Mechanisms of orthopnoea in patients with advanced COPD

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Orthopnoea, a troublesome symptom in patients with severe COPD, is associated with increased neural drive to the diaphragm and heightened respiratory effort to compensate for abrupt augmentation of load–capacity imbalance of the inspiratory muscles https://bit.ly/2ZLvyiI

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ABSTRACT Many patients with severe chronic obstructive pulmonary disease (COPD) report an unpleasant respiratory sensation at rest, which is further amplified by adoption of a supine position (orthopnoea). The mechanisms of this acute symptomatic deterioration are poorly understood.

Sixteen patients with advanced COPD and a history of orthopnoea and 16 age- and sex-matched healthy controls underwent pulmonary function tests (PFTs) and detailed sensory–mechanical measurements including inspiratory neural drive (IND) assessed by diaphragm electromyography (EMG_{di}), oesophageal pressure (P_{es}) and gastric pressure (P_{ga}), in both sitting and supine positions.

Patients had severe airflow obstruction (forced expiratory volume in 1 s (FEV_1): 40±18% pred) and lung hyperinflation. Regardless of the position, patients had lower inspiratory capacity (IC) and higher IND for a given tidal volume (V_T) (*i.e.* greater neuromechanical dissociation (NMD)), higher intensity of breathing discomfort, higher minute ventilation (V'_E) and higher breathing frequency (f_B) compared with controls (all p<0.05). For controls in a supine position, IC increased by 0.48 L *versus* sitting erect, with a small drop in V'_E, mainly due to reduced f_B (all p<0.05). By contrast, IC remained unaltered in patients with COPD, but dynamic lung compliance (C_{Ldyn}) decreased (p<0.05) in the supine position. Breathing discomfort, inspiratory work of breathing (WOB), inspiratory effort, IND, NMD and neuroventilatory uncoupling all increased in COPD patients in the supine position (p<0.05), but not in the healthy controls. Orthopnoea was associated with acute changes in IND (r=0.65, p=0.01), neuroventilatory uncoupling (r=0.76, p=0.001) and NMD (r=0.73, p=0.002).

In COPD, onset of orthopnoea coincided with an abrupt increase in elastic loading of the inspiratory muscles in recumbency, in association with increased IND and greater NMD of the respiratory system.

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Introduction

Dyspnoea is the most common respiratory symptom in patients with chronic obstructive pulmonary disease (COPD) and, in those with severe airflow obstruction, can be distressing even at rest [1]. In such patients, breathing discomfort can become further amplified on adoption of the supine position (*i.e.* orthopnoea) [2–4]. Indeed, in many individuals, orthopnoea may be problematic at night and may disrupt sleep. The precise mechanisms of orthopnoea are unknown and their investigation presents a new opportunity to advance our understanding of the neurophysiology of dyspnoea.

Proposed factors contributing to orthopnoea include impedance of diaphragmatic motion in the supine position, which may result in further mechanical disadvantage requiring compensatory increases in ribcage and accessory muscle activity to maintain ventilation [2, 5]. Heijdra *et al.* [5] have shown lower maximum inspiratory mouth pressure (MIP) and lower maximum expiratory mouth pressure (MEP) in the supine *versus* sitting positions in patients with severe COPD, reflecting increased functional weakness of various respiratory muscles in recumbency. Increased airway resistance (R_{aw}) in the supine position, due to lower end-expiratory lung volume (EELV), is potentially important although it is unclear whether this is relevant in patients with severe lung hyperinflation [3, 6–8]. Additionally, worsening pulmonary gas exchange abnormalities, due to gravitational effects and cephaloid shift of abdominal contents, could potentially stimulate chemoreceptors to increase inspiratory neural drive (IND), further compounding respiratory discomfort in some patients [9, 10].

Important studies have shown that certain positions adopted by individual patients to relieve dyspnoea, *e.g.* "forward-leaning", are associated with improved ability to generate maximal inspiratory pressures and improved length–tension relationships, neuromechanical efficiency of the diaphragm and reduced neuromechanical dissociation (NMD) of the respiratory system [2, 4, 11]. This raises the question of whether the opposite is true, *i.e.* that orthopnoea reflects acute increases in inspiratory muscle dysfunction and reduced diaphragmatic efficiency. Collectively, most studies undertaken to date lacked validated measurements of dyspnoea intensity and included participants with heterogeneous physiological abnormalities. Therefore, they have not permitted any definitive or unitary conclusions about the origins of orthopnoea in COPD.

Current constructs of the origins of dyspnoea in chronic lung diseases emphasise the importance of increased IND from cortical motor centres in the brain, secondary to load-capacity imbalance of the respiratory muscles [12, 13]. Advanced COPD patients show higher IND at rest (estimated by diaphragm electromyography (EMG_{di})) compared to healthy controls [14]. Recent studies, in which exercise was used as the provocative stimulus for dyspnoea, have shown that increased exertional dyspnoea intensity ratings are strongly associated with increased IND and increased disparity between IND and the mechanical response of the respiratory system (*i.e.* NMD) [15–19]. Moreover, interventions that reduced mechanical loading of the inspiratory muscles (*e.g.* bronchodilators) or that improved their strength (*e.g.* inspiratory muscle training) are associated with reduced IND and dyspnoea intensity in COPD [20, 21]. Accordingly, we postulated that orthopnoea is related to acute amplification of IND and NMD due to sudden deterioration in the load–capacity ratio of already compromised inspiratory muscles in the supine position. To test this hypothesis, we measured changes in dyspnoea intensity, IND, NMD, dynamic lung mechanics and pulmonary gas exchange during the transition from a seated to a supine position in patients with advanced COPD with known orthopnoea and in healthy controls.

Methods

Subjects

We included 16 patients with COPD (age: ⩾45 years; post-bronchodilator forced expiratory volume in 1 s (FEV_1): <80% pred; cigarette smoking history: ⩾20 pack-years; clinically stable but with long-standing orthopnoea). Exclusion criteria were: body mass index (BMI) >35 $kg{\cdot}m^{-2}$; use of oxygen; history of asthma or other respiratory/cardiovascular disease that could contribute to dyspnoea or orthopnoea (*e.g.* heart failure). Sixteen non-smoking, age-matched healthy control subjects were also included. Participants were recruited from a database of volunteers at the Respiratory Investigation Unit and respiratory outpatient clinics at Kingston Health Sciences Centre (Kingston, ON, Canada).

Study design

This cross-sectional prospective study received ethical approval from the Queen's University and Affiliated Teaching Hospitals Research Ethics Board (DMED-1989-16). After providing informed consent, participants completed one visit which included eligibility screening, symptom questionnaires, quality of life (QoL) questionnaires [22–25] and pulmonary function tests (PFTs). EMG_{di} and respiratory pressures were continuously measured at rest while sitting erect and then, after 10 min, in a supine position (using a double-ballooned, multi-electrode oesophageal catheter). In each position, participants performed a series

of cough, sniff and inspiratory capacity (IC) manoeuvres. Participants spent at least 5 min quiet breathing while using a mouth piece, in order to collect breath-by-breath breathing pattern and metabolic parameters.

