Does apneic oxygenation prevent desaturation during emergency airway management? A systematic review and meta-analysis

L'oxygénation apnéique prévient-elle la désaturation au cours de la gestion des voies respiratoires en urgence? Revue systématique de la littérature et méta-analyse

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Abstract

Purpose Apneic oxygenation (AO) via nasal cannulae is a potential method for preventing oxygen desaturation during emergency intubations. The purpose of this systematic review was to determine the effectiveness of AO in preventing oxygen desaturation during emergency intubations.

Source Three electronic databases (MEDLINE, EMBASE and CINAHL) were systematically searched to identify studies that examined the prevention of oxygen desaturation using AO via nasal cannulae. Our primary outcome was the incidence of oxygen desaturation as defined by each individual study; we secondarily assessed the incidence of severe oxygen desaturation ($SpO_2 < 80\%$). A meta-analysis of studies reporting data on oxygen desaturation as defined by each study and in patients with severe desaturation was performed to generate a pooled effect estimate.

Principal findings A total of 544 studies were screened, of which ten studies (2,322 patients) met all eligibility criteria. Compared with no AO, the use of AO was associated with a reduction of oxygen desaturation (relative risk [RR], 0.76; 95% confidence interval [CI], 0.61 to 0.95; $P = 0.02$), but not associated with a reduction in severe oxygen desaturation (RR, 0.65; 95% CI, 0.38 to 1.11; $P = 0.12$). Nevertheless, significant heterogeneity in patient factors, interventions, and

oxygen desaturation definitions was present between studies.

Conclusion Our findings suggest that AO via nasal cannulae is associated with a lower risk of oxygen desaturation during emergency intubations. Nevertheless, as there was significant heterogeneity between the studies, more high-quality trials are required to determine which patients may benefit from AO in emergency intubations.

Résumé

Objectif L'oxygénation apnéique (OA) par lunettes nasales est une méthode de prévention de la désaturation en oxygène au cours des intubations en urgence. L'objectif de cette revue systématique était de déterminer l'efficacité de l'OA sur la prévention de la désaturation en oxygène au cours des intubations en urgence.

Source Des recherches systématiques ont été effectuées dans trois bases de données électroniques (MEDLINE, EMBASE et CINAHL) pour identifier les études portant sur la prévention de la désaturation en oxygène au moyen de l'OA par lunettes nasales. Notre critère d'évaluation principal était l'incidence des désaturations telle que définie dans chaque étude; nous avons ensuite évalué l'incidence de la désaturation sévère en oxygène ($SpO_2 < 80\%$). Une méta-analyse a été effectuée sur les études présentant des données sur la désaturation en oxygène telle que définie par chaque étude et chez des patients ayant une désaturation sévère pour générer une estimation groupée de l'effet.

Constatactions principales Au total, 544 études ont été examinées, parmi lesquelles dix (2 322 patients) satisfaisaient tous les critères d'éligibilité. Comparativement à l'absence d'OA, l'utilisation de cette méthode a été associée à une réduction de la désaturation

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en oxygène (risque relatif [RR] : 0,76; intervalle de confiance à 95% [IC] : 0,61 à 0,95; $P = 0,02$), mais n'a pas été associée à une réduction de la désaturation sévère (RR, 0,65; IC à 95% : 0,38 à 1,11; $P = 0,12$). Néanmoins, il y avait une hétérogénéité significative des facteurs liés aux patients, des interventions et des définitions de la désaturation en oxygène entre les études.

Conclusion Nos constatations suggèrent que l'OA par lunettes nasales est associée à un moindre risque de désaturation en oxygène au cours des intubations en urgence. Cependant, compte de tenu de l'hétérogénéité des études, d'autres essais de grande qualité sont nécessaires pour déterminer quels patients pourraient bénéficier de l'OA au cours des intubations d'urgence.

Oxygen desaturation is a potentially dangerous complication that commonly occurs during endotracheal intubation in the intensive care unit (ICU), emergency department (ED), and out-of-hospital settings.¹⁻⁵ Desaturation during intubation places patients at risk for cardiac dysrhythmias, hemodynamic decompensation, and cerebral ischemia and may ultimately result in death.⁶ Despite advances in intubation sequences and techniques,⁷ emergency intubation is associated with a reported oxygen desaturation rate of 10.9-33.5%.¹⁻⁵ Severe hypoxemia, defined as an oxygen desaturation of $< 80\%$, can occur in up to 25% of cases.⁸ Prevention of hypoxemia is critical as a UK national review of emergency intubation identified hypoxemia as a cause of death in 50% of ICU and 27% of ED patients requiring intubation.⁹ Therefore, additional methods to prevent this life-threatening complication of hypoxemia are essential.

