



Mechanisms of exercise intolerance in Global Initiative for Chronic Obstructive Lung Disease grade 1 COPD

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ABSTRACT The purpose of this study was to determine if a dissociation existed between respiratory drive, as estimated by diaphragmatic electromyography (EMGdi), and its pressure-generating capacity during exercise in mild chronic obstructive pulmonary disease (COPD) and whether this, if present, had negative sensory consequences.

Subjects meeting spirometric criteria for mild COPD ($n=16$) and age and sex-matched controls ($n=16$) underwent detailed pulmonary function testing and a symptom limited cycle test while detailed ventilatory, sensory and respiratory mechanical responses were measured.

Compared with controls, subjects with mild COPD had greater ventilatory requirements throughout submaximal exercise. At the highest equivalent work rate of 60 W, they had a significantly higher: total work of breathing (32 ± 17 versus 16 ± 7 J·min⁻¹; $p<0.01$); EMGdi (37.3 ± 17.3 versus $17.9 \pm 11.7\%$ of maximum; $p<0.001$); and EMGdi to transdiaphragmatic pressure ratio (0.87 ± 0.38 versus 0.52 ± 0.27 ; $p<0.01$). Dyspnoea-ventilation slopes were significantly higher in mild COPD than controls (0.17 ± 0.12 versus 0.10 ± 0.05 ; $p<0.05$). However, absolute dyspnoea ratings reached significant levels only at high levels of ventilation.

Increased respiratory effort and work of breathing, and a wider dissociation between diaphragmatic activation and pressure-generating capacity were found at standardised work rates in subjects with mild COPD compared with controls. Despite these mechanical and neuromuscular abnormalities, significant dyspnoea was only experienced at higher work rates.



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Introduction

Despite having relatively preserved spirometry, patients with milder chronic obstructive pulmonary disease (COPD) show increased mortality [1], increased hospitalisations, and decreased health-related quality of life [2–5] compared with nonsmoking controls. Many of these patients also experience exertional dyspnoea [6], which may partially explain their reduced physical activity levels [7]. Despite these findings, this subpopulation has not been extensively studied and no evidence-based recommendations currently exist for their management beyond smoking cessation. Therefore, the optimal management of patients with mild COPD awaits a better understanding of their underlying pathophysiology.

The clinical presentation of patients with mild airway obstruction is highly variable and depends on the integration of several factors such as the nature and extent of their physiological impairment, the attendant compensatory respiratory system adjustments, and complex behavioural adaptations (e.g. activity avoidance). The heterogeneous physiological abnormalities of patients with mild airway obstruction include: increased peripheral airway resistance, early airway closure, maldistribution of ventilation, impaired pulmonary gas exchange and gas trapping [8–12]. Recent studies have shown that these physiological abnormalities are amplified during exercise [6, 13, 14]. Thus, the combination of ventilatory inefficiency and abnormal ventilatory mechanics can force the respiratory system to prematurely reach its physiological limits at lower exercise intensities than in healthy controls [13].

The current study extends previous work [15–17] to determine if a dissociation exists between diaphragmatic activation and pressure generation or between respiratory muscle effort and the mechanical output of the respiratory system during exercise in patients with mild COPD and whether such factors have negative sensory consequences. Therefore, the current study tested the hypotheses that: 1) dissociation between respiratory neural drive and the muscular/mechanical response of the respiratory system would be present in mild COPD at lower work rates than in healthy controls; and 2) these compensatory adjustments to support the increased ventilatory demands of exercise would be associated with an earlier onset of intolerable dyspnoea.

Methods

Subjects

The study included 16 subjects with Global Initiative for Chronic Obstructive Lung Disease grade 1 COPD (forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) <0.70 and FEV₁ ≥80% predicted) and 16 healthy age- and sex-matched controls. Subjects were recruited through advertisements and through the respiratory clinic at Kingston General Hospital (Kingston, ON, Canada). Individuals with cardiovascular, metabolic, neuromuscular or any other disease that could contribute to dyspnoea or interfere with exercise testing were excluded.

Study design

This study received ethical approval from the Queen's University and Affiliated Hospitals Research Ethics Board (DMED-1285-10). Subjects participated in two testing visits. On visit one, a detailed medical history was completed, followed by chronic activity-related dyspnoea questionnaires, pre- and post-bronchodilator (400 µg salbutamol) pulmonary function testing and a symptom-limited incremental cycle test for familiarisation purposes. On visit two, subjects performed pulmonary function testing followed by the same exercise protocol but with additional measurements of diaphragmatic electromyography (EMGdi) and respiratory pressures. COPD subjects refrained from using their short- and long-acting bronchodilators for 6 and 24 h prior to testing, respectively, and avoided caffeine, heavy meals and alcohol for at least 4 h prior to testing.

Pulmonary function

Spirometry, body plethysmography, single-breath diffusing capacity of the lung for carbon monoxide (DLCO), single-breath nitrogen test, maximal mouth pressures and impulse oscillometry were performed using an automated testing system (Vs62j Body Plethysmograph, Vmax229d Encore and Masterscreen IOS; SensorMedics, Yorba Linda, CA) according to established guidelines and expressed as % pred of normal values.