Procedures

Spirometry, plethysmography, diffusing capacity of the lung for carbon monoxide (D_{LCO}), MIP and MEP tests were performed (Vmax229d, AutoboxV62J; SensorMedics, Yorba Linda, CA, USA). Questionnaires included the modified Medical Research Council (mMRC) dyspnoea scale [23], the baseline dyspnoea index (BDI) [22], the COPD assessment test (CAT) [25] and the St George's Respiratory Questionnaire (SGRQ) [24]. Breath-by-breath breathing pattern and metabolic parameters (Vmax229d, SensorMedics), oxygen saturation measured by pulse oximetry (S_{pO_2}) and heart rate (HR) (12-lead electrocardiogram) were collected continuously.

At the end of the quiet breathing period, participants were asked to rate their intensity of breathing discomfort using the modified 10-point Borg scale [26] ("how strong?", with 0 indicating no discomfort and 10 indicating the maximum discomfort they ever experienced or could imagine experiencing), as well as the quality of their breathing discomfort in five domains [27] ("what breathing feels like?", with regard to overall intensity, difficulty breathing in, difficulty breathing out, increased work/effort and unpleasantness).

EMG_{di} and respiratory pressure data represent 30 participants, as one participant in each group declined catheter insertion after initial agreement. A multi-electrode EMG_{di} catheter with oesophageal and gastric balloons was inserted nasally [16]. EMG_{di} and respiratory pressures were recorded continuously and analysed [14, 16, 28]. Raw EMG_{di} signal data was sampled at 2000 Hz (PowerLab ML880, ADInstruments, Bella Vista, Australia), band-pass filtered between 20 Hz and 1000 Hz (Bioamplifier RA-8, Guanzhou Yinghui Medical Equipment Co., Guangzhou, China) and converted into a root mean square (RMS) value. For each breath, data from the electrode pair (of the five pairs) with the largest inspiratory RMS value were used for analysis. $EMG_{di,max}$ was determined during maximal sniff or IC manoeuvres. The oesophageal and gastric balloons were connected to differential pressure transducers to obtain oesophageal (P_{es}) and gastric (P_{ga}) pressures. Transdiaphragmatic pressure (P_{di}) was calculated as the difference between P_{es} and P_{ga}. $P_{di,max}$ and $P_{es,max}$ were determined during maximal sniff manoeuvres [29]. Tidal EMG_{di} as a percentage of $EMG_{di,max}$ ($EMG_{di,\%max}$) and tidal P_{di} as a percentage of $P_{di,max}$ (tidal $P_{di,\%max}$) were used as indices of IND to the crural diaphragm and inspiratory effort, respectively [14, 16, 28]. Ratios of $EMG_{di,\%max}$:tidal volume (V_T)/predicted vital capacity (pred VC), $EMG_{di,\%max}$:tidal $P_{di,\%max}$ and $EMG_{di,\%max}$:minute ventilation (V'_E) were used as indices of NMD, neuromuscular efficiency of the diaphragm and neuroventilatory coupling, respectively. Expiratory flow limitation (EFL) was assessed as the percentage of V_T that overlapped the maximal flow–volume loop (V_{FL}) of each position [30]. The PowerLab system received continuous flow signal input from the Vmax229d system for analysis. R_{aw}, dynamic lung compliance (C_{Ldyn}) and work of breathing (WOB) were calculated as previously described [16]. More details are provided in the supplementary material.

Statistics

A sample size of 16 was estimated to provide 80% power to detect a one Borg unit difference in dyspnoea intensity between groups, based on a standard deviation (SD) of one unit, an α-value of 0.05 and a two-tailed test of significance. An unpaired t-test was used for between group comparisons and a paired t-test was used to compare responses in the sitting *versus* the supine position within groups. Linear regression was used to test the relationship between a change in dyspnoea intensity on supine–sitting position change and relevant independent variables. Statistical significance was set at $p<0.05$.

Results

Subject characteristics and PFTs

Thirty COPD patients were screened and 14 were excluded either because they didn't report long-standing orthopnoea and/or declined catheter insertion. Subject characteristics are given in table 1 and supplementary table E1. Groups were matched for age, sex, height and BMI. Three controls with normal PFTs had an insignificant smoking history and had stopped smoking for >30 years at the time of the study. Patients had greater activity-related dyspnoea (mMRC dyspnoea scale and BDI), higher CAT scores and poorer QoL compared with the control group (all $p<0.001$). None of the participants had any clinical evidence of significant cardiac or pulmonary vascular disease that could contribute to orthopnoea. Other comorbidities and medications are shown in the supplementary material.

Compared to the control group, patients had higher residual volume (RV)/total lung capacity (TLC) and lower D_{LCO}, sitting IC, maximum voluntary ventilation (MVV), MIP and MEP (all $p<0.01$) (table 1 and

TABLE 1 Subjects characteristics and pulmonary function test (PFT) data

Variable	COPD group (n=16, M:F=9:7)		Control group (n=16, M:F=8:8)	
	Value	% predicted[#]	Value	% predicted[#]
Characteristics				
Age years	66±7		69±7	
Height cm	168±10		167±7	
Body mass kg	71±17		76±11	
BMI $kg \cdot m^{-2}$	25±6		27±3	
Smoking history pack-years	52.2±24.9[¶]		1.8±3.5	
Current smokers %	25		0	
mMRC dyspnoea scale score (04)	2.7±0.9[¶]		0.2±0.4	
BDI focal score (0–12)	5.0±1.8[¶]		11.6±0.7	
PFTs				
FEV_1 L	0.96±0.39[¶]	40±18[¶]	2.70±0.63	115±28
FVC L	2.67±0.86[¶]	73±15[¶]	3.74±0.66	110±15
FEV_1/FVC %	37±14[¶]	53±20[¶]	70±7	101±11
PEF $L \cdot s^{-1}$	3.54±1.28[¶]	53±22[¶]	7.40±1.32	113±15
$FEF_{25-75\%}$ $L \cdot s^{-1}$	0.35±0.18[¶]	14±8[¶]	1.82±0.96	75±38
IC L	1.89±0.55[¶]	69±16[¶]	2.99±0.74	114±20
FRC L	4.92±1.77[¶]	151±42[¶]	3.15±0.63	100±16
TLC L	6.81±1.91	113±18	6.05±0.93	105±10
RV L	3.80±1.43[¶]	172±60[¶]	2.11±0.54	94±18
RV/TLC %	55±11[¶]		35±7	
D_{LCO} $mL \cdot min^{-1} \cdot mmHg^{-1}$	7.67±2.85[¶]	40±18[¶]	17.72±3.61	89±17
D_{LCO}/V_A $mL \cdot min^{-1} \cdot mmHg^{-1} \cdot L^{-1}$	2.06±0.69[¶]	52±24[¶]	3.38±0.53	92±13
V_A L	3.85±0.87[¶]		5.25±0.80	
V_A/TLC	0.53±0.19[¶]		0.87±0.06	
sR_{aw} $cmH_2O \cdot s$	28.9±16.4[¶]	686±385[¶]	7.7±4.6	184±104
MVV $L \cdot min^{-1}$	35.8±11.0[¶]	32±13[¶]	109.6±27.3	107±20
MIP cmH_2O	66±21[¶]	80±39[¶]	100±32	134±39
MEP cmH_2O	114±40	57±30[¶]	133±61	79±27

Data are presented as mean±SD, unless otherwise stated. COPD: chronic obstructive pulmonary disease; BMI: body mass index; mMRC: modified Medical Research Council; BDI: baseline dyspnoea index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PEF: peak expiratory flow; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC; IC: inspiratory capacity; FRC: functional residual capacity; TLC: total lung capacity; RV: residual volume; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V_A: alveolar volume; D_{LCO}/V_A: D_{LCO} corrected for V_A; sR_{aw}: specific airway resistance; MVV: maximum voluntary ventilation; MIP: maximum inspiratory mouth pressure; MEP: maximum expiratory mouth pressure. [#]: percentage of predicted normal values; [¶]: p<0.05 (COPD group *versus* control group).

supplementary figure E1). The ratio of alveolar volume (V_A), measured by single-breath gas diffusion, to plethysmographic TLC was lower in patients compared with the control group (p<0.0001), while TLC was not different between groups.