Recently, a technique known as apneic oxygenation (AO) has been described to determine whether its use can reduce the rate of desaturation during an intubation.¹⁰ Apneic oxygenation is the passive movement of oxygen to the alveoli without spontaneous or artificial ventilation. This technique provides continuous oxygen delivery using nasal cannulae,¹¹ thereby extending the safe apnea time. Apneic oxygenation has also been shown to prevent hypoxia during intubations performed in the operating room,^{10,12,13} prolonging the time to desaturation from 3.5-5.3 min using 5 L·min⁻¹ of flow¹³ and up to 17 min using high flow (60 L·min⁻¹) humidified nasal oxygenation.¹⁰

Studies examining the benefit of AO in ED and ICU settings have yielded conflicting results.¹⁴⁻¹⁷ It is challenging to estimate the true rate of desaturation, as studies often utilize inconsistent definitions of hypoxemia.¹⁻⁵ The primary objective of this systematic review was to examine studies evaluating patients

undergoing an emergency intubation (defined as intubation occurring in the ICU, ED, or out of hospital) to determine whether AO (using nasal cannulae) compared with conventional therapy (i.e., no AO and no initial bag valve mask [BVM] therapy) would prevent or minimize oxygen desaturation (as defined in each individual paper). The secondary objective of this review was to establish whether the use of AO results in a lower incidence of severe oxygen desaturation as defined by an incidence of oxygen saturation (SpO_2) $< 80\%$.

Methods

Data sources and search strategy

A systematic review was performed using the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.¹⁸ Potential studies were identified by searching three electronic databases (MEDLINE [1950-7 August 2017], EMBASE [1947-7 August 2017], and CINAHL [1961-7 August 2017]). The search strategy was developed in collaboration with an experienced librarian and modified as needed for each database (see Appendix). Additional search methods included hand searching key journals and reviewing the bibliographies of retrieved articles. The final search outcome was collated in Refworks (Proquest Software, Ann Arbor, MI, USA) where duplicate references were removed.

Study selection

All case-controlled, cohort and randomized-control trials (RCTs) were included in the analysis, providing that they met the following inclusion criteria: 1) design, primary study of original data involving human participants; 2) population, adult patients (as individually defined in each paper) undergoing emergency intubation (i.e., in the ICU, ED, or out of hospital); 3) exposure, patients receiving AO via nasal cannulae (either conventional nasal or high-flow nasal cannulae [HFNC]); 4) outcome, oxygen desaturation (as defined by the individual studies), as well as the incidence of severe oxygen desaturation ($\text{SpO}_2 < 80\%$). Studies were excluded if they did not provide a comparison group to the intervention or if initial BVM ventilation was used during the apneic period or in conjunction with AO. Articles that were identified through the search for which only an abstract was available were excluded if no primary data were included (though an attempt was made to contact the corresponding authors for primary data).

The title and abstract of each included article were screened for relevance by two reviewers (E.T. and O.L.); any studies not meeting the inclusion criteria were

excluded. The full texts of remaining studies were assessed by both reviewers. Any disagreements were resolved through consensus; if consensus could not be reached, a third reviewer (N.K.) was consulted to resolve the disagreement.

Data extraction

A standardized data extraction form was created and data were extracted for the following elements: authorship, year of publication, study design, number of patients, patient population, age, body mass index (BMI), gender, definition and incidence of oxygen desaturation, time to intubation, control of the upper airway (defined as an attempt to maintain a patent upper airway during the apneic phase [i.e., a protocol that described the use of a jaw thrust, chin lift, or use of an oral/nasal airway during the apneic period]), incidence of patients experiencing $\text{SpO}_2 < 80\%$, and the partial pressure arterial oxygen/fraction of the inspired oxygen ($\text{PaO}_2/\text{F}_i\text{O}_2$) ratio.

Outcomes

The primary outcome was the incidence of oxygen desaturation in patients undergoing emergency intubation with or without AO. This outcome was based on the definition or measurement of oxygen desaturation described by the individual studies. As a secondary outcome, we assessed the incidence of severe oxygen desaturation (defined as $\text{SpO}_2 < 80\%$), as previously described in studies of critically ill patients.^{19,20} A planned meta-analysis was performed to combine the results of a subgroup of independent studies based on the common outcome of severe oxygen desaturation $< 80\%$.

Quality assessment

The methodologic quality of each study was assessed by one investigator (E.T.), using the Newcastle-Ottawa Scale (NOS) for non-randomized studies and the Cochrane Collaboration Risk of Bias Tool for RCTs.^{21,22} Potential for publication bias was assessed by visually inspecting a funnel plot of the risk ratio vs standard error.²³

Statistical analysis

Descriptive statistics for categorical variables are presented as frequencies and percentages, and continuous variables are reported as mean (standard deviation [SD]) or median [interquartile range (IQR)]. A meta-analysis was performed on the primary outcome (oxygen desaturation) and the results of a subgroup of independent studies based on the secondary outcome. Continuous variables were pooled

with a random-effects generic-inverse-variance method, providing the summary point estimates and associated 95% confidence interval (CI). Dichotomous outcomes were pooled with a random-effect generic-inverse-variance method, providing summary point estimates and associated 95% CI.

