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Title Page

Oxygen delivery through high-flow nasal cannulae increase end expiratory lung volume and reduce respiratory rate in post cardiac surgical patients

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Running Title

High flow nasal cannulae use post cardiac surgery

Australia and New Zealand Clinical Trial Registry

Clinical Trial No - ACTRN12609000037202

URL - http://www.anzctr.org.au/trial_view.aspx?ID=83413

Summary

Background: High-flow nasal cannulae (HFNC) create positive oropharyngeal airway pressure but it is unclear how their use affects lung volume. Electrical impedance tomography (EIT) allows assessment of changes in lung volume by measuring changes in lung impedance. Primary objectives were to investigate the effects of HFNC on airway pressure (P_{aw}) and end-expiratory lung volume (EELV), and to identify any correlation between the two. Secondary objectives were to investigate the effects of HFNC on respiratory rate (RR), dyspnoea, tidal volume and oxygenation; and the interaction between body mass index (BMI) and EELV.

Methods: Twenty patients prescribed HFNC post-cardiac surgery were investigated. Impedance measures, P_{aw} , PaO_2/FiO_2 ratio, RR and modified Borg scores were recorded first on low flow oxygen (nasal cannula or Hudson face mask) and then on HFNC.

Results: A strong and significant correlation existed between P_{aw} and end-expiratory lung impedance (EELI) ($r=0.7$, $p<0.001$). Compared with low flow oxygen, HFNC significantly increased EELI by 25.6% (95% CI 24.3, 26.9) and P_{aw} by 3.0 cmH₂O (95% CI 2.4, 3.7). RR reduced by 3.4 breaths per minute (95% CI 1.7, 5.2) with HFNC use, tidal impedance variation increased by 10.5% (95% CI 6.1, 18.3) and PaO_2/FiO_2 ratio improved by 30.6 mmHg (95% CI 17.9, 43.3). HFNC improved subjective dyspnoea scoring ($p=0.023$). Increases in EELI were significantly influenced by BMI, with larger increases associated with higher BMIs ($p<0.001$).

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Conclusions: This study suggests that HFNC improve dyspnoea and oxygenation by increasing both EELV and tidal volume, and are most beneficial in patients with higher BMIs.

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Key words: Lung - volume, Oxygen - therapy, Surgery – cardiovascular.

Introduction

Pulmonary complications post cardiac surgery are common ¹ and are associated with adverse outcomes, including prolonged mechanical ventilation times, increased use of sedation, increased risk of ventilator-associated pneumonia, and prolonged Intensive Care Unit (ICU) and hospital lengths of stay ²⁻³. Alveolar collapse and atelectasis is observed in up to 90% of post surgical cases ⁴ and subsequently results in a reduction in functional residual capacity (FRC) of approximately 20% ¹. Physiotherapy and early mobilisation may provide some benefit, but respiratory dysfunction is still commonplace ⁵. Non-invasive ventilation can be useful in avoiding reintubation in such patients, but this treatment prevents early mobilisation; is associated with gastric distension which may further reduce FRC; restricts effective communication and oral nutrition; and is poorly tolerated in some patients ⁶.

High-flow nasal cannulae (HFNC) deliver high flow humidified air and oxygen via wide bore nasal cannulae at a prescribed fraction of inspired oxygen (FIO₂). Whereas conventional nasal prongs are generally limited to flows of 5 litre min⁻¹ due to the potential drying effects of cold oxygen on the nasal mucosa ⁷, oxygen at up to 50 litre min⁻¹ may be delivered when the warmed gas is optimally humidified, making it less irritant to the nasal mucosal. The therapy is well established in neonatal and paediatric populations ⁸⁻⁹ and HFNC use has recently been described in adult populations ¹⁰⁻¹¹.

A number of studies have described the generation of positive airway pressure at the level of the pharynx associated with HFNC ¹²⁻¹⁴. However, there is no data regarding the translation of this pharyngeal positive pressure effect to the lungs, nor any data describing associated changes in lung volumes. This is essential in understanding if HFNC provide any clinically relevant benefit.