Cardiopulmonary exercise testing

Exercise was performed on an electronically-braked cycle ergometer (Ergometrics 800S; SensorMedics) using a cardiopulmonary testing system (Vmax229d; SensorMedics). Testing involved a rest period and a 1 min warm-up of unloaded pedalling followed by stepwise increases of 20 W per 2 min until symptom limitation. Standard cardiopulmonary measurements were collected on a breath-by-breath basis. Blood pressure, heart rate and oxyhaemoglobin saturation were monitored using sphygmomanometry, electrocardiography, and pulse oximetry, respectively. Inspiratory capacity (IC) measurements were

performed at rest, every second minute during exercise and at the end of exercise [18]. Subjects rated the intensity of their “breathing discomfort” and “leg discomfort” at rest, every second minute during exercise and at the end of exercise using the modified 10-point Borg scale [19]. Subjects were asked to report their primary reason for stopping exercise and to select qualitative phrases that described how their breathing felt at peak exercise [20]. An inflection in tidal volume (V_T) relative to minute ventilation (V'_E) was determined for each subject during exercise [21]. The highest equivalent work rate (HEWR) was defined as the highest work rate achieved by all subjects.

Diaphragmatic EMG and respiratory pressures

A combined electrode-balloon catheter was passed through the nose and positioned as previously described [22]. Raw EMGdi signals were sampled at 2000 Hz (PowerLab, model ML880; ADInstruments, Castle Hill, Australia), band-pass filtered between 20–1000 Hz (Bio-amplifier model RA-8; Guangzhou Yinghui Medical Equipment Co. Ltd, Guangzhou, China) and converted into a root mean square. The mean root mean square for each inspiration was determined by manually selecting the EMGdi signal that fell between cardiac QRS complexes. The electrode pair with the largest EMGdi amplitude was used for the analysis. Maximal EMGdi ($EMG_{di,max}$) was determined as the highest EMGdi amplitude from any IC manoeuvre [22, 23]. The ratio between $EMG_{di}/EMG_{di,max}$ and $V_T/(predicted\ vital\ capacity\ (VC_{pred}))$ was used as an index of neuromechanical dissociation of the respiratory system.

Oesophageal and gastric balloon catheters were connected to calibrated differential pressure transducers (model DP15-34; Validyne Engineering, Northridge, CA, USA). Transdiaphragmatic pressure (P_{di}) was calculated as the difference between P_{ga} and P_{es} . Maximal P_{di} ($P_{di,max}$) and P_{es} ($P_{es,max}$) were determined during maximal IC and sniff manoeuvres, respectively. The work of breathing was determined as the area within an averaged tidal P_{es} –volume loop and was further subdivided into the inspiratory resistive and inspiratory elastic work of breathing [24]. The breath selection occurred over the same 30 s as all other cardiorespiratory and EMG data (*i.e.* the first 30 s of each second minute of exercise). An index of ventilatory muscle recruitment was calculated as the difference between end-inspiratory and end-expiratory P_{ga} divided by the difference between end-inspiratory and end-expiratory P_{es} ($\Delta P_{ga}/\Delta P_{es}$) [25].

Data analysis

Between-group comparisons of subject characteristics, and physiological and sensory variables at each time point during exercise were performed using unpaired t-tests. Qualitative descriptors of dyspnoea at peak exercise and the reasons for stopping exercise were analysed using Fisher’s exact test. To evaluate the relationship between dyspnoea intensity (dependent variable) and relevant independent variables during exercise, the following were included in a multivariable linear regression model: the independent variable of interest, group as a categorical effect, an interaction term to determine whether the relationship being tested was similar across groups (independent variable \times group), and subjects were treated as random effects to account for serial measurements (subject nested within group). Results are reported as mean \pm SD, unless otherwise specified. A p-value <0.05 was used for statistical significance.

Results

Subjects

Descriptive characteristics of the mild COPD subjects ($n=16$) and controls ($n=16$) are summarised in table 1. Subjects with mild COPD had a significant smoking history (range 15–111 pack-years) including 12 ex-smokers and four current smokers. Only two control subjects had a smoking history of 2.5 and 2 pack-years each, while all other controls were never-smokers. Nine COPD subjects used respiratory medications on a regular basis: short-acting β_2 -agonist as needed ($n=7$), short-acting anticholinergic ($n=2$), long-acting anticholinergic ($n=5$), inhaled corticosteroid ($n=1$), and a long-acting β_2 -agonist combined with an inhaled corticosteroid ($n=6$). Comorbidities in the COPD group included the following: hypertension ($n=10$), diabetes mellitus type 2 ($n=4$), hypercholesterolaemia ($n=3$), osteoarthritis ($n=3$), anxiety ($n=2$), gastro-oesophageal reflux ($n=1$), and sleep apnoea ($n=1$). Comorbidities in the healthy control group included the following: hypertension ($n=3$), osteoarthritis ($n=3$), hypercholesterolaemia ($n=1$), sleep apnoea ($n=1$), and anaemia ($n=1$). None of the COPD subjects had participated in pulmonary rehabilitation.

All but one COPD subject was below the lower limit of normal for FEV_1/FVC [26]. Compared with controls, subjects with mild COPD had significantly greater activity-related dyspnoea, airway resistance, N_2 slope, resonant frequency, functional residual capacity, residual volume, and a greater difference between total lung capacity and alveolar volume. They also had a significantly reduced IC, $DLCO$ and static respiratory muscle strength.

