ORIGINAL ARTICLE

Physiological Characterization of Preserved Ratio Impaired Spirometry in the CanCOLD Study

Implications for Exertional Dyspnea and Exercise Intolerance

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Abstract

Rationale: It is increasingly recognized that adults with preserved ratio impaired spirometry (PRISm) are prone to increased morbidity. However, the underlying pathophysiological mechanisms are unknown.

Objectives: Evaluate the mechanisms of increased dyspnea and reduced exercise capacity in PRISm.

Methods: We completed a cross-sectional analysis of the CanCOLD (Canadian Cohort Obstructive Lung Disease) population-based study. We compared physiological responses in 59 participants meeting PRISm spirometric criteria (post-bronchodilator $FEV_1 < 80\%$ predicted and $FEV_1/FVC \geq 0.7$), 264 control participants, and 170 ever-smokers with chronic obstructive pulmonary disease (COPD), at rest and during cardiopulmonary exercise testing.

Measurements and Main Results: Individuals with PRISm had lower total lung, vital, and inspiratory capacities than healthy controls (all $P < 0.05$) and minimal small airway, pulmonary gas exchange, and radiographic parenchymal lung abnormalities. Compared with healthy controls, individuals with PRISm had higher dyspnea/$\dot{V}O_2$ ratio at peak exercise (4.0 ± 2.2 vs. 2.9 ± 1.9 Borg units/L/min; $P < 0.001$) and lower $\dot{V}O_{2peak}$ ($74 \pm 22\%$ predicted vs. $96 \pm 25\%$ predicted; $P < 0.001$). At standardized submaximal work rates, individuals with PRISm had greater VT/inspiratory capacity (VT%IC; $P < 0.001$), reflecting inspiratory mechanical constraint. In contrast to participants with PRISm, those with COPD had characteristic small airways dysfunction, dynamic hyperinflation, and pulmonary gas exchange abnormalities. Despite these physiological differences among the three groups, the relationship between increasing dyspnea and VT%IC during cardiopulmonary exercise testing was similar. Resting IC significantly correlated with $\dot{V}O_{2peak}$ ($r = 0.65$; $P < 0.001$) in the entire sample, even after adjusting for airflow limitation, gas trapping, and diffusing capacity.

Conclusions: In individuals with PRISm, lower exercise capacity and higher exertional dyspnea than healthy controls were mainly explained by lower resting lung volumes and earlier onset of dynamic inspiratory mechanical constraints at relatively low work rates.

Clinical trial registered with www.clinicaltrials.gov (NCT00920348).

Keywords: preserved ratio impaired spirometry; exercise capacity; dyspnea; pulmonary function; spirometry

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A complete list of CanCOLD Collaborative Research Group and the Canadian Respiratory Research Network members may be found before the beginning of the References.

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The term preserved ratio impaired spirometry (PRISm), defined as post-bronchodilator $FEV_1 < 80\%$ predicted and an FEV_1/FVC ratio $\geqslant 0.7$ or greater than or equal to the lower limit of normal (LLN) (1–3), has variously been described as restrictive pulmonary function (4, 5), Global Initiative for Chronic Obstructive Lung Disease (GOLD)-unclassified chronic obstructive pulmonary disease (COPD) (6), or, as originally suggested by Hyatt and colleagues (7), the nonspecific pattern, defined as reduced FEV_1 and FVC but a normal FEV_1/FVC and TLC. Recent COPD population studies in patients with PRISm have included nonsmokers (8, 9), whereas others have not (2, 3, 10). Regardless of smoking history, adults with PRISm, reported to have a variable population prevalence of 3–20%, are more likely to have chronic dyspnea, exercise limitation, poor quality of life, and increased mortality (2, 3, 6, 8, 11–18). However, the pathophysiological mechanisms of increased dyspnea and reduced exercise capacity in both ever- and never-smokers with PRISm and the overlap with COPD remain unstudied (1, 18, 19). Previous studies have used different FEV_1/FVC criteria for PRISm definition, some favoring fixed ratio > 0.7 (8–11, 20) and others $>$ LLN (3, 21). However, the impact of using either of these spirometric criteria on the assessment of its underlying pathophysiology of PRISm is unknown and may have clinical relevance.

Based on several previous studies in various clinical populations (22–25), it is plausible that heightened dyspnea and reduced exercise tolerance in PRISm, compared with healthy controls, may reflect a lower-than-normal baseline VC and inspiratory capacity (IC), which would reduce maximal ventilatory capacity during a cardiopulmonary exercise test (CPET). A lower baseline IC in individuals with expiratory flow limitation would mean that the operating limits for tidal volume (V_T) expansion are significantly reduced during exercise. In this context, a relatively diminished inspiratory reserve volume (IRV) indicates earlier onset of significant inspiratory mechanical constraints (22, 23, 26). Thus, earlier elastic mechanical loading of the inspiratory muscles, as V_T encroaches on minimal IRV, near the upper reaches of the respiratory system's pressure–volume relation, would undoubtedly heighten inspiratory neural drive from respiratory control centers and have negative sensory consequences, contributing to earlier exercise termination (22, 23, 27). This situation would likely be compounded further in a subset of smokers fitting PRISm criteria, by the coexistence of smoking-related inflammatory injury of the airways, parenchyma, and vasculature that characterize COPD. Here, in those with low baseline VC or IC, the combination of expiratory flow limitation, lung hyperinflation, and concomitant high ventilatory requirements due to pulmonary gas exchange abnormalities, could lead to the onset of severe dynamic inspiratory mechanical constraints and limiting dyspnea at even lower exercise intensities (22–24, 28–33). It is conceivable, therefore, that a low baseline VC or IC in PRISm has the potential to negatively influence exercise performance, regardless of whether such patients have pathophysiological features of COPD. Thus, we postulated that low resting VC and/or IC, regardless of cause, can strongly influence the time course of development of critical dynamic mechanical constraints and the associated dyspnea and exercise intolerance.

Accordingly, the overarching objective of the current study was to evaluate the pathophysiological mechanisms of increased dyspnea and reduced exercise capacity in those with PRISm identified in a large population-based sample. We first undertook a careful clinical characterization of each individual and compared incremental exercise test responses in PRISm with healthy control participants to identify physiological mechanisms of dyspnea and exercise limitation. Second, to better understand interactions between PRISm and spirometrically defined COPD, we examined common mechanisms of exertional dyspnea in these two groups and, in particular, the role of dynamic inspiratory mechanical constraints. Third, we wished to determine the impact of smoking history on underlying pathophysiological responses in PRISm and whether choice definitions of PRISm (fixed ratio or LLN) could alter pathophysiological assessments and their clinical interpretation.

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This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article.

At a Glance Commentary

Scientific Knowledge on the Subject: Adults with preserved ratio impaired spirometry (PRISm), defined as post-bronchodilator $FEV_1 < 80\%$ predicted and an FEV_1/FVC ratio ≥ 0.7, are more likely to have chronic activity-related dyspnea and reduced exercise capacity. However, the pathophysiological mechanisms of increased dyspnea and reduced exercise capacity in PRISm are unclear.

