

## Research Article

# Rationale and Design of a Randomised Controlled Trial of High-Flow Nasal Oxygen (Optiflow™) and Standard Oxygen Therapy in High-Risk Patients after Cardiac Surgery

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Submitted: 16 September 2015

Accepted: 10 October 2015

Published: 12 October 2015

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## Keywords

- High-flow nasal oxygen
- Pulmonary complications
- Acute respiratory failure
- Cardiac surgery
- Non-invasive ventilation

## Abstract

Patients after cardiac surgery are at risk of respiratory complications that may lead to prolonged hospital stay and worse outcomes. The incidence of respiratory complications is increased in patients with intrinsic respiratory disease. Continuous positive airway pressure administered prophylactically postoperatively can improve functional performance and decrease respiratory complications. However, these are poorly tolerated and their use may be limited by increased staffing and monitoring requirements. Nasal high-flow oxygen is well tolerated and can be administered on a standard postoperative ward. It also provides a low level of continuous positive airway pressure and reduces the work of breathing. In a recent randomized controlled trial we showed that high-flow nasal oxygen, administered for 24 hours after thoracic lung resection surgery, reduced hospital stay and improved functional patient-reported recovery. Routine use of high-flow nasal oxygen after extubation in patients undergoing a normal postoperative trajectory after low risk cardiac surgery is not recommended. The therapeutic effectiveness of high-flow nasal oxygen in high-risk cardiac surgical patients has not been studied before. Our hypothesis is that prophylactic use of nasal high-flow oxygen therapy for at least 24 hours in cardiac surgical patients at high-risk of developing post-operative pulmonary complications, is associated with shorter hospital length of stay (days).

## INTRODUCTION

## Study Aims

## Primary Aim:

- To determine if prophylactic nasal high flow oxygen (NHFO) therapy in cardiac surgical patients at high-risk of developing post-operative pulmonary complications, is associated with shorter hospital length of stay (days).

## Secondary Aims:

- To determine if prophylactic nasal high flow oxygen (NHFO) therapy after high-risk cardiac surgery improves patients' early postoperative recovery, as determined by

performance on a 6 minute walking test (6MWT), compared with patients who receive standard (soft face mask or nasal prongs) oxygen therapy.

- To evaluate if high-risk cardiac surgical patients treated prophylactically with NHFO have better early postoperative lung function, tested by spirometry, than patients treated with standard oxygen.
- To evaluate the tolerability and practicality of prophylactic NHFO in patients after high-risk cardiac surgery compared with standard oxygen.
- To determine if prophylactic NHFO therapy in high-risk

cardiac surgical patients, is associated with reduced intensive care unit (ICU) readmission rate.

- To determine if prophylactic NHFO therapy in high-risk cardiac surgical patients, is associated with shorter ICU length of stay (days).
- To determine if prophylactic NHFO in high-risk cardiac surgical patients, is associated with reduced requirement for escalation of respiratory support (invasive or non-invasive respiratory support).

## BACKGROUND

Patients undergoing cardiac surgery are at significant risk of postoperative pulmonary complications, and these complications may increase morbidity and mortality and lead to prolonged intensive care unit (ICU) and hospital length of stay [1]. The reported incidence of pulmonary complications following cardiac surgery ranges from 8% to 79% [2]. Postoperative pulmonary complications manifest early as arterial hypoxaemia, during the later course as pneumonia, and in rare cases also as acute respiratory distress syndrome [3].

The incidence of respiratory complications is increased in patients with intrinsic respiratory disease and lower airway obstruction (asthma or chronic obstructive pulmonary disease (COPD)), or current heavy smokers [4]. These patients often stay longer on the ICU after surgery because of lower respiratory tract infections, impaired ventilation and prolonged requirement for ventilatory support. They are also more likely to require re-admission to ICU for continuous positive airway pressure (CPAP), non-invasive or invasive mechanical ventilation. Therefore, hospital stay is prolonged compared with low-risk patients after cardiac surgery [5-7].

A contributing mechanism of postoperative respiratory complications is atelectasis, which has been shown to affect up to 90% of patients undergoing cardiac surgery [1, 8]. Postoperative interventions effective in the reduction of pulmonary complications include chest physiotherapy, incentive spirometry, and non invasive continuous positive airway pressure (CPAP) ventilation [1].

