Apnoeic oxygenation during intubation in the intensive care unit: A systematic review and meta-analysis

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ABSTRACT

Hypoxaemia increases the risk of cardiac arrest and mortality during intubation. The reduced physiological reserve and reduced efficacy of pre-oxygenation in intensive care patients makes their intubation particularly dangerous. Apnoeic oxygenation is a promising means of preventing hypoxaemia in this setting. We sought to ascertain whether apnoeic oxygenation reduces the incidence of hypoxaemia when used during endotracheal intubation in the intensive care unit (ICU). A systematic review of five databases for all relevant studies published up to November 2016 was performed. Eligible studies investigated apnoeic oxygenation during intubation in the ICU, irrespective of design. All studies were assessed for risk of bias and level of evidence. A meta-analysis was performed on all data using Revman 5.3. Six studies including 318 patients were retrieved. The study found level 1 evidence of a significant reduction in the incidence of critical desaturation (RR = 0.69, CI = 0.48–1.00, p = 0.05) and a significant increase in the lowest SpO2 value by 2.83% (CI = 2.28–3.38, p < 0.00001). There was a significant reduction in ICU stay (WMD = –2.89, 95%CI = –3.25 to –2.51, p < 0.00001). There was no significant difference between groups regarding mortality (RR = 0.77, 95%CI = 0.59–1.03, p = 0.08), first pass intubation success (RR = 1.17, 95% CI = 0.67 to 2.03, p = 0.58), arrhythmia during intubation (RR = 0.58, 95%CI = 0.08 to 4.29, p = 0.60), cardiac arrest during intubation (RR = 0.33, 95%CI = 0.01 to 7.84, p = 0.49) and duration of ventilation (WMD = –1.97, 95%CI = –5.89 to 1.95, p = 0.32). Apnoeic oxygenation reduces patient hypoxaemia during intubation performed in the ICU. This meta-analysis found evidence that apnoeic oxygenation may significantly reduce the incidence of critical desaturation and significantly raises the minimum recorded SpO2 in this setting. We recommend apnoeic oxygenation be incorporated into ICU intubation protocol.

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Introduction

Apnoeic oxygenation uses cannulae to supply a constant stream of oxygen to the patient devoid of respiratory effort (Table 1). First described in 1959, the technique aims to prevent hypoxemic by delivering high volumes of oxygen to the pharynx, from where it can diffuse into the alveoli. The process is effective so long as patients have a patent airway and are free of significant cardiopulmonary shunting.

Endotracheal intubation is a life-saving treatment used in multiple hospital settings. The risk of intubation increases when performed outside of the operating theatre, where the clinical setting may be less controlled and the facilities and support staff less equipped. The intensive care unit (ICU) patient’s physiological reserve is often reduced due to acute and chronic illness, and up to 25–39% of intubations of critically ill patients result in complications.

Hypoxemia is a particular risk during intubation, increasing the possibility of cardiac arrest and death. Pre-oxygenation prior to intubation maximizes the patient’s reserve and reduces the risk of hypoxemia.1,2,3
intubation is a well-established technique used to ameliorate the risk of hypoxemia and prolong the ‘safe apnea time’ – the window of time following induction before desaturation occurs. However in the critically-ill population, pre-oxygenation is significantly less efficacious. Apneic oxygenation is commonly employed to improve oxygen saturations during intubation, including in the ICU. The technique uses high-flow nasal prongs, which supply concentrated oxygen to the nasopharynx at flow rates of between 15 L and 60 L per minute, whilst intubation is taking place.

Trials have assessed the use of apneic oxygenation during intubation in a broad variety of settings. These studies are difficult to compare given the vastly different protocols used and patient groups studied. In an attempt to produce a clinically meaningful analysis for intensive care professionals, only studies carried out in the ICU were included in this meta-analysis. The primary aim of this systematic review and meta-analysis was to evaluate the efficacy of apneic oxygenation in reducing hypoxemia (lowest SpO2 and incidence of critical desaturation) during intubation performed in the ICU. The secondary aims were to assess the impact of apneic oxygenation on post-apnoea oxygen saturation and on the incidence of adverse outcomes both during and after intubation such as duration of ventilation and mortality.

Methods

Search strategy

Commencing on 1st November 2016, a systematic search of five databases (SCOPUS, Web of Science, CINAHL, Medline and PubMed) was performed by two independent reviewers (RH, LW) and included articles published up to and including the 19th November 2016. Search terms used were: ((apneic OR apneic) oxygenation) AND ((endotracheal OR tracheal) intubation). The reference lists of recent papers were then manually checked for additional studies.

