BMJ Open Respiratory Research

Haemodynamic compensations for exercise tissue oxygenation in early stages of COPD: an integrated cardiorespiratory assessment study

Ruddy Richard ,[1,2,3] Dennis Jensen,[4] Julianne Touron,[1] Costes Frederic,[1,3] Aurélien Mulliez,[5] Bruno Pereira,[5] Laura Filaire ,[6] Darcy Marciniuk,[7] François Maltais,[8] Wan Tan,[9] Jean Bourbeau ,[10] Hélène Perrault[11]

To cite: Richard R, Jensen D, Touron J, *et al*. Haemodynamic compensations for exercise tissue oxygenation in early stages of COPD: an integrated cardiorespiratory assessment study. *BMJ Open Respir Res* 2024;**11**:e002241. doi:10.1136/bmjresp-2023-002241

Received 7 December 2023
Accepted 23 February 2024

For numbered affiliations see end of article.

Correspondence to
Dr Ruddy Richard;
ruddy.richard@uca.fr

ABSTRACT

Background Cardiovascular comorbidities are increasingly being recognised in early stages of chronic obstructive pulmonary disease (COPD) yet complete cardiorespiratory functional assessments of individuals with mild COPD or presenting with COPD risk factors are lacking. This paper reports on the effectiveness of the cardiocirculatory-limb muscles oxygen delivery and utilisation axis in smokers exhibiting no, or mild to moderate degrees of airflow obstruction using standardised cardiopulmonary exercise testing (CPET).

Methods Post-bronchodilator spirometry was used to classify participants as 'ever smokers without' (n=88), with 'mild' (n=63) or 'mild-moderate' COPD (n=56). All underwent CPET with continuous concurrent monitoring of oxygen uptake ($V'O_2$) and of bioimpedance cardiac output (Qc) enabling computation of arteriovenous differences ($a\text{-}vO_2$). Mean values of Qc and $a\text{-}vO_2$ were mapped across set ranges of $V'O_2$ and Qc isolines to allow for meaningful group comparisons, at same metabolic and circulatory requirements.

Results Peak exercise capacity was significantly reduced in the 'mild-moderate COPD' as compared with the two other groups who showed similar pulmonary function and exercise capacity. Self-reported cardiovascular and skeletal muscle comorbidities were not different between groups, yet disease impact and exercise intolerance scores were three times higher in the 'mild-moderate COPD' compared with the other groups. Mapping of exercise Qc and $a\text{-}vO_2$ also showed a leftward shift of values in this group, indicative of a deficit in peripheral O_2 extraction even for submaximal exercise demands. Concurrent with lung hyperinflation, a distinctive blunting of exercise stroke volume expansion was also observed in this group.

Conclusion Contrary to the traditional view that cardiovascular complications were the hallmark of advanced disease, this study of early COPD spectrum showed a reduced exercise O_2 delivery and utilisation in individuals meeting spirometry criteria for stage II COPD. These findings reinforce the preventive clinical management approach to preserve peripheral muscle circulatory and oxidative capacities.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A reduced capacity for exercise, impairments in cardiocirculatory function and alterations muscle oxidative capacity and mitochondrial function are common findings of advanced chronic obstructive pulmonary disease (COPD). The heterogeneity of early COPD disease manifestation is increasingly recognised, yet cardiopulmonary exercise assessment to provide insight of functional decline in individuals with mild COPD or presenting with COPD risk factors is lacking.

WHAT THIS STUDY ADDS

⇒ Using continuous concurrent measurements of cardiac output and pulmonary gas exchange during incremental exercise in some 200 participants, this study is to date the largest set of data to provide an integrated perspective of early COPD impact. Results suggest that active tobacco smoking per se does not compromise the integrity of the cardiopulmonary exercise response. However, with aggravating airflow obstruction manifestations skeletal muscle peripheral oxygen extraction and exercise stroke volume expansion are impacted. Using the Global Initiative for Obstructive Lung Disease classification of disease, the threshold for significant negative repercussion on oxygen transport was stage 2 airflow obstruction criteria. The present findings indicate that the circulatory impact of COPD occurs not only in advanced stages of disease reinforcing the need for early dyspnoea symptom relief interventions to preserve functional capacity through peripheral O_2 delivery and utilisation capacities.