Electrical impedance tomography (EIT) is a non-invasive radiation-free bedside imaging technique used to provide real-time images and data of regional lung ventilation and lung volumes (Figure 1) ¹⁵. Its use has been validated in a number of clinical applications including optimisation of mechanical ventilatory strategies such as lung recruitment manoeuvres ¹⁶; detection of pulmonary complications including lung collapse, pleural effusion and pneumothorax ¹⁷⁻¹⁸; and ensuring correct placement of the endotracheal tube ¹⁹. EIT allows the effects of HFNC on lung volumes to be accurately assessed.

The primary aims of this prospective interventional study were to compare the differences in airway pressure (P_{aw}) and end-expiratory lung volume (EELV) between HFNC and low flow oxygen, and to determine any relationship between changes in P_{aw} and EELV. Secondary aims were to investigate the changes in respiratory rate (RR), subjective rating of dyspnoea (modified Borg score), tidal volume (V_t), and oxygenation (PaO_2/FiO_2 ratio) between the two therapies. Due to the association between increased body mass index and decreased in FRC in the post-operative period ²⁰, we assessed the interaction between BMI and changes in EELV in patients on HFNC.

Methods

Following approval from the Institutional Human Research and Ethics Committee (EC27105), this study was conducted at a tertiary referral hospital in Australia specialising in cardiothoracic surgery and medicine. The study was registered with the Australian Clinical Trials Registry (Clinical Trial No: ACTRN12609000037202).

Participants

Written informed consent was obtained from all participants. Patients were included in the study if they were deemed by the treating intensive care specialist to be displaying signs of respiratory dysfunction (including one or more of decreasing PaO_2 [PaO_2/FiO_2 ratio of < 300], subjective dyspnoea, increased use of accessory muscles, increase in respiratory rate) and requiring HFNC; post-cardiac surgery (on cardio-pulmonary bypass); and ≥ 18 years of age. Patients were excluded if they had ongoing air leak post-surgery, a requirement for electrical cardiac pacing or an open sternum.

Electrical Impedance Tomography

Lung volume changes were assessed using EIT. Previous studies have demonstrated that changes in end-expiratory lung impedance (EELI) as measured by EIT have a strong linear correlation with changes in EELV ^{21 22}. Similarly, V_t changes are correlated with tidal impedance variation (VART) ²². Therefore the effect of HFNC at a pulmonary, rather than an oropharyngeal airway level, can be accurately assessed.

EIT measurements were performed with the EIT Evaluation Kit 2 (Dräger Medical, Lübeck, Germany) which had been calibrated and self-tested according to manufacturer's instructions. EIT files were automatically saved to the device's hard drive, analysed by the Dräger review software V5.1 and then downloaded as a Microsoft™ Excel spreadsheet.

Study protocol

Patients were assessed in an upright position either in bed (at a head of bed elevation of at least 45 degrees as measured by an angle measurement device) or sitting in a straight backed chair. Pain levels were assessed, and analgesia administered if necessary, to ensure patients could breathe without discomfort and restriction. After instillation of Co-phenylcaine Forte Nasal spray into the nares, an eight French feeding tube (Unomedical, Sydney, Australia) was inserted nasally to the level of the oropharynx. Correct placement was confirmed both by visual inspection and capnography (Marquette monitor, GE Medical Systems Information Technologies Inc., Wisconsin, USA). The tube was then connected to a precision pressure transducer (PPT-001, DWWW2V, Honeywell international Ltd, Minneapolis, USA) to measure P_{aw} and the data downloaded directly to a Microsoft™ Excel spreadsheet. Figure 2 shows a representative example of the airway pressure tracing obtained.

