Randomized controlled trial of high concentration oxygen in suspected community-acquired pneumonia

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DECLARATIONS

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None declared

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Summary

Objective To determine whether high concentration oxygen increases the $PaCO_2$ in the treatment of community-acquired pneumonia.

Design Randomized controlled clinical trial in which patients received high concentration oxygen (8 L/min via medium concentration mask) or titrated oxygen (to achieve oxygen saturations between 93 and 95%) for 60 minutes. Transcutaneous CO_2 ($PtCO_2$) was measured at 0, 20, 40 and 60 minutes.

Setting The Emergency Departments at Wellington, Hutt and Kenepuru Hospitals.

Participants 150 patients with suspected community-acquired pneumonia presenting to the Emergency Department. Patients with chronic obstructive pulmonary disease (COPD) or disorders associated with hypercapnic respiratory failure were excluded.

Main outcome variables The primary outcome variable was the proportion of patients with a rise in $PtCO_2$ ≥4 mmHg at 60 minutes. Secondary outcome variables included the proportion of patients with a rise in $PtCO_2$ ≥8 mmHg at 60 minutes.

Results The proportion of patients with a rise in $PtCO_2$ ≥4 mmHg at 60 minutes was greater in the high concentration oxygen group, 36/72 (50.0%) vs 11/75 (14.7%), relative risk (RR) 3.4 (95% CI 1.9 to 6.2), $P < 0.001$. The high concentration group had a greater proportion of patients with a rise in $PtCO_2$ ≥8 mmHg, 11/72 (15.3%) vs 2/75 (2.7%), RR 5.7 (95% CI 1.3 to 25.0), $P = 0.007$. Amongst the 74 patients with radiological confirmation of pneumonia, the high concentration group had a greater proportion with a rise in $PtCO_2$ ≥4 mmHg, 20/35 (57.1%) vs 5/39 (12.8%), RR 4.5 (95% CI 1.9 to 10.6) $P < 0.001$.

Conclusions We conclude that high concentration oxygen therapy increases the $PtCO_2$ in patients presenting with suspected community-acquired pneumonia. This suggests that the potential increase in $PaCO_2$ with high concentration oxygen therapy is not limited to COPD, but may also occur in other respiratory disorders with abnormal gas exchange.

recruited patients; Mark Weatherall undertook statistical analyses; All authors contributed to the design of the study and writing of the manuscript

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Reviewer

Julie Morris

Introduction

Community-acquired pneumonia is a common respiratory condition associated with significant morbidity and risk of mortality.[1] Patients presenting with suspected community-acquired pneumonia routinely receive oxygen therapy, however there are no randomized controlled trials of the benefits or risks of this approach. Hence, it is not known whether high concentration oxygen therapy in this setting might increase arterial CO_2 tension ($PaCO_2$) similar to the physiological response to such therapy in chronic obstructive pulmonary disease (COPD) exacerbations.[2,3] In support of this possibility, it has been demonstrated that in COPD the increase in $PaCO_2$ with oxygen therapy may result not only from suppression of the hypoxic respiratory drive, but also from the release of hypoxic pulmonary vasoconstriction.[4–7] This leads to worsening ventilation perfusion inequality, resulting in an increase in the physiological dead space and thus CO_2 retention. Furthermore, there is evidence that oxygen therapy may also result in an increase in $PaCO_2$ in severe asthma,[8–10] suggesting that this physiological response may be present in other acute respiratory conditions in which ventilation/perfusion abnormalities are present.

In this randomized controlled trial, we sought to investigate the effects of high concentration oxygen therapy on $PaCO_2$ in patients presenting to the Emergency Department (ED) with suspected community-acquired pneumonia. Comparison was made with oxygen therapy titrated as required to relieve hypoxaemia but avoid hyperoxaemia, with a target oxygen saturation of between 93 and 95%. The current study was designed to test the hypothesis that uncontrolled high concentration oxygen would result in an increase in the $PaCO_2$ compared with the titrated oxygen regime.

Methods

Subjects

Patients aged 18 to 75 years presenting to the Wellington (tertiary referral public), Kenepuru and Hutt (secondary referral public) Hospital EDs with suspected community-acquired pneumonia were enrolled in the study. Inclusion criteria were the presence of cough, a respiratory rate >18 breaths per minute, and at least one systemic feature of sweating, rigors or fever >37.8°C, representing the criteria for the clinical diagnosis of pneumonia. Patients with a diagnosis of COPD, or disorders associated with hypercapnic respiratory failure such as neuromuscular disease, or obesity hypoventilation syndrome were excluded from the study, due to the potential for confounding. Patients presenting with respiratory failure requiring mechanical ventilation, acute ECG changes suggesting ischaemia or suspected neutropenic sepsis were also excluded. The study was approved by the Central Regional Ethics Committee, and informed consent was obtained from each patient.