Pooled results were reported as relative risk (RR) and a $P < 0.05$ was considered significant. Between-study heterogeneity of effect size was quantified using the I^2 statistic.²⁴ Review Manager (RevMan Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to pool and analyze results from the individual studies.

Results

A total of 544 articles were identified from the described search. After removal of 109 duplicates, we screened the titles and abstracts of the remaining 435 articles for eligibility. We identified 34 potentially eligible articles and reviewed the full text of each. Ten studies met all of the inclusion and exclusion criteria. A flow diagram outlining the search strategy and final selection is shown in Fig. 1.

Study characteristics

Data were extracted from the ten studies involving 2,322 participants. There were four prospective cohort studies,^{14,15,25,26} four RCTs,^{16,17,27,28} and two retrospective cohort studies.^{29,30} Table 1 summarizes the characteristics of each included study. The patient populations in the included studies were diverse, with three studies examining intubation in the ED,^{15,25,28} two studies describing out-of-hospital intubation,^{29,30} four studies investigating intubation in the ICU,^{14,16,17,28} and one in a mixed ICU and ED population.²⁸ Patients were predominately male (55–71%), and mean (SD) age ranged from 45 (21) to 62 (14) yr. Three studies reported mean (SD) BMI^{16,17,28} that ranged from 26.1 (6.2) to 28.6 (SD not reported), and the mean (SD) severity of hypoxia based on the $\text{PaO}_2/\text{F}_i\text{O}_2$ was described in two studies^{16,27} as 118 (59) and 203 (58). Regarding controlling for confounding factors, all trials used neuromuscular blockers for the intubation, with seven using a rapid sequence induction (RSI) as part of their protocol.^{14,15,25,27–30} Two studies reported controlling for patency of the upper airway during the intubation procedure, which was described as maintenance of a jaw thrust or chin lift during the apneic phase of the intubation.^{14,28} Five of the studies recorded the mean (SD) time to intubation^{14,16,17,27,28} in each population group, which ranged from 34 (22) sec to 150 (SD not reported) sec.

Fig. 1 Flow diagram of studies selected for inclusion in the review

Table 2 summarizes the oxygen flow rate of AO through the nasal cannulae used in each study. Two studies compared a variable flow of AO,^{15,25} five studies 15 L·min⁻¹,^{17,26,28-30} and three studies compared AO using humidified HFNC at 50-60 L·min⁻¹ with conventional therapy.^{14,16,27}

Preoxygenation

Table 3 summarizes the preoxygenation techniques described in each of the studies. Overall, preoxygenation using a non-rebreather mask was used in 1,882 (81.5%) patients, BVM in 225 (9.7%) patients, HFNC in 133 (5.7%) patients, non-invasive ventilation in 102 (4.4%) patients, and other methods of preoxygenation in 15 (0.6%) patients. In all study groups that used nasal cannulae for AO, preoxygenation with nasal cannulae was performed in combination with the described preoxygenation technique.

Oxygen desaturation

Table 4 summarizes the level of oxygen desaturation experienced by patients in the included studies. In the two studies that defined oxygen desaturation as SpO₂ < 93%,^{26,29} the incidence of desaturation was 13-17% in patients that received AO compared with 20-23% in patients that did not receive the intervention. Five studies defined oxygen desaturation as SpO₂ < 90%^{15,17,25,28,30}; in these patients, the incidence of oxygen desaturation was 7-45% in those that received AO and 15-47% in the control group. Three studies defined oxygen desaturation as SpO₂ < 80%^{14,16,27}; in these patients the incidence of oxygen desaturation was 2-26% in those that received AO and 14-25% in the control group. A meta-analysis was performed comparing AO vs conventional therapy using the definition of oxygen desaturation as defined in each of the ten included

Table 1 Characteristics of included studies

Study	Design	No. of patients	Population	Mean or median age (SD), [IQR] (% male)	Gender	Mean or median BMI (SD), [IQR]	Control for upper airway ¹	Mean or median PaO ₂ /F _i O ₂ (SD), [IQR]
Sakles <i>et al.</i> (1) 2016	Prospective observational study	127	Intracerebral hemorrhage requiring ED intubation	50 (20.5)	70.9	NR	No	NR
Wimalasena <i>et al.</i> 2015	Retrospective	728	Out of hospital	46 ⁴ [NR]	68.5	NR	No	NR
Sakles <i>et al.</i> (2) 2016	Prospective observational study	635	ED	50.6 (19.0)	64.3	NR	No	NR
Vourc'h <i>et al.</i> 2015	RCT	119	ICU	62.2 (14.2)	65.5	27.6 (6.5)	No	118 (59.1)
Dyett <i>et al.</i> 2015	Prospective observational study	129	ICU, ED	54 ⁴ [35-69]	59.7	NR	No	NR
Semler <i>et al.</i> 2016	RCT	150	ICU	60 ⁴ [NR]	60.7	28.6 ⁴ [NR]	No	NR
Miguel-Montanes <i>et al.</i> 2015	Prospective quasi-experimental	101	ICU	60 ⁴ [NR]	64.4	NR	Yes ³	NR
Simon <i>et al.</i> 2016	RCT	40	ICU	58.5 (11.5)	55	26.1 (6.2)	NR	202.5 (58)
Caputo <i>et al.</i> 2016	RCT	200	ED	54.6 (1.1)	58.5	NA	Yes	NR
Riyapan <i>et al.</i> 2016	Case cohort study	93	Out of hospital	45.4 (21.2)	69.9	NA	NR	NR

