

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 (V_E) and physiological dead space to tidal volume ratio (V_D/V_T) among people with stable untreated OHS, with comparison to healthy controls.

Methods In a double-blind randomised crossover study, participants breathed oxygen concentrations (F_IO₂) 0.28 and 0.50, each for 20 min, separated by a 45 min washout period. Arterialised-venous PCO₂ (PavCO₂) and pH, V_E and V_D/V_T 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) F_IO₂ 0.28 and 0.50 maintained oxygen saturation 98–100%. After 20 min of F_IO₂ 0.28, PavCO₂ change (ΔPavCO₂) was 0.3±0.2 kPa (p=0.013), with minimal change in V_E and rises in V_D/V_T of 1±5% (p=0.012). F_IO₂ 0.50 increased PavCO₂ by 0.5±0.4 kPa (p=0.012), induced acidaemia and increased V_D/V_T by 3±3% (p=0.012). V_E fell by 1.2±2.1 L/min within 5 min then recovered individually to varying degrees. A negative correlation between ΔV_E and ΔPavCO₂ (r=−0.60, p=0.024) suggested that ventilatory responses were the key determinant of PavCO₂ rises. Among controls, F_IO₂ 0.28 and 0.50 did not change PavCO₂ or pH, but F_IO₂ 0.50 significantly increased V_E and V_D/V_T.

Conclusion Commonly used oxygen concentrations caused hypoventilation, PavCO₂ rises and acidaemia 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

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 (V_D/V_T) 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 V_D/V_T.

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.

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.⁷ 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

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frequent admission to intensive care and increased hospital length of stay and mortality.^{9–11} Hyperoxia-induced hypercapnia in COPD has been attributed to increased ventilation/perfusion (V/Q) inequality, mediated by the reversal of hypoxic vasoconstriction^{12–14}; however recent evidence suggests that hypoventilation may be a quantitatively more important mechanism.^{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 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, 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/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 (F_iO₂) 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 (F_iO₂ 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 CO₂ absorber and a T-connector at the participant interface. Gas was continuously sampled at the interface using oxygen/CO₂ sensors. A stable F_iO₂ was maintained through titration of bottled air and oxygen using continuous real-time feedback from the oxygen sensor. Immediately after each F_iO₂ change, the circuit was flushed to allow stabilisation at the new F_iO₂ 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.¹⁷ 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 (V_E), tidal volume (V_T) and respiratory rate (RR). Breath-by-breath physiological dead space (V_Dphys) was calculated using a CO₂ expirogram method¹⁸ and adjusted by subtracting apparatus dead space, then divided by V_T to obtain V_Dphys to V_T ratio (V_D/V_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

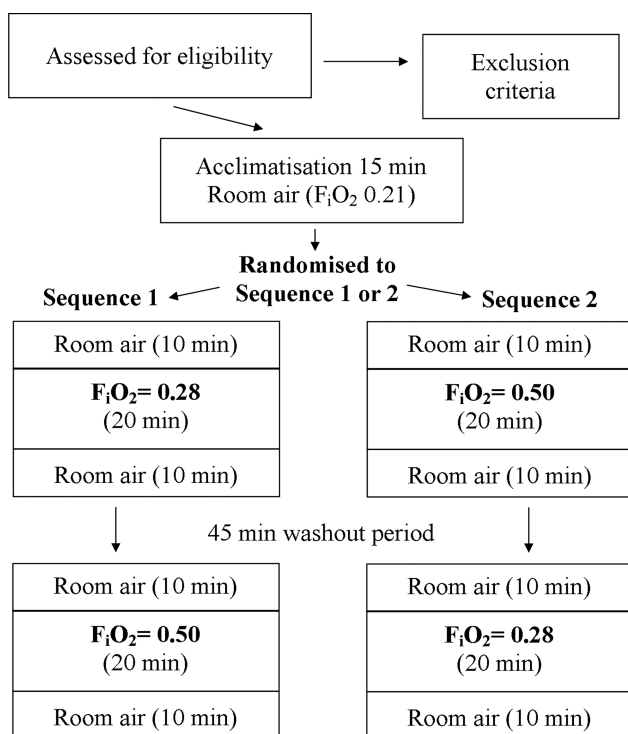
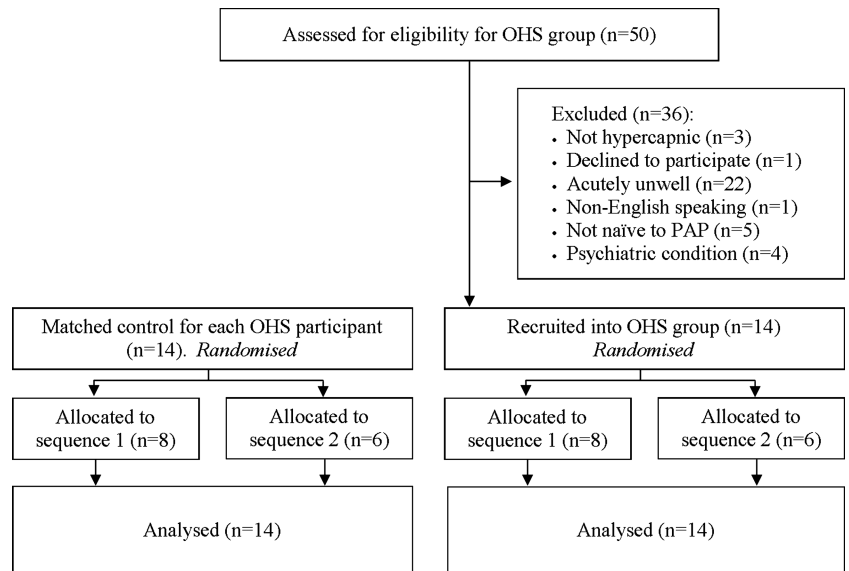


