Effectiveness of Apneic Oxygenation During Intubation: A Systematic Review and Meta-analysis

Lucas Oliveira J. e Silva; Daniel Cabrera, MD; Patricia Barrionuevo, MD; Rebecca L. Johnson, MD; Patricia J. Erwin, MLS; M. Hassan Murad, MD, MPH; M. Fernanda Bellolio, MD, MS*

*Corresponding Author. E-mail: Bellolio.Fernanda@mayo.edu, Twitter: @mfbellolio, @lucasojesilva12.

Study objective: We conduct a systematic review and meta-analysis to evaluate the effectiveness of apneic oxygenation during emergency intubation.

Methods: We searched Ovid MEDLINE, Ovid EMBASE, Ovid CENTRAL, and Scopus databases for randomized controlled trials and observational studies from 2006 until July 2016, without language restrictions. Gray literature, clinicaltrials.gov, and reference lists of articles were hand searched. We conducted a meta-analysis with random-effects models to evaluate first-pass success rates, incidence of hypoxemia, and lowest peri-intubation SpO_2 between apneic oxygenation and standard oxygenation cases.

Results: A total of 1,386 studies were screened and 77 selected for full-text review. A total of 14 studies were included for qualitative analysis, and 8 studies (1,837 patients) underwent quantitative analysis. In the meta-analysis of 8 studies (1,837 patients), apneic oxygenation was associated with decreased hypoxemia (odds ratio [OR] 0.66; 95% confidence interval [CI] 0.52 to 0.84), but was not associated with decreased severe hypoxemia (6 studies; 1,043 patients; OR 0.86; 95% CI 0.47 to 1.57) or life-threatening hypoxemia (5 studies; 1,003 patients; OR 0.90; 95% CI 0.52 to 1.55). Apneic oxygenation was associated with increased first-pass success rate (6 studies; 1,658 patients; OR 1.59; 95% CI 1.04 to 2.44) and increased lowest peri-intubation SpO_2 (6 studies; 1,043 patients; weighted mean difference 2.2%; 95% CI 0.8% to 3.6%).

Conclusion: In this meta-analysis, apneic oxygenation was associated with increased peri-intubation oxygen saturation, decreased rates of hypoxemia, and increased first-pass intubation success. [Ann Emerg Med. 2017;■:1-12.]

Please see page XX for the Editor's Capsule Summary of this article.

0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2017.05.001

INTRODUCTION

Background

Apneic oxygenation consists in the administration of oxygen during the apneic period of the intubation procedure to extend the safe apnea time beyond that which can be achieved by preoxygenation alone.[1-5] This concept was first introduced in the operating room setting,[6] and more recently its use has been rapidly adopted during airway management in the emergency department (ED) and ICU.[7-10] The rationale for apneic oxygenation revolves around the physiologic capacity of continuous oxygen capture by alveoli through a passive process without providing ventilation.[6,11] During laryngoscopy, apneic oxygenation may be provided as continuous oxygen delivery throughout the intubation with nasal cannulas, nasopharyngeal catheters, and modified laryngoscopes.

Importance

Airway management is commonly performed by anesthesiologists, emergency physicians, and critical care providers as part of their daily practice. Most intubations are performed in the operating room under controlled, often ideal situations. However, out-of-operating-room intubations have been associated with higher risks of adverse events because they are frequently performed urgently in critically ill patients,[12] for whom the rates of severe complications can be as high as 28%.[13] Hypoxemia is an adverse effect that can occur during intubation.[14] If oxygen were administered through the pharynx during the apneic period, one could increase the uptake of oxygen into the bloodstream, thus reducing occurrences of potentially harmful oxygen desaturation events.

Goals of This investigation

The use of apneic oxygenation has been recommended by experts for management of high-risk airway situations, including emergency intubations in the ED,[10] and for patients at risk for difficult laryngoscopy and intubation in the operating room[15]; however, the evidence supporting

Editor's Capsule Summary

What is already known on this topic

Apneic oxygenation may prolong safe apnea time and increase first-pass success during emergency intubation.

What question this study addressed

Is apneic oxygenation, typically delivered by high-flow nasal cannula, associated with lower peri-intubation hypoxemia and higher first-pass intubation success?

What this study adds to our knowledge

In this meta-analysis of 8 emergency department and ICU studies comprising 1,837 patients, apneic oxygenation was associated with lower odds of peri-intubation hypoxemia (SpO_2 <93%; odds ratio 0.66; 95% confidence interval 0.52 to 0.85) and higher odds of first-pass intubation success (odds ratio 1.59; 95% confidence interval 1.04 to 2.44).

How this is relevant to clinical practice

These results support the role of apneic oxygenation in emergency intubation.

apneic oxygenation is still not well established. The objective of this systematic review and meta-analysis was to evaluate the effectiveness of apneic oxygenation on hypoxemia, first-pass success, and lowest oxygen saturation during emergency intubation.

MATERIALS AND METHODS

Study Design

This was a systematic review and meta-analysis conducted to evaluate the effectiveness of apneic oxygenation during intubations performed in the ED and ICU settings. A protocol was developed a priori and it is available for access in the PROSPERO Web site. This report adheres to recommendations made in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[16]

Eligibility Criteria

We included original research articles, including randomized controlled trials and observational studies, in which apneic oxygenation was used as part of the intubation procedure. We did not exclude any studies according to language, and only studies published in the past 10 years were included. This time restriction was based on the recent implementation of apneic oxygenation in clinical practice and advances in capnography and intubation monitoring in the included settings.

Studies of pediatric and adult patients who received apneic oxygenation during the apneic period of intubation in the ED or ICU were included. Studies performed in the out-of-hospital setting and in the operating room were excluded. There was no restriction by age, sex, or any other baseline characteristic.

To meet the eligibility criteria, patients had to have received oxygen during the apneic period. All types of oxygen devices were considered, including standard nasal cannula, high-flow nasal cannula, nasopharyngeal catheters, modified laryngoscopes, or any other device. Apneic oxygenation is most commonly performed with high-flow nasal cannula through the transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) technique and with standard nasal cannula through the technique of nasal oxygen during efforts securing a tube (NO DESAT). The THRIVE technique consists of the use of a high-flow warmed humidified oxygen delivery system up to 70 L/min to perform both preoxygenation and apneic oxygenation. This technique combines the benefits of apneic oxygenation with continuous positive airway pressure and gaseous exchange through flow-dependent dead-space flushing.[17,18] The technique of NO DESAT uses a standard nasal cannula with cold dry oxygen set as high as 15 L/min, together with the traditional techniques of preoxygenation, and allows apneic oxygenation to continue while attempts at intubation are performed.[10,19]

Outcome Measures and Study Selection

The following outcomes were included: lowest SpO_2 peri-intubation; first-pass success (success on the first laryngoscopy attempt); incidences of hypoxemia (SpO_2 <93%), severe hypoxemia (SpO_2 <80%), and life-threatening hypoxemia (SpO_2 <70%) during the procedure; duration of mechanical ventilation; ICU length of stay; and mortality in the ICU. In studies in which an episode of hypoxemia was defined by SpO_2 less than 90%, these events were included as episodes of SpO_2 less than 93%.

A medical librarian (P.J.E.) designed and conducted a comprehensive search of 4 electronic databases, including Ovid MEDLINE, Ovid EMBASE, Ovid CENTRAL, and Scopus from 2006 to July 2016. The initial search was designed in Ovid MEDLINE (Appendix E1, available online at http://www.annemergmed.com) and then translated into terms appropriate to Ovid CENTRAL and Ovid EMBASE. The strategies used a combination of controlled vocabulary (in MEDLINE, this is Medical

Subject Headings), eg, "intubation," "intratracheal," text words. This was done for each concept: intubation, setting (eg, ED), purpose (apneic oxygenation), and outcomes (eg, hypoxemia). Gray literature databases suggested by the Cochrane handbook,[20] ongoing trials (through clinicaltrials.gov), and reference lists of eligible articles were hand searched.

In phase 1, 2 investigators (L.O.J.S. and D.C.), working independently, screened all titles and abstracts for eligibility. Records considered potentially relevant were assessed in full text for eligibility by 2 independent reviewers (L.O.J.S. and D.C.) in phase 2. We used Cohen's unweighted κ to measure chance corrected agreement between reviewers for phase 2. Disagreements were discussed with the senior author (M.F.B.) and resolved by consensus. All studies were included for qualitative analysis and only those with available data were included for the quantitative analysis.

Primary Data Analysis

Pertinent data were extracted with a standardized predefined form. Data from the first 10 studies were extracted at the beginning of the process independently in duplicate by 2 reviewers (L.O.J.S. and P.B.) to identify variables prone to misinterpretation. Extracted data included study design, study size, study setting, study population, details of the intubation procedure, and outcomes of interest. In regard to the intubation procedure, data collected included clinical predictors of difficult intubation (ie, Cormack-Lehane grades III and IV), methods of preoxygenation, use of rapid sequence intubation, context for intubation, proceduralist expertise (trainee versus expert), and type of laryngoscope used. Trainee proceduralist was defined as physicians undergoing a training program (residents and fellows). Expert proceduralist was defined as emergency physicians, intensivists, and anesthesiologists.

For randomized controlled trials, we assessed the risk of bias with the Cochrane Collaboration Bias Appraisal Tool.[20] We assessed the risk of bias for observational studies with a modified Newcastle-Ottawa Scale tool.[21] Quality assessment of all studies included was performed in duplicate and independently by 2 reviewers (L.O.J.S. and P.B.). The quality of evidence for the main outcomes was evaluated with the Grading of Recommendations Assessment, Development and Evaluation methods.[22]

We collected the outcomes included in the published reports, and authors were contacted by e-mail if data were missing or unclear. Most studies contained the desired clinical outcomes. We directly contacted the authors of the 14 studies and received additional data from 12. One conference abstract of an ongoing trial had no data for outcomes of interest.[23]

We considered it reasonable to pool the data from ED and ICU studies to have a better understanding of the overall benefit of apneic oxygenation in an emergency setting. Data were managed following Cochrane recommendations.[20] We used Review Manager (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for meta-analyses, using a random-effects model as described by DerSimonian-Laird.[24] The pooled-effect estimates of using apneic oxygenation during intubation versus not using it were reported as odds ratio (OR) and weighted mean difference with 95% confidence intervals (CIs). Statistical heterogeneity was assessed among studies by the I^2 statistic proposed by Higgins and Thompson.[25] Between-studies heterogeneity was also evaluated visually. To account for the clinical and statistical heterogeneity between studies, we used a random-effects model.