What This Study Adds to the Field: This study is the first to examine physiological responses at rest and during exercise in individuals with PRISm compared with healthy control participants and individuals with chronic obstructive pulmonary disease. Heightened exertional dyspnea and reduced exercise capacity in ever- and never-smokers with PRISm, compared with health, was mainly explained by reduced vital and inspiratory capacities and a lower operating limit for V_T expansion during exercise. The observation that participants with PRISm (with lung volume reduction but preserved small airway function and pulmonary gas exchange) were as dyspneic and functionally impaired as adults with moderate chronic obstructive pulmonary disease (with both small airway dysfunction and pulmonary gas exchange derangements) points to the primacy of resting lung volumes as a strong contributor of exertional dyspnea and exercise intolerance, regardless of the underlying respiratory pathophysiology.

Methods

Study Participants

All study participants provided written informed consent to take part in the multicenter CanCOLD (Canadian Cohort Obstructive Lung Disease) study, which received approval by the ethical review boards at each site. In brief, CanCOLD is a prospective longitudinal cohort study investigating adults from the community (>40 yr old) at baseline, 18 months, 3 years, and beyond (34, 35). The sampling for CanCOLD is described elsewhere (31, 34–37). The current study completed a cross-sectional analysis from visit 1, which included a medical history, symptom assessment, pulmonary function tests (PFTs), a CPET, and a chest computed tomography (CT) scan. In the present study, 1,250 individuals had complete CPET data available for analysis. We identified 59 individuals with PRISm ($FEV_1 < 80\%$ predicted and $FEV_1/FVC \geq 0.7$ post-bronchodilator), 264 never-smokers with normal lung function, and 170 ever-smokers with COPD ($FEV_1/FVC < 0.7$ post-bronchodilator and FEV_1 50–79% predicted). A flowchart detailing participant selection is shown Figure E1 in the online supplement.

Outcomes

Spirometry, body plethysmography, D_{LCO}, and K_{CO} were performed using automated equipment following established guidelines (38–40). Select PFT parameters were expressed in absolute values and relative to predicted normal values (41–43). CT images were acquired at each of the nine sites using various CT system models, as previously described (31, 44). Standardized symptom-limited, stepwise incremental (10 W/min) CPETs were conducted on an electronically braked cycle ergometer using a CPET system (Vmax, SensorMedics [seven sites]; TrueOne, Parvomedics [one site]; Ergocard, Medisoft [one site]) (34). Additional details, including definitions of key CPET outcomes (Table E1), are provided in the online supplement.

Statistical Analysis

Data are presented as mean ± SD, relative frequency (percentage of subgroup), or estimated marginal means (5–95% confidence intervals) unless otherwise specified. A $P < 0.05$ level of significance was used *a priori* for all inferential analyses. ANOVA was used for between-group (PRISm, COPD, and never-smoking controls) comparison of demographics and select PFT and CT variables. In addition, analysis of covariance was used for between-group comparison of select PFT and CPET variables. Model covariates included age, sex, height, body mass index (BMI), and history of cardiovascular disease (CVD).

A linear mixed model was used to determine between-group (PRISm vs. control) by exercise intensity interactions on ventilation, breathing pattern, operating lung volumes, and dyspnea intensity during incremental CPET. If a significant group or group by exercise intensity interaction was observed, the groups were compared with Bonferroni correction at each exercise intensity (i.e., baseline, 20 W, 40 W, and 50% predicted peak exercise [WR_{peak}]). For 50% predicted WR_{peak}, we used the closest available data point that was within a ±10% range (i.e., 40–60% predicted WR_{peak}). These submaximal exercise points were included for analyses as data were available in all 323 participants ($n = 264$ control subjects, $n = 59$ individuals with PRISm) for baseline, 20 W, and 40 W intensities and in 314/323 participants for 50% predicted WR_{peak}. In addition to group, intensity, and their interaction, this mixed model included age, sex, height, BMI, and history of CVD as covariates. Exercise intensity was modeled as a categorical repeated factor. The model used unstructured within-subject covariance to account for the repeated measure design. See the online supplement for details on comparisons between individuals with PRISm, individuals with COPD, and control subjects.

Fisher exact tests were used to compare frequencies of categorical variables of interest. To explore the pathophysiology of PRISm, two-sample *t* test analysis was completed to determine between-group differences in select demographics, PFT, CPET, and CT data in ever-smokers versus never-smokers within the PRISm subgroup ($n = 59$). Similar analysis was completed to explore between-group differences in our original PRISm group versus an additional 43 participants, characterized as PRISm using the FEV_1/FVC greater than or equal to LLN cutoff. Pearson's correlation was used to test associations between continuous variables of interest (i.e., resting IC, peak $\dot{V}O_2$ [$\dot{V}O_{2peak}$]). Stepwise multivariable linear regression was used to estimate the standardized β coefficient values between select PFT and CT variables (independent) and $\dot{V}O_{2peak}$ and dyspnea–$\dot{V}O_2$ ratios at peak exercise (dependent variables), while adjusting for age, sex, height, BMI, and history of CVD. Additional details on exploratory two-sample *t* test and multivariable regression analysis procedures are provided in the online supplement. All statistical analysis was performed using Statistical Package for the Social Sciences version 28 (IBM).

Table 1. Participant Demographics

	Control	PRISm	COPD
Demographics			
n	264	59	170
Male:female	121:143	30:29	98:72
Age, yr	66 ± 10	66 ± 9	66 ± 10
Height, cm	165 ± 10	167 ± 10	170 ± 9
Weight, kg	77 ± 14	82 ± 18	79 ± 17
BMI, kg/m^2	27.5 ± 4.8	29.2 ± 4.4*	28.0 ± 5.2
Pack-years	0 ± 0	20 ± 26†	35 ± 22*‡
Joint-years	1.1 ± 6.8	0.8 ± 1.9†	4.1 ± 12.8*‡
Current smoker	0 (0)	16 (27)*	51 (30)‡
Biomass exposure years	3 ± 8	3 ± 6	3 ± 8
Occupational exposure	10 (8)	8 (14)	20 (13)
History of CVD	125 (48)	37 (63)*	95 (56)‡
History of diabetes	57 (22)	16 (27)	39 (23)
History of HDHTDM	138 (53)	40 (68)	108 (63)
History of any cancer	49 (19)	12 (20)	31 (18)
History of physician-diagnosed asthma	35 (13)	13 (22)*†	60 (35)‡
History of interstitial lung disease	0 (0)	0 (0)	0 (0)
Any respiratory medication	27 (10)	12 (20)*†	82 (48)‡
Symptoms			
MRC, 1–5	1.2 ± 0.5	1.7 ± 0.8*	1.7 ± 0.7‡
MRC ⩾ 2, % sample	23	52*	56‡
CAT, 0–40	5 ± 4	9 ± 6*	10 ± 6‡
CAT ⩾ 10, % sample	14	42*	43‡

Definition of abbreviations: BMI = body mass index; CAT = chronic obstructive pulmonary disease assessment test; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; HDHTDM = heart disease, systemic hypertension and/or diabetes mellitus; MRC = Medical Research Council dyspnea scale; PRISm = preserved ratio impaired spirometry.
Data are presented as mean ± SD or *n* (%) unless otherwise stated. Joint-years: marijuana exposure quantified as the number of joints smoked per day multiplied by years; biomass exposure: lifetime exposure in years to the use of indoor fire using coal or coke, wood, crop residues, or dung (*see* Reference 37); occupational exposure: any work-related exposure (yes or no) to poor air quality, including indoor fire using (*see* Reference 37).
*$P < 0.05$ PRISm versus control.
†$P < 0.05$ PRISm versus COPD.
‡$P < 0.05$ COPD versus control.

