CrossMark

Oxygen versus air-driven nebulisers for exacerbations of chronic obstructive pulmonary disease: a randomised controlled trial

George Bardsley[1,2] , Janine Pilcher[1,2,3] , Steven McKinstry[1,2,3] , Philippa Shirtcliffe[1,2] , James Berry[2,4] , James Fingleton[1,2] , Mark Weatherall[4] and Richard Beasley[1,2,3*]

Abstract

Background: In exacerbations of chronic obstructive pulmonary disease, administration of high concentrations of oxygen may cause hypercapnia and increase mortality compared with oxygen titrated, if required, to achieve an oxygen saturation of 88–92%. Optimally titrated oxygen regimens require two components: titrated supplemental oxygen to achieve the target oxygen saturation and, if required, bronchodilators delivered by air-driven nebulisation. The effect of repeated air vs oxygen-driven bronchodilator nebulisation in acute exacerbations of chronic obstructive pulmonary disease is unknown. We aimed to compare the effects of air versus oxygen-driven bronchodilator nebulisation on arterial carbon dioxide tension in exacerbations of chronic obstructive pulmonary disease.

Methods: A parallel group double-blind randomised controlled trial in 90 hospital in-patients with an acute exacerbation of COPD. Participants were randomised to receive two 2.5 mg salbutamol nebulisers, both driven by air or oxygen at 8 L/min, each delivered over 15 min with a 5 min interval in-between. The primary outcome measure was the transcutaneous partial pressure of carbon dioxide at the end of the second nebulisation (35 min). The primary analysis used a mixed linear model with fixed effects of the baseline $PtCO_2$, time, the randomised intervention, and a time by intervention interaction term; to estimate the difference between randomised treatments at 35 min. Analysis was by intention-to-treat.

Results: Oxygen-driven nebulisation was terminated in one participant after 27 min when the $PtCO_2$ rose by > 10 mmHg, a predefined safety criterion. The mean (standard deviation) change in $PtCO_2$ at 35 min was 3.4 (1.9) mmHg and 0.1 (1.4) mmHg in the oxygen and air groups respectively, difference (95% confidence interval) 3.3 mmHg (2.7 to 3.9), $p < 0.001$. The proportion of patients with a $PtCO_2$ change ≥4 mmHg during the intervention was 18/45 (40%) and 0/44 (0%) for oxygen and air groups respectively.

Conclusions: Oxygen-driven nebulisation leads to an increase in $PtCO_2$ in exacerbations of COPD. We propose that air-driven bronchodilator nebulisation is preferable to oxygen-driven nebulisation in exacerbations of COPD.

Trial registration: Australian New Zealand Clinical Trials Registry number ACTRN12615000389505. Registration confirmed on 28/4/15.

Keywords: Air, Bronchodilator agents, Hypercapnia, Nebulisation, Oxygen

---

* Correspondence: richard.beasley@mrinz.ac.nz
[1]Capital and Coast District Health Board, Wellington, New Zealand
[2]Medical Research Institute of New Zealand, Box 7902, Wellington, PO 6242, New Zealand
Full list of author information is available at the end of the article

Bardsley *et al. BMC Pulmonary Medicine* (2018) 18:157

Page 2 of 9

Background

In acute exacerbations of chronic obstructive pulmonary disease (AECOPD), administration of high concentration oxygen may cause profound hypercapnia and increase mortality, compared with oxygen titrated to achieve an oxygen saturation of between 88 to 92% [1, 2]. Titrated oxygen regimens require two components: titrated supplemental oxygen to achieve a particular target arterial oxygen saturation measured by pulse oximetry (SpO_2), and bronchodilators delivered by either air-driven nebulisation or metered-dose inhalers with a spacer. Oxygen-driven nebulisation inadvertently exposes patients to high concentrations of inspired oxygen, particularly with prolonged or repeated use as may occur in patients with severe exacerbations during long pre-hospital transfers or if the mask is inadvertently left in place.

We have shown that air-driven bronchodilator nebulisation prevents the increase in arterial partial pressure of carbon dioxide ($PaCO_2$) that results from use of oxygen-driven nebulisers in patients with stable COPD [3]. However, there are only two small non-blinded randomised controlled trials of air compared to oxygen-driven nebulisation in patients admitted to hospital with AECOPD [4, 5]. These trials reported that administration of a single bronchodilator dose using oxygen-driven nebulisation increases the $PaCO_2$ in COPD patients who have baseline hypercapnia.

Robust determination of the risks of oxygen-driven nebulisation in AECOPD could identify whether widespread implementation of air-driven nebulisers, or use of metered-dose inhalers through a spacer, are required to ensure safe delivery of bronchodilators to this high-risk patient group. The objective of this study was to compare the effects on $PaCO_2$ of air- and oxygen-driven bronchodilator nebulisation in AECOPD. Our hypothesis was that two doses of oxygen-driven bronchodilator nebulisation would increase the $PaCO_2$ compared with air-driven nebulisation in patients hospitalised with an AECOPD.

Methods

Trial design and patients

This was a parallel-group double-blind randomised controlled trial at Wellington Regional Hospital, New Zealand. The full study protocol is available in the online supplement.

Participants were hospital inpatients, ≥40 years of age, with an admission diagnosis of AECOPD. Exclusion criteria included requirement for ≥4 L/min of oxygen via nasal cannulae to maintain SpO_2 between 88 to 92%; current requirement for non-invasive ventilation (NIV); baseline transcutaneous partial pressure of carbon dioxide ($PtCO_2$) > 60 mmHg; inability to provide written informed consent; and any other condition which at the Investigator's discretion, was believed may present a safety risk or impact on the feasibility of the study

results. Written informed consent was obtained before any study-specific procedures. The study was undertaken on the ward during the hospital admission. Ethics approval was obtained from the Health and Disability Ethics Committee, New Zealand (Reference 14/NTB/200). The full study protocol (original and updated version) can be found on the OLS (see Additional file 1 and 2).

