

Study Title:

**Pre- and Apnoeic high flow oxygenation for RApid sequence
intubation in The Emergency dept (Pre-AeRATE)**

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2. INTRODUCTION: BACKGROUND INFORMATION AND CLINICAL SIGNIFICANCE

2.1 Background information and clinical significance

Rapid sequence intubation (RSI) is the most common method of intubation used in the ED.¹ RSI involves the immediate administration of a paralytic agent following delivery of an induction agent that brings about unresponsiveness; a procedure which aims for successful endotracheal intubation with no ventilation via bag-valve-mask while awaiting the onset of paralysis. Under these circumstances, the maintenance of oxygen saturation during the apnoeic phase depends on the patient's underlying oxygen reserve, the adequacy of pre-oxygenation and the ability to insufflate the apnoeic lungs with oxygen (apnoeic oxygenation).

Critically ill patients have shorter safe apnoeic time (defined as duration of apnoea where SpO_2 remains $\geq 90\%$)² due to physiological stressors that accompany critical illnesses, such as decreased cardiac output, increased shunting and reduced pulmonary reserves. Once the SpO_2 reading approaches 90%, it can rapidly drop to $< 70\%$ (a critical hypoxic state) within seconds³ for two reasons. Firstly, a SpO_2 of 90% represents the steep gradient of the oxygen dissociation curve (Figure 1), where a small change in the arterial partial pressure of oxygen (PaO_2) results in a large change in haemoglobin oxygen binding capacity.⁴ Secondly, the pulse oximeter devices routinely used to measure SpO_2 have dampened circuitry to prevent fluctuating readings. However, this property may delay recognition of falling haemoglobin oxygen saturation⁵ and up to 47% of patients may experience latency in SpO_2 readings of up to 2 minutes.⁶ Furthermore, with increasing prevalence of obesity in Singapore⁷ from increasing affluence, a large proportion of our critically ill patients are also obese, and obesity can further shorten safe apnoeic times. Benumof et al. estimated that a moderately ill normal-sized adult would reach an SpO_2 of 90% at slightly under 5 minutes, while a 127kg obese adult would reach such a level within 2.5 to 3 minutes⁸ (Figure 2).

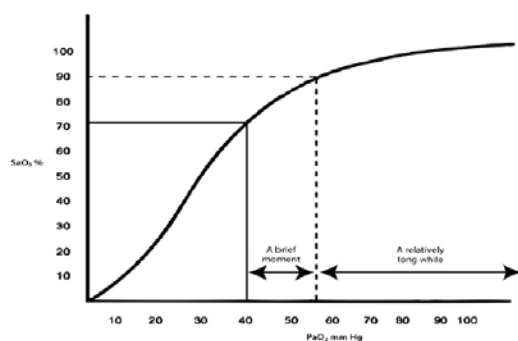


Figure 1. Oxyhaemoglobin dissociation curve of a healthy individual⁴

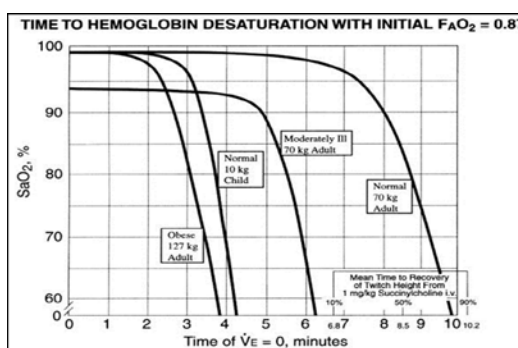


Figure 2. Arterial oxyhaemoglobin saturation (SpO_2) versus time of apnoea in an obese adult, a 10kg, and in a moderately ill adult, compared with a healthy adult. F_{AO_2} , Fractional alveolar oxygen concentration; \dot{V}_E , expired volume⁷

Profound hypoxaemia during intubation results in higher proportions of peri-intubation cardiac arrest, brain injury and death.^{3,9} The risk of adverse outcomes escalates with increasing number of attempts at endotracheal intubation and with development of hypoxia.¹⁰⁻¹² Prolongation of safe apnoea time would ameliorate some of these negative outcomes, by preventing hypoxia and allowing more time to achieve successful intubation without resorting to bag-mask ventilation to re-oxygenate the patient.

