ORIGINAL ARTICLE

Moderate concentrations of supplemental oxygen worsen hypercapnia in obesity hypoventilation syndrome: a randomised crossover study

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ABSTRACT

Introduction In people with obesity hypoventilation syndrome (OHS), breathing 100% oxygen increases carbon dioxide (PCO2), but its effect on pH is unknown. This study investigated the effects of moderate concentrations of supplemental oxygen on PCO2, pH, minute ventilation (V̇E) and physiological dead space to tidal volume ratio (VD/VT) among people with stable untreated OHS, with comparison to healthy controls.

Methods In a double-blind randomised crossover study, participants breathed oxygen concentrations (FiO2) 0.28 and 0.50, each for 20 min, separated by a 45 min washout period. Arterialised-venous PCO2 (PavCO2) and pH, V̇E and VD/VT were measured at baseline, then every 5 min. Data were analysed using general linear model analysis.

Results 28 participants were recruited (14 OHS, 14 controls). Among OHS participants (mean±SD arterial PCO2 6.7±0.5 kPa; arterial oxygen 8.9±1.4 kPa) FiO2 0.28 and 0.50 maintained oxygen saturation 98–100%. After 20 min of FiO2 0.28, PavCO2 change (ΔPavCO2) was 0.3±0.2 kPa (p=0.013), with minimal change in V̇E and rises in VD/VT of 1±5% (p=0.012). FiO2 0.50 increased PavCO2 by 0.5±0.4 kPa (p=0.012), induced acidaemia and increased VD/VT by 3±3% (p=0.012). V̇E fell by 1.2±2.1 L/min within 5 min then recovered individually to varying degrees. A negative correlation between ΔV̇E and ΔPavCO2 (r=−0.60, p=0.024) suggested that ventilatory responses were the key determinant of PavCO2 rises. Among controls, FiO2 0.28 and 0.50 did not change PavCO2 or pH, but FiO2 0.50 significantly increased V̇E and VD/VT.

Conclusion Commonly used oxygen concentrations caused hypoventilation, PavCO2 rises and acidemia among people with stable OHS. This highlights the potential dangers of this common intervention in this group.

INTRODUCTION

In obesity hypoventilation syndrome (OHS), chronic hypercapnia develops as a consequence of obesity. This condition is associated with alveolar hyperventilation, restricted pulmonary function, severe sleep-disordered breathing and higher rates of morbidity, mortality and healthcare costs compared with eucapnic obesity.1–4 OHS affects approximately 0.15–0.3% of the US population5 and over 50% of hospital inpatients with body mass index (BMI)>50 kg/m2.1 Despite this, OHS frequently goes undiagnosed among hospital inpatients with obesity.1 Supplemental oxygen is a common medical intervention6 and may be administered to patients with OHS in a range of healthcare settings. British Thoracic Society guidelines on emergency oxygen prescription identify patients with OHS as a group among whom excessive concentrations of supplemental oxygen, causing hyperoxia, could increase carbon dioxide (CO2) levels and lower pH.6 The basis of the guidelines relies upon expert opinion and data from COPD, because very few studies have investigated the effects of supplemental oxygen in OHS. Among patients with obesity and elevated transcutaneous CO2 pressure (PCO2), breathing 100% oxygen induced an average rise in transcutaneous PCO2 of 0.7 kPa (with rises of >1.3 kPa in three patients).7 However, the effect of oxygen on pH, an important prognostic indicator,2–8–9 was not reported. Furthermore, 100% oxygen is rarely used in clinical practice.2–8 Hence, the clinical relevance of these data is uncertain.

During acute exacerbations of COPD, hyperoxia arising from supplemental oxygen worsens hypercapnia and pH, and has been linked to more


Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2013-204389).

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Received 19 August 2013
Revised 24 October 2013
Accepted 31 October 2013
Published Online First 19 November 2013

What is the key question?
▸ What are the effects of moderate concentrations of supplemental oxygen on CO2, pH, ventilation and physiological dead space to tidal volume ratio (VD/VT) in people with obesity hypoventilation syndrome (OHS)?

What is the bottom line?
▸ In OHS, breathing moderate concentration supplemental oxygen for 20 min worsened hypercapnia and induced acidaemia due to hypoventilation and a worsening of VD/VT.

