

# Apnoeic oxygenation was associated with decreased desaturation rates during rapid sequence intubation in multiple Australian and New Zealand emergency departments

Adrian Perera ,<sup>1</sup> Hatem Alkouri,<sup>2,3</sup> Toby Fogg,<sup>4</sup> John Vassiliadis,<sup>4,5</sup> John Mackenzie,<sup>6</sup> Yashvi Wimalasena<sup>7,8</sup>

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For numbered affiliations see end of article.

## Correspondence to

Dr Adrian Perera, Emergency Department, Royal Free London NHS Foundation Trust, London NW3 2QG, UK; adrian\_perera@icloud.com

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## ABSTRACT

Apnoeic oxygenation (ApOx) has been demonstrated to reduce the incidence of desaturation, although evidence of benefit has been conflicting depending on the technique used. The aim of this study was to compare the incidence of desaturation between patients who received ApOx via conventional nasal cannula (NC) and those who did not, using a large, multicentre airway registry.

**Methods** This study is an analysis of 24 months of prospectively collected data in the Australia and New Zealand Emergency Department Airway Registry (June 2013–June 2015). The registry includes information on all intubated adults from 43 emergency departments. Patients intubated during cardiac arrest (n=393), those who received active ventilation prior to the first intubation attempt (n=486), and where the use of ApOx was not recorded either way (n=312) were excluded. The proportion of patients who desaturated ( $\text{SaO}_2 < 93$ ) in the group that received ApOx and those that did not were compared. To evaluate the association of ApOx with patient desaturation, a logistic regression model based on factors expected to influence desaturation was performed.

**Results** Of 2519 patients analysed, 1669 (66.3%) received ApOx via NC while 850 (33.7%) did not. Desaturation in the cohort receiving ApOx was 10.4% compared with standard care (no ApOx) 13.7%. ApOx had a protective effect for desaturation (OR 0.71, 95% CI 0.53 to 0.95). Single intubation attempt was associated with reduced risk of desaturation of (OR 0.10, 95% CI 0.06 to 0.17); this was increased on second attempt (OR 0.37, 95% CI 0.21 to 0.68). Desaturation was also associated with the physician recording that they had anticipated a difficult airway (OR 1.83, 95% CI 1.34 to 2.48).

**Conclusion** This large multicentre registry study provides evidence that ApOx delivered through a conventional NC is associated with a lower incidence of desaturation in patients undergoing rapid sequence intubation.

**Trial registration number** ACTRN12613001052729.

## Key messages

### What is already known on this subject

► Multiple meta-analyses have demonstrated that apnoeic oxygenation (ApOx) decreases the incidence of desaturation during emergency department rapid sequence intubation. The most readily available technique delivers wall supply oxygen at 15 L/min via conventional nasal cannula. However, studies using this technique have reported conflicting results.

### What this study adds

► This analysis, using prospectively collected data from a large airway registry in Australia and New Zealand, demonstrates the delivery of ApOx via conventional nasal cannula is associated with reduced incidence of desaturation. The study also confirms prior studies showing the desaturation is more likely to occur in patients with anticipated difficult airway and those requiring multiple intubation attempts.  
► As predicting which patients will require more than one intubation attempt is challenging, this study suggests ApOx should be applied as standard care.

As a result, RSI performed out of the operating theatres has higher risk of complications, such as pulmonary aspiration, hypoxia, airway trauma, hypotension or procedural failure.<sup>1</sup> The use of potent sedatives and muscle relaxants to create optimal intubating conditions for an RSI will induce a period of apnoea prior to and during intubation. This risks hypoxia which, if severe and prolonged, may precipitate hypotension and cardiac arrest.<sup>2</sup> Moreover, the incidence of desaturation is strongly associated with the number of attempts at intubation.<sup>3</sup> Desaturation rates have been reported to be up to 37.8% in patients who had multiple attempts at intubation compared with 9.2% successful on first attempt.<sup>4</sup>

Apnoeic oxygenation (ApOx) allows passive diffusion of oxygen via a patent airway to the alveoli along a diffusion gradient when the patient is not breathing. This net pressure gradient across alveoli