Adequate pre-oxygenation is the cornerstone of successful RSI and an essential step to achieving prolonged safe apnoeic times during intubation.² Pre-oxygenation with high fraction of inspired oxygen (FiO_2) de-nitrogenates the lungs, maximises oxygen reserve and oxygen saturation in the bloodstream.³ The standard of care is to apply a non-rebreather mask (NRM) with tidal volume breathing for 3 minutes for pre-oxygenation. However, depending on the patients respiratory rate and depth of breathing (i.e. their minute volume) the actual FiO_2 delivered varies from 0.8 to 0.6,¹³ sometimes even lower. Other more efficacious methods such as applying positive airway pressure and pre-oxygenating in a head-up position of 20 degrees have been described, but are not always possible in emergency situations or with obtunded patients.^{14,15}

High flow nasal cannula (HFNC) oxygenation has been gaining interest as an alternative method of pre-oxygenation and apnoeic oxygenation.¹⁶ It can deliver up to 60L/min of oxygen and FiO_2 of 1.0. As it is

humidified and heated, the high flow is well tolerated by awake patients.¹⁷ Moreover, the high flow has been shown to wash out carbon dioxide in anatomical dead space, create positive airway pressure adequate enough for alveolar recruitment and maintain a constant FiO_2 , regardless of the patient's minute volume.¹⁶ Additionally, it has the convenience of continuing oxygenation during the apnoeic phase after induction and paralysis, since the high flow maintains a positive end expiratory pressure and can insufflate the lungs, resulting in apnoeic oxygenation. Apnoeic oxygenation is possible due to differential solubility of oxygen and carbon dioxide in blood. Carbon dioxide is more soluble and therefore moves less readily down its concentration gradient from the bloodstream into the alveoli during apnoea. As a result, more oxygen moves from the alveoli into the bloodstream. This creates a sub-atmospheric pressure in the alveoli, allowing oxygen to flow from the pharynx to the alveoli during apnoea. Despite this sensible physiological rationale, a recent large randomised controlled trial reported no difference in median lowest arterial oxygen saturation in ICU patients with apnoeic oxygenation using 15L/min of nasal cannula compared with no apnoeic oxygenation at all.¹⁸ However, limitations in this study prevent definitive conclusions to be drawn. Firstly, the oxygen flow of 15L/min was delivered through routine nasal cannulae, which are not designed for such flows. Secondly, a flow rate of 15L/min may not be high enough to provide apnoeic oxygenation. It has been shown that flows of 30L/min are necessary to generate positive airway pressures.¹⁹ Thirdly, the cohort in the study consisted of mostly medical ICU patients with advanced respiratory failure, where 15L/min of oxygenation may not generate enough positive airway pressure to overcome pulmonary shunting. Furthermore, the results cannot be generalised to patients who do not typically present to medical ICUs, for instance patients with severe trauma or a surgical diagnosis.

There have been conflicting results from previous studies evaluating pre-oxygenation and apnoeic oxygenation using true HFNC. The PREOXYFLOW trial is the largest randomised controlled trial (RCT) to date (n=124) and found no difference in the lowest SpO_2 achieved when HFNC oxygenation was compared to high fraction-inspired oxygen facial mask for pre-oxygenation.²⁰ These results differ from another quasi-experimental before-after study (n=101), which showed that patients who were pre-oxygenated with HFNC had significantly higher SpO_2 during the apnoeic phase.²¹ Both studies were conducted in ICU patients and continued the HFNC during the apnoeic phase for apnoeic oxygenation. In addition to the contradictory findings by the 2 studies, it is also difficult to conclude whether the favourable results were attributable to the effect of HFNC during pre-oxygenation or apnoeic oxygenation.

Until now, there have been no studies conducted in the ED investigating the use of HFNC for pre- and apnoeic oxygenation. The incidence of failed intubations in the emergency setting is estimated to be 20 times that compared to intubation done electively²² and ED patients differ from ICU patients because they are less likely to have been fasted, increasing the risk of aspiration if re-oxygenation with bag valve mask is required during the intubation attempts. Aspiration of gastric contents contributes to increased risk of death during intubation.²³ Furthermore, hypoxia from failure to intubate is associated with increased ICU length of stay, irreversible brain damage, increased number of ventilated days and higher incidence of tracheostomy.²⁴ This translates to longer hospital stays, adversely affecting overall bed occupancy, as well as higher healthcare costs. Given the existing high occupancy in Singapore's restructured hospitals, which is expected to worsen as the population ages, it is vital that we prevent such adverse events from occurring by prolonging safe apnoea times for intubation (i.e. maintain lowest SpO_2 above 90%), without the need for bag-valve-mask ventilation for re-oxygenation during RSI. If our hypothesis is confirmed, the results from this study could potentially change current clinical practice and reduce demands on an already stressed healthcare system.