Figure 1 Study design. F_iO₂, inspired oxygen fraction.

Figure 2 Flow diagram of enrolment, randomisation/allocation and analysis phases. OHS, obesity hypoventilation syndrome, PAP, positive airway pressure.



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 (PavCO_2) and secondary (pH, V_E and V_D/V_T) outcomes; between baseline and supplemental oxygen (factor: time) for primary, secondary and tertiary (V_T , RR, V_D Phys) outcomes; and between the two oxygen concentrations (factor: concentration) for PavCO_2 . 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

PavCO_2 after 20 min (ΔPavCO_2) of F_iO_2 0.50, including baseline PaCO_2 , bicarbonate (HCO_3^-) and arterial oxygen saturation (SaO_2), ΔV_E , and $\Delta V_D/V_T$. The study was powered to detect a ΔPavCO_2 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 SpO_2 in OHS increasing to $99 \pm 1\%$ during F_iO_2 0.28 and $100 \pm 0\%$ during F_iO_2 0.50. Figure 3 depicts time courses of PavCO_2 , V_E and V_D/V_T . There was no significant effect of test order on PavCO_2 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 PavCO_2 and pH (figure 3, table 3), but not for V_E after adjustment. There were no significant between-group differences or interaction effects for V_D/V_T , hence data from both groups were combined to analyse the effects of time for V_D/V_T .

OHS group: responses to supplemental oxygen

Amongst OHS participants, significant increases in PavCO_2 occurred after 20 min of F_iO_2 0.28 (0.3 ± 0.2 kPa, adj.p=0.013) and F_iO_2 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 F_iO_2 0.50 (7.346 ± 0.030 , adj. p=0.011). There was a significant difference in PavCO_2 between the two oxygen concentrations, but this became non-significant after adjustment (raw p=0.021, adj.p=0.315).

Table 1 Participant characteristics, baseline arterial blood gases and spirometry

	OHS	Controls	p Value
Age (years)	48±12	48±12	0.987
Gender (F/M)	3/11	3/11	–
BMI (kg/m^2)	53±7	25±4	<0.001
Weight (kg)	154±21	73±15	<0.001
pH	7.395±0.030	7.414±0.019*	0.055
PaCO_2 (kPa)	6.7±0.5	5.5±0.4*	<0.001
PaO_2 (kPa)	8.9±1.4	14.3±1.1*	<0.001
SaO_2 (%)	92±3	98±1*	<0.001
HCO_3^- (mmol/L)	30.3±1.7	25.8±1.2*	<0.001
A-aDO ₂ (kPa)	3.6±1.4	0.9±1.2*	<0.001
Haemoglobin (g/L)	153±20	143±11	0.156
FEV_1 (L)	2.39±0.72	3.71±0.71	0.001
FEV_1 % predicted	73±14	106±11	<0.001
FVC (L)	3.03±0.85	4.54±0.77	<0.001
FVC % predicted	77±14	107±13	<0.001
FEV_1/FVC (%)	79±6	82±5	0.231

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; FEV_1 , forced expired volume in 1 s; FVC, forced vital capacity; HCO_3^- , bicarbonate; OHS, obesity hypoventilation syndrome; PaCO_2 , arterial partial pressure of CO₂; PaO_2 , arterial partial pressure of O₂.