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## INTRODUCTION

Patients undergoing rapid sequence intubation (RSI) in the emergency department (ED) are often critically unwell with significantly deranged physiology.



occurs as oxygen consumption remains constant at approximately 250 mL/min while carbon dioxide absorbed in the blood stream is exchanged.<sup>4</sup> Giving ApOx during the apnoeic period between induction and insertion of the endotracheal tube can therefore maintain lung oxygenation and prolong the time to desaturation during RSI.<sup>5</sup>

There are currently two modes of ApOx oxygen delivery during the apnoeic phase. The most commonly used is the so-called nasal oxygen during efforts securing a tube (NO DESAT) technique, where nasal cannula (NC) oxygen is delivered from a wall supply. The flow rate is, therefore, limited to approximately 15 L/min. Oxygen delivery through transnasal humidified rapid-insufflation ventilator exchange (THRIVE) can deliver rates of flow >60 L/min. Such high-flow rates increase positive end expiratory pressure, and improve ventilation-perfusion mismatch.<sup>6</sup>

Evidence in single centre studies on the application of NO DESAT ApOx has been conflicting. Both Wimalasena *et al*<sup>7</sup> and Sakles *et al*<sup>8</sup> have demonstrated the reduction in incidence of desaturation with the application of ApOx. However, Riyapan *et al*, and the FELLOWS study examined the same technique and both found no benefit of ApOx.<sup>9 10</sup> The ENDAO study investigated the lowest mean saturations on ED RSIs and identified no difference between ApOx and standard care.<sup>11</sup>

Several meta-analyses have aggregated data to demonstrate the benefits of ApOx; reducing incidence of desaturation and improving peri-intubation oxygen saturations with a mortality benefit.<sup>5 12</sup> However, in each meta-analysis, the effects of THRIVE and NO DESAT techniques are combined. The difference of the modality of oxygen delivery during the apnoeic phase may have significantly influenced the aggregated data.<sup>13</sup>

To date there are no published multicentre registry database studies that have examined the effects of NO DESAT ApOx during ED RSI.

## AIM OF STUDY

The aim of this study is to investigate if use of NO DESAT ApOx during ED RSI decreases the incidence of desaturation as a complication of RSI, in Australian and New Zealand EDs. The secondary aim is to examine the contribution of ApOx in the incidence of desaturation in the context of other potentially contributing factors.

## METHODS

### Study design and setting

The Australia and New Zealand ED Airway Registry (ANZEDAR) is a prospective observational study of the practice of ED RSI.<sup>14</sup> The ANZEDAR enrolled 43 EDs in Australia (39, 5% of total public hospitals) and New Zealand (4, 10% of total public hospitals), which prospectively recorded intubation data over 24 months between June 2013 and June 2015. Of the participating EDs, 17 are classified as major referral (39.5%), 13 urban district (30.2%) and 13 regional or rural (30.2%). Annual patient attendances ranged from 20 000 to 120 000. Two EDs that participated in the study were adult only. Overall, 14 (32%) of the participating sites are major trauma centres. This is further detailed in online supplemental appendix 1.

Data for the registry were reported by the intubating doctor close to the time of intubation, using a paper form. Data requested were: Patient demographics, indication for intubation, prediction of airway difficulty, and vital signs preintubation and postintubation. Interventions such as preoxygenation, patient positioning, medication, intubator seniority and experience, use of a preintubation checklist, devices and blades used, intubation

manoeuvres, number of intubation attempts, adverse events and patient disposition.

### Inclusion criteria

#### Participants

All patients who were intubated in participating EDs were eligible for inclusion in the ANZEDAR registry and were therefore eligible for inclusion in this analysis. There was no restriction by age, gender or underlying pathology. Patients were excluded if they were intubated during cardiac arrest or who received active ventilation by bag valve mask (BVM) or non-invasive ventilation (NIV) during the apnoeic period between induction of anaesthesia and the first laryngoscopy. However, patients who required more than one attempt at intubation and hence had rescue ventilation between attempts at laryngoscopy were not excluded, as this reflects conventional practice.

