# Mechanisms of Orthopnoea in Patients with Advanced COPD

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## ONLINE DATA SUPPLEMENT

## Methods

### Pulmonary function test

Spirometry, body plethysmography, single-breath lung diffusing capacity for carbon monoxide ($D_LCO$) and maximal inspiratory (MIP) and expiratory (MEP) mouth pressures were performed using automated equipment (Vmax229d, AutoboxV62J; SensorMedics, Yorba Linda, CA). Measurements were expressed relative to predicted normal values (1,2).

### Diaphragm electromyography and respiratory pressure measurements

Diaphragm electromyography (EMGdi), oesophageal pressure (Pes) and gastric pressure (Pga) were measured continuously using a combined electrode-balloon catheter system (3-7). The EMGdi signal was sampled at 2000 Hz (PowerLab, model ML880; ADInstruments, CastleHill, NSW, Australia), band-pass filtered between 20-1000 Hz (Bioamplifier model RA-8; Guanzhou Yinghui Medical Equipment Co. Ltd, Guangzhou, China) and converted to a root mean square (RMS) to assess respiratory neural activity. The data from the electrode pair showing the highest RMS value from the five electrode pairs in each inspiration was used for analysis. The oesophageal and gastric balloons were inflated with 1.0 mL and 1.2 mL of air, respectively. Pes and Pga were measured using differential pressure transducers (model DP15-34; Validyne Engineering, Northridge, CA, USA) and sampled at a rate of 100 Hz (PowerLab); trans-diaphragmatic pressure (Pdi) was calculated by subtraction of Pes from Pga. The continuous flow signal from the Vmax229d system (SensorMedics, Yorba Linda, CA) was simultaneously input into the data-acquisition system for analysis.

Maximal EMGdi (EMGdi,max) was determined as the highest inspiratory RMS from any sniff/inspiratory capacity manoeuvre performed during the test (8). Inspiratory sniffs were used to obtain maximum Pes (Pes,max) and maximum Pdi (Pdi,max) (6,9). Tidal Pes swings (Pes,tidal) were defined as the amplitude between the maximum expiratory value and minimum inspiratory value for each respiratory cycle. The tidal Pdi swing was defined as the amplitude of the Pdi waveform during tidal breathing.

End-inspiratory (EI) and end-expiratory (EE) data points of zero flow for Pes and Pga were collected. Dynamic compliance (CL,dyn) was calculated as the change in lung volume divided by change in Pes between EE and EI (10). Lung elastic work was calculated from the dynamic relation between Pes and lung volume in Campbell diagrams (11,12). Airway resistance was calculated as the difference in Pes divided by the difference in flow at inspiratory mid-volume and expiratory iso-volume (ΔPes/Δflow) (10).

$EMGdi_{\%max}$ was used as an index of inspiratory neural drive (IND) to the crural diaphragm. The ratio between $EMGdi_{\%max}$ and tidal volume expressed relative to predicted vital capacity ($EMGdi_{\%max}$:$VT_{\%predVC}$) was used as an index of neuromechanical dissociation (NMD) of the respiratory system (9). Neuromuscular efficiency of the diaphragm was defined as the ratio of $EMGdi_{\%max}$:tidal $Pdi_{\%max}$ (6).

**Results**

Compared with healthy controls, patients with COPD had greater COPD assessment test (CAT) score, poorer health-related quality of life (St. George's Respiratory Questionnaire) and lower habitual physical activity (Community Healthy Activities Model Program for Seniors questionnaire), all $p<0.001$ (**table E1**). In average, patients had severe airflow obstruction [forced expiratory volume in one-second ($FEV_1$): 40±18 %predicted] and 4/16 had moderate severity ($80>FEV_1\geq50$ %predicted). **Table E1** also shows subjects' comorbid conditions and medications.

None of the subjects had significant cardiovascular or pulmonary vascular disease that could contribute to dyspnoea or orthopnoea.