Intervention

After written consent, participants had continuous $PtCO_2$ and heart rate monitoring using the SenTec® (SenTec AG, Switzerland) device and oxygen saturation (SpO_2) measured by pulse oximetry (Novametrix 512, Respironics, Carlsbad, USA). Participants were randomised to receive two nebulisations, both driven either by air or oxygen, at 8 L/min, each delivered over 15 min with a five minute break in-between. Randomisation was 1:1 by a block randomised computer generated sequence (block size six), provided in sealed opaque envelopes by the study statistician who was independent of recruitment and assessment of participants.

The participants and blinded investigator, who recorded heart rate and $PtCO_2$ were masked to the randomised treatments. If both oxygen and air ports were available in hospital on the wall behind the participant, these were used for driving nebulisation. If only oxygen ports were available, identical portable oxygen and air cylinders were placed behind the participant's bed prior to randomisation and used instead. Both the participant and blinded investigator faced forward for the full duration of the study. In addition, the blinded investigator sat towards the end of the bed - ahead of the participant, such that they could not see the participant's interventions. Likewise, the blinded investigator and patient could not view the SpO_2 on the Sentec device, as this was covered during the interventions, or the pulse oximeter which could only be viewed by the unblinded investigator. Interaction between blinded and unblinded investigators would only occur if a rise in $PtCO_2$ of ≥10 mmHg was demonstrated (a predefined safety criterion to abort intervention).

An initial 15 min wash-in and titration period was administered by the unblinded investigator using nasal cannulae, if required, to ensure that participant's SpO_2 were within 88 to 92%. If saturations were ≥88% on room air, no supplemental oxygen was required. Randomisation was performed after the 15 min wash-in period, when both patient and blinded investigator were already in a forward-facing position to maintain blinding. The unblinded investigator recorded SpO_2 on a separate pulse-oximeter from then onwards.

Immediately before the first nebulisation, denoted by the baseline reading at time-point zero, $PtCO_2$, SpO_2 and heart rate were recorded. Participants then received two administrations of 2.5 mg salbutamol by nebulisation,

Bardsley *et al. BMC Pulmonary Medicine* (2018) 18:157

Page 3 of 9

delivered by either air or oxygen - each for 15 min duration at a flow rate of 8 L/min. Hudson RCI Micro Mist Nebuliser Masks (Hudson RCI, Durham, North Carolina, USA) were used. The nebulisations were delivered by the unblinded investigator at time zero and at 20 min, allowing for a five minute interval between nebulisations. Recordings were continued for 45 min after completion of the last nebulisation (80 min after baseline). Measurements of $PtCO_2$, SpO_2 and heart rate were recorded at five minute intervals, and at six minutes after the start of each nebulisation, in view of the British Thoracic Society (BTS) guideline's recommendation for limiting oxygen-driven nebulisation to six-minutes in ambulance care, if air-driven nebulisation is unavailable [6].

Immediately before the first nebulisation and just before completion of the second nebulisation, at 35 min, a capillary blood gas sample was taken from the fingertip for measurement of $PcapCO_2$ and pH.

Oxygen delivery

During the wash-in and between the nebulisations oxygen was titrated, if required, via nasal prongs to maintain oxygen saturations between 88 to 92%. Participants in the air-driven group who were receiving oxygen at the start of nebulisation continued to receive titrated supplemental oxygen via nasal prongs underneath the nebuliser mask. Those in the oxygen-driven group had the prongs removed at the start, and reapplied after the completion of each nebulisation. At 35 min, oxygen was delivered via nasal prongs to participants at the flow rate they last received during titration (i.e. at 35 min and 20 min in the air-driven and oxygen-driven groups, respectively). From 35 min until 80 min, the oxygen flow rate was only increased (or initiated) if a participant's SpO_2 fell below 85%.

Outcomes

The primary outcome was originally planned to be $PcapCO_2$ at 35 min, at completion of the second nebulisation. However, after the first 14 participants had been studied, it was evident that obtaining adequate amounts of blood to fill the capillary tubes from some participants was difficult. At this stage of recruitment 4/14 (29%) of participants had missing data. The primary outcome variable was therefore changed to $PtCO_2$ at 35 min, with $PcapCO_2$ at 35 min reverting to a secondary outcome variable. Other secondary outcomes were the individual $PtCO_2$ measurements at each time point; the proportion of participants who had a rise in $PtCO_2$ or $PcapCO_2$ of ≥ 4 and ≥ 8 mmHg; capillary pH at 35 min, and heart rate and SpO_2 measurements at each time point.

Sample size calculation and statistical analysis

A rise in $PtCO_2$ from baseline of ≥ 4 mmHg is considered a physiologically significant change and ≥ 8 mmHg

a clinically significant change, based on previous criteria [7, 8]. In our study of oxygen versus air-driven nebulisers in stable COPD patients, the standard deviation (SD) of baseline $PtCO_2$ was 5.5 mmHg [3]. With 90% power and alpha of 5%, 82 patients were required to detect a 4 mmHg difference. Assuming a drop-out rate of 10% our target recruitment was 90 patients.