Impact of COPD on dyspnoea, IND and ventilatory mechanics

Tables 2 and 3 summarise measurements taken in the supine and sitting positions. In both positions, patients had greater dyspnoea in all five domains when compared to the control group (all p<0.05) (table 2). In addition, COPD patients had consistently higher V'_E and ventilatory inefficiency (ventilatory equivalent for carbon dioxide (V'_E/carbon dioxide production (V'_{CO_2}))) when compared with controls, regardless of body position, in the presence of lung hyperinflation (higher EELV, lower IC and inspiratory reserve volume (IRV)) and greater EFL (V_{FL}) (all p<0.01). V_T and end-tidal carbon dioxide tension (P_{ETCO_2}) were not different from the controls in both positions (figure 1 and table 2). $P_{di,max}$ and $P_{es,max}$ were lower and R_{aw}, total WOB, tidal EMG_{di}, IND, inspiratory effort and neuroventilatory uncoupling were all greater in the COPD group *versus* the control group, in both positions (all p<0.05) (table 3).

Impact of supine posture on dyspnoea, IND and ventilatory mechanics

Dyspnoea ratings increased significantly in the transition from a seated to a supine position in COPD patients (p<0.05), while controls reported no breathlessness (table 2 and supplementary figure E2).

TABLE 2 Cardio–respiratory and metabolic measurements in the sitting and supine positions

Variable	COPD group (n=16)		Control group (n=16)	
	Sitting	Supine	Sitting	Supine
V'_{O_2} L·min^{-1}	0.26±.0.05	0.26±0.06	0.28±0.06	0.29±0.05
V'_{CO_2} L·min^{-1}	0.21±0.05	0.21±0.05	0.23±0.05	0.21±0.04
V'_E L·min^{-1}	12.11±1.7¶	11.20±1.76¶	9.75±1.97#	8.46±1.87
IC L	2.05±0.73¶	2.13±0.78¶	3.02±0.79#	3.49±0.77
V_T L	0.65±0.16	0.62±0.19	0.68±0.14	0.67±0.12
f_B breaths·min^{-1}	19.9±4.4¶	19.7±6.1¶	15.3±3.0#	13.4±3.3
t_I/t_{TOT}	35.3±5.8¶	37.1±7.2¶	44.8±5.3#	55.1±9.5
t_I s	1.19±0.26¶	1.58±1.17¶	2.03±0.70#	3.06±1.22
IRV L	1.35±0.57#,¶	1.46±0.61¶	2.33±0.72	2.70±1.13
V'_E/V'_{O_2}	47.7±6.1#,¶	42.5±5.8¶	35.9±6.0#	29.3±3.5
V'_E/V'_{CO_2}	59.1±9.6#,¶	54.3±8.1¶	44.6±6.2#	40.1±4.5
P_{ETCO_2} mmHg	31.8±4.7#	33.0±4.2	34.2±3.2	34.6±1.9
HR beats·min^{-1}	72±8	70±9	70±10#	65±7
S_{pO_2} %	94.5±2.4#	93.8±2.6	95.4±1.4#	94.2±1.1
V_{FL} %	83.7±12.0#,¶	95.6±5.9¶	25.5±29.6#	67.0±27.0
Dyspnoea (Borg scale 0–10)				
Overall intensity	0.78±0.89#,¶	2.00±1.20¶	0.0±0.0	0.0±0.0
Difficulty breathing in	0.50±0.82#,¶	1.38±1.30¶	0.0±0.0	0.0±0.0
Difficulty breathing out	0.56±0.85#,¶	1.25±1.24¶	0.0±0.0	0.0±0.0
Work/effort	0.44±0.77#,¶	1.72±1.53¶	0.0±0.0	0.0±0.0
Unpleasantness	0.53±0.85#,¶	1.69±1.48¶	0.03±0.13	0.10±0.21

Data are presented as mean±SD. COPD: chronic obstructive pulmonary disease; V'_{O_2}: oxygen uptake; V'_{CO_2}: carbon dioxide production; V'_E: minute ventilation; IC: inspiratory capacity; V_T: tidal volume; f_B: breathing frequency; t_I: inspiratory time; t_{TOT}: total time of the respiratory cycle; t_I/t_{TOT}: inspiratory duty cycle; IRV: inspiratory reserve volume; V'_E/V'_{O_2}: ventilatory equivalent for oxygen; V'_E/V'_{CO_2}: ventilatory equivalent for carbon dioxide; P_{ETCO_2}: end-tidal carbon dioxide tension; HR: heart rate; S_{pO_2}: oxygen saturation measured by pulse oximetry; V_{FL}: percentage of V_T that overlapped the maximal flow–volume loop. #: p<0.05 (sitting *versus* supine within the COPD or control groups); ¶: p<0.05 (COPD group *versus* control group).

IC increased in the control group by 0.48 L (p<0.001) in a supine position *versus* a sitting position (supplementary figure E1), likely reflecting lower EELV. This was associated with lower V'_E, V'_E/V'_{CO_2}, ventilatory equivalent for oxygen (V'_E/oxygen uptake (V'_{O_2})) and breathing frequency (f_B) (all p<0.05), with no change in V_T (figure 1 and table 2). In contrast to controls, patients' IC, EELV, V'_E and f_B did not change in the supine position (table 2 and figure 1), while V_T also remained unchanged. Patients had lower V'_E/V'_{O_2} and V'_E/V'_{CO_2} (p=0.001) in the supine position *versus* the sitting position, reflecting a slightly lower V'_E (p=0.07), while V'_{O_2} and V'_{CO_2} remained unchanged. P_{ETCO_2} did not change with position in the control group, but increased slightly (by 1.2 mmHg) in COPD patients for the supine position *versus* the sitting position (p=0.003). There was a minor drop in S_{pO_2} of 1.2% in the control group (p=0.003) and of 0.7% in the patient group (p=0.02) for the supine position *versus* the sitting position (table 2).

