Nasal high flow oxygen therapy in patients with COPD reduces respiratory rate and tissue carbon dioxide while increasing tidal and end-expiratory lung volumes: a randomised crossover trial

Abstract

Patients with COPD using long-term oxygen therapy (LTOT) over 15 h per day have improved outcomes. As inhalation of dry cold gas is detrimental to mucociliary clearance, humidified nasal high flow (NHF) oxygen may reduce frequency of exacerbations, while improving lung function and quality of life in this cohort. In this randomised crossover study, we assessed short-term physiological responses to NHF therapy in 30 males chronically treated with LTOT. LTOT (2–4 L/min) through nasal cannula was compared with NHF at 30 L/min from an AIRVO through an Optiflow nasal interface with entrained supplemental oxygen. Comparing NHF with LTOT: transcutaneous carbon dioxide ($TcCO_2$) (43.3 vs 46.7 mm Hg, p<0.001), transcutaneous oxygen (TcO_2) (97.1 vs 101.2 mm Hg, p=0.01), I:E ratio (0.75 vs 0.86, p=0.02) and respiratory rate (RR) (15.4 vs 19.2 bpm, p<0.001) were lower; and tidal volume (Vt) (0.50 vs 0.40, p=0.003) and end-expiratory lung volume (EELV) (174% vs 113%, p<0.001) were higher. EELV is expressed as relative change from baseline (%Δ). Subjective dyspnoea and interface comfort favoured LTOT. NHF decreased $TcCO_2$, I:E ratio and RR, with a concurrent increase in EELV and Vt compared with LTOT. This demonstrates a potential mechanistic rationale behind the improved outcomes observed in long-term treatment with NHF in oxygen-dependent patients.

Trial registration number

ACTRN12613000028707.

INTRODUCTION

The burden of COPD is increasing globally, and its physiological, economical and mortality costs are enormous, with >65 million people affected by moderate-to-severe COPD.

Long-term oxygen therapy (LTOT) improves health outcomes and reduces mortality.[1] However, further optimisation of respiratory support may diminish symptomatic breathlessness, ameliorate COPD-associated cachexia, reduce hypercarbia, improve right ventricular function and provide psychological benefits.

Nasal high flow (NHF) oxygen, an emerging therapy developed for acute care areas for respiratory support, may have the potential for domiciliary use. NHF delivers heated and humidified air/oxygen with flows up to 60 L/min. NHF produces pharyngeal pressures of 2–8 cm H_2O[2], which transmit to the alveoli, contributing to lung recruitment and upper airway splinting.[3] Nasopharyngeal dead space washout has been proposed to reduce CO_2 rebreathing, thus providing a fresh reservoir of oxygen from which to breathe.[4] The observed clinical effects of high gas flows in patients with COPD include improvements in exercise tolerance, oxygenation and reduced dyspnoea.[5 6] NHF has been demonstrated to increase tidal volumes in a number of cohorts,[7] while reducing work of breathing by lowering inspiratory resistance and generating positive expiratory pressure.[5] NHF has been shown to be non-inferior to non-invasive ventilation in the prevention of treatment failure in patients with acute respiratory failure postcardiac surgery[8] and reduce mortality (both in the intensive care unit and at 90 days) in patients with acute respiratory failure.[9]

A randomised crossover study was commenced to assess the short-term physiological effects of NHF oxygen in patients with chronic stable COPD.

METHODS

The online repository for this research letter contains details on study inclusion and exclusion criteria, study procedures and statistical analysis.

Study protocol

A randomised crossover design was used to study subjects on their own LTOT (low flow oxygen, 2–4 L/min through nasal cannula) and NHF using air supplemented with the equivalent fraction of inspired oxygen (FiO_2) to a total flow of 30 L/min from an AIRVO through an Optiflow nasal interface (Fisher & Paykel Healthcare, Auckland, New Zealand). Data collected included transcutaneous oxygen (TcO_2) and transcutaneous carbon dioxide ($TcCO_2$); pulse oximetry; tidal volume (Vt) and minute volume (MV), respiratory rate (RR) and I:E ratio via respiratory inductance plethysmography; end-expiratory lung impedance (EELI) via electrical impedance tomography; heart rate (HR) via standard ECG monitoring; subjective dyspnoea and comfort scores (0=no dyspnoea/discomfort to 10=maximum dyspnoea/discomfort); and videography of the patients' torso to identify inconsistencies during data analysis such as coughing and sneezing.

Patients remained on LTOT during the 20 min set-up period while baseline recordings were taken. Patients received the first randomised therapy (LTOT or NHF) for 20 min, followed by a 20 min washout period of LTOT, after which they crossed over to the second therapy (LTOT or NHF) for 20 min.

RESULTS

Details regarding the numbers of patients screened and subsequently excluded are contained in the online repository. Thirty patients were included in the study (see tables in online repository for patient characteristics). Results are contained in table 1.

When comparing NHF with LTOT, TcO_2, $TcCO_2$, RR and I:E ratio were significantly lower when using NHF. On NHF, Vt and EELI were significantly higher than on LTOT. Figure 1 illustrates the decrease in $TcCO_2$ and RR. No significant difference between groups was found in SpO_2, MV or HR.