INTRODUCTION

Active tobacco smoking plays an overwhelming role in the development of chronic obstructive pulmonary disease (COPD) and is considered a major cardiovascular risk factor.[1 2] A diagnosis of COPD confirmed on the basis of a low (<0.70) post-bronchodilator ratio of the forced expiratory volume in 1 s (FEV_1) to the forced vital capacity (FVC), is found in 10%–26% of the general population

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ While differentiation of disease manifestation in patients with confirmed COPD is increasingly being recognised, insufficient attention has been devoted to interactions of risk factors, functional repercussions of disease progression and management of interventions such as physical training, to delay symptom burden and impact. The present findings reinforce the need for early dyspnoea symptom relief enabling exercise interventions to preserve functional capacity, peripheral O_2 delivery and utilisation capacities.

with a higher prevalence seen in ever-smokers.[3 4] Based on the Global Initiative for Obstructive Lung Disease (GOLD) classification, approximately half of these people meet criteria for the presence of an airflow limitation defined as 'mild' or stage 1 disease severity.[5 6] Individuals with GOLD 1 stage COPD exhibit a heterogeneous set of manifestations and respiratory symptoms, with various levels of exercise tolerance impairment, lung diffusing capacity with decrements in lower limb muscle strength reported in some, but not all patients.[7 8]

Evidence is also growing that a large proportion of former and current smokers who do not meet the spirometry criterion for COPD, also present with respiratory symptoms and a reduced exercise capacity.[7 9] Contrary to the common belief that cardiovascular complications are hallmark features of only the advanced states of COPD, recent clinical and epidemiological studies have reported cardiovascular structural anomalies and comorbidities in early stages of COPD.[1 2 10] An impaired exercise haemodynamics in early stage disease was also found to be associated with the expected exercise-induced lowering of pulmonary vascular resistance failing to occur.[11]

Deciphering the pathophysiological markers of disease progression is complicated by the overlapping symptoms and manifestation for spirometry-based criteria defining the early-stage spectrum of disease severity. Thus, the need for assessments beyond the exclusive reliance of spirometry and the value of exercise stress testing to unmask or amplify anomalies have been widely acknowledged.[5 7 12] Standardised cardiopulmonary exercise testing (CPET) is particularly valuable to provide insight into the effectiveness of the integrated oxygen (O_2) transport conductance across the lung, circulatory and skeletal muscle components.[5 10] To capture and reflect the integrated perspective of O_2 delivery and utilisation, the combined and concurrent measurements of systemic oxygen uptake ($V'O_2$) and cardiac output (Qc) are required.

Access to the Canadian Cohort of Obstructive Lung Disease (CanCOLD) dataset[13] provided such an opportunity as it involves a large non-clinical random-based sample of individuals with confirmed and unconfirmed COPD in whom standardised CPET with concurrent continuous of $V'O_2$ and impedance Qc monitoring have been achieved. The aim of this study was thus to use the large CanCOLD data set to compare the O_2 delivery and utilisation functions of ever-smokers without confirmed airflow obstruction and of those meeting spirometry criteria for GOLD stages 1 and 2 COPD over comparable ranges of exercise-induced O_2 and Qc requirements.

METHODS

Study design

CanCOLD is a multi-centre study with random sampling of Canadian men and women aged ≥40 years (NCT00920348). A full account of the CanCOLD study, eligibility criteria and design was published by Bourbeau *et al*.[13]

This study reports a subset of data on exercise physiology parameters and cardiac impedance-derived Qc from 207 participants for whom a valid and complete set of concurrent gas exchange and cardiac output data was obtained. Participants were classified as 'Ever-smokers without COPD' (N=88), GOLD 1 (N=63) and GOLD 2 COPD (N=56). Participants were divided into groups based on post-bronchodilator FEV_1/FVC, with those exhibiting a FEV_1/FVC ratio ≤0.70 being further classified into people with GOLD 1 (80% FEV_1 predicted) or GOLD 2 (FEV_1 50%–80% predicted) according to the National Health And Nutrition Examination Survey III predicted values. A group of ever smokers who did not meet spirometry-based criteria confirming COPD diagnosis was also included.

Patients and public involvement

Patients were recruited as part of the longitudinal CanCOLD study involving nine centres across Canada, carrying out the same exercise assessments including a non-invasive measurement of cardiac output in four of these centres. Patients were recruited randomly from a population of at least 250 000 people per research site.[13] Data presented in this study constituted the initial evaluations of a multi-year follow-up.

Sample characteristics, pulmonary function and symptoms

Body height and mass were taken during the introductory visit. Participants also took part in structured interviews for reporting of sociodemographic, and health information. All also completed the Community Healthy Activities Models Programme for Seniors[14] and the St. George Respiratory Questionnaires[15] to assess regular physical activity, symptoms and disabilities. Participant underwent pulmonary function tests in accordance with recommended techniques for measurements of post-bronchodilator spirometry, diffusing capacity of the lungs for carbon monoxide, and lung volumes by body plethysmography.

Cardiopulmonary exercise test

The CPET was carried out using an electromagnetically braked cycle ergometer and a computer driven cardiopulmonary exercise gas analysis testing system according to recognised guidelines. The CPET protocol

was standardised across participating institutions and consisted of a three-to-ten-minute sitting rest period, 1 min of unloaded cycling followed by 10 W/min increments starting at 10 W until symptom limitation. A 12 lead-ECG, gas exchange and breathing parameters were monitored at baseline and throughout the exercise. Exercise variables (VE, $V'O_2$, VCO_2, Fbr, Ti, Ti/Ttot) were measured and averaged over the last 30 s of every minute of exercise and at symptom-limited peak exercise. A maximal voluntary inspiratory manoeuvre (inspiratory capacity (IC)) was performed at baseline and during the last 30 s of each 2 min exercise stage as well as immediately on stopping exercise for determination of IC. Exercise-induced changes in operational lung volumes were evaluated from measurements of dynamic IC, assuming that total lung capacity remained constant during exercise. The highest IC value was used as an indicator of the near-peak value.