In the control group, supine positioning was associated with a small reduction in $P_{es,max}$ (p=0.01), $P_{di,max}$ (p<0.01) and $EMG_{di,max}$ (p=0.004) (table 3 and supplementary figures E3 and E4). There were no differences in tidal EMG_{di}, IND, R_{aw}, WOB, inspiratory effort, NMD, neuromuscular efficiency of the diaphragm or neuroventilatory coupling; however, C_{Ldyn} was lower (p=0.04) and V_{FL} was higher (p=0.001) in the supine position *versus* the sitting position (table 3 and figure 2). Expiratory muscle activity was reduced while supine, *i.e.* lower tidal expiratory $P_{ga,max}$ (p=0.004) and lower end-expiratory P_{ga} (p=0.047) in the supine position *versus* the sitting position (table 3).

In a similar fashion to the control group, supine posture in COPD patients was associated with reductions in $EMG_{di,max}$, $P_{di,max}$, C_{Ldyn} and expiratory muscle activity (all p<0.05), with no change in R_{aw} (table 3 and supplementary figures E3 and E4). Absolute tidal EMG_{di} was not different on average but was raised in 53% of patients while supine (supplementary figure E3). Moreover, in patients with COPD, supine posture was associated with greater IND, NMD, neuroventilatory uncoupling and total inspiratory WOB (all p<0.05), but neuromuscular efficiency of the diaphragm was unaltered (table 3 and figure 2). Elastic WOB was also greater in the supine position *versus* the sitting position (p=0.06) (table 3). Unlike the control

TABLE 3 Respiratory pressures and diaphragm electromyography (EMG_{di}) measurements in the sitting and supine positions

Variable	COPD group (n=15)		Control group (n=15)	
	Sitting	Supine	Sitting	Supine
Inspiratory muscle activity				
Inspiratory $P_{es,max}$ cmH_2O	44.9±11.0¶	43.0±13.6¶	67.4±17.0#	61.2±17.6
Tidal inspiratory P_{es} cmH_2O	9.9±2.8¶	10.5±3.8¶	3.2±1.7	4.2±2.4
Tidal $P_{es,\%max}$ %	24±11#¶	29±17¶	5±3#	7±5
$P_{di,max}$ cmH_2O	79±23#¶	69±20¶	96±18#	80±21
Tidal P_{di} cmH_2O	10.4±2.6¶	11.6±3.2¶	5.4±2.6	5.8±3.8
Tidal $P_{di,\%max}$ %	14±5#¶	19±10¶	6±3	8±6
Tidal $P_{di,\%max}$:V_T/pred VC	0.75±0.31#¶	1.10±0.65¶	0.30±0.17	0.40±0.29
Expiratory muscle activity				
Tidal expiratory $P_{ga,max}$ cmH_2O	24.6±13.4#	18.1±12.9	17.7±9.7#	12.6±7.3
End expiratory P_{ga} cmH_2O	22.3±14.2#	17.0±13.5	15.0±10.8#	11.2±7.9
EMG_{di} measurements				
$EMG_{di,max}$ µV	185±42#	160±58	164±33#	139±26
Tidal EMG_{di} µV	46.9±17.4¶	50.4±19.6¶	20.1±8.0	17.4±6.8
$EMG_{di,\%max}$ (IND) %	25±7#¶	33±13¶	13±6	13±5
$EMG_{di,\%max}$:V'_E	2.10±0.69#¶	2.93±1.17¶	1.37±0.64	1.57±0.74
$EMG_{di,\%max}$:V_T/pred VC (NMD)	1.35±0.49#¶	1.92±1.10¶	0.66±0.37	0.65±0.28
$EMG_{di,\%max}$:tidal $P_{di,\%max}$	2.06±1.08	2.21±1.29	2.74±1.41	3.05±2.87
Other respiratory mechanics				
C_{Ldyn} $mL{\cdot}cmH_2O^{-1}$	168±96#¶	120±77¶	281±83#	232±106
R_{aw} $cmH_2O{\cdot}L^{-1}{\cdot}s^{-1}$	7.40±3.09¶	7.74±3.45¶	1.80±1.14	2.42±1.60
Total inspiratory WOB J	7.17±2.37#¶	10.16±4.14¶	1.87±1.28	2.46±1.86
Total expiratory WOB J	1.76±0.81¶	1.36±1.20¶	0.16±0.21	0.17±0.24
Elastic WOB J	3.10±0.98¶	4.21±2.39¶	1.16±0.75	1.64±1.20
Resistive WOB J	4.07±1.60¶	4.95±2.35¶	0.71±0.66	0.82±0.71

Data are presented as mean±SD. COPD: chronic obstructive pulmonary disease; P_{es}: oesophageal pressure; P_{di}: transdiaphragmatic pressure; VC: vital capacity; V_T: tidal volume; P_{ga}: gastric pressure; tidal expiratory $P_{ga,max}$: maximum expiratory P_{ga} during tidal breathing; V'_E: minute ventilation; IND: inspiratory neural drive; IND:V'_E: neuroventilatory coupling; NMD: neuromechanical dissociation; IND:tidal $P_{di,\%max}$: neuromuscular efficiency of the diaphragm; C_{Ldyn}: dynamic lung compliance; R_{aw}: airway resistance; WOB: work of breathing. #: p<0.05 (sitting *versus* supine within the COPD or control groups); ¶: p<0.05 (COPD group *versus* the control group).

group, the patient group had greater inspiratory effort and a greater ratio of $P_{di,\%max}$:V_T/pred VC in the supine position *versus* the sitting position (table 3 and figure 2). A descriptive summary of the physiological changes associated with supine posture compared to sitting posture, in both the control group and patients with COPD, is shown in table 4.

In COPD patients, the sitting-to-supine change in C_{Ldyn} correlated with corresponding changes in the elastic WOB (r=0.74, p=0.003). In addition, the sitting-to-supine change in dyspnoea intensity correlated with corresponding changes in IND (r=0.65, p=0.01), NMD (r=0.73, p=0.002) and neuroventilatory uncoupling (r=0.76, p=0.001) (figure 3).

Discussion

These results support the hypothesis that, compared with healthy controls, transition from the sitting position to the supine position in mechanically compromised patients with COPD was associated with acutely increased dyspnoea intensity linked to corresponding increases in NMD of the respiratory system due to sudden decreases in C_{Ldyn}.

This study included a well-characterised group of patients with severe airway obstruction, lung hyperinflation, persistent chronic dyspnoea and orthopnoea. Compared with healthy controls, patients had higher ventilatory requirements, IND (~two-fold), inspiratory effort and WOB, together with lower IC and IRV, regardless of the position. Additionally, patients had higher resistive and elastic loading of the functionally-weaker inspiratory muscles compared with controls.

In healthy individuals, supine positioning was associated with a small (albeit significant) drop in V'_E at a given V'_{CO_2}, primarily due to reduced f_B (figure 1), without any change in respiratory sensation [31, 32].