Table 1 Two-way (paired) comparisons between the long-term oxygen therapy (LTOT) and nasal high flow (NHF) groups

Variable	LTOT	NHF	p Value
Oxygen saturation (%)*	95.8 (94.6 to 96.9)	95.7 (93.1 to 97.1)	0.06
Transcutaneous O_2 (mm Hg)	101.2 (22.5)	97.1 (24.2)	0.01
Transcutaneous CO_2 (mm Hg)	46.7 (9.4)	43.3 (9.5)	<0.001
Respiratory rate (breaths/min)	19.2 (6.3)	15.4 (4.8)	0.001
Inspiratory:expiratory ratio	0.86 (0.20)	0.75 (0.25)	0.02
Tidal volume (L)*	0.40 (0.34, 0.46)	0.50 (0.41, 0.54)	0.003
Minute volume (L/min)*	6.20 (4.84, 8.18)	6.18 (4.75, 7.69)	0.88
Heart rate (beats/min)	70.1 (59.1, 79.3)	69.8 (61.3, 79.8)	0.21
End-expiratory lung impedance (%Δ)*	113 (98, 128)	174 (161, 187)	<0.001

A p value <0.05 was considered significant. Normally distributed data are presented as mean (SD) while non-normal data are presented as median (IQR). End-expiratory lung impedance data are presented as percentage change from baseline (%Δ). All variables returned to baseline values during the washout periods and subsequently during the recovery period.
*A paired t test was used for the normally distributed data while a Wilcoxon signed rank test was used for the non-normal data.

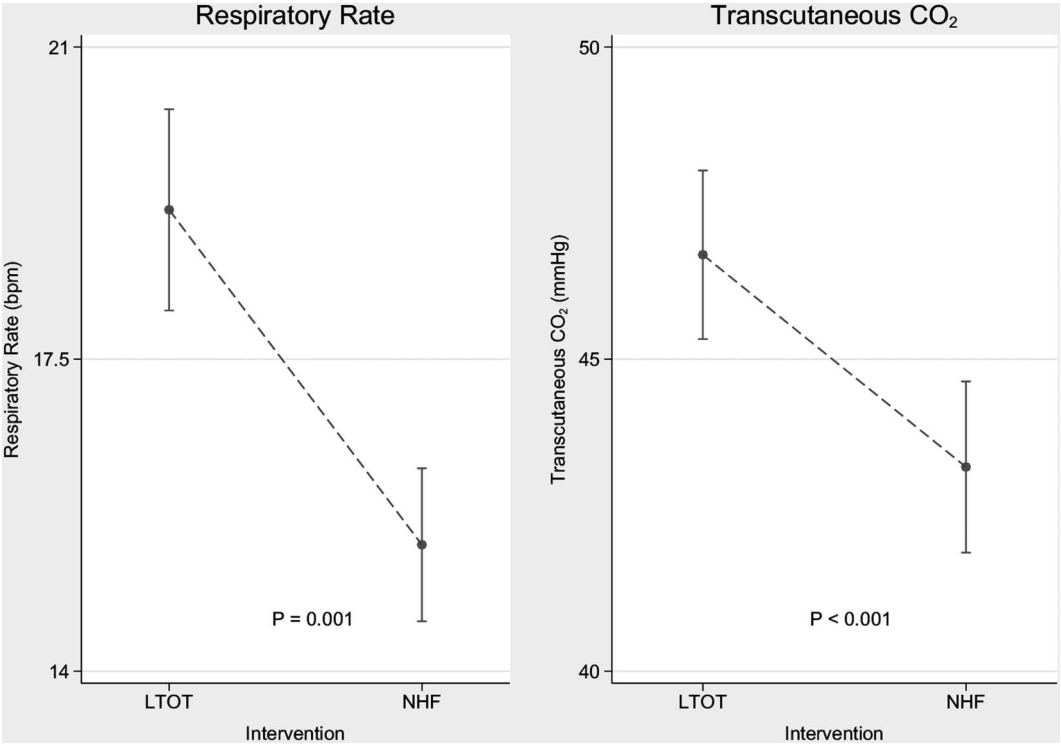

Figure 1 Observed decreases in respiratory rate and transcutaneous carbon dioxide level between the long-term oxygen therapy (LTOT) group and the nasal high flow (NHF) group. Data are presented as mean and vertical 95% CI bars.

Median subjective dyspnoea scores were significantly higher during NHF compared with LTOT (LTOT: median 0.5 [range 0–3.5]; NHF: 2.00–[5], p<0.001). Similarly with interface comfort, LTOT was more comfortable than NHF (LTOT: 9;[7–10] NHF: 8 [2.5–10], p<0.02).

DISCUSSION

In this study, NHF in patients with stable oxygen-dependent COPD led to a significant reduction in $TcCO_2$ levels. NHF use also resulted in increases in Vt, end-expiratory lung volume (EELV) and I:E ratio with corresponding decreases in RR, without changes to MV. These short-term findings, if confirmed over a longer duration in subsequent studies, could imply a role for NHF in the domiciliary management of patients with COPD dependent on LTOT.