### Definitions

ApOx was defined as the provision of oxygen up to 15 L/min via NC during the apnoeic period following induction of anaesthesia.<sup>15</sup> Although there may be variation of wall supplied oxygen and NC delivery device, oxygen flow was assumed to be 15 L/min. Humidified high flow devices were not typically available and thus not identified for exclusion.

Standard care was defined as the absence of NC delivering oxygen during the apnoeic period of intubation.

Desaturation was defined as a fall in the patient's peripheral oxygen saturation ( $\text{SaO}_2$ ) to below 93% measured by pulse oximeter. This cut-off was chosen as 93% represents an inflection point of the oxygen dissociation curve,<sup>14</sup> after this point, the rate of decline may be rapid, particularly when coupled with the lag in pulse oximetry.<sup>16</sup> This cut-off is widely used in other Australasian studies. -

Intubation attempt: Each insertion of the laryngoscope blade into a patient's mouth was defined as an intubation attempt.

### Outcome measures

The primary outcome was the report of desaturation to <93% by the intubating physician.

### Data quality

Each recruited ED had a nominated senior emergency medicine clinician as a principal investigator (PI), listed in online supplemental appendix 1. To ensure accuracy and quality control, site data were reviewed by the PI prior to inclusion in ANZEDAR. The PI contacted the intubating physician requesting completion of missing or incomplete forms within a month.

Registry quality control included checking cases collected against records in resuscitation room or medications logbooks, or electronic medical records. Site compliance with a data set of 90% or more of all intubations for a minimum period of 6 months was required for inclusion.

The deidentified data sets were collated to a Microsoft Excel 2010 spread sheet (Microsoft, Redmond, Washington, USA) by the site PI and sent to the Emergency Care Institute for inclusion in the registry on a monthly basis.

### Data analysis

Intubation records were transposed to SPSS V.26 (SPSS) for statistical analysis. A  $\chi^2$  test was applied to establish baseline differences among patients who received ApOx versus standard care. To determine independent predictors of desaturation, we performed a logistic regression analysis, where the dependent

variable was desaturation. Candidate predictors were: age and weight as continuous variables; gender, ApOx, intubation attempt, anticipated difficult intubation, preoxygenation modality, trauma system designation, indication, specialty of the intubating doctor and intubating experience as categorical variables. These variables were selected a priori, based on considered scientific rationale. Blank data fields were coded as missing data, and deleted listwise by SPSS from the model. Thus, if there was a missing value for a modelled variable, the entire case was excluded from analysis.

Statistical significance is assumed when  $p < 0.05$ . Bonferroni correction was considered; when applied to the testing of 19 terms, corrected  $p$  value was  $< 0.003$ . Although this protects from type I error, the Bonferroni correction is overly conservative and vulnerable to a type 2 error, so the correction was not applied. The adequacy of the logistic regression model was verified by the Akaike's information criterion (AIC). This is a measure of the loss of information resulting from the use of the model and can be later used to assess better fitting models set a priori.<sup>17</sup> To test the approximation of the model to the data, a residual analysis by plotting standardised deviance residual vs predicted value of linear predictor was performed.

### Patient and public involvement

No patients were involved in the design of the study.

## RESULTS

The registry contained records for 3710 intubated patients. Patients intubated during cardiac arrest were excluded (393 (10.6%)). Patients who were ventilated during the apnoeic period via BVM (418 (11.2%)) or NIV (68 (1.9%)) were excluded from this analysis. Thus 2831 eligible intubated patients were analysed. In 312 cases, (11%) whether ApOx had been used was

not recorded and these cases were excluded from further analysis. Of the 2519 remaining, overall the median age was 48 years (IQR 30–65), and gender:female 985 (39.1%), male 1518 (60.3%) and missing 16 (0.6%). Prior experience of intubations was grouped as  $> 100$  997 (39.6%); 10–100 1141 (45.3%);  $< 10$  323 (12.8%); missing 58 (2.3%). The majority of intubations were due to a medical indication 1833 (72.8%); while trauma accounted for 644 (25.6%) and other 36 (1.4%).