Cardiac output measurement

A cardiac impedance device (Physioflow, Manatec Biomedical, France) was used for continuous recording at baseline and throughout the CPET. A full description of the technique-validation has been published elsewhere.[16 17] Briefly, measurement of Qc using bioimpedance relies on changes in transthoracic conductance to reflect cardiac ejection to calculate stroke volume (SV). Sets of transmitting and sensing electrodes are placed at upper and lower thorax extremities while two other electrodes are positioned for single lead ECG recording. The ECG signal and impedance waveform are used to calculate the maximal rate of decrease in impedance for a given heartbeat over the ventricular ejection time. The first derivative of the change in thoracic impedance (dZ/dt_{max}) is used to calculate SV. Heart rate (Hr) was taken from the R-R interval determined on the ECG first derivative. Beat-to-beat Qc was computed as Hr×SV, data being stored as five second averages for the entire CPET duration.

For each participant, Physioflow data was extracted and synchronised with the CPET variables ensuring alignment on power output and time. Systemic arterial-venous oxygen difference ($a\text{-}vO_2$) was used to reflect exercise-induced peripheral O_2 extraction and was calculated from the application of the standard Fick equation to contemporaneous gas exchange-derived $V'O_2$ and bioimpedance-derived Qc, such that,

$a\text{-}vO_2$ ($mLO_2/L\ min^{-1}$)=$V'O_2$ ($L\ min^{-1}$)/Qc ($L\ min^{-1}$).

Statistical analyses

Statistical analyses were performed using Stata software (V.15). All tests were two-sided, with a type I error set at 5%. Continuous data were expressed as mean±SEM.

Between-group comparisons of continuous variables were achieved using analysis of variance (ANOVA), or a Kruskal-Wallis test if ANOVA assumptions were not met. When p value <0.05, post-hoc multiple comparisons were performed using Tukey-Test after ANOVA and Dunn after Kruskal-Wallis. For categorical variables, between-group comparisons were carried out using χ^2 or Fisher's exact tests.

A random-effects model for repeated measures with group×time-point evaluation interactions was used to examine response patterns taking into account the relationships between O_2 delivery (Qc, SV, Hr) and peripheral O_2 extraction ($a\text{-}vO_2$) related variables across exercise-induced increases in $V'O_2$, with time as fixed effect, and individual as random-effect for between and within individual variability.

RESULTS

Participant characteristics

As seen in table 1, participants of all three groups showed similar comorbidity characteristics except for the prevalence of physician diagnosed asthma which was higher in the GOLD 2 COPD than in the other two groups. Comparisons of demographics showed no statistical difference between groups except for a higher smoking history (pack-years) in the GOLD 2 COPD group. As expected from the classification criteria, pulmonary function was also more impaired in this group compared with the two others. Results from the St. George Respiratory Questionnaire also showed significantly higher scores for respiratory symptoms, impact of disease and regular physical activity in the GOLD 2 COPD group.

CPET symptom-limited end-point exercise measurements

Measurements of power output, cardiocirculatory, ventilatory and gas exchange parameters obtained at the end of the incremental CPET are presented for all groups in table 2. Results from the ever-smokers and the GOLD 1 COPD groups were not significantly different, except that the former group reached a higher percentage of age-predicted peak heart rate than the two others. Similarly, the GOLD 2 COPD showed lower peak power at symptom limitation, lower values of $V'O_2$, ventilation (VE), tidal volume (V_T), IC and lower peak SV, Qc and $a\text{-}vO_2$ compared with the two other groups. There was no difference in peak diastolic, systolic and mean arterial blood pressures or in total peripheral resistance estimated from mean arterial pressure/Qc (mmHg/($L\cdot min^{-1}$) (ever smokers: 1408±31; GOLD 1: 1495±96; GOLD 2: 1422±43).

Oxygen delivery and utilisation patterns

For a better understanding of the O_2 delivery and utilisation system dynamics, components were anchored to the same absolute $V'O_2$ ($L\cdot min^{-1}$). A series of exercise $V'O_2$ values between 0.5 and 2.0 ($L\cdot min^{-1}$) were used as anchorage point to derive and graphically display the Qc versus $a\text{-}vO_2$ functions resulting from application of the Fick equation. The set of VO_2 isolines serves as reference for the interpretation of the measured Qc and $a\text{-}vO_2$ data.