Hypercarbia, respiratory acidosis and failure are all associated with increased risk of acute deterioration and poor outcomes for patients with COPD. Home NHF use with titrated or low-level supplemental oxygen may assist in avoiding these problems. How long patients should be maintained on this strategy for the benefits of NHF to be sustained is unclear; however, in a recent study of long-term domiciliary use of NHF, the actual exposure time to NHF was 1.6 h/day.[10] The supplemental benefit of reduced $TcCO_2$, reduced RR and increased EELV and Vt, combined with adequate oxygen to prevent hypoxia and pulmonary hypertension, is unknown, indicating the need for a long-term study in the domiciliary setting. This reduction in $TcCO_2$ correlates with the consistent rise in Vt, and we believe this increase may be accompanied by dead space and subsequent CO_2 washout, as seen in preceding COPD studies.[6]

The ability of NHF to reduce RR is consistent with a reduction in work of breathing. The mechanism is most likely the reduced anatomical dead space assisted by the positive expiratory pressure effect of NHF, which allows for improved ventilation and perfusion matching. Additionally, matching the inspiratory flow demands with NHF overcomes nasopharyngeal inspiratory resistance, thereby diminishing resistive work of breathing.[5]

In this NHF-naive cohort, higher dyspnoea and lower comfort scores were observed during NHF, perhaps due to commencing a new treatment in a cohort known to suffer from anxiety.

This study has some limitations that are contained in the online repository.

CONCLUSIONS

This study demonstrates that in the stable home-oxygen-dependent male COPD patient, short-term NHF use results in reductions in $TcCO_2$ and RR, with increased Vt and EELV, when compared to LTOT. However, this cohort rated their LTOT interface more comfortable and providing more dyspnoea relief than NHF. This short-term study demonstrates adequate physiological rationale to proceed with trialling these devices in the long-term management of COPD, with the hope of reducing further physiological decay, improving quality of life and reducing hospital admissions.

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REFERENCES

1 Kent BD, Mitchell PD, McNicholas WT. Hypoxemia in patients with COPD: cause, effects, and disease progression. *Int J Chron Obstruct Pulmon Dis* 2011;6:199–208.
2 Parke RL, McGuinness SP. Pressures delivered by nasal high flow oxygen during all phases of the respiratory cycle. *Respir Care* 2013;58:1621–4.
3 Corley A, Caruana LR, Barnett AG, *et al*. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. *Br J Anaesth* 2011;107:998–1004.
4 Dysart K, Miller TL, Wolfson MR, *et al*. Research in high flow therapy: mechanisms of action. *Respir Med* 2009;103:1400–5.
5 Chatila W, Nugent T, Vance G, *et al*. The effects of high-flow vs low-flow oxygen on exercise in advanced obstructive airways disease. *Chest* 2004;126:1108–15.
6 Okuda M, Kashio M, Tanaka N, *et al*. Nasal high-flow oxygen therapy system for improving sleep-related hypoventilation in chronic obstructive pulmonary disease: a case report. *J Med Case Rep* 2014;8:341.
7 Bräunlich J, Beyer D, Mai D, *et al*. Effects of nasal high flow on ventilation in volunteers, COPD and idiopathic pulmonary fibrosis patients. *Respiration* 2013;85:319–25.
8 Stéphan F, Barrucand B, Petit P, *et al*. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery. A randomized clinical trial. *JAMA* 2015;313:2331–9.
9 Frat JP, Thille AW, Mercat A, *et al*. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372:2185–96.
10 Rea H, McAuley S, Jayaram L, *et al*. The clinical utility of long-term humidification therapy in chronic airways disease. *Respir Med* 2010;104:525–33.

ONLINE REPOSITORY MATERIAL

INTRODUCTION

Cost estimates associated with the disease are over 50 billion dollars in the USA[1] and over a billion pounds in the UK[2]. Most acute exacerbations are secondary to infection[3] but many are associated with the inexorable decline in cardio-respiratory status[4]. Acute exacerbations descend into increased metabolism and work of breathing, resulting in increased carbon dioxide (CO_2) production of up to 23% greater than normal[5]. This increased work of breathing and CO_2 production necessitates medical intervention and frequently ventilatory assistance, most commonly invasive or non-invasive ventilation[6].

The value of high inspired oxygen concentrations in managing acute exacerbations of COPD has been questioned recently[7]. Several studies have demonstrated poorer outcomes due to associated hypercarbia and respiratory acidosis, when compared to titrated oxygen flows maintaining oxygen saturations between 88-90%[8]. In a recent randomised controlled trial[9], the delivery of long-term humidification to COPD patients reduces exacerbations, improves lung function and quality of life and is associated with high compliance.

METHODS

This study was conducted at a tertiary referral hospital. This trial was registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12613000028707). Patients who were treated by a respiratory team at our hospital and who were registered for home oxygen were screened for suitability. All patients were outpatients. Written and informed consent was obtained from all participants prior to study commencement. Patients were eligible if they were male, ≥18 years with COPD receiving LTOT and were able to attend hospital for a 2.5-3 hour data collection period. Exclusion criteria were previous lung resections, hemidiaphragm palsy, active respiratory infection (diagnosed by treating physician), frequent purse-lip breathing or anxiousness using an alternate

respiratory device.

The order of therapy was allocated using sequentially-numbered, sealed envelopes which were not prepared by study staff. All patients were studied in a semi-recumbent position in a chair and monitoring equipment was applied. As a safety precaution participants were placed on LTOT and monitored for a final 20 minutes to ensure they could return to usual activities of daily living.