TABLE 1 Subject characteristics

	Controls	Mild COPD
Subjects, n	16	16
Males/females, n	8/8	8/8
Age years	63±9	67±7
Body mass index kg·m⁻²	27.5±2.5	26.8±6.1
Smoking history pack-years	0.3±0.8	46.9±28.8***
Baseline Dyspnoea Index focal score	11.3±0.9	9.1±2.2**
Oxygen cost diagram mm	89±11	74±14**
COPD Assessment Test	4±4	13±8***
Peak incremental V'O₂ L·min⁻¹	2.55±0.88	1.61±0.48***
Peak incremental V'O₂ % predicted	114±27	80±14***
Peak incremental work rate W	178±62	102±30***
Peak incremental work rate % pred	116±21	76±20***
Pulmonary function		
Post-bronchodilator		
FEV1 % pred	120±12	93±9***
FEV1/FVC %	77±5	63±4***
Pre-bronchodilator		
FEV1 % pred	116±13	86±9***
FEV1/FVC %	74±6	59±5***
SVC % pred	116±13	105±11*
IC % pred	116±17	99±19*
FRC % pred	89±21	109±19**
RV % pred	81±20	110±23***
TLC % pred	102±14	104±9
PEF % pred	120±19	92±16***
FEF25-75 % pred	91±34	33±10***
sRaw % pred	132±57	245±104***
DLCO % pred	102±15	82±21**
MIP % pred	113±25	87±37*
MEP % pred	89±20	70±18**
N ₂ slope % pred	206±69	416±230**
R5 cmH ₂ O·L ⁻¹ ·s ⁻¹	4.36±1.16	5.22±1.74
R5-20 cmH ₂ O·L ⁻¹ ·s ⁻¹	12.5±7.3	22.7±9.8**
X5 cmH ₂ O·L ⁻¹ ·s ⁻¹	-1.12±0.54	-1.77±0.86*
Fres Hz	12.1±3.5	16.2±4.7*
TLC-VA L	0.63±0.41	1.15±0.32***

Data are presented as mean±SD, unless otherwise stated. COPD: chronic obstructive pulmonary disease; V'O₂: oxygen uptake; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; SVC: slow vital capacity; IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; PEF: peak expiratory flow; FEF25-75: force expiratory flow at 25–75% of FVC; sRaw: specific airway resistance; DLCO: diffusing capacity of the lung for carbon monoxide; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; N₂: nitrogen; R5: resistance at 5 Hz; R5-20: difference in resistance between 5 Hz and 20 Hz; X5: distal capacitive reactance at 5 Hz; Fres: resonant frequency during impulse oscillometry; VA: alveolar volume. *: p<0.05; **: p<0.01; ***: p<0.001.

Physiological responses to exercise

Peak work rate and oxygen uptake (V'O₂) were significantly lower in subjects with mild COPD compared with controls. Selected sensory and physiological parameters at rest, the HEWR, and peak exercise are shown in table 2. Figure 1 shows the metabolic and ventilatory responses to exercise. Compared with controls, subjects with mild COPD had greater ventilatory inefficiency (fig. 1b), higher ventilatory requirements (fig. 1c), and higher operating lung volumes during exercise (fig. 1f). A discernible VT/V'E inflection occurred in all subjects except for one subject with mild COPD. The VT/V'E inflection (denoted as triangles in the figure) occurred at a significantly lower V'O₂, V'E and work rate in the subjects with mild COPD compared with controls.

TABLE 2 Selected sensory and physiological parameters at rest, the HEWR, and peak exercise

	Rest		HEWR (60 W)		Peak	
	Controls	Mild COPD	Controls	Mild COPD	Controls	Mild COPD
Dyspnoea Borg scale	0.0±0.0	0.1±0.2	0.6±0.7	1.4±1.4*	6.0±3.1	4.7±1.8
Leg discomfort Borg scale	0.1±0.3	0.1±0.2	0.7±0.7	2.1±1.7**	6.8±3.2	5.4±1.8
$\dot{V}O_2$ L·min ⁻¹	0.35±0.12	0.32±0.08	1.13±0.12	1.11±0.17	2.55±0.88	1.61±0.48***
Work rate W					178±62	102±30***
Heart rate beats·min ⁻¹	73±15	81±13	101±18	116±17*	155±16	142±17*
SaO ₂ %	97±1	97±2	97±1	96±2	94±3	95±2
$\dot{V}E$ L·min ⁻¹	10.4±3.6	11.2±3.1	27.7±4.3	33.9±8.1*	92.7±30.1	55.7±16.4***
$\dot{V}T$ L	0.79±0.24	0.69±0.18	1.33±0.19	1.32±0.28	2.35±0.69	1.57±0.44***
f_R breaths·min ⁻¹	14.3±5.2	17.2±5.1	21.4±4.5	26.9±8.9*	39.5±6.8	36.1±7.2
$\dot{V}E/\dot{V}CO_2$	40.0±4.9	46.3±7.6**	28.9±2.2	33.3±4.0***	33.0±4.3	33.3±4.1
PETCO ₂ mmHg	35.1±2.7	32.3±3.6*	39.9±3.2	35.2±4.5**	33.6±4.0	33.6±3.9
IC L	3.06±0.87	2.56±0.61	3.31±0.84	2.53±0.52**	3.16±0.80	2.29±0.46***
ΔIC L			0.25±0.34	-0.03±0.38*	0.10±0.53	-0.28±0.47*
IRV L	2.27±0.78	1.87±0.55	1.98±0.86	1.21±0.40**	0.81±0.34	0.71±0.40
EELV/TLC %	48.2±8.6	55.9±9.3*	43.6±8.7	56.8±5.8***	46.5±7.2	61.1±3.4***
EILV/TLC %	61.7±8.7	67.8±8.4	67.0±10.2	79.6±5.2***	86.3±5.3	87.9±6.4
Work of breathing J·min ⁻¹	3±1	4±3*	16±7	32±17**	177±112	87±38**
EMG _{di} /EMG _{di,max} %	7.8±4.3	12.8±3.4**	17.9±11.7	37.3±17.3***	59.3±12.6	59.5±17.5
(EMG _{di} /EMG _{di,max})/(P _{di} /P _{di,max})	0.30±0.20	0.35±0.10	0.52±0.27	0.87±0.38**	1.31±0.40	1.26±0.41
P _{es} /P _{es,max} %	8.4±4.0	10.5±3.3	14.6±5.0	23.3±7.7***	38.5±11.9	38.2±8.1
VMR ($\Delta P_g/\Delta P_{es}$)	-1.26±1.01	-1.62±1.28	-0.34±0.64	-0.14±0.58	0.00±0.48	0.13±0.88