Table 1 Sample demographics and characteristics

Reported comorbidity	Ever smokers (N=88)	GOLD 1 (N=63)	GOLD 2 (N=56)
Physician diagnosed asthma	13	11	25†
Myocardial infraction	5	1	4
Angina symptoms	7	1	2
Hypertension	23	23	22
Depression	2	2	4
Diabetes	10	4	4
Muscular disorders	38	34	25
Osteoporosis	7	11	10
Demographics			
Age (years)	65 (0.9)	69 (1.1)	65 (1.3)
Body mass (kg)	78 (1.7)	76 (1.6)	74 (2.3)
Body mass index ($kg{\cdot}m^{-2}$)	27.45 (0.54)	26.42 (0.52)	26.57 (0.70)
Proportion of women (%)	39	37	53
Smoking (pack-years)	21.06 (19.88)	20.47 (20.40)	28.68† (27.02)
St. George's Respiratory Questionnaire			
Total score	7.89 (0.98)	9.52 (1.16)	18.77† (1.89)
Symptoms	14.76 (1.45)	15.46 (1.82)	26.73† (2.89)
Activity	10.99 (1.63)	14.24 (2.02)	28.43† (3.12)
Impacts	3.96 (0.83)	4.96 (0.95)	10.78† (1.70)
Pulmonary functions			
FEV_1 post-BD (L)	2.92 (0.08)	2.68 (0.08)	1.95† (0.08)
FEV_1/FVC post-BD (%)	77.3 (0.49)	64.27 (0.61)	58.38† (1.0)
VC (L)	3.89 (0.12)	4.34 (0.13)	3.01† (0.12)
TLC (L)	6.44 (0.15)	7.09 (0.20)	6.44 (0.20)
FRC (% NHANES predicted)	108 (2.5)	120 (3.7)	126* (4.4)
RV (% NHANES predicted)	120.5 (3.0)	130.5 (4.3)	147† (5.3)
DL_{CO} ($mL{\cdot}min^{-1}{\cdot}mm\ Hg^{-1}$)	24.1 (0.69)	22.9 (0.89)	21.1* (1.01)

Values are mean (SEM).
Statistical significance GOLD 2 versus the two other groups.
*p≤0.05.
†p≤0.001.
DL_{co}, diffusion capacity of lung for carbon monoxide; FEV_1/FVC post-BD, post-bronchodilation forced expiratory volume in 1 s/forced vital capacity; FEV_1 post-BD, post bronchodilation forced expiratory volume in 1 s; GOLD, Global Initiative for Obstructive Lung Disease; NHANES, National Health And Nutrition Examination Survey; RV, residual volume; TLC, total lung capacity FRC; VC, vital capacity.

Group responses obtained throughout the incremental CPET until the exercise intensity at which a satisfactory IC manoeuvre was obtained in all groups, are illustrated in figure 1. Group means for Qc and a-vO_2 were superimposed on the axes used to generate the isoVO_2 lines to enable comparisons over the set range of V'O_2. Moving from lower to higher V'O_2 isolines, the graph shows all groups responding to the increasing exercise intensity by a right and upward displacement. No differences were seen between the exercise Qc versus a-vO_2 patterns of the ever-smokers and of the GOLD 1 COPD. For V'O_2 isolines above $1.0\,L{\cdot}min^{-1}$, the GOLD 2 data points are positioned to the left of other groups on account of a statistically significant lower a-vO_2 difference. The data points between the 1.0 and $1.5\,L{\cdot}min^{-1}$ V'O_2 isolines are seen shifted slightly upward compared with other groups and a lower end-point Qc is observed. The bar graph inserted to the upper right, shows the mean a-vO_2 and Qc computed for each group at for a same VO_2 of $1.5\,L{\cdot}min^{-1}$.

Figure 2 illustrates exercise induced cardio-dynamic adaptive strategies using a similar approach as previous but generating Qc isolines from the Hr versus SV functions. A set of three Qc isolines ranging between 5 and $15\,L{\cdot}min^{-1}$ were generated with Hr and SV group mean values being displayed for the corresponding Qc isoline. As can be seen both Hr and SV contribute to the increase in Qc between the 5 and the $10\,L{\cdot}min^{-1}$ Qc isolines While

Table 2 Exercise measurements (at peak inspiratory capacity)

