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Supine hyperinflation and expiratory flow limitation are associated with respiratory arousals and nocturnal hypoventilation in COPD

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ABSTRACT

Introduction Subjective sleep disturbance is common in chronic obstructive pulmonary disease (COPD) and is related to hyperinflation when supine and tidal expiratory flow limitation (EFL). We hypothesised that abnormalities in supine lung mechanics disturb sleep and impair gas exchange in COPD. We aimed to assess relationships between supine lung derecruitment, EFL and hyperinflation, and polysomnographic measures of sleep disturbance and gas exchange in COPD.

Methods In this prospective, observational study, supine oscillometry was performed in stable COPD patients to assess lung derecruitment (reactance at 5 Hz (Xrs_5) z-score) and EFL (difference between mean inspiratory and expiratory reactance (ΔXrs_5)). Hyperinflation was assessed by supine inspiratory capacity (IC_{supine}) z-score. In-laboratory polysomnography was used to assess sleep disturbance, measured by Apnoea-Hypopnoea Index (AHI), Oxygen Desaturation Index (ODI) and AHI during rapid eye movement sleep (AHI REM). Monitoring of transcutaneous carbon dioxide ($TcCO_2$), and measurements of partial pressure of arterial carbon dioxide ($PaCO_2$) and HCO_3^- were performed in a subgroup.

Results 28 COPD patients were enrolled (13 female, mean age (SD) 67.5 (8.71) years and mean forced expiratory volume in 1second (FEV1) z-scores (SD) −2.61 (1.06)). Worse $Xrs_{5(supine)}$ correlated with greater respiratory arousals (AHI r_s =0.47, p=0.01; ODI r_s=−0.58, p=0.001), as did greater $\Delta Xrs_{5(supine)}$ (AHI REM r_s=0.53, p=0.005). $Xrs_{5(supine)}$ correlated with peripheral oxygen saturation nadir (r_s=0.43, p=0.02). IC_{supine} correlated negatively with hypoventilation ($PaCO_2$ r_s=−0.77, p=0.001; HCO_3^- r_s=−0.78, p=0.001, n=15), as did $Xrs_{5(supine)}$ (rise in $TcCO_2$ r_s=−0.65, p=0.009).

Conclusion Lung derecruitment, EFL and supine hyperinflation likely contribute to sleep disturbance and sleep-related gas exchange impairment in COPD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sleep disturbance in chronic obstructive pulmonary disease (COPD) is common, but its underlying mechanisms are poorly understood.

WHAT THIS STUDY ADDS

⇒ For the first time, we demonstrate that impaired supine lung mechanics, including worse expiratory flow limitation, more severe supine hyperinflation and lung derecruitment, are associated with increased sleep disturbance, worse oxygen desaturation and nocturnal hypoventilation in COPD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings may allow identification of COPD patients at risk of sleep disturbance.

⇒ This raises the potential for future research targeted at overcoming supine expiratory flow limitation and hyperinflation, thus improving sleep outcomes.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction, causing breathlessness, reduced exercise capacity, impaired quality of life and premature death. Sleep disturbances are common in COPD, but under-recognised, with up to 78% of patients reporting difficulties with sleep initiation, frequent nocturnal wakenings, sleep dissatisfaction and daytime fatigue.[1] Poor sleep is an independent predictor of COPD exacerbations and is associated with worse overall quality of life.[1–3] Despite its importance, the underlying mechanisms and risk factors are poorly understood.

Although airflow obstruction in COPD is the obvious and likely cause of sleep impairment, the gold standard measurement, using spirometry, does not correlate with sleep quality parameters, such as sleep efficiency, sleep disturbance or nocturnal hypoventilation.[4–7] Resting and dynamic hyperinflation are key mechanical characteristics of COPD and are not captured well by spirometry. Hyperinflation can persist in

the supine position, defined by failure to increase inspiratory capacity (IC) which would occur in healthy individuals. Decreased IC to total lung capacity (IC/TLC) ratio correlates with sleep efficiency, independently of Apnoea-Hypopnoea Index (AHI) in COPD.[6] This may be due to impaired diaphragmatic function, as measured by a reduced length of the zone of apposition, which also correlates with reduced sleep efficiency and total sleep time in COPD.[8] Furthermore, supine hyperinflation is closely linked to tidal expiratory flow limitation (EFL)[9] in which flow cannot be increased during tidal breathing, despite increased alveolar driving pressure. Supine EFL is likely important in sleep, being associated with orthopnoea, nocturnal symptoms and subjective sleep disturbance in COPD.[10] Overcoming tidal EFL with carefully titrated expiratory positive airway pressure (EPAP) has been shown to reduce ineffective respiratory efforts and has the potential to reduce nocturnal hypercapnia in COPD.[11]