BMI = body mass index; ED = emergency department; ICU = intensive care unit; IQR = interquartile range; NA = not available; NR = not reported; RCT = randomized-controlled trial; SD = standard deviation

F_iO₂/PaO₂ = partial pressure arterial oxygen/fraction of inspired oxygen

¹ Upper airway patency controlled for in the study (i.e., jaw thrust or pharyngeal airway)

² Mean PaO₂/F_iO₂ ratio to quantify the severity of hypoxic respiratory failure

³ Not mentioned in the study protocol; information obtained through contact with primary author. Airway maintained with jaw thrust in all patients

⁴ Mean of the reported medians; for these no IQR can be reported (NR)

Table 2 Type of apneic oxygenation and measurement of desaturation

Study	Intervention ¹	Primary outcome	Secondary outcome	Use of neuromuscular blocker for the intubation ²	Mean ³ or Median time to intubation in seconds (SD or IQR)
Sakles <i>et al.</i> 2016	Varying levels of AO (5, 10, 15, > 15 L·min ⁻¹) vs none	Incidence of desaturation < 90%	Incidence of desaturation < 80% and < 70%	Yes (RSI)	NR
Wimalasena <i>et al.</i> 2015	AO with 15 L·min ⁻¹ vs none	Incidence of desaturation < 93%	NR	Yes (RSI)	NR
Sakles <i>et al.</i> 2016	AO with 0, 5, 10, 15, > 15 vs none	Incidence of desaturation < 90%	NR	Yes (RSI)	NR
Vour'h <i>et al.</i> 2015	AO with HFNC 60 L·min ⁻¹ vs none	Lowest oxygen saturation (SpO ₂)	Quality of preoxygenation, including duration, ability of device to improve SpO ₂ ; quality of ETI procedure, including adverse events during ETI and in next hour, difficult intubation rate and IDS; organ failure during first 5 days (SOFA score); PaO ₂ /F _i O ₂ ratio during following hour and first 5 days; ICU morbidity (time on ventilator, length of stay, ventilation-free days, occurrence of ventilator-associated pneumonia and 28-day mortality)	Yes (89%)	60 ⁴ (NR)
Dyett <i>et al.</i> 2015	AO was subgroup (if used 15 L·min ⁻¹)	Incidence of desaturation < 93%	NR	Yes (90%)	NR
Semler <i>et al.</i> 2016	AO with 15 L·min ⁻¹ vs conventional	Lowest saturation (SpO ₂)	Incidence of hypoxemia	Yes (97%)	150 ⁴ (NR)
Miguel-Montanes <i>et al.</i> 2015	AO with 6 L·min ⁻¹ flow through NP catheter vs 60 L·min ⁻¹	Lowest saturation (SpO ₂)	Median SpO ₂ obtained during intubation, after preoxygenation, and after intubation and SpO ₂ < 80%	Yes (RSI)	120 ⁴ (NR)
Simon <i>et al.</i> 2016	HFNC (50 L·min ⁻¹) vs BVM (No bagging during apnea)	Lowest saturation (SpO ₂)	Changes in ABG 30 min post intubation	Yes (RSI)	33.5 (22)
Caputo <i>et al.</i> 2016	AO with > 15 L·min ⁻¹ through NC	Lowest saturation (SpO ₂)	Rates of first pass success, desaturation below SpO ₂ 90%, and desaturation below SpO ₂ 80%	Yes (RSI)	61 (3.6)
Riyapan <i>et al.</i> 2016	AO with > 15 L·min ⁻¹ through NC	Incidence of desaturation < 90%	NR	Yes (RSI)	NR

ABG = arterial blood gas; AO = apneic oxygenation group; BVM = bag valve mask; ETI = endotracheal intubation; HFNC = high flow nasal cannulae; ICU = intensive care unit; IDS = intubation difficulty score; NC = nasal cannulae; NP = nasal prongs; NR = not reported; RSI = rapid sequence intubation; SpO₂ = oxygen saturation

PaO₂/F_iO₂ = partial pressure arterial oxygen/fraction of inspired oxygen

¹ Flow of nasal cannulae used for apneic oxygenation and the control group. In all trials AO with NP was used during preoxygenation as well as the apneic period

² Numbers in quotations represent the percentage of patients who received neuromuscular blockers for the intubation or RSI, which was part of the study protocol where 100% received neuromuscular blockers

³ Average documented time of induction of medication to securing the airway

⁴ Mean of the reported medians, for those no IQR can be reported (NR)

