Mechanisms of Exertional Dyspnea in Symptomatic Smokers without COPD

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ONLINE DATA SUPPLEMENT

METHODS

Oxygen Cost Diagram

The oxygen cost diagram was used to evaluate self-reported tolerance of daily activities. This scale consists of a 100 mm line listing everyday activities in proportion to their approximate oxygen cost between zero and 100. Subjects were asked to indicate the point on the line, beyond which they became breathless. The distance from point zero was measured and reported in mm (E1).

Pulmonary Function Tests

Detailed pulmonary function tests were performed using automated equipment (Vmax229d and Autobox V62J; and MasterScreen impulse oscillometry (IOS); SensorMedics, Yorba Linda, CA); measurements were expressed relative to predicted normal values (E2-E7).

Anaerobic Threshold Assessment

The anaerobic threshold (AT) was assessed using the V-slope method (E8,E9). For corroboration of the V-slope method, we also employed the ventilatory equivalent method (E10,E11). Furthermore, two different investigators independently verified the identification of the AT.

Diaphragm Electromyography and Respiratory Pressure Measurements

Diaphragm electromyography (EMGdi), esophageal pressure (Pes) and gastric pressure (Pga) were measured continuously using a combined electrode-balloon catheter system (E12-E21).

Due to the subjective analysis of the EMGdi analysis, the same investigator examined data for both smokers and healthy controls in a blinded fashion. 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; the largest value from the five electrode pairs in each inspiration was used for analysis. The esophageal 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); transdiaphragmatic pressure (Pdi) was calculated by electronic subtraction of Pes from Pga. The continuous flow signal from the cardiopulmonary exercise testing system (Vmax229d; SensorMedics, Yorba Linda, CA) was simultaneously input into the data acquisition system for analysis.

Maximal EMGdi (EMGdi,max) was determined during serial inspiratory capacity (IC) maneuvers at rest and throughout exercise (E17,E22); EMGdi,max measured in this way often produces greater values than during sniff maneuvers, and has been shown to be highly reproducible and remains unchanged during ventilatory stimulation by exercise or hypercapnia (E15,E23,E24). EMGdi/EMGdi,max was used as an index of inspiratory neural drive to the crural diaphragm. IC maneuvers at rest and throughout exercise were used to obtain dynamic peak inspiratory Pdi (Pdi,max) (E19,E20). Inspiratory Pdi was the peak tidal value during inspiration; inspiratory Pdi/Pdi,max was used as an index of diaphragmatic effort. Tidal Pes swings were defined as the amplitude between the maximum inspiratory and expiratory values for each respiratory cycle. Tidal Pes swings were expressed as a fraction of the difference between the maximum values during the IC maneuvers and the baseline vital capacity maneuver;

Pes/Pes,max was used as an index of global respiratory effort. The expiratory rise in Pga (Pga,exp.rise) was used as an index of expiratory muscle activity (E25).

End-inspiratory (EI) and end-expiratory (EE) data points of zero flow for Pes and Pga were collected. Dynamic compliance ($C_L$dyn) was calculated as the difference in lung volume divided by difference in Pes between EE and EI (E26). Total lung resistance was calculated as the difference in Pes divided by the difference in flow at inspiratory mid-volume and expiratory iso-volume (ΔPes/Δflow) (E26). The tension time index of the diaphragm (TTIdi) and the inspiratory muscles (TTIes) was calculated as the product of tidal Pdi and Pes and the ratio of inspiration time to breath cycle (E27,E28). The mechanical work of breathing was determined as the area within an ensemble averaged tidal Pes–volume loop with the addition of that portion of a triangle representing work that fell outside of the pressure-volume loop (i.e., part of the elastic work of breathing) (E29) and was further subdivided into the inspiratory resistive and inspiratory elastic work of breathing (E30).

RESULTS

Subjects

Comorbidities within the smokers group included stable: hypertension (n=5), gastro-esophageal reflux disease (n=4), mild liver disease (n=2), previous myocardial infarction (n=1), and diabetes mellitus (n=1). None were treated for congestive heart failure. All smokers did not meet spirometric criteria for COPD, i.e., a post-bronchodilator FEV_1/FVC was > 0.7 and higher than the predicted lower limit of normal (LLN), except one subject who had a ratio lower than LLN by only 0.5%. In support of successful asthma exclusion, none of the smokers demonstrated significant bronchodilator reversibility.

Cardiopulmonary Exercise Test

Smokers had a reduced peak work rate and oxygen uptake ($\dot{V}O_2$) compared with controls; however, $\dot{V}O_2$-work rate relationships were superimposed in both groups throughout exercise (**Figure E1**). Heart rate and oxygen pulse responses were similar throughout exercise but smokers reached a lower peak heart rate than controls (mean±SD): 75±15 versus 94±7 %predicted ($P<0.05$) (**Figure E1**). Intensity ratings of leg discomfort during exercise were significantly greater in smokers compared to controls (**Figure E1**).

The ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) was not different at its nadir during exercise between the two groups (28.7±3.3 versus 27.9±3.3; smokers versus controls). However, those (n=10) with values above the median of 28 (n=10) had a significantly lower peak $\dot{V}O_2$ than those below the median (n=10): 56±24 versus 101±41 %predicted, respectively ($P=0.007$). Within smokers, the $\dot{V}_E/\dot{V}CO_2$ nadir correlated well with peak $\dot{V}O_2$ ($R= -0.598$, $P=0.005$) (**Figure E2**).