Study Design

On presentation, if oxygen saturations were >92% whilst breathing room air, patients remained off oxygen for 10 minutes, while eligibility for inclusion was assessed and informed consent obtained. If the oxygen saturations were ≤92% on presentation, patients received titrated oxygen to achieve an oxygen saturation of 93 to 95% for this 10 minute period. Patients were then randomly assigned using a computer-generated method, to one of two oxygen regimes for one hour. All patients in the high concentration oxygen group received 8 L/min via a medium concentration mask (Hudson RCI, Durham NC, USA) which delivers a FiO_2 of between 0.4 and 0.78.[11,12] Patients in the titrated group received oxygen only if their saturation was ≤92% on room air, with oxygen titrated as required at 5 minute intervals, to achieve an oxygen saturation of 93 to 95% according to the protocol outlined in the online supplement. A computerized randomization sequence was generated by the biostatistician (MWe) and the patients were enrolled and assigned to their treatment group by the clinical research fellows (MWi, KP, BH, KW, SB and RBo). Allocation concealment was achieved by using a secure database which contained the randomization sequence. Allocation was revealed to the researchers only when the subjects name was entered. The clinical research fellows and patients could not be blinded to the treatment regimes, due to the requirement to

titrate oxygen therapy in the control group. The administration of oxygen therapy prior to hospital attendance and randomization was not documented.

A full history was taken and each patient underwent a physical examination. Empirical antibiotics were administered in accordance with published guidelines,[1] and other therapies such as analgesia and intravenous fluids were administered at the discretion of the attending investigator. All patients underwent a chest radiograph.

Measures

Transcutaneous partial pressure of carbon dioxide ($PtCO_2$) was used to estimate arterial $PaCO_2$ using a combined oxygen saturation/$PtCO_2$ monitor (TOSCA, Radiometer, Basel, Switzerland). A sensor was attached via a low-pressure clip to the patient's earlobe and heated to 42°C to enhance blood flow and to 'arterialize' the underlying capillaries. Baseline measurements of $PtCO_2$ and oxygen saturation were recorded. Patients remained in a semi-recumbent position during the study protocol.

Measurements of $PtCO_2$, respiratory rate and heart rate were made at baseline (0 minutes) and at 20, 40 and 60 minutes. The oxygen saturation was measured continuously throughout the study period and recorded at 5 minute intervals.

Arterial blood gas (ABG) measurements were performed according to clinical need and were not part of the study protocol.

Statistical analysis

The pre-specified primary outcome variable was the proportion of patients with a $PtCO_2$ >38 mmHg at 60 minutes. However, after initial recruitment and clinical monitoring of patients, it was apparent that this outcome was inappropriate to determine if a physiologically relevant increase in $PtCO_2$ had occurred, as it was primarily determined by the presenting $PtCO_2$. For this reason, the primary outcome was changed to the proportion of patients with a $PtCO_2$ rise of ≥4 mmHg at 60 minutes and the proportion of patients with a $PtCO_2$ rise of ≥4 mmHg and a $PtCO_2$ ≥38 mmHg at 60 minutes was included as a secondary outcome variable. Other secondary outcome variables included the mean change from baseline $PtCO_2$, the mean change in respiratory rate and heart rate, and the need for hospital admission. The proportion of patients with a $PtCO_2$ rise of ≥8 mmHg was included as a *post-hoc* analysis. Whether the risk of a $PtCO_2$ rise of ≥4 mmHg at 60 minutes was influenced by the presence or absence of a pulmonary infiltrate on the chest radiograph consistent with pneumonia, was tested by an interaction term in a logistic regression model.

The rate of change of $PtCO_2$ was determined using a mixed linear model with random intercept and slope terms. Continuous outcome variables were analysed as change from baseline using independent sample *t*-tests or for achieved oxygen saturation, for which normality assumptions were not met, by a Mann-Whitney test. Analysis was by intention to treat. SAS version 9.1 and Minitab version 14 were used.