Oscillometry is a practical way to measure breathing mechanics in COPD and provides clinically relevant information. Multi-frequency pressure waves are superimposed over tidal breathing to derive parameters of resistance (Rrs), reflecting overall airway calibre, and reactance (Xrs), reflecting the oscillatory (or dynamic) elastic properties of the respiratory system. Both Rrs and, in particular, Xrs are sensitive to airway narrowing and closure, and heterogeneous ventilation.[12] Xrs is not a measure of static stiffness of the respiratory system; rather, it is a measure of lung de-recruitment. When there is severe small airway narrowing and closure, the volume of lung that the oscillation signal 'sees' is reduced; the 'communicating lung size' is smaller and the lung mechanically behaves stiffer (ie, reduced dynamic compliance) and hence, Xrs becomes more negative. That is, more negative Xrs indicates greater lung derecruitment due to worse airways disease. Xrs as a measure of lung de-recruitment has been demonstrated in comparisons of Xrs against plethysmographic lung volume and single breath alveolar volume[13] and hyperpolarised helium 3 MRI images, which provide detailed visualisation of low-ventilated lungs.[14] Both studies demonstrate a close correlation between Xrs and communicating lung volume. EFL can be measured by a decrease of Xrs (worsening derecruitment) in expiration. Reduction in reactance in expiration compared with inspiration (ΔXrs) indicates the presence of EFL.[15] Furthermore, Xrs can also be measured in supine posture which is more relevant to sleep.

Our aims were to assess the relationships between gas trapping, hyperinflation and ΔXrs on nocturnal obstructive respiratory events, nocturnal oxygen desaturation and hypoventilation during sleep in patients with COPD. We hypothesised that hyperinflation, worse Xrs and ΔXrs would be associated with apnoeas and hypopnoeas, nocturnal oxygen desaturation and hypoventilation in patients with COPD.

A subset of the data, including seated and supine oscillometry and seated lung function, was previously published in a study assessing the relationship between supine persistent hyperinflation and oscillatory mechanics.[9]

METHODS

Subjects

Current or ex-smokers with at least a 10 pack-year smoking history, aged over 40 years, with a physician diagnosis of COPD, and no known history of sleep-disordered breathing or hypercapnic respiratory failure were recruited from outpatient services at the Royal North Shore Hospital, a large tertiary referral hospital in metropolitan Sydney, and the patient volunteer database at the Woolcock Institute of Medical Research. Patients with a recent (<8 weeks) exacerbation of COPD or significant comorbid cardiorespiratory disease were excluded. The diagnosis of COPD was confirmed by a post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced inspiratory vital capacity (FVC) ratio below the lower limit of normal.

Study design

This was a prospective, observational study in which subjects underwent seated and supine oscillometry and IC manoeuvres, followed by spirometry and body plethysmography. Subjects completed the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI), the St George's Respiratory Questionnaire (SGRQ) and a clinical questionnaire on medical history, medication use and cigarette smoking. Patients also completed the COPD Asthma Sleep Impact Scale (CASIS) and the COPD assessment test. The CASIS is a 0–100 point scale designed to specifically measure the effect of respiratory disease on sleep, with a higher score indicating greater severity of sleep disturbance.[16] All patients then underwent a full in-laboratory polysomnography, with patients who consented having evening and morning arterial blood gas measurements and overnight transcutaneous CO_2 monitoring.

Lung function

Impedance as a measure of lung mechanics was assessed using a TremoFlo oscillometry device (Thorasys, Thoracic Medical Systems) as per European Respiratory Society (ERS) recommendations, using a 5–37 Hz multi-frequency pressure oscillation. Calibration was checked daily using a test load of 15 $cmH_2O/(L/s)$ resistance, supplied by the manufacturer. A minimum of three technically acceptable 30 s trials were performed in the seated and supine position. Subjects were instructed to breathe normally through an anti-bacterial filter while wearing a nose clip, holding their head in a slightly chin-up position and supporting their own cheeks. After a period of breathing stabilisation, three 30 s recordings of tidal breathing were made with the operator monitoring the subject's head position, and observing for leaks,

swallowing or coughing. Three maximal deep inspiratory breaths were performed in the seated position from which IC was calculated. Subjects were moved into the supine position, supported with one pillow under their head. In the supine posture, the same neutral neck position was maintained with the operator holding the device in position, and tidal breathing and IC breaths were again recorded.

Trials containing artefacts were excluded and measurements repeated. Measurements were assessed off-line for quality (MS). Any breaths containing resistances that were negative or were >5 SDs above the mean were excluded. Supine persistent hyperinflation was measured by supine IC, supine IC/TLC ratio and the difference between seated and supine IC. Tremoflo version 1.0.44.40 (2019) was used for offline analysis of data and data export. We report only the impedance results for 5 Hz. The mean Rrs and Xrs of each acquisition was calculated, from which the mean of the three recordings was calculated (Rrs_{mean} and Xrs_{mean}). Rrs and Xrs z-scores were calculated using Oostveen *et al* or Brown *et al*.[17 18] We also calculated Rrs and Xrs of expiration and inspiration separately, and calculated the difference between the mean inspiratory and expiratory Xrs (ΔXrs) as the mean of all inspiratory Xrs in the acquisition minus the mean of all expiratory Xrs, then calculated the mean difference of the three acquisitions. This method is slightly different from the technique described by Dellacà and colleagues where within-breath differences in inspiratory and expiratory Xrs were calculated. Due to technical difficulties, we were unable to calculate intra-breath differences and given that both methods yield similar results, we proceeded to use the threshold value of ΔXrs≥2.8 $cmH_2O/(L/s)$ during tidal volume breathing indicating that significant EFL was present.[15]

