ORIGINAL ARTICLE

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

Carly Ann Hollier,1,2 Alison Rosemary Harmer,2 Lyndal Jane Maxwell,3 Collette Menadue,1 Grant Neville Willson,4 Gunnar Unger,5 Daniel Flunt,1 Deborah Ann Black,4 Amanda Jane Piper1,5

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 acidemia 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 hypoventilation, 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 intervention5 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.6 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
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 ≥ 30 kg/m\textsuperscript{2}) and daytime hypercapnia (arterial PCO\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 (±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 co-investigator 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} expirogram 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}/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±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

![Figure 1](http://thorax.bmj.com/)
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), ΔV̇E, and ΔV̇D/V̇T. 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 2 shows all variables at baseline and after 20 min of breathing each oxygen concentration. In both groups, supplemental oxygen induced hyperoxia, with SpO2 in OHS increasing to 99±1% during FIO2 0.28 and 100±0% during FIO2 0.50. Figure 3 depicts time courses of PavCO2, V̇E and V̇D/V̇T. There was no significant effect of test order on PavCO2 for either group. General linear model comparisons are detailed in table E1, online data supplement.

Between-group comparisons

Responses to supplemental oxygen were significantly different between groups for PavCO2 and pH (figure 3, table 3), but not for V̇E after adjustment. There were no significant between-group differences or interaction effects for V̇D/V̇T hence data from both groups were combined to analyse the effects of time for V̇D/V̇T.

OHS group: responses to supplemental oxygen

Amongst OHS participants, significant increases in PavCO2 occurred after 20 min of FIO2 0.28 (0.3±0.2 kPa, adj.p=0.013) and FIO2 0.50 (0.5±0.4 kPa, adj.p=0.012) (table 3, figure 3). Consequently, proportional changes in pH were observed, resulting in acidaemia after 20 min of FIO2 0.50 (7.346±0.030, adj. p=0.011). There was a significant difference in PavCO2 between the two oxygen concentrations, but this became non-significant after adjustment (raw p=0.021, adj.p=0.315).
Figure 3  Time course of changes in PavCO₂, V̇e and V̇o₂/V̇t 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; PavCO₂, arterialised-venous CO₂; V̇e, minute ventilation; V̇o₂/V̇t, dead space to tidal volume ratio.

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>OHS group</th>
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<th>Control group</th>
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<tbody>
<tr>
<td></td>
<td>Room air baseline</td>
<td>20 min Adj. p value</td>
<td>Room air baseline</td>
<td>20 min Adj. p value</td>
</tr>
<tr>
<td>FiO₂ 0.28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>94±3</td>
<td>99±1</td>
<td>98±1</td>
<td>100±1</td>
</tr>
<tr>
<td>PavCO₂ (kPa)</td>
<td>7.1±0.6</td>
<td>7.4±0.6</td>
<td>5.5±0.4</td>
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<td>pH</td>
<td>7.37±0.019</td>
<td>7.359±0.027</td>
<td>7.408±0.023</td>
<td>7.397±0.010</td>
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<tr>
<td>V̇e (L/min)</td>
<td>9.9±2.3</td>
<td>9.9±2.8</td>
<td>7.5±1.6</td>
<td>7.5±1.7</td>
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<tr>
<td>V̇o₂/V̇t (ratio)</td>
<td>0.28±0.05</td>
<td>0.29±0.03</td>
<td>0.27±0.05</td>
<td>0.29±0.04</td>
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<tr>
<td>V̇o₂phys (mL)</td>
<td>200±55</td>
<td>196±26</td>
<td>232±79</td>
<td>237±53</td>
</tr>
<tr>
<td>V̇t (mL)</td>
<td>633±149</td>
<td>597±129</td>
<td>813 (353)</td>
<td>754 (356)</td>
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<tr>
<td>RR (br/min)</td>
<td>17.5±5.2</td>
<td>18.2±4.7</td>
<td>10.3±4.2</td>
<td>10.5±4.5</td>
</tr>
<tr>
<td>FiO₂ 0.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>94±3</td>
<td>100±1</td>
<td>98±1</td>
<td>100±1</td>
</tr>
<tr>
<td>PavCO₂ (kPa)</td>
<td>7.2±0.6</td>
<td>7.3±0.6</td>
<td>5.4±0.3</td>
<td>5.4±0.4</td>
</tr>
<tr>
<td>pH</td>
<td>7.373±0.021</td>
<td>7.346±0.030</td>
<td>7.407±0.020</td>
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<tr>
<td>V̇e (L/min)</td>
<td>9.6±2.1</td>
<td>9.3±2.0</td>
<td>7.5±1.8</td>
<td>8.6±1.9</td>
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<tr>
<td>V̇o₂/V̇t (ratio)</td>
<td>0.29±0.05</td>
<td>0.32±0.05</td>
<td>0.28±0.04</td>
<td>0.32±0.04</td>
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<tr>
<td>V̇o₂phys (mL)</td>
<td>194±56</td>
<td>192±37</td>
<td>244±123</td>
<td>263±97</td>
</tr>
<tr>
<td>V̇t (mL)</td>
<td>578±105</td>
<td>487±107</td>
<td>751 (285)</td>
<td>751 (264)</td>
</tr>
<tr>
<td>RR (br/min)</td>
<td>18.1±4.9</td>
<td>18.1±4.2</td>
<td>10.6±3.7</td>
<td>11.8±3.6</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.