Atelectasis has however been shown to be resistant to simple techniques such as patient positioning and incentive spirometry [9]. Lung recruitment manoeuvres and positive airway pressure may reduce atelectasis formation, but this effect is lost after extubation [10].

Prophylactic nasal CPAP has been shown to reduce pulmonary complications after cardiac surgery [11]. CPAP is however costly, and requires more intensive involvement by hospital staff, and in many hospitals its use requires admission of patients to at least a high dependency or even intensive care unit, thus further increasing costs. Physiological and therapeutic effects of CPAP comprise improvement in arterial oxygenation, shift of the pressure volume curve of the lung to the right, reduction in the work of breathing required, and atelectasis re-expansion [12, 13]. Aside from the expense and extra healthcare provision costs, common potential side effects from CPAP include mask discomfort, skin abrasions, patient discomfort, inability

to communicate effectively, inability to eat or drink whilst the device is in use, inability to mobilise, and irritation from device noise [12, 14].

Nasal high-flow oxygen therapy (NHFO) delivers low level, flow-dependent positive airway pressure, and may be better tolerated than CPAP or non-invasive ventilation and enhance washout of nasopharyngeal dead space, thus improving oxygenation [15-18]. NHFO has been shown to be both safe and non-inferior to conventional CPAP in providing prophylactic support to very preterm neonates after extubation [19]. The incidence of nasal trauma was also significantly lower in the nasal cannulae group than in the CPAP group in this study. We have demonstrated that use of NHFO immediately after thoracic lung resection surgery, in the recovery and for 24 hours after surgery, reduces hospital length of stay and improves functional patient-reported recovery.

NHFO has the potential to be more effective than simple standard oxygen due to a combination of five potential mechanisms [20]:

- washout of nasopharyngeal deadspace- the most common reasons for needing to switch to invasive ventilation are hypercapnia, and apnoea secondary to hypercapnia. Therefore, if deadspace in the nasopharyngeal cavity is reduced, alveolar ventilation will be a greater fraction of minute ventilation
- Reduced work of breathing- the nasopharyngeal surface area, distensibility of the nasopharynx and gas volume contributes resistance to gas flow. NHFO therapy provides nasopharyngeal gas flows that are equal to, or greater than, a patient's peak expiratory flow, thereby decreasing resistance, which in turn translates into a reduction in resistive work of breathing.
- Improved mechanics- even short periods inspiring gas at ambient temperature and humidity can significantly decrease pulmonary compliance and conductance during mechanical ventilation in infants. Improved respiratory compliance has been documented in infants receiving NHFO therapy for oxygen support. These results indicate that, by reducing distending pressure and therefore also functional residual volume, adequate conditioning of inspired gases during NHFO therapy affects physiological responses in the lung.
- Reduced metabolic cost of gas conditioning- there is an energy cost associated with conditioning of the inspired gases by the upper airway. This cost is higher when gas is cooler and dry. Furthermore the increase in minute ventilation that often accompanies lung pathologies means that the volume of gas requiring conditioning is greater. Use of NHFO therapy system that warms and humidifies inspired gases should reduce the energy required for gas conditioning.
- Provision of distending pressure- ventilatory mechanics can be improved by providing distending pressure to the lungs which then improves lung compliance and gas exchange. There is potential CPAP to be generated during NHFO therapy. NHFO therapy increased airway pressure by 3.0cm H<sub>2</sub>O over that achieved with low flow oxygen therapy, and this increase was correlated with the increase in end expiratory lung impedance

[21]. This airway pressure development is dependent on the leak rate which in turn is highly dependent on the relationship between the size of nasal prongs and the nose, and requires the mouth to be closed.

A previous study has shown that HFNO did not improve outcomes as assessed by oxygen saturations in low-risk patients after cardiac surgery but did reduce the requirement for escalation of respiratory support [22]. In a recent randomized controlled trial, Corley and colleagues compared prophylactic extubation onto HFNO for 8 hours, with standard care post-cardiac surgery in obese patients (body mass index  $\geq 30$  kg/m<sup>2</sup>). Primary outcome was atelectasis on post-operative chest radiograph. Prophylactic extubation onto HFNO did not lead to improvements in respiratory function or statistically significant difference in the ICU length of stay [23]. Among the limitations of the study were the limited HFNO exposure time (8 hours) and use of a surrogate outcome (atelectasis score) as a primary outcome rather than a patient-oriented outcome.