Spirometry and body plethysmography were performed according to American Thoracic Society/ERS criteria. All pulmonary functions were expressed as z-scores, using Global Lung Function Initiative equations for spirometry and lung volumes, and reference values from Quanjer *et al* for functional residual capacity/TLC.[19 20]

In-laboratory polysomnography

All patients underwent in-laboratory overnight polysomnography with electroencephalogram PSG montage with electro-oculogram, chin electromyogram, nasal airflow pressure (nasal cannula), thoracic and abdominal respiratory effort, finger pulse oximetry (SpO_2%), body position and leg electromyography measurements. ECG data were collected using three electrodes placed in the standard lead II configuration with a sampling rate of 512 Hz. Lead placement was standardised as per the American Academy of Sleep Medicine (AASM) guidelines version 2.6. A radiometer TCM5 device was used to measure transcutaneous carbon dioxide monitoring ($TcCO_2$). A significant rise in $TcCO_2$ was defined as ≥1.33 kPa (equivalent to ≥10 mm Hg).

Sleep staging and scoring were performed by registered sleep technologists using Recommended Standards and Specifications outlined by the AASM Manual for the Scoring of Sleep and Associated Events, version 2.2. The sleep parameters of interest were: (1) sleep efficiency—total sleep time as a percent of total time in bed, (2) AHI—the number of apnoeas or hypopnoeas recorded during the study per hour of sleep. An apnoea was defined as a complete (≥90%) obstruction to airflow lasting ≥10 s, while a hypopnoea was defined as a partial (≥30%) reduction in airflow lasting ≥10 s associated with either an arousal from sleep or an oxygen desaturation of ≥3% from baseline, (3) oxygen desaturation nadir and (4) the Oxygen Desaturation Index (ODI)—the number of oxygen desaturations ≥3% per hour of sleep, averaged over the total sleep time and (5) Apnoea-Hypopnoea Index in rapid eye movement (REM) (AHI_{REM}).

Patient and public involvement

Patients or the public were not directly involved in the design, reporting or dissemination plans of our research.

Statistical analysis

Data were analysed using Jamovi V.2.3.28 and SPSS Statistics. Graphs were generated using GraphPad Prism V.10.2.2. Data are presented as mean (SD) or median (IQR) as appropriate. To address the hypothesis that supine hyperinflation, Xrs and ΔXrs are associated with sleep parameters, we used a univariate Spearman's correlation due to non-normally distributed data.

Z-score measurements were used in these correlations to account for the impact of sex, body habitus and age.

Receiver operator curve (ROC) was calculated in Jamovi V.2.3.28 for $Xrs_{5supine}$ and moderate-severe obstructive sleep apnoea (OSA).

Statistical significance was determined using the method of Benjamini and Hochberg, which accounts for multiple comparisons in a small sample size, assuming a false discovery rate of 0.2.[21]

Sample size

There are no published data on the relationship between Xrs_5, ΔXrs or hyperinflation, and respiratory arousals, nocturnal desaturation or hypoventilation. Based on previous data by Kwon *et al* and Krachman *et al*[6 8] who assessed the relationship between seated hyperinflation and sleep parameters, we anticipated a linear correlation coefficient of approximately 0.5 between $Xrs_{5supine}$ and AHI to arrive at a sample size of 29, with a power of 80% and type 1 error 0.05.

Table 1 Baseline demographic and lung function parameters

Age, years	67.5 (8.71)
Female, N (%)	13 (46.4%)
BMI	26.8 (5.06)
Pack years	40 (19.5)
SGRQ	40.6 (15.4)
FEV1 z-score	–2.61 (1.06)
FEV1% predicted	57 (18.9)
FVC z-score	–0.54 (1.04)
FEV1/FVC	47.3 (12)
TLC z-score	0.75 (1.05)
RV/TLC z-score	1.84 (1.09)
IC_{Seated} (L)	2.03 (0.69)
IC_{Seated} z-score	–2.94 (0.85)
IC_{Supine} (L)	2.09 (0.67)
IC_{Supine} z-score	–2.64 (0.92)
$Rrs_{5(Seated)}$ $cmH_2O/(L/s)$	5.49 (2.34)
$Rrs_{5(Seated)}$ z-score	1.82 (1.45)
$Rrs_{5(Supine)}$ $cmH_2O/(L/s)$	6.83 (2.69)
$Rrs_{5(Supine)}$ z-score	2.66 (1.34)
$Xrs_{5(Seated)}$ $cmH_2O/(L/s)$	–4.04 (2.63)
$Xrs_{5(Seated)}$ z-score	–4.81 (4.03)
$Xrs_{5(Supine)}$ $cmH_2O/(L/s)$	–6.04 (3.02)
$Xrs_{5(Supine)}$ z-score	–7.88 (3.74)
$\Delta Xrs_{5(Seated)}$	2.25 (2.74)
$\Delta Xrs_{5(Supine)}$	4.81 (4.1)