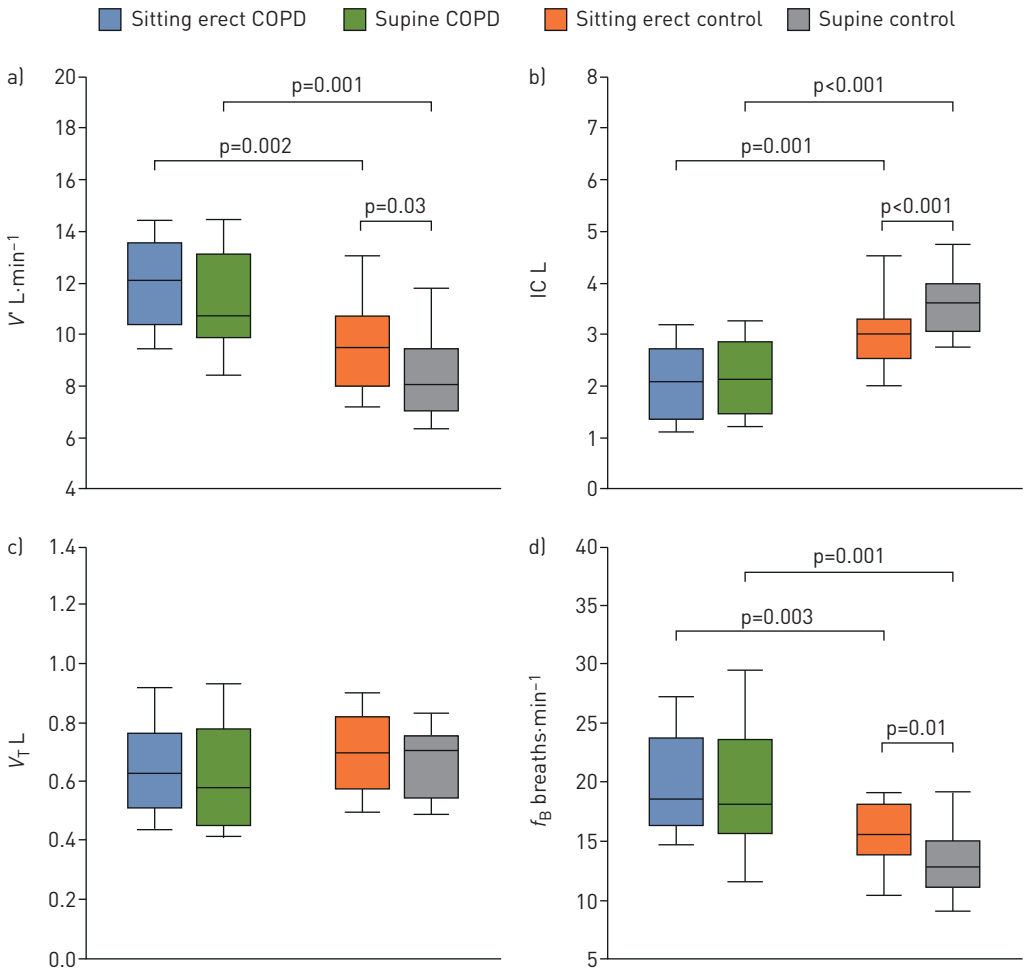

FIGURE 1 Breathing pattern parameters a) ventilation ($\dot{V}$); b) inspiratory capacity (IC); c) tidal volume (V_T); and d) breathing frequency (f_B), in the sitting and supine positions, in patients with advanced chronic obstructive pulmonary disease (COPD) and in age-matched healthy controls. Box plots depict the first to third quartiles, with the median denoted by a horizontal central line. Projecting bars denote the 10th to 90th percentile range.

Interestingly, IC increased in recumbency in the current study (by 0.48 L) (figure 1), which is consistent with an earlier report by Brody *et al.* [33]. This increase in IC suggests a relatively large decrease in supine EELV, assuming TLC remained unchanged as previously reported [34, 35]. It is noteworthy that inspiratory $P_{es,max}$ and $P_{di,max}$ decreased slightly in recumbency, suggesting reduced functional static inspiratory muscle strength. Based on previous studies, reduction in supine EELV is likely due to a combination of decreased chest wall compliance, increased thoracic blood volume, gravitational redistribution of visceral weight and cephaloid shift of the diaphragm [33, 36–38]. Recumbency in the healthy elderly is associated with increased small airway closure, more uneven distribution of inspired gas and ultimately greater heterogeneity in mechanical time constants (*i.e.* the product of compliance and resistance), with preferential ventilation of alveolar units with fast time constants for emptying [7, 8]. Indeed, EFL (as crudely assessed by the V_T *versus* maximal flow–volume loop method [30]) was increased and C_{Ldyn} was decreased in the supine position in our control group (average age 69 years), with little change in total R_{aw} [6]. The decrease in C_{Ldyn} in the supine position did not have a deleterious effect on respiratory symptoms in healthy controls. It led to a slight, albeit insignificant, increase in elastic WOB, which was accommodated by normally-functioning inspiratory muscles in the setting of normal respiratory mechanics.

As such, despite these acute dynamic mechanical changes and small decreases in maximal inspiratory pressures, IND for a given V_T or V'_E, WOB and neuromuscular efficiency of the diaphragm were not different in the supine position *versus* the seated position for the control group (table 3 and figure 2). This latter finding is in keeping with previous observations that effective compensatory mechanisms are at play in health [39, 40]. One such adaptation is that cephaloid shift of the diaphragm is associated with