2.2 Potential benefits and risks

Potential benefits include a longer safe apnoeic time during rapid sequence intubation (i.e. SpO_2 maintains more than or equal to 90% after intubation til successful intubation). Although well tolerated by most patients, delivering HFNC oxygenation may have the following side effects or risks such as:

- Mild discomfort due to the high flow (approximately 12% risk),
- Dryness of the nose (level of dryness approximately 50% with high flow oxygenation compared with 95% in conventional oxygen therapy), and
- Low oxygen saturation during the intubation process (less than 5% risk): this will be similar for control and intervention groups.

Continuous SpO₂ monitoring will be performed to ensure that SpO₂ is maintained above 95% for pre-oxygenation. Previous studies using nasal oxygenation for pre-oxygenation prior to intubation were also able to maintain saturations at 100%,²¹ and showed no difference in SpO₂ at end of pre-oxygenation between the use of high flow face mask or nasal cannula.²⁰

3. **SPECIFIC AIMS & HYPOTHESIS**

The purpose of this clinical trial is to determine the best practices for maintaining oxygenation during rapid sequence intubation of critically ill patients in the emergency department (ED). Therefore, this multicentre randomised clinical trial is designed to test the hypothesis that the use of humidified high flow oxygenation via nasal cannula at 60L/min for **pre-oxygenation** and **apnoeic oxygenation** maintains higher oxygen saturation (SpO₂) compared with current usual care of non-rebreather mask for pre-oxygenation and standard nasal cannula of 15L/min for apnoeic oxygenation.

We expect to confirm our hypotheses by demonstrating that the use of humidified high flow oxygenation at 60L/min via nasal cannula (HFNC) during pre-oxygenation, as well as for apnoeic oxygenation, would improve the lowest recorded SpO₂ during intubation, and consequently increase the safe apnoeic time during rapid sequence intubation in the ED.

4. **STUDY DESIGN**

4.1 Description of study design

Overview

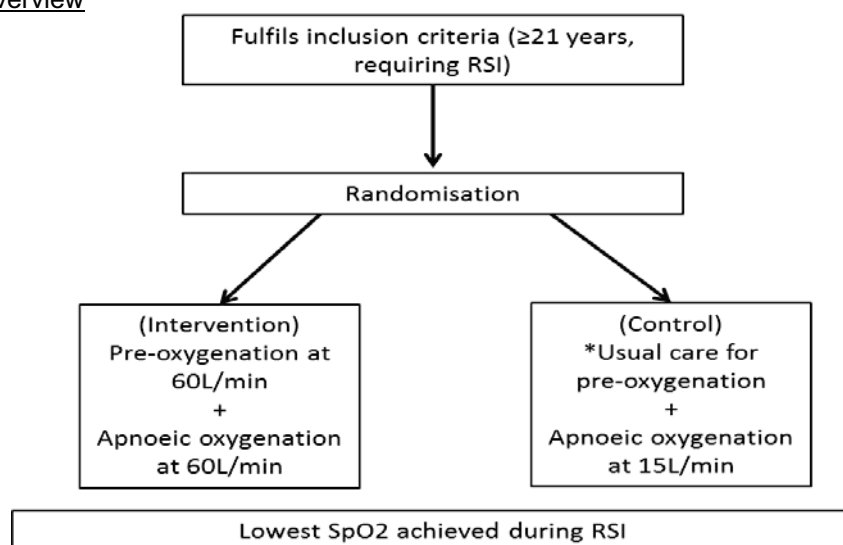


Figure 3.
Randomisation flow chart.

*Usual care for pre-oxygenation involves the use of non-rebreather mask

Target population and study site

This will be a randomised controlled study (Figure 3), enrolling adult patients aged 21 years and above, who require RSI due to medical, surgical and traumatic conditions, in the Emergency Departments of National University Hospital and Ng Teng Fong General Hospital, Singapore.

Randomisation

Subjects will be randomised at equal ratio into 2 treatment combinations (Figure 3). Random blocks of variable sizes will be selected via a web-based randomisation service. The block lengths will be kept unknown to the site as per ICH E9 guideline. However, block randomisation will ensure the numbers in each group will remain similar throughout the study, should we fail to recruit the targeted number of patients.