n=28. Values are mean (SD).
BMI, body mass index; FRC/TLC, functional residual capacity/total lung capacity ratio; Rrs_5, respiratory resistance at 5 Hz; RV/TLC, residual volume/total lung capacity ratio; SGRQ, St George's Respiratory Questionnaire; Xrs_5, respiratory reactance at 5 Hz; ΔXrs_5, difference between inspiratory and expiratory reactance at 5 Hz.

RESULTS

Patient demographics

Participant demographics and baseline lung function are summarised in table 1. 28 COPD patients with a mean age (SD) of 67.5 (8.71) years were enrolled in the study. Patients demonstrated moderate airflow obstruction (mean (SD) FEV1 z-score –2.61 (1.06); mean (SD) FEV1% predicted 57 (18.9)) and mild baseline hyperinflation on average. There was mild impairment of mean seated Rrs_5 and severely reduced mean Xrs_5. Both mean Rrs_5 and mean Xrs_5 z-score worsened in the supine position. Absolute values for Rrs_5 and Xrs_5 are provided in table 1. Flow limitation (EFL-$\Delta Xrs_5 \geq 2.8$ $cmH_2O/(L/s)$) was present in 42.8% of patients in the seated position, increasing to 67.8% in the supine position. There was minimal change in IC seated to supine.

Table 2 Sleep parameters

Total sleep time, minutes	308 (228–359)
Sleep efficiency %	70.8 (56.2–78.9)
AHI (/hour)	8.4 (3.3–21.2)
Presence of OSA (AHI≥5) n (%)	17 (60.7)
AHI≥15 n (%)	9 (32.1)
ODI (/hour)	3.65 (1.05–11.8)
Arousal index (/hour)	18.4 (13.1–23.6)
REM % of TST	15.3 (8.57–21)
AHI_{REM} (/hour)	22.5 (7.1–36.2)
Mean nocturnal SpO_2 (%)	92.5 (90.5–94)
SpO_2 nadir (%)	86 (80–88.3)
% TST sats<90%	1.85 (0–48.1)
ESS median	6 (3–8.5)
PSQI	8 (5-11)
CASIS	33.8 (19.1)*
ESS>9 n (%)	7 (25)
PSQI≥5 n (%)	23 (82.1)

n=28. Values are mean (SD) or median (IQR).
*19 patients included only.
AHI, Apnoea-Hypopnoea Index; CASIS, COPD Asthma Sleep Impact Scale; ESS, Epworth Sleepiness Score; ODI, Oxygen Desaturation Index; OSA, obstructive sleep apnoea; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement; SPO_2, peripheral oxygen saturation; TST, total sleep time.

Sleep parameters

Sleep parameters are outlined in table 2. The median sleep efficiency was mildly reduced (70.8% IQR 56.2%–78.9%) and median percentage of REM sleep was moderately reduced (15.3% IQR 8.6%–21.0%). Arousal index was within the normal range. Median AHI was increased at 8.4/hour (IQR 3.3–21.2/hour) with 60.7% of patients having OSA (AHI≥5). Moderate-severe OSA (AHI≥15/hour) was present in 32.1% of patients. Median sleep efficiency and percentage of REM sleep were similar when only those with OSA (AHI≥5) were evaluated (sleep efficiency 70.0% IQR 52.8%–77.6%; REM sleep percentage 16.3% IQR 11.7%–20.4%).

Median nocturnal oxygen saturations were mildly reduced (92.5%, IQR 90.5%–94.0%) and median oxygen desaturation nadir was 86% (IQR 80.0%–88.3%). Most patients (82.1%) reported poor sleep quality with a PSQI≥5, and 25% of patients reported increased daytime sleepiness with an ESS≥10. Mean (SD) CASIS score was mildly elevated at 33.8 (19.1).