Inclusion criteria

Papers were included in our study if they compared apneic oxygenation during intubation with a control group in adult patients. Only studies carried out in the intensive care setting were eligible for inclusion in this analysis. Assessment for inclusion was made by two reviewers (RH, LW). There was no limitation on study design. Published abstracts were included.

Exclusion criteria

Studies performed outside the ICU setting or without a control group were excluded. Papers unavailable in English and unpublished studies were excluded.

Quality assessment

The Centre for Evidence Based Medicine (CEBM) levels of evidence (introductory document) was used to evaluate each study. These studies were subsequently evaluated for methodological quality and risk of bias using the Cochrane Collaboration’s tool for assessing the risk of bias.

Data extraction

Extracted data included indication for intubation, apneic oxygenation intervention and patient outcomes. Data was independently extracted by two reviewers (RH, LW). Collected data was subsequently assessed for homogeneity.

Outcome measures

The pooled data was analyzed for short, intermediate and long-term outcomes. Short-term outcomes included lowest measured SpO2 during intubation, critical desaturation during intubation, timing of desaturation, successful first-pass intubation, cardiac arrest, arrhythmias during the procedure and mortality (Table 1). Intermediate measures included duration of ventilation and ICU stay. The long-outcome of all-cause mortality was included.

Statistical analyses

RevMan 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark) was used to interrogate the combined data. Relative risk (RR) with 95% confidence interval (CI) was calculated for dichotomous outcomes and the weighted mean difference (WMD) with 95% CI was found for continuous results.

Table 1

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apneic oxygenation</td>
<td>Oxygen administered via nasal cannula to the patient devoid of respiratory effort.</td>
</tr>
<tr>
<td>Low-flow apneic oxygenation</td>
<td>Apneic oxygenation with oxygen flow rates of 15 L/min or less.</td>
</tr>
<tr>
<td>High-flow apneic oxygenation</td>
<td>Apneic oxygenation with oxygen flow rates of 50–60 L/min.</td>
</tr>
<tr>
<td>Critical desaturation</td>
<td>Fall in oxygen saturation (SpO2) to below 80% during intubation.</td>
</tr>
<tr>
<td>Mortality</td>
<td>Death in ICU or within 28 days of intubation.</td>
</tr>
</tbody>
</table>