Table 2 Physiological variables at baseline and at the end of F_{iO_2} 0.28 and F_{iO_2} 0.50 tests

	F_{iO_2} 0.28			F_{iO_2} 0.50		
	Room air baseline	20 min	Adj. p value	Room air baseline	20 min	Adj. p value
OHS group						
SpO ₂ (%)	94±3	99±1	–	94±3	100±0	–
PavCO ₂ (kPa)	7.1±0.6	7.4±0.6	0.013	7.2±0.6	7.7±1.0	0.012
pH	7.371±0.019	7.359±0.027	0.406*	7.373±0.021	7.346±0.030	0.011
V _E (L/min)	9.9±2.3	9.9±2.8	0.997	9.6±2.1	9.3±2.9	0.224*
V _D /V _T (ratio)	0.28±0.05	0.29±0.03	0.012	0.29±0.05	0.32±0.05	0.012
V _D phys (mL)	200±55	196±26	>0.999	194±56	192±37	>0.999
V _T (mL)	633±149	597±129	0.012	578±105	489±107	0.012
RR (br/min)	17.5±5.2	18.2±4.7	>0.999	18.1±4.9	18.1±4.2	>0.999
Control group						
SpO ₂ (%)	98±1	100±1	–	98±1	100±0	–
PavCO ₂ (kPa)	5.5±0.4	5.6±0.2	0.726	5.4±0.3	5.4±0.4	>0.999
pH	7.408±0.023	7.397±0.010	>0.999	7.407±0.020	7.407±0.023	>0.999
V _E (L/min)	7.5±1.6	7.5±1.7	>0.999	7.6±1.8	8.6±1.9	0.019
V _D /V _T (ratio)	0.27±0.05	0.29±0.04	0.012	0.28±0.04	0.32±0.04	0.012
V _D phys (mL)	232±79	237±53	0.085*	244±123	263±97	0.085*
V _T (mL)	813 (353)	754 (356)	>0.999	751 (285)	751 (264)	>0.999
RR (br/min)	10.3±4.2	10.5±4.5	0.195*	10.6±3.7	11.8±3.6	0.195*

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.

F_{iO_2} , inspired oxygen fraction; PavCO₂, arterialised-venous carbon dioxide; RR, respiratory rate; SpO₂, pulse oxygen saturation; V_D/V_T, physiological dead space to tidal volume ratio; V_Dphys, physiological dead space; V_E, minute ventilation; V_T, tidal volume.

