectively; P < 0.05]. Similarly, Ramachandran et al.[13] studied 30 obese patients randomized to an apneic oxygenation group receiving oxygen at a rate of 5 L·min^{-1} via nasal prongs or a control group without apneic oxygenation. The apneic oxygenation group had a significantly longer mean (SD) time to desaturation (SpO$_2$ < 95%) than the control group [5.29 (1.02) min *vs* 3.49 (1.33) min, respectively; P < 0.05]. In addition, the lowest mean SpO$_2$ recorded was significantly higher in the apneic oxygenation group compared with the control group [94.3 (4.4) % *vs* 87.7 (9.3) %, respectively; P < 0.05].

In Taha et al.'s[14] study, 30 patients were randomized into an apneic oxygenation group receiving oxygen at a rate of 5 L·min^{-1} via nasopharyngeal catheter or a non-apneic oxygenation control group. The apneic oxygenation group maintained maximum oxygen saturation longer than the control group [SpO$_2$ = 100% at 6 min *vs* SpO$_2$ < 95% in 3.65 (1.15) min, respectively; P value not stated]. In a

Table 1 Apneic oxygenation studies in the operating room

Paper	Design	Setting/Situation	Sample Size	Control Group	Apneic Oxygenation (AO) Group(s)	Results
Baraka et al. 2007[12]	Randomized-controlled trial	Hospital OR: ASA I/II, BMI > 35 kg·m⁻², Gastric bypass, gastric band surgery	34 = 17 control, 17 intervention	Preoxygenation alone Mean (SD) BMI = 42.7(5.4) kg·m⁻²	Nasopharyngeal catheter: O_2 at 5 L·min⁻¹ Mean (SD) BMI = 41.8(6.9) kg·m⁻²	Time to SpO_2 < 95% AO: SpO_2 100% maintained in 16/17 patients at 4 min* Control: 145 (27) sec
Ramachandran et al. 2010[13]	Randomized-controlled trial	University hospital: 30 < BMI < 35 kg·m⁻² Elective surgery	30 = 15 control, 15 intervention	No additional nasal O_2	Nasal prongs: O_2 at 5 L·min⁻¹	1) Duration SpO_2 > 95% (max 6 min): AO: 5.29 (1.02) min* Control: 3.49 (1.33) min 2) Lowest SpO_2: AO: 94.3 (4.4) %* Control: 87.7 (9.3) %
Taha et al. 2006[14]	Randomized-controlled trial	Hospital OR: ASA I/II Elective surgery	30 = 15 control, 15 intervention	No nasopharyngeal O_2 insufflation	Nasopharyngeal catheter O_2 at 5 L·min⁻¹	Time to SpO_2 < 95% (max 6 min): AO: SpO_2 100% maintained in 15/15 patients at 6 min Control: 3.65 (1.15) min
Teller et al. 1988[15]	Randomized-controlled trial: double-blind crossover study	Hospital OR: ASA I/II Elective surgery	12	Placebo - no O_2 insufflation through catheter	Nasopharyngeal catheter O_2 at 3 L·min⁻¹	1) Time to SaO_2 < 92% (max 10 min): AO: SaO_2 > 97% all 10 min* Control: 6.8 (0.6) min 2) Minimum SaO_2: AO: 95%* Control: 91(1) %
Christodoulou et al. 2013[16]	Randomized-controlled double-blind study	Hospital OR: ASA I-III Elective surgery	41 = 14 control 27 intervention (13 at 5 L·min⁻¹, 14 at 10 L·min⁻¹)	No O_2 insufflation	Nasal prongs O_2 at 1) 5 L·min⁻¹ or 2) 10 L·min⁻¹	1) Time* 2) Treatment effect* 3) Mean PaO_2 10 L·min⁻¹ > 5 L·min⁻¹, and 0 L·min⁻¹ at 4 min*
Lee 1998[17]	Randomized-controlled trial	Hospital OR: ASA I/II, Tympanomastoidectomies	46 = 23 control, 23 intervention	No additional O_2	Nasal prongs O_2 at 5 L·min⁻¹	Apneic for 3 min 1) PaO_2 decrease: AO: 479 (48) mmHg → 345 (78) mmHg* Control: 479 (58) mmHg → 256 (81) mmHg 2) $PaCO_2$ increase: AO: 35.6 (3.4) mmHg → 47 (4.7) mmHg* Control: 35 (6.1) mmHg → 53.6 (5.3) mmHg
Millar et al. 2001[18]	Randomized-controlled trial	Hospital OR: ASA I/II Elective surgery	17 = 10 control, 7 intervention	No Eschmann tracheal tube introducer, no AO during intubation	Eschmann tracheal tube introducer inserted orally, tip in trachea, with O_2 at 8 L·min⁻¹	Time to SpO_2 90%: AO: 14.23 min* Control: 5.1 min