During the development of the protocol, we planned to perform subgroup analyses by proceduralist expertise, study design, and risk of bias. Sensitivity analyses were conducted excluding studies with high risk of bias.

RESULTS

The search strategy identified 1,386 studies for review (Figure 1). After screening the titles and abstracts and removing duplicates, we identified 77 potentially relevant studies. After full-text review, a total of 14 studies met the inclusion criteria: 6 ICU studies,[26-31] 6 ED studies,[23,32-36] and 2 mixed ED and ICU studies.[37,38] Interobserver agreement (κ) for phase 2 of study selection was moderate (κ 0.54; 95% CI 0.34 to 0.74), with an overall agreement of 79.2% (95% CI 70.2% to 88.3%).

Among the studies including patients intubated in the ED or ICU, there were 9 observational studies and 5 randomized controlled trials (Table 1 and Appendix E2, available online at http://www.annemergmed.com).

The included studies involved 2,023 participants, with 1,168 patients receiving apneic oxygenation during intubation and 855 not receiving it. Eight studies,[26,27,29-32,35,38] including 982 patients receiving apneic oxygenation and 855 not receiving it, underwent meta-analysis. Three studies had no control groups,[33,34,37] 1 study had both arms receiving apneic oxygenation,[28] and 1 conference abstract did not have enough data details.[23] There were 2 studies with overlapping cohorts, and we included only the most comprehensive one in the meta-analyses.[35,36] Two ED studies included pediatric patients within a mixed pediatric and adult cohort,[32,38] with a median age greater

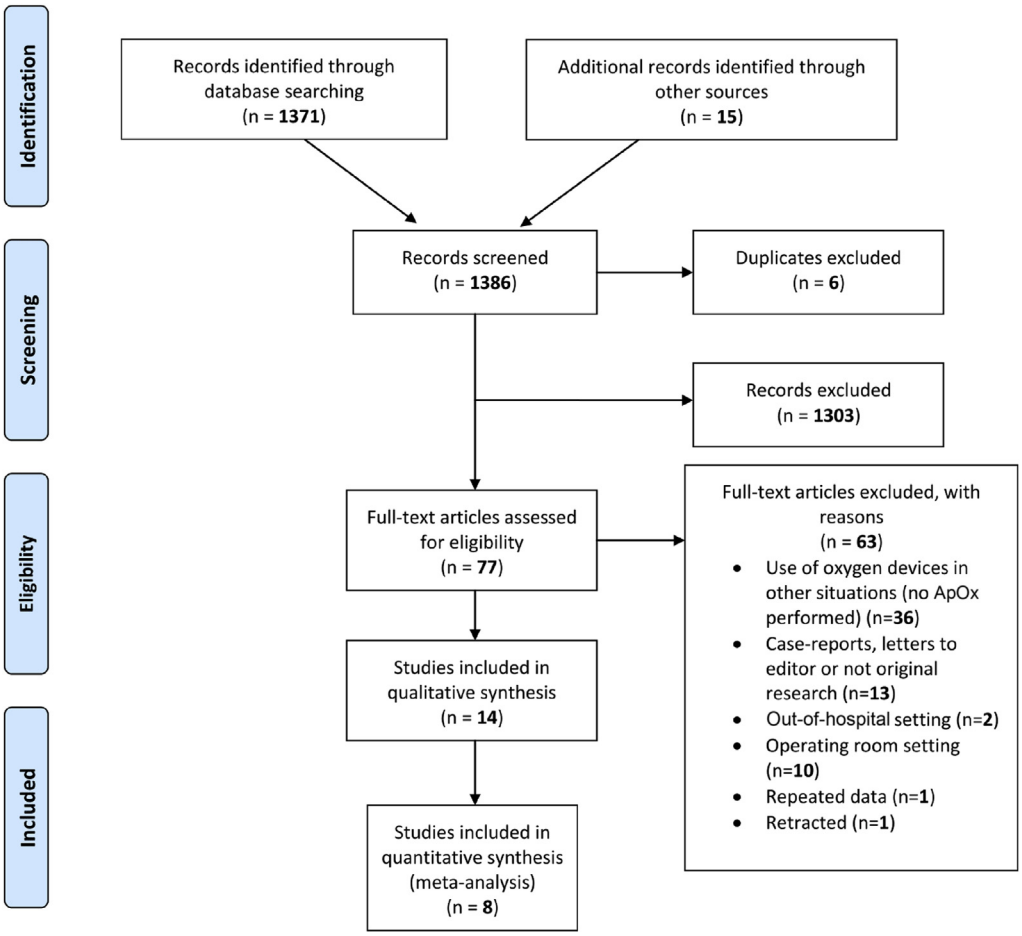

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses study flow. *ApOx*, Apneic oxygenation.

than 50 years. Most studies included patients with acute respiratory failure requiring emergency intubation.

Apneic oxygenation was performed through high-flow nasal cannula in most studies,[26,28,30,31,34,37] with the oxygen flow set as high as 60 L/min. Standard nasal cannula with oxygen set as high as 15 L/min, used in combination with traditional techniques of preoxygenation, was mostly used in the ED studies.[32,35,36,38]

Main Results

We evaluated the body of evidence for the main outcomes with the Grading of Recommendations Assessment, Development and Evaluation approach, which assessed the confidence in our meta-analytic effects accounting for different criteria rather than the risk of bias alone (Table 2 and Appendix E3, available online at http://www.annemergmed.com). Sources of clinical heterogeneity included setting and context for intubation, approaches to preoxygenation and apneic oxygenation, and proceduralist expertise.

The timeframe for measurement of the lowest peri-intubation SpO_2 and incidences of hypoxemia were unclear in most studies; among those that reported it in detail, it was measured from drug injection until the initiation of mechanical ventilation.

In the meta-analysis of 6 studies including 1,043 patients,[26,27,29-31,35] the lowest peri-intubation SpO_2 was higher for apneic oxygenation than standard oxygenation (difference 2.21%; 95% CI 0.81% to 3.61%; I^2=0%) (Figure 2*A*).

In the meta-analysis of 6 studies including 1,658 patients,[25,26,28,30,31,34] apneic oxygenation during intubation was associated with increased first-pass success rates (OR 1.59; 95% CI 1.04 to 2.44; I^2=48%) (Figure 2*B*).

Hypoxemia was defined differently across studies. For the meta-analysis, we defined hypoxemia as SpO_2 less than 93%. In studies in which an episode of hypoxemia was defined by SpO_2 less than 90%, these events were included as episodes of SpO_2 less than 93%. In the meta-analysis of 8 studies including 1,837 patients,[26,27,29-32,35,38] apneic oxygenation during intubation was associated with decreased incidence of hypoxemia (OR 0.66; 95% CI 0.52 to 0.84; I^2=0%) (Figure 2*C*).

Table 1. ED and ICU studies: main baseline characteristics.

Study	Study Design	Setting	Population	Proceduralist Expertise	Intervention [Number of Participants]	Comparison [Number of Participants]
Besnier, 2016[26]	Observational study	ICU	Adult patients with ARF intubated in the ICU	Majority of intubations performed by an expert	THRIVE technique PreOx: HFNC (50 L/min, FiO_2 100%) ApOx: HFNC (50 L/min, FiO_2 100%) [n=13]	PreOx: NIV (FiO_2 100%, PEEP minimum of 5 cm H_2O ApOx: not used [n=39]
Dyett, 2015[38]	Observational study	ED, ICU, and wards	Adults and children urgently intubated in the ED, ICU, and wards. ARF was the most common underlying cause for intubation.	Majority of intubations performed by trainees	NO DESAT technique PreOx: most common was BVM ApOx: standard NC (15 L/min) [n=47]	PreOx: most common was BVM ApOx: not used [n=92]
Fogg, 2016[32]	Observational study	ED	Adults and children intubated in the ED. Overdose was the most common underlying cause for intubation.	Majority of intubations performed by an expert.	NO DESAT technique as part of a new airway protocol PreOx: not described ApOx: standard NC (15 L/min). Few patients in the postimplementation period did not receive ApOx [n=360]	Period before the implementation of a new airway protocol PreOx: not described ApOx: not used [n=259]
Horan, 2016[23]	RCT	ED	Patients (age not specified) who underwent RSI in a community ED	Not specified	Method of ApOx not specified [n=13]	Not specified
Jaber, 2016[27]	RCT	ICU	Adult patients with severe hypoxemic ARF intubated in the ICU	Majority of intubations performed by an expert	PreOx: HFNC (60 L/min, FiO_2 100%) plus NIV (PS 10 cm H_2O, PEEP 5 cm H_2O, FiO_2 100%) ApOx: HFNC (60 L/min, FiO_2 100%) [n=23]	PreOx: NIV (PS 10 cm H_2O, PEEP 5 cm H_2O, FiO_2 100%) ApOx: not used [n=24]
Sakles, 2016[35]	Observational study	ED	Adult patients intubated in the ED. Patients intubated mostly for airway protection.	All intubations performed by a trainee	NO DESAT technique PreOx: NRB face mask (15 L/min) plus standard NC (different flows) ApOx: standard NC (different flows, but mostly $\geq$15 L/min) [n=380]	PreOx: NRB face mask (15 L/min) ApOx: not used [n=255]
Sakles, 2016[36]	Observational study	ED	Adult patients with ICH intubated in the ED	All intubations performed by a trainee	NO DESAT technique PreOx: NRB face mask (15 L/min) plus standard NC (different flows) ApOx: standard NC (different flows, but mostly $\geq$15 L/min) [n=72]	PreOx: NRB face mask (15 L/min) ApOx: not used [n=55]
Semler, 2016[29]	RCT	ICU	Adult patients intubated in the ICU. ARF was the most common underlying cause for intubation.	Majority of intubations performed by a trainee	NO DESAT technique PreOx: BVM was the most common method ApOx: standard NC (15 L/min, FiO_2 100%) [n=77]	PreOx: NRB face mask was the most common method ApOx: not used [n=73]
Simon, 2016[30]	RCT	ICU	Adult patients with ARF intubated in the ICU	All intubations performed by an expert	THRIVE technique PreOx: HFNC (50 L/min, FiO_2 100%) ApOx: HFNC (50 L/min, FiO_2 100%) [n=20]	PreOx: BVM without PEEP valve (10 L/min) ApOx: not used [n=20]

Table 1. Continued.