Allocation concealment will be maintained until registration and randomisation process is completed.

However, due to the nature of the intervention, it will not be possible to blind the treating clinician, ED staff members or patient after allocation has occurred. A possible concern is whether the results will be biased due to lack of blinding. As the outcome measures in our study are objective physiological measurements, the risk of bias remains low.²⁷ Clinicians in the admitting ICU will be blinded to the patients' allocation to any of the study arms.

Treatment protocol

In the intervention arm, the patients will receive oxygenation with 60L/min using the AIRVO™ 2 Humidifier with Integrated Flow Generator (Fisher & Paykel Healthcare, Auckland, New Zealand) during the pre- and apnoeic oxygenation phases.

The control group will be managed in accordance with current best practice by performing pre-oxygenation using NRM that has a FiO₂ of 0.6 to 0.8¹³ and given 15L/min of oxygen via nasal cannula (non-humidified, from wall supply).

Both groups will receive 3 minutes of pre-oxygenation.^{3,28,29} Premedication (if required) will be given 3 minutes prior to RSI, i.e. at the start of pre-oxygenation.³⁰ The lowest SpO₂ achieved from time of administration of paralytic agent until quantitative end-tidal CO₂ (ETCO₂) is detected for the first intubation attempt will be measured for all groups, together with the variables listed below.

4.2 Study endpoints

1. Primary endpoint

- Lowest SpO₂ achieved during first intubation attempt
 - From time of administration of paralytic agent until quantitative ETCO₂ is detected post-intubation
 - First intubation attempt is defined as first attempt to insert endotracheal tube into oropharynx

SpO₂ will be measured using the pulse oximeter of Philips Intellivue MP30 Patient Monitor.

2. Secondary endpoints

- Number of attempts at intubation
- Safe apnoea time during intubation
- Incidence of SpO₂ < 90%
- Peri-intubation adverse events (see below under Study Procedures)
- Length of time to successful intubation
- Incidence of ventilator associated pneumonia and aspiration pneumonia
- Number of ventilated days
- In-hospital mortality in ICU and on discharge
- Highest Sequential Organ Failure Assessment (SOFA) score
- Incidence of acute respiratory distress syndrome (ARDS)
- Lowest PaO₂ : FiO₂ ratio while intubated

5. STUDY ENROLMENT AND WITHDRAWAL

5.1 Inclusion criteria

Adult patients aged 21 years and above, who require RSI due to medical, surgical and traumatic conditions, in the Emergency Departments of National University Hospital will be eligible for study enrolment.

5.2 Exclusion criteria

- Patients with “do-not-resuscitate” orders
- Crash, awake or delayed sequence intubations
- Patients requiring non-invasive positive pressure ventilation
- Cardiac arrest
- Clinical suspicion or confirmed diagnosis of base of skull fractures or severe facial trauma that precludes nasal cannula placement

- Vulnerable patient populations (e.g. pregnant women, prisoners)

6. STUDY DEVICE

In the treatment group for pre- and apnoeic oxygenation using HFNC, the patients will be pre-oxygenated and oxygenated during apnoea with 60L/min of warm and humidified oxygen using the AIRVO™ 2 Humidifier with Integrated Flow Generator (Fisher & Paykel Healthcare, Auckland, New Zealand).



Figure 4. (a) Image of AIRVO™ 2 Humidifier with Integrated Flow Generator (left); (b) Nasal cannula interface (middle); and (c) heating tube (right).



Figure 5: Image showing how the nasal cannula will be connected to the AIRVO™ 2 system and patient.

7. STUDY PROCEDURES

Method of oxygenation for each patient will be dependent on the treatment combination randomised and assigned as described above.

Patients will be **pre-oxygenated for 3 minutes** with 60L/min using the AIRVO™ 2 Humidifier with Integrated Flow Generator **or** non-rebreather mask depending on treatment group randomised to. Premedication (if required) will be given 3 minutes prior to RSI, i.e. at the start of pre-oxygenation. Once 3 minutes of pre-oxygenation is completed, induction medications are administered and apnoeic oxygenation commenced as per assigned treatment group, which comprised of nasal cannula oxygenation at 15L/min **or** HFNC at 60L/min. Intubation attempts starts after 30 to 45 seconds (onset time of paralytic agent, typically succinylcholine or rocuronium). If the intubator is of resident grade, only 2 attempts are allowed before escalating to an EM specialist. Each attempt is defined as passage of laryngoscope through mouth.