The primary analysis used a mixed linear model with fixed effects of the baseline $PtCO_2$, time, the randomised intervention, and a time by intervention interaction term; to estimate the difference between randomised treatments at 35 min. A power exponential in time correlation structure was used for the repeated measurements. The secondary outcome variables of $PtCO_2$ at the other time points, SpO_2 and heart rate used similar mixed linear models. $PcapCO_2$ and pH were compared by Analysis of Covariance with the baseline measurement as a continuous co-variate. As a post-hoc analysis we compared the difference in $PtCO_2$ between the 15 and 6 min, and the 35 and 26 min time points.

Comparison of categorical variables, $PtCO_2$ or $PcapCO_2$ change of ≥ 4 and 8 mmHg, was by estimation of a risk difference, and Fishers' exact test. As a post-hoc analysis we also compared the difference in paired proportions for those with $PtCO_2$ change of ≥ 4 mmHg in the oxygen arm only using McNemar's test and an appropriate estimate for the difference in paired proportions. The time for $PtCO_2$ to return to baseline during the observation period (defined as the time until the $PtCO_2$ was first equal to or below the baseline value, between 40 and 80 min), was compared using Kaplan-Meier survival curves and a Cox Proportional Hazards model. A simple t-test was used to compare the lowest value of the SpO_2 between 40 and 80 min, compared to baseline. SAS version 9.4 was used.

Results

Patients

The trial recruited between May 14th 2015 and June 29th 2016. The CONSORT diagram of the flow of the 90 recruited participants through the trial is shown in Fig. 1. One participant withdrew after 18 min of air-driven nebulisation because of feeling flushed, and so complete data was available for $PtCO_2$ for 89 participants. The baseline $PtCO_2$ for this participant was 34.3 mmHg and at the time of withdrawal it was 34.6 mmHg. Oxygen-driven nebulisation was stopped in another participant at 27 min when the $PtCO_2$ rose by > 10 mmHg from baseline, a pre-defined safety criterion. The baseline $PtCO_2$ for this participant was 43.4 mmHg and at the time of withdrawal it was 54.1 mmHg. This participant had study measurements continued after this for the full duration of the study. No clinical adverse events were noted during the intervention periods.

Bardsley *et al. BMC Pulmonary Medicine* (2018) 18:157

Page 4 of 9

Fig. 1 Participant flow through the study and allocation of interventions
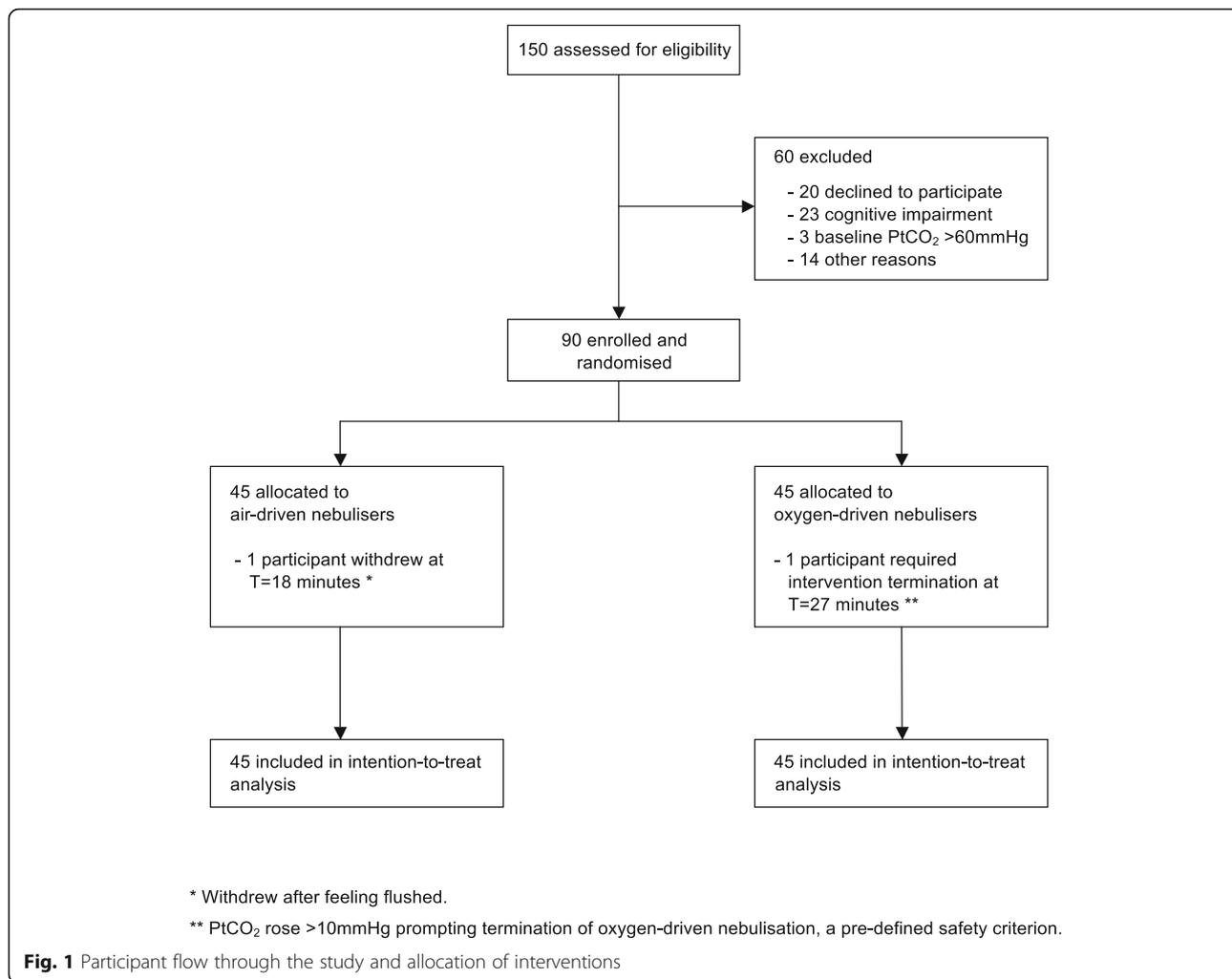
A summary of baseline participant characteristics are shown in Table 1. Participants predominantly had severe airflow obstruction with a mean FEV_1 of 34.5% predicted. The mean (range) baseline $PtCO_2$ was 37.6 mmHg (24.3 to 58.5 mmHg), and mean SpO_2 was 93%. Patients randomised to the oxygen group were more likely to have required assisted ventilation previously. The mean (SD) time for the nebulised salbutamol to dissipate from the chamber was 5.2 (1.2) minutes.