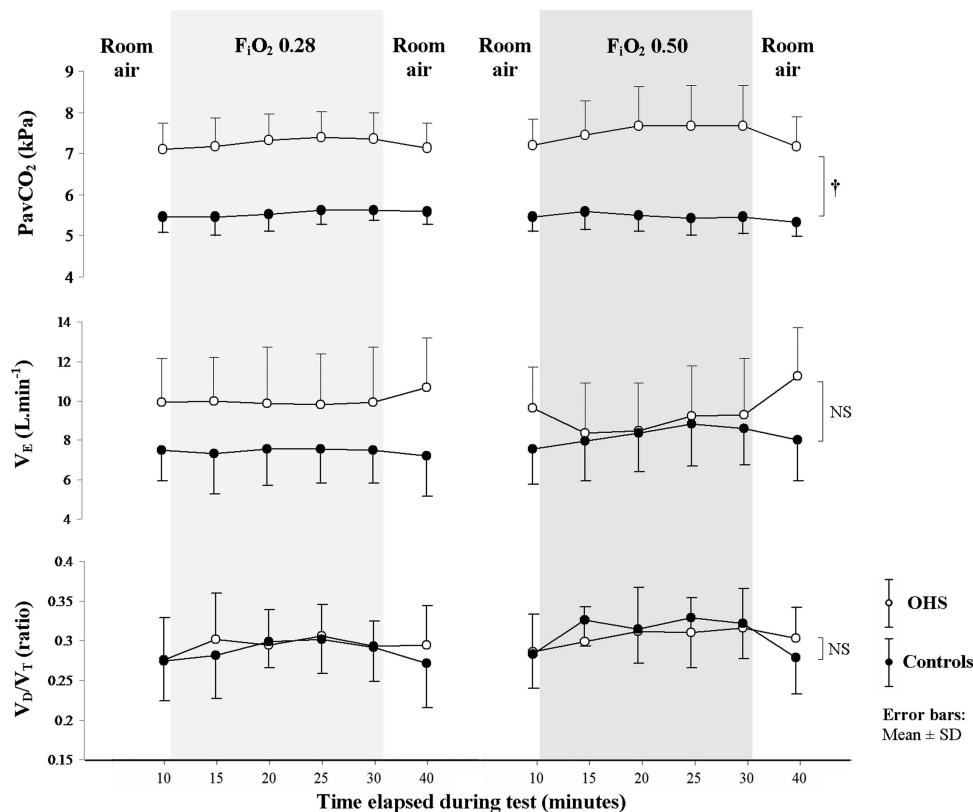


Figure 3 Time course of changes in PavCO₂, V_E and V_D/V_T during air/oxygen breathing tests for OHS group (open circles) and control group (closed circles), with results of general linear model analysis of between-group differences (factor: group, and group by time). †Adjusted p value=0.01; F_{iO_2} , inspired oxygen fraction; NS, non-significant; OHS, obesity hypoventilation syndrome; PavCO₂, arterialised-venous CO₂; V_E, minute ventilation; V_D/V_T, dead space to tidal volume ratio.

Table 3 Between-group comparisons of responses to supplemental oxygen

	MD (Δ at 20 min)*	95% CI	Main effect: group		Interaction: time by group	
			Raw p value	Adj. p value	Raw p value	Adj. p value
PavCO ₂ (kPa)	0.31	0.13 to 0.49	<0.001	0.010	<0.001	0.014
pH	-0.014	-0.023 to -0.005	<0.001	0.011	0.001	0.019
V _E (L/min)	-0.8	-1.3 to -0.38	0.045	0.585	0.051	0.612
V _D /V _T (ratio)	0.01	-0.03 to 0.01	0.085	0.850	0.128	>0.999

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; V_D/V_T, physiological dead space to tidal volume ratio; V_Dphys, physiological dead space; V_E, minute ventilation.

There was a positive correlation between Δ PavCO₂ (F_iO₂ 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 Δ PavCO₂ and Δ V_E was found ($r=-0.60$, $p=0.024$), but not Δ V_D/V_T ($r=0.42$, $p=0.18$).

There was no significant change in V_E when breathing F_iO₂ 0.28 (table 2). In contrast, during F_iO₂ 0.50 a consistent fall in V_E of 1.2 ± 2.1 L/min ($12 \pm 22\%$) 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 $3 \pm 20\%$ 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_T as RR was unchanged.

During F_iO₂ 0.28 and 0.50, V_D/V_T increased by $1 \pm 5\%$ and $3 \pm 3\%$, respectively (adj. $p=0.012$), in the absence of significant changes in V_Dphys.

Control group: responses to supplemental oxygen

Among the controls, there were no significant changes in PavCO₂ or pH during either F_iO₂ (table 2, figure 3), and no significant differences for PavCO₂ between concentrations. During F_iO₂ 0.28 there were no significant changes in V_E, V_T or RR. However, breathing F_iO₂ 0.50 increased V_E by $15 \pm 11\%$ 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 $1 \pm 3\%$ and $4 \pm 3\%$ were observed during F_iO₂ 0.28 and 0.50 respectively (adj. $p=0.012$). This was accompanied by small rises in V_Dphys which became non-significant after adjustment (raw $p<0.001$, adj. $p=0.085$).