Arterial blood gas and transcutaneous carbon dioxide measurements were measured in 15 participants. Mean (SD) pH was normal at 7.4 (0.02), mean (SD) PaO2 was mildly reduced at 9.67 (1.45) kPa and mean (SD) bicarbonate was 25.3 (2.85) mmol/L. Three of 15 patients (20%) had a significant (>1.33 kPa) rise in transcutaneous carbon dioxide trace ($TcCO_2$), with a mean (SD) increase of 0.95 (0.63) kPa. Mean (SD) morning arterial carbon

Table 3 Univariate correlations between lung function and sleep and gas exchange parameters

	AHI	ODI	REM %TST	AHI_{REM}	SpO_2 nadir	$PaCO_2$	HCO_3^-	Rise in $TcCO_2$
$IC_{(Supine)}$ z-score	−0.01 (0.97)	−0.17 (0.39)	0.19 (0.36)	−0.28 (0.15)	0.24 (0.23)	**−0.78 (0.001)**	**−0.78 (0.001)**	−0.12 (0.67)
$IC_{(Supine)}$/TLC	0.04 (0.83)	−0.06 (0.78)	−0.04 (0.85)	−0.12 (0.54)	0.24 (0.23)	−0.50 (0.06)	**−0.53 (0.04)**	0.22 (0.43)
$Rrs_{5(Supine)}$ z-score	0.15 (0.45)	0.19 (0.33)	0.05 (0.82)	0.2 (0.32)	0.07 (0.72)	0.32 (0.25)	0.35 (0.20)	−0.19 (0.50)
$Xrs_{5(Supine)}$ z-score	**−0.47 (0.01)**	**−0.58 (0.001)**	0.09 (0.64)	−0.23 (0.25)	**0.43 (0.02)**	−0.44 (0.10)	**−0.55 (0.03)**	−0.33 (0.24)
$\Delta Xrs_{5(Supine)}$	0.20 (0.31)	0.26 (0.18)	0.1 (0.63)	**0.53 (0.005)**	−0.19 (0.26)	0.34 (0.22)	0.48 (0.07)	0.34 (0.21)
$Rrs_5Z_{(Supine–upright)}$	0.07 (0.72)	0.03 (0.88)	0.31 (0.10)	0.10 (0.61)	0.03 (0.89)	**0.54 (0.04)**	0.32 (0.24)	0.25 (0.37)
$Xrs_5Z_{(Supine–upright)}$	0.16 (0.430)	0.23 (0.23)	0.15 (0.45)	−0.27 (0.17)	**0.52 (0.003)**	**−0.51 (0.05)**	−0.30 (0.29)	**−0.65 (0.009)**

n=28 for sleep parameters. n=15 had arterial blood gas and $TcCO_2$ measurements. Values are Spearman correlation coefficients (p values). Bold denotes statistical significance.
AHI, Apnoea-Hypopnoea Index; AHI_{REM}, Apnoea-Hypopnoea Index in rapid eye movement sleep; HCO_3^-, partial pressure of bicarbonate; IC, inspiratory capacity; ODI, Oxygen Desaturation Index; $PaCO_2$, partial pressure of arterial carbon dioxide; REM % TST, Percentage of total sleep time in rapid eye movement sleep; Rrs_5, respiratory resistance at 5 Hz; $Rrs_5Z_{(Supine–upright)}$, supine-seated Rrs_5 z-score; $SpO_{2\ nadir}$, lowest recorded oxygen saturations; $TcCO_2$, maximum increase in transcutaneous carbon dioxide; Xrs_5, respiratory reactance at 5 Hz; $Xrs_5Z_{(Supine–upright)}$, supine-seated Xrs_5 z-score; ΔXrs_5, difference between inspiratory and expiratory reactance.

dioxide (partial pressure of arterial carbon dioxide ($PaCO_2$)) was normal at 5.59 (0.80) kPa, however 5 of 15 participants (33.3%) had $PaCO_2 \geq 6.0$ kPa.

Relationships between lung function and sleep parameters

Univariate correlations between lung function and sleep parameters and gas exchange parameters are outlined in table 3 and figures 1 and 2. Lung derecruitment in the seated position ($Xrs_{5(seated)}$) correlated with ODI (see online supplemental table 2) but no other parameters. In contrast, Xrs_5 in the supine position ($Xrs_{5(supine)}$) correlated with AHI, ODI, SpO_2 nadir and arterial bicarbonate (see table 3 and figure 1). There were no significant associations between $\Delta Xrs_{5(seated)}$ and either sleep or gas exchange parameters; however, $\Delta Xrs_{5(supine)}$ correlated with AHI in REM sleep. A greater decrease in $Xrs_{5(supine-upright)}$ also correlated with lower nocturnal oxygen saturation and a greater increase in $TcCO_2$ (see table 3).

SEATED AND SUPINE HYPERINFLATION (IC_{SEATED} Z-SCORE AND IC_{SUPINE} Z-SCORE) BOTH CORRELATED WITH ALVEOLAR HYPOVENTILATION WITH INCREASED ARTERIAL BICARBONATE AND $PACO_2$ (SEE TABLE 3, ONLINE SUPPLEMENTAL TABLE 3 AND FIGURE 2).

Univariate relationships for other parameters can be found in online supplemental file 1, but seated spirometry and $Rrs_{5(Supine)}$ were unrelated to sleep disturbance or gas exchange. There were no significant correlations between any lung function parameters and either sleep efficiency or arousals.