Results

Participant Characteristics

Participant characteristics are provided in Table 1. There were no between-group differences (PRISm, COPD, and control) in age, sex, and height. BMI was greater in individuals with PRISm than in control subjects ($P < 0.001$). A total of 39/59 individuals with PRISm and all individuals with COPD were ever-smokers. Only 16 individuals with PRISm and 51 individuals with COPD were active smokers at the time of study enrollment. There were no between-group differences in biomass exposure or occupational exposure to noxious air quality (all $P > 0.05$). The presence of significant comorbidities was similar between groups, except for a greater prevalence of physician-diagnosed asthma and history of CVD in individuals with PRISm and COPD compared with control subjects (both $P < 0.01$). Prescribed respiratory medication use was greater in individuals with PRISm compared with control subjects ($P < 0.001$) but lower in individuals with PRISm compared with those with COPD ($P < 0.001$). Medical Research Council dyspnea scale values were uniformly greater in individuals with PRISm and COPD than in controls (both $P < 0.001$).

PFT and CT values are provided in Table 2. Individuals with PRISm and COPD had similar FEV_1, and both were lower than controls (both $P < 0.001$). Individuals with PRISm and COPD both had low VC and IC compared with controls (both $P < 0.01$). TLC was lower in individuals with PRISm than in controls ($P < 0.001$) but not different between controls and individuals with COPD ($P = 0.60$). Despite the reduction in TLC, only 9/59 individuals with PRISm had TLC greater than LLN. The VC–FVC difference, forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75}$), $FEF_{25–75}$/FVC, FRC, residual volume (RV), and specific airways resistance (sRAW) were not different between individuals with PRISm and controls (all $P > 0.05$). $FEF_{25–75}$ and $FEF_{25–75}$/FVC were lower and sRAW, FRC, and RV were higher in individuals with COPD compared with those with PRISm and controls (all $P < 0.01$). D_{LCO} was uniformly lower in individuals with PRISm and COPD compared with controls (both $P < 0.001$). V_A was lower in individuals with PRISm compared with control subjects ($P < 0.001$) but greater than individuals with COPD ($P < 0.001$). K_{CO} and V_A/TLC were not different between individuals with PRISm and controls (both $P > 0.05$) but were consistently lower in individuals with COPD (both $P < 0.001$). Quantitative CT-derived emphysema percentage and probability measure of functional small airway disease and emphysema were not different between individuals with PRISm and controls (all $P > 0.05$) but were consistently greater in COPD (all $P < 0.001$). Qualitative CT analysis revealed no between-group differences in prevalence of consolidation, honeycombing, ground glass, mosaic attenuation, or reticular abnormalities (all $P > 0.05$). In addition,

Table 2. Selected Pulmonary Function, Radiographic Imaging, and Cardiopulmonary Exercise Test Measurements

	Control	PRISm	COPD
Post-bronchodilator lung function			
FEV_1, L	2.8 ± 0.8 (102 ± 13)	2.0 ± 0.5* (72 ± 6*)	2.0 ± 0.5‡ (71 ± 7‡)
FVC, L	3.6 ± 1.1 (104 ± 11)	2.6 ± 0.7*† (75 ± 8*†)	3.3 ± 0.8 (91 ± 13)
FEV_1/FVC	0.78 ± 0.05	0.75 ± 0.04†	0.60 ± 0.07‡
$FEF_{25–75}$, L/s	2.5 ± 0.9 (110 ± 31)	1.6 ± 0.5*† (69 ± 18*†)	0.8 ± 0.4‡ (33 ± 11‡)
$FEF_{25–75}$/FVC	0.63 ± 0.15	0.59 ± 0.15‡	0.24 ± 0.09‡
Prebronchodilator lung function			
TLC, L	5.9 ± 1.3 (108 ± 16)	5.2 ± 1.1 *† (96 ± 15*†)	6.1 ± 1.3 (110 ± 18)
FRC, L	3.1 ± 0.9 (105 ± 25)	2.9 ± 0.7† (97 ± 24†)	3.7 ± 1.0‡ (121 ± 31‡)
FRC/TLC, %	54 ± 8	54 ± 9†	59 ± 9‡
VC, L	3.8 ± 1.1 (113 ± 22)	2.9 ± 0.8 *† (87 ± 14*†)	3.4 ± 0.9‡ (97 ± 17‡)
VC–FVC, L	0.23 ± 0.36	0.28 ± 0.26†	0.04 ± 0.36‡
IC, L	2.8 ± 0.8 (113 ± 24)	2.3 ± 0.6*† (94 ± 19*†)	2.6 ± 0.8‡ (102 ± 23‡)
IC/TLC, %	46 ± 8	45 ± 8†	41 ± 9‡
ERV, L	1.0 ± 0.7	0.6 ± 0.4*†	0.8 ± 0.5‡
ERV/TLC	15 ± 10	12 ± 8	13 ± 7
RV, L	2.2 ± 0.6 (108 ± 27)	2.3 ± 0.6† (110 ± 32†)	2.9 ± 0.8‡ (144 ± 43‡)
RV/TLC, %	38 ± 8	44 ± 8*	46 ± 9‡
sRAW, cm H_2O/s	6.1 ± 2.8	7.1 ± 3.1†	11.5 ± 5.9‡
V_A, L	5.3 ± 1.4 (98 ± 21)	4.5 ± 1.2*† (83 ± 27*†)	5.0 ± 1.3 (90 ± 20)
D_{LCO}, ml/min/mm Hg	22 ± 7 (99 ± 21)	19 ± 6* (83 ± 22*)	19 ± 6‡ (81 ± 20‡)
K_{CO} ml/min/mm Hg/L	4.1 ± 0.8 (99 ± 17)	4.1 ± 1.0† (99 ± 26†)	3.7 ± 1.1‡ (90 ± 25‡)
V_A/TLC, %	88 ± 10	87 ± 10†	81 ± 12‡
CT imaging			
n	210	53	151
LAA_{950}, %	2.9 ± 2.6	2.1 ± 2.3†	5.6 ± 5.2‡
LAA_{856}, %	21 ± 17	17 ± 13†	31 ± 18‡
DPM fSAD, %	42 ± 17	45 ± 15	49 ± 15‡
DPM emphysema, %	2.6 ± 3.6	1.5 ± 1.8†	6.3 ± 6.8‡
$LV_{inspiration}$, L	5.2 ± 1.4	4.4 ± 1.1*†	5.6 ± 1.2
Consolidation, *n* (% sample)	1 (0.5)	1 (0.5)	5 (3.3)
Honeycombing, *n*	0	0	0
Ground glass, *n* (% sample)	7 (3.3)	2 (3.3)†	14 (9.2)‡
Mosaic attenuation, *n* (% sample)	7 (3.3)	1 (0.9)	8 (5.2)
Reticular abnormalities, *n*	23 (11)	7 (12)	12 (8)
Cardiopulmonary exercise test			
$\dot{V}O_{2peak}$, % predicted	95 ± 25	74 ± 22*	77 ± 20‡
Change in IC (rest − peak), L	−0.05 ± 0.37	−0.09 ± 0.40†	−0.25 ± 0.36‡
Sp_{O_2} at peak, %	97.1 ± 2.1	96.3 ± 2.9	95.9 ± 2.8
Nadir $V_E/\dot{V}CO_2$	30 ± 5	31 ± 8†	33 ± 6‡
Dyspnea, 0–10 Borg units	5.2 ± 2.8	5.1 ± 2.6	5.1 ± 2.5
Dyspnea/$\dot{V}O_2$ ratio, Borg units/L/min	3.2 ± 2.1	4.0 ± 2.2*	3.9 ± 2.6‡
Dyspnea/V_E ratio, Borg units/L/min	0.09 ± 0.06	0.11 ± 0.06*	0.11 ± 0.06‡
Leg discomfort, 0–10 Borg units	6.0 ± 2.6	5.8 ± 2.7	6.2 ± 2.5
Leg discomfort/$\dot{V}O_2$ ratio, Borg units/L/min	3.2 ± 2.1	4.0 ± 2.2*	3.9 ± 2.6‡