Table 3 Preoxygenation technique prior to intubation as described in the studies

Study	No. of patients	No. of NRB patients (%)	No. of BVM patients (%)	No. of HFNC patients (%)	No. of NIV patients (%)	No. of other patients (%) ²
Sakles <i>et al.</i> (1) 2016	127	126 (99.2)	-	-	-	1 (0.8)
Wimalasena <i>et al.</i> 2015	728	728 (100)	-	-	-	-
Sakles <i>et al.</i> (2) 2016	635	635 (100)	-	-	-	-
Vourc'h <i>et al.</i> 2015	119	57 (47.9)	-	62 (52.1)	-	-
Dyett <i>et al.</i> 2015	129	14 (10.1)	97 (69.8)	-	27 (19.4)	1 (0.7)
Semler <i>et al.</i> 2016 (1)	150	57 (38)	64 (42.7)	-	46 (30.1)	9 (6.0)
Miguel-Montanes <i>et al.</i> 2015	101	50 (50)	-	51 (50)	-	-
Simon <i>et al.</i> 2016	40	-	20 (50)	20 (50)	-	-
Caputo <i>et al.</i> 2016	200	166 (83)	5 (2.5)	-	29 (14.5)	-
Riyapan <i>et al.</i> 2016	93	49 (52.7)	39 (41.9)	-	-	4 (5.4)

BVM = bag valve mask; HFNC = high-flow nasal cannulae; NIV = non-invasive ventilation and other; NRB = non-rebreather mask

¹ Study data presented as per article. Noted in the article that each participant may have received more than one method of preoxygenation

² Other methods of preoxygenation, which may include regular nasal cannulae or other methods not described

Table 4 Definition of desaturation across included studies

Study	Definition of desaturation ¹	Number of patients		Patients who desaturated ² n (%)		Severe desaturation (SpO ₂ < 80%) ³ n (%)	
		AO	No AO	AO	No AO	AO	No AO
Sakles <i>et al.</i> 2016	SpO ₂ < 90%	72	55	5 (7)	16 (29)	3 (4)	10 (18)
Wimalasena <i>et al.</i> 2015	SpO ₂ < 93%	418	310	70 (17)	71 (23)	-	-
Sakles <i>et al.</i> 2016	SpO ₂ < 90%	380	255	78 (18)	79 (31)	-	-
Vourc'h <i>et al.</i> 2015	SpO ₂ < 80%	62	57	15 (26)	13 (22)	15 (26)	13 (22)
Dyett <i>et al.</i> 2015	SpO ₂ < 93%	47	92	6 (13)	18 (20)		
Semler <i>et al.</i> 2016	SpO ₂ < 90%	77	73	34 (45)	34 (47)	12 (15.8)	18 (25)
Miguel-Montanes <i>et al.</i> 2015	SpO ₂ < 80%	51	50	1 (2)	7 (14)	1 (2)	7 (14)
Simon <i>et al.</i> 2016	SpO ₂ < 80%	20	20	5 (25)	5 (25)	5 (25)	5 (25)
Caputo <i>et al.</i> 2016	SpO ₂ < 90%	100	100	17 (17)	15 (15)	3 (3)	4 (4)
Riyapan <i>et al.</i> 2016	SpO ₂ < 90%	29	64	5 (17.2)	14 (21.9)	-	-

AO = apneic oxygenation group; No AO = control group; SpO₂ = oxygen saturation

¹ Definition of desaturation as defined by each study

² Frequency of patients who desaturated as defined by each study

³ Frequency of patients who desaturated to an SpO₂ < 80%

studies. Overall, there was a significant reduction in the incidence of desaturation (RR, 0.76; 95% CI, 0.61 to 0.95; $P = 0.02$) with low heterogeneity ($I^2 = 37\%$, $P = 0.11$), which favoured AO as an intervention to prevent oxygen desaturation.

Severe oxygen desaturation

We performed a sub-group meta-analysis of six studies (four RCTs^{16,17,27,28} and two observational studies),^{14,15}

which examined the incidence of severe desaturation (SpO₂ < 80%). In the AO group, the incidence of severe desaturation was 2-26%, whereas the incidence of severe desaturation was 4-25% in the control group. A meta-analysis was performed for severe oxygen desaturation in the six identified articles. Overall there was no significant reduction in the incidence of severe oxygen desaturation (RR, 0.65; 95% CI, 0.38 to 1.11; $P = 0.12$) with low heterogeneity ($I^2 = 39\%$, $P = 0.15$) (Figs. 2 and 3).

Fig. 2 Incidence of oxygen desaturation as defined in each study. Forest plot comparing apneic oxygenation vs no apneic oxygenation during emergency intubations in ten studies under the random effects

meta-analysis. The sizes of the boxes in the figure are in proportion to the weight assigned to each study, whereas the horizontal bar is the reported 95% confidence interval for each risk ratio.