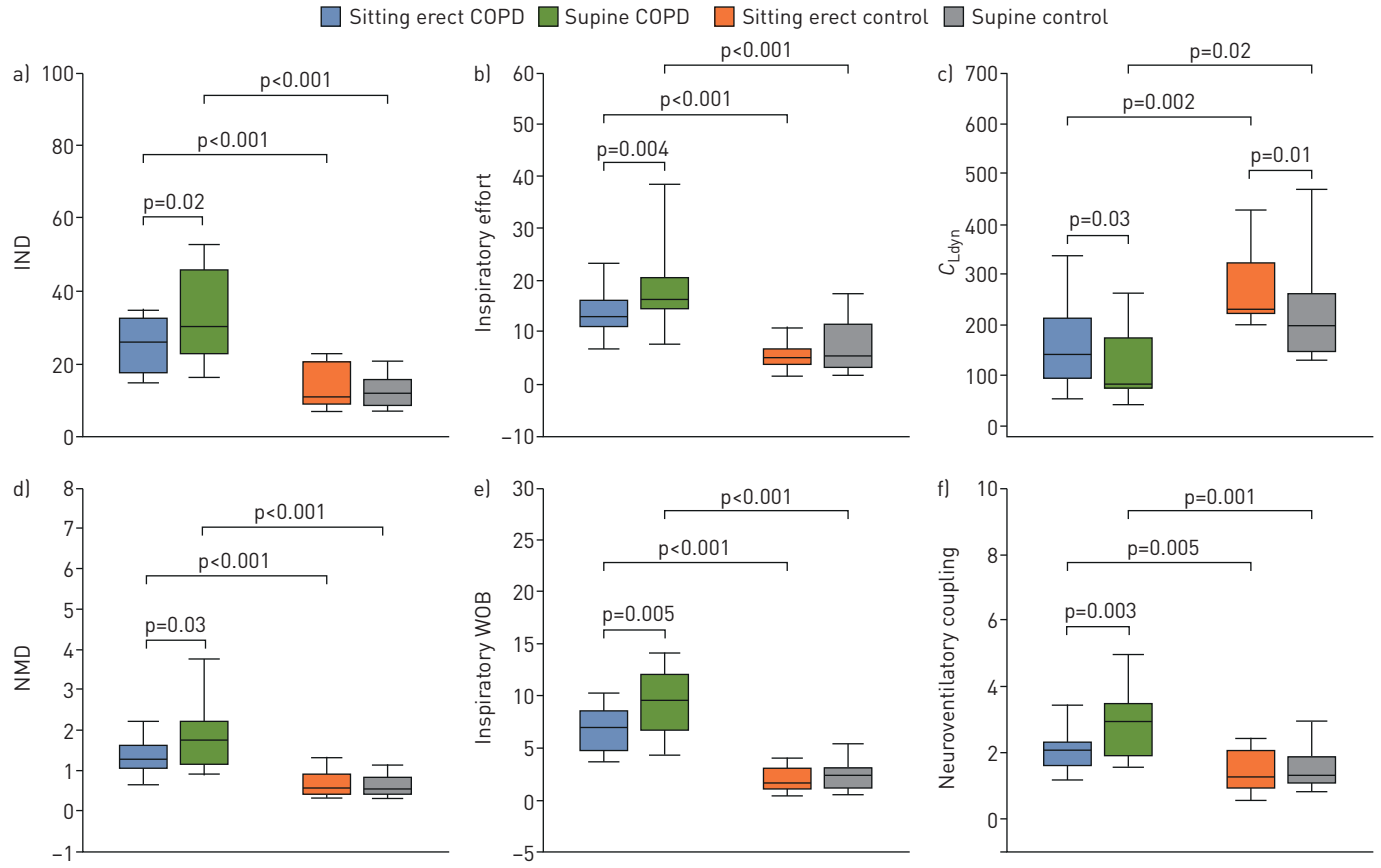

FIGURE 2 a) Inspiratory neural drive (IND) ($EMG_{di,\%max}$) by diaphragm electromyography (EMG_{di}) and respiratory pressure measurements; b) inspiratory effort (tidal $P_{di,\%max}$); c) dynamic lung compliance (C_{Ldyn}) (mL·cmH_2O^{-1}); d) neuromechanical dissociation (NMD) ($EMG_{di,\%max}$:V_T/pred VC); e) inspiratory work of breathing (WOB); and f) neuroventilatory coupling ($EMG_{di,\%max}$:V'_E), in the sitting and supine positions, in patients with advanced chronic obstructive pulmonary disease (COPD) and in age-matched healthy controls. Box plots depict the first to third quartiles, with the median denoted by a central horizontal line. Projecting bars denote the 10th to 90th percentile range. P_{di}: transdiaphragmatic pressure; VC: vital capacity; V_T: tidal volume; V'_E: minute ventilation.

TABLE 4 Summary of physiological changes associated with supine posture *versus* sitting posture in patients with advanced chronic obstructive pulmonary disease (COPD) and in healthy controls

Variable	COPD group with orthopnoea	Control group
IC L	no change	increase
EELV L	no change	decrease
V'_E L·min^{-1}	no change	decrease
V'_E/V'_{CO_2}	decrease	decrease
V_T L	no change	no change
C_{Ldyn} mL·cmH_2O^{-1}	decrease	decrease
Inspiratory effort (tidal $P_{di,\%max}$)	increase	no change
Expiratory muscle activity	decrease	decrease
Total inspiratory WOB J	increase	no change
IND (tidal $EMG_{di,\%max}$)	increase	no change
NMD ($EMG_{di,\%max}$:V_T/pred VC)	increase	no change
Neuroventilatory uncoupling	increase	no change
Dyspnoea Borg rating	increase	no change

IC: inspiratory capacity; EELV: end-expiratory lung volume; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; V'_E/V'_{CO_2}: ventilatory equivalent for carbon dioxide; V_T: tidal volume; C_{Ldyn}: dynamic lung compliance; P_{di}: transdiaphragmatic pressure; WOB: work of breathing; IND: inspiratory neural drive; EMG_{di}: diaphragm electromyography; NMD: neuromechanical dissociation; VC: vital capacity.

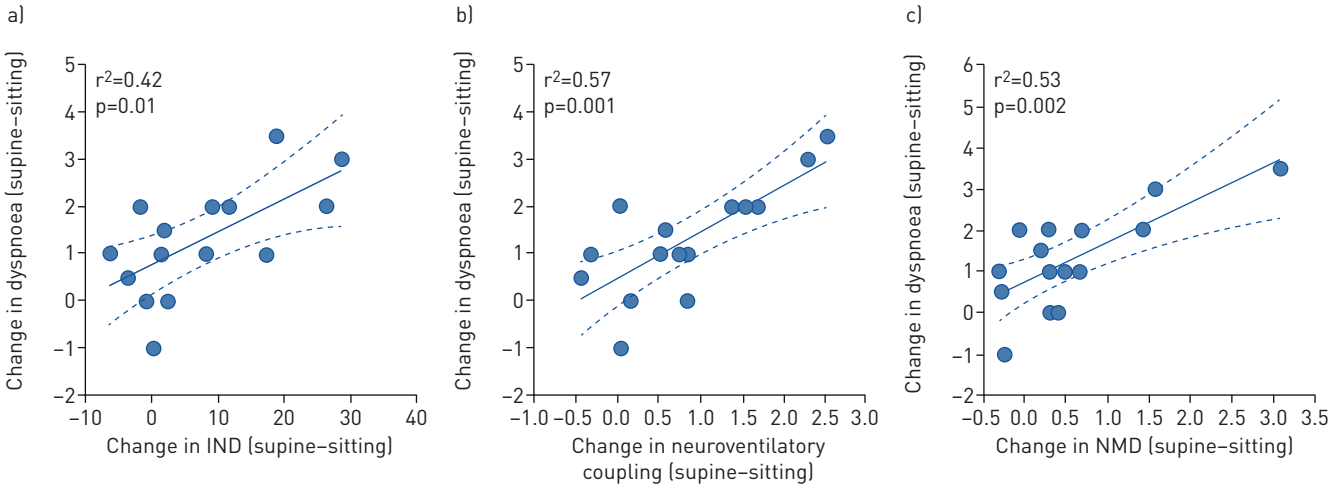

FIGURE 3 Correlation between change in dyspnoea intensity (supine–sitting) on the Borg scale and corresponding changes in: a) inspiratory neural drive (IND) (r^2=0.42, p=0.01); b) neuroventilatory coupling (r^2=0.57, p=0.001); and c) neuromechanical dissociation (NMD) (r^2=0.53, p=0.002) in patients with COPD. Dashed lines represent the 95% confidence interval (CI) for the slope of the regression line.

improvement in the length–tension relationship and increased zone of apposition, which helps to preserve ventilatory function and mitigate a fall in alveolar ventilation in the supine position [39, 40].

COPD patients transitioning to the supine position reported abrupt onset of unpleasant respiratory sensations (table 2 and supplementary figure E2). In contrast to the control group, the relatively diminished seated IC remained unchanged on recumbency, suggesting an unaltered EELV (figure 1 and supplementary figure E1) which is not surprising in the setting of severe resting lung hyperinflation [10, 33, 35, 41]. In addition, V_T was well preserved and there was no supine decrease in f_B as seen in controls.

Inspiratory $P_{es,max}$ was similar in both positions, but $P_{di,max}$ and expiratory $P_{ga,max}$ decreased on recumbency, suggesting reduced contribution of the diaphragm to overall pressure generation by the respiratory pump. In other words, additional inspiratory and accessory muscles were likely recruited during the maximal inspiratory manoeuvre to TLC while supine.