Ḟo₂, inspired oxygen fraction; PavCO₂, arterialised-venous carbon dioxide; RR, respiratory rate; SpO₂, pulse oxygen saturation; V̇o₂/V̇t, physiological dead space to tidal volume ratio; V̇o₂phys, physiological dead space; V̇t, minute ventilation; V̇e, tidal volume.

There was a positive correlation between ΔPavCO2 (FiO2 0.50) and PaCO2 (r=0.60, p=0.023) and HCO3− (r=0.58, p=0.030), but not SaO2 (r=−0.48, p=0.08). Furthermore, a negative correlation between ΔPavCO2 and ΔVE was found (r=−0.60, p=0.024), but not ΔVD/VT (r=0.42, p=0.18).

There was no significant change in VE when breathing FiO2 0.28 (table 2). In contrast, during FiO2 0.50 a consistent fall in VE of 1.2±2.1 L/min (12±22%) below baseline occurred within 5 min (figure 3). Thereafter, a varying recovery in VE was observed (figure 4C), such that after 20 min VE remained below baseline in six participants, returned to baseline in four participants and exceeded baseline VE by >5% in four participants. After 20 min, group mean VE was 3±20% below baseline, which became non-significant after adjustment (raw p=0.014, adj.p=0.224). Decreases in VE were attributable to significant falls in V̇E as RR was unchanged.

During FiO2 0.28 and 0.50, V̇D/V̇T increased by 1±5% and 3±3%, respectively (adj.p=0.012), in the absence of significant changes in VDphys.

**Control group: responses to supplemental oxygen**

Among the controls, there were no significant changes in PavCO2 or pH during either FiO2 (table 2, figure 3), and no significant differences for PavCO2 between concentrations. During FiO2 0.28 there were no significant changes in V̇E, V̇T or RR. However, breathing FiO2 0.50 increased V̇E 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 V̇D/V̇T of 1±3% and 4±3% were observed during FiO2 0.28 and 0.50 respectively (adj.p=0.012). This was accompanied by small rises in VDphys 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>PavCO2 (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>V̇E (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>V̇D/V̇T (ratio)</td>
<td>0.01</td>
<td>−0.03 to 0.01</td>
<td>&lt;0.001</td>
<td>0.014</td>
<td>&lt;0.001</td>
<td>0.014</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 Δ values at 20 min.

OHS, obesity hypoventilation syndrome; PavCO2, arterialised-venous carbon dioxide; V̇D/V̇T, physiological dead space to tidal volume ratio; VDphys, physiological dead space; V̇E, minute ventilation.

**Figure 4** Individual and group responses to supplemental oxygen concentration (FiO2) 0.28 and 0.50 for OHS group (A and C) and control group (A and D), showing change in arterialised-venous carbon dioxide from room air baseline (ΔPavCO2) (A and B), and change in minute ventilation from room air baseline (V̇E) (C and D). Each figure includes individual changes at 20 min for FiO2 0.28 and group mean±SD on the left, and individual changes at 20 min for FiO2 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 F1O2 0.28 and F1O2 0.50 caused significant rises in PavCO2. Accordingly, pH decreased, resulting in acidaemia during F1O2 0.50. Breathing F1O2 0.50 was accompanied by hypoventilation and increases in VD/VT. However, changes in VE were the key determinant of PavCO2 rises. Breathing F1O2 0.50 also increased VD/VT in the control group, but controls maintained a stable PavCO2 and pH through a 15% increase in VE. 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.