Data are presented as mean±SD. HEWR: highest equivalent work rate; COPD: chronic obstructive pulmonary disease; $\dot{V}O_2$: oxygen uptake; SaO₂: arterial oxygen saturation; $\dot{V}E$: minute ventilation; $\dot{V}T$: tidal volume; f_R : respiratory frequency; $\dot{V}CO_2$: carbon dioxide production; PETCO₂: end-tidal carbon dioxide tension; IC: inspiratory capacity; ΔIC : change in IC from rest; IRV: inspiratory reserve volume; EELV: end-expiratory lung volume; TLC: total lung capacity; EILV: end-inspiratory lung volume; EMG_{di}: diaphragmatic electromyography; EMG_{di,max}: maximal EMG_{di}; P_{di}: transdiaphragmatic pressure; P_{di,max}: maximal P_{di}; P_{es}: tidal oesophageal pressure; P_{es,max}: maximal P_{es}; VMR: ventilatory muscle recruitment; ΔP_g : change in gastric pressure. *: p<0.05; **: p<0.01; ***: p<0.001.

Respiratory mechanics and diaphragmatic function

The total work of breathing and the inspiratory elastic and resistive work of breathing were significantly elevated in mild COPD throughout submaximal exercise compared with controls (fig. 2). At the HEWR, the total work of breathing was two-fold higher in mild COPD *versus* controls. Peak exercise work of breathing was higher in the controls reflecting their higher peak $\dot{V}E$. EMG_{di} and mean P_{di} were higher in mild COPD at rest and throughout submaximal exercise (fig. 2d and 2e, respectively). The ratio between EMG_{di}/EMG_{di,max} and P_{di}/P_{di,max} was also significantly higher during exercise in subjects with mild COPD (fig. 2f). Subjects with mild COPD had lower $\dot{V}T$ and $\dot{V}E$, and a modestly higher P_{di} for any given EMG_{di} (fig. 3a–c). Total respiratory effort (P_{es}/P_{es,max}) was similar between groups for any given EMG_{di} (fig. 3d). Neuromechanical dissociation of the respiratory system, whether expressed as (EMG_{di}/EMG_{di,max})/($\dot{V}T/\dot{V}C_{pred}$) or (P_{es}/P_{es,max})/($\dot{V}T/\dot{V}C_{pred}$), was significantly higher in mild COPD for any given work rate (fig. 4) or $\dot{V}E$ compared with the controls.

Sensory responses to exercise

Breathing discomfort, alone or in combination with leg discomfort was selected as the primary reason for stopping exercise in 69% of subjects with mild COPD *versus* 25% of healthy controls (p=0.07). Leg discomfort alone was the primary reason for stopping exercise in 19% of subjects with COPD *versus* 69% of healthy controls (p<0.05). Other reasons for stopping exercise in mild COPD included “general fatigue” (n=2). One healthy control subject stopped due to a “dry mouth and throat”. Phrases alluding to “inspiratory difficulty” were selected more frequently in subjects with mild COPD *versus* controls at peak exercise (69% *versus* 25% of subjects, p<0.05). Dyspnoea– $\dot{V}E$ slopes were significantly higher in subjects with mild COPD *versus* controls (0.17±0.12 *versus* 0.10±0.05; p<0.05). Dyspnoea intensity ratings were also significantly higher in mild COPD subjects at the HEWR (fig. 5a). Despite this, absolute dyspnoea ratings in the mild COPD group remained relatively low up to the $\dot{V}T/\dot{V}E$ inflection, corresponding to a $\dot{V}E$ of 40.8±13.2 L·min⁻¹. Dyspnoea increased similarly in both groups as a function of increasing EMG_{di} throughout exercise (fig. 5b). Dyspnoea intensity during exercise correlated best with $\dot{V}E$ (% of maximum