Fig. 3 Incidence of severe desaturation ($SpO_2 < 80\%$). Forest plot comparing apneic oxygenation vs no apneic oxygenation during emergency intubations in six studies under the random effects meta-

analysis. The sizes of the boxes in the figure are in proportion to the weight assigned to each study, whereas the horizontal bar is the reported 95% confidence interval for each risk ratio.

Risk of bias

The quality assessment of each study is presented in Tables 5 and 6. The risk of bias of the four RCTs was graded as low risk overall (Table 5). For the six non-randomized trials, the NOS scores for the included studies ranged from 7–10 (Table 6). Visual inspection of the funnel plot (Fig. 4) showed some asymmetry indicating that potential for publication bias may exist.

Discussion

This systematic review identified ten studies that compared AO via nasal cannulae with conventional therapy during an emergency intubation. Based upon the definitions used in each study, AO was associated with an overall reduction of oxygen desaturation compared with conventional therapy (RR, 0.76; 95% CI, 0.61 to 0.95; $P = 0.02$). In our subgroup meta-analysis examining severe oxygen desaturation, AO was not associated with a reduction in

the incidence of severe oxygen desaturation compared with conventional therapy (RR, 0.65; 95% CI, 0.38 to 1.11; $P = 0.12$). Our findings suggest that AO may be more effective than conventional therapy for preventing oxygen desaturation during an emergency intubation.

Life-threatening desaturation is a common complication of emergency intubation, occurring in up to 25% of all intubations in critically ill patients.⁸ Preoxygenation prior to intubation is required to prevent desaturation during the apneic period after induction and paralysis and during intubation. Non-rebreather masks and bag valve devices are routinely used for preoxygenation in emergency situations.²⁸ Although oxygen desaturation is often a transient event, several studies have determined that desaturation during the intubation procedure is a significant risk factor for cardiovascular collapse during the intubation process.^{9,31,32} Nevertheless, to date no study has correlated this transient hypoxemia with worse long-term outcomes such as mortality or time on ventilator. Despite this paucity of data to implicate worse outcomes from transient hypoxemia, the high incidence of oxygen

Table 5 Cochrane risk of bias for randomized control trials

Study	Bias domain	Source of bias	Review authors' judgement	Support for judgement
Semler <i>et al.</i> 2016	Selection	Random sequence generation	Low risk	Block randomization sequence of study group assignments was generated via a computerized algorithm using permuted blocks of 4, 8, and 12
		Allocation concealment	Low risk	Study group assignments were placed in sequentially numbered opaque envelopes that remained sealed until the decision had been made that a patient required intubation and was enrolled in the study
	Performance	Blinding of participants and personnel	Low risk	Open labelled however this should not affect results
	Detection	Blinding of outcome assessment	Low risk	Open labelled and physicians would know lowest SpO ₂
	Attrition	Incomplete outcome data	Low risk	No patients lost to follow-up, no data missing. All patients accounted for with indications why patients were excluded
	Reporting	Selective reporting	Low risk	All pre-specified data points were reported
	Other	Anything else, ideally pre-specified		
Vourc'h <i>et al.</i> 2015	Selection	Random sequence generation	Low risk	Randomization used fixed blocks of four patients (ratio 1:1) and was stratified by center
		Allocation concealment	Low risk	Patients were allocated to one of the two preoxygenation strategies (HFNC or HFFM) using a secure computer-generated online remote system (Clinisight software) controlled by the independent research promotion unit at the University Hospital of Nantes, which had no role in patient recruitment
	Performance	Blinding of participants and personnel	Low risk	Open labelled however this should not affect results
	Detection	Blinding of outcome assessment	Low risk	Open labelled and physicians would know lowest SpO ₂
	Attrition	Incomplete outcome data	Low risk	All patients accounted for. 6 (4.9%) patients were excluded after randomization with clear documentation
	Reporting	Selective reporting	Low risk	All data points were recorded
	Other	Anything else, ideally pre-specified		
Simon <i>et al.</i> 2016	Selection	Random sequence generation	Low risk	Randomization was accomplished by computer-generated random number sequence allocation
		Allocation concealment	Low risk	study team blinded by using numbered, opaque, and sealed envelopes
	Performance	Blinding of participants and personnel	Low risk	Open labelled however this should not affect results
	Detection	Blinding of outcome assessment	Low risk	Open labelled and physicians would know lowest SpO ₂
	Attrition	Incomplete outcome data	Low risk	All patients accounted for. No drop out after randomization
	Reporting	Selective reporting	Low risk	All data points recorded
	Other	Anything else, ideally pre-specified		
Caputo <i>et al.</i> 2016	Selection	Random sequence generation	Low risk	Randomization was accomplished by predetermined randomization
		Allocation concealment	Low risk	Study recorder, blinded to study outcome not involved in the procedure recorded the data
	Performance	Blinding of participants and personnel	Low risk	Open labelled however this should not affect results
	Detection	Blinding of outcome assessment	Low risk	Open labelled and physicians would know lowest SpO ₂
	Attrition	Incomplete outcome data	Low risk	A total of 206 patients enrolled with 6 accidentally receiving the wrong intervention. They were excluded from the analysis
	Reporting	Selective reporting	Low risk	All data points recorded
	Other	Anything else, ideally pre-specified		