Why read on?
▸ This is the first study to evaluate the effects of moderate concentration supplemental oxygen on blood gases and respiratory variables in OHS and highlights the potential risks of this common intervention among this unique population.
frequent admission to intensive care and increased hospital length of stay and mortality.\textsuperscript{9-11} Hyperoxia-induced hypercapnia in COPD has been attributed to increased ventilation/perfusion (V/Q) inequality, mediated by the reversal of hypoxic vasoconstriction\textsuperscript{12-14}; however recent evidence suggests that hypventilation may be a quantitatively more important mechanism.\textsuperscript{15 16}

Whether or not these mechanisms apply to OHS, which has a vastly different pathophysiology to COPD, has yet to be determined.

The aims of the present study were to document the time course of changes in PCO\textsubscript{2}, pH and respiratory variables in response to clinically relevant, moderate concentrations of supplemental oxygen among people with OHS in comparison to a healthy control group; and to examine physiological mechanisms that may explain any oxygen-induced changes in PCO\textsubscript{2}.

**METHODS**

Written informed consent was obtained from all participants. The study was approved by the Ethics Committees of Royal Prince Alfred Hospital (protocol no. X12-0067 and HREC/12/RPAH/109) and the University of Sydney (Ref. 14935) and registered on the Australian and New Zealand Clinical Trials Registry (ACTRN1260800172303).

**Participants**

Patients referred to the Sleep Unit, Royal Prince Alfred Hospital with obesity and possible hypercapnia were screened for eligibility. Inclusion criteria were the combination of obesity (BMI \geq 30 kg/m\textsuperscript{2}) and daytime hypercapnia (arterial PCO\textsubscript{2} (PaCO\textsubscript{2}) > 6 kPa). Patients were excluded in the case of any other potential cause of hypercapnia, current use of positive airway pressure, acute respiratory/cardiac illness within the previous month, acidemia or psychiatric illness. A control group was recruited concurrently from a sample of convenience. Each control participant was age (\pm 3 years) and gender matched with an OHS participant, non-smoking, with BMI < 30 kg/m\textsuperscript{2}, normal spirometry and no history of cardiorespiratory disease.

**Study design and protocol**

Using a double-blind randomised crossover design (figure 1), each participant breathed two fractions of inspired oxygen (FiO\textsubscript{2} 0.28 and 0.50 in random order (sequence 1 or 2), via a breathing circuit, after a circuit acclimatisation period. Each test began with a 10 min period of breathing room air via the circuit (baseline), followed by a 20 min period of supplemental oxygen (FiO\textsubscript{2} 0.28 or 0.50), and then a 10 min period of breathing room air (recovery). A 45 min washout period separated the two supplemental oxygen tests.

Randomisation of sequence was generated using an online randomisation programme (http://www.randomization.com), with allocation concealed via sealed opaque envelopes. The chief investigator and participants remained blinded throughout. An unblinded coinvestigator operated equipment and instructed participants. Testing began between 8:30am and 10:00am. All participants had fasted and abstained from caffeine from midnight.

**Instrumentation**

The closed breathing circuit comprised a dry rolling-seal spirometer, a bias-flow generator, a soda-lime CO\textsubscript{2} absorber and a T-connector at the participant interface. Gas was continuously sampled at the interface using oxygen/CO\textsubscript{2} sensors. A stable FiO\textsubscript{2} was maintained through titration of bottled air and oxygen using continuous real-time feedback from the oxygen sensor. Immediately after each FiO\textsubscript{2} change, the circuit was flushed to allow stabilisation at the new FiO\textsubscript{2} within 2 min. Participants breathed through the circuit via a nasal mask (dead space 175 mL) with the mouth closed (n=25), or in the case of nasal obstruction, via a mouthpiece (dead space 100 mL) with a nose peg (n=3).

**Outcome measures**

On the day of testing, baseline measures of height, weight, spirometry and arterial blood gases (ABGs) were performed. Arterialised-venous blood was repeatedly sampled to obtain surrogate measures of arterial PCO\textsubscript{2} (PavCO\textsubscript{2}) and pH. We previously described and validated this method in OHS.\textsuperscript{17} An oximeter continuously measured pulse oxygen saturation (SpO\textsubscript{2}) (Radical, Masimo, Irvine, California, USA). Signals from the oxygen/CO\textsubscript{2} sensors and spirometer were recorded by a computer programme and used to derive and/or display breath-by-breath minute ventilation (V\textsubscript{E}), tidal volume (V\textsubscript{T}) and respiratory rate (RR). Breath-by-breath physiological dead space (V\textsubscript{D}phys) was calculated using a CO\textsubscript{2} expirgram method\textsuperscript{18} and adjusted by subtracting apparatus dead space, then divided by V\textsubscript{T} to obtain V\textsubscript{D}phys to V\textsubscript{T} ratio (V\textsubscript{D}phys/V\textsubscript{T}). Data affected by leak or artefact were systematically excluded. Subsequently, breath-by-breath data were averaged over 60 s.