$PtCO_2$

The mean (SD) change in $PtCO_2$ after 35 min was 3.4 (1.9) mmHg in the oxygen group ($n = 45$), compared to 0.1 (1.4) mmHg in the air group ($n = 44$). The difference (95% CI) in $PtCO_2$ for oxygen compared to air-driven nebulisations after 35 min was 3.3 mmHg (2.7 to 3.9), $p < 0.001$. (Table 2 and Fig. 2). After adjustment for baseline $PtCO_2$, a history of assisted ventilation, previous hypercapnia and baseline SpO_2, were not associated with the $PtCO_2$ at 35 min in either randomised group.

In 18/45 (40%) participants receiving oxygen-driven nebulisation, $PtCO_2$ increased from baseline by ≥ 4 mmHg at some stage during the intervention compared to none of the participants receiving air-driven nebulisation, risk difference (95% CI) 40% (25.7 to 54.3), $p < 0.001$. The full data description and comparisons at each time point are shown in the OLS. Two participants receiving oxygen-driven nebulisation had a rise in $PtCO_2 \geq 8$ mmHg, one of whom required intervention termination, exceeding the predefined safety criterion of a rise ≥ 10 mmHg from baseline.

The estimate (95% CI) of the time-related difference, 15 min minus six minutes, for oxygen compared to air, was 0.73 mmHg (0.11 to 1.35), $P = 0.021$; and for 35 min minus 26 min, 0.43 mmHg (-0.19 to 1.06), $P = 0.17$. In the oxygen treatment arm the proportion of patients in whom the $PtCO_2$ increased from baseline by ≥ 4 mmHg at 6 min was less than the proportion at 15 min: 6/45 (13.3%) and 13/45 (28.9%) respectively, paired difference in proportions (95% CI) 15.6% (3.3 to 27.8), $P = 0.013$

Bardsley *et al. BMC Pulmonary Medicine* (2018) 18:157

Page 5 of 9

Table 1 Participant Characteristics

	Mean (SD)		P
	Oxygen N=45[a]	Air N=45[a]	
Age (years)	70·4 (10·3)	72·3 (8·3)	0.34
Age at diagnosis of COPD (years)	58·6 (12·1) N = 40	58·8 (12·2) N = 44	0.92
BMI (kg/m^2)	27·2 (7·7)	25·5 (8·9)	0.33
Smoking pack years	39·3 (31·1)	51·2 (39·2)	0.11
FEV$_1$ (L)	0·81 (0·33) N = 35	0·85 (0·31) N = 37	0.69
FEV$_1$% predicted	35·0 (11·5) N = 35	34·0 (11·8) N = 37	0.73
mMRC	2·38 (1·09)	2·33 (1·04)	0.84
Baseline Transcutaneous Data			
PtCO$_2$ (mmHg)	38·0 (7·7)	37·2 (6·8)	0.59
SpO$_2$ (%)	92·6 (2·4)	92·6 (2·3)	0.93
Heart Rate (per minute)	89·6 (15·7)	87·0 (16·0)	0.89
Baseline capillary blood gas			
pH	7·42 (0·04) N = 43	7·44 (0·03) N = 41	0.11
PcapCO$_2$ (mmHg)	40·2 (7·0) N = 43	38·5 (5·9) N = 41	0.23
	N/45 (%)		P
	Oxygen	Air	
Male	17 (38)	24 (53)	0.20
Ethnicity			0.49
European	24 (53)	31 (69)	
Māori	7 (16)	4 (9)	
Pacific	5 (11)	4 (9)	
Other	9 (20)	6 (13)	
Previous Ventilation (ever)	12 (27)	3 (7)	0.02
Previous Ventilation Type			0.03
NIV	10 (22)	3 (7)	
Intubation	2 (4)	0 (0)	
Previous hypercapnia	23 (51)	17 (38)	0.29
Home Oxygen	2 (4)	1 (2)	0.99
Home Nebulisers	5 (11)	12 (27)	0.10
Comorbidities			
Heart Failure	8 (18)	3 (7)	0.20
Asthma	6 (13)	2 (4)	0.27
Bronchiectasis	3 (7)	4 (9)	0.99

COPD Chronic Obstructive Pulmonary Disease, *BMI* Body Mass Index, *FEV$_1$* Forced Expiratory Volume in 1 s at time of randomisation, *mMRC* Modified Medical Research Council dyspnea scale, *PtCO$_2$* Transcutaneous partial pressure of carbon dioxide, *SpO$_2$* peripheral oxygen saturation, *PcapCO$_2$* Capillary partial pressure of carbon dioxide, *NIV* non-invasive ventilation
[a]Unless indicated

(Additional file 1: Table S1). The proportion of patients in whom the PtCO$_2$ increased from baseline by ≥4 mmHg at 26 min (6 min into the second oxygen-driven nebulisation) was also less than the proportion at 35 min (completion of the second oxygen-driven nebulisation), although this difference was not statistically significant: 10/45 (22%)

and 14/45 (31%) respectively, paired difference in proportions (95% CI) 8.9% (– 3.3 to 20.9), P = 0.15.