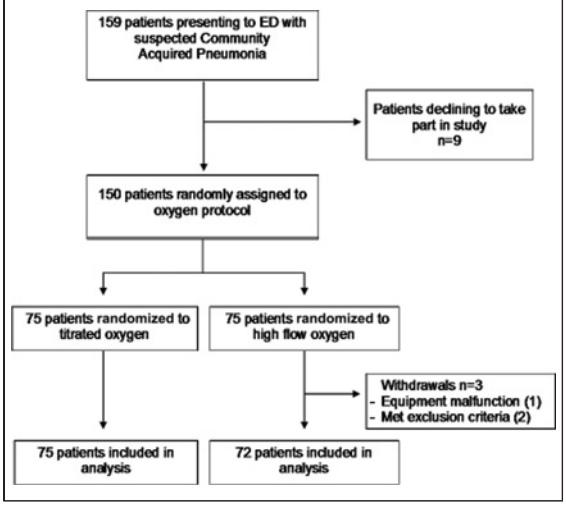
Based on previous research,[10] we calculated that to detect a difference in the main outcome variable of 20% in the high concentration oxygen group and 5% in the titrated group, with power of 80% at a type 1 error rate of 5%, 75 patients were required in each group.

Results

Patient Characteristics

Eligible patients were recruited from July 2007 to April 2009. Figure 1 shows the flow of the 150 patients through the study, with 75 randomized to high concentration oxygen and 75 randomized to titrated oxygen. Three patients were withdrawn from the high concentration oxygen group prior to the administration of oxygen due to the inability to obtain $PtCO_2$ recordings ($n = 1$) and two protocol violations which included the inadvertent enrolment of a patient with COPD and another with obesity hypoventilation syndrome. As a result, there were 72 and 75 patients included in the high concentration and titrated oxygen groups respectively. The two groups were similar in age, sex, respiratory rate, oxygen saturation, $PtCO_2$, CRB-65 score and radiological confirmation of pneumonia at baseline, as outlined in Table 1. In 74/146 (50.7%) patients (one patient refused a chest radiograph), there was radiological confirmation of pneumonia, with the

Figure 1
Flow of subjects through the study



presence of a pulmonary infiltrate on the chest radiograph.

There was a wide range of $PtCO_2$ levels at baseline ranging from 17 to 49 mmHg (Figure 2). Most (134/147) (91.2%) presented with an oxygen saturation >92% at baseline. In the titrated oxygen group, 68/75 (90.7%) patients did not require oxygen therapy throughout the 60 minute treatment period as their oxygen saturations remained >92%. In the titrated oxygen group, 6 of 75 (8%) patients required oxygen between 1 to 4 litres per minute via nasal prongs and 1 of 75 (1.4%) patient required >4 litres per minute via medium concentration mask to achieve oxygen saturations ≥93%. In the high concentration oxygen group, the oxygen saturation at 60 minutes was ≥99% in 65/72 (90.3%) of patients and was between 93 and 98% in the remaining 7/72 (9.7%) patients.

Changes in $PtCO_2$

The proportion of patients with an increase in $PtCO_2$ of ≥4 mmHg at 60 minutes was significantly greater in the high concentration group, compared with the titrated oxygen group, 36/72 (50.0%) vs 11/75 (14.7%) with a relative risk of 3.4 (95% CI 1.9 to 6.2; P < 0.001) (Table 2). The proportion of patients with a rise in $PtCO_2$ ≥4 mmHg was also greater in the high concentration group at the 20 and 40 minute time points (Table 3). In both groups the proportion of patients with a $PtCO_2$ ≥4 mmHg progressively increased throughout the 60 minute time course.

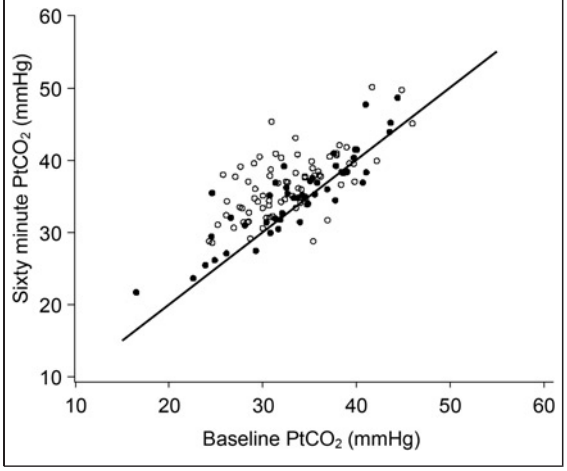
The change in $PtCO_2$ from baseline was significantly greater in the high concentration oxygen compared with the titrated oxygen group, with a mean difference of 2.7 mmHg (95% CI 1.5 to 3.9; $P < 0.001$) at 60 minutes (Table 3). The rate of increase in $PtCO_2$ in the high concentration