An appropriately-sized electrode belt was placed around the circumference of the patient's chest, **at the level of the anterior intercostal space 5–6**, and an optimal EIT signal was confirmed prior to data collection. For female patients, the placement of the belt was standardised to underneath the breast tissue. Data were collected first on low flow oxygen, then on HFNC. **The order of data collection was unable to be randomised as the participants were requiring HFNC as part of their treatment.** Prior to the measurement of the low flow oxygen data, patients were asked to rate their dyspnoea level using the Modified Borg Dyspnoea Scale ²³ and asked to keep their mouth closed if possible during the measurement period. The patient's mouth status (open or closed) was tracked every 30 seconds during the measurement period. Simultaneous 2 minute P_{aw} , EELI and VART readings were then recorded while the patient was receiving oxygen therapy via a low flow system (either nasal cannula or Hudson face mask) at the flow rate the patient was receiving prior to HFNC prescription. FiO_2 on low

flow was estimated using a previously described standardised algorithm²⁴. An arterial blood gas (ABG) was taken at this time in all patients if an intra-arterial line (IAL) was *in situ*.

HFNC (Optiflow™ system, MR850 heated humidified, RT202 delivery tubing & RT050/051 nasal cannulae, Fisher and Paykel Healthcare Ltd, Auckland, New Zealand) were applied with the humidifier temperature set to 37°C to optimise humidification. The FiO₂ was titrated to patient need to maintain SpO₂ levels ≥ 95% and flow was commenced at 35 litre min⁻¹. This flow rate was titrated upwards to a maximum of 50 litre min⁻¹ as determined by patient tolerance, as is the clinical practice in the unit. A 15 minute washout period was used between therapies to counter any cumulative treatment effect. The patient was again asked to score their dyspnoea whilst reminded to keep their mouth closed if possible. After optimal signals were confirmed on both the EIT and pressure transducer, simultaneous 2 minute EIT and P_{aw} measurements were repeated in addition to an ABG.

Supplementary data included patient demographics, including height and weight to assess BMI. Data analysed from the EIT files were EELI, VART and RR. Mean P_{aw} was measured in cm H₂O from the pressure transducer files.

Initially, the investigators chose to exclude patients requiring cardiac pacing as there was no safety data regarding the interaction between EIT and cardiac pacing. After consultation with colleagues who routinely use EIT to study post cardiac surgical neonates with temporary epicardial pacing, it was found that in a 12 month period, no adverse events occurred. Therefore, late in the study, this exclusion criterion was removed. Only one patient was recruited using the amended exclusion criteria.

Statistical Analysis

To investigate the changes in lung volumes (EELI and VART) for the EIT data, a mixed effects regression model was used. A mixed model extends a standard regression model by allowing repeated results from the same individual which we modelled using a random intercept. The dependent variable was EIT and the independent variable was HFNC (yes/no). Spearman's correlation coefficient was used to determine any correlation between EELI and P_{aw} change. A second

independent variable of mouth closed (yes/no) was added to test its effect on EELI. An interaction term was included to examine if the effectiveness of the HFNC depended on BMI. To investigate changes V_t , RR, modified Borg score and PaO_2/FiO_2 ratio, a paired t-test was used. Any p values less than 0.05/6=0.008 were considered significant after making a Bonferroni adjustment for multiple comparisons. Data was assessed using an intention to treat analysis. All analyses were performed using the R statistical software (www.r-project.org).

Results

Twenty seven patients were eligible for inclusion into the study and were approached for informed consent. Two patients refused insertion of the nasopharyngeal catheter, two patients required epicardial pacing to be commenced just prior to the study period, one male patient could not be fitted with a correctly-sized EIT belt due to their chest circumference and the EIT was unable to pass the manufacturer's self test in a further two patients. Therefore, twenty patients who were prescribed HFNC by the intensive care specialist post-cardiac surgery were recruited, 15 of whom were male. The mean (and range) age of participants was 65.3 (51–77) years; height was 171.1 (160–183); weight was 93.3 (60–123); and BMI was 32 (22–45) $kg\ m^{-2}$. Selected clinical parameters of participants are shown in Table 1. Two patients were unable to provide complete data due to the absence of an IAL in one patient and the inability to tolerate the nasopharyngeal catheter in the other. Using an intention to treat analysis, data from these two patients was included.