The median (25th to 75th percentile) time taken for PtCO$_2$ to return to baseline after cessation of the second nebulisation was 40 (40 to 45) minutes in the air group compared to 50 (45 to 50) minutes in the oxygen group, hazard ratio (95% CI) 1.59 (1.01 to 2.52), P = 0.047.

PcapCO$_2$ and pH
Data summaries for capillary blood gas sampling are shown in Table 3. The difference (95% CI) between oxygen and air for PcapCO$_2$ after 35 min was 2.0 mmHg (1.1 to 2.8), $p < 0.001$. Thirteen (31.7%) participants receiving oxygen had a rise in PcapCO$_2$ of ≥4 mmHg compared with three (7.7%) receiving air; risk difference (95% CI) 24% (7.5 to 40.5), $p = 0.01$. In addition to the two participants in whom the PtCO$_2$ increased by ≥8 mmHg, there were two additional participants with capillary data receiving oxygen who had a rise in PcapCO$_2$ of ≥8 mmHg and none from the air group. The mean (95% CI) difference in pH after 35 min was 0.015 units (0.008 to 0.024, $p < 0.001$) lower for oxygen nebulisation compared to air. One participant experienced a reduction in pH of 0.06 units (from 7.38 to 7.32) in association with a rise in PcapCO$_2$ of 9 mmHg (55 to 64 mmHg).

SpO$_2$ and heart rate
The SpO$_2$ was higher throughout both the nebulisation and initial washout periods in the oxygen compared with the air group (see Additional file 3: Table S2). Figure 3 shows the trend for the SpO$_2$ in the oxygen group to fall below that of the air group after cessation of the second nebulisation. At the end of the observation period (80 min), the SpO$_2$ was lower in the oxygen group (difference – 1.22%, 95% CI -2.04 to – 0.39, p = 0.004). The maximum reduction in SpO$_2$ from baseline was 0·8% (95% CI -0.2 to 1.7, P = 0.10) lower after oxygen compared with air nebulisation. The heart rate was slower in the oxygen group at 35 min by 3.3 bpm (95% CI 0.31 to 6.25), p = 0.031 (see Additional file 1: Table S3).

Methods of PCO$_2$ measurement
Due to the requirement to change the primary outcome measure, a post-hoc analysis was undertaken to compare the two methods of measuring PaCO$_2$. Based on data for 80 paired PtCO$_2$ and PcapCO$_2$ measurements at baseline and 35 min, the mean (SD) change in PtCO$_2$ was 1.7 mmHg (2.2) with a range of – 2.5 to 8.0 mmHg, and the mean (SD) change in PcapCO$_2$ was 1.7 mmHg (2.3), with a range – 3.0 to 9.0 mmHg. The estimate of bias for change in PcapCO$_2$ minus PtCO$_2$ was – 0.03 mmHg (95% CI -0.44 to 0.38), P = 0.89. The limits of agreement between PtCO$_2$ and PcapCO$_2$ were +/– 3.8 mmHg for each individual measurement obtained.

Table 2 PtCO$_2$ by time and randomised group

Action	Time	PtCO$_2$ Mean (SD) [N = 45 for each unless specified]		Oxygen minus air (95% CI)	P
		Oxygen	Air		
Baseline	0	38·0 (7·7)	37·2 (6·8)		
1st nebulisation	5	39·9 (8·3)	37·0 (7·1)	2·10 (1·49 to 2·71)	< 0·001
	6	40·1 (8·4)	37·0 (7·1)	2·24 (1·63 to 2·86)	< 0·001
	10	40·8 (8·6)	37·2 (6·9)	2·76 (2·15 to 3·37)	< 0·001
	15	41·1 (8·8)	37·3 (6·9)	2·97 (2·36 to 3·59)	< 0·001
	20	38·6 (7·8)	37·0 (6·4)[a]	0·86 (0·25 to 1·48)	0·006
2nd nebulisation	25	40·5 (8·3)	36·8 (6·8)[b]	2·77 (2·15 to 3·39)	< 0·001
	26	40·6 (8·4)	36·8 (6·8)[b]	2·88 (2·26 to 3·50)	< 0·001
	30	41·1 (8·5)	37·1 (6·6)[a]	3·20 (2·59 to 3·82)	< 0·001
	35	41·3 (8·6)	37·3 (6·5)[a]	3·31 (2·70 to 3·93)	< 0·001
Observation period	40	39·0 (8·1)[a]	37·0 (6·7)[a]	1·14 (0·52 to 1·76)	< 0·001
	45	38·1 (7·5)	36·7 (6·3)[a]	0·61 (− 0·01 to 1·22)	0·053
	50	37·9 (7·4)	36·6 (6·2)[a]	0·59 (− 0·02 to 1·21)	0·059
	55	37·9 (7·3)	36·6 (6·0)[a]	0·51 (− 0·10 to 1·13)	0·1
	60	37·9 (7·3)	36·7 (6·1)[a]	0·51 (− 0·10 to 1·13)	0·1
	65	38·1 (7·2)	36·7 (6·1)[a]	0·63 (0·01 to 1·25)	0·045
	70	37·5 (6·5)[a]	36·7 (6·1)[a]	0·60 (− 0·02 to 1·21)	0·059
	75	37·8 (6·8)	36·7 (6·1)[a]	0·42 (− 0·20 to 1·03)	0·18
	80	37·9 (6·9)	36·7 (6·3)[a]	0·40 (− 0·21 to 1·02)	0·2