HFNC = high-flow nasal cannulae; HFFM = high-flow face mask; SPO₂ = oxygen saturation

Table 6 Newcastle-Ottawa scale for risk of bias and quality assessment of included studies

Case control studies	Selection	Comparability				Exposure		Total			
		Case definition	Representativeness of the cases	Selection of controls	Definition of controls	Study controls for use of apneic oxygenation	Study controls for BMI, age and gender		Ascertainment of exposure	Ascertainment for cases and controls	Non-response rate
Wimalasena <i>et al.</i> 2015	☆	☆	☆	☆	-	☆	-	☆	☆	☆	7
Riyapan <i>et al.</i> 2016	☆	☆	☆	☆	-	☆	-	☆	☆	☆	7
Cohort studies											
	Selection	Comparability				Outcomes		Total			
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Study controls for use of apneic oxygenation	Study controls for BMI, age and gender		Assessment of outcomes	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts
Sakles <i>et al.</i> 2016	☆	☆	☆	☆	☆	☆	☆	☆	☆	☆	10
Sakles <i>et al.</i> 2016	☆	☆	☆	☆	☆	☆	☆	☆	☆	☆	10
Miguel-Montanes <i>et al.</i> 2015	☆	☆	☆	☆	☆	☆	☆	☆	☆	☆	10
Dyett <i>et al.</i> 2015	☆	☆	☆	☆	☆	☆	☆	-	☆	☆	9

BMI = body mass index

Fig. 4 Funnel plot of the risk ratio (RR) of included studies against the standard error (SE) of the log RR. Individual study results are represented by open circles. The pooled effect size is represented by the vertical line in the plot. Asymmetry of the funnel plot suggests publication bias.

desaturation in this patient population highlights the need to develop improved methods to minimize any complications that may arise.

Apneic oxygenation via nasal cannulae is a recently described airway technique, which prevents oxygen desaturation during intubation.^{11–13} First described in 1959,³³ AO is a method of providing alveolar oxygen delivery despite the lack of active respiration (apnea). Alveolar oxygen delivery is thought to occur through the generation of a pressure gradient between the lungs and oropharynx. During apnea, there is a discrepancy in the absorption of oxygen and the generation of CO₂ in the lung alveoli.^{34,35} The subsequent gas deficit results in sub-atmospheric pressures in the alveolar space, generating a pressure gradient between the oropharynx (higher pressure) and the lungs (lower pressure), causing bulk flow of air from the upper airway into the alveoli.

Only recently have studies explored the benefits of using AO via nasal cannulae during endotracheal intubation. Results from case control and observational studies suggest that AO may reduce desaturation events in critically ill patients.^{14,15,29} To date, there have been no documented adverse effects from the use of AO via nasal cannulae including nasal trauma or interference of laryngoscopy.³⁶ Effective AO relies on the availability of an oxygen source, nasal prongs, and a patent upper airway. Patency of the upper airway is a critical factor in the success of AO; an obstructed upper airway prevents oxygen diffusion from the nasal pharynx to the trachea.³⁶

The few studies carried out to date in elective surgery patients have showed a clear benefit for the extension of safe apnea time when using AO.^{10,13} Conversely, AO literature in critically ill patients has shown mixed results for prolongation of oxygen desaturation during emergency

intubation.^{14,16} Possible explanations for the difference in these findings are the severity of illness in the patient population and variation of airway technique. Patients requiring emergency intubations are generally unstable compared with those seen in the operating room. Sepsis, respiratory distress, and respiratory failure increase the cardiac output and metabolic demand in critically ill patients, which results in a higher rate of oxygen consumption to maintain homeostasis.³⁷ In addition, pulmonary pathology (e.g., infection and pulmonary edema) may lead to pulmonary shunting, which may contribute to the lack of significant benefit of AO in preventing oxygen desaturation in emergency intubation compared with during induction of anesthesia for elective surgery.

Studies of AO during anesthesia may have also benefited from the use of airway protocols. All operating room studies were protocolized in their airway set-up including maintenance of the upper airway with a jaw thrust, chin lift, oral airway, or suspension laryngoscopy.^{10,12,13} This is in contrast to the majority of studies included in this review, where airway management was the responsibility of each individual physician performing the intubation and the study methodology did not specifically account for patency of the upper airway. Maintenance of the upper airway is critical for AO to work and, as currently described, the maintenance of the upper airway patency is not part of a rapid sequence intubation, though it does recommend cricoid pressure, which may exacerbate an upper airway obstruction.³⁸ As the majority of the studies utilized an RSI for their intubations, it is possible that many of the patients in the reviewed studies did not have a patent upper airway during the intubation procedure, which may impact the demonstrated effectiveness of AO as reported in more stable patients.

