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 (VE) 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.

Key messages

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. Hyperoxia-induced hypercapnia in COPD has been attributed to increased ventilation/perfusion (V/Q) inequality, mediated by the reversal of hypoxic vasoconstriction; however recent evidence suggests that hypoventilation may be a quantitatively more important mechanism. 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 PCO2, 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 PCO2.

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/m2) and daytime hypercapnia (arterial PCO2 (PaCO2) > 6 kPa). Patients were excluded in the case of any other potential cause of hypercapnia, current use of positive airway pressure, 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/m2, 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 (FiO2) 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 (FiO2 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 CO2 absorber and a T-connector at the participant interface. Gas was continuously sampled at the interface using oxygen/CO2 sensors. A stable FiO2 was maintained through titration of bottled air and oxygen using continuous real-time feedback from the oxygen sensor. Immediately after each FiO2 change, the circuit was flushed to allow stabilisation at the new FiO2 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 PCO2 (PavCO2) and pH. We previously described and validated this method in OHS. An oximeter continuously measured pulse oxygen saturation (SpO2) (Radical, Masimo, Irvine, California, USA). Signals from the oxygen/CO2 sensors and spirometer were recorded by a computer programme and used to derive and/or display breath-by-breath minute ventilation (Vb), tidal volume (VT) and respiratory rate (RR). Breath-by-breath physiological dead space (VDPHYS) was calculated using a CO2 expiratory method and adjusted by subtracting apparatus dead space, then divided by VT to obtain VDPHYS to VT ratio (VDPHYS/VT). 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
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, VD/Phys) 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. 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), ΔVE, and ΔVD/VT. The study was powered to detect a ΔPavCO₂ of 0.4 kPa 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, VE and VD/VT. 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 2, figure 3). Consequently, proportional changes in pH were observed, resulting in acidemia 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).
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>FiO2 0.28</th>
<th></th>
<th>Adj. p value</th>
<th>FiO2 0.50</th>
<th></th>
<th>Adj. p value</th>
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<tr>
<td></td>
<td>Room air baseline</td>
<td>20 min</td>
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<td>Room air baseline</td>
<td>20 min</td>
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<td>OHS group</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<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>PavCO2 (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>Vt (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>Vphys (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>
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<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>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<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>PavCO2 (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>
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<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>Vt (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>Vphys (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; PavCO2, arterialised-venous carbon dioxide; RR, respiratory rate; SpO2, pulse oxygen saturation; Vd/Vt, physiological dead space to tidal volume ratio; Vphys, physiological dead space; Vt, minute ventilation; VT, tidal volume.

Figure 3  Time course of changes in PavCO2, Vt 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). Adj. p value=0.01; FiO2, inspired oxygen fraction; NS, non-significant; OHS, obesity hypoventilation syndrome; PavCO2, arterialised-venous CO2; Vt, minute ventilation; Vd/Vt, dead space to tidal volume ratio.
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 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 V̇Dphys.