Study	Study Design	Setting	Population	Proceduralist Expertise	Intervention [Number of Participants]	Comparison [Number of Participants]
Vourc'h, 2015[31]	RCT	ICU	Adult patients with hypoxemic ARF intubated in the ICU	Majority of intubations performed by a trainee	THRIVE technique PreOx: HFNC (60 L/min, FiO_2 100%) ApOx: HFNC (60 L/min, FiO_2 100%) [n=62]	PreOx: NRB high FiO_2 face mask (15 L/min) ApOx: not used [n=57]
Doyle, 2016[37] (ED/ICU cohort)	Observational study	ED and ICU	Adult patients intubated in the ICU and ED. ARF was the most common underlying cause for intubation.	Not specified	THRIVE technique PreOx: HFNC (60 L/min) ApOx: HFNC (60 L/min) [n=34]	No control group
Grant, 2016[33]	Observational study	ED	Adult patients intubated in the ED deemed to be clinically at high risk of oxygen desaturation	Not specified	NO DESAT technique PreOx: NIV (NIV-ST mode, PEEP 5 cm H_2O, PS 10 cm H_2O) plus standard NC (15 L/min) ApOx: standard NC (15 L/min) [n=8]	No control group
Kim, 2016[34]	Observational study	ED	Adult patients intubated in the ED. ARF was the most common underlying cause for intubation.	Majority of intubations performed by an expert	THRIVE technique PreOx: HFNC (50 L/min, FiO_2 100%) ApOx: HFNC (50 L/min, FiO_2 100%) [n=30]	No control group
Miguel-Montanes, 2015[28]	Observational study	ICU	Adult patients intubated in the ICU. Shock patients, altered mental status, and ARF (mild to moderate) were the most common underlying causes for intubation.	Majority of intubations performed by a trainee	THRIVE technique PreOx: HFNC (60 L/min, FiO_2 100%) ApOx: HFNC (60 L/min, FiO_2 100%) [n=51]	PreOx: NRB face mask (15 L/min) ApOx: nasopharyngeal catheter (6 L/min) [n=50]

ARF, Acute respiratory failure; *FiO_2*, fraction of inspired oxygen; *PreOx*, preoxygenation; *HFNC*, high-flow nasal cannula; *NIV*, noninvasive ventilation; *PS*, pressure support; *PEEP*, positive end-expiratory pressure; *BVM*, bag-valve-mask; *NC*, nasal cannula; *RCT*, randomized controlled trial; *RSI*, rapid sequence intubation; *NRB*, nonrebreather; *ICH*, intracranial hemorrhage.

Table 2. Summary of evidence findings for main outcomes using the Grading of Recommendations Assessment, Development and Evaluation approach.

Quality Assessment							No. of Patients (%)		Effect		
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations*	Use of ApOx	Controls Without ApOx	Relative (95% CI)	Absolute (95% CI)	Quality
Lowest SpO_2 peri-intubation											
6	4 RCTs 2 Observ.	Not serious	Serious[†‡]	Not serious	Not serious	None	575	468	—	MD 2.21% higher (0.81 higher to 3.61 higher)	⊕⊕⊕◯ Moderate
First-pass success											
6	3 RCTs 2 Observ.	Serious[§]	Serious[‡‖]	Not serious	Not serious	None	807/915 (88.2)	594/743 (79.9)	OR 1.59 (1.04–2.44)	64 more per 1.000 (from 6 more to 107 more)	⊕⊕◯◯ Low
Hypoxemia (SpO_2 <93%)											
8	4 RCTs 4 Observ.	Serious[¶]	Serious[†‡]	Not serious	Not serious	None	163/982 (16.6)	209/855 (24.4)	OR 0.66 (0.52–0.84)	68 fewer per 1.000 (from 31 fewer to 100 fewer)	⊕⊕◯◯ Low
Severe hypoxemia (SpO_2 <80%)											
6	4 RCTs 2 Observ.	Not serious	Serious[†‡]	Not serious	Serious[#]	None	62/575 (10.8)	65/468 (13.9)	OR 0.86 (0.47–1.57)	17 fewer per 1.000 (from 63 more to 68 fewer)	⊕⊕◯◯ Low
Life-threatening hypoxemia (SpO_2 <70%)											
5	3 RCTs 2 Observ.	Not serious	Serious[†‡]	Not serious	Serious[#]	None	32/555 (5.8)	33/448 (7.4)	OR 0.90 (0.52–1.55)	7 fewer per 1.000 (from 34 fewer to 36 more)	⊕⊕◯◯ Low

Observ., Observational studies; *MD*, mean difference.

*Other considerations include assessment of publication bias, magnitude of effect, plausible confounding, and dose-response gradient.

[†]ApOx may have a larger effect in less sick populations intubated in the ED/ICU, as shown indirectly by the increased safe apnea time when using ApOx in elective intubated patients in the operating room without cardiorespiratory disease.

[‡]Different approaches to ApOx (NO DESAT vs THRIVE) could also play a role in the direction of effect.

[§]Inclusion of a before-after observational study with high risk of bias (Fogg[32]); however, when sensitivity analysis was performed excluding this study, there was still a benefit of using ApOx.

[‖]ApOx may have larger effect when trainees perform intubations.

[¶]Inclusion of 2 studies with high risk of bias (Fogg[32] and Dyett[38]); however, when sensitivity analysis excluding these studies was performed, there was still a benefit of using ApOx.

[#]95% CI around the pooled estimate of effect includes both benefit and no benefit of using ApOx.

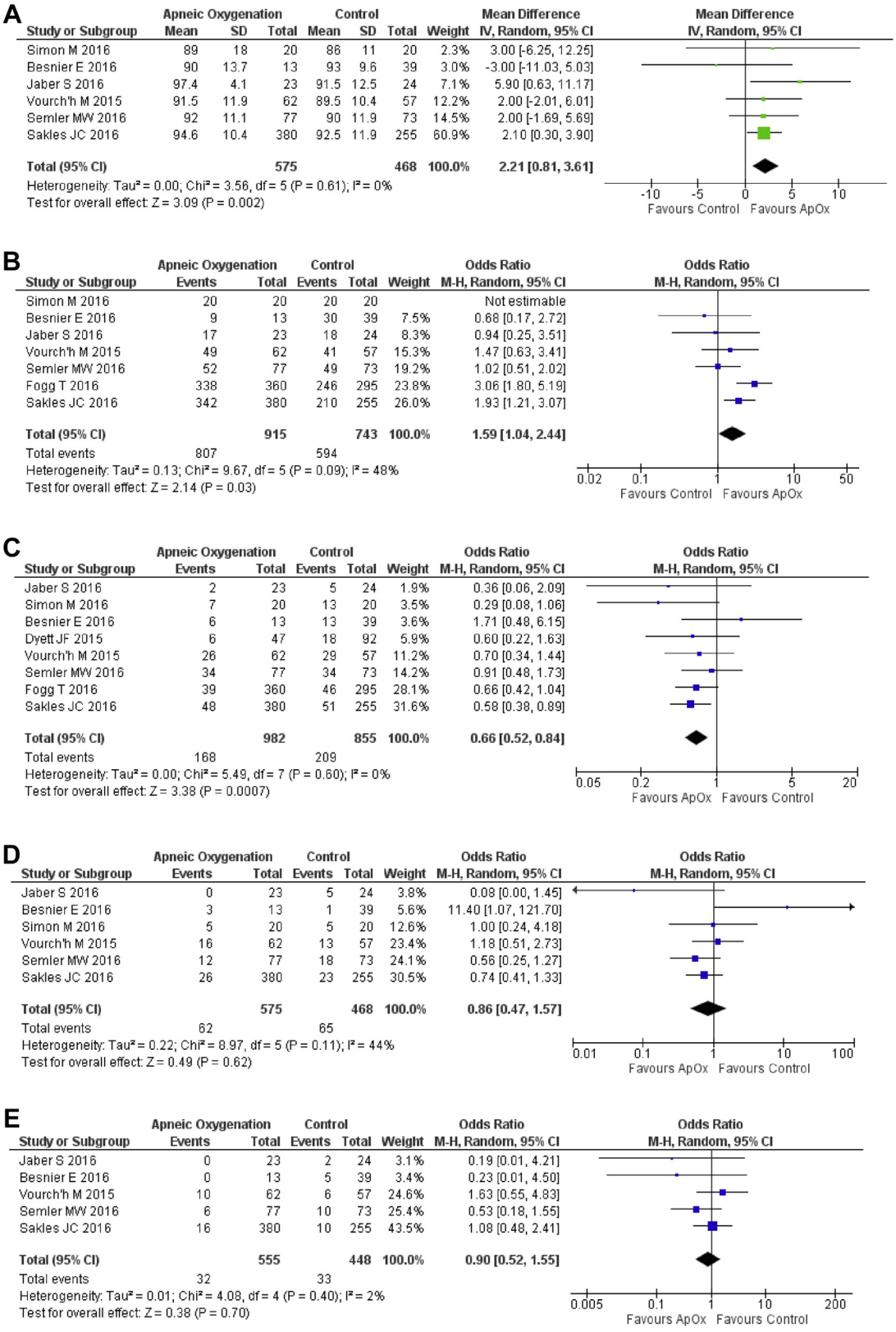

Figure 2. Forest plots of meta-analyses on periprocedural outcomes. *A*, Lowest oxygen saturation (SpO_2) peri-intubation. *B*, First-pass success. *C*, Hypoxemia (SpO_2 <93%). *D*, Severe hypoxemia (SpO_2 <80%). *E*, Life-threatening hypoxemia (SpO_2 <70%).

In the meta-analysis of 6 studies including 1,043 patients,[26,27,29-31,35] apneic oxygenation during intubation was not associated with severe hypoxemia (SpO_2 <80%) (OR 0.86; 95% CI 0.47 to 1.57; I^2=44%) (Figure 2*D*).