Fig. 1. Systematic database search strategy.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Number of Patients</th>
<th>Mean Age (range)</th>
<th>Number of female gender (%)</th>
<th>Site of study</th>
<th>Patient Group</th>
<th>Pre-oxygenation (control; intervention)</th>
<th>Intervention (patient number)</th>
<th>Control</th>
<th>Primary Outcome(s)</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besnier et al. (2016)</td>
<td>Prospective Cohort</td>
<td>52</td>
<td>61 (50–63)</td>
<td>27 (52)</td>
<td>France</td>
<td>ICU- Respiratory Failure</td>
<td>&gt;3 mins 100% NIV; &gt;3 mins 50 L/min HFNC</td>
<td>50 L/min via HFNC (Optiflow&lt;sup&gt;a&lt;/sup&gt;, Fisher &amp; Paykel, New Zealand) (13)</td>
<td>0 L/min (39)</td>
<td>1) Desaturation (SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 95%) 2) Incidence of Critical Desaturation (SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 80%)</td>
<td>2</td>
</tr>
<tr>
<td>Jaber et al. (2016)</td>
<td>RCT</td>
<td>47</td>
<td>61 (57–68)</td>
<td>11 (22)</td>
<td>France</td>
<td>ICU- Respiratory Failure</td>
<td>4 mins 100% NIV; 4 mins 100% NIV + 60 L/min HFNC</td>
<td>60 L/min via HFNC (Optiflow&lt;sup&gt;a&lt;/sup&gt;, Fisher &amp; Paykel Healthcare, Auckland, NZ) (23)</td>
<td>0 L/min, HFNC in place with nil flow (24)</td>
<td>1) Lowest SpO2 2) Incidence of Critical Desaturation (SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 80%) 3) First Pass Success 4) SpO2 5 and 30 Minutes Post-Intubation 5) Arrhythmia During Intubation 6) Cardiac Arrest During Intubation 7) Short Term Mortality 8) Length of ICU Stay</td>
<td>1</td>
</tr>
<tr>
<td>Miguel-Montanes et al. (2015)&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Prospective Cohort 'Quasi-experimental'</td>
<td>101</td>
<td>60 (36–74)</td>
<td>36 (36)</td>
<td>France</td>
<td>ICU- Respiratory Failure</td>
<td>&gt;3 mins 15 L NRM (both groups)</td>
<td>60 L/min via HFNC (Optiflow; Fisher &amp; Paykel, Auckland, New Zealand) (51)</td>
<td>0 L/min (50)</td>
<td>1) Lowest SpO2 2) Incidence of Critical Desaturation (SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 80%) 3) PaO&lt;sub&gt;2&lt;/sub&gt; Post-Intubation 4) SpO2 5 and 30 Minutes Post-Intubation 5) Arrhythmia During Intubation 6) Cardiac Arrest During Intubation 7) Short Term Mortality 8) Length of ICU Stay</td>
<td>2</td>
</tr>
<tr>
<td>Semler et al. (2016)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>RCT</td>
<td>150</td>
<td>60 (50–68)</td>
<td>49 (38)</td>
<td>USA</td>
<td>ICU patients</td>
<td>&gt;3 mins 100% NIV, 100% BVM 15 L/min HFNC or 15 L HM (both groups)</td>
<td>15 L/min via HFNC (Comfort Soft Plus; Westmed, Inc., Tucson, AZ) (77)</td>
<td>0 L/min (73)</td>
<td>1) Lowest SpO2 2) Incidence of Critical Desaturation (SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 80%) 3) First Pass Success 4) Duration of Ventilation 5) Short Term Mortality 6) Length of ICU Stay</td>
<td>1</td>
</tr>
<tr>
<td>Simon et al. (2016)&lt;sup&gt;16&lt;/sup&gt;</td>
<td>RCT</td>
<td>40</td>
<td>58 (28–80)</td>
<td>18 (45)</td>
<td>Germany</td>
<td>ICU- Respiratory Failure</td>
<td>&gt;3 mins 100% BVM; &gt;3 mins 50 L/min HFNC</td>
<td>50 L/min via HFNC (not stated) (20)</td>
<td>0 L/min (20)</td>
<td>1) Lowest SpO2 2) Incidence of Critical Desaturation (SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 80%) 3) First Pass Success 4) Duration of Ventilation 5) Short Term Mortality</td>
<td>1</td>
</tr>
<tr>
<td>Vourch et al. (2015)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>RCT</td>
<td>118</td>
<td>63 (36–82)</td>
<td>41 (34)</td>
<td>France</td>
<td>ICU- Hypoaxemic Respiratory Failure</td>
<td>4 mins 15 L/min HFFM; 4 mins 60 L/min HFNC</td>
<td>60 L/min via HFNC (OptiflowTM; Fisher &amp; Paykel Healthcare, Auckland, NZ) (61)</td>
<td>0 L/min (57)</td>
<td>1) Lowest SpO2 2) Incidence of Critical Desaturation (SpO&lt;sub&gt;2&lt;/sub&gt; &lt; 80%) 3) First Pass Success 4) Duration of Ventilation 5) Short Term Mortality</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: NIV- non-invasive ventilation; HFNC- high-flow nasal cannula; NRM- non-rebreather mask; BVM- bag-valve-mask; HM- Hudson mask; HFFM- high FiO<sub>2</sub> face mask.

<sup>a</sup> Level of Evidence assessed using the Centre for Evidence Based Medicine (CEBM): Levels of Evidence Introduction Document.12
The Mantel-Haenszel (M-H) fixed effects model was implemented. Chi squared and $I^2$ statistics were used to assess for heterogeneity. An $I^2>50\%$ indicated significant study heterogeneity. When assessing RR, WMD or $I^2$, statistical significance was confirmed by a $P$ value of $<0.05$. Following the initial analysis, where possible, a subgroup analysis including only high quality RCTs was performed.