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CT = computed tomography; DPM-emphysema = CT-derived disease probability measure of emphysema; DPM-fSAD = CT-derived disease probability measure of functional small airway disease; ERV = expiratory reserve volume; $FEF_{25–75}$ = forced expiratory flow between 25% and 75% of the FVC maneuver; IC = inspiratory capacity; LAA_{856} = full-expiration low-attenuation areas of the lung below −856 Hounsfield units; LAA_{950} = low-attenuation areas of the lung below −950 Hounsfield units; $LV_{inspiration}$ = lung volume on inspiration; PRISm = preserved ratio impaired spirometry; RV = residual volume; Sp_{O_2} = pulse oximetry–derived oxygen saturation; sRAW = specific airways resistance; VC = vital capacity; $V_E/\dot{V}CO_2$ = ventilatory equivalents for carbon dioxide; $\dot{V}O_{2peak}$ = peak oxygen uptake.

Data are presented as mean ± SD (absolute [% predicted]) or frequency (*n*) unless otherwise specified. Analysis of variance and Fisher exact test were used for between-group comparisons.

*$P < 0.05$ PRISm versus control.

†Indicates $P < 0.05$ in PRISm versus COPD.

‡Indicates $P < 0.05$ in COPD versus control.

there was no radiographic report of thoracic cage deformity in any participant. Within participants with PRISm, the presence of reticular abnormalities did not affect key CPET responses (Table E2).

Tables 3 provides detailed comparisons between never- and ever-smokers within participants with PRISm. There were no between-group differences in key PFT, CT, or CPET metrics. Tables E3–E5 provide detailed comparisons between the main PRISm group ($n = 59$) and 43 additional participants in the PRISm LLN subgroup. Pack- and joint-years were greater; FEV_1/FVC, $FEF_{25–27}$, and K_{CO} were lower; and

CT-derived emphysema percentage was greater in individuals with PRISm LLN compared with the main PRISm group (all $P < 0.05$; Tables E3 and E4). PRISm LLN had a greater reduction in IC from rest to peak during CPET compared with the main PRISm group ($P < 0.001$; Table E5). All other CPET responses were similar between PRISm groups.

CPET Responses: Individuals with PRISm versus Healthy Controls

Detailed CPET data are presented in Tables 2 and E6. $\dot{V}O_{2peak}$ was reduced in individuals with PRISm compared with controls ($P < 0.001$). At standardized submaximal work rates, adjusted $\dot{V}E$, $\dot{V}E/\dot{V}CO_2$, partial pressure of end-tidal CO_2, and pulse oximetry–derived oxygen saturation were not different between individuals with PRISm and controls (all $P > 0.05$) (Figures 1A–1D). Individuals with PRISm had a rapid and shallow breathing pattern compared with controls (Figures 1E and 1F). At rest and throughout exercise, adjusted IC was lower in individuals with PRISm than in controls ($P < 0.01$) (Figure 1G). The change in IC from rest to peak exercise was similar between groups ($P = 0.50$). Adjusted VT%IC was higher throughout exercise in individuals with PRISm compared with controls ($P < 0.001$) (Figure 1H).

CPET Responses: Individuals with PRISm versus Individuals with COPD

At standardized submaximal work rates, $\dot{V}E/\dot{V}CO_2$ was greater in individuals with COPD compared with individuals with PRISm ($P < 0.01$) (Figures 2A and E2), after adjusting for covariates. Individuals with PRISm breathed at relatively low operating lung volumes (low end-expiratory and inspiratory lung volumes, whereas operating lung volumes were higher in COPD ($P < 0.05$) (Figures 2B). At rest and during exercise, adjusted IC was lower in individuals with PRISm than in those with COPD ($P < 0.01$) (Figures 3A and E3), and individuals with PRISm had a rapid shallow breathing pattern compared with those with COPD (Figure 2C). Despite different mechanisms, a lower fixed IC in individuals with PRISm, and dynamic reductions in IC (pulmonary gas trapping) in individuals with COPD, the adjusted VT%IC ratio was not different in these two groups ($P = 0.90$) but similarly higher than controls (both $P < 0.01$) (Figure E3). Adjusted $\dot{V}O_{2peak}$ was lower in individuals with PRISm and individuals with COPD compared with controls (Figure 3B).

Table 3. Demographic, Lung Structure/Function, and Exercise Characteristics in Never-Smokers and Ever-Smokers within Preserved Ratio Impaired Spirometry

	Never-Smokers	Ever-Smokers
Demographics		
n	20	39
Male:female	10:10	10:19
Age, yr	68 ± 9	68 ± 10
Height, cm	169 ± 8	167 ± 10
BMI, kg/m^2	30 ± 6	29 ± 5
Pack-years	0 ± 0	30 ± 26
Current smoker, *n*	0	16
MRC 1–5	1.7 ± 0.8	1.7 ± 0.8
CAT 0–40	7.8 ± 4.8	8.7 ± 6.1
Post-bronchodilator lung function		
FEV_1, % predicted	72 ± 6	72 ± 6
FVC, % predicted	74 ± 8	75 ± 8
FEV_1/FVC	0.75 ± 0.4	0.75 ± 0.4
$FEF_{25–75}$, L	71 ± 15	68 ± 20
Prebronchodilator lung function and imaging		
TLC, % predicted	92 ± 14	97 ± 14
FRC, % predicted	91 ± 24	99 ± 23
FRC/TLC, %	55 ± 8	56 ± 8
VC, % predicted	86 ± 12	87 ± 14
IC, % predicted	93 ± 19	95 ± 21
RV, % predicted	106 ± 33	115 ± 32
RV/TLC, %	44 ± 9	43 ± 8
ERV/TLC, %	12.1 ± 0.7	12.5 ± 0.9
sRAW, cm H_2O/s	6.7 ± 2.4	8.0 ± 3.8
V_A, % predicted	82 ± 38	83 ± 20
D_{LCO}, % predicted	88 ± 22	81 ± 21
K_{CO}, % predicted	104 ± 27	96 ± 24
V_A/TLC, %	85 ± 12	87 ± 12
LAA_{950}, %	2.3 ± 3.3	2.0 ± 1.5
LAA_{856}, %	16 ± 13	17 ± 13
DPM fSAD, %	46 ± 15	45 ± 16
DPM emphysema, %	1.2 ± 1.3	1.5 ± 2.1
Cardiopulmonary exercise test		
$\dot{V}O_{2peak}$, % predicted	73 ± 19	75 ± 24
$\dot{V}E_{peak}$, L/min	46 ± 18	48 ± 18
Change in IC (rest − peak), L	−0.05 ± 0.34	−0.10 ± 0.43
EILV/TLC/$\dot{V}E$ at peak, %/L/min	2.1 ± 0.6	2.1 ± 0.8
Nadir $\dot{V}E/\dot{V}CO_2$	30 ± 5	31 ± 9
Dyspnea/$\dot{V}O_2$ at peak, Borg units/L/min	4.1 ± 1.9	4.0 ± 2.4
Dyspnea/$\dot{V}E$ at peak, Borg units/L/min	0.12 ± 0.06	0.11 ± 0.07