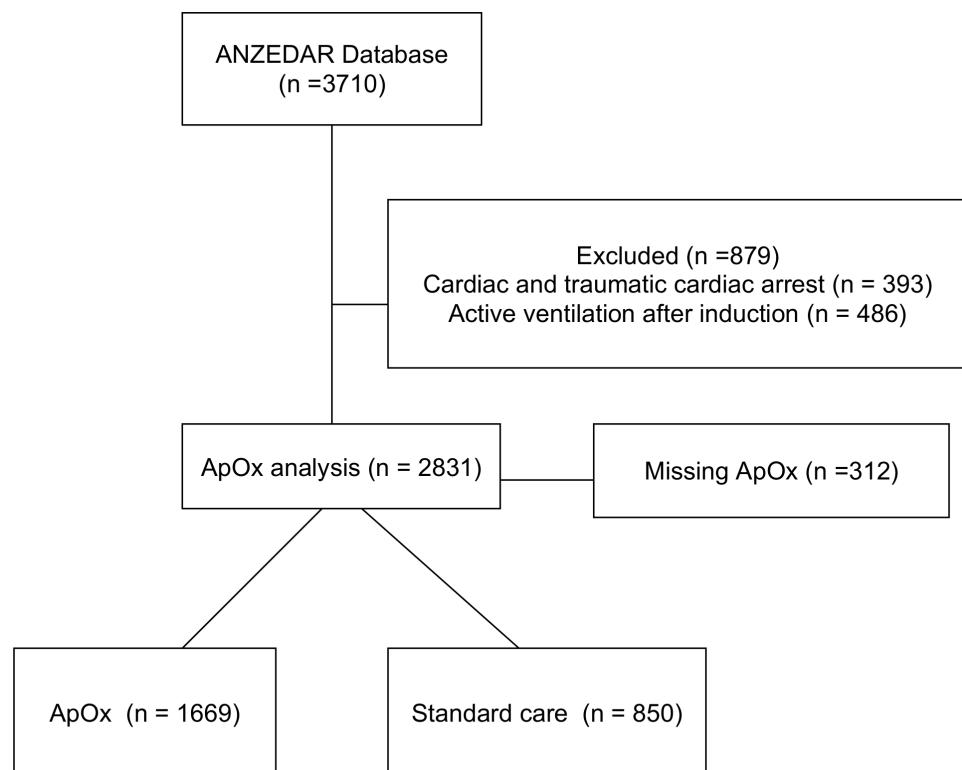
A total of 1669 (58.9%) patients received ApOx while 850 (30%) did not. Patient eligibility at each stage of selection is illustrated in a flow diagram (figure 1). The characteristics of patients receiving ApOx compared with standard care are demonstrated in table 1.

The intubating specialty was predominately emergency medicine. Anaesthetics and intensive care medicine (ICM) specialties were grouped together due to small group size for data management and similar level of airway expertise.

Chi square analysis identified that non-rebreath mask pre-oxygenation, Emergency medicine specialty, number of prior intubations  $< 10$ , and major trauma centre were significantly associated with use of ApOx as opposed to standard care ( $p < 0.01$ ).

Among those receiving ApOx, 173 (10.4%) desaturated, while among those who received standard care, 117 (38%) desaturated ( $p < 0.01$ ). In the logistic regression, those receiving ApOx had significantly reduced likelihood of desaturation (OR=0.71 95% CI 0.53 to 0.95) (table 2) compared with those receiving standard care.

Of the other variables, gender, anticipated difficult airway, number of intubation attempts and intubation by anaesthetics/critical care medicine were statistically significant. The OR of desaturation in females was significantly lower (OR 0.72, 95% CI 0.53 to 0.98) relative to males. Anticipated difficult airway was significantly associated with desaturation (OR 1.82 95% CI 1.34



**Figure 1** ANZEDAR participants through selection criteria and treatment. ANZEDAR, Australia and New Zealand Emergency Department Airway Registry; ApOx, apnoeic oxygenation.