Expiratory muscle activity (tidal expiratory $P_{ga,max}$ and end-expiratory P_{ga}) was lower in the supine position *versus* the sitting position, suggesting reduced abdominal muscle contribution to ventilation [42–44], as previously shown by DRUZ and SHARP [42].

The reduced fixed IC means that V_T continues to be positioned close to TLC and to the upper poorly-compliant portion of the relaxed respiratory system pressure–volume relationship in COPD (where there is increased elastic threshold loading of functionally-weakened inspiratory muscles). This is further compounded in recumbency by acutely decreased $C_{L,dyn}$ (by 48 mL·cmH_2O^{-1}) in the setting of a stable breathing pattern and lack of a significant increase in R_{aw}. The cause of reduced $C_{L,dyn}$ is multifactorial and potentially includes factors mentioned above (increased small airway closure with variable atelectasis and regional lung hyperinflation, increased EFL as suggested by V_T/maximal flow–volume loop overlap calculations, maldistribution of inspired gas and greater mechanical time constant inhomogeneity) [45]. Other possible contributors established from previous studies include gravitational effects such as increased pulmonary blood volume and increased thoraco-abdominal asynchrony, and chest wall distortion leading to reduced lung distensibility [7, 45].

Unlike the situation in the control group, acute elastic loading of this nature had immediate deleterious consequences in our COPD patients who were already mechanically compromised (by resting hyperinflation and impaired inspiratory muscle function). Effort and WOB of the inspiratory muscles increased in association with an augmented IND. While neuromuscular efficiency of the diaphragm was largely unaltered, overall compensatory strategies were less effective than in controls. Thus, the wide disparities between increased IND and the mechanical and ventilatory responses of the respiratory system evident while sitting were acutely amplified by adopting a supine posture.

On recumbency and despite the compensatory increase in IND in patients with COPD, there was a modest reduction in V'_E; however, the ventilatory equivalent for CO_2 (*i.e.* V'_E/V'_{CO_2}), which would be expected to rise due to decreased ventilatory efficiency, actually fell significantly (by 5 L·min^{-1}) in keeping with acute mechanical deterioration and associated ventilatory constraints. This was associated with a small rise in P_{ETCO_2} and a reduction in S_{pO_2} of uncertain clinical significance.

Mechanisms of orthopnoea in patients with COPD

Dyspnoea intensity (severity) in our patients was increased in the supine position *versus* the sitting position by an average of 1.2 Borg units (table 2). In qualitative terms, patients described greater difficulty in breathing in and out, and reported "my breathing requires more work or effort" and "my breathing feels unpleasant". In general, greater dyspnoea is associated with greater IND and inspiratory effort as a result of greater mechanical loading of the inspiratory muscles, increased chemical drive or both in combination [16]. The sudden increase in acute elastic mechanical loading worsened load/capacity imbalance of the inspiratory muscles, such that compensatory increases in IND were required. Accordingly, the data support the postulation that increased central command output from cortical motor centres to the inspiratory muscles and the attendant increased central corrolary discharge from these centres to the somato-sensory cortex, are key mechanisms of orthopnoea [46]. However, altered afferent inputs (from abundant sensory receptors throughout the respiratory system) in response to sudden increases in elastic loading, which cannot be easily measured, also likely influenced perception of the intensity and quality of dyspnoea. Certainly it is reasonable to implicate short-term alterations in afferent feedback from mechanoreceptors in the inspiratory muscles and the chest wall (muscle spindles and Golgi tendon organs) in the genesis of such unpleasant respiratory sensations [47]. In the current study, the consistent association between increases in respiratory discomfort in the sitting–supine transition and parallel increases in measures of IND, NMD and neuroventilatory mismatching (explaining 40–50% of the variance in orthopnoea) further support this contention (figure 3).

Limitations

The sample size was small but was sufficient to uncover significant differences in the parameters of interest, both between patients and controls and within the patient group [15, 16]. We obtained electromyography measurements of the crural diaphragm only and cannot comment on concomitant electrical activity of the ribcage and accessory muscles. When considering positional differences in the mechanical properties of the lungs, we must acknowledge that intra-oesophageal pressure can deviate from intrapleural pressure in the supine position due to a direct pressure of the heart or other mediastinal structures on the oesophagus [6]. Our study did not permit us to assess potential "peripheral" influences on the intensity/quality of perceived orthopnoea, which may arise directly from altered afferent feedback from various sensory receptors in the respiratory muscles, chest wall, lungs and cardiovascular system. Lastly, we acknowledge that our results cannot be generalised to all COPD patients; those without orthopnoea or those with significant comorbidities.

Conclusion

In patients with severe COPD, the onset of orthopnoea coincided with an abrupt increase in the amplitude of IND from an already elevated sitting value. This increased IND occurred in response to acute elastic loading of the functionally-weakened inspiratory muscles and further amplified the pre-existing disparity between increased IND and the mechanical and ventilatory responses of the respiratory system.

Our study is the first to demonstrate that the presence of persistent orthopnoea in patients with advanced COPD points to the existence of severe mechanical compromise and very high resting IND and NMD, even in the absence of significant pulmonary gas exchange abnormalities. The corollary is that a central goal of management in such patients must be, as recently demonstrated, to improve respiratory mechanics so as to effectively reduce IND and NMD [48]. To the extent that orthopnoea can seriously disrupt sleep in patients with advanced COPD, every effort should be made to individualise bronchodilator treatment to achieve sustained "24-h" bronchodilatation and lung deflation.

Author contributions: All authors played a role in developing the content and writing the manuscript. D.E. O'Donnell was the principal investigator and provided the original idea for the study. D.E. O'Donnell and A.F. Elbehairy had input into the study design and the conduct of the study. A.F. Elbehairy and H. McIsaac collected the data. A.F. Elbehairy and A. Faisal performed the data analysis and prepared it for presentation.

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Conflict of interest: None declared.