It is challenging to determine whether the flow of AO impacted the effect on oxygen desaturation because of the differences between studies. Higher AO flows (i.e., HFNC) have been shown to be effective at prolonging the time to oxygen desaturation time in anesthesia¹⁰ as it can help to ensure a higher concentration of oxygen in the nasal/oral pharynx as well as provide some positive end-expiratory pressure during the apneic period.¹¹ The most common flow of AO used in our studies was 15 L·min⁻¹; however, flow rates among studies varied from 5–60 L·min⁻¹. Due to this heterogeneity, it was not possible to perform subgroup analysis to test whether higher flow was superior in AO. When examining studies that used HFNC, we found mixed outcomes—two studies showing no difference,^{16,27} while a third study showed a possible benefit.¹⁴ Therefore, based on the findings of this review,

it is unclear whether a higher flow of AO results in greater benefit.

The major limitations of the review stem from the wide heterogeneity of patient factors and measurements among the included studies; therefore, the results should be interpreted with caution. Many studies did not account for conditions known to increase the risk of oxygen desaturation during intubation such as increased BMI and severity of hypoxia.³⁹ In addition, significant heterogeneity existed in the definition of oxygen desaturation—i.e., there were three different definitions ($\text{SpO}_2 < 93$, 90, and 80%) used in the studies included. Anticipating that there would be a heterogeneous definition of oxygen desaturation in the literature, we elected to use a predefined and more clinically significant measurement ($\text{SpO}_2 < 80\%$) of desaturation⁸ as our secondary outcome and combined the results from six studies in a subgroup meta-analysis. Agreement on a standard definition of oxygen desaturation would improve our ability to compare and generalize the findings of future studies. Another potential limitation was the inclusion of both randomized and non-randomized studies in the meta-analysis. Based upon a growing body of evidence recommending the inclusion of non-randomized studies into meta-analyses, a decision was made to include both study groups in the analysis.^{40–42}

The strength of this review lies in the patient selection for emergency intubations. As highlighted above, intubations in the ICU, out of hospital, and in the ED have a larger incidence of severe complications and examining the benefit of AO in this vulnerable patient population is critical. The results from this review are in keeping with results found with other systematic reviews suggesting that AO via nasal cannulae may reduce the overall incidence of oxygen desaturation.^{43–47} When examining the effects of AO on severe oxygen desaturation there are conflicting results.^{43–47} Some reviews suggest that AO resulted in a decreased incidence of severe oxygen desaturation,^{43–45} while others have concluded that there was no difference in AO compared with no AO.^{46,47} The inconsistent results, as well as the significant clinical heterogeneity of the published studies, suggest that more well-designed clinical trials are required before standard implementation of AO during an emergency intubation should be recommended. Future studies would benefit from a standard airway protocol for the intubation process (standard preoxygenation, positioning, and attempts to maintain patency of the upper airway with a jaw thrust, chin lift, or nasal/oral airway). Furthermore, having a consistent definition of oxygen desaturation and accurate documentation of important airway variables, including the time to intubation and severity of hypoxemia for intubation ($\text{PaO}_2/\text{F}_i\text{O}_2$ ratio), are recommended.

Conclusion

The results of this review suggest that AO via nasal cannulae is associated with a decreased incidence of oxygen desaturation in emergency intubations. To ascertain whether any patient- or system-level factors affect the outcome of AO on oxygen desaturation in emergency intubations, we suggest that further clinical trials are required.

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Appendix

MEDLINE

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((("intubation"[MeSH Terms] OR intubat*[tw]) OR
("laryngoscopy"[MeSH Terms] OR laryngoscop*[tw]))
AND((((apneic oxygenation*[tw]) OR (((transnasal[tw]
OR nasal cannul*[tw]) OR nasal prong*[tw]) OR nose
prong*[tw])) AND (apne*[tw] OR apnoe*[tw] OR
hypox*[tw] OR desaturat*[tw])))))
```

CINAHL

```
((("MH "Intubation")) OR ((MH "Laryngoscopy")) OR
intubat* OR laryngoscop*) AND (((MH "Nasal
Cannula")) OR (apneic N1 oxygen*) OR transnasal OR
(nasal N1 cannul*) OR (nasal N1 prong*) OR (nose N1
prong*)) AND (((MH "Apnea")) OR ((MH "Anoxia"))
OR apne* OR apnoe* OR hypoxi* OR desaturat*)
```

EMBASE

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('intubation'/de OR intubat*:ab,ti OR 'respiratory tract
intubation'/exp OR ('laryngoscopy'/exp OR
laryngoscop*:ab,ti)) AND ('nasal cannula'/exp OR
((apneic OR apnoeic) NEAR/1 oxygen*):ab,ti OR
```

transnasal:ab,ti OR ((nasal OR nose) NEAR/1 (cannul* OR prong*)):ab,ti) AND ('apnea'/exp OR 'anoxia'/exp OR apne*:ab,ti OR apnoe*:ab,ti OR hypoxi*:ab,ti OR desaturat*:ab,ti)

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