**Table 1** Baseline characteristics of groups ApOx and standard caret

	No ApOx n=850	ApOx n=1669
Age		
Median (IQR)	45 (29–65)	49 (31–65)
Missing	8 (0.9)	17 (1.0)
Weight		
Median (IQR)	75 (65–85)	75 (65–90)
Missing	70 (8.2)	118 (7.1)
Gender		
Female	349 (41.1)	636 (38.1)
Male	494 (58.1)	1024 (61.4)
Missing	7 (0.8)	9 (0.5)
Indication		
Medical	628 (73.9)	1205 (72.2)
Trauma	203 (23.9)	441 (26.4)
Other	16 (1.9)	20 (1.2)
Missing	3 (0.4)	3 (0.2)
Anticipated difficult airway		
No	558 (65.6)	1121 (67.2)
Yes	270 (31.8)	528 (31.6)
Missing	22 (2.6)	20 (1.2)
Preoxygenation*		
BVM +PEEP	107 (12.6)	251 (15.0)
BVM	455 (53.5)	779 (46.7)
NIV	58 (6.8)	77 (4.6)
LMA	13 (1.5)	23 (1.4)
NRBM	205 (24.1)	522 (31.3)
Missing	12 (1.4)	17 (1.0)
Successful attempt		
1	720 (84.7)	1416 (84.8)
2	99 (11.6)	208 (12.5)
≥3	31 (3.6)	45 (2.7)
Specialty*		
Emergency medicine	672 (79.1)	1488 (89.2)
Anaesthetics/ICM	159 (18.7)	157 (9.4)
Other	16 (1.9)	20 (1.2)
Missing	3 (0.4)	4 (0.2)
No of prior intubations*		
<10	80 (9.4)	243 (14.6)
10–100	362 (42.6)	779 (46.7)
>100	381 (44.8)	616 (36.9)
Missing	27 (3.2)	31 (1.9)
Trauma service*		
Trauma unit	174 (20.5)	296 (17.7)
Regional centre	107 (12.6)	155 (9.3)
Major centre	569 (66.9)	1218 (73.0)

\*P&lt;0.01.

†Data are presented as n (%) unless otherwise indicated.

ApOx, apnoeic oxygenation; BVM, bag valve mask; ICM, intensive care medicine; NIV, non invasive ventilation; NRBM, non-rebreath mask; PEEP, peak end-expiratory pressure.

to 2.48) relative to normal airway. In the patients not anticipated to have a difficult airway (1679), desaturation still occurred in 8.3% (139). In patients requiring ≥3 intubation attempts (85), difficult airway was anticipated in 64.7% of cases. Preoxygenation via laryngeal mask airway (LMA) was significantly associated with an increased risk of desaturation, OR 2.82 (95% CI 1.66 to 4.78). This likely reflects the underlying respiratory

**Table 2** Factors predicting desaturation: logistic regression results

	OR	95% CI for OR		P Value
		Lower	Upper	
ApOx	0.710	0.530	0.951	0.022
No ApOx	1			
Age	0.993	0.986	1.000	0.046
Weight	1.010	1.004	1.016	0.002
Female	0.721	0.530	0.980	0.037
Male	1			
Indication				
Medical	2.618	0.344	19.922	0.353
Trauma	2.216	0.287	17.093	0.445
Other	1			
Anticipated difficult airway	1.826	1.344	2.48	<0.001
Predicted normal airway	1			
Preoxygenation				
BVM +PEEP	1.107	0.713	1.719	0.651
BVM	0.867	0.619	1.213	0.404
LMA	2.823	1.666	4.786	<0.001
NIV	0.216	0.028	1.675	0.143
NRBM	1			
Attempt				
1	0.098	0.056	0.172	<0.001
2	0.375	0.206	0.684	0.001
≥3	1			
Intubating specialty				
Emergency medicine	0.405	0.149	1.101	0.077
Anaesthetics/critical care	0.287	0.096	0.852	0.025
Other	1			
Previous intubation				
>100	1.507	0.937	2.426	0.091
10–100	1.346	0.857	2.116	0.197
<10	1			
Trauma designation				
Major centre	1.232	0.876	1.733	0.230
Regional centre	0.779	0.472	1.286	0.329
Trauma unit	1			

OR represents the constant effect of factor on the likelihood that desaturation will occur, either as continuous increment of factor or relative to factor where OR=1

ApOx, apnoeic oxygenation; BVM, bag valve mask; LMA, laryngeal mask airway; NIV, non-invasive ventilation; NRBM, non-rebreath mask; PEEP, peak end-expiratory pressure.