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References

1 Buist AS, McBurnie MA, Vollmer WM, *et al.* International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007; 370: 741–750.
2 O'Neill S, McCarthy DS. Postural relief of dyspnoea in severe chronic airflow limitation: relationship to respiratory muscle strength. *Thorax* 1983; 38: 595–600.
3 Eltayara L, Ghezzo H, Milic-Emili J. Orthopnea and tidal expiratory flow limitation in patients with stable COPD. *Chest* 2001; 119: 99–104.
4 Sharp JT, Drutz WS, Moisan T, *et al.* Postural relief of dyspnea in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1980; 122: 201–211.
5 Heijdra YF, Dekhuijzen PN, van Herwaarden CL, *et al.* Effects of body position, hyperinflation, and blood gas tensions on maximal respiratory pressures in patients with chronic obstructive pulmonary disease. *Thorax* 1994; 49: 453–458.
6 Attinger EO, Monroe RG, Segal MS. The mechanics of breathing in different body positions. I. In normal subjects. *J Clin Invest* 1956; 35: 904–911.
7 Granath A, Horie E, Linderholm H. Compliance and resistance of the lungs in the sitting and supine positions at rest and during work. *Scand J Clin Lab Invest* 1959; 11: 226–234.
8 Sharp JT. The effect of body position change on lung compliance in normal subjects and in patients with congestive heart failure. *J Clin Invest* 1959; 38: 659–667.
9 Ries AL, Kaplan RM, Chang J. Effect of posture on arterial oxygenation in patients with chronic obstructive pulmonary disease. *Respiration* 1992; 59: 317–321.
10 Erwin WS, Zolov D, Bickerman HA. The effect of posture on respiratory function in patients with obstructive pulmonary emphysema. *Am Rev Respir Dis* 1966; 94: 865–872.
11 Bhatt SP, Guleria R, Luqman-Arafath TK, *et al.* Effect of tripod position on objective parameters of respiratory function in stable chronic obstructive pulmonary disease. *Indian J Chest Dis Allied Sci* 2009; 51: 83–85.
12 O'Donnell DE, Neder JA. The enigma of dyspnoea in COPD: a physiological perspective. *Respirology* 2020; 25: 134–136.
13 Jolley CJ, Luo YM, Steier J, *et al.* Neural respiratory drive and breathlessness in COPD. *Eur Respir J* 2015; 45: 355–364.
14 Jolley CJ, Luo YM, Steier J, *et al.* Neural respiratory drive in healthy subjects and in COPD. *Eur Respir J* 2009; 33: 289–297.
15 Elbehairy AF, Guenette JA, Faisal A, *et al.* Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *Eur Respir J* 2016; 48: 694–705.
16 Faisal A, Alghamdi BJ, Ciavaglia CE, *et al.* Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. *Am J Respir Crit Care Med* 2016; 193: 299–309.
17 Guenette JA, Chin RC, Cheng S, *et al.* Mechanisms of exercise intolerance in global initiative for chronic obstructive lung disease grade 1 COPD. *Eur Respir J* 2014; 44: 1177–1187.
18 Laveneziana P, Webb KA, Ora J, *et al.* Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. *Am J Respir Crit Care Med* 2011; 184: 1367–1373.
19 O'Donnell DE, Hamilton AL, Webb KA. Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. *J Appl Physiol* 2006; 101: 1025–1035.
20 Langer D, Ciavaglia C, Faisal A, *et al.* Inspiratory muscle training reduces diaphragm activation and dyspnea during exercise in COPD. *J Appl Physiol* 2018; 125: 381–392.
21 Qin YY, Li RF, Wu GF, *et al.* Effect of tiotropium on neural respiratory drive during exercise in severe COPD. *Pulm Pharmacol Ther* 2015; 30: 51–56.
22 Eakin EG, Sassi-Dambron DE, Ries AL, *et al.* Reliability and validity of dyspnea measures in patients with obstructive lung disease. *Int J Behav Med* 1995; 2: 118–134.
23 Mahler DA, Weinberg DH, Wells CK, *et al.* The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984; 85: 751–758.
24 Ferrer M, Alonso J, Prieto L, *et al.* Validity and reliability of the St George's Respiratory Questionnaire after adaptation to a different language and culture: the Spanish example. *Eur Respir J* 1996; 9: 1160–1166.
25 Jones PW, Harding G, Berry P, *et al.* Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009; 34: 648–654.
26 Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982; 14: 377–381.
27 O'Donnell DE, Hong HH, Webb KA. Respiratory sensation during chest wall restriction and dead space loading in exercising men. *J Appl Physiol* 2000; 88: 1859–1869.
28 Luo YM, Moxham J, Polkey MI. Diaphragm electromyography using an oesophageal catheter: current concepts. *Clin Sci* 2008; 115: 233–244.
29 Sinderby C, Beck J, Spahija J, *et al.* Voluntary activation of the human diaphragm in health and disease. *J Appl Physiol* 1998; 85: 2146–2158.
30 Johnson BD, Weisman IM, Zeballos RJ, *et al.* Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. *Chest* 1999; 116: 488–503.
31 Weissman C, Abraham B, Askanazi J, *et al.* Effect of posture on the ventilatory response to CO_2. *J Appl Physiol Respir Environ Exerc Physiol* 1982; 53: 761–765.
32 Baydur A, Behrakis PK, Zin WA, *et al.* Effect of posture on ventilation and breathing pattern during room air breathing at rest. *Lung* 1987; 165: 341–351.
33 Brody JS, Glazier JB. The effect of position on pulmonary function in chronic obstructive lung disease. *Am Rev Respir Dis* 1965; 92: 579–588.
34 Watson RA, Pride NB. Postural changes in lung volumes and respiratory resistance in subjects with obesity. *J Appl Physiol* 2005; 98: 512–517.
35 Tucker DH, Sieker HO. The effect of change in body position on lung volumes and intrapulmonary gas mixing in patients with obesity, heart failure, and emphysema. *Am Rev Respir Dis* 1960; 82: 787–791.
36 Craig AB, Jr. Effects of position on expiratory reserve volume of the lungs. *J Appl Physiol* 1960; 15: 59–61.
37 Banzett RB, Mead J. Reflex compensation for changes in operational length of inspiratory muscles. *In*: Roussos CH, Macklem PT, eds. The thorax. Part A. Lung biology in health and disease. New York, Marcel Dekker, 1985; pp. 595–605.

38 Behrakis PK, Baydur A, Jaeger MJ, *et al.* Lung mechanics in sitting and horizontal body positions. *Chest* 1983; 83: 643–646.
39 Takazakura R, Takahashi M, Nitta N, *et al.* Diaphragmatic motion in the sitting and supine positions: healthy subject study using a vertically open magnetic resonance system. *J Magn Reson Imaging* 2004; 19: 605–609.
40 De Troyer A. Mechanical role of the abdominal muscles in relation to posture. *Respir Physiol* 1983; 53: 341–353.
41 Marini JJ, Tyler ML, Hudson LD, *et al.* Influence of head-dependent positions on lung volume and oxygen saturation in chronic air-flow obstruction. *Am Rev Respir Dis* 1984; 129: 101–105.
42 Druz WS, Sharp JT. Activity of respiratory muscles in upright and recumbent humans. *J Appl Physiol Respir Environ Exerc Physiol* 1981; 51: 1552–1561.
43 Lopata M, O'Connor TD, Onal E. Effects of position on respiratory muscle function during CO_2 rebreathing. *Respiration* 1985; 47: 98–106.
44 Vellody VP, Nassery M, Druz WS, *et al.* Effects of body position change on thoracoabdominal motion. *J Appl Physiol Respir Environ Exerc Physiol* 1978; 45: 581–589.
45 Linderholm H. Lung mechanics in sitting and horizontal postures studied by body plethysmographic methods. *Am J Physiol* 1963; 204: 85–91.
46 Gandevia SC, Leeper JB, McKenzie DK, *et al.* Discharge frequencies of parasternal intercostal and scalene motor units during breathing in normal and COPD subjects. *Am J Respir Crit Care Med* 1996; 153: 622–628.
47 Parshall MB, Schwartzstein RM, Adams L, *et al.* An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012; 185: 435–452.
48 Domnik NJ, James MD, Scheeren RE, *et al.* Deterioration of nighttime respiratory mechanics in COPD: impact of bronchodilator therapy. *Chest* 2021; 159: 116–127.