Delivered FiO_2 was calculated using a nasal cannula FiO_2 and AIRVO FiO_2 conversion table[10]. Oxygenation was measured using transcutaneous oxygen (TcO_2) and carbon dioxide ($TcCO_2$) monitoring (Radiometer TCM4, Brønshøj, Denmark) which involved applying a probe (Sensor E52800) to the inner forearm. $TcCO_2$ measurements, while primarily used in neonates, were chosen to approximate $PaCO_2$ levels. $TcCO_2$ has been shown to correlate acceptably with arterial measurements in adults[11] and can also be used to follow trends[12]. In line with common practice, a correction was automatically applied to the transcutaneous data to better approximate arterial values[13]. Pulse oximetry (504, Criticare Systems, Wisconsin, USA) was applied to the fingertip to measure oxygen saturations (SaO_2).

Tidal volume (Vt), minute volume (MV), respiratory rate (RR) and I:E ratio were monitored with respiratory inductance plethysmography (RespiTrace Plus, Viasys®, San Diego, USA). Two Respitrace bands were placed around the patient's chest and abdomen. The patient was asked to breathe through a low-resistance pneumotacograph for two minutes prior to and following study completion to calibrate the Respitrace system.

Changes in end-expiratory lung impedance (EELI) were measured using Electrical impedance tomography (EIT) (PulmoVista 500, Dräger, Lübeck, Germany). An electrode belt was placed around the chest at nipple level to monitor end-expiratory lung volumes (EELV). Previous studies have demonstrated that changes in EELI as measured by EIT have a strong linear correlation with changes in EELV[14, 15].

Additionally, heart rate (HR) was monitored via standard ECG monitoring and a video camera recorded images of the patients' torso to identify any inconsistencies during data analysis such as coughing and sneezing.

Two minute EIT recordings were taken at 18 minutes during each study period. Patients were asked to rate their dyspnoea and comfort level on the therapy at 15 minutes in each study period on a 0 to 10 scale where 0=no dyspnoea or discomfort and 10=maximal dyspnoea/discomfort. All other measurements (TcO_2, $TcCO_2$, SpO_2, Vt, MV, HR, RR and I:E ratio) were recorded continuously throughout the study.

Patients were withdrawn immediately from the study if their SaO_2 fell >10% below baseline, TcO_2 increased >50% from baseline, became tachypnoeic at >50% from baseline or if they experienced any anxiety during the study.

Statistical Analysis

The statistician was blinded to treatment allocation – LTOT was labelled treatment 1 and NHF was labelled treatment 2. Data were checked for completeness and errors and corrected if necessary. Data were presented as mean (SD) for normally distributed data, median (IQR) for non-normal data or as a simple proportion for binary data. The normality of each variable was checked using a Shapiro-Wilk test. Accounting for the time series nature of the data, statistical modelling was performed to examine the adequacy of the washout periods with reference to both the baseline and the recovery periods. A Wilcoxon signed-rank test was used for analysing non-normal data and a paired t-test was used for normally distributed data. The level of significance was set at $P < 0.05$. STATA (v12.0) was used throughout. The order of intervention was tested as an independent predictor in a univariate time-series regression analysis using the individual variables as the outcome variable in each case. Based on our previous work[16], a reduction in respiratory rate of 4 breaths

per minute in the NHF group was estimated. To find this difference with 80% power using a 5% significance level required 30 patients.

RESULTS

Fifty-two chronic LTOT patients were eligible for the study. Thirteen patients could not attend a study visit, two patients had hemidiaphragmatic palsy and seven patients refused to participate. No patients became unstable or met withdrawal criteria during the study. Table 1 shows patient demographics. Table 2 shows mean baseline data for all variables.

Table 1 Patient Demographics

Variable	***Mean (SD)***	***Range***
Age, years	74.5 (8.8)	56 - 91
Height (m)	1.71 (0.07)	1.59 – 1.89
Weight (kg)	77.4 (23.5)	48.0 – 160.0
BMI, kg/m^2	26.1 (6.4)	18.1 – 47.8
COPD severity (GOLD guidelines)	**n**	**%**
• Stage I	3	10
• Stage II	7	23.3
• Stage III	10	33.3
• Stage IV	9	30
• Unclassifiable	1	3.3

Table 2 Median baseline data. Results are tabulated with their measurement units. It is noted that inspiratory:expiratory ratio, tidal volume and end expiratory lung volume are dimensionless.

Variable	***Median***	***IQR***
Oxygen saturation (%)	94.9	92.5 – 97.6
Transcutaneous O_2 (mmHg)	105.6	94.6 – 118.6
Transcutaneous CO_2 (mmHg)	46.2	38.4 – 52.3
Respiratory rate (breaths/min)	19.2	15.8 – 21.6
Inspiratory:Expiratory ratio	0.83	0.68 – 0.87
Tidal volume (impedance units)	0.44	0.35 – 0.53
Minute volume (impedance units)	6.81	5.35 – 8.62
End-expiratory lung volume	928.7	396.3 – 1461.1
Heart rate (beats/min)	72.1	62.4 – 81.6

The washout period was found to be adequate with return to baseline after each test condition. As the data were not normally distributed, baseline data were compared with washout and recovery data in a pairwise fashion using the Wilcoxon signed-rank test. Similarly, order of intervention was found to be not significant for any of the variables. See Table 3.