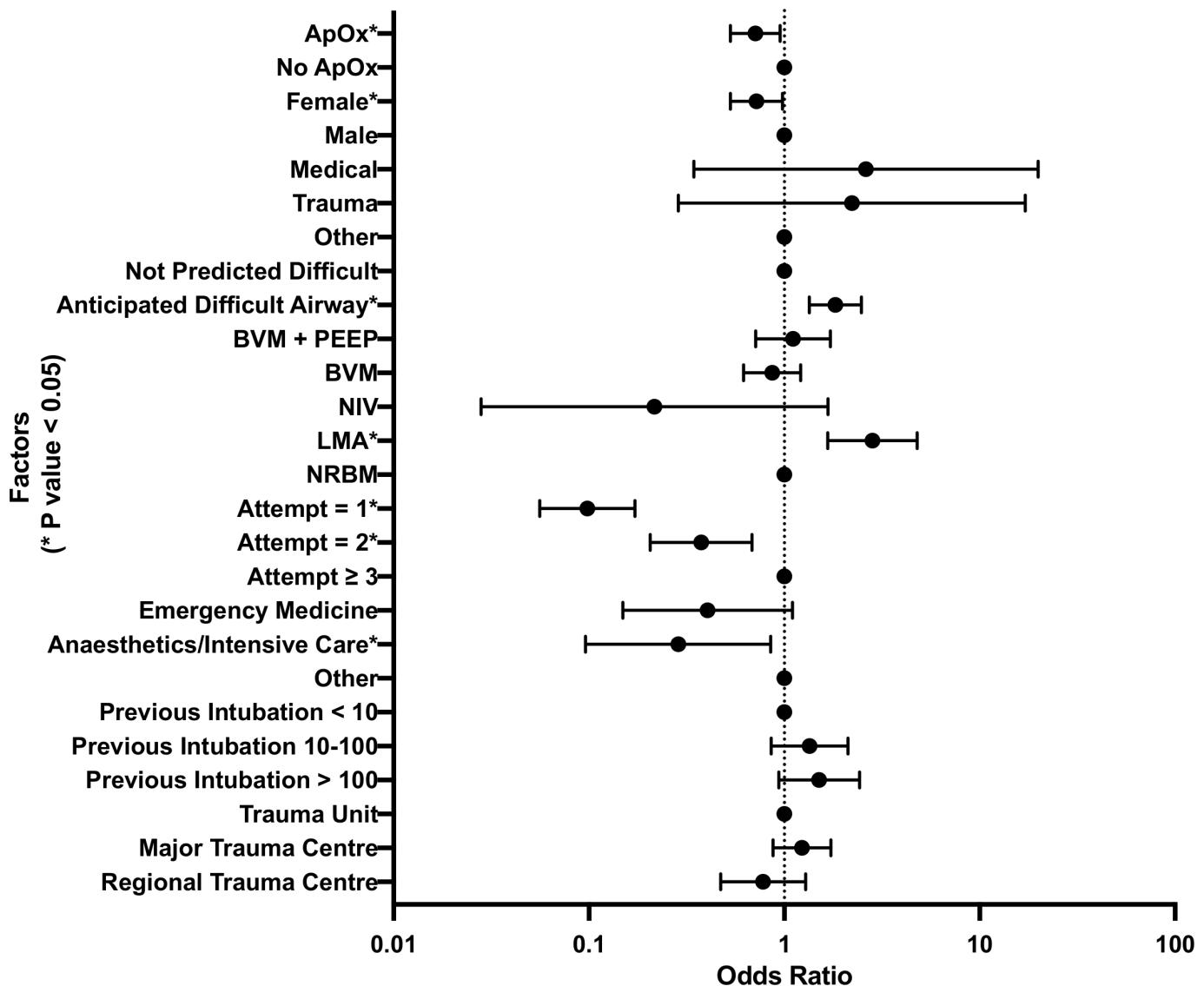
pathology and requires a sufficiently obtunded or sedated patient to tolerate LMA. Single intubation attempt was associated with risk of desaturation (OR 0.10, 95% CI 0.06 to 0.17); this risk was increased on second attempt (OR 0.37, 95% CI 0.21 to 0.68), measured relative to three or more attempts. Patient age, weight, trauma system designation and intubating experience were not found to be significant (figure 2).