Among participants with OHS, hyperoxia induced by supplemental oxygen significantly worsened hypercapnia and lowered pH. In an earlier study, breathing 100% oxygen increased transcutaneous PCO2 in obesity-associated hypercapnia, but the clinical relevance of this report was unclear because pH was not measured and transcutaneous PCO2 was used, inherently adding potential errors to PCO2 measures and preventing a definitive diagnosis of OHS. 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 PCO2 in OHS has not been defined, in the present study the rise in PavCO2 during F1O2 0.50 (0.5±0.4 kPa) was considered clinically significant because it induced acidaemia. In patients with COPD, hyperoxia-related acidaemia is associated with higher in-hospital morbidity, and this may apply to acutely unwell patients with OHS 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, VD/VT 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, PavCO2 and pH remained relatively stable, albeit with some individual variation (figure 4B). During F1O2 0.50, stable PavCO2 levels were achieved by a 15±11% increase in VE. This is consistent with previous observations among healthy controls breathing 100% O2 and is indicative of normal ventilatory control. Hyperoxic hyperventilation in healthy individuals is usually preceded by a fall in VE (∼5–12%) 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 PaO2 range. However, the washout time of circuit gases prevented this being captured in the present study. Quickly thereafter, VE increases above baseline due to transient increases in PavCO2 from initial hyperventilation, the Haldane effect, increases in VD/VT and possibly in part through direct stimulation of chemoreceptors.

Obesity hypoventilation syndrome
Participants with OHS also experienced increases in VD/VT during hyperoxia. However, unlike the controls, breathing F1O2 0.50 was invariably characterised by marked hyperventilation for the first 5–10 min, followed by a partial recovery in VE. The recovery of VE was usually insufficient to overcome the increase in VD/VT hence PavCO2 was elevated after 20 min of F1O2 0.50 in most participants (figure 4). There was a negative correlation between ∆VE and ∆PavCO2, but ∆VD/VT was not associated with ∆PavCO2. These results suggest that the PavCO2 rises observed amongst OHS participants were largely a result of inadequate ventilatory control. Impaired respiratory chemosensitivity is a common feature of OHS and may explain why the initial decrease in VE during hyperoxia was of a larger magnitude, with much slower recovery, than that reported in controls. Blunted hypercapnic ventilatory responses could also explain why an elevation of PavCO2 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, 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 PavCO2 observed during hyperoxia.

Factors potentially influencing VD/VT in controls and OHS
In both groups, VD/VT increased significantly during hyperoxia, although the contribution of this small change towards potential PavCO2 rises is uncertain. Increased VD/VT could arise from an increase in VD/phys, a decrease in VT or both. In studies measuring V/Q distributions in healthy controls, and patients with OHS, breathing 100% oxygen has been shown to increase perfusion to poorly ventilated regions of lung through the release of local hypoxic vasoconstriction. This results in underperfusion of well ventilated regions, thereby increasing VD/phys. This mechanism is plausible among the control group, in whom a small increase in Vphys was observed during F1O2 0.50. However, this change became non-significant after statistical adjustment. In contrast, no change was observed in Vphys among the OHS group. It has been shown that Vphys has a proportional relationship with VE and has been offset by the concomitant fall in VE. Given the lack of increase in Vphys during hyperoxia among OHS participants, rises in VD/VT are largely attributable to the reduction in VE (via the reduction in VT), which is consistent with previous observations in patients with obesity-associated hypercapnia whilst breathing 100% oxygen. 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 F1O2 0.28 caused minimal changes in pH or VE, while F1O2 0.50 caused hyperventilation and acidaemia. Furthermore, compared with responses to F1O2 0.50 in our OHS participants, even more marked changes in PCO2 and VE occurred during 100% oxygen in obesity-associated hypercapnia. 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 F1O2 0.28 may be less harmful than F1O2 0.50 or 1.0.

Substantial inter-individual variability in ∆PavCO2 during hyperoxia was evident among the OHS group; as has been reported in obesity-associated hypercapnia and COPD.
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. Elevated HCO3− may also directly blunt hypercapnic ventilatory responses in OHS, through an increased acid-buffering capacity. Previous data also suggest that people with more severe hypoxaemia may experience larger PCO2 rises during hyperoxia, although this was not evident amongst our mildly hypercapnic 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, which recommend that in OHS, supplemental oxygen should be titrated to maintain SpO2 88−92%, thereby avoiding hyperoxia and hypoxaemia. Oxygen supplementation should also include close monitoring and periodic reassessment of ABGs.

Limitations
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 ventilation 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 clinical practice guidelines.

CONCLUSION
Among people with mild, stable untreated OHS, breathing moderate concentrations of supplemental oxygen increased PavCO2, sufficient to induce acidosis 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.

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