**Title**

High-flow Oxygen and Nitric Oxide inhalation versus high-flow oxygen alone to prevent intubation in hypoxaemic Respiratory failure (HONOR): a pilot randomised controlled trial.

# **Investigators**

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# **Resources**

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# **Abbreviations**

ABG Arterial blood gas

AE Adverse event

AHRF Acute hypoxaemic respiratory failure

AR Adverse reaction

ARF Acute respiratory failure

COT Conventional Oxygen Therapies

CRF Case report form

CXR Chest X-ray

FiO2 Fraction of inspired oxygen

GCP Good clinical practice

GCS Glasgow Coma Scale

HFNC High flow nasal cannulae

HFO2 High flow oxygen

HREC Human Research Ethics Committee

ICU Intensive care unit

IMV Invasive mechanical ventilation

iNO Inhaled nitric oxide

LOS Length of stay

NIV Non-Invasive Ventilation

NO Nitric oxide

NO2 Nitrogen dioxide

PaCO2 Partial pressure of arterial carbon dioxide

PaO2 Partial pressure of arterial oxygen

PEEP Positive end-expiratory pressure

PF ratio of PaO2 to fraction of inspired oxygen

PI Principal Investigator

PPM Parts per million

SAE Serious adverse event

SM Safety monitor

SpO2 Pulse oximetry

TPCH The Prince Charles Hospital

WOB Work of breathing

# **INTRODUCTION**

## Background and Rationale

Acute respiratory failure (ARF) is a common and life-threatening consequence of a diverse group of diseases (1, 2). When patients with ARF fail conventional oxygen therapies (COT) (≤15L/min oxygen via nasal prongs, cannula or mask) (3) or non-invasive ventilation (NIV), invasive mechanical ventilation (IMV) is considered the last option. However, outcomes of IMV are highly dependent on aetiology, age, co-morbidities and severity of illness. The use of IMV is common throughout the world and is increasing annually (4, 5). Mechanically ventilated patients represent approximately 3% of acute hospitalisations and 30% of Intensive Care Unit (ICU) admissions both internationally and in Australia (1, 2, 6-8). In 2017, 1176 patients were admitted to The Prince Charles Hospital (TPCH) with ARF, and of these, 330 were admitted to the ICU with 172 receiving IMV.

Previous studies have demonstrated significant increases in hospital length of stay (LOS) and ICU LOS for patients receiving IMV compared with non-ventilated patients (6, 9). IMV is also associated with an increased cost burden, ranging from 25-59% extra per ICU patient per day receiving IMV (7, 10, 11). Whilst often a life-saving intervention, intubation and ventilation are not without inherent risks. Risks include (but are not limited to) laryngeal injury, injury to lung parenchyma, adverse haemodynamic consequences (e.g. decreased venous return, drops in blood pressure and decreased cardiac output) and predisposition to infection (e.g. ventilator-associated pneumonia) (12-15). Furthermore, 30-40% of patients requiring IMV do not survive their ICU admission (1, 2, 16), with many survivors experiencing a significantly compromised quality of life, including symptoms of posttraumatic stress disorder (PTSD) (17-19). In 2017, 58 of the 172 patients (33%) admitted with ARF who received IMV in the TPCH ICU did not survive their hospital admission.

Emergent endotracheal intubation in acutely ill patients carries a high risk of morbidity, with reported intubation-related cardiac arrest (occurring within 20 minutes after successful intubation) rates of up to 23% (20). Additionally, despite being at a higher risk of mortality and morbidity, patients over 65 years of age receive IMV at rates three to five times higher than the national average compared with younger patient cohorts (2). Therefore, reducing the incidence, risks and costs of IMV is a major priority for providers, health system administrators, tax payers and policymakers (6). By averting an artificial airway, ARF patients supported with less invasive means can often avoid intravenous sedation and costly complications, such as ventilator-associated pneumonia, critical illness weakness, sinusitis, and line sepsis (6). Avoiding such consequences of intubation allows patient-centric aims of early rehabilitation, speech and oral feeding to be achieved in ICU, improves patient outcomes and reduces length of ICU and hospital stay that are tightly linked to costs of care.