Air Air-driven nebuliser group, *Oxygen* Oxygen-driven nebuliser group, *PtCO$_2$* Transcutaneous partial pressure of carbon dioxide
[a]*N* = 44
[b]*N* = 43

Fig. 2 PtCO$_2$ change from baseline (*T* = 0) to *T* = 35 min. Mean PtCO$_2$ with error bars showing one SD, by time and intervention

Bardsley *et al. BMC Pulmonary Medicine* (2018) 18:157

Page 7 of 9

Table 3 Capillary blood gas measurements according to randomised treatment

Time (mins)	$P_{cap}CO_2$ Mean (SD)		Difference[a] (95% CI)	P
	Oxygen	Air		
0	40·2 (7·0) N = 43	38·5 (5·9) N = 41	–	–
35	42·6 (8·3) N = 41	39·0 (6·4) N = 39	2·0 (1.1 to 2·8)	< 0·001
Time (mins)	pH Mean (SD)		Difference[b] (95% CI)	P
	Oxygen	Air		
0	7·42 (0·04) N = 43	7·44 (0·03) N = 41	–	–
35	7·41 (0·04) N = 41	7·43 (0·04) N = 39	-0·015 (− 0·024 to − 0·008)	< 0·001

$P_{cap}CO_2$ Capillary partial pressure of carbon dioxide
[a]$P_{cap}CO_2$ at 35 min, adjusted for baseline
[b]pH at 35 min, adjusted for baseline

Discussion

In this study, oxygen-driven nebulisation increased the $PtCO_2$ in hospital in-patients with an AECOPD compared with air-driven nebulisation. Despite the small mean increase in $PtCO_2$ of 3.4 mmHg, the physiological relevance of this response is suggested by the increase in $PtCO_2$ of at least 4 mmHg in 18/45 (40%) of participants receiving oxygen-driven nebulisation, whereas no patient had an increase of 4 mmHg or more following air-driven nebulisation. The clinical relevance of this physiological response is suggested by the requirement to withdraw one participant during the second oxygen-driven nebulisation due to the $PtCO_2$ increasing by > 10 mmHg, and the increase of $PtCO_2$ or $PcapCO_2$ of at least 8 mmHg in 4/45 (9%) patients receiving oxygen-driven nebulisation, one of

whom had a fall in pH of 0.06 into the acidotic range (7.32). These findings suggest that air-driven nebulised bronchodilator therapy represents an important component of the conservative titrated oxygen regimen which has been shown to reduce the risk of hypercapnia, acidosis and mortality in AECOPD [1].

There are a number of methodological issues relevant to the interpretation of the study findings. Both the randomised controlled design and double-blinding of this study allow for robust and reliable data capture. The length of the nebuliser regimen was chosen to ensure adequate time for complete nebulisation to occur, and to replicate 'real-world' back to back treatments in the acute setting, by using two nebulisations separated by five minutes. It is possible that the magnitude of the
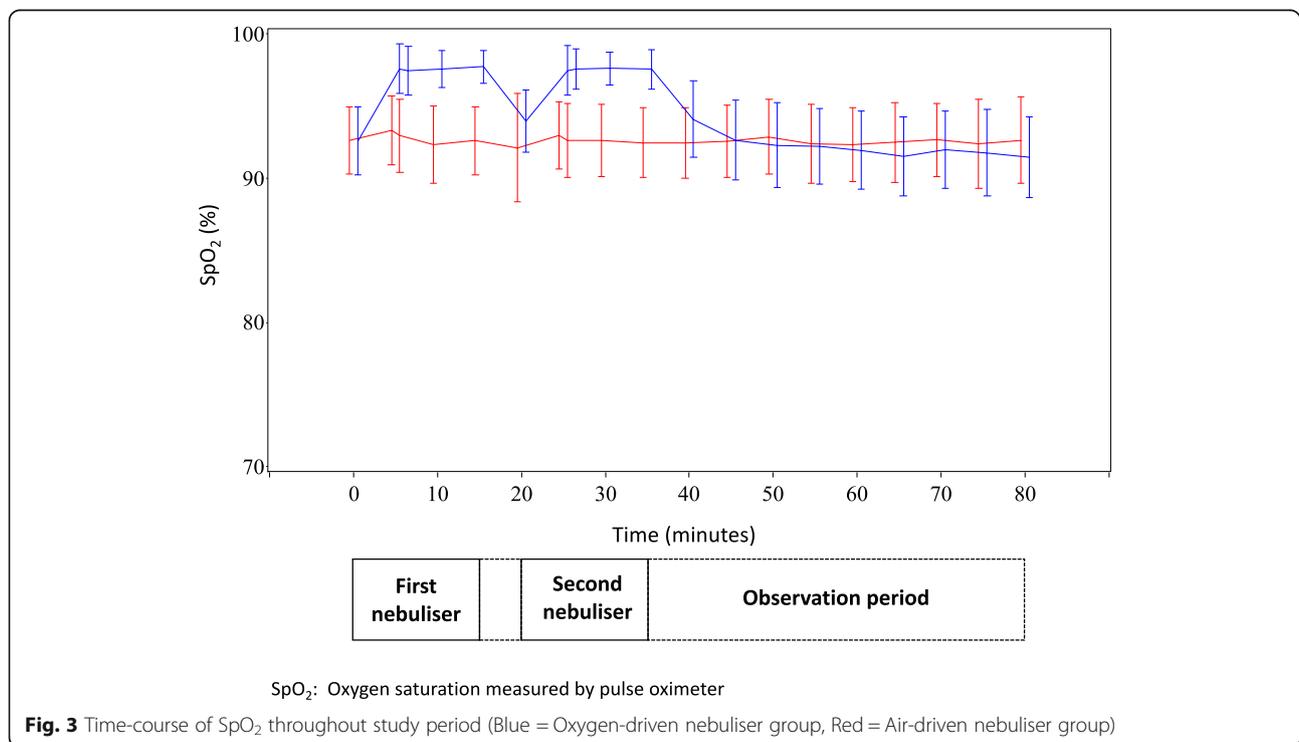
Fig. 3 Time-course of SpO_2 throughout study period (Blue = Oxygen-driven nebuliser group, Red = Air-driven nebuliser group)