When those with moderate-severe OSA (AHI>15) were excluded from analysis, the relationships between $Xrs_{5(Supine)}$ and ODI, SpO_2 nadir and bicarbonate persisted as did the relationship between IC_{supine} z-score and arterial bicarbonate and $PaCO_2$ (see online supplemental tables 4 and 5).

Age and body mass index were correlated with higher ESS scores. A greater reduction in $Xrs_{5(Supine)}$ z-score was associated with a lower PSQI. Spirometry, ΔXrs_5, $Xrs_{5(Supine)}$, AHI, ODI, SpO_2 nadir, $PaCO_2$ and hyperinflation were unrelated to any subjective sleep scores (see online supplemental table 1).

DISCUSSION

In this prospective observational study of moderate to severe COPD patients without a pre-existing diagnosed sleep disorder, we found that worse supine lung derecruitment ($Xrs_{5(Supine)}$) had important relationships with respiratory disturbance (as measured by AHI), as well as gas exchange (nocturnal oxygen desaturation and ODI) (see figure 1). In contrast, as shown in figure 2, supine hyperinflation was related to indices of alveolar hypoventilation (bicarbonate and $PaCO_2$). Although FEV_1 and FEV_1/FVC ratio are important measurements of disease severity and airflow obstruction, they were unrelated to polysomnographic sleep disturbance, gas exchange or alveolar ventilation during sleep. These findings may be clinically helpful in identifying subjects who may benefit from interventions to improve sleep.

A novel finding in our study was that Xrs_5, particularly in the supine position, was consistently related to AHI and ODI and oxygen desaturation, whereas Rrs_5 and spirometry were not. There were no correlations between lung function parameters and sleep efficiency or arousal