To prevent intubation, high flow oxygen (HFO2) delivered through nasal cannula and non-invasive positive pressure ventilation (NIV) have been attempted, with HFO2 now commonly used in treatment of ARF (21-23). In a recent randomised clinical trial in patients with non-hypercapnic, hypoxic ARF, HFO2 therapy demonstrated a non-significant reduction in need for IMV compared with COT and NIV, but resulted in a better 90-day survival (24). In this study, the rates of intubation for patients treated with HFO2, COT and NIV were 38%, 47% and 50% respectively. The leading cause of intubation was worsening ARF and hypoxia (> 70%).

Hypoxaemia in some of these patients can be corrected by the addition of Nitric Oxide (NO) gas (25, 26) to nasal HFO2, thereby potentially avoiding IMV. NO is a potent vasodilator and when administered via inhalation, has the ability to provide selective pulmonary vascular dilation in well-ventilated sections of the lungs, improving ventilation-perfusion mismatch (26, 27). Significant improvements in oxygenation have been demonstrated in infants with ARF on nasal continuous positive airway pressure and NO (28), however results within the adult population remain inconsistent. A 2017 systematic review investigating NO use in patients with acute respiratory distress syndrome (ARDS) demonstrated improved fraction of inspired oxygen (PF) ratios in adults at 24 hours (29), however the benefits were transient or not sustained after this period (30-33). Furthermore, NO was either delivered via COT or mechanical ventilation and not via nasal HFO2. Literature demonstrating the effects of NO combined with HFO2 remains sparse. One multicentre cohort study evaluated the effectiveness of HFO2+NO in a specific patient population with respiratory failure from coronavirus disease (COVID-19) (34). In this patient population, HFO2+NO did not reduce oxygen requirements in the majority of patients, however in the subset of patients considered responders (defined as a decrease in supplemental oxygen delivered via HFNC 12 hours after inhaled nitric oxide (iNO) initiation), there was a trend toward decreased need for IMV compared to non-responders (34). Outside of this patient population, only case reports exist of successful HFO2+NO in preventing IMV, demonstrating improvements in oxygenation within the hospital setting and maintaining safe oxygen levels during transport to and from hospital (35, 36). Despite these early promising results, the lack of studies within this area is apparent. Therefore, to further investigate the potential benefits of HFO2+NO in preventing IMV, reducing the risks and costs of critical care in general, we believe this innovative idea merits further rigorous scientific investigation.

## Objectives

## The objective of this study is to examine the feasibility and clinical outcomes of comparing HFO2+NO gas inhalation over HFO2 alone to prevent IMV in patients with hypoxic, non-hypercapnic ARF. Based on the physiologic rationale (25, 37), precedence (28, 35, 36) and our anecdotal experience, we hypothesise that HFO2+NO therapy is superior to HFO2 in preventing IMV in patients with ARF.

This pilot study is a requisite initial step in exploring the proposed intervention (38). In preparation for a larger scale, multi-centre definitive trial, this pilot study will assess the feasibility and safety of the study protocol and processes to inform budget and protocol development; and provide initial effect estimates to inform sample size calculation.

## Design

Single-centre, pilot (n=40), randomised controlled trial. This will be an open label, non-cross over, pilot randomised controlled trial of nasal HFO2+NO gas inhalation versus HFO2 alone in patients with hypoxic, non-hypercapnic AHRF.

# **RESEARCH METHODOLOGY**

## Setting and sample

This single centre study will enrol adult patients admitted to ICU at The Prince Charles Hospital. Patients presenting with type I acute hypoxic respiratory failure (AHRF) (PaO2 < 60 mmHg with normal or subnormal PaCO2) (39) will have arterial blood gas sampling as per standard care for hypoxic respiratory failure. Aligning with previous research investigating HFO2 in ARF (40), if the ratio of PaO2 to PF is less than 300, they will be screened for suitability to participate in the study by a member of the research team. The patients will receive all appropriate treatments as determined by the treating clinician.