Table 3 Effect of washout period and order of intervention for each variable.

Variable	***Baseline vs washout***	***Baseline vs recovery***	***Order of intervention***

	(P-value)	*(P-value)*	*(P-value)*
Oxygen saturation	0.75	0.39	0.96
Transcutaneous O_2	0.11	0.70	0.82
Transcutaneous CO_2	0.62	0.43	0.12
Respiratory rate	0.96	0.25	0.94
Inspiratory:Expiratory ratio	0.87	0.38	0.57
Tidal volume	0.56	0.64	0.95
Minute volume	0.71	0.66	0.29
End-expiratory lung volume	0.88	0.39	0.28
Heart rate	0.27	0.11	0.08

DISCUSSION

Pham et al[17] demonstrated that NHF offloads the diaphragm and reduced work of breathing in bronchiolitic infants. The one study[18] examining work of breathing in adult COPD patients found no difference between low flow oxygen and NHF therapies however the delivered rate of high flow therapy in this study was lower than in the current study (20L/min vs 30 L/min).

Interestingly, a recent study comparing NHF with non-invasive ventilation demonstrated that the reduction in $PaCO_2$ occurred more quickly with NHF, again most likely due to increased tidal volumes and washout of carbon dioxide from the anatomical deadspace[19].

While TcO_2 fell on NHF, SaO_2 remained unchanged. This may indicate that the patients were on the upper region of the oxygen dissociation curve. During LTOT, the supplemental oxygen is diluted by a much smaller fraction than is seen in the NHF treatment where dilution is greater due to its high flow rate. Clinicians may consider whether an increased oxygen flow for entrainment should be administered during NHF to offset this dilution effect and maintain the desired arterial pO_2.

Our cohort of LTOT users stated that NHF was different and "not as comfortable" as their familiar LTOT. However it must be noted that dyspnoea and discomfort scores were low with both therapies and no study patient requested discontinuation of NHF due to dyspnoea or discomfort. Future studies have been planned to examine the effects and acceptance of NHF over a longer period of time. This would also allow the patient to become more accustomed to the NHF therapy, thus negating the effects if any, of 'unfamiliarity' with the system.

Our findings are consistent with Braunlich et al[20] who examined the delivery of NHF at 24 L/min in COPD patients and also observed significant reductions in RR and pCO_2, significant increases in Vt and no change in I:E ratio when compared with low flow oxygen. Chatila et al[18] studied COPD patients during exercise and similarly found reductions in RR and pCO_2 and increased exercise tolerance on NHF at 20 L/min. We observed no difference in oxygenation (using saturation levels) between NHF and LTOT which differs from existing data in COPD patients[18].

This study has several limitations. Firstly, we studied only males thus the results seen cannot be generalised to women suffering COPD. However, as twice as many males than females are affected by COPD, these results are still relevant to the majority of chronic, oxygen-dependent COPD patients[21]. Secondly, it could be seen as a limitation that patients were studied on LTOT during baseline and washout periods within the crossover design. Nonetheless, this study was a pragmatic one and we considered it unethical to deny oxygen-dependent patients of oxygen during these periods. Thirdly, with the growing financial burden of COPD on the healthcare system, economic

analyses are needed to assess the cost effectiveness of treatment modalities. An economic analysis was not performed as part of this study but is planned for the subsequent larger study. Lastly, the randomised crossover design precludes the investigation of longer term outcomes therefore the effects of NHF on longer-term outcomes such as quality of life indices and mortality were not assessed. More work is required in robust randomised controlled trials to determine if long-term domiciliary use of NHF results in improvements in clinically important long-term outcomes for patients.

REFERENCES

1. Pasquale MK, Sun SX, Song F, et al. Impact of exacerbations on health care cost and resource utilization in chronic obstructive pulmonary disease patients with chronic bronchitis from a predominantly Medicare population. Int J Chron Obstruct Pulmon Dis 2012;7:757-64.

2. Sullivan SD, Ramsey SD, Lee TA. The economic burden of COPD. Chest 2000;117:5S-9S.

3. Wedzicha JA, Singh R, Mackay AJ. Acute COPD exacerbations. Clinics in chest medicine 2014;35(1):157-63.

4. Connors AF, Dawson NV, Thomas C, Harrell FE, Desbiens N, Fulkerson WJ, Kussin P, Bellamy P, Goldman L, Knaus WA. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med 1996;154(4):959-67.

5. Vermeeren MA, Schols AM, Wouters EF. Effects of an acute exacerbation on nutritional and metabolic profile of patients with COPD. Eur Respir J 1997;10(10):2264-9.

6. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23(6):932-46.

7. Cameron L, Pilcher J, Weatherall M, Beasley R, Perrin K. The risk of serious adverse outcomes associated with hypoxaemia and hyperoxaemia in acute exacerbations of COPD. Postgrad Med J. 2012;88(1046):684–689.)

8. Austin MA, Wills KE, Blizzard L, et al. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. BMJ 2010;341:c5462.

9. Rea H, McAuley S, Jayaram L, et al. The clinical utility of long-term humidification therapy in chronic airways disease. Respiratory Medicine 2010;104:525-33.