### Results

The initial systematic search revealed 2011 citations and the manual reference check of relevant papers found 15 additional citations (Fig. 1). After removal of duplicates and screening of records based on the title 30 abstracts were identified for review. Twenty-four of these failed to meet the inclusion criteria. Six studies were included in the meta-analysis with 518 patients. 14–16 Quality assessment concluded that of the six studies, four were high-quality randomized controlled trials and two were low quality level two trials 14–16(Table 2, and 3). Ten outcome measures from the ICU patient 20,21 and critical desaturation occurs during up to 50% of intubations performed in the ICU.6,22 Pre-oxygenation is universally employed as a means of delaying desaturation but it may perform unpredictably in some patients.23 It follows that any additional options for patient oxygenation are of great benefit to this scenario. The primary aim of this systematic review and meta-analysis was to evaluate the efficacy of apneic oxygenation in reducing hypoxemia (lowest SpO2 and incidence of critical desaturation) during intubation performed in the ICU. The effect on hypoxemia was assessed via a number of outcome measures, the most clinically significant being the lowest recorded SpO2 and the incidence of critical desaturation during intubation. The lowest recorded SpO2 was 2.83% higher than recorded in the control group ($p < 0.01$). The sigmoid relationship between oxygen saturation and the blood's partial pressure of oxygen describes that changes in oxygen saturation above 80% indicate larger alterations in oxygen partial pressure.24,25 Under normal physiological conditions, oxygen saturations of 90% equate to a generally satisfactory partial pressure of oxygen of 60 mmHg.26 Considering that patients

### Discussion

This is the first systematic review with meta-analysis to assess the utility of apneic oxygenation during intubation specifically within the intensive care setting. We found that apneic oxygenation significantly reduces the prevalence of hypoxemia and critical desaturation during intubation without impeding first-pass success rates. However, the technique did not alter the rates of adverse outcomes or mortality. Hypoxemia is a commonly used marker for poor prognosis in the ICU patient 20,21 and critical desaturation occurs during up to 50% of intubations performed in the ICU.5,22 Pre-oxygenation is universally employed as a means of delaying desaturation but it may perform unpredictably in some patients.23 It follows that any additional options for patient oxygenation are of great benefit to this scenario. The primary aim of this systematic review and meta-analysis was to evaluate the efficacy of apneic oxygenation in reducing hypoxemia (lowest SpO2 and incidence of critical desaturation) during intubation performed in the ICU. The effect on hypoxemia was assessed via a number of outcome measures, the most clinically significant being the lowest recorded SpO2 and the incidence of critical desaturation during intubation. The lowest recorded SpO2 was 2.83% higher than recorded in the control group ($p < 0.01$). The sigmoid relationship between oxygen saturation and the blood’s partial pressure of oxygen describes that changes in oxygen saturation above 80% indicate larger alterations in oxygen partial pressure.24,25 Under normal physiological conditions, oxygen saturations of 90% equate to a generally satisfactory partial pressure of oxygen of 60 mmHg.26 Considering that patients

### Table 3

Screening of bias and methodological quality based on the Cochrane Collaboration’s tool for assessing the risk of bias.13

<table>
<thead>
<tr>
<th>Study</th>
<th>Random Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Blinding of Patients</th>
<th>Blinding of outcome Assessors</th>
<th>Incomplete Outcome Data</th>
<th>Selective Reporting</th>
<th>Other</th>
<th>Quality Score (Quality Classification)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besnier et al. (2016)15</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>3 (Low)</td>
</tr>
<tr>
<td>Jaber et al. (2016)15,16</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7 (High)</td>
</tr>
<tr>
<td>Miguel-Montanes et al. (2015)16</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>3 (Low)</td>
</tr>
<tr>
<td>Semler et al. (2016)17</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7 (High)</td>
</tr>
<tr>
<td>Simon et al. (2016)18</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6 (High)</td>
</tr>
<tr>
<td>Vourc’h et al. (2015)19</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7 (High)</td>
</tr>
</tbody>
</table>

*Fig. 2. Lowest recorded SpO2 level during intubation with and without apneic oxygenation.*
intubated in the ICU often record lowest saturations near this value, a near 3% improvement in saturations is important.\textsuperscript{15–17} For instance, a shift from 89% to 91.8% would mean an increase in pO2 of over 6 mmHg, a shift exaggerated by the acidosis that often accompanies respiratory failure necessitating intubation in the ICU.\textsuperscript{11,24,27} Three of the four studies reporting this outcome were level one RCTs, qualifying the result as level one evidence. Similarly, our paper showed a significant reduction in the incidence of critical desaturation during intubation. However, this effect was rendered insignificant on subgroup analysis excluding the two low quality level two studies. Critical desaturation may therefore be unaffected the use of apneic oxygenation.