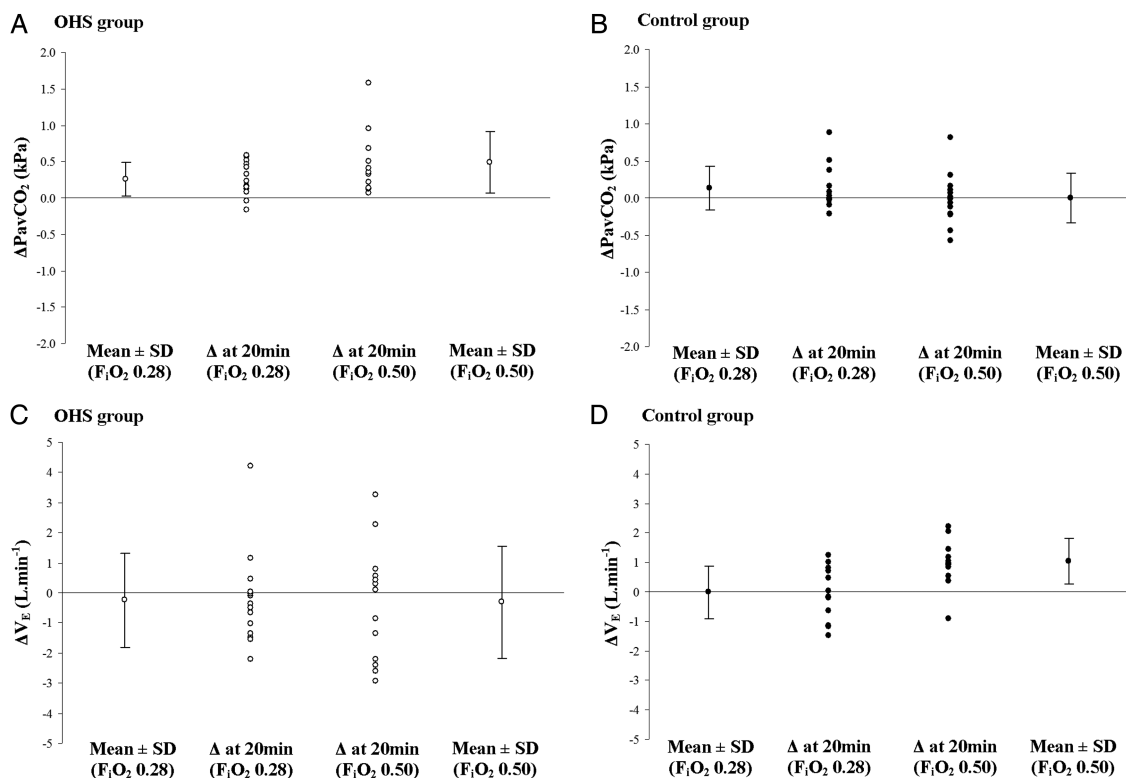


Figure 4 Individual and group responses to supplemental oxygen concentration (F_iO₂) 0.28 and 0.50 for OHS group (A and C) and control group (A and D), showing change in arterialised-venous carbon dioxide from room air baseline (Δ PavCO₂) (A and B), and change in minute ventilation from room air baseline (V_E) (C and D). Each figure includes individual changes at 20 min for F_iO₂ 0.28 and group mean \pm SD on the left, and individual changes at 20 min for F_iO₂ 0.50 and group mean \pm 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 PCO_2 and pH, V_D/V_T and V_E and its determinants among people with OHS. In OHS, hyperoxia induced by breathing $F_i\text{O}_2$ 0.28 and $F_i\text{O}_2$ 0.50 caused significant rises in PavCO_2 . Accordingly, pH decreased, resulting in acidaemia during $F_i\text{O}_2$ 0.50. Breathing $F_i\text{O}_2$ 0.50 was accompanied by hypoventilation and increases in V_D/V_T . However, changes in V_E were the key determinant of PavCO_2 rises. Breathing $F_i\text{O}_2$ 0.50 also increased V_D/V_T in the control group, but controls maintained a stable PavCO_2 and pH through a 15% increase in V_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.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_2 in obesity-associated hypercapnia,⁷ but the clinical relevance of this report was unclear because pH was not measured and transcutaneous PCO_2 was used, inherently adding potential errors to PCO_2 measures and preventing a definitive diagnosis of OHS.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_2 in OHS has not been defined, in the present study the rise in PavCO_2 during $F_i\text{O}_2$ 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,⁹ and this may apply to acutely unwell patients with OHS^{2, 8} 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_D/V_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_2 and pH remained relatively stable, albeit with some individual variation (figure 4B). During $F_i\text{O}_2$ 0.50, stable PavCO_2 levels were achieved by a $15 \pm 11\%$ increase in V_E . This is consistent with previous observations among healthy controls breathing 100% O_2 ^{20–23} and is indicative of normal ventilatory control. Hyperoxic hyperventilation in healthy individuals is usually preceded by a fall in V_E (~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 PaO_2 range.^{20, 21, 23} However, the washout time of circuit gases prevented this being captured in the present study. Quickly thereafter, V_E increases above baseline due to transient increases in PaCO_2 from initial hypoventilation,^{22, 23} the Haldane effect,²² increases in V_D/V_T and possibly in part through direct stimulation of chemoreceptors.²²