For final analysis, data obtained during the following periods were included: the final minute of the 10 min baseline, the final minute of each 5 min epoch of supplemental oxygen, and the final minute of the 10 min recovery. Arterialised-venous blood samples were drawn within the last 10 s of each of these periods.

**Statistical analysis**

Data are presented as mean\pm SD or median (IQR), and mean difference (MD) and 95% CI for between-group comparisons. A significance level of p<0.05 was used for all comparisons. Between-group MDs in baseline variables were compared using
independent t-tests. General linear model (univariate, repeated measures) analysis compared responses to supplemental oxygen between participant groups (factor: group; factor interaction: time-by-group) for primary (PavCO2) and secondary (pH, VE and VD/VT) outcomes; between baseline and supplemental oxygen (factor: time) for primary, secondary and tertiary (VT, RR, VDPhys) outcomes; and between the two oxygen concentrations (factor: concentration) for PavCO2. For non-parametric data, the Friedman test was used to evaluate effects of time. To account for multiple comparisons the level of significance was adjusted (adj.p) using Holm’s Bonferroni procedure.19 Within the OHS group only, Pearson’s correlation coefficient was calculated to examine potential factors associated with the change in PavCO2 after 20 min (ΔPavCO2) of FIO2 0.50, including baseline PaCO2, bicarbonate (HCO3−) and arterial oxygen saturation (SaO2), ΔVt, and ΔVD/Vt. The study was powered to detect a ΔPavCO2 of 0.4 kPa16 from baseline during supplemental oxygen within the OHS group, with an SD estimate of 0.45 kPa (using data from the first five OHS participants), power of 0.8, α of 0.05. A sample of 14 OHS participants (hence 14 matched controls) was required. Data were analysed using PASW 18 (IBM, Armonk, New York, USA).

RESULTS
Fourteen participants with OHS and 14 controls were recruited between August 2008 and February 2012 (figure 2). Baseline characteristics (table 1) show that groups were well matched for age and gender. Participants with OHS presented with super-obesity, mild hypercapnia and hypoxaemia, and mild pulmonary restriction.

Table 1 Participant characteristics, baseline arterial blood gases and spirometry

<table>
<thead>
<tr>
<th>OHS</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48±12</td>
<td>48±12</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>3/11</td>
<td>3/11</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>53±7</td>
<td>25±4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>154±21</td>
<td>73±15</td>
</tr>
<tr>
<td>pH</td>
<td>7.395±0.030</td>
<td>7.414±0.019*</td>
</tr>
<tr>
<td>PaCO2 (kPa)</td>
<td>6.76±0.5</td>
<td>5.5±0.4*</td>
</tr>
<tr>
<td>PaO2 (kPa)</td>
<td>8.9±1.4</td>
<td>14.3±1.1*</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>92±3</td>
<td>98±1*</td>
</tr>
<tr>
<td>HCO3− (mmol/L)</td>
<td>30.3±1.7</td>
<td>25.8±1.2*</td>
</tr>
<tr>
<td>a-ADO2 (kPa)</td>
<td>3.6±1.4</td>
<td>0.9±1.2*</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>15±20</td>
<td>14±11</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>2.39±0.72</td>
<td>3.71±0.71</td>
</tr>
<tr>
<td>FEV1% predicted</td>
<td>73±14</td>
<td>106±11</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.03±0.85</td>
<td>4.54±0.77</td>
</tr>
<tr>
<td>FVC% predicted</td>
<td>77±14</td>
<td>107±13</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>79±6</td>
<td>82±5</td>
</tr>
</tbody>
</table>

Data presented as mean±SD; p value represents two-tailed significance from independent t tests comparing control and OHS groups.

*Data reported from n=13, as arterial blood gas could not be performed in one control participant.