Anaesthetics and ICM specialties had significantly lower odds of desaturation, (OR 0.29, 95% CI 0.01 to 0.85) compared with other specialties such as general practice or paediatrics.

The adequacy of the logistic regression model was found to be AIC. Further details of the residual plot analysis are provided in online supplemental appendix.

## DISCUSSION

This study demonstrated that the use of NO DESAT ApOx is associated with an adjusted OR of desaturation during RSI of



**Figure 2** Forest plot of factors in association with desaturation. ApOx, apnoeic oxygenation; BVM, bag valve mask; LMA, laryngeal mask airway; NRBM, non-rebreath mask.

0.71 (95% CI 0.53 to 0.95), in Australian and New Zealand EDs compared with standard care, after controlling for other potential predictors of desaturation. The risk of desaturation was significantly lower for first and second intubation attempts compared with three or more attempts. While desaturation was associated with anticipation of a difficult airway, desaturation still occurred in 8.3% of patients with anticipated normal airway. Three previous meta-analyses have considered ApOx, and all found that it reduced the risk of desaturation. Oliveira J E Silva *et al*<sup>12</sup> demonstrated an OR 0.66 for in eight studies, and an improvement in the peri-intubation oxygen saturations in six of these. Binks *et al*<sup>18</sup> found the same protective effect on desaturation. Pavlov *et al*<sup>5</sup> demonstrated a relative risk reduction of 30% with mortality benefit. White *et al*<sup>19</sup> found a similar reduction in relative risk of desaturation with ApOx. Each of these meta-analyses, however, included both NO DESAT and THRIVE techniques of ApOx.

Prior evidence for the NO DESAT technique has been conflicting. Riyapan and Lubin examined the incidence of desaturation in the prehospital environment and found no benefit of NO DESAT ApOx.<sup>9</sup> The FELLOWS trial found no difference

in incidence of desaturation with NO DESAT ApOx in an intensive care unit population. However, the majority of patients were intubated due to failure of NIV therapy and there were a variety of preoxygenation techniques.<sup>10</sup> Furthermore, 30% of patients were ventilated before laryngoscopy with BVM or non-invasive ventilation (NIV), confounding the effects of NO DESAT ApOx. The ENDAO study investigated the lowest mean saturations on 208 ED RSIs using NO DESAT and showed no difference in the lowest mean saturations between the groups.<sup>11</sup> Several other studies have found a benefit of NO DESAT ApOx reducing the incidence of desaturation; however, these have been limited to single-centre observational studies<sup>8 20</sup> or retrospective analysis.<sup>7</sup>

This large study, using prospectively collected data from 43 different EDs, demonstrates the reduced incidence of desaturation with the use of NO DESAT ApOx in ED.

Further analysis is required to determine what factors predict patients at greatest risk of desaturation during RSI, and which of these patients would benefit most from ApOx. The retrospective documentation of anticipated difficult airway does not support the statistical predictive power of airway assessment tools. This

would lead us to recommend the use of ApOx for all patients requiring RSI in ED.<sup>21 22</sup>

## LIMITATIONS

As a retrospective analysis of a prospectively collected database, the selection of patients to receive ApOx was not randomised.  $\chi^2$  analysis of baseline characteristics found a significant difference between patients whom received ApOx versus standard care. The greater use of ApOx by emergency medicine novice (<10) intubators in major trauma centres would suggest a greater awareness of the technique for those in supervised training positions at larger centres. Patient-dependant variables were equal between ApOx and standard care.