	Ever smoker (N=88)	GOLD 1 (N=63)	GOLD 2 (N=56)
Power output (W)	133 (5.2)	128 (5.46)	101† (4.5)
$V'O_2$ ($L \cdot min^{-1}$)	1.93 (0.07)	1.83 (0.07)	1.51† (0.07)
$V'O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	24.7 (1.3)	24.1 (1.1)	20.3† (1.7)
Hr ($beats \cdot min^{-1}$)	143* (2.3)	134 (2.7)	135 (2.7)
Hr (% predicted)	85* (1.2)	81 (1.5)	80 (1.5)
SV (mL)	95 (2.7)	98 (2.5)	89‡ (2.3)
Qc ($L \cdot min^{-1}$)	12.9 (0.37)	12.7 (0.37)	11.5* (0.36)
a-vO_2 ($mLO_2 \cdot L^{-1}$blood)	153 (5.0)	152 (5.6)	140† (4.9)
O_2 pulse ($mL \cdot beats^{-1}$)	14.01 (2.19)	14.27 (1.99)	11.82* (1.86)
SBP (mmHg)	189 (2.6)	187 (3.1)	182 (3.37)
DBP (mmHg)	85.3 (0.8)	83.4 (1.6)	87.2 (1.6)
MAP (mmHg)	119 (1.5)	116 (1.8)	117 (1.9)
VE ($L \cdot min^{-1}$)	68.0 (2.8)	67.8 (3.0)	52.6† (2.3)
VE (% predicted)	66.8 (2.0)	72.0 (2.3)	79.0† (2.6)
V_T (L)	2.03 (0.07)	2.16 (0.08)	1.66† 0.07)
Fbr ($breaths \cdot min^{-1}$)	34 (0.8)	33 (1.0)	33 (1.0)
IC (L)	3.30 (0.10)	3.40 (0.10)	2.68† (0.11)

Values are mean (SEM); statistical significance between the other two groups.
*p≤0.05.
†p≤0.001.
‡p≤0.10.
a-vO_2, systemic arterio-venous oxygen difference; DBP, diastolic blood pressure; Fbr, breathing frequency; GOLD, Global Initiative for Obstructive Lung Disease; Hr, heart rate; IC, inspiratory capacity; MAP, mean arterial pressure estimated as (DBP+1/3SBP-DBP); O_2 pulse, oxygen pulse (mL $beats^{-1}$); Qc, cardiac output; SBP, systolic blood pressure; SV, stroke volume; VE, ventilation; $V'O_2$, rate of oxygen consumption; V_T, tidal volume.

a similar pattern is seen in the three groups, the GOLD 2 group SV coordinates are positioned leftward of other groups resulting in significantly lower values at the peak exercise (not shown on graph). The plot also shows a predominant contribution of Hr for further exercise-induced increases in Qc above the $10\,L \cdot min^{-1}$ isoline.

The pattern of exercise-induced adjustment in IC andV_T is shown in figure 3 with respect to levels of minute VE. In the GOLD 2 group, IC values throughout the CPET were markedly and significantly lower compared with the other two groups with a progressive decline for increasing levels of VE. The graph also shows V_T levelling off for increasing levels of minute VEs above $40\,L \cdot min^{-1}$ in the GOLD 2 COPD group while values continued to increase significantly to higher peak in the ever smokers and the GOLD 1 COPD groups.

Figure 4 shows mean values of SV and IC measured concurrently throughout the CPET. A significant difference in patterns (p<0.001) was observed between groups with curves generated for the ever-smokers and the GOLD 1 COPD groups positioned upward and leftward compared with the GOLD 2 COPD alignment. With increasing exercise intensity, a pattern of decreasing IC and blunting of SV expansion is seen in the GOLD 2 COPD group but not in the two other groups.

DISCUSSION

Main findings

This study advances the understanding of early phases of airflow obstruction by providing evidence of functional repercussions in both central and peripheral circulatory exercise adaptations. There was no difference in end-point exercise physiology parameters between groups of ever-smokers without COPD and GOLD 1 COPD, but values were significantly lower in the GOLD 2 COPD group. By anchoring cardiocirculatory measurements to set levels of $V'O_2$, our study enabled a representation of O_2 transport determinants as prescribed by the Fick equation, enabling group comparisons over a range of exercise demands. Results showed a clear shift in Qc versus a-vO_2 coordinates in GOLD 2 COPD compared with the two other groups indicating a reduced O_2 peripheral extraction, unrelated to premature exercise cessation. Using a similar approach to anchor SV and Hr on exercise cardiac outputs we observed a distinctive blunting of SV in the GOLD 2 COPD, again unrelated to premature exercise cessation. This appeared only partially compensated by tachycardia since it was insufficient to correct Qc at end-point exercise. The contribution of chronic heart or neuromuscular disease to explain the distinctive pattern of the GOLD 2 COPD group is unlikely as