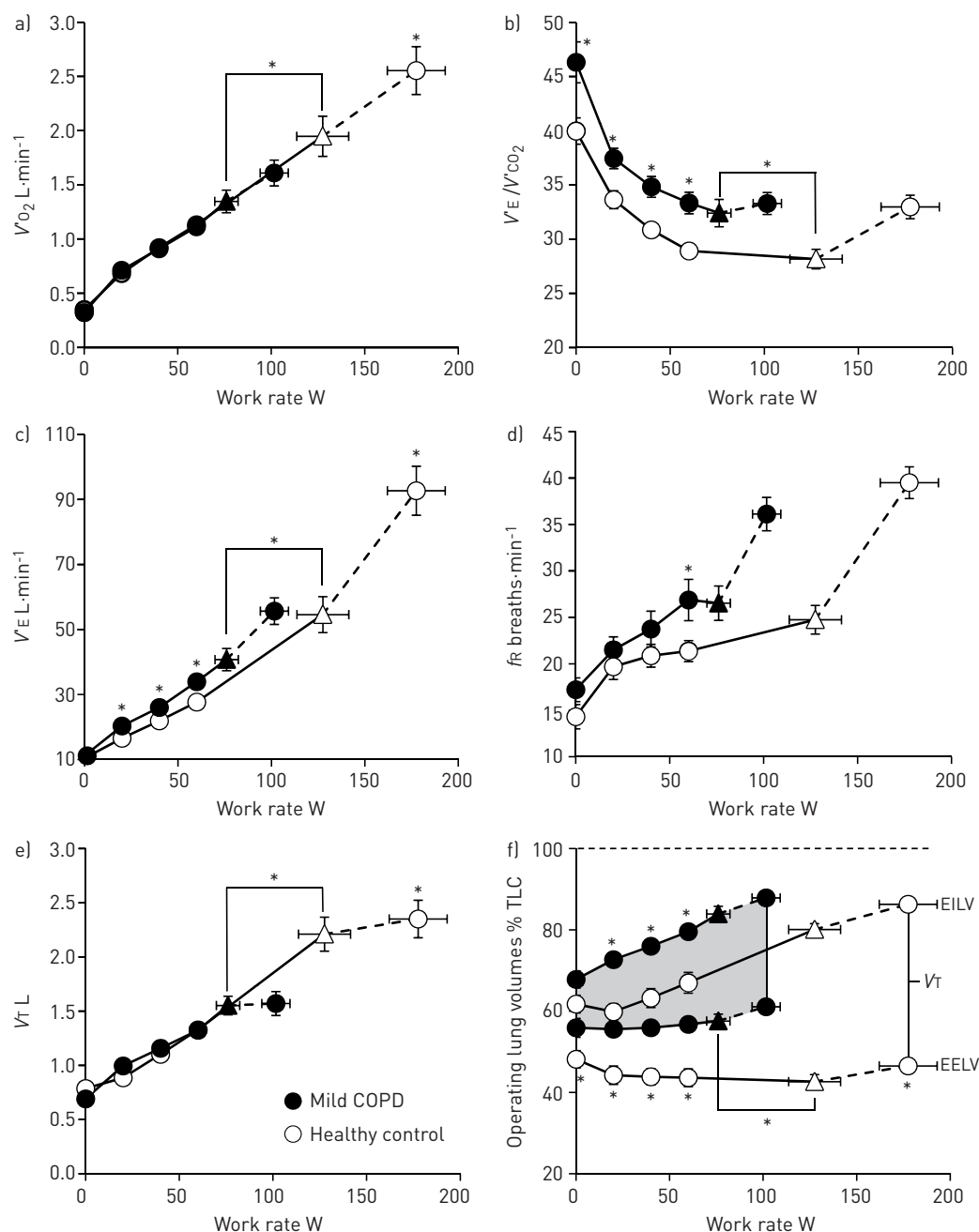


FIGURE 1 Metabolic and ventilatory responses to exercise. a) Oxygen uptake ($\dot{V}O_2$), b) minute ventilation ($\dot{V}E$)/carbon dioxide production ($\dot{V}CO_2$), c) $\dot{V}E$, d) respiratory frequency (f_R), e) tidal volume (V_T) and f) operating lung volumes at different work rates. COPD: chronic obstructive pulmonary disease; TLC: total lung capacity; EILV: end-inspiratory lung volume; EELV: end-expiratory lung volume. Data are presented as mean \pm SEM. Triangles represent the $V_T/\dot{V}E$ inflection. *: $p < 0.05$.

voluntary ventilation), $P_{es}/P_{es,max}$ and $EMG_{di}/EMG_{di,max}$ (all $p < 0.0005$); these relationships were similar across groups. Indices of neuromechanical dissociation (*i.e.* P_{es}/V_T and EMG/V_T ratios) were more weakly associated with dyspnoea, but these relationships showed a significant ($p < 0.005$) group interaction.

Discussion

The novel findings of this study are as follows. 1) The resistive and elastic loads on the respiratory muscles were significantly increased resulting in increased diaphragmatic activation, respiratory effort and work of breathing in mild COPD relative to controls at standardised work rates. 2) In COPD, there was a widening