The technique of ApOx may not be uniformly executed: for example the rate of oxygen flow via NC during ApOx was not recorded and assumed to be 15 L/min. A previous study by Sakles *et al* similarly found a wide variation in the flow rate used for ApOx, and implementation over a 2-year observational study.<sup>8</sup> For ApOx to be effective the patency of the airway must be maintained throughout the peri-intubation period. While this is a key airway skill, it cannot be assured.

The duration of preoxygenation was assumed to be the accepted 3 min or eight vital capacity breaths. Ineffective preoxygenation could result in a shorter time to desaturation regardless of the continuous oxygen delivery during apnoea. A previously published study demonstrated NC oxygen can achieve 7% (95% CI 5% to 9%) greater preoxygenation end tidal oxygen ( $ETO_2$ ) at 1 min compared with BVM.<sup>23</sup> However, this benefit may only be compensating for the presence of a mask leak.<sup>24</sup> It is not possible to determine if ApOx has an additive effect on preoxygenation or if the continuous flow of oxygen during apnoea was protective.

As with most observational studies, missing data and potential error in recording poses reporter or recall bias and confounding factors. As the cases were not recorded by centre in the ANZEDAR, it is not possible to account for clustering in the analysis. Each patient was deidentified once entered into ANZEDAR; as such some patients may have been entered from repeated RSI encounters. It is unknown how this contributed to the dataset and thus cannot be mitigated.

The retrospective recording of anticipated difficult airway assessment, as requested by the registry form, permits potential recall bias after difficult intubation and desaturation. This has a compromising influence on the regression model. It remains possible further factors related to the medical cause of the pre-*RSI* hypoxia were not considered.

Recognition of desaturation endpoint is a key adverse event in emergency airway management. However, within the literature the threshold of desaturation is variable between 88% and 95%. If desaturation was under-reported, it is likely that it would be under-reported in both the ApOx and standard care groups, given that intubators were not aware that an analysis would be performed on this variable. To reach a consensus across 43 geographically widespread locations is challenging, thus  $SaO_2 < 93\%$  threshold was set a priori.

## CONCLUSION

This large multicentre study of prospectively collected data provides evidence supporting the use of NO DESAT ApOx using a conventional NC with wall-supplied oxygen to prevent incidence of desaturation in RSI. Patients with anticipated difficult airway and those requiring preoxygenation via LMA were demonstrated to have greater odds of desaturation. A randomised

controlled trial is required to conclude the benefit of NO DESAT ApOx against desaturation and determine its efficacy in difficult airways and multiple intubation attempts.

## Author affiliations

<sup>1</sup>Intensive Care, Royal Free London NHS Foundation Trust, London, UK

<sup>2</sup>Emergency Care Institute, New South Wales Agency for Clinical Innovation, Sydney, New South Wales, Australia

<sup>3</sup>Faculty of Medicine, University of New South Wales School of the Arts and Media, Sydney, New South Wales, Australia

<sup>4</sup>Emergency Department, Royal North Shore Hospital, Sydney, New South Wales, Australia

<sup>5</sup>Medical Education, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia

<sup>6</sup>Acute Care Adult and Paediatrics, Prince of Wales Hospital, Sydney, New South Wales, Australia

<sup>7</sup>Emergency Medicine, University Hospitals Coventry & Warwickshire NHS Trust, Birmingham, UK

<sup>8</sup>GSA HEMS, NSW Ambulance Service, Sydney, New South Wales, Australia

**Twitter** Adrian Perera @perera\_adrian

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**Collaborators** Sally McCarthy; Matthew Murray; Maysaa Daher; Helen Badge.

**Contributors** YW prosed the subgroup analysis. HA, TF, JV, JM were involved in data generation and establishment of ANZEDAR. AP and HA prepared the manuscript, data analysis and submission. All listed authors partook in several stages of the review and preparation of the submitted manuscript.

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## ORCID iD

Adrian Perera <http://orcid.org/0000-0002-1753-2586>

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