In the meta-analysis of 5 studies including 1,003 patients,[26,27,29,31,35] apneic oxygenation during intubation was not associated with life-threatening hypoxemia (SpO_2 <70%) (OR 0.90; 95% CI 0.52 to 1.55; I^2=2%) (Figure 2*E*).

In the meta-analysis of 4 studies including 368 patients,[26,27,29,31] apneic oxygenation during intubation was not associated with decreased duration of mechanical ventilation (weighted mean difference 1.42 days; 95% CI 0.59 to 3.42; I^2=63%) (Figure 3*A*). In the meta-analysis of 4 studies including 368 patients,[26,27,29,31] apneic oxygenation during intubation was associated with a decreased ICU length of stay of 2.88 days (95% CI 1.40 to 4.37 days; I^2=0%) (Figure 3*B*). In the meta-analysis of 4 studies including 258 patients,[26,27,30,31] apneic oxygenation was not associated with ICU mortality (OR 0.82; 95% CI 0.38 to 1.76; I^2=32%). Deaths included 36 of 118 patients (30.5%) in the apneic oxygenation group and 49 of 140 (35.0%) in the control group, with an absolute difference of –4% (95% CI –18% to 14%) (Figure 3*C*).

Additional Analyses

Forest plots of subgroup analyses by proceduralist expertise, study design, and risk of bias are shown in Appendix E4, available online at http://www.annemergmed.com. Apneic oxygenation favored the trainees' subgroup when proceduralist expertise was evaluated; however, differences between subgroups were not statistically significant. Sensitivity analysis excluding the study with high risk of bias[32] did not significantly change the pooled effect estimates. When randomized controlled trials and studies with low risk of bias were analyzed separately, apneic oxygenation was not associated with better periprocedural outcomes.

We were unable to statistically assess the presence of publication bias because the number of studies included in each analysis was small, which makes analysis of funnel plots unreliable.[39]

LIMITATIONS

There are several limitations in this systematic review and meta-analysis. The major limitation relates to the quality of included studies, which warrants a moderate to low level of certainty in the estimates. Another important limitation is the different approaches used to apneic

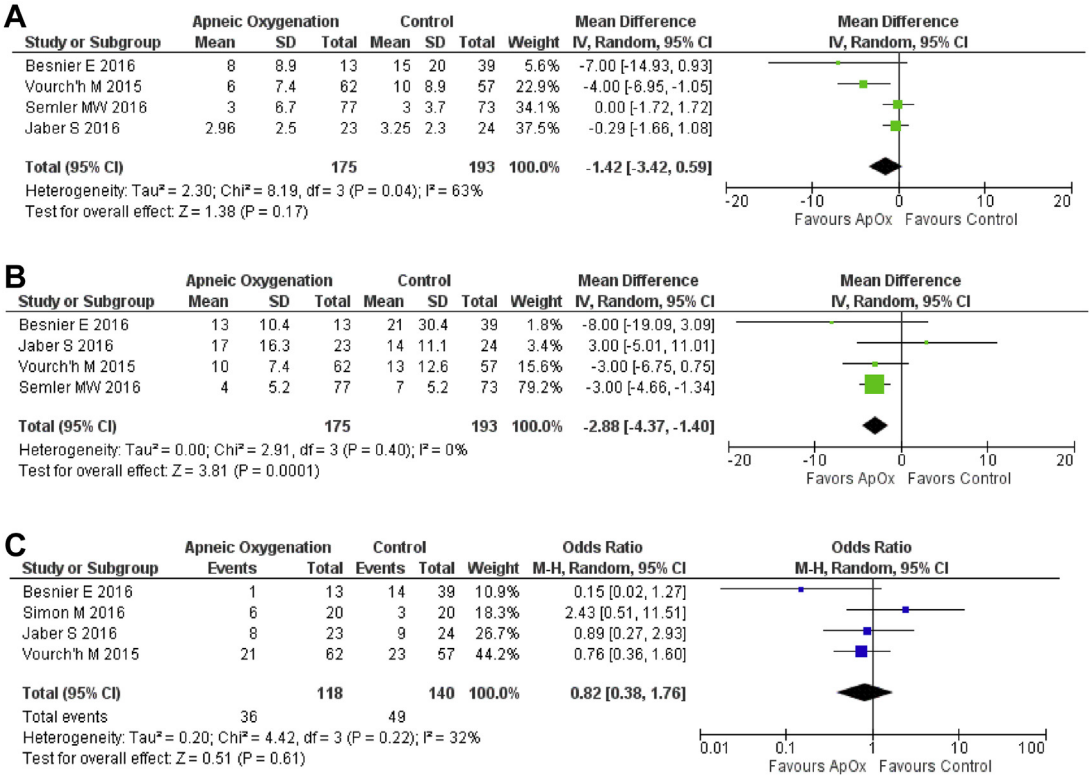

Figure 3. Forest plots of meta-analyses on postprocedural outcomes. *A*, Duration of mechanical ventilation. *B*, ICU length of stay. *C*, ICU mortality.

oxygenation in terms of preoxygenation and other peri-intubation variables and cointerventions. The different methods of preoxygenation between groups could affect the likelihood of developing hypoxemia during the apneic period; therefore, the effect of apneic oxygenation was not isolated in some of the included studies. The maintenance of airway patency during apneic oxygenation was not described in most of the studies, and that might affect the quality of this intervention. The clinical heterogeneity of patients intubated in the ED and ICU in regard to their cardiorespiratory baseline status is also an important factor to be considered, and which approach is better among the spectrum of sickness in patients requiring emergency intubation still has to be studied.

To decrease selection bias, we included all eligible studies including those published in gray literature and not indexed in PubMed or major databases, and abstracts. We included all studies even if they had a low number of participants or high risk of bias. This likely introduced heterogeneity into the analyses. However, we assessed clinical and statistical heterogeneity and accounted for this in the statistical analyses. To mitigate some of these limitations, we used subgroup analyses. Also we contacted the authors when published data were not clear or missing, and we received several responses.

DISCUSSION

This systematic review and meta-analysis demonstrated that the use of apneic oxygenation during intubation appears to be associated with increased peri-intubation oxygen saturation and first-pass success rates, as well as decreased incidence of hypoxemia in patients intubated in the ED or ICU. The use of apneic oxygenation was associated with a decrease in ICU length of stay, but there was no difference in duration of mechanical ventilation and ICU mortality. We found no reports of adverse events related to the use of apneic oxygenation, despite different approaches and settings.

The concept and use of apneic oxygenation for the optimization of peri-intubation conditions, especially apnea time, has been introduced in the practice of emergency medicine after ED observational studies,[32,35,38] anesthesiology literature,[1,3,4] and recommendations by experts in the field.[10,19] EDs and ICUs have used different techniques for apneic oxygenation, with most ICU studies using high-flow nasal cannula and most ED studies using the standard nasal cannula.[32,35,36,38] The THRIVE technique combines preoxygenation and apneic oxygenation using a high-flow nasal cannula up to 70 L/min, creating a flow-dependent positive pharyngeal pressure, with potentially more benefit for patients with more severe respiratory disease.[8,40]

The relative simplicity and safety of this intervention and the potential to turn intubation in a safer procedure, with higher success rates and fewer complications, led to a rapid and widespread use of the concept and to its even being considered by some as standard of care despite relatively scarce evidence to support its use.[10] Recently, ICU-based studies have shown conflicting results on the effectiveness of apneic oxygenation using different approaches.[26-31]

Patients intubated outside of the operating room represented emergency intubations in the setting of critical illness in an ED or ICU environment, in whom the lowest SpO_2 and incidences of hypoxemia during the peri-intubation period are different from those in the elective operating room population. Although there was variable level of bias and heterogeneity in the included studies, apneic oxygenation was associated with increased SpO_2 peri-intubation, increased first-pass success rates, and decreased incidence of hypoxemia in patients intubated in the ED or ICU. Severe and life-threatening hypoxemia was not affected. These findings likely represent an overall benefit of using apneic oxygenation during emergency intubations, reflecting better periprocedural outcomes and prolonged safe apnea time. The physiologic improvements noted likely have little effect on the underlying disease, which may explain the lack of improvement in mortality.

In the subgroup analysis, proceduralist experience showed that peri-intubation oxygen saturation, first-pass success, and hypoxemia were improved in the trainees' subgroup; however, these outcomes were not significantly improved in the experts' subgroup. The potential decrease in hypoxemia in urgently intubated patients with the use of apneic oxygenation might have allowed less experienced operators more time for laryngoscopy, and thus led them to achieve higher first-pass success rates. Apneic oxygenation may be of less benefit to operators who are very skilled at laryngoscopy and can complete intubation quickly.[35] Higher first-pass success rates could also explain the decreased incidence of hypoxemia, given the direct relationship between number of attempts and the incidence of desaturations,[9,35,41] and secondary increase in patients' safety.[35] Subgroup analysis by risk of bias showed that when only studies with low risk of bias were included, none of the outcomes analyzed showed an improvement with the use of apneic oxygenation, likely because the sample sizes were significantly reduced; however, this also raises a concern about the quality of the evidence of the available studies in regard to the use of apneic oxygenation.

In summary, in this meta-analysis apneic oxygenation was associated with increased peri-intubation SpO_2, decreased hypoxemia, and increased first-pass intubation success. Apneic oxygenation is a potentially important adjunct for emergency airway management.

Supervising editor: Henry E. Wang, MD, MS

Author affiliations: From the Department of Emergency Medicine (Silva, Cabrera, Bellolio), Knowledge Synthesis and Kern Center for the Science of Health Care Delivery (Barrionuevo, Murad), Department of Anesthesiology and Perioperative Medicine (Johnson), Division of Preventive, Occupational and Aerospace Medicine, Department of Medicine (Murad), and Department of Health Science Research, Division of Health Care Policy and Research (Bellolio), Mayo Clinic, Rochester, MN; Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil (Silva); and Mayo Clinic Libraries, Rochester, MN (Erwin).

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

Publication dates: Received for publication March 16, 2017. Revisions received April 10, 2017; April 13, 2017, and April 20, 2017. Accepted for publication May 1, 2017.