Table 1 continued

Paper	Design	Setting/Situation	Sample Size	Control Group	Apneic Oxygenation (AO) Group(s)	Results
Achar et al. 2014[4]	Randomized-controlled trial	Hospital OR: ASA I/II Elective surgery	56 = 28 control 28 intervention	AO via nasal prongs 5 L·min^{-1}	Nasopharyngeal catheter AO at 5 L·min^{-1}	Patients with SpO$_2$ < 95% (max 10 min): Nasopharyngeal catheter: 0/28 patients = 0%* Nasal prong: 9/28 patients = 32%
Frumin et al. 1959[19]	Prospective study No control	Hospital OR: Minor operations	8	None	Cuffed tracheal catheter 100% F$_1$O$_2$ via circle system at 8 L·min^{-1}	1) Duration of apnea: 18-55 min 2) Lowest SaO$_2$%: 98-100%
Babinski et al. 1985[20]	Prospective study No control	Hospital OR: Elective gynecological procedures	5 = 4 trans-abdominal hysterectomy, 1 transvaginal hysterectomy	None	Two endobronchial catheters inserted into right and left main stem bronchi with O$_2$ at 0.6-0.7 L·min^{-1} for 30 min	1) PaO$_2$: 30 min without significant desaturation, 321 (46) mmHg at start to 299 (37) mmHg at 30 min 2) PaCO$_2$: 37.0 (1.9) mmHg at start to 54.9 (4.0) mmHg at 30 min*
Rudlof et al. 2013[2]	Retrospective analysis No control	Teaching hospital OR: Panendoscopies	47	None	8-French catheter inserted into trachea with O$_2$ at 0.5 L·min^{-1}	Average apnea time = 24.7 (8.7) min
Patel et al. 2015[3]	Prospective study No control	Hospital OR: Difficult airways	25 = 15 male 10 female	None	High-flow nasal cannula with O$_2$ at 70 L·min^{-1}	1) Median IQR apnea time = 14 [9-19] min 2) No patient SpO$_2$ <90%

Values for Results are expressed as mean (standard deviation) unless otherwise indicated. AO = apneic oxygenation; ASA = American Society of Anesthesiologists physical status classification system; BMI = body mass index; IQR = interquartile range; OR = operating room; SD = standard deviation. *Statistically significant as compared with control, $P < 0.05$

Table 2 Apneic oxygenation studies outside the operation room

Paper	Design	Setting/Situation	Sample Size	Control Group	Apneic Oxygenation (AO) Group(s)	Results
Miguel-Montanes et al. 2015[21]	Prospective quasi-experimental before/after	University hospital ICU	101 = 50 control 51 intervention	Standard preoxygenation then 6 L·min⁻¹ O₂ flow via nasopharyngeal catheter during apnea	Preoxygenation with HFNC at 60 L·min⁻¹ and F₁O₂ 1.0, device maintained during apnea	1) Median IQR lowest SpO₂: AO: 100 [95-100]%* Control: 94 [83-98.5]% 2) Overall SpO₂: AO > control* 3) Hypoxemia (SpO₂ < 80%): AO: 2%* Control: 14%
Vourc'h et al. 2015[22]	Randomized-controlled trial	ICU	119 = 57 control 62 intervention	Standard preoxygenation. No AO	Preoxygenation 4 min with Optiflow HFNC (60 L·min⁻¹), maintained after induction	1) Lowest SpO₂ during intubation: Median IQR HFNC: 91.5 [80-96] % Control: 89.5 [81-95]% 2) Mean (SD) PaO₂/F₁O₂: HFNC: 120.2 (55.7) Control: 115.7 (63)
Semler et al. 2015[23]	Randomized, open-label trial	Medical ICU	150 = 73 control 77 intervention	No supplemental O₂ during laryngoscopy	Nasal cannula O₂ at 15 L·min⁻¹ during laryngoscopy	1) Lowest SpO₂: Median IQR AO: 92 [84-99] % Control: 90 [80-96] % 2) No difference in incidence of SpO₂ < 90%, SpO₂ < 80%, or decrease in SpO₂ > 3%
Wijewardena et al. 2014[24]	Prospective controlled study	ICU and ED	36 = 10 control 26 intervention	No AO	HFNC for preoxygenation and during intubation	SpO₂ decline: AO: 0-6% decline Control: 0-15% decline
Dyett et al. 2015[25]	Prospective observational study	ICU, ED, and wards	139 intubations = 76 had AO	No AO	Nasal cannula O₂ at 15 L·min⁻¹	1) Overall, hypoxemia AO = 12.8% Control = 19.6% 2) Patients without respiratory failure subgroup AO = 0%* Control = 16.7%