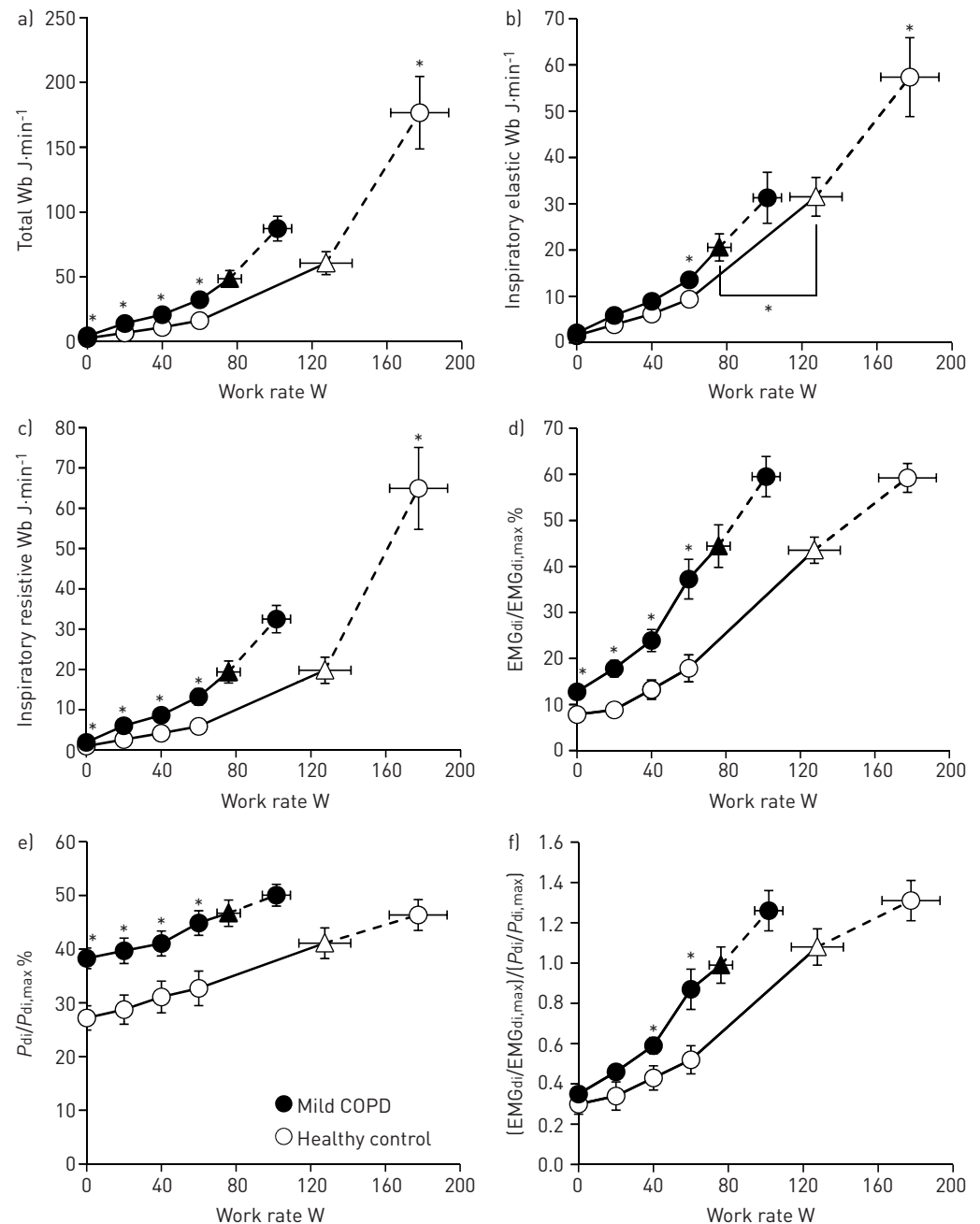


FIGURE 2 Work of breathing and diaphragmatic function in response to exercise. a) Total work of breathing (W_b), b) inspiratory elastic W_b, c) inspiratory resistive W_b, d) ratio of diaphragmatic electromyography (EMG_{di}) to maximal EMG_{di} (EMG_{di,max}), e) ratio of transdiaphragmatic pressure (P_{di}) to maximal P_{di} (P_{di,max}) and f) ratio of EMG_{di}/EMG_{di,max} to P_{di}/P_{di,max} at different work rates. Data are presented as mean ± SEM. Triangles represent the tidal volume/minute ventilation inflection. COPD: chronic obstructive pulmonary disease. *: p < 0.05.

dissociation between indices of respiratory neural drive and the muscular and mechanical response of the respiratory system at lower work rates compared with controls. 3) Despite the mechanical and neuromuscular adaptations needed to support increased ventilation, subjects with mild COPD did not experience significant dyspnoea during moderate submaximal work rates.

Although the mild COPD group had only minor spirometric abnormalities and minimal lung hyperinflation at rest, they had evidence of significant peripheral airway dysfunction as indicated by a reduction in mid-volume maximal expiratory flows, maldistribution of ventilation, pulmonary gas trapping and negative frequency dependence of resistance. These subjects also had mild-to-moderate activity-related