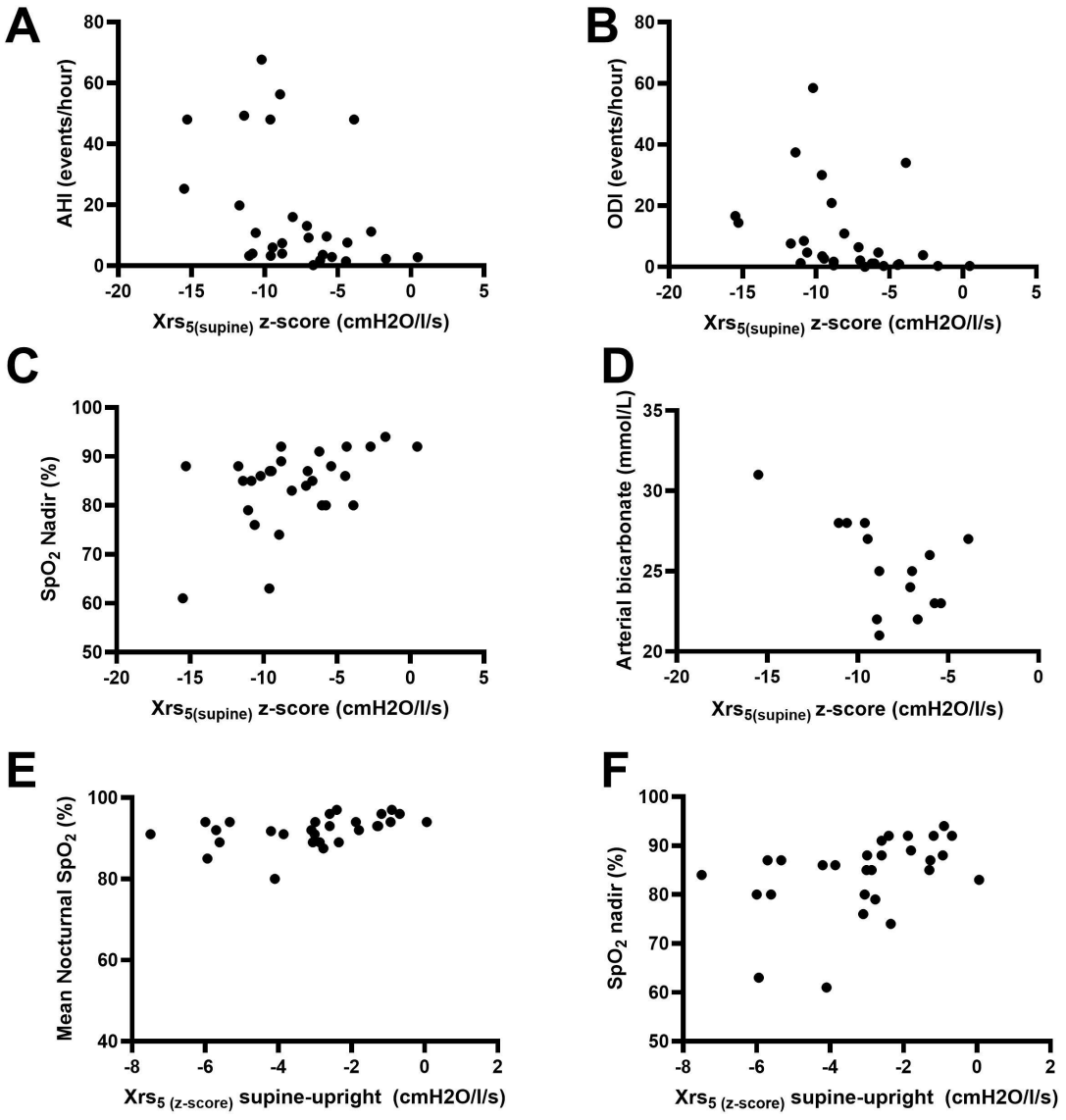

Figure 1 Relationships between supine Xrs_5 z-scores and (A) Apnoea-Hypopnoea Index (AHI) r_s=0.47, p=0.01, (B) Oxygen Desaturation Index (ODI) r_s=0.58, p=0.001, (C) peripheral oxygen saturation nadir (SpO_2 nadir) r_s =0.43, p=0.02 and (D) arterial bicarbonate r_s=−0.52, p=0.03. N=28 for AHI, ODI, mean nocturnal SpO_2 and SpO_2 nadir, n=15 for bicarbonate. Graphs (E) and (F) show relationships between the change in Xrs_5 z-scores supine-upright and mean nocturnal SpO_2 r_s=0.54, p=0.03 and SpO_2 nadir r_s=0.52, p=0.003, respectively. Xrs5, respiratory reactance at 5 Hz.

index. In contrast, previous studies demonstrated correlations between FEV_1 and arousals[22] and sleep efficiency.[8] Explanations for the discordance may be sample size, with much larger numbers studied by Mcsharry *et al*,[22] although participant numbers in the study of Krachman *et al*[8] were similar to our study. A major difference, however, which may account for the discordance, was the severity of FEV_1 impairment; the mean FEV_1 was 57±18.9% of predicted in our study, compared with approximately 30% of predicted in the aforementioned studies.

In the supine position, there was a significant decrease in mean Xrs_5 despite no change in IC. In a prior publication, we reported this decrease in supine, compared with seated Xrs_5, independent of lung volume which we speculated was due to a change in distribution of airway closure.[9] Supine Xrs_5 and ΔXrs_5 parameters were more strongly correlated with impaired sleep and gas exchange parameters, compared with seated measures, suggesting that the mechanical disadvantage of the supine position has implications for the COPD patient during sleep.

The underlying mechanisms explaining the relationship between Xrs_5 and measures of OSA including AHI and ODI are unknown. Xrs_5 reflects lung derecruitment due to its associations with reduced alveolar volume,[13 14] increased RV/TLC ratio and intrinsic positive end expiratory pressure (iPEEP).[23] At 5 Hz, Xrs correlates strongly with oesophageal balloon measurements[24] and is reduced in airway diseases due to airway narrowing and closure.[25] During sleep—especially REM—lung derecruitment and iPEEP would increase the work of breathing, impair ventilation/perfusion (V/Q) matching and reduce minute ventilation. This is due to the need for greater alveolar

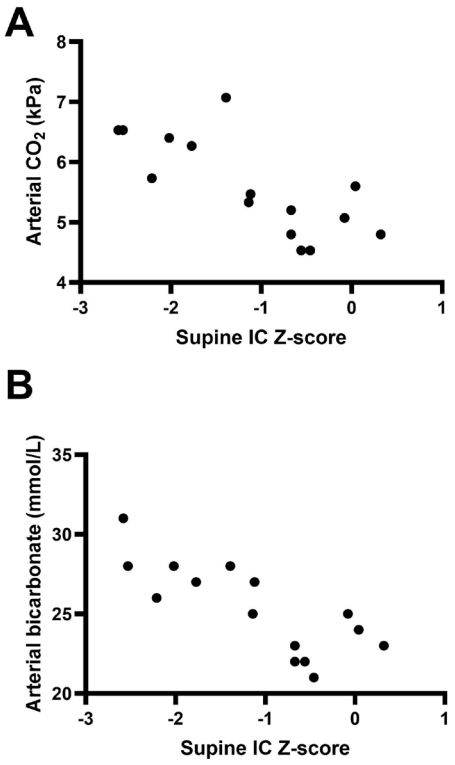

Figure 2 Relationships between supine IC z-scores and (A) $PaCO_2$ r_s=−0.78, p=0.001 and (B) arterial bicarbonate r_s=−0.78, p=0.001 (n=15). IC, inspiratory capacity; $PaCO_2$, partial pressure of arterial carbon dioxide.

pressure to ventilate a smaller lung volume and the inspiratory threshold imposed by iPEEP. Poorly ventilated lung regions increase the risk of V/Q mismatch, particularly if hypoxic pulmonary vasoconstriction is impaired, such as with infection or bronchodilator use.