Definition of abbreviations: BMI = body mass index; CAT = chronic obstructive pulmonary disease assessment test; CT = computed tomography; DPM-emphysema = CT-derived disease probability measure of emphysema; DPM-fSAD = CT-derived disease probability measure of functional small airway disease; EILV = end-inspiratory lung volume; ERV = expiratory reserve volume; $FEF_{25–75}$ = forced expiratory flow between 25% and 75% of the FVC maneuver; IC = inspiratory capacity; LAA_{856} = full-expiration low-attenuation areas of the lung below −856 Hounsfield units; LAA_{950} = low-attenuation areas of the lung below −950 Hounsfield units; MRC = Medical Research Council dyspnea scale; PRISm = preserved ratio impaired spirometry; RV = residual volume; sRAW = specific airways resistance; VC = vital capacity; $\dot{V}E/\dot{V}CO_2$ = ventilatory equivalents for carbon dioxide; $\dot{V}O_{2peak}$ = peak oxygen uptake; $\dot{V}E$ = minute ventilation.
Data are presented as mean ± SD unless otherwise noted.

Sensory Responses to CPET

At all standardized submaximal work rates, dyspnea was similarly increased in individuals with PRISm and individuals with COPD compared with controls as a function of increasing work rate ($P < 0.001$) (Figure 4A), after adjusting for covariates. At peak exercise, VT%IC and dyspnea ratings were similar between groups, albeit at a relatively lower peak $\dot{V}E$ and $\dot{V}O_2$ in both individuals with PRISm and

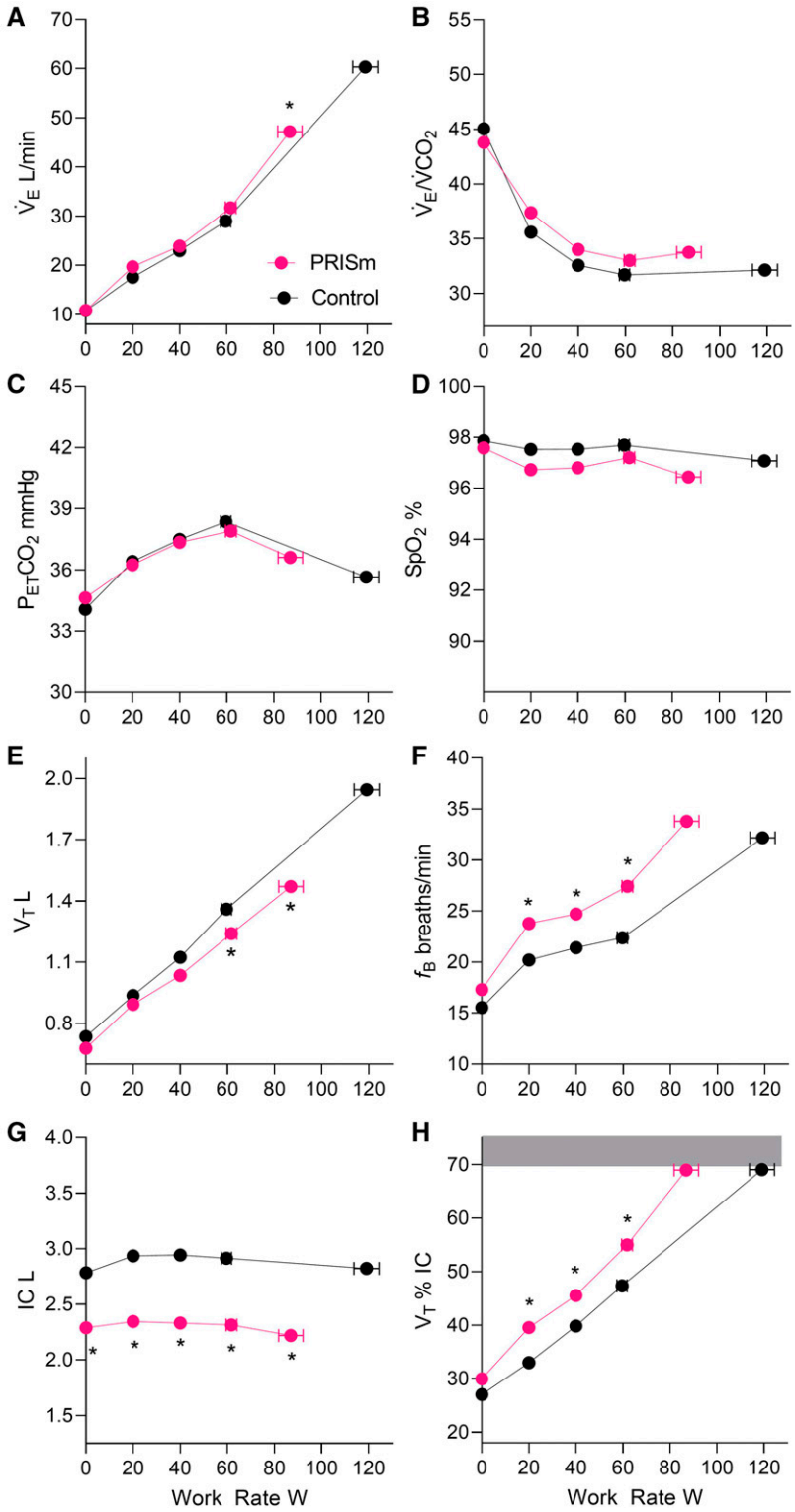

Figure 1. (*A* and *B*) Ventilatory, (*C* and *D*) pulmonary gas exchange, (*E* and *F*) breathing pattern, and (*G* and *H*) dynamic lung volume responses to incremental cycle ergometry exercise in 59 participants with preserved ratio impaired spirometry (PRISm) and 264 healthy controls. Gray shaded area in (*H*) represents critically high tidal volume (V_T) % inspiratory capacity (IC) of 70%. Comparisons were made using linear mixed modeling. Covariates included in the model were: age, sex, height, body mass index, and history of cardiovascular disease. Data are presented as estimated marginal means (adjusted for covariates) ± SEM. *$P < 0.05$ PRISm versus control. f_B = breathing frequency; $P_{ET_{CO_2}}$ = partial pressure of end-tidal carbon dioxide; Sp_{O_2} = pulse oximetry–derived oxygen saturation; $\dot{V}_E$ = minute ventilation; $\dot{V}_E/\dot{V}CO_2$ = ventilatory equivalent for carbon dioxide.