A-aDO2, alveolar-arterial oxygen difference; BMI, body mass index; FEV1, forced expired volume in 1 s; FVC, forced vital capacity; HCO3−, bicarbonate; OHS, obesity hypoventilation syndrome; PaCO2, arterial partial pressure of CO2; PaO2, arterial partial pressure of O2.
**Table 2** Physiological variables at baseline and at the end of FiO₂ 0.28 and FiO₂ 0.50 tests

<table>
<thead>
<tr>
<th></th>
<th>Room air baseline</th>
<th>20 min</th>
<th>Adj. p value</th>
<th>Room air baseline</th>
<th>20 min</th>
<th>Adj. p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OHS group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>94±3</td>
<td>99±1</td>
<td>-</td>
<td>94±3</td>
<td>100±0</td>
<td>-</td>
</tr>
<tr>
<td>PacCO₂ (kPa)</td>
<td>7.1±0.6</td>
<td>7.4±0.6</td>
<td>0.013</td>
<td>7.2±0.6</td>
<td>7.7±1.0</td>
<td>0.012</td>
</tr>
<tr>
<td>pH</td>
<td>7.37±0.019</td>
<td>7.359±0.027</td>
<td>0.406*</td>
<td>7.37±0.021</td>
<td>7.346±0.030</td>
<td>0.011</td>
</tr>
<tr>
<td>VE (L/min)</td>
<td>9.9±2.3</td>
<td>9.9±2.8</td>
<td>0.997</td>
<td>9.6±2.1</td>
<td>9.3±2.9</td>
<td>0.224*</td>
</tr>
<tr>
<td>Vd/VT (ratio)</td>
<td>0.28±0.05</td>
<td>0.29±0.03</td>
<td>0.012</td>
<td>0.29±0.05</td>
<td>0.32±0.05</td>
<td>0.012</td>
</tr>
<tr>
<td>Vdphys (mL)</td>
<td>200±55</td>
<td>196±26</td>
<td>&gt;0.999</td>
<td>194±56</td>
<td>192±37</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>VT (mL)</td>
<td>633±149</td>
<td>597±129</td>
<td>0.012</td>
<td>578±105</td>
<td>489±107</td>
<td>0.012</td>
</tr>
<tr>
<td>RR (br/min)</td>
<td>17.5±5.2</td>
<td>18.2±4.7</td>
<td>&gt;0.999</td>
<td>18.1±4.9</td>
<td>18.1±4.2</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>98±1</td>
<td>100±1</td>
<td>-</td>
<td>98±1</td>
<td>100±0</td>
<td>-</td>
</tr>
<tr>
<td>PacCO₂ (kPa)</td>
<td>5.5±0.4</td>
<td>5.6±0.2</td>
<td>0.726</td>
<td>5.4±0.3</td>
<td>5.4±0.4</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>pH</td>
<td>7.408±0.023</td>
<td>7.397±0.010</td>
<td>&gt;0.999</td>
<td>7.407±0.020</td>
<td>7.407±0.023</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>VE (L/min)</td>
<td>7.5±1.6</td>
<td>7.5±1.7</td>
<td>&gt;0.999</td>
<td>7.6±1.8</td>
<td>8.6±1.9</td>
<td>0.019</td>
</tr>
<tr>
<td>Vd/VT (ratio)</td>
<td>0.27±0.05</td>
<td>0.29±0.04</td>
<td>0.012</td>
<td>0.28±0.04</td>
<td>0.32±0.04</td>
<td>0.012</td>
</tr>
<tr>
<td>Vdphys (mL)</td>
<td>232±79</td>
<td>237±53</td>
<td>0.085*</td>
<td>244±123</td>
<td>263±97</td>
<td>0.085*</td>
</tr>
<tr>
<td>VT (mL)</td>
<td>813 (353)</td>
<td>754 (356)</td>
<td>&gt;0.999</td>
<td>751 (285)</td>
<td>751 (264)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>RR (br/min)</td>
<td>10.3±4.2</td>
<td>10.5±4.5</td>
<td>0.195*</td>
<td>10.6±3.7</td>
<td>11.8±3.6</td>
<td>0.195*</td>
</tr>
</tbody>
</table>

Data presented as mean±SD or median (IQR). Adj. p value: significance level from general linear model analysis, change over time (ie room air vs oxygen) after Holm’s Bonferroni correction (refer to table E1, online supplement for full details).

*Raw p value significant but adj. p value=non-significant.