Table 2 continued

Paper	Design	Setting/Situation	Sample Size	Control Group	Apneic Oxygenation (AO) Group(s)	Results
Sakles et al. 2015[26]	Prospective controlled study	ED neurologically injured patients	90 = 51 control 39 intervention	No AO	Nasal cannula 1) AO 5 L·min⁻¹ (n = 9) 2) AO 10 L·min⁻¹ (n = 4) 3) AO ≥ 15 L·min⁻¹ (n = 26)	$SpO_2 < 90\%$ during intubation: AO: 7.7% (95% CI, 1.6 to 20.9) Control: 29.4% (95% CI, 17.5 to 43.8) aOR 4.8 (95% CI, 1.2 to 19.9)*
Wimalasena et al. 2015[27]	Retrospective before/ after	Helicopter emergency service - out-of-hospital and interhospital	728 = 310 control 418 intervention	Pre-implementation of AO	Nasal Cannula Post-implementation of AO	$SpO_2 < 93\%$ at any time: AO: 70/418 patients = 16.5% Control: 71/310 patients = 22.6% Difference = 6.1%*

AO = apneic oxygenation; aOR = adjusted odds ratio; CI = confidence interval; ED = emergency department; HFNC = high-flow nasal cannula; ICU = intensive care unit; IQR = interquartile range; SD = standard deviation. * Statistically significant as compared with control ($P < 0.05$)

crossover study, Teller et al.[15] examined 12 patients randomized to an apneic oxygenation group receiving oxygen at a rate of 3 L·min⁻¹ via nasal catheter or a control placebo group, with the two groups switching interventions in the second part of the study. Time to desaturation ($SaO_2 < 92\%$) was significantly longer in the apneic oxygenation group compared with the control group [$SaO_2 > 97\%$ all 10 min vs $SaO_2 < 92\%$ in 6.8 (0.6) min, respectively; $P < 0.01$]. The lowest mean SaO_2 recorded was significantly higher in the apneic oxygenation group vs the control group [$SaO_2 = 95\%$ vs $SaO_2 = 91 (1)\%$, respectively; $P < 0.001$].

Christodoulou et al.[16] examined the difference amongst patients randomized during tracheal intubation into three groups: apneic oxygenation via nasal prongs at a rate of 5 L·min⁻¹ ($n = 13$), 10 L·min⁻¹ ($n = 14$), or no apneic oxygenation control group ($n = 14$). Apneic oxygenation provided a significant difference in time to desaturation ($P = 0.028$) compared with the control group. The arterial oxygenation (i.e., PaO_2) in the 10 L·min⁻¹ group was significantly higher than both the 5 L·min⁻¹ group and the control group at four minutes ($P = 0.004$). Lee[17] studied 46 patients randomized to an apneic oxygenation group with oxygen rate at 5 L·min⁻¹ via nasal prongs or to a control group without apneic oxygenation. At three minutes, the mean PaO_2 decline in the apneic oxygenation group was significantly less than in the control group [PaO_2 479 (48) mmHg to 345 (78) mmHg vs PaO_2 479 (58) mmHg to 256 (81) mmHg, respectively; $P < 0.05$].