Trial registration number: PROSPERO (Study ID: CRD42016052438)

REFERENCES

1. Baraka AS, Taha SK, Siddik-Sayyid SM, et al. Supplementation of pre-oxygenation in morbidly obese patients using nasopharyngeal oxygen insufflation. *Anaesthesia*. 2007;62:769-773.
2. Heard A, Toner AJ, Evans JR, et al. Apneic oxygenation during prolonged laryngoscopy in obese patients: a randomized, controlled trial of buccal RAE tube oxygen administration. *Anesth Analg*. 2017;124:1162-1167.
3. Jain S, Agarawal M, Dali J. Role of nasopharyngeal oxygen insufflation on haemoglobin desaturation following preoxygenation. *J Anaesthesiol Clin Pharmacol*. 2009;25:454-458.
4. Ramachandran SK, Cosnowski A, Shanks A, et al. Apneic oxygenation during prolonged laryngoscopy in obese patients: a randomized, controlled trial of nasal oxygen administration. *J Clin Anesth*. 2010;22:164-168.
5. Taha SK, Siddik-Sayyid SM, El-Khatib MF, et al. Nasopharyngeal oxygen insufflation following pre-oxygenation using the four deep breath technique. *Anaesthesia*. 2006;61:427-430.
6. Frumin MDMJ, Epstein MD, Robert M, et al. Apneic oxygenation in man. *Anesthesiology*. 1959;20:789-798.
7. Moran C, Karalapillai D, Darvall J, et al. Is it time for apnoeic oxygenation during endotracheal intubation in critically ill patients? *Crit Care Resusc*. 2014;16:233-235.
8. Mosier JM, Hypes CD, Sakles JC. Understanding preoxygenation and apneic oxygenation during intubation in the critically ill. *Intensive Care Med*. 2017;43:226-228.
9. Ricard JD. Hazards of intubation in the ICU: role of nasal high flow oxygen therapy for preoxygenation and apneic oxygenation to prevent desaturation. *Minerva Anestesiol*. 2016;82:1098-1106.
10. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. *Ann Emerg Med*. 2012;59:165-175.e161.
11. Holmdahl MH. Pulmonary uptake of oxygen, acid-base metabolism, and circulation during prolonged apnoea. *Acta Chir Scand Suppl*. 1956;212:1-128.
12. Bowles TM, Freshwater-Turner DA, Janssen DJ, et al. Out-of-theatre tracheal intubation: prospective multicentre study of clinical practice and adverse events. *Br J Anaesth*. 2011;107:687-692.
13. Jaber S, Jung B, Corne P, et al. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive Care Med*. 2010;36:248-255.
14. Mort TC. The incidence and risk factors for cardiac arrest during emergency tracheal intubation: a justification for incorporating the ASA guidelines in the remote location. *J Clin Anesth*. 2004;16:508-516.
15. Berkow L, Hagberg CA, Crowley M. Airway management for induction of general anesthesia. 2016. Available at: http://www.uptodate.com/contents/airway-management-for-induction-of-general-anesthesia. Accessed November 15, 2016.
16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6:e1000100.
17. Patel A, Nouraei SA. Nasal ventilation: oxygenation, NO DESAT, and THRIVE. 2016. Available at: http://www.anesthesiologynews.com/Review-Articles/Article/08-16/Nasal-Ventilation-Oxygenation-NO-DESAT-and-THRIVE/37294/ses=ogst. Accessed November 15, 2016.
18. Patel A, Nouraei SAR. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. *Anaesthesia*. 2015;70:323-329.
19. Levitan RM. NO DESAT! Nasal oxygen during efforts securing a tube. 2010. Available at: http://www.epmonthly.com/features/current-features/no-desat-/. Accessed November 15, 2016.
20. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. Copenhagen, Denmark: Cochrane Collaboration; 2011.
21. Wells G, Shea B, O'Connell D, et al. *Quality Assessment Scales for Observational Studies*. Ottawa, Canada: Ottawa Health Research Institute; 2004.
22. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64:401-406.
23. Horan T, Berns AL, Malone M, et al. Use of apneic oxygenation in rapid sequence intubation (RSI) patients in the emergency department [abstract 172]. SAEM annual meeting abstracts. *Acad Emerg Med*. 2016;23:S81.
24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
25. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539-1558.
26. Besnier E, Guernon K, Bubenheim M, et al. Pre-oxygenation with high-flow nasal cannula oxygen therapy and non-invasive ventilation for intubation in the intensive care unit. *Intensive Care Med*. 2016;42:1291-1292.

27. Jaber S, Monnin M, Girard M, et al. Apnoeic oxygenation via high-flow nasal cannula oxygen combined with non-invasive ventilation preoxygenation for intubation in hypoxaemic patients in the intensive care unit: the single-centre, blinded, randomised controlled OPTINIV trial. *Intensive Care Med*. 2016;42:1877-1887.
28. Miguel-Montanes R, Hajage D, Messika J, et al. Use of high-flow nasal cannula oxygen therapy to prevent desaturation during tracheal intubation of intensive care patients with mild-to-moderate hypoxemia. *Crit Care Med*. 2015;43:574-583.
29. Semler MW, Janz DR, Lentz RJ, et al. Randomized trial of apneic oxygenation during endotracheal intubation of the critically ill. *Am J Respir Crit Care Med*. 2016;193:273-280.
30. Simon M, Wachs C, Braune S, et al. High-flow nasal cannula versus bag-valve-mask for preoxygenation before intubation in subjects with hypoxemic respiratory failure. *Respir Care*. 2016;61:1160-1167.
31. Vourc'h M, Asfar P, Volteau C, et al. High-flow nasal cannula oxygen during endotracheal intubation in hypoxemic patients: a randomized controlled clinical trial. *Intensive Care Med*. 2015;41:1538-1548.
32. Fogg T, Alkhouri H, Vassiliadis J. The Royal North Shore Hospital Emergency Department airway registry: closing the audit loop. *Emerg Med Australas*. 2016;28:27-33.
33. Grant S, Khan F, Keijzers G, et al. Ventilator-assisted preoxygenation: protocol for combining non-invasive ventilation and apnoeic oxygenation using a portable ventilator. *Emerg Med Australas*. 2016;28:67-72.
34. Kim TH, Hwang SO, Cha YS, et al. The utility of noninvasive nasal positive pressure ventilators for optimizing oxygenation during rapid sequence intubation. *Am J Emerg Med*. 2016;34:1627-1630.
35. Sakles JC, Mosier JM, Patanwala AE, et al. First pass success without hypoxemia is increased with the use of apneic oxygenation during rapid sequence intubation in the emergency department. *Acad Emerg Med*. 2016;23:703-710.
36. Sakles JC, Mosier JM, Patanwala AE, et al. Apneic oxygenation is associated with a reduction in the incidence of hypoxemia during the RSI of patients with intracranial hemorrhage in the emergency department. *Intern Emerg Med*. 2016;11:983-992.
37. Doyle AJ, Stolady D, Mariyaselvam M, et al. Preoxygenation and apneic oxygenation using transnasal humidified rapid-insufflation ventilatory exchange for emergency intubation. *J Crit Care*. 2016;36:8-12.
38. Dyett JF, Moser MS, Tobin AE. Prospective observational study of emergency airway management in the critical care environment of a tertiary hospital in Melbourne. *Anaesth Intensive Care*. 2015;43:577-586.
39. Lau J, Ioannidis JPA, Terrin N, et al. The case of the misleading funnel plot. *BMJ*. 2006;333:597-600.
40. Papazian L, Corley A, Hess D, et al. Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review. *Intensive Care Med*. 2016;42:1336-1349.
41. Hasegawa K, Shigemitsu K, Hagiwara Y, et al. Association between repeated intubation attempts and adverse events in emergency departments: an analysis of a multicenter prospective observational study. *Ann Emerg Med*. 2012;60:749-754.e742.

Appendix E1. Search strategies: Epub ahead of print, in-process and other non-indexed citations, Ovid MEDLINE daily, and Ovid MEDLINE; 1946 to present.

#	Searches	Results	Type
1	Intubation, Intratracheal/	31593	Advanced
2	((intratracheal or endotracheal or tracheal) adj3 intubat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	38137	Advanced
3	1 or 2 or intubat*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	72200	Advanced
4	(((apneic or apnoeic) adj2 oxygenation*) or "ap ox").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	168	Advanced
5	(preoxygenat* or "pre oxygenat*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	648	Advanced
6	((passive adj2 oxygen*) or (diffusion adj2 respirat*) or (oxygen* adj2 insufflat*) or (mask* adj2 flow* adj2 ventilat*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	479	Advanced
7	((nasal or nasopharyngeal*) adj2 (cannula* or prong*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1313	Advanced
8	(("high flow" or "high frequency") adj3 (nasal or nasopharyng*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	436	Advanced
9	(hfnc or hfnp or hhfnox).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	148	Advanced
10	(((noninvasive or "non invasive") adj2 (positive or respirat* or ventil*)) or nppv or ninppv or nippv).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	6025	Advanced
11	(operating room* or "OR" or emergent or emergency* or ards or (respiratory adj2 (distress* or fail*)) or icu*1 or ccu*1 or "critical care" or "intensive care" or "airway manage*" or urgen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7563071	Advanced
12	postoperative complications/or intraoperative complications/	331681	Advanced
13	exp Intensive Care Units/	64939	Advanced
14	(critical* adj2 ill*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	44998	Advanced
15	Critical Care/or rsi.mp. or "rapid sequence."mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	46529	Advanced
16	or/11-15	7778162	Advanced
17	or/4-10	8407	Advanced
18	3 and 16 and 17	1783	Advanced
19	3 and laryngoscop*.mp. and 17 [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	88	Advanced
20	3 and 15	2946	Advanced
21	17 and 20	239	Advanced
22	18 or 19 or 21	1803	Advanced
23	22 and (desaturat* or hypox* or anox* or success* or sp02 or "first pass" or outcome* or death* or mortality or complicat* or surviv* or los or optimi*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1440	Advanced
24	23 and (apneic or preoxygen* or "pre oxygen*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	171	Advanced
25	23 or 24	1440	Advanced
26	25 and (compar* or study or studies or observation* or trial* or prospective* or series or cohort*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1123	