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 V̇Dphys 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>Main effect: group</th>
<th>Interaction: time by group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raw p value</td>
<td>Adj. p value</td>
<td>Raw p value</td>
<td>Adj. p value</td>
</tr>
<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>
</tr>
<tr>
<td>pH</td>
<td>−0.014</td>
<td>−0.023 to −0.005</td>
<td>0.001</td>
<td>0.011</td>
</tr>
<tr>
<td>V̇E (L/min)</td>
<td>−0.8</td>
<td>−1.3 to −0.38</td>
<td>0.045</td>
<td>0.585</td>
</tr>
<tr>
<td>V̇D/VT (ratio)</td>
<td>0.01</td>
<td>−0.03 to 0.01</td>
<td>0.085</td>
<td>0.850</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/VT, physiological dead space to tidal volume ratio; V̇Dphys, physiological dead space; V̇E, minute ventilation.
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, V̇₀₂/V̇ₜ and V̇ₑ and its determinants among people with OHS. In OHS, hyperoxia induced by breathing F₂O₂ 0.28 and F₂O₂ 0.50 caused significant rises in PavCO₂. Accordingly, pH decreased, resulting in acidemia during F₂O₂ 0.50. Breathing F₂O₂ 0.50 was accompanied by hypoventilation and increases in V̇₀₂/V̇ₑ. However, changes in V̇ₑ were the key determinant of PavCO₂ rises. Breathing F₂O₂ 0.50 also increased V̇₀₂/V̇ₑ in the control group, but controls maintained a stable PavCO₂ and pH through a 15% increase in V̇ₑ. 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 F₂O₂ 0.50 (0.5±0.4 kPa) was considered clinically significant because it induced acidemia. In patients with COPD, hyperoxia-related acidemia 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, V̇₀₂/V̇ₜ 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 F₂O₂ 0.50, stable PavCO₂ levels were achieved by a 15±11% increase in V̇ₑ. 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 V̇ₑ (~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, V̇ₑ increases above baseline due to transient increases in PaCO₂ from initial hypoventilation, the Haldane effect, increases in V̇₀₂/V̇ₜ and possibly in part through direct stimulation of chemoreceptors.

Obesity hypoventilation syndrome

Participants with OHS also experienced increases in V̇₀₂/V̇ₜ during hyperoxia. However, unlike the controls, breathing F₂O₂ 0.50 was invariably characterised by marked hypoventilation for the first 5–10 min, followed by a partial recovery in V̇ₑ. The recovery of V̇ₑ was usually insufficient to overcome the increase in V̇₀₂/V̇ₜ hence PavCO₂ was elevated after 20 min of F₂O₂ 0.50 in most participants (figure 4). There was a negative correlation between ΔV̇ₑ and ΔPavCO₂, but ΔV̇₀₂/V̇ₜ was not associated with ΔPavCO₂. 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 V̇ₑ 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 V̇₀₂/V̇ₜ in controls and OHS

In both groups, V̇₀₂/V̇ₜ increased significantly during hyperoxia, although the contribution of this small change towards potential PavCO₂ rises is uncertain. Increased V̇₀₂/V̇ₜ could arise from an increase in V̇₀₂ phys, a decrease in V̇ₜ 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 V̇₀₂ phys. This mechanism is plausible among the control group, in whom a small increase in V̇₀₂ phys was observed during F₂O₂ 0.50. However, this change became non-significant after statistical adjustment. In contrast, no change was observed in V̇₀₂ phys among the OHS group. It has been shown that V̇₀₂ phys has a proportional relationship with V̇ₑ. Therefore, in OHS participants, increases in V̇₀₂ phys occurring due to increased V/Q inequality may have been offset by the concomitant fall in V̇ₑ. Given the lack of increase in V̇₀₂ phys during hyperoxia among OHS participants, rises in V̇₀₂/V̇ₜ are largely attributable to the reduction in V̇ₑ (via the reduction in V̇ₜ), 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 F₂O₂ 0.28 caused minimal changes in pH or V̇ₑ, while F₂O₂ 0.50 caused hypoventilation and acidemia. Furthermore, compared with responses to F₂O₂ 0.50 in our OHS participants, even more marked changes in PCO₂ and V̇ₑ occurred during 100% oxygen in obesity-associated hypercapnia. The mechanisms by which hyperoxia induces hypoventilation 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 F₂O₂ 0.28 may be less harmful than F₂O₂ 0.50 or 1.0.

Substantial inter-individual variability in ΔPavCO₂ 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 hypoxia and hypercapnia. 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 acidocaemia 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, CM: contributed to design and implementation of the study, data collection, and editing of manuscript; GNW: contributed to original concept and design of the study, and statistical analysis, preparation and editing of manuscript; DAB: contributed to design of the study, and editing of manuscript; AJP: contributed to design of 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. T08-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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