Millar et al.[18] compared 17 patients randomized to an apneic oxygenation group receiving 8 L·min⁻¹ of oxygen via an Eschmann® tracheal tube introducer in the trachea extending 2-3 cm beyond the vocal cords or a control group receiving no apneic oxygenation. The apneic oxygenation group had a significantly longer time to desaturation (time taken for SpO_2 to fall to 90%) compared with the control group (average of 14 min 14 sec vs 5 min 6 sec, respectively; $P < 0.001$). Achar et al.[4] compared the effectiveness of nasal prongs with that of a nasopharyngeal catheter in providing apneic oxygenation to 56 randomized patients, with both methods insufflating oxygen at a rate of 5 L·min⁻¹. The nasopharyngeal catheter was significantly more effective, as no patient desaturated in the nasopharyngeal group ($SpO_2 < 95\%$), while nine patients (32%) desaturated ($P = 0.001$) in the nasal prongs group.

There were four prospective studies that examined the effectiveness of apneic oxygenation without a control group. In an early study (1959), Frumin et al.[19] found that, in eight healthy patients, apneic oxygenation during intubation with an endotracheal catheter maintained adequate SpO_2 for 18-55 min, with the lowest SpO_2 recorded at 98-100%. Babinski et al.[20] performed a study on five females scheduled for elective gynecology

procedures and analyzed the effectiveness of 0.6-0.7 $L \cdot min^{-1}$ of oxygen insufflation via two endobronchial catheters inserted into the right and left main stem bronchi. All patients underwent 30 min of apnea without significant oxygen desaturation [PaO_2 = 321 (46) mmHg at the start and 299 (37) mmHg at 30 min). Patel and Nouraei[3] studied 25 patients with known difficult airways at high risk of oxygen desaturation during endotracheal intubation. Patients received oxygen via the Optiflow device at 70 $L \cdot min^{-1}$ using Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) until the trachea was successfully intubated. Median [interquartile range (IQR)] apnea time was 14 [9-19] min, and no patient desaturated to SpO_2 < 90%.

Rudlof and Hohenhorst[2] performed a retrospective study analyzing 47 patients who underwent a panendoscopy under apneic oxygenation at 0.5 $L \cdot min^{-1}$ using a catheter inserted into the trachea. The median SpO_2 at the end of the apneic period was 100%. Additionally, the mean (SD) apnea time was measured to be 24.7 (8.7) min with no adverse effects.

In summary, eight comparative studies showed that apneic oxygenation in the operating room through various routes (nasal, nasopharyngeal, tracheal, or endobronchial administration) prolongs time to oxygen desaturation and reduces the incidence of oxygen desaturation without adverse effects. Four single-device studies also showed maintenance of adequate SpO_2 with prolonged apnea.

The use of apneic oxygenation outside the operating room, including the ICU, emergency department, and pre-hospital encounters (Table 2)

Miguel-Montanes et al.[21] studied 101 patients requiring tracheal intubation in the ICU. The intervention group (n = 51) received preoxygenation using Optiflow HFNC at 60 $L \cdot min^{-1}$, which was maintained throughout the intubation. This technique was compared with a control group (n = 50) preoxygenated with a non-rebreathing bag reservoir face mask at 15 $L \cdot min^{-1}$ for three minutes, followed by 6 $L \cdot min^{-1}$ via nasopharyngeal catheter during the intubation. High-flow nasal cannula exceeded the control, with a higher median lowest SpO_2 (100% vs 94%, respectively; P < 0.0001), a smaller decrease in SpO_2 throughout (P < 0.0001), and a lower hypoxemic (SpO_2 < 80%) rate (2% vs 14%, respectively; P < 0.03).

In a conference abstract, Vourc'h et al.[22] randomized 119 patients into one of two groups. The apneic oxygenation group used Optiflow HFNC at 60 $L \cdot min^{-1}$ from induction until completion of intubation. The control group received face mask preoxygenation at 15 $L \cdot min^{-1}$ but no supplemental oxygen during the intubation attempt.