Ovid EMBASE; 1988 to 2016 week 29

#	Searches	Results	Type
1	Intubation, Intratracheal/	34159	Advanced
2	((intratracheal or endotracheal or tracheal) adj3 intubat*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	38219	Advanced
3	1 or 2 or intubat*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	84322	Advanced
4	(((apneic or apnoeic) adj2 oxygenation*) or "ap ox").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	141	Advanced
5	(preoxygenat* or "pre oxygenat*").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	875	Advanced
6	((passive adj2 oxygen*) or (diffusion adj2 respirat*) or (oxygen* adj2 insufflat*) or (mask* adj2 flow* adj2 ventilat*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	394	Advanced
7	((nasal or nasopharyngeal*) adj2 (cannula* or prong*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2521	Advanced
8	(("high flow" or "high frequency") adj3 (nasal or nasopharyng*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	781	Advanced
9	(hfnc or hfnp or hhfnox).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	284	Advanced
10	(((noninvasive or "non invasive") adj2 (positive or respirat* or ventil*)) or nppv or ninppv or nippv).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	11265	Advanced
11	(operating room* or "OR" or emergent or emergency* or ards or (respiratory adj2 (distress* or fail*)) or icu*1 or ccu*1 or "critical care" or "intensive care" or "airway manage*" or urgen*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	8291392	Advanced
12	postoperative complications/or intraoperative complications/	40776	Advanced
13	exp Intensive Care Units/	103859	Advanced
14	(critical* adj2 ill*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	65337	Advanced
15	Critical Care/or rsi.mp. or "rapid sequence."mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	61564	Advanced
16	or/11-15	8329344	Advanced
17	or/4-10	14769	Advanced
18	3 and 16 and 17	3549	Advanced
19	3 and laryngoscop*.mp. and 17 [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	179	Advanced
20	3 and 15	4740	Advanced
21	17 and 20	444	Advanced
22	18 or 19 or 21	3571	Advanced
23	22 and (desaturat* or hypox* or anox* or success* or sp02 or "first pass" or outcome* or death* or mortality or complicat* or surviv* or los or optimi*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2946	Advanced
24	23 and (apneic or preoxygen* or "pre oxygen*").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	267	Advanced
25	23 or 24	2946	Advanced
26	25 and (compar* or study or studies or observation* or trial* or prospective* or series or cohort*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2213	Advanced
27	clinical study/or exp case control study/or exp case study/or exp clinical trial/or exp "clinical trial (topic)"/ or exp intervention study/or exp major clinical study/or exp prospective study/or exp retrospective study/	3498048	Advanced
28	26 and (27 or observational*.mp. or cohort*.mp.) [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1431	Advanced
29	25 and 27	1238	Advanced
30	28 or 29	1431	Advanced
31	limit 30 to human	1376	Advanced
32	31 not case report/	1361	Advanced
33	remove duplicates from 32	1322	

Scopus

(TITLE-ABS-KEY(intubat*) AND TITLE-ABS-KEY(preoxygenat* OR "pre oxygen*" OR "ap ox" OR ((apneic OR apnoeic OR passive OR insufflat*) W/2 oxygen*) OR (("high flow" OR "high frequency" OR cannula* OR prong*) W/2 (nose OR nasal OR binasal OR nasopharyn*)) OR hfnc OR hfnp OR hhfnox)) AND AFT 2005 AND NOT (PMID(1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)) 183.

Ovid CENTRAL: 253 results

The asterisk (*) is a commonly used "wildcard" symbol that broadens a search by finding words that start with the same letters. Use it with distinctive word stems to retrieve variations of a term with less typing.

APPENDIX E3

Risk-of-Bias Assessment of ED and ICU Studies

Cochrane Collaboration's tool for assessment of risk of bias in randomized controlled trials.

Study	Adequate Sequence Generation	Adequate Allocation Concealment	Adequate Blinding of Personnel and Outcome Assessors	Incomplete Outcome Data Addressed	Free of Selective Outcome Reporting	Free of Other Bias	Overall Risk of Bias
Horan[23]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Jaber[27]	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Semler[29]	Yes	Yes	Yes	Yes	Yes	Unclear	Low risk
Simon[30]	Yes	Yes	Unclear	Yes	Yes	No	Moderate risk
Vourc'h[31]	Yes	Yes	Unclear	Yes	Yes	Unclear	Moderate risk

Modified Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies.

Study	Representative of Exposed	Selection of the Nonexposed Cohort (May Not Be Included)	Ascertainment of Exposure (Description of ApOx)	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on Basis of Design or Analysis	Assessment of Outcome	For Case Series: Consecutive Selection of Patients	Overall Risk of Bias
Besnier[26]	Somewhat	Same community	Good	Yes	Yes	Other than the proceduralist	—	Low risk
Dyett[38]	Truly	Same community	Poor	No description	No description	Other than the proceduralist	—	High risk
Fogg[32]	Truly	Same community	Poor	No description	No description	Assessed by proceduralist	—	High risk
Sakles[35]	Somewhat	Same community	Good	Yes	Yes	Assessed by proceduralist	—	Moderate risk
Sakles[36]	Somewhat	Same community	Good	Yes	Yes	Assessed by proceduralist	—	Moderate risk
Doyle[37]	Truly	N/A	Good	Yes	N/A	No description	Yes	Moderate risk
Grant[33]	Somewhat	N/A	Good	N/A	N/A	No description	Unclear	High risk
Kim[34]	Truly	N/A	Good	Yes	N/A	No description	Unclear	High risk
Miguel-Montanes[28]	Truly	Same community	Good	Yes	Yes	No description	—	Moderate risk

APPENDIX E4

Subgroup Analyses

Subgroup analysis by proceduralist expertise.

Outcomes	Trainees Subgroup	Experts Subgroup
Lowest oxygen saturation, SpO_2, % (WMD, 95% CI)	2.07 (0.57 to 3.57) [n=904]	2.59 (−2.83 to 8.00) [n=139]
First-pass success, OR (95% CI)	1.53 (1.04 to 2.25) [n=904]	1.47 (0.52 to 4.16) [n=754]
Hypoxemia, OR (95% CI)	0.66 (0.49 to 0.90) [n=1,043]	0.64 (0.35 to 1.16) [n=794]
Severe hypoxemia, OR (95% CI)	0.77 (0.51 to 1.17) [n=904]	1.08 (0.10 to 11.90) [n=139]

WMD, Weighted mean difference.

Subgroup analysis by study design.

Outcomes	RCTs	Observational
Lowest oxygen saturation, SpO_2, % (WMD, 95% CI)	2.83 (0.49 to 5.16) [n=356]	1.11 (−2.83 to 5.06) [n=687]
First-pass success, OR (95% CI)	1.14 (0.70 to 1.87) [n=316]	2.02 (1.13 to 3.62) [n=1,342]
Hypoxemia, OR (95% CI)	0.68 (0.44 to 1.06) [n=356]	0.65 (0.48 to 0.87) [n=1,481]
Severe hypoxemia, OR (95% CI)	0.75 (0.38 to 1.47) [n=356]	2.26 (0.16 to 31.65) [n=687]

Forest Plots for the Subgroup Analyses

Proceduralist Expertise (Trainees vs Experts)

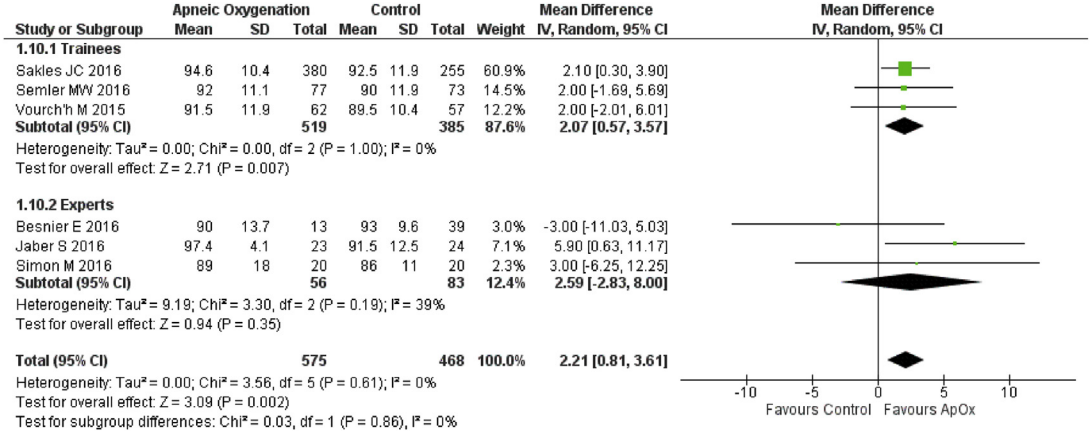

Figure E1. Lowest peri-intubation SpO_2 by proceduralist expertise.

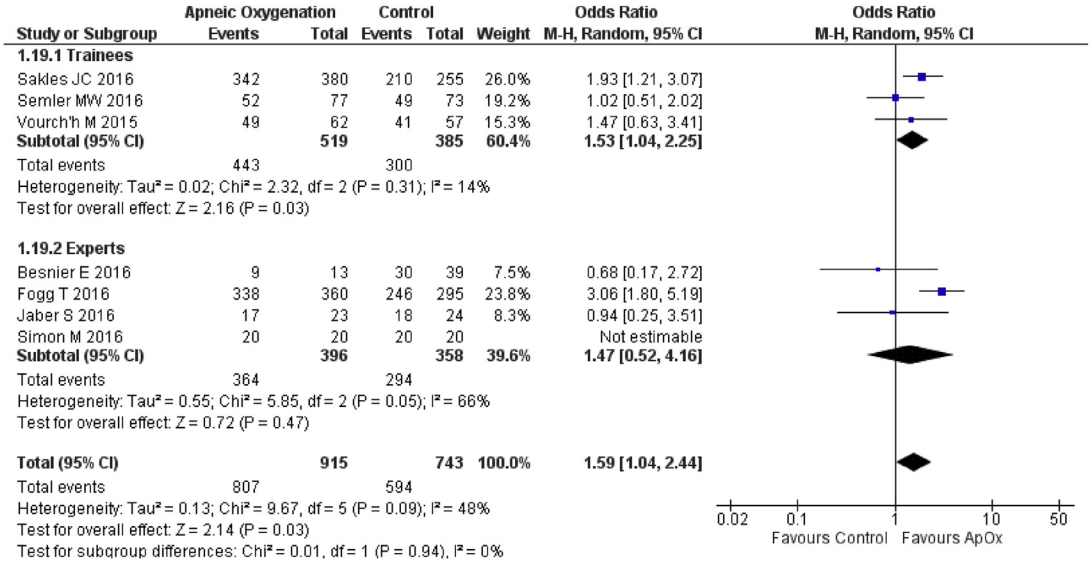

Figure E2. First-pass success by proceduralist expertise.