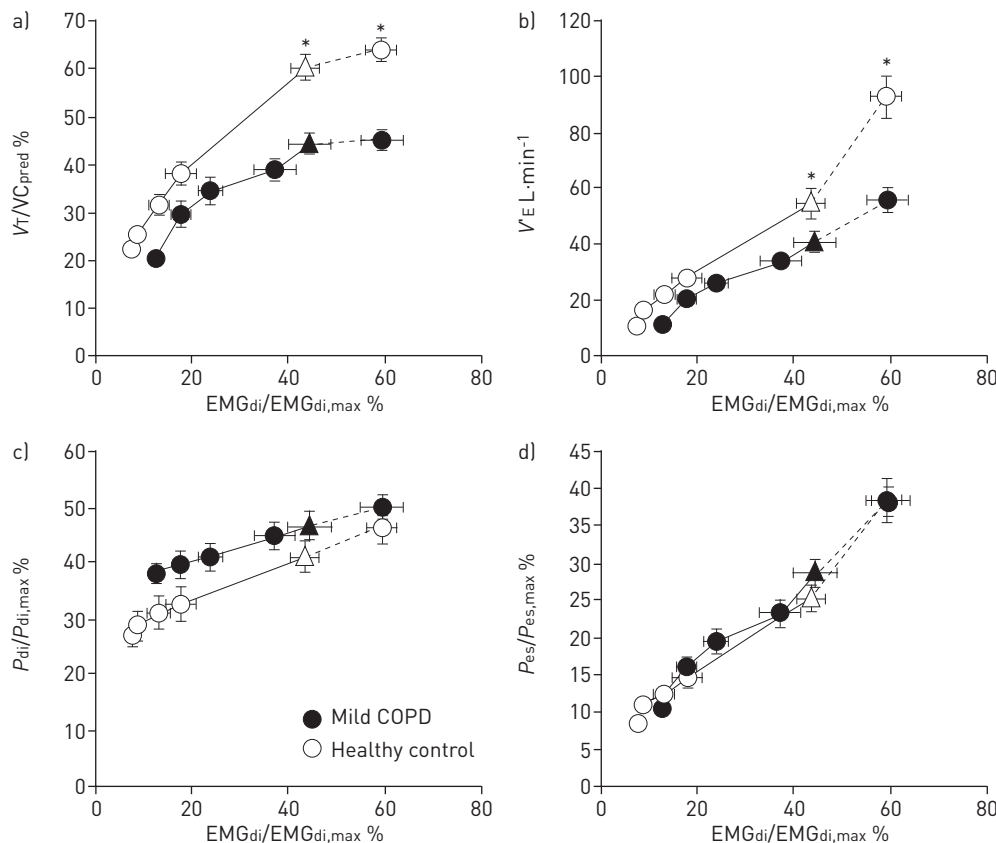


FIGURE 3 Ventilatory and respiratory pressure responses for a given level of diaphragmatic activation. a) Ratio of tidal volume (V_t) to predicted vital capacity (VC_{pred}), b) minute ventilation (V'_E), c) ratio of transdiaphragmatic pressure (P_{di}) to maximal P_{di} ($P_{di,max}$) and d) ratio of tidal oesophageal pressure (P_{es}) to maximal P_{es} ($P_{es,max}$) at different diaphragmatic electromyography (EMG_{di}) to maximal EMG_{di} (EMG_{di,max}) ratios. Data are presented as mean \pm SEM. Triangles represent the V_t/V'_E inflection. Statistical comparisons were performed at the V_t/V'_E inflection and at peak exercise. COPD: chronic obstructive pulmonary disease. *: $p < 0.05$.

dyspnoea and moderately impaired health status. Absolute peak work rate and $V'O_2$ were significantly lower in the COPD group relative to controls and predicted values. Collectively, these results demonstrate that subjects with mild airway obstruction can have important physiological and clinical abnormalities despite having relatively preserved spirometry.

Our results confirm previous reports of significant ventilatory abnormalities in subjects with mild COPD during exercise (fig. 1) [6, 14, 27]. For example, greater ventilatory inefficiency (high V'_E /carbon dioxide production ($V'CO_2$)) was present at rest and during exercise in mild COPD, likely reflecting an increased physiological dead space due to regional increases in ventilation/perfusion ratios. Our mild COPD group also had evidence of dynamic hyperinflation at peak exercise (~ 0.3 L), along with greater tachypnoea and an earlier V_t inflection, indicating that the end-inspiratory lung volume encroached on total lung capacity (TLC) (88% of TLC) at a lower work rate (102 versus 178 W) and V'_E (55.7 versus 92.7 L·min⁻¹) than in the controls.

Compared with controls, subjects with mild COPD had greater resistive and elastic loading of the inspiratory muscles resulting in an increased total work of breathing for any given submaximal work rate. At the HEWR, the total work of breathing was two-fold greater in mild COPD relative to controls and this was predominantly driven by a higher inspiratory resistive work of breathing. Respiratory muscle effort was also markedly higher in mild COPD subjects across all submaximal work rates. Thus, to perform the same standardised physical task, subjects with mild COPD consistently had greater erosion of their respiratory reserve than healthy individuals.

Diaphragmatic function and dynamic respiratory mechanics

To our knowledge, this is the first study to examine detailed measures of diaphragmatic function in individuals with mild airway obstruction. EMG_{di} was markedly higher in this group at rest and throughout all submaximal work rates. The ratio of EMG_{di} to P_{di} was also significantly higher relative to controls,

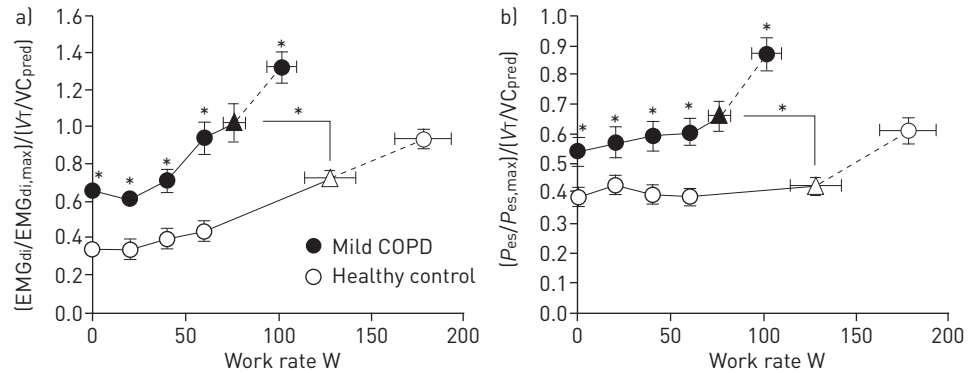


FIGURE 4 Neuromechanical dissociation of the respiratory system. As exercise progresses there is an increasing disparity between a) the ratio of diaphragmatic electromyography (EMG_{di}) to maximal EMG_{di} (EMG_{di,max}) or b) the ratio of tidal oesophageal pressure (P_{es}) to maximal P_{es} (P_{es,max}) and the tidal volume (V_t) response in mild chronic obstructive pulmonary disease (COPD) compared with healthy controls. VC_{pred}: predicted vital capacity. Data are presented as mean ± SEM. Triangles represent the V_t/V_E inflection. *: p < 0.05.

indicating some degree of neuromuscular dissociation of the diaphragm. This higher ratio was driven, in part, by the more rapid increase in EMG_{di} since the rate of increase in P_{di} was similar in both groups and increased linearly with increasing exercise intensity (fig. 2e). This is in contrast with the work by SINDERBY *et al.* [17] in moderate-to-severe COPD, where a plateau in P_{di} occurred relatively early during exercise despite a continued increase in EMG_{di}. The authors proposed that this was the result of reduced pressure generating capacity of the diaphragm due to lung hyperinflation. Patients with moderate-to-severe COPD have been shown to have an EMG_{di} of 70% of maximum at peak incremental exercise corresponding to a V_E of 32.3 ± 9.6 L·min⁻¹ using the same catheter as used in the present study [28]. At a similar absolute V_E (33.9 ± 8.1 L·min⁻¹), we found that patients with mild COPD have an EMG_{di} of 37% of maximum, suggesting that respiratory neural drive increases dramatically with advancing COPD severity. Accordingly, the relatively preserved pressure generating capacity of the diaphragm in our mild COPD subjects probably reflects the presence of less severe mechanical constraints. In keeping with this, the pattern of ventilatory muscle recruitment during exercise was not different in mild COPD and controls. Nevertheless, the higher diaphragmatic activation and EMG_{di} to P_{di} ratio in mild COPD indicates the presence of important compensatory physiological adaptations. Specifically, the combination of increased mechanical loading and pulmonary gas exchange abnormalities led to an increase in neural activation of the diaphragm and total respiratory muscle contractile effort, which permitted subjects to achieve the alveolar ventilation required to meet the metabolic demands of moderate physical work.