Obesity hypoventilation syndrome

Participants with OHS also experienced increases in V_D/V_T during hyperoxia. However, unlike the controls, breathing $F_i\text{O}_2$ 0.50 was invariably characterised by marked hypoventilation for the first 5–10 min, followed by a partial recovery in V_E . The recovery of V_E was usually insufficient to overcome the increase

in V_D/V_T , hence PavCO_2 was elevated after 20 min of $F_i\text{O}_2$ 0.50 in most participants (figure 4). There was a negative correlation between ΔV_E and ΔPavCO_2 , but $\Delta V_D/V_T$ was not associated with ΔPavCO_2 . These results suggest that the PavCO_2 rises observed amongst OHS participants were largely a result of inadequate ventilatory control. Impaired respiratory chemosensitivity is a common feature of OHS^{24–26} and may explain why the initial decrease in V_E during hyperoxia was of a larger magnitude, with much slower recovery, than that reported in controls.^{21, 23} Blunted hypercapnic ventilatory responses could also explain why an elevation of PavCO_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,^{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_2 observed during hyperoxia.

Factors potentially influencing V_D/V_T in controls and OHS

In both groups, V_D/V_T increased significantly during hyperoxia, although the contribution of this small change towards potential PavCO_2 rises is uncertain. Increased V_D/V_T could arise from an increase in $V_{D\text{phys}}$, a decrease in V_T or both. In studies measuring V/Q distributions in healthy controls,²⁷ and patients with OHS,²⁸ breathing 100% oxygen has been shown to increase perfusion to poorly ventilated regions of lung through the release of local hypoxic vasoconstriction.²⁷ This results in underperfusion of well ventilated regions, thereby increasing $V_{D\text{phys}}$.²⁷ This mechanism is plausible among the control group, in whom a small increase in $V_{D\text{phys}}$ was observed during $F_i\text{O}_2$ 0.50. However, this change became non-significant after statistical adjustment. In contrast, no change was observed in $V_{D\text{phys}}$ among the OHS group. It has been shown that $V_{D\text{phys}}$ has a proportional relationship with V_T .^{29, 30} Therefore in OHS participants, increases in $V_{D\text{phys}}$ occurring due to increased V/Q inequality may have been offset by the concomitant fall in V_T . Given the lack of increase in $V_{D\text{phys}}$ during hyperoxia among OHS participants, rises in V_D/V_T are largely attributable to the reduction in V_E (via the reduction in V_T), which is consistent with previous observations in patients with obesity-associated hypercapnia whilst breathing 100% oxygen.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 $F_i\text{O}_2$ 0.28 caused minimal changes in pH or V_E , while $F_i\text{O}_2$ 0.50 caused hypoventilation and acidaemia. Furthermore, compared with responses to $F_i\text{O}_2$ 0.50 in our OHS participants, even more marked changes in PCO_2 and V_E occurred during 100% oxygen in obesity-associated hypercapnia.⁷ 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 $F_i\text{O}_2$ 0.28 may be less harmful than $F_i\text{O}_2$ 0.50 or 1.0.

Substantial inter-individual variability in ΔPavCO_2 during hyperoxia was evident among the OHS group; as has been reported in obesity-associated hypercapnia⁷ and COPD.¹⁶

Therefore it would be clinically useful to identify features that may predict adverse responses to hyperoxia. Strong associations between ΔPavCO_2 and baseline PaCO_2 and HCO_3^- were observed, suggesting that patients with OHS and severe hypercapnia (and associated elevated HCO_3^- levels) are more likely to develop worsening hypercapnia during hyperoxia. This is plausible, given the tendency for people with OHS and a higher PaCO_2 to have lower hypercapnic ventilatory responses than those with lower PaCO_2 .^{24–26} Elevated HCO_3^- 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 PCO_2 rises during hyperoxia,⁷ 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 in OHS, supplemental oxygen should be titrated to maintain SpO_2 88–92%, thereby avoiding hyperoxia and hypoxaemia. Oxygen supplementation should also include close monitoring and periodic reassessment of ABGs.⁶

Limitations

In this study, we documented acute responses to breathing supplemental oxygen for 20 min. Based on the time course of PavCO_2 (figure 3), a plateau in PavCO_2 occurred after 10 min of breathing oxygen. However, due to the large capacity of the body for CO_2 storage, CO_2 equilibrium is not usually achieved until 20–30 min after a change in ventilation³³ and therefore participants may not have reached CO_2 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 PavCO_2 , sufficient to induce acidemia during F_iO_2 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 SpO_2 range and monitoring of ABGs during supplemental oxygen administration.