10. Fisher & Paykel Healthcare Ltd. AIRVO: Hospital use operating manual. Auckland: Fisher & Paykel Healthcare Ltd, 2010.

11. Phan CQ, Tremper KK, Lee SE, et al. Noninvasive monitoring of carbon dioxide: a comparison of the partial pressure of transcutaneous and end-tidal carbon dioxide with the partial pressure of arterial carbon dioxide. J Clin Monit 1987;3(3):149-54.

12. Rithalia SV, Ng YY, Tinker J. Measurement of transcutaneous PCO2 in critically ill patients. Resuscitation 1982;10(1):13-8.

13. Severinghaus JW, Stafford M, Bradley AF. tcPCO2 electrode design, calibration and temperature gradient problems. Acta Anaesthesiol Scand Suppl 1978;68:118-22.

14. van Genderingen HR, van Vught AJ, Jansen JR. Estimation of regional lung volume changes by electrical impedance pressures tomography during a pressure-volume maneuver. Intensive Care Med 2003;29(2):233-40.

15. Hinz J, Hahn G, Neumann P, et al. End-expiratory lung impedance change enables bedside monitoring of end-expiratory lung volume change. Intensive Care Med 2003;29(1):37-43.

16. Corley A, Caruana LR, Barnett AG, et al. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. Br J Anaesth 2011;107(6):998-1004.35.

17. Pham TM, O'Malley L, Mayfield S, et al. The effect of high flow nasal cannula therapy on the work of breathing in infants with bronchiolitis. Pediatr Pulmonol 2014;50(7):713-20.

18. Chatila W, Nugent T, Vance G, et al. The effects of high-flow vs low-flow oxygen on exercise in advanced obstructive airways disease. Chest 2004;126(4):1108-15.

19. Stéphan F, Barrucand B, Petit P, et al. High-Flow Nasal Oxygen vs Noninvasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery. A Randomized Clinical Trial. JAMA 2015;313(23):2331-39.

20. Braunlich J, Beyer D, Mai D, et al. Effects of nasal high flow on ventilation in volunteers, COPD and idiopathic pulmonary fibrosis patients. Respiration 2013;85(4):319-25.

21. Raherison C, Girodet PO. Epidemiology of COPD. Eur Respir Rev 2009;18(114):213-21.

The use of heated humidified nasal high flow oxygen (NHF) in patients with COPD

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Background

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide [1]. In addition to generating high healthcare costs [2], COPD imposes a significant burden in terms of disability and impaired quality of life [3]. Unlike many leading causes of death and disability, COPD is projected to increase in much of the world as smoking frequencies rise and the population ages [4, 5].

Oxygen as a therapeutic agent was first introduced by Alvin Barach [6] in 1922 and since then it has become an important form of home therapy for hypoxic chronic obstructive pulmonary disease (COPD). Its use has increased dramatically over the last 20 years since two pivotal studies demonstrated improved survival in hypoxic COPD patients receiving continuous oxygen [7,8].

Domiciliary long term oxygen therapy (LTOT) is usually delivered via loose fitting nasal cannulae, which allow room air to be breathed around the cannula. This room air dilutes the oxygen, providing the inspired oxygen concentration required by the patient. The oxygen is neither warmed nor humidified and high flows of cold dry gas are uncomfortable and may lead to airway obstruction by thickened secretions.

An alternative therapy now available is a nasal high flow (NHF) of humidified air, which can be enriched with oxygen, and delivered at up to 60L/min by a comfortable nasal cannula (Airvo and Optiflow, Fisher & Paykel Healthcare, Auckland, NZ). NHF therapy has been successfully trialled in a long-term study in New Zealand on COPD patients [8] which showed a lowering of exacerbations, improved lung function and quality of life, and high compliance.

This randomised crossover observational study aims to assess the short term physiological respiratory changes caused by using NHF versus the currently used LTOT.

Aims

We aim to establish if NHF:

- reduces respiratory rate
- improves oxygenation
- improves subjective scoring of dyspnoea
- increases tidal volume and end expiratory lung volume

Study Population

Thirty male COPD patients attending the respiratory clinic of The Prince Charles Hospital. Patients will be selected by the respiratory physician in collaboration with the research nurse.

Inclusion Criteria

- Male COPD patients requiring home oxygen
- ≥18 years
- able to attend hospital for a 2.5-3 hour data collection period

Exclusion Criteria

- previous lung resections
- hemidiaphragm palsy
- active respiratory infection (diagnosed by treating physician)
- frequent purse-lip breathing or anxiousness using an alternate respiratory device

Withdrawal Criteria

- Anxiety during the study
- Oxygen saturation falling by more than 10% below baseline
- Transcutaneous carbon dioxide level rising by more than 50% above baseline
- Tachypnea more than 50% above baseline

Identification of patients and consent

In collaboration with the respiratory physician, the research nurse will identify suitable patients from the respiratory clinic of The Prince Charles Hospital. All patients registered for home oxygen will be screened for suitability. The research nurse will approach the patient at the respiratory clinic, explain the study and obtain informed consent to undertake the study at the patient's next clinic visit.