FiO₂, inspired oxygen fraction; PacCO₂, arterialised-venous carbon dioxide; RR, respiratory rate; SpO₂, pulse oxygen saturation; Vd/VT, physiological dead space to tidal volume ratio; Vdphys, physiological dead space; VE, minute ventilation; VT, tidal volume.

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**Figure 3** Time course of changes in PacCO₂, VE and Vd/VT during air/oxygen breathing tests for OHS group (open circles) and control group (closed circles), with results of general linear model analysis of between-group differences (factor: group, and group by time). *Adjusted p value=0.01; FiO₂, inspired oxygen fraction; NS, non-significant; OHS, obesity hypoventilation syndrome; PacCO₂, arterialised-venous CO₂; VE, minute ventilation; Vd/VT, dead space to tidal volume ratio.
There was a positive correlation between \( \Delta P_{\text{avCO}_2} \) (FiO\(_2\) 0.50) and PaCO\(_2\) (\(r=0.60, p=0.023\)) and HCO\(_3^-\) (\(r=0.58, p=0.030\)), but not SaO\(_2\) (\(r=-0.48, p=0.08\)). Furthermore, a negative correlation between \( \Delta P_{\text{avCO}_2} \) and \( \Delta V_E \) was found (\(r=-0.60, p=0.024\)), but not \( \Delta V_{D/V_T} \) (\(r=0.42, p=0.18\)).

There was no significant change in \( V_E \) when breathing FiO\(_2\) 0.28 (table 2). In contrast, during FiO\(_2\) 0.50 a consistent fall in \( V_E \) of 1.2±2.1 L/min (12±22%) below baseline occurred within 5 min (figure 3). Thereafter, a varying recovery in \( V_E \) was observed (figure 4C), such that after 20 min \( V_E \) remained below baseline in six participants, returned to baseline in four participants and exceeded baseline \( V_E \) by >5% in four participants. After 20 min, group mean \( V_E \) was 3±20% below baseline, which became non-significant after adjustment (raw \(p=0.014\), adj.\(p=0.224\)). Decreases in \( V_E \) were attributable to significant falls in \( V_E \) as RR was unchanged.

During FiO\(_2\) 0.28 and 0.50, \( V_{D/V_T} \) increased by 1±5% and 3±3%, respectively (adj.\(p=0.012\)), in the absence of significant changes in \( V_{D/phys} \).

**Control group: responses to supplemental oxygen**

Among the controls, there were no significant changes in PaCO\(_2\) or pH during either FiO\(_2\) (table 2, figure 3), and no significant differences for PaCO\(_2\) between concentrations. During FiO\(_2\) 0.28 there were no significant changes in \( V_E, V_T \) or RR. However, breathing FiO\(_2\) 0.50 increased \( V_E \) by 15±11% after 20 min (adj.\(p=0.019\)), due to a slight, non-significant increase in RR (raw \(p=0.01\), adj.\(p=0.170\)).

Significant increases in \( V_{D/V_T} \) of 1±3% and 4±3% were observed during FiO\(_2\) 0.28 and 0.50 respectively (adj.\(p=0.012\)). This was accompanied by small rises in \( V_{D/phys} \) which became non-significant after adjustment (raw \(p<0.001\), adj.\(p=0.085\)).

### Table 3 Between-group comparisons of responses to supplemental oxygen

<table>
<thead>
<tr>
<th></th>
<th>MD (Δ at 20 min)*</th>
<th>95% CI</th>
<th>Raw p value</th>
<th>Adj. p value</th>
<th>Raw p value</th>
<th>Adj. p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PavCO(_2) (kPa)</td>
<td>0.31</td>
<td>0.13 to 0.49</td>
<td>&lt;0.001</td>
<td>0.010</td>
<td>&lt;0.001</td>
<td>0.014</td>
</tr>
<tr>
<td>pH</td>
<td>−0.014</td>
<td>−0.023 to −0.005</td>
<td>0.045</td>
<td>0.585</td>
<td>0.051</td>
<td>0.612</td>
</tr>
<tr>
<td>(V_E) (L/min)</td>
<td>−0.8</td>
<td>−1.3 to −0.38</td>
<td>0.085</td>
<td>0.850</td>
<td>0.128</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>(V_E/V_T) (ratio)</td>
<td>0.01</td>
<td>−0.03 to 0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adj. p value: significance level from general linear model analysis, OHS versus controls, after Holm’s Bonferroni correction.