No study has assessed the effect of prophylactic use of NHFO on hospital length of stay in cardiac surgical patients with significant risk factors for perioperative pulmonary complications. We therefore plan to study high-risk patients with pre-existing lung disease (COPD, asthma, recent lower respiratory tract infection), current heavy smokers or morbidly obese patients, who we expect to stay longer in ICU and hospital due to increased respiratory complications. The hypothesis that this study sets out to test is that routine administration of NHFO leads to reduced length of hospital stay after high risk cardiac surgery compared with usual care oxygen therapy.

## METHODS

Patients are eligible for inclusion if:

- they are aged over 18 years
- are undergoing elective cardiac surgery (coronary artery bypass grafting, valve surgery or both)
- They have one or more patient-related risk factor for post-operative pulmonary complications (COPD, asthma, lower respiratory tract infection in last 4 weeks, body mass index  $\geq 35$  kg/m<sup>2</sup> current (last 6 weeks) heavy smokers (> 10 packyears)).
- They are capable of performing a 6MWT - The 6MWT is a clinical exercise test, and is popular in clinical practice because it aids clinical decision making, and because of the belief that it provides a better estimate of functional capacity than resting cardiorespiratory measurements [24]. The 6MWT is the most popular clinical exercise test, which is used for postoperative evaluation after lung surgery and has also been validated in cardiac surgery [24, 25].

Exclusion criteria are:

- Contraindication to high flow nasal oxygen such as nasal septal defect.
- Not met extubation criteria by 10am the day after surgery (Day 1).
- Need for CPAP pre-operatively.

Written informed consent will be obtained from all study participants prior to any study related procedures.

## Pre-operative Procedures

- 6 minute walk test

All study participants will undergo a 6 minute walk test before the operation, and this will be performed according to the guidelines of the American Thoracic Society. The 6MWT will be conducted in a standard manner by a physiotherapist familiar with the guidelines of the American Thoracic Society. Patients will be dressed comfortably for the test and have taken their bronchodilator therapy beforehand. Patients will rest for 15 minutes before the test, and have their blood pressure, heart rate, oxygen saturation, and dyspnoea score recorded. The Borg scale is the dyspnoea score which will be used, and it is scaled from 1 to 10 in accordance with dyspnoea severity. Before the test the patients will be instructed to walk as quickly as possible around the track for 6 minutes, aiming to cover as much ground as possible. Patients will be told that they may slow down or stop during the test if they feel that they need to, and they will be monitored for signs of difficulty or distress, but they will also be encouraged to continue with the test as far as is possible.

At the end of the test, patients will be allowed to rest, and oxygen saturation, heart rate, blood pressure, and dyspnoea score will be immediately recorded. The distance covered will be recorded. Patients will be allowed rest after the test until they are comfortable.

- Spirometry

Additionally, patients will undergo pre-operative spirometry testing. Patients will be asked to take the deepest breath they can, and then exhale into the spirometer as hard as possible, for as long as possible, preferably at least 6 seconds. This will be repeated 3 times, and average values for forced vital capacity (FVC), forced expiratory volume at one second (FEV<sub>1</sub>) calculated.

## Peri-operative Procedures

- Questionnaire

PQRS will be completed on the day of admission, before discharge (approximately one week after surgery), and again one month following their surgery by telephone.

- Anesthesia

The anaesthetic technique and surgical procedure performed will not be affected by patients' participation in this study. Anaesthesia will be induced with midazolam, fentanyl and propofol, neuromuscular blockade with pancuronium, and maintained with continuous infusions of both propofol, and/or inhalational anaesthetic agent at the discretion of the attending anaesthetist. Participating patients will be randomized to either the HFNO or standard oxygen therapy groups whilst they are in the operating room.

- Cardiac recovery/intensive care unit

Once surgery has finished, patients will be transferred to the cardiac recovery unit, part of the ICU at Papworth hospital. Occasionally, due to lack of beds or closure of cardiac recovery

unit over the weekends, patients will be admitted to ICU where same care bundle will be followed.