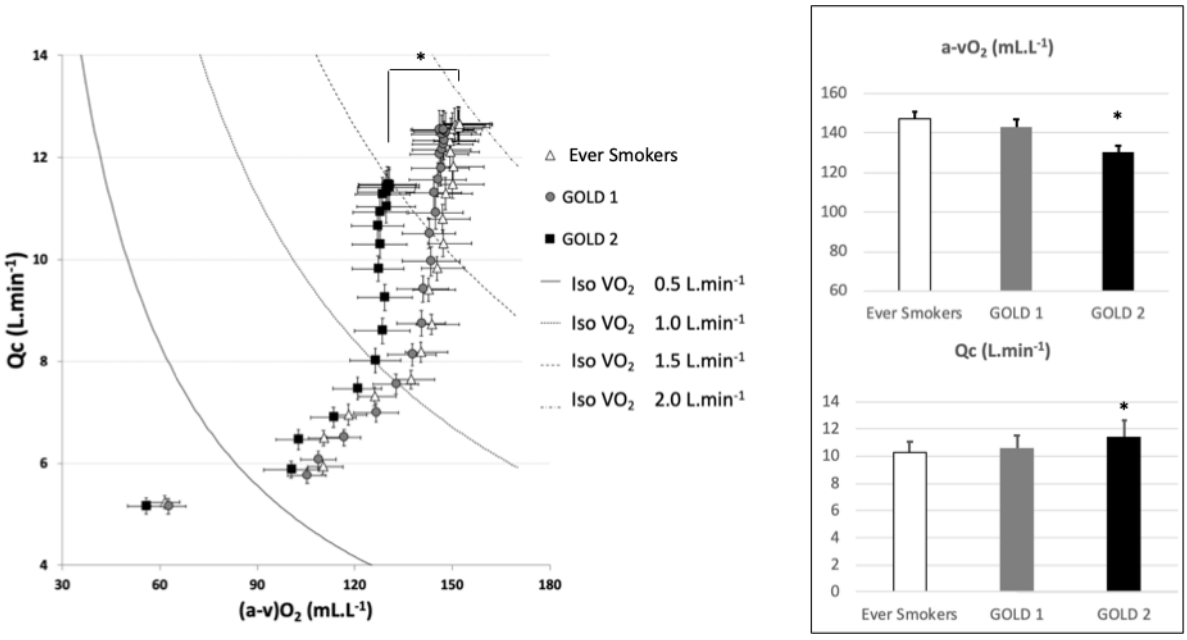

Figure 1 Exercise-induced adjustments in Qc and systemic oxygen extraction across V'O2 isolines through near maximal cardiopulmonary exercise testing. Values are group means of Qc and a-vO2 ± their respective SEM. *Significant ($p<0.05$) difference in the Qc/a-vO_2 kinetics between the GOLD 2 COPD and the other groups. The boxed graph shows group mean values taken at the 1.5 L·min^{-1} VO_2 isolines for a-vO_2 (upper) and Qc (lower). a-vO_2, systemic arterio-venous oxygen difference; GOLD, Global Initiative for Obstructive Lung Disease; Qc, cardiac output; V'O_2, rate of oxygen consumption.

self-reported cardiovascular and skeletal muscle comorbidities were not different between groups. However, unlike participants from the other groups, the GOLD 2 COPD group showed baseline lung inflation as reflected by their lower baseline and exercise IC for given minute VE compared with other groups. Levelling of exercise SV for reduced exercise IC was also seen to occur prematurely in this group. Participants in the GOLD 2 COPD group also presented with an overwhelming difference in disease burden reflected by three times higher total scores for symptoms, disease impact and physical inactivity. Our findings indicate that a deficit in peripheral skeletal muscle O_2 extraction, presumably the result of physical deconditioning secondary to respiratory symptoms and a deficit in exercise SV expansion related to lung hyperinflation coexist as early cardiocirculatory manifestations of COPD. Consideration should therefore be given to include standardised monitoring of

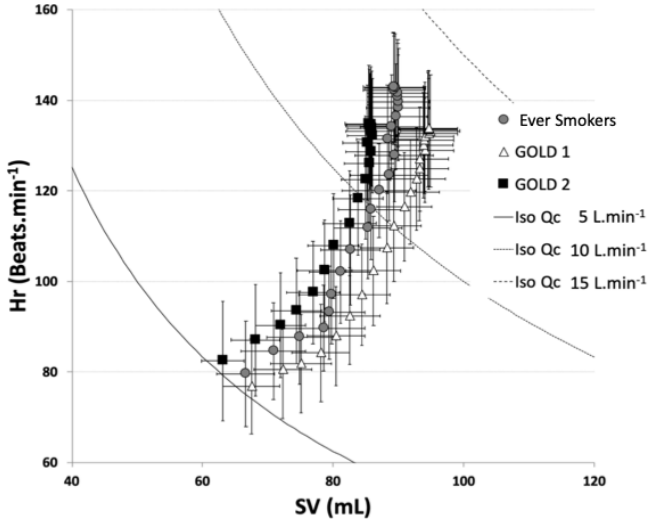

Figure 2 Exercise-induced adjustments in Hr and SV across Qc isolines through near maximal cardiopulmonary exercise testing. Values are group means of Hr and SV ± their respective SEM. A leftward shift in the Hr×SV combination is seen for the GOLD 2 group resulting in a lower SV measured at the exercise endpoint. GOLD, Global Initiative for Obstructive Lung Disease; Hr, heart rate; Qc, cardiac output; SV, stroke volume.