*MD: mean difference (OHS-control) for \( \Delta \) values at 20 min.

OHS, obesity hypoventilation syndrome; PavCO\(_2\), arterIALIZED-venous carbon dioxide; \(V_{D/V_T}\), physiological dead space to tidal volume ratio; \(V_{D/phys}\), physiological dead space; \(V_E\), minute ventilation.

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**Figure 4** Individual and group responses to supplemental oxygen concentration (FiO\(_2\)) 0.28 and 0.50 for OHS group (A and C) and control group (A and D), showing change in arterIALIZED-venous carbon dioxide from room air baseline (\(\Delta P_{\text{avCO}_2}\)) (A and B), and change in minute ventilation from room air baseline (\(\Delta V_E\)) (C and D). Each figure includes individual changes at 20 min for FiO\(_2\) 0.28 and group mean±SD on the left, and individual changes at 20 min for FiO\(_2\) 0.50 and group mean±SD on the right. OHS, obesity hypoventilation syndrome.
DISCUSSION
To our knowledge, this is the first study to investigate the effects of clinically relevant, moderate concentrations of supplemental oxygen on PCO2 and pH, VD/VT and VE and its determinants among people with OHS. In OHS, hyperoxia induced by breathing F\textsubscript{O2} 0.28 and F\textsubscript{O2} 0.50 caused significant rises in PavCO\textsubscript{2}. Accordingly, pH decreased, resulting in acidemia during F\textsubscript{O2} 0.50. Breathing F\textsubscript{O2} 0.50 was accompanied by hypoventilation and increases in V\textsubscript{D}/V\textsubscript{T}. However, changes in V\textsubscript{E} were the key determinant of PavCO\textsubscript{2} rises. Breathing F\textsubscript{O2} 0.50 also increased V\textsubscript{D}/V\textsubscript{T} in the control group, but controls maintained a stable PavCO\textsubscript{2} and pH through a 15\% increase in V\textsubscript{E}. The findings of the present study bring into question the safety of moderate concentrations of supplemental oxygen among patients with untreated OHS and provide evidence to substantiate current clinical guidelines on oxygen prescription.\textsuperscript{6}

Among participants with OHS, hyperoxia induced by supplemental oxygen significantly worsened hypercapnia and lowered pH. In an earlier study, breathing 100\% oxygen increased transcutaneous PCO\textsubscript{2} in obesity-associated hypercapnia,\textsuperscript{2} but the clinical relevance of this report was unclear because pH was not measured and transcutaneous PCO\textsubscript{2} was used, inherently adding potential errors to PCO\textsubscript{2} measures and preventing a definitive diagnosis of OHS.\textsuperscript{5} The present study provided further physiological detail and insight into the clinical relevance of the effects of hyperoxia in OHS. Although the minimal important difference for PCO\textsubscript{2} in OHS has not been defined, in the present study the rise in PavCO\textsubscript{2} during F\textsubscript{O2} 0.50 (0.5\pm0.4 kPa) was considered clinically significant because it induced acidaemia. In patients with COPD, hyperoxia-related acidaemia is associated with higher in-hospital morbidity,\textsuperscript{2} and this may apply to acutely unwell patients with OHS\textsuperscript{5,6} but has not been addressed. Therefore, in light of the results of the present study, the influence of supplemental oxygen usage on morbidity, mortality and healthcare utilisation in people with OHS requires investigation.

Ventilatory responses to hyperoxia

Controls
Interestingly, V\textsubscript{D}/V\textsubscript{T} increased among the control group with both oxygen concentrations, with rises of the same magnitude as those of the OHS group (figure 3). Despite this, PavCO\textsubscript{2} and pH remained relatively stable, albeit with some individual variation (figure 4B). During F\textsubscript{O2} 0.50, stable PavCO\textsubscript{2} levels were achieved by a 15\% increase in V\textsubscript{E}. This is consistent with previous observations among healthy controls breathing 100\% O\textsubscript{2}\textsuperscript{20-23} and is indicative of normal ventilatory control. Hyperoxic hyperventilation in healthy individuals is usually preceded by a fall in V\textsubscript{E} (\textasciitilde5–12\%) within the first 30 s to 2 min of breathing 100\% oxygen via inhibition of the peripheral chemoreceptors, which are tonically active within a normal Pa\textsubscript{O2} range.\textsuperscript{20,21,23} However, the washout time of circuit gases prevented this being captured in the present study. Quickly thereafter, V\textsubscript{E} increases above baseline due to transient increases in PA\textsubscript{CO2} from initial hyperventilation,\textsuperscript{22} the Haldane effect,\textsuperscript{22} increases in V\textsubscript{D}/V\textsubscript{T} and possibly in part through direct stimulation of chemoreceptors.\textsuperscript{22}