Fourteen subjects in each group accepted the insertion of the EMGdi-pressure catheter. Indices of global inspiratory muscle effort (inspiratory Pes/Pi,max) and expiratory muscle activity (Pga expiratory rise) were similar between both groups (**Figure E1, E3**). EMGdi relative to maximum (EMGdi/EMGdi,max), inspiratory Pdi/Pdi,max and total lung resistance were significantly ($P<0.05$) higher for a given ventilation ($\dot{V}_E$) in smokers compared with controls (**Figure E3**).

Looking at individual EMGdi data, there were several smokers with tidal EMGdi values at rest and early in exercise that were higher than any seen in the control group. In addition, the majority of smokers had EMGdi,max values during their serial IC maneuvers in the low range (i.e., <100 µV) in contrast to the control group where the majority had values in the higher range (i.e., >150 µV) (**Figure E4)**; EMGdi,max during the highest IC was lower in smokers versus controls (113±65 versus 165±56 μV, *P*=0.028). Thus, the higher EMGdi/EMGdi,max reflected differences in both the numerator (tidal EMGdi) and the denominator (EMGdi,max) which varied between smokers. Of note, EMGdi/EMGdi,max was significantly higher in smokers at rest and throughout exercise whether EMGdi,max was calculated during serial IC maneuvers, the highest IC throughout the test, or the highest inspiratory maneuver (either IC or sniff) throughout the test (**Figure E5**). Values of pre- and post-exercise maximal respiratory pressures and EMGdi during sniff and IC maneuvers are summarized in **Table E1**.

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TABLE E1. Pre- and post-exercise maximal respiratory pressures and EMGdi during sniff and IC maneuvers

Variable	**Smokers without COPD**		**Healthy Controls**	
	Pre-exercise	**Post-exercise**	**Pre-exercise**	**Post-exercise**
Pes,sniff, cmH_2O	69 ± 14	71 ± 14	70 ± 13	69 ± 16
Pes,IC, cmH_2O	39 ± 10	42 ± 10	41 ± 11	41 ± 10
Pdi,sniff, cmH_2O	96 ± 23	89 ± 22†	108 ± 17	95 ± 24†
Pdi,IC, cmH_2O	64 ± 19	57 ± 17†	76 ± 23	60 ± 20†
EMGdi,sniff, μV	117 ± 51*	116 ± 58*	159 ± 66	150 ± 50
EMGdi,IC, μV	98 ± 55*	101 ± 64*	150 ± 47	153 ± 48

Values are means ± SD.

**P*<0.05 smokers without COPD versus healthy controls. †*P*<0.05 pre- versus post-exercise within each group.

Abbreviations: IC = inspiratory capacity; EMGdi = diaphragm electromyography; Pes = esophageal pressure; Pdi = transdiaphragmatic pressure.

FIGURES LEGENDS

Figure E1. Intensity ratings of leg discomfort (**a**) oxygen uptake (**b**), heart rate (**c**), oxygen pulse (**d**), Pes/Pi,max (**e**), Pga expiratory rise (**f**) are plotted against work rate during incremental cycle exercise in smokers without COPD and in age-matched healthy controls. Values are mean±SEM. *$P<0.05$ smokers without COPD vs. healthy controls at standardized work rates or at peak exercise. *Abbreviations:* VO_2 = oxygen uptake; Pes = esophageal pressure; Pes/Pi,max = inspiratory esophageal pressure relative to maximum and used as an index of global inspiratory muscle effort; Pga = gastric pressure; Pga expiratory rise = an index of expiratory muscle activity.

Figure E2. There was a significant inverse relationship between the ventilatory equivalent for carbon dioxide (V_E/VCO_2) at its nadir and peak VO_2 during exercise in smokers without COPD ($R=-0.598$, $P=0.005$).

Figure E3. Diaphragm electromyography (EMGdi) and select pressure-derived respiratory mechanical measurements are shown during incremental cycle exercise in smokers without COPD and age-matched healthy controls. Values are mean±SEM. *$P<0.05$ smokers without COPD vs. healthy controls at a standardized ventilation or at peak exercise. *Abbreviations:* EMGdi/EMGdi,max = EMGdi relative to maximum is an indirect measure of inspiratory neural drive to the crural diaphragm; tidal Pes/Pes,max = tidal esophageal pressure relative to maximum is an index of total respiratory muscle effort; tension time index, es = tension time index derived from esophageal pressure is an index of the oxygen cost of breathing; inspiratory Pdi/Pdi,max = inspiratory transdiaphragmatic pressure relative to maximum is an index of diaphragmatic effort; Pga = gastric pressure; WOB = work of breathing.

Figure E4. Individual diaphragm electromyography (EMGdi) data are shown during incremental cycle exercise in smokers without COPD and age-matched healthy controls. Data are shown as absolute tidal inspiratory EMGdi (*panels a and c*) and as maximum values during serial IC maneuvers (*panels b and d*) at rest and during exercise in both smokers and healthy controls. *Abbreviations:* IC = inspiratory capacity; insp = inspiratory.

Figure E5. Diaphragm electromyography (EMGdi) relative to maximum (EMGdi,max) is shown during incremental cycle exercise in smokers without COPD and age-matched healthy controls. EMGdi,max was derived during concurrent serial inspiratory capacity (IC) maneuvers (*panel a*), during the highest IC maneuver throughout the test (*panel b*), or during the highest inspiratory maneuver (either IC or sniff) throughout the test (*panel c*). Values are mean±SEM. *$P<0.05$ smokers without COPD vs. healthy controls at rest or at a standardized work rates.