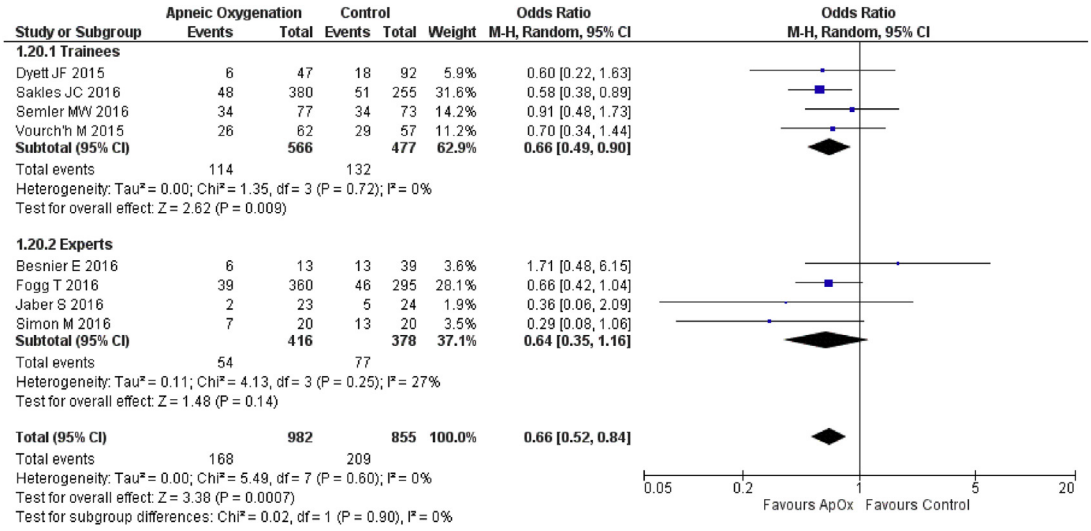

Figure E3. Hypoxemia (SpO_2 <93%) by proceduralist expertise.

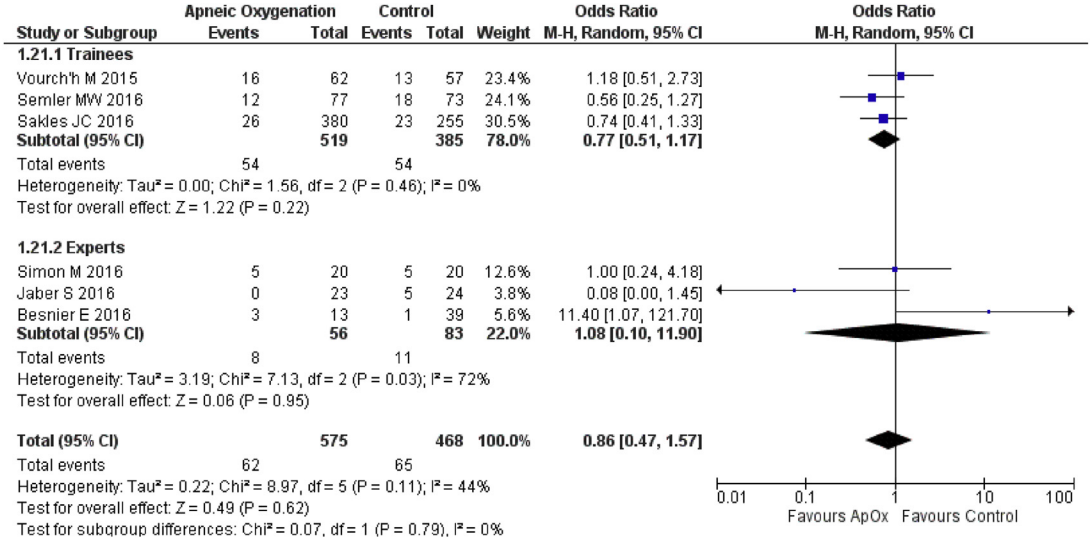

Figure E4. Severe hypoxemia (SpO_2 <80%) by proceduralist expertise.

Study Design (RCTs vs Observational Studies)

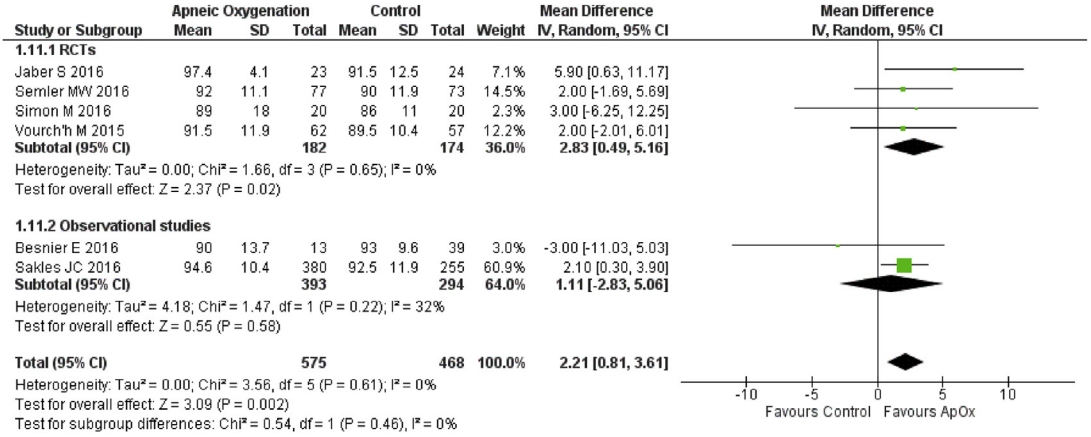

Figure E5. Lowest peri-intubation SpO_2 by study design.

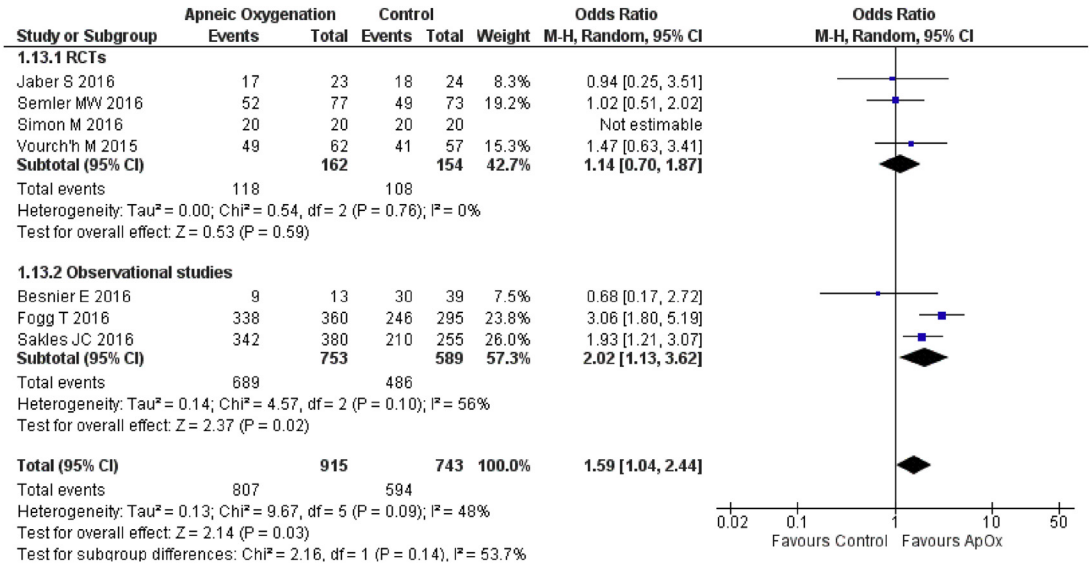

Figure E6. First-pass success by study design.

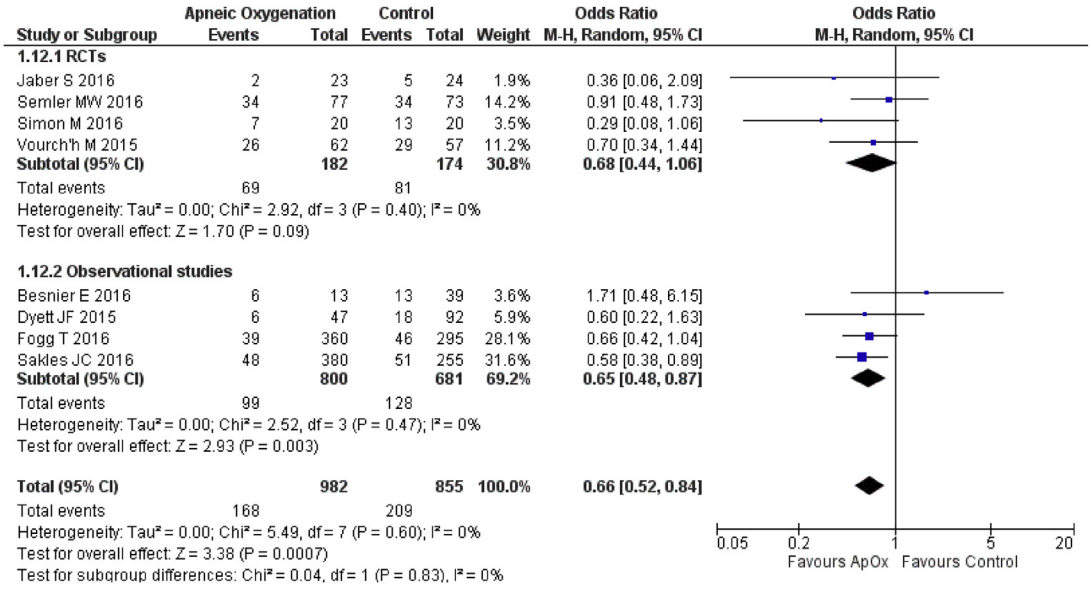

Figure E7. Hypoxemia (SpO_2 <93%) by study design.