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Online data supplement

Table E1. All general linear model comparisons, with details of Holm's Bonferroni adjustment

Variable	Factor	Raw p value	Partial eta squ.	p value rank	Adj. p value	Interaction	Adj. p value
Between group comparisons:							
PavCO ₂	Group	<0.001	0.759	1	0.010	Time*group	0.014
pH	Group	<0.001	0.555	3	0.011	Time*group	0.019
V _E	Group	0.045	0.146	16	0.585	Time*group	0.612
V _D /V _T ^a	Group	0.085	0.110	19	0.850	Time*group	>0.999 ^a
OHS group, response to oxygen:							Raw p value
PavCO ₂ (FiO ₂ 0.28) ^b	Time	<0.001	0.33	6	0.013	Time*concentration	0.046 ^b
PavCO ₂ (FiO ₂ 0.50) ^b	Time	<0.001	0.47	4	0.012	Time*concentration	0.046 ^b
PavCO ₂	Concentration	0.021	0.35	14	0.315	Concentration*group	0.013
pH (FiO ₂ 0.28) ^b	Time	0.029	0.18	15	0.406	Time*concentration	0.003 ^b
pH (FiO ₂ 0.50) ^b	Time	<0.001	0.58	2	0.011	Time*concentration	0.003 ^b
V _E (FiO ₂ 0.28) ^b	Time	0.997	0.00	29	>0.999	Time*concentration	0.041 ^b
V _E (FiO ₂ 0.50) ^b	Time	0.014	0.21	13	0.224	Time*concentration	0.041 ^b
V _D phys	Time	0.133	0.13	21	>0.999	Time*concentration	0.580
V _T	Time	<0.001	0.43	5	0.012	Time*concentration	0.229
RR	Time	0.334	0.08	23	>0.999	Time*concentration	0.648
Control group, response to oxygen:							Raw p value
PavCO ₂ (FiO ₂ 0.28) ^b	Time	0.066	0.15	18	0.726	Time*concentration	0.043 ^b
PavCO ₂ (FiO ₂ 0.50) ^b	Time	0.303	0.09	22	>0.999	Time*concentration	0.043 ^b
PavCO ₂	Concentration	0.372	0.06	24	>0.999	Concentration*group	0.013
pH	Time	0.464	0.07	27	>0.999	Time*concentration	0.128
V _E (FiO ₂ 0.28) ^b	Time	0.878	0.02	28	>0.999	Time*concentration	0.013 ^b
V _E (FiO ₂ 0.50) ^b	Time	0.001	0.31	9	0.019	Time*concentration	0.013 ^b
V _D phys	Time	0.005	0.75	11	0.090	Time*concentration	0.085
V _T (FiO ₂ 0.28) ^c	Time	0.223	-	26	>0.999	-	-
V _T (FiO ₂ 0.50) ^c	Time	0.145	-	25	>0.999	-	-
RR	Time	0.01	0.22	12	0.170	Time*concentration	0.195
OHS & controls combined, response to oxygen:							Raw p value
V _D V _T ^a	Time	<0.001	0.22	7	0.012	Time*concentration	0.121 ^a

FiO₂: fraction of inspired oxygen; PavCO₂: arterialised-venous carbon dioxide; V_E: minute ventilation; V_D/V_T: physiological dead space to tidal volume ratio; V_Dphys: physiological dead space; V_T: tidal volume; RR: respiratory rate. Raw p: significance level before Bonferroni adjustment; Adj. p value: significance level after Bonferroni adjustment; partial eta squ.: effect size, partial eta squared; p value rank: rank of raw p value for Bonferroni adjustment. ^adata from both groups and both concentrations analysed together, as there were no interaction effects; ^bdata from FiO₂ 0.28 and FiO₂ 0.50 test analysed separately due to significant interaction effect, time*concentration; ^c Friedman test performed (non-parametric data).