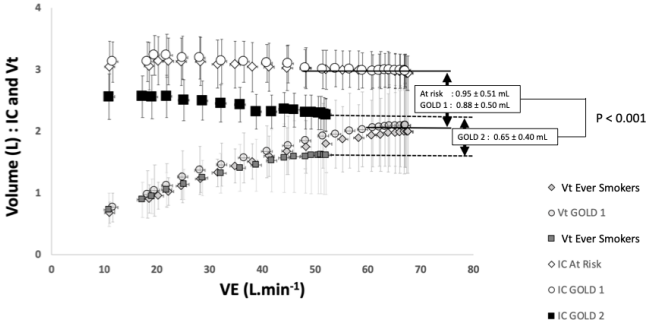

Figure 3 Exercise-induced responses in V_T and in IC with respect to exercise-induced V'E responses. Values are mean±SEM. Significant differences between the GOLD 2 chronic obstructive pulmonary disease and the other two groups are shown for the exercise-induced changes to peak exercise in IC and in V_T. GOLD, Global Initiative for Obstructive Lung Disease; IC, inspiratory capacity; SV, stroke volume; VE, ventilation; V_T, tidal volume.

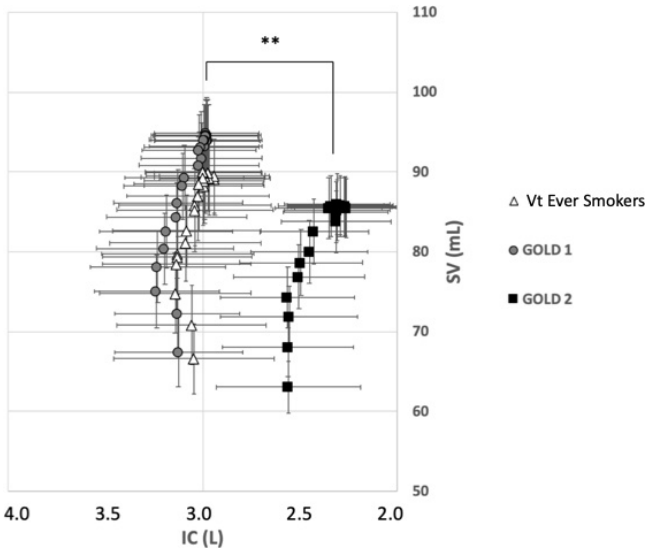

Figure 4 Concurrent cardiopulmonary exercise testing induced responses in SV and IC. Values are mean±SEM. Top bars indicates a significant (**p<0.001) difference in response curve between the GOLD 2 chronic obstructive pulmonary disease group and the two others. GOLD, Global Initiative for Obstructive Lung Disease; IC, inspiratory capacity; SV, stroke volume; V_T, tidal volume.

symptoms, exacerbations and regular physical activity levels in the surveillance of early stages of airflow obstruction allowing for early symptom relief interventions and potentially physical exercise training to preserve function.

Comparisons with other studies

Exercise intolerance on account of exertional dyspnea is a hallmark of advancing COPD.[5 10] Less is known on cardio-circulatory related functional repercussions in less severe COPD disease. To our knowledge, this study currently stands as the most robust and largest set of standardised continuous and concurrent exercise gas exchange and Qc measurements in early phases of airflow obstruction. Results from large random population studies have reported associations between subclinical pulmonary function impairments and clinical markers of heart disease with both reduced and preserved systolic function.[2 10] In our study, neither reported cardiovascular comorbidities nor Qc resting measurements were different between groups, despite group-related difference in pulmonary functions. Peak exercise variables measured in the non-COPD group and the GOLD 1 COPD group showed near complete agreement with normative exercise data collected on healthy adults from the CanCOLD cohort study[18] suggesting a minimal impact if at all of mild airflow obstruction.

Exercise Qc was also within the range of expected $V'O_2$ predicted values in all groups attesting to preservation of the expected Qc adaptive function. Nonetheless, participants in the GOLD 2 COPD group reached an earlier symptom-limited endpoint resulting in lower values of VE, VO_2, Qc and Hr at the common point of exercise termination. The symptom-limited values obtained in our GOLD 2 COPD group are in keeping with recent reports using cardiac impedance in people with GOLD stages 2 to 4 COPD, alone or with overlapping heart failure showing lower peak values as well as slower central haemodynamic adjustments to submaximal exercise.[19–24] In earlier studies using direct Fick Qc measurements a lesser Qc exercise expansion in advanced COPD was also found and attributed to an exaggerated increase in ventricular afterload.[25–28]

