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 (PCO_2), but its effect on pH is unknown. This study investigated the effects of moderate concentrations of supplemental oxygen on PCO_2, 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_iO_2) 0.28 and 0.50, each for 20 min, separated by a 45 min washout period. Arterialised-venous PCO_2 ($PavCO_2$) 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 PCO_2 6.7±0.5 kPa; arterial oxygen 8.9±1.4 kPa) F_iO_2 0.28 and 0.50 maintained oxygen saturation 98–100%. After 20 min of F_iO_2 0.28, $PavCO_2$ change ($\Delta PavCO_2$) 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_iO_2 0.50 increased $PavCO_2$ 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 $\Delta PavCO_2$ (r=−0.60, p=0.024) suggested that ventilatory responses were the key determinant of $PavCO_2$ rises. Among controls, F_iO_2 0.28 and 0.50 did not change $PavCO_2$ or pH, but F_iO_2 0.50 significantly increased V_E and V_D/V_T.

Conclusion Commonly used oxygen concentrations caused hypoventilation, $PavCO_2$ rises and acidaemia 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 CO_2, 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.

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 population[5] and over 50% of hospital inpatients with body mass index (BMI)>50 kg/m^2.[1] Despite this, OHS frequently goes undiagnosed among hospital inpatients with obesity.[1]

Supplemental oxygen is a common medical intervention[6] 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 (CO_2) 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 CO_2 pressure (PCO_2), breathing 100% oxygen induced an average rise in transcutaneous PCO_2 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

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 PCO_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_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^2) and daytime hypercapnia (arterial PCO_2 ($PaCO_2$) > 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, acidaemia 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^2, normal spirometry and no history of cardiorespiratory disease.

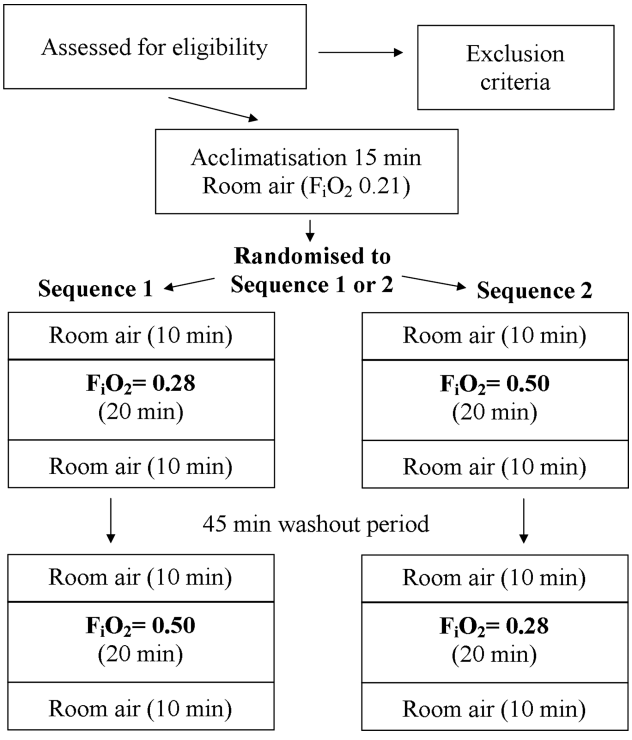

Figure 1 Study design. F_iO_2, inspired oxygen fraction.