This is a pilot trial and as such is not required to be powered to detect statistical significance, therefore a sample of 40 patients will be recruited over a period of 12-18 months. Assuming the proportion of patients who progress to IMV is 0.38 (24), a sample of 20 per group will produce an exact 95% CI of width 0.44. Participants will be randomly allocated in a 1:1 ratio, with the use of the sealed envelope system to either the control or intervention arm. The patients will need to meet all inclusion criteria and nil exclusion criteria to be eligible to participate.

## ELIGIBILITY CRITERIA

**INCLUSION CRITERIA**

* Age ≥ 18 years, meeting the following criteria
  + *De novo* type I respiratory failure (hypoxaemia in the absence of chronic lung condition) (41)
  + PF ratio <300mmHg
  + High flow nasal cannula determined by ICU medical team to be primary method for delivery of oxygen therapy
  + Anticipated HFO2 requirement >24 hours
  + Arterial line in-situ for blood gas sampling
* Ability to provide informed consent, or consent via a substitute decision maker
  + Where emergency treatment is required rapidly, and the involvement in the research carries no more risk to participants than not participating, a consent waiver may be initiated, until a time point where the patient or their substitute decision maker can give informed consent

**EXCLUSION CRITERIA**

* Underlying chronic respiratory failure or exacerbation of asthma (including COPD or another chronic respiratory disease)
* Documented cardiogenic pulmonary oedema or acute coronary syndrome
* Hypercapnic respiratory failure with PaCO2 > 45mmHg
* Deterioration of neurologic status demonstrated by Glasgow Coma Scale (GCS) ≤ 12
* Urgent need for intubation (evaluated by the medical officer in charge)
* Haemodynamic instability (defined by systolic arterial blood pressure <90mm Hg or mean arterial blood pressure <65 mmHg)
* Use of vasopressors
* Do not intubate orders
* Enrolled in any other trial of targeted oxygen therapy

## STUDY INTERVENTIONS

**High Flow Oxygen (HFO2) alone (control group)**:

* Initial FiO2 set at 100% with an initial flow of 60L/min
* Down titrate FiO2 in the first hour, targeting SpO2> 92% and PaO2> 60mm Hg
* Further down titrate FiO2 every subsequent two hours maintaining SpO2> 92% and PaO2> 60mm Hg
* Down titrate flows in increments of 10L/min if needed for tolerance, to a minimum of 30L/min corresponding with FiO2 listedin the table below:

|  |  |
| --- | --- |
| Flow rate | FiO2 |
| 50-60L/min | 0.6 – 1.0 |
| 40L/min | 0.4-0.6 |
| 30L/min | 0.21-0.4 |

* Humidification to ensure delivery of HFO2 into the nares at a temperature set at 37°C

**High Flow Oxygen and Nitric Oxide (HFO2+NO) (intervention group):**

* Initial FiO2 set at 100% with an initial flow of 60L/min
* Down titrate FiO2 in first hour, targeting SpO2 > 92% and PaO2>60mmHg
* Further down titrate FiO2 every subsequent two hours maintaining SpO2> 92% and PaO2> 60mm Hg
* NO set at 20ppm via HFNC as per clinical work unit guideline (see Appendix for further details)
* Down titrate flows in increments of 10L/min if needed for tolerance, to a minimum of 30L/min corresponding with FiO2 listedin the table below:

|  |  |
| --- | --- |
| Flow rate | FiO2 |
| 50-60L/min | 0.6 – 1.0 |
| 40L/min | 0.4-0.6 |
| 30L/min | 0.21-0.4 |

* HFO2+NO support for a minimum of 24 hours
* Humidification to ensure delivery of HFO2 to the nares at a temperature set at 37°C