We suggest that supine hyperinflation (IC_{Supine}) is clinically relevant because it correlated with hypoventilation (increased morning $PaCO_2$ and bicarbonate) and may indicate a lack of respiratory reserve, such as during exercise when it is also associated with worsening hypercapnia.[26] The relationship between supine hyperinflation and sleep disturbance is concordant with published relationships of upright hyperinflation[6] and gas trapping[8] with reduced sleep efficiency. As expected, supine hyperinflation and $\Delta Xrs_{5(Supine)}$ were correlated (r_s=0.475, p=0.011) and may be mechanistically linked.[9] $\Delta Xrs_{5(Supine)}$ correlated with AHI in REM, presumably due to the propensity to hypoventilation in REM sleep[27 28] which would likely lead to a small decrease in PaO_2. However, since PaO_2 in COPD may be around 8.0 kPa or less, small decreases in PaO_2 would lead to desaturation that is enough to be deemed a respiratory event on polysomnography. Therefore, these interrelated phenomena of EFL, particularly in the supine position, supine hyperinflation and gas trapping may contribute to respiratory disturbance in REM sleep.

The $Xrs_{5(supine)}$ results may help to identify patients with OSA as ROC analysis showed supine Xrs_5 of less than or equal to −9.5 predicted moderate to severe OSA, with a sensitivity of 84.2% and specificity of 66.7%, corresponding to an area under the curve of 0.8, suggesting that there is potential for oscillometry to be used as a screening tool for OSA in COPD. Studies with greater numbers and range of severity would be required to better evaluate this.

Overcoming supine EFL, hyperinflation and gas trapping is a potential treatment target in COPD. CPAP has been shown to increase IC and reduce airway resistance in COPD.[29 30] Recent studies have demonstrated that titration of external positive end expiratory pressure (EPAP) to abolish tidal EFL reduces transdiaphragmatic inspiratory pressure swings and neural respiratory drive in patients with COPD and hypercapnic respiratory failure[31] and has the potential to reduce nocturnal hypercapnia and ineffective respiratory efforts.[11] It is unclear whether this improves patient-reported sleep outcomes or is generalisable to non-hypercapnic patients, but it is an important area of further study given the lack of treatment options for nocturnal symptoms and the comparative ease and accessibility of CPAP compared with non-invasive ventilation.

The findings from this study cannot be generalised across the spectrum of COPD, given the small sample size and moderate spirometric impairment. The relationships between supine hyperinflation and hypoventilation were in a subgroup and so must be interpreted cautiously. No causal relationship has been identified between tidal EFL, supine lung derecruitment and sleep disturbance; however, we suggest that there is a mechanistic plausibility that underlies such relationships, given the interrelationship between EFL, hyperinflation and iPEEP. Interestingly, there were no consistent relationships between measurements of lung mechanics and subjective measures of sleep impairment. However, we recognise that the ESS and PSQI are not validated in COPD. Abnormal supine Xrs_5 could also indicate increased upper airway obstruction due to compliant tissues, which could become more abnormal during sleep. We standardised head position, but the upper airway contribution was not estimated in our study since we could not estimate the pressure drop across the upper airways.

Only univariate correlations were assessed due to the small sample size and therefore, the impact of confounders, including underlying OSA, could not be determined. However, the use of z-score measurements in the analysis does account for age, sex and body habitus. We also demonstrated a persistent significant relationship between $Xrs_{5(supine)}$, $\Delta Xrs_{5(supine)}$ and supine IC and measures of sleep disturbance and gas exchange when those with moderate-severe OSA were excluded from analysis.

In conclusion, in this study of participants with moderate COPD but no previous diagnosis of sleep-disordered breathing, more severe supine lung derecruitment and EFL were associated with greater risk of sleep disturbance (AHI, ODI and AHI REM) and nocturnal

oxygen desaturation (SpO_2 nadir and ODI) on nocturnal polysomnography, while supine hyperinflation indicated greater risk of hypoventilation (morning $PaCO_2$ and bicarbonate). Polysomnographic parameters were dissociated from spirometry. Supine parameters of ventilatory impairment may therefore be useful in identifying patients for polysomnography, although intervention studies to determine if there is any improvement in sleep parameters and/or impedance measures are still needed.

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Contributors MS and GGK conceived and designed the research; MS, KP, DGC, KECB and DT performed experiments; MS and GGK analysed the data; MS and GGK interpreted results of experiments. MS and GGK prepared figures and drafted the manuscript. All authors contributed to revising the article, gave final approval for the version to be published and agreed to be accountable to all aspects of the work. GGK is the guarantor for this work.

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Competing interests GGK is a non-executive board member of Cyclomedica Ltd, Australia. He has received honouraria for consultancy services from AstraZeneca, Chiesi, GSK and Sanofi. He receives grants from Cyclomedica and philanthropic trusts. KOT has received honouraria for consultancy services from AstraZeneca and Chiesi. ASLC and PC have received honouraria for consultancy services from Somnomed. PC has also received consulting fees from ResMed, Signifier Medical and Sunrise Medical. All other authors have no competing interests to declare.

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