Study design and protocol

Using a double-blind randomised crossover design (figure 1), each participant breathed two fractions of inspired oxygen (F_iO_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 (F_iO_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_2 absorber and a T-connector at the participant interface. Gas was continuously sampled at the interface using oxygen/CO_2 sensors. A stable F_iO_2 was maintained through titration of bottled air and oxygen using continuous real-time feedback from the oxygen sensor. Immediately after each F_iO_2 change, the circuit was flushed to allow stabilisation at the new F_iO_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_2 ($PavCO_2$) and pH. We previously described and validated this method in OHS.[17] An oximeter continuously measured pulse oxygen saturation (SpO_2) (Radical, Masimo, Irvine, California, USA). Signals from the oxygen/CO_2 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 ($V_D$phys) was calculated using a CO_2 expirogram method[18] and adjusted by subtracting apparatus dead space, then divided by V_T to obtain $V_D$phys 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

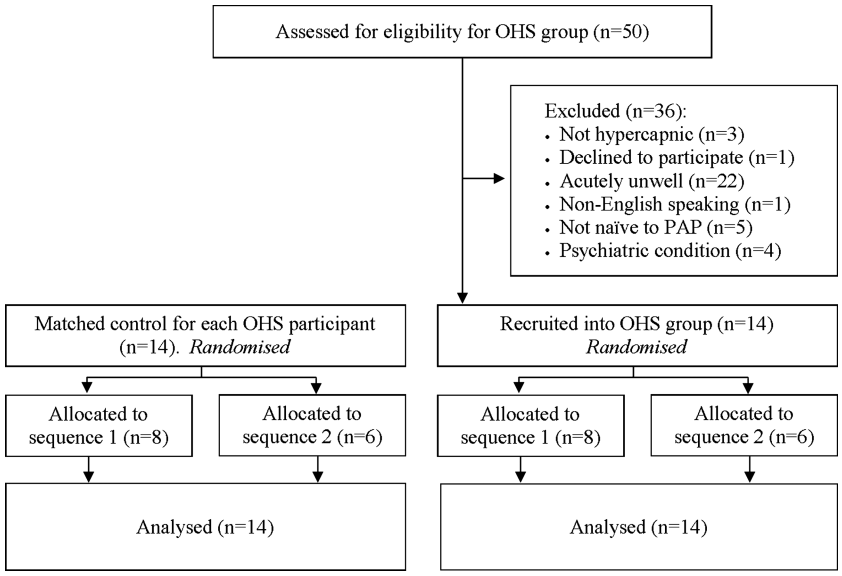

Figure 2 Flow diagram of enrolment, randomisation/allocation and analysis phases. OHS, obesity hypoventilation syndrome, PAP, positive airway pressure.

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_DPhys) 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 ($\Delta PavCO_2$) 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 $\Delta PavCO_2$ of 0.4 kPa[16] 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).

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-aDO_2, 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 CO_2; PaO_2, arterial partial pressure of O_2.

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±1% during F_iO_2 0.28 and 100±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 acidaemia 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 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; $PavCO_2$, arterialised-venous carbon dioxide; RR, respiratory rate; SpO_2, pulse oxygen saturation; V_D/V_T, physiological dead space to tidal volume ratio; $V_D$phys, physiological dead space; V_E, minute ventilation; V_T, tidal volume.