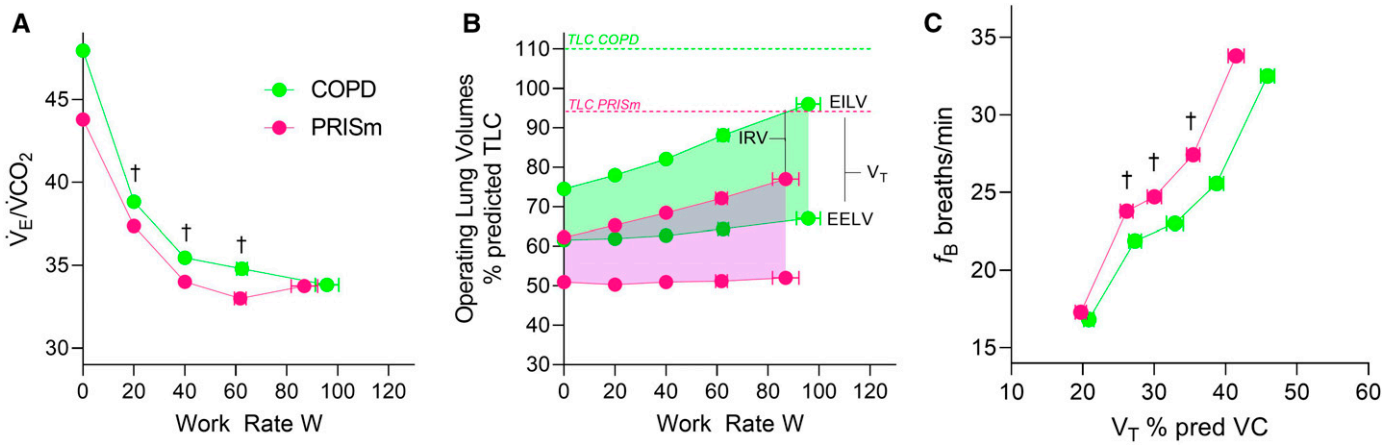

Figure 2. (*A*) Ventilatory, (*B*) operating lung volume, and (*C*) breathing pattern responses to incremental cycle ergometry exercise in 59 participants with preserved ratio impaired spirometry (PRISm) and 170 participants meeting criteria for chronic obstructive pulmonary disease (COPD). The green dashed line represents the mean TLC value (percentage predicted) for COPD. The pink dashed line represents the mean TLC value (percentage predicted) for PRISm. In (*C*), † symbols indicate between-group differences ($P < 0.05$) in breathing frequency (f_B) at standardized work rates. Comparisons were made using linear mixed modeling. Covariates included in the model were: age, sex, height, body mass index, and history of cardiovascular disease. Data are presented as estimated marginal means (adjusted for covariates) ± SEM. $^{\dagger}P < 0.05$ PRISm versus COPD. EELV = end-expiratory lung volume; EILV = end-inspiratory lung volume; IRV = inspiratory reserve volume; $\dot{V}_E/\dot{V}CO_2$: ventilatory equivalent for carbon dioxide; f_B: breathing frequency.

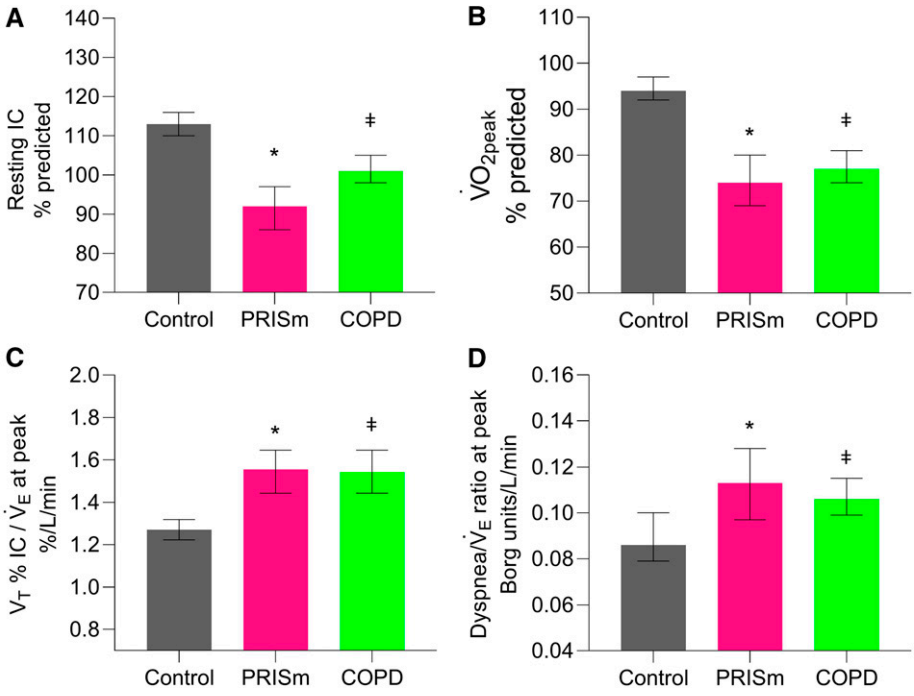

Figure 3. (*A*) Resting inspiratory capacity, (*B*) exercise capacity, (*C*) dynamic lung volumes adjusted for $\dot{V}_E$ at peak exercise, and (*D*) dyspnea/ventilation ratios at peak exercise during incremental cycle ergometry exercise in 59 participants with preserved ratio impaired spirometry (PRISm), 170 participants meeting criteria for chronic obstructive pulmonary disease (COPD), and 264 healthy control subjects. Body mass index and history of cardiovascular disease were included as covariates in ANOVA models in all panels. In addition, age, sex, and height were included as covariates in panels C and D. Data are presented as estimated marginal means (adjusted for covariates) with upper and lower 95% confidence intervals. $^{*}P < 0.05$ PRISm versus control and $^{\ddagger}P < 0.05$ COPD versus control. IC = inspiratory capacity; $\dot{V}O_{2peak}$ = peak oxygen uptake (index of exercise capacity); $\dot{V}_E$ = minute ventilation; V_T % IC/$\dot{V}_E$ = tidal volume relative to inspiratory capacity adjusted for $\dot{V}_E$ at peak exercise (index of inspiratory constraint).

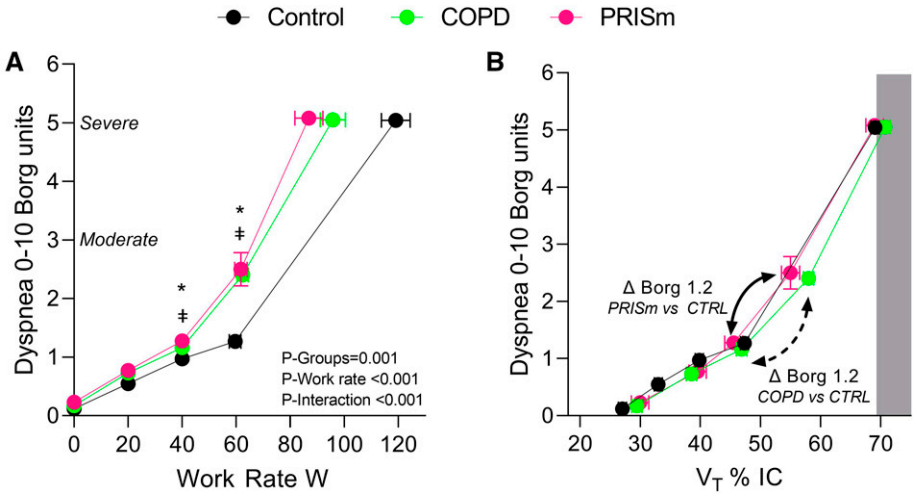

Figure 4. Exertional dyspnea as a function of (*A*) increased work rate, and (*B*) dynamic lung volumes during incremental cycle ergometry exercise in 59 participants with preserved ratio impaired spirometry (PRISm), 170 participants meeting criteria for chronic obstructive pulmonary disease (COPD), and 264 healthy control participants. In (*B*), the black solid arrow indicates between-group difference (PRISm vs. control) of 1.2 Borg units in dyspnea at 50% predicted peak work rate. In (*B*), the black dashed arrow indicates between-group difference (COPD vs. control) of 1.2 Borg units in dyspnea at 50% predicted peak work rate. V_T % IC = tidal volume relative to inspiratory capacity. Comparisons in (*A*) were made using linear mixed modeling and *post hoc* ANOVA. Covariates included in the model were: age, sex, height, body mass index, and history of cardiovascular disease. Data are presented as estimated marginal means (adjusted for covariates) ± SEM. $^{*}P < 0.05$ PRISm versus control and $^{‡}P < 0.05$ COPD versus control.