Study Procedures

The research nurse and scientist will prepare and calibrate the research equipment (as per the checklist below). The respiratory physician will confirm that the patient is otherwise well and fit to undertake the study.

All patients will be placed on a bed in a semi-recumbent position, using their own LTOT at their usual oxygen flow rate.

The following physiological monitoring equipment will be attached. Before each is attached, the purpose will be explained to the patient.

- Radiometer TCM4 transcutaneous oxygen and carbon dioxide monitor will be attached to the inner forearm using the supplied adhesive attachment ring.
- 504 Criticare systems pulse oximeter will be placed on a finger tip to measure oxygen saturation.
- Dräger Electrical impedance Tomography (EIT) electrode belt will be placed around the chest at nipple level to monitor end-expiratory lung volumes.
- Viasys Respitrace bands will be placed around the chest and abdomen to monitor breath volumes. The Respitrace system will be calibrated by having the patient breath through a low resistance pneumotacograph for two minutes.
- Continuous ECG monitoring will be applied to measure heart rate
- A video camera will be used to record from the mouth to above the waist during the study in order to identify any "glitches" in the recorded data, such as coughs, sneezes or sighs. It is imperative to monitor this to exclude any erroneous data which will affect the final analysis.

<u>Measurements</u>
A 20 minute baseline recording will be performed (on LTOT). After the baseline period the patient will be randomised using sealed opaque envelopes to either: NHF followed by LTOT OR LTOT followed by NHF. Twenty minutes of data will be recorded using each device with a 20 minute washout period between the two modes of oxygen delivery. During the washout period, the patient will be on their own cannulae.

Data collected during each measurement period is as follows:

- EIT measurements will be undertaken at 18 minutes into the study period
- all other physiological data will be recorded continuously
- dyspnoea level using a Visual analogue scale (a scale of 0-10) 15 minutes into the treatment period

The patient will remain monitored on their own LTOT for another twenty minute period as a safety precaution. At the end of the period, the patient will again breathe through a low resistance pneumotacograph for two minutes to validate the calibration of the Respitrace system. If the patient meets any of the pre-specified withdrawal criteria or if the patient does not wish to continue with the study for any reason, the study will be immediately stopped.

Pre-Study Equipment Checklist

- Emergency equipment in place and staff aware of study
- AIRVO system disinfection cycle completed.
- AIRVO circuit in place, set for 30L/min and warmed up
- AIRVO cannulae in multiple sizes
- Oxygen flowmeter and tubing
- Masimo Radical 7 oximeter – test probe on researcher's finger
- Radiometer TCM4, calibrated
- TCM4 attachment rings and contact fluid
- Respitrace system on and working
- Respitrace bands in various sizes
- EIT system self-tests passed
- EIT bands and electrodes in various sizes
- Face mask and pneumotach
- All data acquisition systems performing satisfactorily

Ethics

This study will be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments and NHMRC National Statement on Ethical Conduct in Research Involving Humans (March 2007).

Data Management

Demographic data will be recorded on prepared forms and kept in a locked filing cabinet in the CCRG. Physiological data and video recordings will be stored on personal computers not connected to networks. Data files will be flagged as "read only" and only remain on the password protected data collection PCs until the end of the study.

On a case-by-case basis, these files will be copied to a password protected external hard drive that will be kept in a locked filing cabinet in the CCRG and to a directory of the QH network with appropriate security and backup.

Following analysis of the data and the use of the video files to identify any "glitches", the video files will be deleted from all storage media.

Only unidentified data will be given to statisticians or others performing data analysis.

Statistical Considerations

All statistical analyses will be performed by the CCRG's visiting statistician, Dr Chris Anstey who will be blinded to whether the patient is receiving LTOT or NHF. The sample size calculation is based on our previous studies using NHF and a reduction in respiratory rate of 4 breaths per minute in the NHF group is estimated. To find this difference with 80% power using a 5% significance level requires a sample size of 30 patients. Two-way (paired) comparisons by treatment group will be performed. Paired t-tests will be used for normally distributed data and results will be presented as mean and standard deviation. For non-normally distributed data, a Wilcoxon signed rank test will be used and results will be presented as median and interquartile range.

Adverse events

Adverse events (AEs) are defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention and which does not necessarily have to have a causal relationship with this treatment (adapted from the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 July 2000).