Obesity hypoventilation syndrome

Participants with OHS also experienced increases in V\textsubscript{D}/V\textsubscript{T} during hyperoxia. However, unlike the controls, breathing F\textsubscript{O2} 0.50 was invariably characterised by marked hypoventilation for the first 5–10 min, followed by a partial recovery in V\textsubscript{E}. The recovery of V\textsubscript{E} was usually insufficient to overcome the increase in V\textsubscript{D}/V\textsubscript{T} hence PavCO\textsubscript{2} was elevated after 20 min of F\textsubscript{O2} 0.50 in most participants (figure 4). There was a negative correlation between A\textsubscript{VCO2} and ΔPavCO\textsubscript{2}, but ΔV\textsubscript{D}/V\textsubscript{T} was not associated with ΔPavCO\textsubscript{2}. These results suggest that the PavCO\textsubscript{2} rises observed amongst OHS participants were largely a result of inadequate ventilatory control. Impaired respiratory chemosensitivity is a common feature of OHS\textsuperscript{24-26} and may explain why the initial decrease in V\textsubscript{E} during hyperoxia was of a larger magnitude, with much slower recovery, than that reported in controls.\textsuperscript{21,23}

Blunted hypercapnic ventilatory responses could also explain why an elevation of PavCO\textsubscript{2} at 20 min was tolerated by most participants. However, hypercapnic ventilatory responses are highly variable between individuals with OHS and are sometimes within the normal range in patients with mild hypercapnia,\textsuperscript{24-26} which may explain the variability in ventilatory responses to hyperoxia in the OHS group. We did not test ventilatory responses and are therefore unable to confirm their role in the changes in PavCO\textsubscript{2} observed during hyperoxia.

Factors potentially influencing V\textsubscript{D}/V\textsubscript{T} in controls and OHS

In both groups, V\textsubscript{D}/V\textsubscript{T} increased significantly during hyperoxia, although the contribution of this small change towards potential PavCO\textsubscript{2} rises is uncertain. Increased V\textsubscript{D}/V\textsubscript{T} could arise from an increase in V\textsubscript{D}phys, a decrease in V\textsubscript{T} or both. In studies measuring V/Q distributions in healthy controls,\textsuperscript{27} and patients with OHS,\textsuperscript{28} breathing 100\% oxygen has been shown to increase perfusion to poorly ventilated regions of lung through the release of local hypoxic vasconstriction.\textsuperscript{27} This results in underperfusion of well ventilated regions, thereby increasing V\textsubscript{D}phys.\textsuperscript{27} This mechanism is plausible among the control group, in whom a small increase in V\textsubscript{D}phys was observed during F\textsubscript{O2} 0.50. However, this change became non-significant after statistical adjustment. In contrast, no change was observed in V\textsubscript{D}phys among the OHS group. It has been shown that V\textsubscript{D}phys has a proportional relationship with V\textsubscript{T}\textsuperscript{29,30} Therefore in OHS participants, increases in V\textsubscript{D}phys occurring due to increased V/Q inequality may have been offset by the concomitant fall in V\textsubscript{T}. Given the lack of increase in V\textsubscript{D}phys during hyperoxia among OHS participants, rises in V\textsubscript{D}/V\textsubscript{T} are largely attributable to the reduction in V\textsubscript{E} (via the reduction in V\textsubscript{T}), which is consistent with previous observations in patients with obesity-associated hypercapnia whilst breathing 100\% oxygen.\textsuperscript{7} However, we did not perform invasive V/Q measures and therefore were unable to characterise the complex interactions between pulmonary ventilation and perfusion, gas exchange and breathing pattern when patients were breathing moderate oxygen concentrations.