individuals with COPD compared with controls (both $P < 0.001$) (Figures 3C and 3D). Dyspnea ratings as a function of increasing V_T%IC were similar among all three groups (Figure 4B).

Associated Factors to Exercise Limitation and Exertional Dyspnea

In the entire sample, unadjusted regression analysis revealed that FEV_1, $FEF_{25–75}$, VC, IC, RV/TLC, K_{CO}, and CT-derived emphysema were associated with $\dot{V}O_{2peak}$ and exertional dyspnea (dyspnea/$\dot{V}O_{2peak}$ ratio at peak exercise) (Table 4). After multivariable regression analyses, low resting IC was the strongest factor associated with

Table 4. Univariate and Multivariable Linear Regression Models to Predict Exercise Capacity and Exertional Dyspnea in the Entire Sample ($N = 493$)

	Unadjusted Analysis		Multivariable Analysis	
	Standardized β	*P* Value	Standardized β (5–95% CI)	*P* Value
$\dot{V}O_{2peak}$, L/min			Model summary $r^2 = 0.55$, $P < 0.001$	
FEV_1, L	0.663	<0.001		
$FEF_{25–75}$, L/s	0.431	<0.001	0.090 (0.013 to 0.166)	0.023
VC, L	0.684	<0.001		
IC, L	0.645	<0.001	0.315 (0.222 to 0.407)	<0.001
RV/TLC	−0.461	<0.001	−0.094 (−0.191 to 0.003)	0.020
K_{CO}, ml/min/mm Hg/L	0.269	<0.001	0.125 (0.047 to 0.204)	<0.001
LAA_{950}, %	0.058	<0.001	—	0.109
Dyspnea/$\dot{V}O_2$ ratio at peak, Borg units/L/min			Model summary $r^2 = 0.10$, $P < 0.001$	
FEV_1, L	−0.302	<0.001		
$FEF_{25–75}$, L/s	−0.184	<0.001	—	0.379
VC, L	−0.268	<0.001		
IC, L	−0.290	<0.001	−0.299 (−0.395 to −0.203)	<0.001
RV/TLC	0.208	<0.001	—	0.109
K_{CO}, ml/min/mm Hg/L	−0.111	0.015	—	0.064
LAA_{950}, %	−0.023	0.642	—	0.209

Definition of abbreviations: CI = confidence interval; $FEF_{25–75}$ = forced expiratory flow between 25% and 75% of the FVC maneuver; IC = inspiratory capacity; RV = residual volume; LAA_{950} = low-attenuation areas of the lung below −950 Hounsfield units.
Both multivariable stepwise multiple regression models were adjusted for age, sex, height, body mass index, and history of cardiovascular disease. Variance inflation factor for all multiple regression models was <2.0. Vital capacity and FEV_1 were removed from regression models because of multicollinearity (variance inflation factor > 4).

low exercise capacity and heightened exertional dyspnea in the entire sample, after accounting for age, sex, height, and BMI (Table 4). Those with a high COPD assessment test score ⩾ 10 had significantly greater adjusted odds of having $\dot{V}O_{2peak}$ less than LLN, compared with CAT < 10 (Figure E4).

Discussion

The main findings are as follows. First, individuals with PRISm had greater exertional dyspnea and lower exercise capacity than healthy controls. Second, although individuals with PRISm, in contrast to those with COPD, had minimal evidence of airway obstruction, lung hyperinflation, and ventilatory inefficiency, both groups had similarly increased dyspnea intensity and decreased exercise capacity. Third, regardless of the marked physiological differences among the three groups, exercise performance was mainly influenced by the degree of prevailing inspiratory mechanical constraints, independent of age, sex, height, BMI, FEV_1, K_{CO} (and $D_{L_{CO}}$), emphysema severity, or history of CVD. The pathophysiological assessment within PRISm of ever- and never-smokers yielded similar results. Different spirometric definitions of PRISm exposed significant differences in overall physiological assessment and clinical interpretation.

In the current study, participants were recruited from a Canadian open population-based study (i.e., CanCOLD) (45). Of those who enrolled in CanCOLD with available CPET data (n = 1,250), the overall prevalence of PRISm was 5% and among ever-smokers was 10%. As reflected by inclusion criteria, participants with PRISm had preserved FEV_1/FVC but showed a statistically lower TLC, VC, and IC than controls. However, only 9/59 participants with PRISm had evidence of static volume restriction on plethysmography (i.e., TLC less than LLN), whereas the remaining 50 participants with TLC greater than LLN would be characterized as nonspecific (46). These findings are consistent with the work of Hyatt and colleagues, who showed that in a majority of individuals with preserved FEV_1/FVC but low FEV_1 and FVC, spirometric patterns were nonspecific when incorporating measurements of TLC (7). Recent studies and reviews have highlighted the importance of identifying smokers or ex-smokers who meet PRISm criteria, because such individuals have poor clinical outcomes (1–3, 8, 10, 11, 18, 47). However, the etiological link between tobacco smoke toxicity and low lung volumes is unclear (1). In the current study, 39/59 participants with PRISm were ever-smokers, 16 of whom were active smokers. In this context, we found no effect of smoking history on lung function within the PRISm group (Table 3). Moreover, resting and exercise physiological measurements and quantitative CT metrics were not different in ever- and never-smokers within the PRISm group (Table 3).

Physiological Characterization of PRISm

Despite the reduced static lung volumes in the PRISm group compared with the control group, there was limited indication of significant small airway dysfunction, as indirect assessments such as sRAW, $FEF_{25–75}$/FVC, ventilation distribution (estimated by the V_A–TLC difference) and CT-derived probability measures of functional small airway disease were similar to controls (Table 2). It is noteworthy that the expiratory reserve volume was slightly diminished and the VC–FVC tended to be larger (with large variability) in individuals with PRISm compared with controls. These findings might be explained by a small (albeit insignificant) increase in RV (by 5%) in the setting of a similar FRC (Table 2), which may in turn indicate early airway closure and mild small airway dysfunction, at least in a subset of participants with PRISm (7, 25, 46, 48–51). To the extent that lower VC in PRISm could not be explained by lower TLC (indicating low inspiratory muscle strength or decreased compliance of the lung and/or chest wall), increased RV/TLC (pulmonary gas trapping) remains the alternative explanation, as proposed by Hyatt and colleagues (7). However, this could not be definitively corroborated in the current study. Thus, although RV/TLC was significantly higher in individuals with PRISm than in control subjects, this ratio was greater than the upper limit of normal in only a third (20/59) of the sample. Moreover, there were no between-group differences in key CPET outcomes (dyspnea, $\dot{V}O_{2peak}$) between individuals with PRISm with higher versus normal RV/TLC (Table E7).