**NITRIC OXIDE WEANING CRITERIA:**

* After 24 hours, wean NO 1ppm every 20 minutes as per clinical work unit guideline (see Appendix 1 for further details) or as directed by the ICU Consultant, provided:
  + PaO2 > 60mmHg and SpO2 > 92% for greater than 6 hours with an FiO2 ≤ 50%
    - FiO2 may be increased up to a maximum of 60% to compensate for any drop-in oxygenation
* If nil decrement in oxygenation seen, NO will be further weaned at a rate of 1ppm/20 minutes to 0ppm) or as directed by ICU Consultant
* If desaturation persists (SpO2 <92%) for >15 minutes, NO will be returned to the most recent level prior to weaning or escalated up to a maximum of 20ppm to maintain patient oxygenation
* NO inhalation will be maintained if the patient in the HFO2+NO arm requires NIV via the ServoU® ventilator with sensing module at the mask end of the delivery tubing (see Appendix for further details)

**TRANSPORT**:

When patients are transported outside the ICU for radiological, surgical or other interventions, no restrictions shall be placed on oxygen use in either treatment group.

**CRITERIA FOR ENDOTRACHEAL INTUBATION**

As per previously established criteria to avoid delayed intubation and mechanical ventilation (MV) in patients receiving HFO2 (40) or at the discretion of the ICU Consultant:

1. Signs of persisting or worsening respiratory failure, defined by at least two of the following criteria:

* A respiratory rate above 40 breaths/min
* Lack of improvement of signs of respiratory-muscle fatigue/high respiratory workload
* Development of copious tracheal secretions
* Acidosis with a pH below 7.35
* SpO2 < 90% for more than 5 minutes without device malfunction
* Intolerance to NIV

1. Signs of haemodynamic instability despite inotropic support, defined by the following:

* Systolic Blood Pressure (SBP) < 90mmHg
* Mean Arterial Pressure (MAP) < 65mmHg

1. Deterioration of Neurological status:

* GCS below 12

## OUTCOMES

#### Primary outcomes

#### 1.Feasibility Outcomes

#### Eligibility (% of screened patients that meet criteria)

#### Recruitment (% of all eligible patients recruited using approved consent methods)

#### Retention (% of pts withdrawing consent)

#### Protocol fidelity (% of pts in intervention group receiving HFO2 + NO for at least 18 hours a day)

#### Missing data (% of primary and secondary outcome data unable to be collected)

#### 2.Clinical Outcomes

#### Serious Adverse Events (SAEs)

1. Methaemaglobin levels measured via ABGs at inclusion, *and then one hour, between four to six hours, 12 hours, 24 hours and 48 hours after randomisation*
2. *Daily serum creatinine and urine output levels will be collected to monitor renal function and/or renal impairment*
3. *Number of patients in each arm progressed to IMV within 28 days*

## Secondary Outcomes

1. Improvement in PaO2 relative to baseline between four to six hours, 12 hours, 24 hours and 48 hours
2. Physiological data (inclusion, and then one hour, between four to six hours, 12 hours, 24 hours and 48 hours after randomisation)
   * Respiratory rate (RR)
   * SpO2
   * SBP
   * Heart rate (HR)
3. Illness severity as estimated by daily sequential organ failure assessment (SOFA) scores (42)
4. Worst daily PF ratio
5. ROX index scores at inclusion, and then one hour, between four to six hours, 12 hours, 24 hours and 48 hours after randomisation
6. Reason for intubation
   * Respiratory failure
   * Circulatory failure
   * Neurological failure
   * Surgery
7. Dyspnoea scores (RPE – see Appendix 2)
8. ICU LOS
9. Hospital LOS
10. Mechanical ventilation hours
11. Number of ventilator free days at day 28
12. Time to mobilisation (Classification 4 (standing) on the ICU mobility score) (43)
13. Best mobility (within first 24 hours and during whole length of stay)
14. Daily delirium incidence (CAM-ICU score)
15. Retrospective pre-ICU EQ-5D-5L questionnaire
16. EQ-5D-5L (collected within 5-7 days of discharge from the ICU)
17. Need for anxiolytic and sedative medication during admission
18. ICU mortality
19. Mortality at 90 days