Bardsley *et al. BMC Pulmonary Medicine* (2018) 18:157

Page 8 of 9

differences in PCO_2 and pH may be even larger with continuous nebulisation which may occur in patients with severe exacerbations not responding to initial treatment or if the nebuliser is inadvertently left in place. The safety-based exclusion criteria of a baseline $PtCO_2 >$ 60 mmHg and an oxygen requirement of ≥4 L/minute (to maintain target SpO_2 of 88 to 92%), effectively excluded patients with the most severe exacerbations of COPD.

Whilst respiratory rate and neurological symptoms were not formally assessed as outcome measures, no adverse events were identified during the interventions. However, we acknowledge that if changes in PCO_2 and pH of this magnitude occurred in more severe patients at the time of their presentation, they would have been at risk of symptoms of hypercapnia and respiratory acidosis, and the requirement to escalate treatment.

The original primary outcome measure and time of measurement was $PcapCO_2$ after 35 min. Following the first 14 study participants, it was evident that obtaining adequate amounts of blood to fill the capillary tubes from some participants was difficult or impossible to the extent that 4 out of 14 participants had one or more missed samples. For this reason, the primary outcome was changed to $PtCO_2$ after 35 min. In other words, the method of capturing the change in PCO_2 was revised, rather than the outcome itself. $PtCO_2$ monitoring enabled continuous assessment to be undertaken, and is accurate in AECOPD, [9] and other acute settings [10–12]. The validity of this method was confirmed by the post hoc analysis of 80-paired samples, where each capillary blood gas sample obtained had a corresponding $PtCO_2$ measurement at the same time-point. This showed that the difference between the $PcapCO_2$ and $PtCO_2$ in the mean change from baseline was − 0·03 mmHg with 95% confidence intervals of − 0.44 to 0.38 mmHg. This data suggests that the use of $PtCO_2$ measurements did not adversely affect our ability to determine change in $PcapCO_2$ from baseline.

We did not investigate the potential mechanisms by which oxygen driven nebulisation increases $PtCO_2$. However as demonstrated in mechanistic studies of oxygen therapy in COPD, it is likely to be due to the combination of a reduction in respiratory drive, release of hypoxic pulmonary vasoconstriction, absorption atelectasis, and the Haldane effect [13, 14]. Furthermore, the study was not designed to assess costs related to each regimen, however it is reasonable to assume that improved clinical outcomes seen by avoiding a rise in $PtCO_2$ and associated acidosis, would lead to a reduction in healthcare costs.

The findings from our study complement those of our previous randomised controlled trial of a similar design in stable COPD patients in the clinic setting, in which there was a mean $PtCO_2$ difference between the oxygen- and air-driven nebulisation treatment arms of 3.1 mmHg (95% CI 1·6 to 4·5), $p < 0·001$, after 35 min. [3] In that study one of the 24 subjects was withdrawn due to an increase in $PtCO_2$ of 10 mmHg after 15 min of the first oxygen-driven nebulisation. As with the previous study, an increase in $PtCO_2$ occurred within 5 min, indicating the rapid time course of this physiological response. We had anticipated a greater effect in this current study as the patients had acute rather than stable COPD however the magnitude of the effect was similar, probably reflecting the similar severity of airflow obstruction, with a mean predicted FEV_1 of 35% and 27% in this and the previous study respectively.

The two previous open crossover studies of inpatients with AECOPD both showed oxygen-driven nebulisation worsened hypercapnia in patients with Type 2 respiratory failure [4, 5]. Gunawardena et al. [4] studied 16 patients with COPD and reported that only those with carbon dioxide retention at baseline ($n = 9$) demonstrated a rise in $PaCO_2$ after 15 min (mean of 7·7 mmHg), and one patient had a rise of 22 mmHg. Similarly, O'Donnell et al [5] reported that 6/10 patients, all with carbon dioxide retention at baseline, showed a rise in $PaCO_2$ after 10 min (mean of 12.5 mmHg).

The current BTS guidelines recommend air-driven nebulisation and, if this is not available in the ambulance service, the maximum use of 6 min for an oxygen-driven nebuliser. This is based on the rationale that most of the nebulised medication will have been delivered, and is categorised as grade D evidence [6]. We observed the mean time for dissipation of salbutamol solution from the nebuliser chamber of 5.2 min confirming that 6 min is adequate for salbutamol delivery. The proportion of participants with a $PtCO_2$ increase ≥4 mmHg was lower after 6 min than 15 min, suggesting some amelioration of risk with the shorter nebulisation treatment. Alternative methods of bronchodilator delivery include air-driven nebulisers or multiple metered dose inhaler actuations via a spacer [15].

The potential for rebound hypoxia after abrupt cessation of oxygen therapy has been observed both in the treatment of asthma and COPD [9, 16, 17]. We identified some evidence consistent with this phenomenon which is a potentially important yet poorly recognised clinical issue.