In supine (vs. sitting), controls' inspiratory capacity (IC) increased by 0.48L ($p<0.001$) (**figure E1**) likely reflecting lower end-expiratory lung volume (EELV). In contrast to controls, patients' IC and EELV were similar in both positions (**figure E1**).

Patients had greater dyspnoea in all 5 domains in both positions compared with healthy controls (all $p<0.05$) and dyspnoea ratings increased significantly in the transition from seated to supine position in patients ($p<0.05$), **figure E2**.

Fifteen of sixteen participants in each group accepted the insertion of the EMGdi-pressure catheter. EMGdi,max and Pdi,max were lower in supine versus sitting positions in both groups ($p<0.05$) (**figure E3 and E4**). While tidal EMGdi and Pdi were not significantly different between positions, values were greater in COPD patients compared with controls regardless of the position.

$EMGdi_{\%max}$ and tidal $Pdi_{\%max}$ were greater in supine versus sitting position only in patients with COPD and values remained unaltered in healthy controls. Looking at individual EMGdi data (**figure E3**), 53% of patients showed a rise in tidal EMGdi in supine versus sitting position and the mean value tended to be higher while supine, though not significant. As such, higher $EMGdi_{\%max}$ in supine versus sitting position in patients with COPD was a result of both higher numerator and lower denominator in variable combination. While in healthy controls, the majority (73%) showed a drop in their tidal EMGdi in supine versus sitting (**figure E3**). Similarly, higher tidal $Pdi_{\%max}$ in supine versus sitting position in COPD patients was a result of higher tidal Pdi (i.e. numerator) and lower Pdi,max (i.e. denominator) in variable combination (**figure E4**).

## References


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**Table E1: Subjects Characteristics**

| Variable | COPD (n=16) | CTRL (n=16) |
|---|---|---|
| CAT score (0-40) | 21.3±7.8* | 4.3±3.5 |
| SGRQ total score | 50.7±14.3* | 3.4±1.8 |
| CHAMPS, kcal/wk for all activities | 2102±1843* | 5342±4240 |
| Comorbidities, no of subjects (%) | | |
| ▪ Hypertension | 7 (44) | 6 (38) |
| ▪ Diabetes Mellitus | 2 (13) | 2 (13) |
| ▪ Ischaemic heart disease | 3 (19) | 0 (0) |
| ▪ Hypercholesterolemia | 6 (38) | 5 (31) |
| ▪ Anxiety | 2 (13) | 2 (13) |
| ▪ Depression | 3 (19) | 2 (13) |
| ▪ Osteoporosis | 3 (19) | 0 (0) |
| Inhaled medication usage, no of subjects (%) | | |
| ▪ SABA | 15 (94) | 0 (0) |
| ▪ SAMA | 7 (44) | 0 (0) |
| ▪ LAMA | 5 (31) | 0 (0) |
| ▪ Combined LABA/LAMA | 8 (50) | 0 (0) |
| ▪ ICS | 7 (44) | 0 (0) |
| ▪ Combined ICS/LABA | 5 (31) | 0 (0) |
| Other medications, no. of subjects (%) | | |
| ▪ Anti-hypertensive | 7 (44) | 6 (38) |
| ▪ Statin | 6 (38) | 5 (31) |
| ▪ Anti-depressant | 3 (19) | 2 (13) |
| ▪ Thyroid replacement | 1 (6) | 1 (6) |
| ▪ Anti-angina medication | 2 (13) | 0 (0) |
| ▪ Aspirin | 2 (13) | 1 (6) |

Values are means±SD.

* $p<0.05$ COPD vs. CTRL group.

*Abbreviations:* CAT= COPD Assessment Test; CHAMPS= Community Healthy Activities Model Program for Seniors questionnaire; COPD= chronic obstructive pulmonary disease; CTRL= healthy controls; ICS= inhaled corticosteroid; LABA= long-acting beta$_2$-agonist; LAMA= long-acting muscarinic antagonist; SABA= short-acting beta$_2$-agonist; SAMA= short-acting muscarinic antagonist; SGRQ= St. George's Respiratory Questionnaire.