## Participant timeline

## RECRUITMENT

Potential participants presenting to ICU at TPCH with acute respiratory failure and a PF ratio ≤300 will be screened according to inclusion and exclusion criteria by a member of the study team. If a patient meets all the inclusion criteria and none of the exclusion criteria, potential participants will be approached about informed consent by study investigators. As patients presenting to ICU may have significant respiratory distress, treatment will not be delayed. HFO2 may be initiated by the treating team as per standard of care. Participants will be randomised (see below) to receive either High Flow O2 via nasal cannula (control) or High Flow O2 and Nitric Oxide (intervention) via nasal cannula.

## CONSENT PROCESS

Screening for suitable participants will occur Monday to Friday. After discussion with the medical team regarding suitability. Written informed consent will be obtained from all the patients, their next of kin, or another surrogate decision maker as appropriate. Where emergency treatment is required rapidly, and the involvement in the research carries no more risk to participants than not participating, a consent waiver may be initiated, until a time point where the patient or their substitute decision maker can give informed consent. HFO2 and NO is currently used as standard of care for this patient cohort in the ICU at TPCH and demonstrated to be safe at levels up to 20ppm (44).

## RANDOMISATION

Participants will be randomly allocated in a 1:1 ratio, with the use of the sealed envelope system to receive HFO2 via nasal cannula (control) or HFO2 and NO (intervention) via nasal cannula. Randomisation and initiation of treatment is required within three hours of informed consent.

# DATA COLLECTION

Feasibility:

As one of the primary outcomes, feasibility data pertaining to the eligibility and recruitment will be gained from the electronic screening log. The screening log will be used to document all patients who have been screened and identify those who consented to enrol in the study and those who were not enrolled remarking the specific reason for exclusion and will contain:

* All patients screened based on admission diagnosis of ARF in ICU
* Inclusion/exclusion criteria
* Recruitment status
* Randomisation (treatment allocation)

Data for the remaining feasibility outcomes (retention, protocol fidelity, percentage of participants in intervention group receiving HFO2 + NO for at least 18 hours a day, missing data and number of patients in each arm progressed to IMV) will be held in a password protected spreadsheet only accessible by the research team.

##### Demographic Data:

Data in relation to demography, physiology, admission severity of illness, haemodynamic data, details of haemodynamic support, hepatic and renal functions will be collected via the Australian and New Zealand Intensive Care Society Centre for Outcomes and Resource Evaluation Adult Patient Database (ANZICS CORE APD).

Data collected for each patient will be collected and stored in a de-identifiable format on a password protected spreadsheet and will include the following data:

* Physiologic parameters including: RR, SpO2 level, SBP and HR will be recorded at inclusion, and then one hour, between four to six hours, 12 hours, and 24 hours after randomisation. Arterial blood gases (ABG) will be recorded at time of inclusion, 12 hours, 24 hours and 48 hours after randomisation.
* Patient subjective respiratory dyspnoea scores will be assessed (1-hour post oxygen strategy) using a modified BORG scale (see Appendix 2)

# STATISTICAL ANALYSIS

Consistent with published recommendations for pilot studies, we will refrain from a detailed inferential statistical analysis in this pilot study [23]. The sample size is based on the pragmatics of recruitment and the necessities for examining feasibility. Inclusion of HFO2 as control group in this pilot is deliberate and will allow realistic examination of recruitment, randomisation and implementation of interventions. Analysis will be performed on an intention-to-treat basis.

Categorical variables will be summarised as frequencies (percentage) and continuous measures will be summarised as mean (SD) or median (IQR) as appropriate. Binary outcome measures for each group will be presented with estimated proportions with 95% confidence intervals to convey precision. Kaplan-Meier curves will be plotted to explore time from enrolment to intubation or death in each group. Associations between baseline factors and intubation will be explored using logistic regression analysis.

# For outcome measures with continuous repeated measures, within-group change, between-group differences and differences in rates of change over time will be explored using mixed effects linear regression modelling with an interaction term for time by group.