Table 1
Baseline characteristics of patients presenting with suspected community-acquired pneumonia, according to randomized oxygen treatment group

	High concentration n = 72	*Titrated n = 75*	*All n = 147*
Sex, male	32	28	60
Age, yr	45.2 (16.3)	46.4 (16.3)	45.8 (16.2)
Respiratory rate, breaths/min	24.2 (6.0)	24.6 (6.6)	24.4 (6.3)
Heart Rate, beats/min	90.5 (16.8)	88.1 (18.2)	89.3 (17.5)
SpO_2, %	96.3 (3.4)	96.2 (3.2)	96.2 (3.3)
$PtCO_2$, mmHg	32.7 (4.6)	33.6 (5.9)	33.1 (5.3)
$PtCO_2$ ≥38 mmHg	11/72 (15.3)	18/75 (24.0)	29/147 (19.7)
CRB-65 Score ≥2	7 (9.7)	7 (9.3)	14 (9.3)
Confirmed pneumonia	35/72 (48.6)	39/75 (52.0)	74/147 (50.3)

Values are mean (SD) for age, respiratory rate, heart rate, SpO_2 and $PtCO_2$, number of participants (percentage) for sex, confirmed pneumonia, $PtCO_2$ ≥38 mmHg and CRB-65 score ≥2.
SpO_2: Oxygen saturation; $PtCO_2$: Transcutaneous carbon dioxide; $PtCO_2$: ≥38 mmHg at baseline; CRB-65 Score: Pneumonia severity score (see text); Confirmed pneumonia: Presence of pulmonary infiltrate on chest radiograph.

Figure 2
The $PtCO_2$ levels at baseline and after 60 minutes in the high concentration (o) and titrated (•) oxygen groups



group was 0.058 (95% CI 0.044 to 0.072) mmHg/min and in the titrated group was 0.017 (95% CI 0.0031 to 0.031) mmHg/min. The difference in the rate of change was 0.041 (95% CI 0.022 to 0.06, $P < 0.001$) mmHg/min.

The proportion of patients with a rise in $PtCO_2$ ≥4 mmHg and a final $PtCO_2$ ≥38 mmHg was significantly greater in the high concentration group with a relative risk of 2.7 (95% CI 1.2 to 6.0, $P = 0.01$). The proportion of patients with a rise in $PtCO_2$ ≥8 mmHg was significantly greater in the high concentration group with a relative risk of 5.7 (95% CI 1.3 to 25.0, $P = 0.007$).

In patients with radiological confirmation of pneumonia, the high concentration oxygen group had a higher proportion with a rise in $PtCO_2$ ≥4 mmHg (20/35 (57.1%) vs 5/39 (12.8%), relative risk 4.5 (95% CI 1.9 to 10.6), compared to those without consolidation 16/37 (43.2%) vs 6/36 (16.7%), relative risk 2.6 (95% CI 1.1 to 5.9), however, this interaction was not statistically significant, $P = 0.28$.

Arterial Blood Gases

ABGs were performed in 12 (8%) patients according to clinical need. The mean (SD) $PaCO_2$ – $PtCO_2$ difference was −0.9 (1.6) mmHg with limits of agreement of plus or minus 3.2 mmHg (−4.1 to +2.3).

Clinical variables

There was no significant difference in the change in respiratory rate (−2.9 vs −2.5 breaths per minute, high concentration vs titrated oxygen groups respectively, $P = 0.63$). The reduction in heart rate was greater in the high concentration compared to the titrated oxygen group (−6.8 vs −2.6 beats per minute, mean difference −4.2, 95% CI −7.3 to −1.2, $P = 0.007$). There were similar rates of hospital admission between the two treatment groups, 36/72 (50%) vs 37/75 (49.3%) for high concentration versus titrated oxygen respectively, relative risk 1.01 (95% CI 0.74 to 1.39, $P = 0.94$). One patient in the titrated group required admission to the intensive care unit.