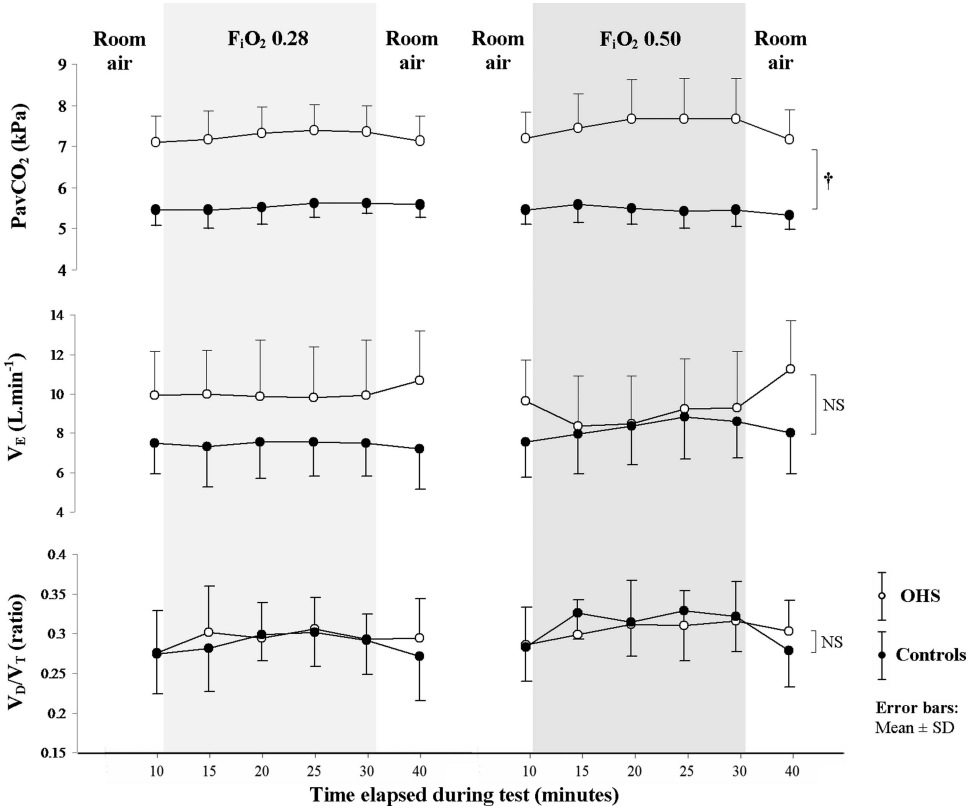

Figure 3 Time course of changes in $PavCO_2$, V_E and V_D/V_T during air/oxygen breathing tests for OHS group (open circles) and control group (closed circles), with results of general linear model analysis of between-group differences (factor: group, and group by time). †Adjusted p value=0.01; F_iO_2, inspired oxygen fraction; NS, non-significant; OHS, obesity hypoventilation syndrome; $PavCO_2$, arterialised-venous CO_2; V_E, minute ventilation; V_D/V_T, dead space to tidal volume ratio.

Table 3 Between-group comparisons of responses to supplemental oxygen

			Main effect: group		Interaction: time by group	
	MD (Δ at 20 min)*	95% CI	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; $PavCO_2$, arterialised-venous carbon dioxide; V_D/V_T, physiological dead space to tidal volume ratio; $V_D$phys, physiological dead space; V_E, minute ventilation.

There was a positive correlation between $\Delta PavCO_2$ (F_iO_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 $\Delta PavCO_2$ and ΔV_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 F_iO_2 0.28 (table 2). In contrast, during F_iO_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_T, as RR was unchanged.

During F_iO_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 $PavCO_2$ or pH during either F_iO_2 (table 2, figure 3), and no significant differences for $PavCO_2$ between concentrations. During F_iO_2 0.28 there were no significant changes in V_E, V_T or RR. However, breathing F_iO_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 F_iO_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).