The median [IQR] lowest saturation was not significantly different between the apneic oxygenation and control groups (91.5 [80-96]% vs 89.5 [81-95]%, respectively)

Semler et al.[23] randomized 150 patients undergoing tracheal intubation in a medical ICU to receive either 100% oxygen at 15 $L \cdot min^{-1}$ via HFNC or no supplemental oxygen during laryngoscopy. They found that the median lowest SpO_2 was 92% with apneic oxygenation vs 90% with usual care (95% confidence interval [CI] for the difference was -1.6 to 7.4; P = 0.16). There were no statistical differences in the incidence of SpO_2 < 90% or SpO_2 < 80% between the groups.

In summary, only one dedicated ICU study showed benefits of sustained SpO_2 using apneic oxygenation compared with standard preoxygenation in patients requiring tracheal intubation. The other two studies, however, showed no benefit of apneic oxygenation. This discrepancy could be the result of heterogeneity in the underlying ICU population and the severity of pulmonary conditions, the device used to deliver high-flow apneic oxygenation, and variations in the oxygenation techniques used in the control group. Furthermore, many ICU patients have major ventilation-perfusion mismatch and shunting, and supplemental oxygenation may have limited value in improving arterial oxygenation.

There were two studies involving a mixed cohort of patients given tracheal intubation outside the operation room. In a study by Wijewardena et al.,[24] patients in the ICU and emergency department receiving apneic oxygenation using HFNC therapy, both during preoxygenation and during intubation (n = 26), were compared with patients receiving standard preoxygenation without apneic oxygenation (n = 10). The decrease in SpO_2 in the apneic oxygenation group (HFNC, with one exception) was 0-6%, while the decrease in the standard preoxygenation group was markedly higher, ranging from 0-15% (P value not stated).

Dyett et al.[25] performed a prospective observational study of patients receiving emergency airway management outside the operating theatres. Seventy-six of the 139 patients in their study received apneic oxygenation. Overall, apneic oxygenation did not reduce the incidence of hypoxemia compared with those without apneic oxygenation (19.6% vs 12.8%, respectively; P = 0.316). In a subgroup of patients receiving tracheal intubation for reasons other than respiratory failure, there were 0/31 (0%) hypoxemic episodes in those receiving apneic oxygenation compared with 10/60 (17%) in those without apneic oxygenation (P = 0.016).

One prospective study and one retrospective study analyzed the use of apneic oxygenation in either the emergency department or in an emergency pre-hospital setting. Sakles et al.[26] assessed 90 neurologically injured

patients in the emergency department undergoing tracheal intubation and compared the difference between patients receiving apneic oxygenation at various levels [5 $L\cdot min^{-1}$ ($n = 9$), 10 $L\cdot min^{-1}$ ($n = 4$), and $\geq$ 25 $L\cdot min^{-1}$ ($n = 26$)] with patients without apneic oxygenation ($n = 51$). The apneic oxygenation group had a significantly lower rate of oxygen desaturation ($SpO_2 < 90\%$) than the non-apneic oxygenation group (7.7%; 95% CI, 1.6 to 20.9 vs 29.4%; 95% CI, 17.5 to 43.8; respectively; $P = 0.03$).

Wimalasena et al.[27] retrospectively examined the difference in the incidences of oxygen desaturation ($SpO_2 < 93\%$) in a 22-month period in both out-of-hospital and interhospital retrievals. They compared patient outcomes before ($n = 310$) and after ($n = 418$) implementation of apneic oxygenation into the rapid sequence intubation protocol. Their study results showed that 22.6% of patients in the pre-apneic oxygenation phase had an episode of desaturation compared with 16.5% of patients in the post-apneic oxygenation phase, resulting in a difference of 6.1% (95% CI, 0.2 to 11.2).

In summary, in four of six studies involving patients undergoing tracheal intubation in ICU, emergency department, and pre-hospital settings, results showed that apneic oxygenation significantly reduces oxygen desaturation when compared with controls. In one observational study in ICU and emergency department patients, apneic oxygenation resulted in no overall reduction in hypoxemia but showed a reduction in hypoxemia in a patient subgroup.