End of intubation is defined as placement of endotracheal tube with confirmation of placement using quantitative end-tidal CO₂.

Clinical data collected (with no identifying data) will include:

(a) Pre-oxygenation	<ul style="list-style-type: none"> • Time pre-oxygenation started • Position adopted for pre-oxygenation • Duration of pre-oxygenation (time of induction = end of pre-oxygenation) • SpO₂ at beginning and end of pre-oxygenation (i.e. prior to induction) • Mode of pre-oxygenation (HFNC, NRM) • Lowest SpO₂ during pre-oxygenation • Name, dosages and timing of pre-medications given
(b) Intubation	<ul style="list-style-type: none"> • Time induction agent given, name of induction agent and dose • Time paralytic agent given, name of paralytic agent and dose • Time of successful intubation • Lowest SpO₂ achieved during subsequent intubation attempts (if unsuccessful at 1st attempt) • SpO₂ at the end of intubation • Type of laryngoscope use (direct/ articulating/ video) • Adjunct devices use (e.g. bougie) • Position of intubation • Cormack-Lehane scoring of laryngeal view (state direct or video view) • Intubator speciality and level of experience (by post-graduate year) • Supervision by EM specialist (yes/no) • Peri-intubation adverse events: hypotension, hypertension, tachycardia, bradycardia, regurgitation, aspiration, cardiac arrhythmia, cardiac arrest during RSI, oropharynx or dental trauma

(c) Clinical outcomes	<ul style="list-style-type: none"> • Length of stay in ICU • As in secondary endpoints
(d) Difficult airway features	<ul style="list-style-type: none"> • Reduced neck mobility or on C collar • Mallampati score • Mouth opening • Thyromental distance • Airway obstruction • Facial trauma (if not severe enough to preclude recruitment as per exclusion criteria) • Blood or vomitus in airway
(e) Others	<ul style="list-style-type: none"> • Demographics (age, gender, ethnicity, body mass index) • Comorbid conditions (congestive cardiac failure, ischemic heart disease, atrial fibrillation, chronic renal disease, chronic obstructive pulmonary disease, asthma, obstructive sleep apnoea, diabetes, previous head and neck radiation, head and neck mass or infection, upper gastrointestinal bleeding) • Pre-intubation vital signs (temperature, heart rate, systolic BP, diastolic BP, mean arterial pressure, Glasgow Coma Scale) • Quick SOFA score at triage and prior to pre-oxygenation • CXR findings • Indication for intubation • Vasopressor use

Only the index ED visit is included in the study. There will be no repeat visits. Patients' clinical outcomes as per secondary endpoints will be followed up electronically from the Computerised Patients' Support System (CPSS-2)

8. STATISTICAL CONSIDERATION

8.1 Sample size calculation

Based on our preliminary data and previous studies, we anticipate a standard deviation of 14% in lowest SpO₂. Enrolment of **184 patients** (92 patients in each of control and intervention groups) will provide statistical power of 80% (with a two-sided α of 0.05) to detect a 6% difference in lowest SpO₂, allowing for a 5% dropout.

8.2 General approach for statistical analysis

The primary analysis will be an intention-to-treat analysis, comparing the primary outcome of lowest SpO₂ achieved between two groups. Descriptive statistics of lowest SpO₂ (e.g. mean, standard deviation, median and interquartile range) will be reported for each group. Comparison of mean (or median) lowest SpO₂ between groups will be made using two-sample *t*-test or non-parametric test as appropriate. 95% confidence intervals of difference in lowest SpO₂ will be provided. Categorical data will be compared using the Fisher's exact test. We will use linear and logistic regression to adjust our findings if there are important differences between the study arms that might confound the results.

9. DATA HANDLING AND RECORD KEEPING

The Research Electronic Data Capture (REDCap) system will be used and maintained at SCRI's secure server. Authorised personnel will be assigned user IDs and passwords to gain access to the database. Entered data will be systematically checked by built-in edit checks.

The study participant's information and research data will be securely stored at the dedicated research computers in the NUH and NTFGH Emergency Departments for internal use during the study. The research computers are password protected and located in the Emergency Department administrative offices which are only accessible to authorised personnel by card access. Individual participants and their research data will be identified by a unique study identification number. Patients' identifiers and research data will be stored separately.

10. **CONFLICT OF INTEREST**

The PI and co-investigators declare no conflict of interests.

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