Discussion

This randomized controlled trial has shown that high concentration oxygen therapy results in a significant increase in $PtCO_2$ when administered to patients presenting to an emergency department with suspected community-acquired pneumonia. The three- and six-fold relative risks of an increase in $PtCO_2$ of at least 4 mmHg and at least 8 mmHg respectively, suggests that this effect may

Table 2
The proportion of patients with a predetermined rise in $PtCO_2$ from baseline at 60 minutes

	High concentration n (%)	*Titrated n (%)*	*Relative risk (95% CI)*	*P value*
Change in $PtCO_2$ ≥4 mmHg	36 (50%)	11 (14.7%)	3.4 (1.9 to 6.2)	<0.001
Change in $PtCO_2$ ≥4 mmHg and $PtCO_2$ ≥38 mmHg	19 (26.4%)	5 (6.7%)	2.7 (1.2 to 6.0)	0.01
Change in $PtCO_2$ ≥8 mmHg	11 (15.3%)	2 (2.7%)	5.7 (1.3 to 25.0)	0.007

Table 3
The time course of the changes in $PtCO_2$ in the treatment groups

(i) *The proportion of patients with a rise in $PtCO_2$ ≥4 mmHg*

Time	*High concentration n (%)*	*Titrated n (%)*	*Relative risk (95% CI)*	*P value*
20 minutes	19 (26.4%)	4 (5.3%)	5.0 (1.8 to 13.8)	<0.001
40 minutes	27 (37.5%)	8 (10.7%)	3.5 (1.7 to 7.2)	<0.001
60 minutes	36 (50.0%)	11 (14.7%)	3.4 (1.9 to 6.2)	<0.001

(ii) *The mean change in $PtCO_2$ (mmHg)*

Time	*High concentration mean (SD)*	*Titrated mean (SD)*	*Difference (95% CI)*	*P value*
20 minutes	1.9 (3.4)	−0.2 (2.7)	2.1 (1.1 to 3.1)	<0.001
40 minutes	2.9 (3.7)	0.5 (3.6)	2.4 (1.2 to 3.6)	<0.001
60 minutes	3.6 (3.9)	0.9 (3.7)	2.7 (1.5 to 3.9)	<0.001

potentially be of both physiological and clinical significance.

There are a number of methodological issues relevant to the interpretation of the study findings. The first is that we used a TOSCA transcutaneous CO_2 monitor to measure $PaCO_2$ rather than the 'gold standard' ABG test. This method was chosen as it allowed continuous $PtCO_2$ monitoring without the discomfort of arterial blood gas sampling or the risk of hand ischemia associated with indwelling radial artery cannulae. The TOSCA has been shown to be an accurate means of estimating both $PaCO_2$ and oxygen saturations from a single probe in healthy subjects,[13,14] in COPD[15] and in critically ill patients.[16] This was confirmed in our subset of patients who had simultaneous ABG and $PtCO_2$ recordings. The $PtCO_2$ device accurately assessed $PaCO_2$ without significant bias and with clinically acceptable limits of agreement when compared to the ABG measurement, thus validating our methodology.

By necessity the study was unblinded, as there was a clinical requirement for the investigator to have knowledge of the oxygen saturations in order to titrate the oxygen therapy in the 'control' treatment group, and an ethical requirement for the investigator to monitor the patient's progress with knowledge of the oxygen administered.

The decision to administer oxygen for 60 minutes was based on the evidence that CO_2 retention in COPD[4–7] and asthma[8–10,17] may occur within this period. However, further increases in $PaCO_2$ may occur beyond this time period and, as a result, the magnitude of the risk of an increased $PtCO_2$ with high concentration oxygen therapy may have been underestimated in our study. This was suggested by our observation that the difference in $PtCO_2$ between the high concentration and titrated oxygen groups progressively increased throughout the 60 minute period. This is clinically relevant as relief of dyspnoea in pneumonia can take many days and oxygen therapy may be continued until the dyspnoea resolves. Previous studies suggest that in some patients a progressive increase in $PaCO_2$ occurs with more prolonged exposure to oxygen therapy.[18,19]

Our pre-specified analysis plan was to use the proportion of subjects with a $PtCO_2$ >38 mmHg at 60 minutes as the primary outcome variable. However, in the early phase of recruitment it was apparent that the pre-specified primary outcome variable did not reflect a physiological increase in $PtCO_2$, as it was primarily determined by the presenting $PtCO_2$, and for this reason we registered a change in the primary outcome variable to the proportion of subjects with a $PtCO_2$ rise of ≥4 mmHg. We acknowledge that changing the primary outcome variable after the start of the study raises the possibility of creating a biased assessment of the outcome of the trial. However, no formal interim statistical analysis, of either the pre-specified outcome variable or the new main outcome variable, was carried out prior to this decision and although the study itself was not masked as to treatment allocation, the decision was made without

reference to the randomized allocation of the research participants.