Once they fulfill standard criteria and they have woken up, patients will be extubated in cardiac recovery unit or in the ICU after their surgery is finished, once they are warm and not bleeding, have established a regular respiratory pattern, have no significant residual muscle block, and do not complain of anything other than mild pain. In cardiac recovery or intensive care unit patients will receive standard post-cardiac surgery monitoring and treatment, in accordance with the established enhanced recovery program already in place at Papworth Hospital. Postoperative pain relief will be provided by regular paracetamol and opioid analgesia for all patients, unless they have a specific contraindication (eg known drug allergy).

After their trachea is extubated patients will receive either HFNO or standard oxygen therapy, i.e. a soft face mask which provides low flow oxygen, according to the randomization. HFNO will be set up and connected to the patients by cardiac recovery or ICU nurses trained and certified to do so by company representatives. The fraction of oxygen delivered will be titrated to that which results in a pulse oxygen saturation of at least 95% (93% for those at risk of hypercapnic respiratory failure such as confirmed COPD patients and morbidly obese patients) according to british thoracic society guidelines for oxygen use in adult patients [26]. Fraction of inspired oxygen will be actively reduced to the minimum level which achieves this goal. The gas flow through the HFNO will be calculated for each patient, based on their body characteristics, and comfort level. The standard starting flow rate will be 30 L/min, and this will be adjusted up or down between a range of 20-50 L/min with the aim of achieving both patient comfort and a respiratory rate of less than 16 breaths per minute.

Patients randomised to receive standard oxygen therapy will be fitted with a soft face mask or nasal prongs, and the oxygen flow titrated to provide pulse oxygen saturation of at least 95% (93% for those at risk of hypercapnic respiratory failure such as confirmed COPD patients and morbidly obese patients). The standard oxygen therapy group will have their oxygen gas flow reduced to the minimum level which provides saturations of at least 95% (93% for those at risk of hypercapnic respiratory failure such as patients with confirmed COPD and morbidly obese patients).

Both groups of patients will have oxygen therapy prescribed for the first 24 hours postoperatively. After this period oxygen therapy will be discontinued, unless clinically indicated (dyspnoea, oxygen saturation <95% or <93% for COPD and morbidly obese patients, respiratory rate >20 breaths per minute). Patients randomized to receive HFNO may have HFNO continued for more than 24 hours if deemed necessary.

Patients who continue to complain of dyspnoea, or show signs of respiratory distress (respiratory rate >20bpm, oxygen saturation <95% or <93% for COPD and morbidly obese patients) will be treated initially by increasing the fraction of delivered oxygen. If this fails to help, then the clinical team may initiate CPAP or non-invasive ventilation, as their standard practice, and if necessary reintubate the patient and support

them with invasive mechanical ventilation. Participation in the study will not preclude any measures which the clinical team caring for the patient feel is necessary. As part of their standard care, all patients will be seen by the physiotherapy team, and be instructed on appropriate respiratory exercises postoperatively.

### Post-operative days 5 and 6

On post-operative day 5 or day 6, patients will have the 6MWT and spirometry testing repeated (on the same day), using the same protocol as before.

PQRS questionnaire will be completed before discharge (approximately one week after surgery), and again one month following their surgery by telephone.

Removal of chest drains will be decided upon by the surgical team, who will also decide when patients will be discharged from the hospital. The surgical team and the physiotherapists will be blinded to group allocation (Figure 1).