It is reasonable to assume, based on previous work, that average reductions of resting VC and IC by 24% and 19%, respectively, compared with controls, negatively influence ventilatory capacity, dyspnea severity, and $\dot{V}O_{2peak}$ (22–24, 28). During CPET, individuals with PRISm had higher dyspnea intensity ratings and lower $\dot{V}O_{2peak}$ (by 25%) than controls (Figure 3). In individuals with PRISm, ventilatory requirements for CO_2 at standardized submaximal exercise work rates and the nadir value (lowest 30-s average) were similar to healthy controls, suggesting normal ventilatory efficiency (Figure 1). In conjunction with a preserved resting K_{CO}, minimal CT-derived parenchymal abnormalities, and normal arterial O_2 saturation at rest and during exercise, it is evident that pulmonary gas exchange was largely preserved in PRISm (31).

As anticipated, participants with PRISm with lower resting VC and IC had a relatively rapid and shallow breathing pattern compared with controls. In keeping with the lack of significant airway dysfunction at rest, there was no evidence of significant dynamic lung hyperinflation (55/59 PRISm $\Delta IC < -0.15$ L rest–peak exercise) (52, 53), despite the relative tachypnea in PRISm (Figure 1).

Putative Mechanisms of Increased Exertional Dyspnea and Exercise Limitation

In participants with PRISm, resting IC was lower, and V_T approached 70% of the relatively fixed IC at a lower ventilation (~14 L/min lower at peak exercise) than controls. Moreover, V_T%IC normalized for $\dot{V}_E$ at peak exercise was greater in individuals with PRISm than in controls (Figure 3B). Based on our current findings and the results of previous studies in respiratory disease, a V_T%IC ~70, at a relatively lower peak work rate, $\dot{V}O_2$, and $\dot{V}_E$ than healthy controls, signifies earlier onset of significant inspiratory mechanical constraint, when end-inspiratory lung volume exceeds ~85% TLC and IRV declines to ~0.7 L (22–24, 28, 54, 55). Thus, when V_T becomes positioned at the upper noncompliant portion of the respiratory system's pressure–volume relation, which is associated with increased elastic loading of the inspiratory muscles, inspiratory neural drive (measured by diaphragm electromyography) must abruptly increase to very high levels to sustain ventilation commensurate with metabolic requirements (22, 23). The excessive inspiratory neural drive is associated with intolerable dyspnea at a relatively low ventilation (22, 23, 27, 29, 30, 56).

At standardized work rates and ventilation, Borg dyspnea ratings were higher to a similar extent in both individuals with COPD and individuals with PRISm, compared with controls (Figure 4A). Notably, the relationship between dyspnea and V_T%IC was similar across all three groups, which is consistent with the results of previous studies (22–24, 28). Our results show that a low resting IC, regardless of the underlying mechanisms, is detrimental to both dyspnea sensation and exercise performance in both PRISm and COPD (Figures 3 and 4) (23, 24, 28, 57–59). Our regression analysis showed that low resting IC was consistently associated with greater exertional dyspnea (i.e., high dyspnea–$\dot{V}O_{2peak}$ ratios) and low $\dot{V}O_{2peak}$ for the group as a whole (Table 4). Importantly, these associations occurred independent of age, sex, height, BMI, FEV_1, $FEF_{25–75}$, RV/TLC, K_{CO} (and $D_{L_{CO}}$), emphysema severity, and history of CVD, all of which have been variably linked to dyspnea intensity and exercise intolerance in health and respiratory disease (24, 31, 32, 56, 60–71). Thus, higher dyspnea ratings in individuals with PRISm and those with COPD at relatively low ventilation (~50 L/min) likely reflect earlier onset of significant ventilatory mechanical constraints and higher inspiratory neural drive than control subjects (Figures 3, 4, and E3) (22, 23, 29, 30, 56). The observation that participants with PRISm (with lower lung volumes but preserved small airway function and pulmonary gas exchange) were as dyspneic and functionally impaired as the COPD group (with both mechanical and pulmonary gas exchange derangements) points to the primacy of resting IC as a strong contributor of exertional dyspnea and exercise intolerance, regardless of the underlying respiratory pathophysiology. Exercise limitation is multifactorial, and factors such as deconditioning and peripheral muscle dysfunction are likely contributory (72–74). In all three groups, perceived leg discomfort ratings were greater than dyspnea ratings at peak exercise, suggesting, but not proving, that such factors were relevant in explaining exercise limitation in all groups.

Defining PRISm: LLN versus Fixed Ratio—Does It Matter?

The definition of an FEV_1/FVC threshold to indicate airflow obstruction is controversial, and different classifications using fixed ratio versus LLN criteria may expose differences in the underlying pathophysiology. The recent Lancet Commission report and others support the use of the 0.7 fixed ratio threshold (19, 75, 76), whereas the recent European Respiratory Society/American Thoracic Society spirometry standard recommended using LLN (46). In the current study, we used fixed ratio criteria to define PRISm, and, incidentally, all participants also met greater than LLN criteria. Interestingly, had we used the LLN criteria alone, an additional 43 individuals (FEV_1/FVC ratio range, 0.60–0.69) would be identified from the CanCOLD database. These individuals were older, had greater smoking history, and had greater small airway dysfunction, RV/TLC, CT-derived emphysema, and dynamic hyperinflation than the fixed-ratio PRISm group (Tables E3–E5). However, CPET outcomes were similar to the fixed-ratio PRISm group. Clearly, exclusive reliance on LLN for PRISm diagnosis uncovered many individuals who have GOLD stage 2 COPD.

Strengths and Limitations

This is the first study in an open population sample that comprehensively examined the physiological mechanisms of exercise limitation in PRISm. However, in the current cross-sectional analysis, the sample size may have been insufficient to establish the precise mechanisms of low VC and IC but nevertheless determined that abnormally low TLC (less than LLN) was not contributory in most. CanCOLD has limited information on early-life demographics (i.e., birth weight, nutritional status, prematurity, history of bronchopulmonary dysplasia), which may be helpful to determine associations with low lung volumes in PRISm. The stability of PRISm over time in the CanCOLD cohort was not established and requires longitudinal follow-up (2, 3).

Conclusions

Participants with PRISm had greater exertional dyspnea and lower exercise capacity than healthy controls, which was explained by lower resting VC and IC, and earlier mechanical constraint during exercise. Ever- and never-smokers within the PRISm group had similar physiological responses at rest and during CPET. Exclusive use of the greater than LLN criterion to define PRISm resulted in inclusion of smokers with pathophysiological features of COPD defined by GOLD criteria. The results show that most individuals fitting PRISm criteria have a nonspecific pattern with preserved TLC and may present to the clinician with significant exertional dyspnea and exercise intolerance. In such individuals, the addition of plethysmographic lung volumes and standardized exercise tests, incorporating measurements of dyspnea and operating lung volumes, can successfully uncover underlying mechanisms of poor exercise tolerance. ■

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