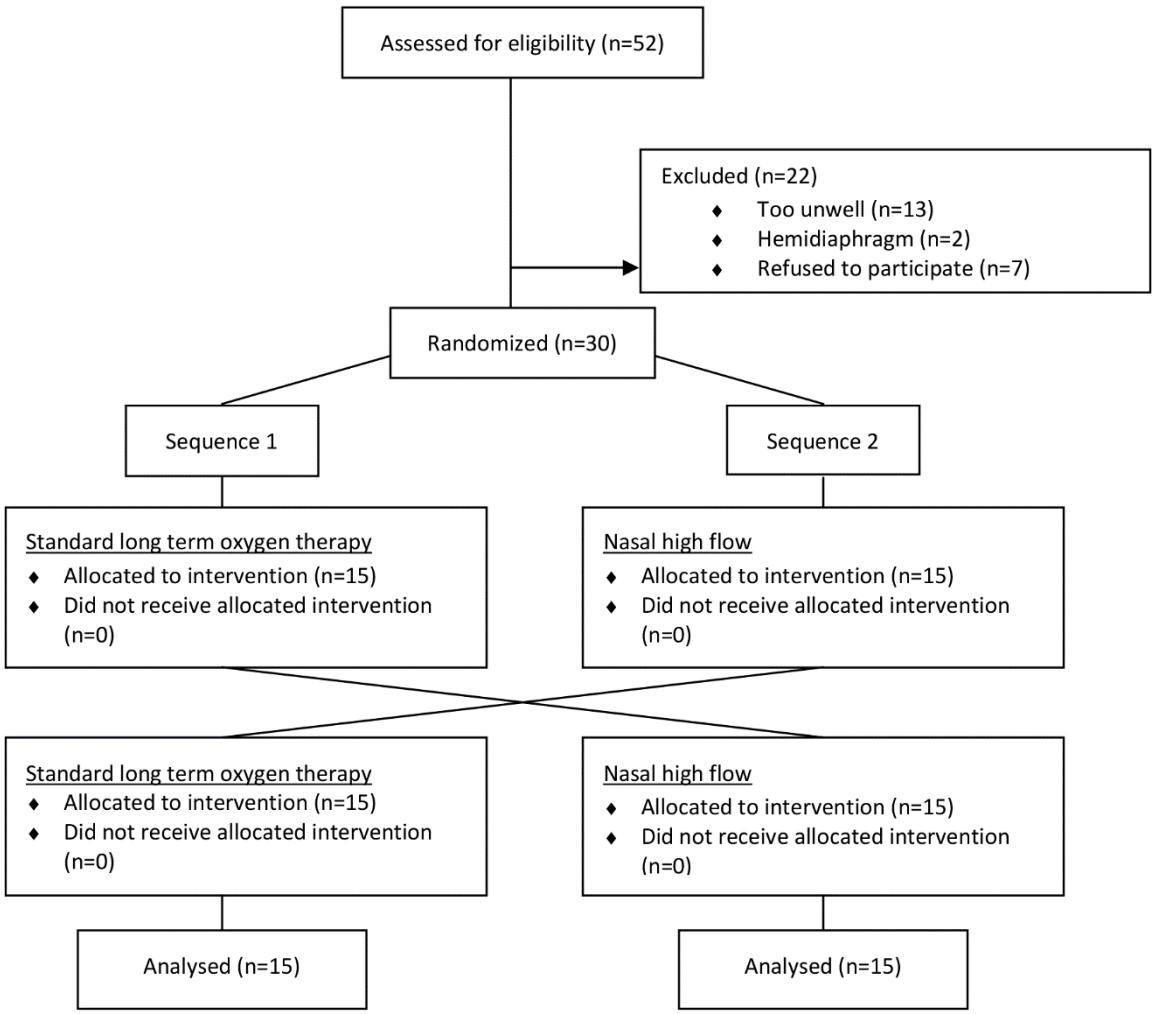
It is recognised that the patient population with COPD will experience aberrations in physiology due to the severity of their underlying disease. These will not necessarily constitute an adverse event unless they require significant intervention or are considered to be of concern in the investigator's clinical judgement.

Serious adverse events

Serious Adverse Events (SAE) are defined in accordance with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) (July 2000) as any untoward medical occurrence that: results in death Is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; is an important medical event which may require intervention to prevent one of the previously listed outcomes.

References

1. Calverley PM, Walker P. Chronic obstructive pulmonary disease. Lancet 2003; 362: 1053–1061.
2. Sullivan SD, Ramsey SD, Lee TA. The economic burden of COPD. Chest 2000; 117: 5S–9S.
3. Ferrer M, Alonso J, Morera J, et al. Chronic obstructive pulmonary disease stage and health-related quality of life. Ann Intern Med 1997; 127: 1072–1079.
4. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. Lancet 1997; 349: 1498–1504.
5. Feenstra TL, van Genugten ML, Hoogenveen RT, Wouters EF, Rutten-van Mölken MP. The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands. Am J Respir Crit Care Med 2001; 164: 590–596.
6. Barach A.L.: The therapeutic use of oxygen. JAMA, 79: 693-8, 1922. Nocturnal oxygen therapy trial group. Continuous or nocturnal oxygen therapy in hypoxaemic chronic obstructive lung disease: A clinical trial. Ann. Intern. Med., 93: 391-8, 1980.
7. Medical Research Working Party. Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet, 1: 681-6, 1981.
8. Rea H., McAuley S., Jayaram L., Garrett J., et al. The clinical utility of long-term humidification therapy in chronic airways disease. Respiratory Medicine 2010; 104, 525-533.


Assessed for eligibility (n=52)
Excluded (n=22)
Too unwell (n=13)
Hemidiaphragm (n=2)
Refused to participate (n=7)
Randomized (n=30)
Sequence 1
Sequence 2
Standard long term oxygen therapy
Allocated to intervention (n=15)
Did not receive allocated intervention (n=0)
Nasal high flow
Allocated to intervention (n=15)
Did not receive allocated intervention (n=0)
Standard long term oxygen therapy
Allocated to intervention (n=15)
Did not receive allocated intervention (n=0)
Nasal high flow
Allocated to intervention (n=15)
Did not receive allocated intervention (n=0)
Analysed (n=15)
Analysed (n=15)