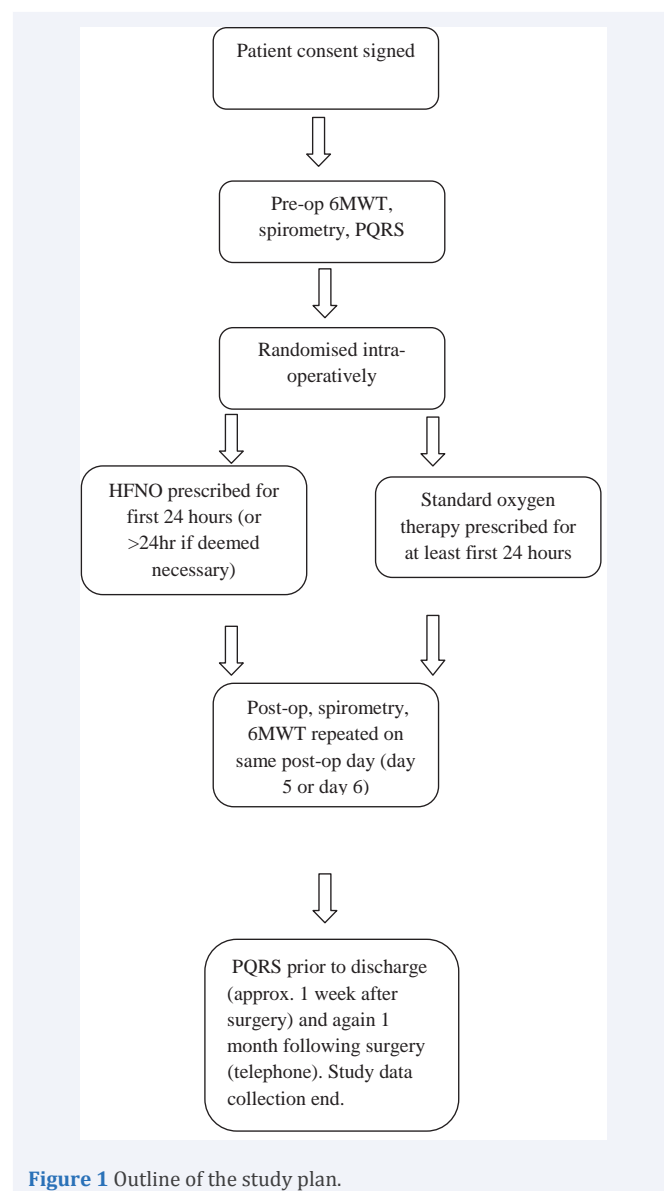


Figure 1 Outline of the study plan.

## Statistical/power analysis

All analyses will be carried out on an intention-to-treat basis. Incidence rates and absolute differences and 95% CIs will be obtained for binary variables in the first instance with subsequent multiple logistic regression adjusted for stratification factors. Sensitivity analysis will also be carried out to determine the effect of missing data from patients that are lost to follow up. Our null hypothesis states that - application of HFNO in high-risk patients after cardiac surgery does not reduce the hospital length of stay (days) compared with standard oxygen therapy.

We expect the mean (SD) length of stay in high-risk patients after cardiac surgery to be 10 (3) days. We expect HFNO to reduce mean length of stay by 2 days (20% relative reduction) to 8 days. We used Wilcoxon rank sum test for 2 independent groups and calculated that 33 patients will be required in each group to achieve 80% power at 5% significance. We plan to randomize a total of 74 patients (37 per arm) in order to allow for a 10% drop out/data loss.

## Data Collection

The following data will be collected:

PQRS (<http://www.pqrsonline.org/>) quality of postoperative recovery, will be completed on the day of admission and before discharge (approximately 1 week after surgery), and again 1 month following their surgery by telephone.

6MWT before surgery and before discharge.

Spirometry before surgery and 48-96 hours post-operatively.

Peripheral capillary oxygen saturation (SpO<sub>2</sub>) before surgery and daily until discharge.

Blood gases in cardiac recovery unit or ICU on arrival (after tracheal extubation) and before discharge to ward.

## FUNDING

This study has been funded by Fisher and Paykel Healthcare Limited.

## ETHICAL CONSIDERATIONS

Patients will be asked to sign a letter in the pre-admission clinic, giving a member of the study team permission to contact them by telephone to discuss the study further and answer any questions. Patients will then be approached by a member of the study team when they are admitted to hospital, either the evening or the morning before surgery, and further questions answered before full written consent is sought. Ethical approval has been granted (NRES Committee East Midlands – Derby, 15 June 2015, REC reference: 15/EM/0251).

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**Cite this article**

Zochios V, Klein A, Jones N, Kriz T, Dunning J, et al. (2015) Rationale and Design of a Randomised Controlled Trial of High-Flow Nasal Oxygen (Optiflow™) and Standard Oxygen Therapy in High-Risk Patients after Cardiac Surgery. *J Cardiol Clin Res* 3(2): 1045.