Patients were excluded if they had a diagnosis of COPD due to the known effect of high concentration oxygen in exacerbations of this disorder.[2] We are confident that patients with established COPD were not included in this study based on their history. We also had immediate access to electronic medical records which document any previous hospital admission, out-patients consultations and spirometry where available, allowing further investigation of a diagnosis of COPD. However, given that we did not perform spirometry on enrolment or prior to discharge, patients with a new diagnosis of airway obstruction may have been included in the study. In clinical practice, when patients present with symptoms to suggest pneumonia, spirometry is rarely available at the first point of oxygen therapy which is usually in the ambulance or ED, thus our study replicates what happens in clinical practice. Indeed, it is likely that greater increases in $PtCO_2$ may occur in an unselected population of patients with community-acquired pneumonia, which is more likely to include those with concomitant COPD or other disorders associated with chronic respiratory failure.

Patients presenting with suspected (rather than confirmed) community-acquired pneumonia were enrolled in the study, as oxygen therapy is usually administered to breathless patients presenting with suspected pneumonia rather than after the diagnosis is confirmed by chest radiography. About half of the patients had pneumonia subsequently confirmed by the presence of consolidation on the chest radiograph. Most of the other patients were likely to have had lower respiratory tract infections, and radiological confirmation of pneumonia would have been possible in a proportion if high-resolution computed tomography had been undertaken.[20,21] This may explain why the presence of radiologically confirmed pneumonia made no significant difference to the risk of a raised $PtCO_2$ with high concentration oxygen therapy. When the analysis was restricted to subjects with radiologically confirmed pneumonia, there was a 4.5-fold increased risk of a rise in $PtCO_2$ $\geq$4 mmHg with high concentration oxygen therapy.

In the absence of a clear view on what represents a 'physiologically' or 'clinically' significant increase in $PtCO_2$ we chose specific levels of $PtCO_2$ increases from baseline. The primary outcome variable was a rise of $\geq$4 mm Hg which was considered to represent an effect of physiological significance given that it is a higher rise that would be expected from the Haldane effect alone.[22] In addition, a change in $PtCO_2$ of $\geq$ 4mmHg is higher than the limits of agreement demonstrated in our published validation study of the $PtCO_2$ device (−3.9 mmHg to +3.7 mmHg)[23] meaning it is likely to represent a true increase. The secondary outcome variable of a rise in $PtCO_2$ of $\geq$8 mmHg was considered to represent an effect of potential clinical significance. The study was not powered to investigate differences in clinical outcomes, in particular the adverse effects of hypercapnia or hyperoxaemia. This issue needs to be addressed in a large study of an unselected group presenting with severe community-acquired pneumonia.

Both treatment groups were hypocapnic on presentation indicating a degree of hyperventilation. Over the course of the 60 minutes, there was a modest reduction in respiratory rate of <3 breaths per minute, with no significant difference between the two groups. This suggests that the greater increase in $PtCO_2$ in the high flow group could not be attributed to differential effects on minute ventilation. High flow oxygen resulted in a reduction in heart rate, which is a well recognised cardiovascular response to oxygen therapy.[24] We consider that this effect is not a marker of clinical benefit, as it is associated with a reduction in cardiac output, increase in blood pressure, and reduction in coronary artery blood flow.[24,25]

In pneumonia, hypoxaemia is primarily due to intrapulmonary shunting and ventilation-perfusion inequalities.[26–29] Treatment with high concentration oxygen in pneumonia has minimal effect on intrapulmonary shunting, however it has the potential to significantly worsen ventilation-perfusion mismatch through release of hypoxic pulmonary vasoconstriction. This could potentially lead to an increase in the physiological dead space and is likely to represent the predominant mechanism responsible for the increase in $PtCO_2$ observed. Importantly, these data suggest that high concentration oxygen therapy may have the potential to cause an increase in $PaCO_2$ across a wide range of

respiratory conditions with abnormal gas exchange. Indeed, this physiological response to high concentration oxygen therapy has now been reported in stable COPD,[5,7] exacerbations of COPD,[2–4,6] asthma,[8–10,17] obesity hypoventilation syndrome,[30,31] and diffuse pulmonary fibrosis or infiltration.[32]

We conclude that high concentration oxygen increases the $PtCO_2$ in patients with community acquired pneumonia. This suggests that the potential increase in $PaCO_2$ with high concentration oxygen therapy is not limited to COPD, but may also occur in other respiratory disorders with abnormal gas exchange.

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