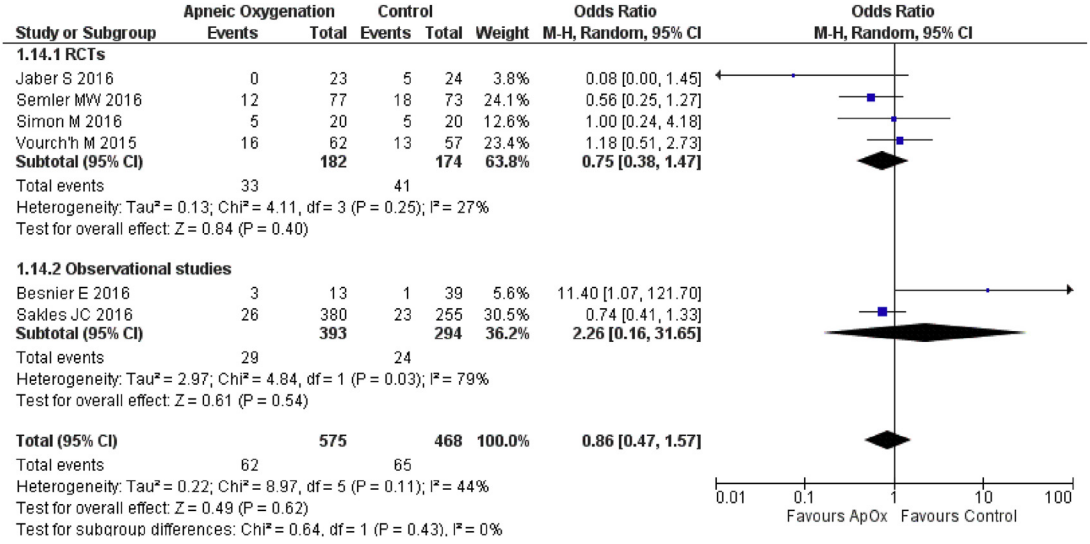

Figure E8. Severe hypoxemia (SpO_2 <80%) by study design.

Risk of Bias

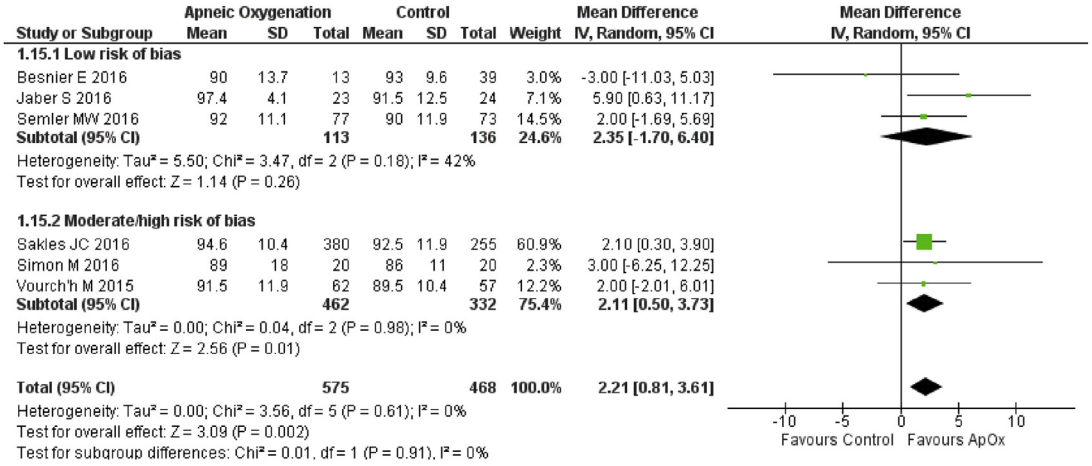

Figure E9. Lowest peri-intubation SpO_2 by risk of bias.

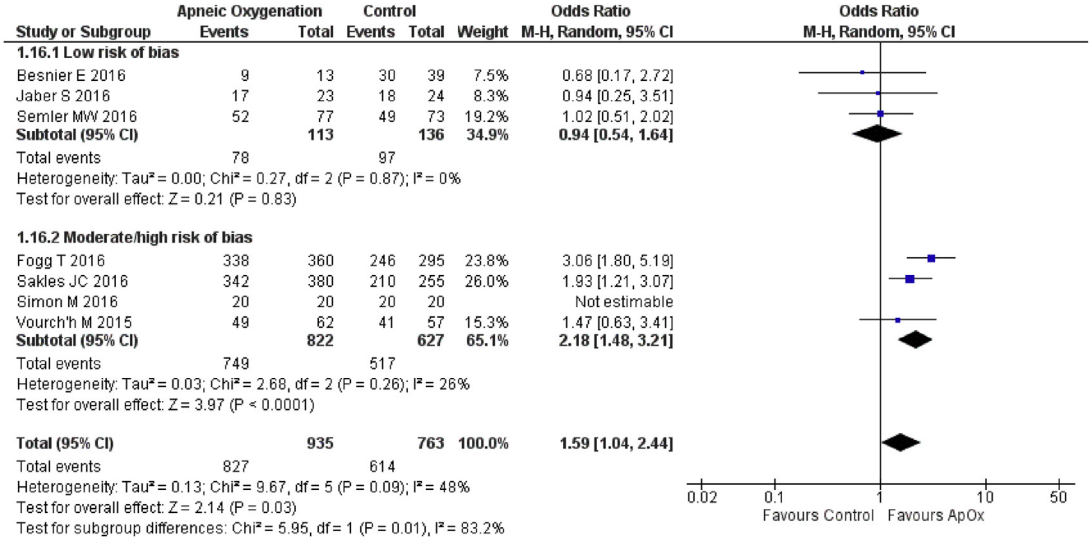

Figure E10. First-pass success by risk of bias.

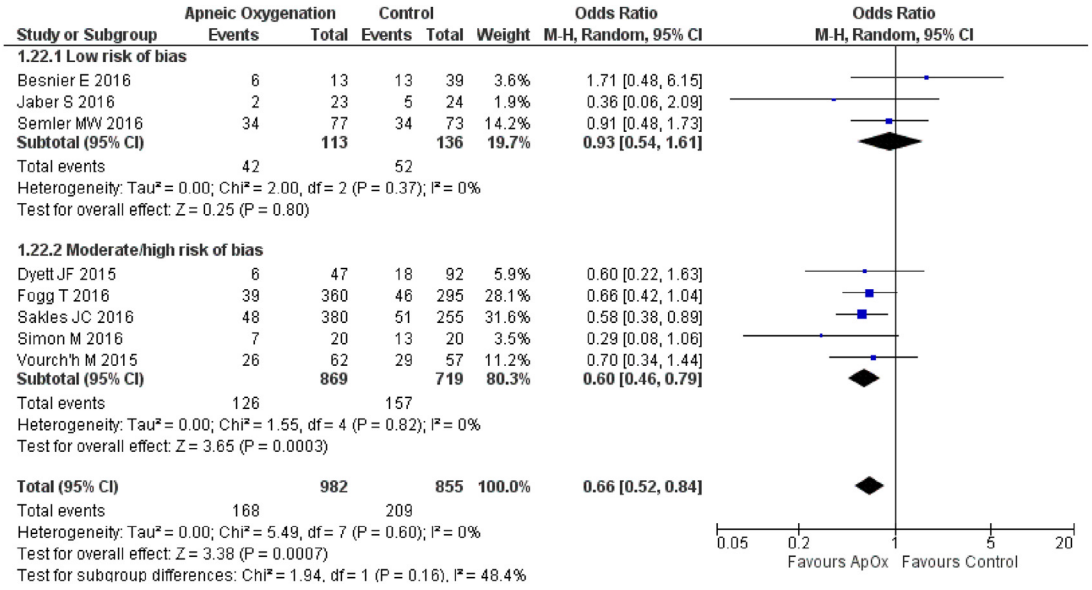

Figure E11. Hypoxemia (SpO_2 <93%) by risk of bias.

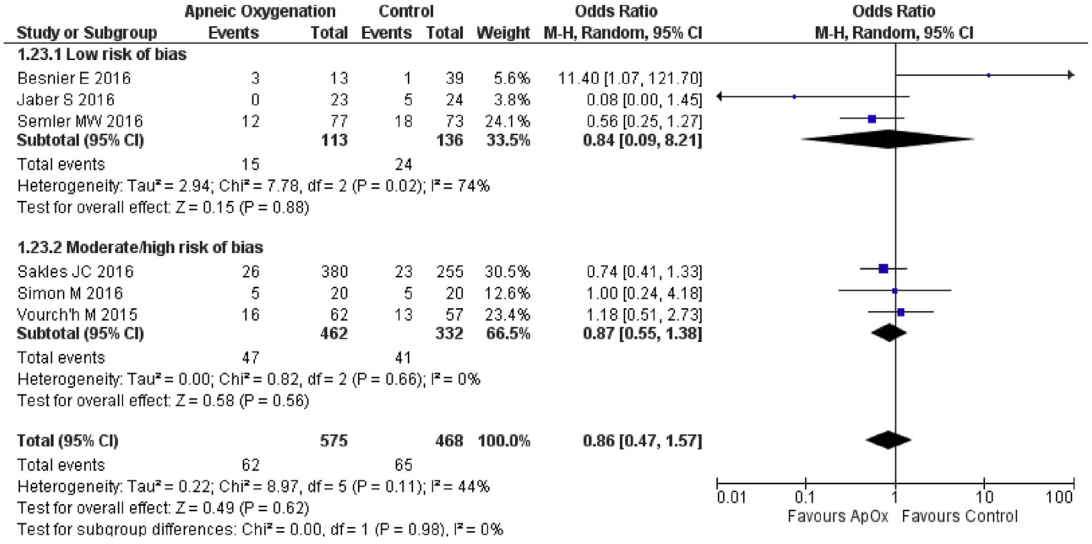

Figure E12. Severe hypoxemia (SpO_2 <80%) by risk of bias.