Limitations of apneic oxygenation

Two main factors may limit the application of apneic oxygenation, i.e., elevation of carbon dioxide and rapid sequence intubation. First, apneic oxygenation can be applied for only a limited amount of time. During apneic oxygenation, CO_2 levels continue to rise, which can lead to a decrease in pH and the development of severe respiratory acidosis.[19,20,28] Measurements of mean CO_2 levels have ranged from 24.5 $mmHg$[29] to 160 $mmHg$,[19] with CO_2 rates increasing from 1.1-3.4 $mmHg\cdot min^{-1}$.[3] The lower rate of CO_2 increase during apneic oxygenation was obtained in a study using HFNC.[3] Many of the studies do not provide data on patients' $PaCO_2$ or end-tidal CO_2. The mean apneic time ranged from 5.29 min[12] to 43 min amongst clinical studies.[19] Many study patients tolerated very long periods of apnea. No significant side effects attributed to hypercapnia were reported. It is possible that hypercapnia might have caused physiologic disturbances that were not captured in the study results. Prolonged apneic oxygenation should be avoided in patients with contraindications to hypercapnia, such as those with increased intracranial pressure, hemodynamic instability, and cardiac dysrhythmia. Second, a patent airway is needed for effective apneic oxygenation. Emergency and ICU patients may require rapid sequence intubation with cricoid pressure, which may cause obstruction between the oropharynx and trachea, thereby preventing mass airflow between these spaces during apnea. Despite this concern, emergency and ICU studies have shown apneic oxygenation to be effective. Third, although the majority of studies utilize nasal prongs or nasopharyngeal catheters in the application of apneic oxygenation, several studies use tracheal or endobronchial catheters. It is clinically impractical to place catheters below the glottis for apneic oxygenation.

Limitations of this review

There are a few limitations to this review. First, a publication bias regarding apneic oxygenation may exist among the articles reviewed. It is possible that studies with positive results were published, while studies with negative results were neither submitted nor published. Second, a small sample size in a few of the prospective studies limits the generalizability of the results. Nevertheless, when all studies were analyzed together, 16 out of 19 studies showed beneficial effects of apneic oxygenation while three studies showed no clear benefit.

Finally, oxygenation, specifically, time to oxygen desaturation and oxygen desaturation rate, are the outcome measures used in the majority of the clinical studies. Oxygen saturation is a surrogate outcome variable which, in itself, has little clinical relevance. In contrast, clinically important outcomes, such as adverse respiratory events or adverse cardiac events, were not assessed in the studies. Furthermore, most of the studies have small sample sizes and were not adequately powered to detect adverse respiratory events or other serious rare complications. Large-scale adequately powered well-designed trials are needed to elucidate whether apneic oxygenation will reduce adverse respiratory events and whether the procedure is safe to use in patients at risk of hypoxemia undergoing tracheal intubation.

Practical guide to the application of apneic oxygenation during tracheal intubation in patients at a higher risk of hypoxemia

First, intubation equipment, a skilled operator, and an assistant should be readily available. Second, nasal cannula should be placed securely on the patient and connected to a dedicated oxygen source flowing minimally at 2-5 $L\cdot min^{-1}$. Third, preoxygenation using a face mask with F_IO_2 close to 1.0 (anesthesia machine or Ambu® bag with non-rebreathing mask) should be applied. If end-tidal O_2 is available, ensure it has reached 85-90%. Fourth, proceed

with general anesthesia, muscle relaxation, and bag mask ventilation. Fifth, increase the nasal oxygen flow to 10-15 $L \cdot min^{-1}$ and remove the face mask. Nasal cannula will provide apneic oxygenation during tracheal intubation. Nasal oxygenation should be continued until tracheal intubation is achieved and confirmed. Finally, apneic oxygenation can have risks and should be used with caution or avoided in clinical situations where hypercarbia could have adverse effects.

Conclusion

This review examined studies pertaining to apneic oxygenation during tracheal intubation in various clinical settings, including the operating room, ICU, emergency department, and pre-hospital situations. All 14 studies in the operating room and emergency departments, and two of five ICU studies, show that apneic oxygenation prolongs time to oxygen desaturation or reduces oxygen desaturation. Nevertheless, the majority of the studies were small in size, did not measure and were not adequately powered to detect adverse respiratory events or other serious rare complications. Prolonged apneic oxygenation (and its consequent hypercarbia) may be risky and should be avoided in patients with conditions such as increased intracranial pressure, metabolic acidosis, hyperkalemia, and pulmonary hypertension.

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