When compared with a low flow oxygen device, HFNC increased mean P_{aw} by 3.0 cm H_2O (95% CI 2.4, 3.7; paired t-test $p<0.001$) and EELI by 1517 impedance units (95% CI 1425, 1608; mixed model $p<0.001$). This translates to an increase in EELI of 25.6% (95% CI 24.3, 26.9; mixed model $p<0.001$) on HFNC, suggesting a similar increase in EELV. No statistically significant difference was found in EELI when the patients' mouth was closed or open (mixed model $p=0.99$). No significant correlation was found between P_{aw} and mouth open or closed ($p=0.99$). A strong and significant correlation was found between P_{aw} and EELI ($r=0.7$, $p<0.001$). RR was lowered by 3.4 breaths per minute (95% CI 1.7, 5.2; paired t-test $p<0.001$) and the Borg dyspnoea score by 0.8 points (95% CI 0.1, 1.4; paired t-test $p=0.023$). HFNC significantly increased VARt by 159 impedance units (95% CI 117, 202; mixed model $p<0.001$), translating to a 10.5% increase (95%CI 6.1, 18.3; mixed model

p<0.001). This finding suggests a similar increase in Vt. PaO₂/FiO₂ ratio was improved by 30.6 (95% CI 17.9, 43.3; paired t-test p<0.001) even though 95% of patients were receiving an equal or lower FiO₂ while on HFNC than when on low flow oxygen. Table 2 summarises the primary and secondary outcome measures.

Higher gas flow rates were found to result in larger increases in EELI. For every one L/min increase in flow rate, the difference in EELI between low flow oxygen device and HFNC increases by a further 0.7% (95% CI 0.1, 1.3; mixed model p-value=0.023).

BMI significantly influenced the positive effect of HFNC on EELI (mixed model p<0.001). A BMI of 25 resulted in a mean increase in EELI of 13.3% (high versus low flow) whereas with a BMI of 40 the increase was 24.4%. Figure 3 shows the mean increases in EELI (expressed as a percentage increase) by BMI.

Discussion

This data indicates for the first time that HFNC are associated with an increase in EELI in patients post cardiac surgery, suggesting an increase in EELV and hence FRC. The increase in EELV was found to be significantly greater in those subjects with a higher BMI. The generation of positive oropharyngeal P_{aw} by HFNC reported in earlier studies¹²⁻¹⁴ was confirmed. In addition, significant decreases were recorded in RR and the patients' perceived dyspnoea, and significant increases were recorded in Vt and oxygenation. The benefits of positive airway pressure and the resultant increase in EELV include a reduction in work of breathing, prevention of small airway closure, and improved oxygenation due to reduced pulmonary shunting²⁵. This increase in EELV, coupled with the reduction in RR and the patients' perceived dyspnoea, could mean that HFNC use in post cardiac surgical patients may be of substantial clinical benefit in the patient with borderline respiratory function post extubation.

Comment [AGB3]: Maybe remove this word?

HFNC have been shown to generate between 0.2 and 4.8 cm H₂O of positive P_{aw} in neonatal and paediatric populations^{26 27}. In healthy adult volunteers, HFNC generated between 5.1 and 8.7 cm H₂O pharyngeal P_{aw}^{12 14}. The findings of our study are similar to the only other published work

investigating the effects of HFNC on P_{aw} in adult intensive care patients¹³. We found no significant correlation between P_{aw} and mouth open or closed ($p=0.99$) in this study, which is at odds with previous studies^{12 14}.

EELI was found to increase with the transition from low to high flow oxygen delivery in 90% of the participants in this study. Due to the strong linear relationship between changes in EELI and EELV demonstrated in previous EIT studies^{21 22}, it can therefore be concluded that the use of HFNC increases EELV. This increase in EELV may be explained by the recruitment of alveoli, and prevention of further alveolar collapse, as a result of the low level positive P_{aw} generated by HFNC. Additionally, the increase could be attributed to further expansion of partially recruited alveoli.