# ETHICAL and SAFETY CONSIDERATIONS

* This study will be conducted in accordance with the ethical principles of human research outlined by the Declaration of Helsinki, the Good Clinical Practice (GCP) guidelines, and in line with the local regulatory statements for ethical conduct of research at each study site.
* Any adverse event associated with the conduct of the study will be reported to the responsible Human Research Ethics Committee by the principal investigator as soon as possible. In addition, regular progress reports will be provided to the ethics committee in line with the local requirement at the study site.

# Data Handling and Record Keeping

CRF’s will be collected initially in hard copy before being transferred to a password protected computer. Paper documents will be stored in a secured locked cabinet under the supervision of the principal investigator. An electronic copy of the data will be maintained via a password protected spreadsheet, and the principal investigator will be responsible for its management. The principal investigator will maintain electronic copies of study data on an encrypted spreadsheet and be responsible for its collation and analysis.

The principal investigator and all associated investigators will ensure all steps are taken to maintain confidentiality and prevent accidental disclosure or destruction of documents. Documents will be maintained for at least 15 years as per Good Clinical Practices.

# Serious Adverse Events:

SAEs will be actively monitored and reported to the relevant Human Research Ethics Committee. The definition of a SAE is one that fulfills at least one of the following:

* Is fatal - results in death
* Is life threatening
* Requires inpatient hospitalisation or prolongation of existing hospitalisation
* Results in persistent or significant disability or incapacity (45)

All SAEs will be reported to the responsible HREC within 24 hours of study staff becoming aware of the occurrence. Reporting will be in accordance with local requirements. A medical professional will be required to assess the causality relationship between the study intervention and the event (possibly, probably or definitely related).

## Duration of study and termination

We expect to recruit 40 participants over a 12-18-month period. The study will be terminated earlier if dictated by the local ethics committee.

## Significance of study:

Given the risks, costs and suboptimal outcomes associated with IMV despite decades of refinements, and in the setting of an ageing population with a higher incidence of pulmonary and other co-morbidities, it is important that less invasive forms of respiratory support such as the one proposed in this research plan are fully explored. Reducing the incidence of IMV and IMV related complications will improve the patient experience, patient outcomes, reduce ICU and hospital length of stay (6) and result in substantial cost saving for the health service. Patients need not go into induced coma, can retain autonomy, eat, drink, exercise and rehabilitate with our innovative approach and this may translate into better long-term physical, cognitive and psychological outcomes and quality of life. Equally, integrating patient’s values, feedback, goals and concerns with the best available evidence about benefits, risks and uncertainties of treatment, to achieve appropriate health care decisions will also reduce distress for patients, families and health care staff.

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**Appendix 1**

Clinical Work Unit Guidelines

* MNHHS (RBWH) Inhaled Nitric Oxide work unit guideline:



* MNHHS (RBWH) Oxygen Therapy and Humidification in Adults:



**Appendix 2**

Modified BORG Scale

Table

Description automatically generated

**Appendix 3**

**Table 3.**

The AKIN classification/staging system of acute kidney injury (46) a

| Stage | SCr | UO |
| --- | --- | --- |
| 1 | ↑ SCr ≥26.5 μmol/L (≥0.3 mg/dL) or ↑SCr ≥150 a 200% (1.5 a 2×) | <0.5 mL/kg/h (>6 h) |
| 2 | ↑ SCr >200 a 300% (>2 a 3×) | <0.5 mL/kg/h (>12 h) |
| 3b | ↑ SCr >300% (>3×) or if baseline SCr ≥353.6 μmol/L (≥4 mg/dL) ↑SCr ≥44.2 μmol/L (≥0.5 mg/dL) | <0.3 mL/kg/h (24 h) oranuria (12 h) |

aSCr, serum creatinine; UO, urine output.

bStage 3 also includes patients requiring RRT independent of the stage (defined by SCr and/or UO) they are in at the moment they initiate RRT.