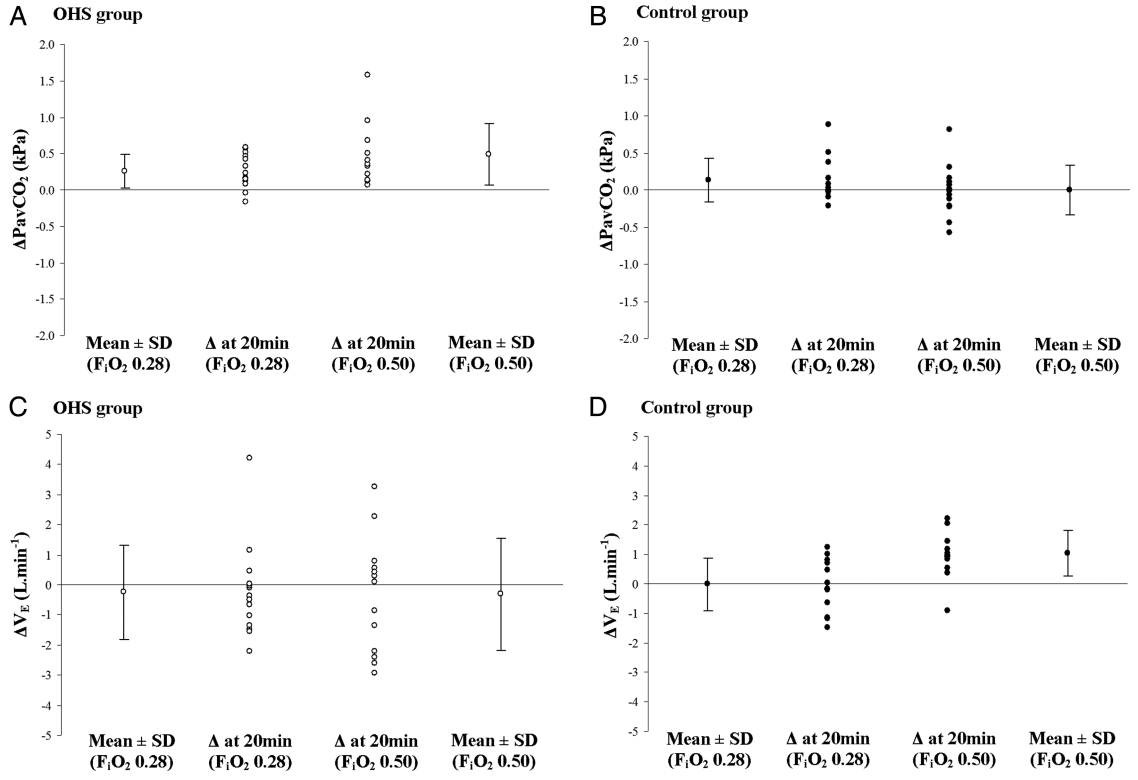

Figure 4 Individual and group responses to supplemental oxygen concentration (F_iO_2) 0.28 and 0.50 for OHS group (A and C) and control group (A and D), showing change in arterialised-venous carbon dioxide from room air baseline ($\triangle PavCO_2$) (A and B), and change in minute ventilation from room air baseline (V_E) (C and D). Each figure includes individual changes at 20 min for F_iO_2 0.28 and group mean±SD on the left, and individual changes at 20 min for F_iO_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 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_iO_2 0.28 and F_iO_2 0.50 caused significant rises in $PavCO_2$. Accordingly, pH decreased, resulting in acidaemia during F_iO_2 0.50. Breathing F_iO_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_iO_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_iO_2 0.50 (0.5±04 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_iO_2 0.50, stable $PavCO_2$ levels were achieved by a 15±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_iO_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_iO_2 0.50 in most participants (figure 4). There was a negative correlation between ΔV_E and $\Delta PavCO_2$, but $\Delta V_D/V_T$ was not associated with $\Delta PavCO_2$. 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 $V_D$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 vascoconstriction.[27] This results in underperfusion of well ventilated regions, thereby increasing $V_D$phys.[27] This mechanism is plausible among the control group, in whom a small increase in $V_D$phys was observed during F_iO_2 0.50. However, this change became non-significant after statistical adjustment. In contrast, no change was observed in $V_D$phys among the OHS group. It has been shown that $V_D$phys has a proportional relationship with V_T.[29 30] Therefore in OHS participants, increases in $V_D$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 $V_D$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_iO_2 0.28 caused minimal changes in pH or V_E, while F_iO_2 0.50 caused hypoventilation and acidaemia. Furthermore, compared with responses to F_iO_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_iO_2 0.28 may be less harmful than F_iO_2 0.50 or 1.0.

Substantial inter-individual variability in $\Delta PavCO_2$ during hyperoxia was evident among the OHS group; as has been reported in obesity-associated hypercapnia[7] and COPD.[16]

Therefore it would be clinically useful to identify features that may predict adverse responses to hyperoxia. Strong associations between $\Delta PavCO_2$ 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 ventilation[33] 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 acidaemia 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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