With a mean BMI of $32 \text{ m}^{-2} \text{ kg}$ in the study cohort, the increase in EELV was significantly greater in those patients with higher BMI (Figure 3). Obese patients are predisposed to post-operative atelectasis and this atelectasis resolves more slowly than in patients with normal body weight (38). Additionally, this group of patients is prone to reduced FRC with an increased risk of developing further respiratory complications²⁹. Therefore it appears that patients with higher BMIs may derive particular benefit from the low level positive airway pressure and increase in EELV that HFNC produce. This may be explained by the pre-existing derangement in respiratory mechanics displayed in obese patients, specifically the higher closing volumes and subsequent reduction in lung volume due to excessive unopposed intra-abdominal pressure³⁰. Subsequently, the obese patient will have a higher number of recruitable alveoli than a patient with a normal BMI and this may account for the beneficial effects seen in the obese group. More work in this area is required to further explore and describe the interaction observed between EELV and BMI, particularly as more than one third of patients undergoing cardiac surgery at this institution have a BMI ≥ 30 .

A statistically significant reduction in RR was observed on HFNC. While no formal measurements of work of breathing were employed, the mean drop in RR of 3.4 breaths per minute may result in a reduction in work of breathing³¹. An improvement in lung compliance and FRC could be significant factors in the improvement in subjective dyspnoea, and may also be partially responsible for the observed decrease in RR.

A higher PaO₂/FiO₂ ratio was demonstrated in patients using HFNC. This could be attributed in part to the observed increase in EELV and resultant increase in alveolar ventilation. However, the PaO₂/FiO₂ ratio would also be improved by the use of higher inspired oxygen concentration, as is seen in high flow oxygen devices. Interestingly, 95% of patients in this study were receiving an equal or lower FiO₂ while on HFNC than when on low flow oxygen, with 50% receiving a lower FiO₂ while on HFNC.

Gas flow rates, which determine inspired oxygen concentration particularly at lower flows, were not standardised across patients in this study. Instead, a clinically driven protocol was chosen which reflected clinical practice and management of these patients and clinical usage of the device. The assessment of the effects of HFNC at different flow rates may be of interest in future studies to further delineate optimal flows.

Whilst the sample size of this study was small, the investigators were able to describe significant differences in clinical markers between low flow oxygen and HFNC usage in a typical post cardiac surgical cohort. A larger sample size will be necessary to investigate the effects of HFNC on longer term outcomes. Our cohort consisted of more males than females at a ratio of 3:1, which is reflective of global trends in cardiac surgery³².

This study confirms that HFNC are effective in providing modest levels of positive airway pressure and, for the first time, clearly demonstrates that this translates to increases in EELV. These increases in lung volume, and the associated improvements in RR, subjective dyspnoea and oxygenation, necessitate further investigation if the clinical significance of HFNC usage and its impact on patients' longer term outcomes is to be established. These questions will be addressed in a subsequent randomised controlled trial which will examine the effects of HFNC on postoperative atelectasis in patients with a BMI ≥ 30 (Australian Clinical Trials Registry, Clinical Trial No: ACTRN12610000942055).

Comment [AGB4]: Probably should delete this as it's no longer statistically significant.

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Conclusions

HFNC generate statistically and clinically relevant increases in oropharyngeal airway pressure, and increases in end expiratory lung volume and tidal volume as demonstrated by changes in lung impedance, particularly in patients with higher BMIs. These changes are associated with reduced respiratory rate, less dyspnoea and improved oxygenation. Thus, HFNC may be a useful treatment option for patients experiencing respiratory dysfunction post-cardiac surgery, particularly those patients who cannot tolerate non-invasive ventilation and those with a higher BMI.

Comment [AGB5]: Maybe here too?
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