It has long been understood that there is a widening disparity between the drive to breathe and the corresponding mechanical output of the impaired respiratory system during exercise in advanced COPD [29]. Since respiratory neural drive cannot be measured directly, we rely on indirect estimates such as

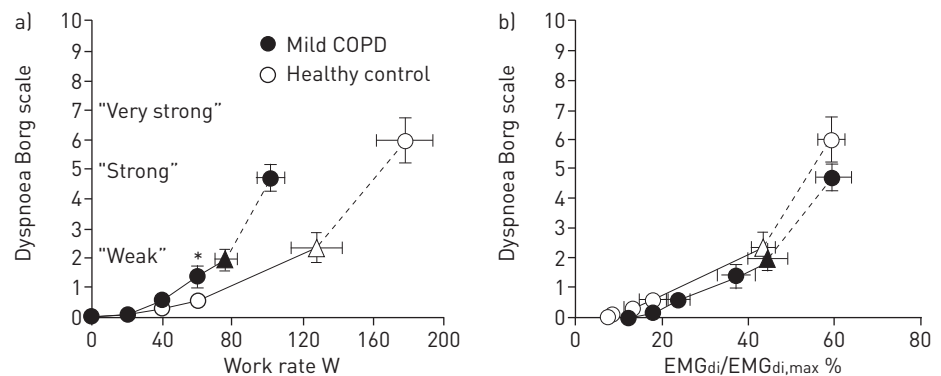


FIGURE 5 Dyspnoea intensity in response to exercise. Dyspnoea measured using the modified 10-point Borg scale in response to exercise measured as a) work rate and b) the ratio of diaphragmatic electromyography (EMG_{di}) to maximal EMG_{di} (EMG_{di,max}). Data are presented as mean ± SEM. Triangles represent the tidal volume/minute ventilation inflection. COPD: chronic obstructive pulmonary disease. *: p < 0.05.

measures of effort (*i.e.* $P_{es}/P_{es,max}$). Unfortunately, this approach can lead to significant underestimation in the setting of severe respiratory mechanical impairment [17, 30, 31]. The additional use of EMG_{di} as a surrogate for respiratory neural drive in mild COPD [32] is unique to this study. Increases in EMG_{di}/EMG_{di,max} and $P_{es}/P_{es,max}$ were closely correlated (fig. 3d) throughout exercise in health and mild COPD, thus supporting the contention that these measures are reasonable surrogates of respiratory neural drive, at least in this population. Remarkably, even in the setting of mild spirometric abnormality, V_T expansion and, thus, V'_E was significantly reduced for a given EMG_{di} (and respiratory muscle effort) compared with controls (fig. 3a and 3b). This inability to appropriately expand V_T is probably explained by the prevailing mechanical ventilatory constraints. This latter contention is bolstered by the previous finding that bronchodilators, by decreasing lung hyperinflation, allow greater V_T expansion during exercise in mild COPD [33, 34].

Dyspnoea

Despite the compensatory increases in diaphragmatic activation and respiratory effort needed to maintain V'_E in pace with increasing metabolic demands, minimal dyspnoea was experienced up to 80 W or a V'_E of ~ 40 L·min⁻¹. The $V'O_2$ at this work rate in mild COPD corresponds to approximately five metabolic equivalents. Thus, by extrapolation, such patients are likely to be able to undertake many daily activities requiring moderate exertion without experiencing significant respiratory discomfort [35]. However, it is clear that more sustained or strenuous tasks would evoke severe dyspnoea. In both groups, dyspnoea increased as a function of increasing EMG_{di}, P_{es} and V'_E , all relative to maximum. Thus, the higher dyspnoea intensity at equivalent work rates in mild COPD compared with controls, generally reflects their higher drive to breathe and respiratory muscle effort requirements. We speculate that this increasing dissociation between neural drive and the muscular/mechanical response of the respiratory system might explain the more frequent selection of the qualitative descriptor inspiratory difficulty at a much lower peak work rate in mild COPD compared with controls [16].

Limitations

This study had a small sample size due to the complexity and invasiveness of the EMG_{di} and respiratory pressure measurements. Despite this, our sample size was sufficient to detect significant differences in dyspnoea intensity and a wide range of physiological and respiratory mechanical outcome variables of interest. The mild COPD subjects who participated in this study had, on average, mild-to-moderate activity-related dyspnoea. Thus, our results may not be generalisable to asymptomatic subjects with mild COPD [36].

Conclusions and implications

In patients with a relatively preserved FEV₁, extensive mechanical and respiratory neuromuscular adaptations were already in place, which allowed them to adequately meet the metabolic demands of moderate physical activity. However, maximal exercise capacity was diminished in these patients, and our study is the first to show that this was associated with the inability of the respiratory system to appropriately increase ventilation in the face of increasing diaphragmatic activation and contractile respiratory muscle effort. These compensatory adjustments in mild COPD appeared to have little negative influence on respiratory sensation until higher levels of ventilation were required to support increased exercise intensities. These results highlight that exclusive reliance on spirometry, to assess severity of airway obstruction in patients with mild COPD, may result in underestimation of clinically important physiological impairment.

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