Clinical implications

Clinically important differences between the two concentrations of oxygen were observed in the present study, that is, hyperoxia induced by F\textsubscript{O2} 0.28 caused minimal changes in pH or V\textsubscript{E}, while F\textsubscript{O2} 0.50 caused hyperventilation and acidemia. Furthermore, compared with responses to F\textsubscript{O2} 0.50 in our OHS participants, even more marked changes in PCO\textsubscript{2} and V\textsubscript{E} occurred during 100\% oxygen in obesity-associated hypercapnia.\textsuperscript{7} The mechanisms by which hyperoxia induces hyperventilation in OHS remain unclear. However, these findings suggest that a greater degree of respiratory depression occurs with higher oxygen concentrations. Therefore, in stable OHS, hyperoxia caused by breathing F\textsubscript{O2} 0.28 may be less harmful than F\textsubscript{O2} 0.50 or 1.0.

Substantial inter-individual variability in ΔPavCO\textsubscript{2} during hyperoxia was evident among the OHS group; as has been reported in obesity-associated hypercapnia\textsuperscript{7} and COPD.\textsuperscript{16}
Therefore it would be clinically useful to identify features that may predict adverse responses to hyperoxia. Strong associations between ΔPavCO2 and baseline PaCO2 and HCO3− were observed, suggesting that patients with OHS and severe hypercapnia (and associated elevated HCO3− levels) are more likely to develop worsening hypercapnia during hyperoxia. This is plausible, given the tendency for people with OHS and a higher PaCO2 to have lower hypercapnic ventilatory responses than those with lower PaCO2.24–26 Elevated HCO3− may also directly blunt hypercapnic ventilatory responses in OHS, through an increased acid-buffering capacity.31 32 Previous data also suggest that people with more severe hypoxaemia may experience larger PCO2 rises during hyperoxia,2 although this was not evident amongst our mildly hypoxaemic group.

Participants in the present study were clinically stable, with mild hypercapnia and hypoxaemia. Therefore our findings probably underestimate the dangers of hyperoxia in people with OHS with severe hypercapnia and/or acute cardiorespiratory illness. The effects of supplemental oxygen in this population warrant further investigation. Even so, the findings of the present study highlight the potential risks associated with the administration of moderate concentrations of supplemental oxygen among people with OHS. These findings also provide an evidence base for current guidelines,6 which recommend that people with more severe hypoxaemia may experience larger PCO2 rises during hyperoxia,2 although this was not evident amongst our mildly hypoxaemic group.

In this study, we documented acute responses to breathing supplemental oxygen for 20 min. Based on the time course of PavCO2 (figure 3), a plateau in PavCO2 occurred after 10 min of breathing oxygen. However, due to the large capacity of the body for CO2 storage, CO2 equilibrium is not usually achieved until 20–30 min after a change in ventilation35 and therefore participants may not have reached CO2 steady state. In clinical practice, patients are usually treated with supplemental oxygen for extended periods. Hence, the effects of longer periods of supplemental oxygen require evaluation to further strengthen the clinical practice guidelines.

CONCLUSION

Among people with mild, stable untreated OHS, breathing moderate concentrations of supplemental oxygen increased PavCO2, sufficient to induce acidaemia during FIO2 0.50. These findings highlight the need for caution during supplemental oxygen administration among people with OHS and support current clinical guidelines which recommend targeting an SpO2 range and monitoring of ABGs during supplemental oxygen administration.

Acknowledgements The authors thank each of the study participants, and Associate Professor Brendon Yee for his assistance.

Contributors CAH: contributed to design and implementation of the study, data collection, statistical analysis, preparation and editing of manuscript; ARH, LJM, CM: contributed to design and implementation of the study, data collection, statistical analysis, preparation and editing of manuscript; DAB: contributed to design of the study, and editing of manuscript; AJP: contributed to design and implementation of the study, and editing of manuscript.

Funding The study was supported by a Cardiorespiratory Physiotherapy Australia Research Grant from the Physiotherapy Research Foundation (grant no. TO8-CAR/JN016).

Competing interests AJP received fees for lectures from ResMed, Asia Pacific and Philips Respironics, Australia. She has also received a grant to evaluate therapy in obesity hyperventilation syndrome from the ResMed Foundation. GNW has previously been a consultant to ResMed, Asia Pacific. He has received fees for lectures from ResMed, Asia Pacific. All other authors have no actual or potential competing interests to disclose.

Ethics approval Respective ethics committees of Royal Prince Alfred Hospital and The University of Sydney, Sydney, Australia.

Provenance and peer review Not commissioned; externally peer reviewed.

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