It has previously been posited that the increased closing pressure of the upper respiratory tract in the sedated patient curtails any benefits of apneic oxygenation during intubation.\textsuperscript{19} Our results appear to refute this claim. Our outcomes also suggest that lower oxygen flow rates may suffice in maintaining alveolar oxygenation. One of the six studies included in this paper used low-flow apneic oxygenation (Table 1).\textsuperscript{17} However, it was Besnier et al. (2016)'s study, using high flow nasal prong oxygenation, which contravened the general trend toward improved oxygen saturations with apneic oxygenation.\textsuperscript{14}

It must be said that direct measurement of arterial oxygen saturation or partial pressure of oxygen would be a more accurate indication of apneic oxygenation’s effectiveness than pulse oximetry. However, oximetry provides fluid, beat-to-beat blood oxygenation data and is imperative to the time-critical decisions required of the intensive care professional during intubation. It is also universally employed, cheap and non-invasive. Its use in the included studies reflects clinical practice.

Despite the reported improvements in patient oxygenation, apneic oxygenation had no effect on adverse events during the intubation procedure, with events such as sustained arrhythmia ($p = 0.60$) and cardiac arrest ($p = 0.49$) being equal across groups. Mortality was also unaffected. However, given the trend ($p = 0.08$), and the magnitude mean difference (23% relative reduction), hope remains that further investigation will reveal true long-term patient mortality benefits with the technique. Given that there was no difference in immediate complications during intubation measured by these studies, potential mortality benefits could lie in the difference in desaturation and the potential consequences for oxygen-sensitive end organs such as the brain and gut.\textsuperscript{11,27}

Only two studies investigated apneic oxygenation’s impact on ICU length of stay. These studies produced contradictory outcomes. Subsequently, and despite the significance of the meta-analytic result, it is impossible to draw meaningful conclusions from this.\textsuperscript{15,17}

Importantly, we found there was no difference in first-pass success rate with the implementation of apneic oxygenation during intubation. It would appear that the nasal cannula used in apneic oxygenation do not obstruct either laryngoscopic blade or endotracheal tube during insertion. It may also be hypothesized that the additional time to desaturation available with apneic oxygenation would aid in location of the laryngeal inlet. Given the need for expedience during intubation, any additional time on offer to the intensive care professional could also help to steady their thought processes and improve performance.

Our findings are in keeping with studies composed in other clinical settings and add to the growing body of evidence in support of apneic oxygenation during intubation \cite{10,11,28–33}. A recent meta-analysis found apneic oxygenation improves rates of hypoxemia when used in the emergency department and retrieval.\textsuperscript{28} Studies have also found success when the technique is used in the operating theatre.\textsuperscript{29,30}

The present meta-analysis includes a relatively small number of patients ($n = 518$) and represents a need for further randomized, controlled trials on the topic. The individual studies were not powered to evaluate for adverse outcomes such as arrhythmia and therefore may have failed to detect the full effect of apneic oxygenation. Future studies must address this if the full potential of apneic oxygenation is to be elicited.

While the majority of the included studies were level 1 RCTs, two were low quality cohort studies, which, as discussed, may have introduced allocation bias to outcomes such as incidence of critical desaturation.
There was variability in the chosen intervention used by studies. One of the six studies used low flow apneic oxygenation (15 L/min) and the other five used high flow oxygen (50–60 L/min). Although there is currently a dearth of evidence recommending one over the other, this may evolve with time and prove our results to be skewed retrospectively. Pre-oxygenation protocols differed between the studies. For instance, some used positive-pressure ventilation in the control groups, which will have increased baseline alveolar recruitment compared to the intervention group.

Each of the studies analyzed had incomplete outcome data. Only two had blinded outcome assessors and all had selective reporting, which may have introduced bias. Clinically significant outcomes such as duration of hemoglobin desaturation and cause of death were not reported in the included papers. Future studies would benefit from their inclusion. Most of the outcomes suffered minimal heterogeneity. However, length of ICU stay showed marked heterogeneity (97%) and may well represent a statistical error.

Conclusions

This study provides level one evidence that apneic oxygenation significantly increases the lowest SpO2 recorded during intubation. There is also evidence that the intervention significantly reduces the incidence of critical desaturation. Both high- and low-flow nasal prong oxygenation appear to be effective. Given that there were no adverse events associated with the use of apneic oxygenation, this study finds that it would be reasonable to incorporate apneic oxygenation into ICU intubation protocols. Future studies powered to detect differences in adverse outcomes and mortality are needed.

References