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.