Conclusions

In summary, air-driven nebulisation avoids the potential risk of increasing the $PaCO_2$ associated with oxygen-driven bronchodilator administration in AECOPD. We propose that air-driven bronchodilator nebulisation is preferable to oxygen-driven nebulisation in AECOPD, and that when the use of oxygen-driven nebulisation is unavoidable, $PtCO_2$ is monitored if possible.

Bardsley *et al. BMC Pulmonary Medicine* (2018) 18:157

Page 9 of 9

Additional files

Abbreviations
AECOPD: Acute exacerbation of chronic obstructive pulmonary disease; BTS: British thoracic society; COPD: Chronic obstructive pulmonary disease; FEV$_1$: Forced expiratory volume over 1 s; FVC: Forced vital capacity; MRINZ: Medical research institute of new zealand; PaCO$_2$: Partial pressure of arterial carbon dioxide; PcapCO$_2$: Partial pressure of capillary carbon dioxide; PIS: Participant information sheet; PtCO$_2$: Partial pressure of transcutaneous carbon dioxide; SD: Standard deviation; Sentec: Transcutaneous monitor brand; SpO$_2$: Oxygen saturation measured by oximetry; StO$_2$: Oxygen saturation measured by transcutaneous monitor

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
RB was the principal investigator for the study, is guarantor for the study, and affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. GB, JP, SM and JB were investigators on the study and collected the data. MW performed the statistical analysis. GB wrote the first draft of the manuscript. RB and PS conceived the study and wrote the first draft of the protocol with JP. GB, JP, SM, PS, JB, JF, MW and RB all contributed to study design, interpretation of results, manuscript writing, and reviewed the final manuscript prior to submission. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. No writing assistance was received. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Ethics approval was obtained from the Health and Disability Ethics Committee, New Zealand (Reference 14/NTB/200). Written informed consent was obtained before any study-specific procedures.

Consent for publication
Not applicable.

Competing interests
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. All authors have no competing interests to declare, other than the MRINZ receiving research funding from Health Research Council of New Zealand.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
[1]Capital and Coast District Health Board, Wellington, New Zealand. [2]Medical Research Institute of New Zealand, Box 7902, Wellington, PO 6242, New Zealand. [3]Victoria University Wellington, Wellington, New Zealand. [4]Wellington School of Medicine & Health Sciences, University of Otago Wellington, Wellington, New Zealand.

References
1. M a A, 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.
2. Murphy R, Driscoll P, O'Driscoll R. Emergency oxygen therapy for the COPD patient. Emerg Med J. 2001;18:333–9.
3. Edwards L, Perrin K, Williams M, et al. Randomised controlled crossover trial of the effect on PtCO2 of oxygen-driven versus air-driven nebulisers in severe chronic obstructive pulmonary disease. Emerg Med J. 2012;29:894–8.
4. Gunawardena KA, Patel B, Campbell IA, et al. Oxygen as a driving gas for nebulisers: safe or dangerous? Br Med J (Clin Res Ed) 1984;288:272–4.
5. O'Donnell D, Kelly CP, Cotter P, Clancy L. Use of oxygen driven nebuliser delivery systems for beta-2 agonists in chronic bronchitis. Ir J Med Sci. 1985;154:198–200.
6. British Thoracic Society Emergency Oxygen Guideline Group. BTS guidelines for oxygen use in adults in healthcare and emergency settings. Br Thorac Soc. 2017;72:1–214.
7. Wijesinghe M, Williams M, Perrin K, et al. The effect of supplemental oxygen on hypercapnia in subjects with obesity-associated hypoventilation: a randomised, crossover, clinical study. Chest. 2011;139:1018–24.
8. Perrin K, Wijesinghe M, Healy B, et al. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. Thorax. 2011;66:937–41.
9. Rudolf M, Turner JA, Harrison BD, et al. Changes in arterial blood gases during and after a period of oxygen breathing in patients with chronic hypercapnic respiratory failure and in patients with asthma. Clin Sci. 1979;57:389–96.
10. Senn O, Clarenbach CF, Kaplan V, et al. Monitoring carbon dioxide tension and arterial oxygen saturation by a single earlobe sensor in patients with critical illness or sleep apnea. Chest. 2005;128:1291–6.
11. Rodriguez P, Lellouche F, Aboab J, et al. Transcutaneous arterial carbon dioxide pressure monitoring in critically ill adult patients. Intensive Care Med. 2006;32:309–12.
12. McVicar J, Eager R. Validation study of a transcutaneous carbon dioxide monitor in patients in the emergency department. Emerg Med J. 2009;26:344–6.
13. Aubier M, Murciano D, Milic-Emili J, et al. Effects of the administartion of O2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am Rev Resp Dis. 1980;122:747–54.
14. Robinson TD, Freiberg DB, Regnis JA, Young IH. The role of hypoventilation and ventilation-perfusion redistribution in oxygen-induced hypercapnia during acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;161:1524–9.
15. van Geffen WH, Douma WR, Siebos DJ, Kerstjens HA. Bronchodilators delivered by nebuliser versus pMDI with spacer or DPI for eaxcerbations of COPD. Cochrane Database Syst Rev 2016 (8): CD011826, Epub 2016 Aug 29.
16. Auerbach D, Hill C, Baughman R, et al. Routine nebulised ipratropium and albuterol together are better than either alone in COPD. Chest. 1997;112:1514–21.
17. Kane B, Turkington PM, Howard LS, et al. Rebound hypoxaemia after administration of oxygen in an acute exacerbation of chronic obstructive pulmonary disease. BMJ. 2011;342:d1557.
18. Bardsley G, McKinstry S, Pilcher J, et al. Oxygen compared to air driven nebulisers for acute exacerbations of COPD: a randomised controlled trial. ERJ. 2017;50:PA684.