The novelty of our report lies in the positioning of data onto ranges of increasing $V'O_2$ enabling an integrated perspective of O_2 transport and utilisation system as defined by the Fick equation. Positioning exercise-induced changes in Qc and in a-vO_2 responses of each group allowed us to compare the relative contribution of the central and peripheral components between groups. Our findings showed a marked deficit in peripheral O_2 extraction in the GOLD 2 COPD group compared with the two other groups. Using a similar approach to assess how Hr and SV contributed to the exercise induced changes in Qc across groups, we found the GOLD 2 COPD group to exhibit a lower SV than that seen in the GOLD 1 COPD. Overall, these observations point to a predominant impact of increasing airflow obstruction severity on the peripheral cardiovascular component as differences in group means computed at a $V'O_2$ of 1.5 $L{\cdot}min^{-1}$ show that a-vO_2 values are 9% lower in stage 2 compared with stage 1 COPD and 12% lower compared with the ever-smoker group. Similar computations for group mean Qc show a difference between of −3% between GOLD 1 and 2 COPD groups and close to −10% between the non-COPD ever smokers and the GOLD 2 COPD. Although this study was not designed to express a trajectory of airflow obstruction impact, these observations suggest a sharp and distinctive circulatory impact occurring as spirometry airflow markers fall below the GOLD 1 current criteria. The difference in mean post-bronchodilator FEV_1 can be computed as an 8% difference in between ever-smokers and the GOLD 1 COPD but of 27% between GOLD 1 and GOLD 2 COPD group. Such differences also translate to distinctive patterns of exercise VE, operating lung volumes and respiratory intrathoracic pressure changes.

In stable COPD patients with pulmonary function and peak exercise characteristics comparable to those from our GOLD 2 COPD group, smaller exercise-induced changes in SV/VO_2 were found in patients exhibiting dynamic lung hyperinflation.[19] Similarly, results from concurrent measurements of oesophageal pressure and open-circuit acetylene-rebreathing Qc during submaximal cycling showed an attenuation of the exercise-induced SV and Qc expansion in patients with moderate COPD compared with age-matched controls. Authors also found that the most severe impairments in central haemodynamics were related to the most severe hyperinflation and to the more negative inspiratory intrathoracic

pressure.[29] Our findings of a down and leftward shift in the SV versus IC values in the GOLD 2 COPD group (figure 4) are in keeping with these reports. The resting and exercise IC of the GOLD 2 COPD patients (figure 3) are as expected values in mild-moderate disease.[19] The data however revealed no significant difference in IC between the ever smokers and the stage 2 COPD group suggesting that a factor other than the progression of airflow obstruction plays a role in the observed impairment. The significant difference in a-vO_2 group means between the GOLD 1 and GOLD 2 COPD seen at the 1.5 L·min^{-1} V'O_2 isoline may be seen as the progression of a peripheral extraction deficit already observable for V'O_2 as low as 0.75 L·min^{-1} and thus not ascribed to factors precipitating exercise endpoint.

Factors affecting peripheral extraction capacity include skeletal muscle histology, capillarisation, oxidative enzyme capacities as well as mitochondrial function. Muscle dysfunction is a common manifestation of COPD on account of multiple factors such as disuse atrophy, malnutrition, medication side-effect, circulating inflammatory cytokines.[12 30] The functional expression of limb muscle alterations in early stages of COPD remain incompletely documented but a deficit in quadriceps muscle strength was recently reported in individual with mild disease.[31] Except for the physician diagnosed asthma, our analysis of self-reported comorbidities including skeletal muscle disorders did not reveal differences between groups. However, St. George Respiratory Questionnaire total scores were two to three times higher in the GOLD 2 COPD compared with other groups with higher symptoms, disease impact and physical inactivity. A concurrent inverse association between self-reported frequency of moderate physical activity and higher symptom burden was also reported for the larger CanCOLD cohort as well as for the moderate-severe COPD subgroups.[8] Thus, the marked distinction in peripheral extraction between patients with GOLD stage 1 and stage 2 COPD may be related to factors triggering worsening of airflow obstruction and respiratory symptoms also operating to reduce regular physical activity. Structural and functional skeletal muscle alterations would then be expected to follow, in part as a result of muscle deconditioning and disuse atrophy as well as circulating factors.[12] Smoking has also been found to negatively impacts skeletal muscle function, presumably though molecular mechanisms promoting muscle protein degradation and impairing muscle protein synthesis.[32 33] Because cigarette smoking exposure was higher in our stage 2 COPD group, it could also have contributed to their peripheral extraction deficit.

Considerations for intervention management

The exercise data from this study was obtained across a range of V'O_2 that encompasses those of regular occupational and recreational physical activities, thus providing insight as to the functional impact of the early disease stage 2 COPD for daily living. Our findings reinforce the view that in addition to spirometry, functional assessments are of value to better characterise daily living exercise capabilities and disabilities of smokers without as well as with only mild airflow obstruction. Our observations suggest that in non-COPD ever smoker factors leading to worsening of airflow obstruction or respiratory symptoms precipitating exercise intolerance may be compounded to induce central and peripheral cardiocirculatory limitations. Consideration should therefore be given for close monitoring and early relief of respiratory symptoms upstream of factors triggering and precipitating a potential spiralling decline, and for interventions to preserve optimal skeletal O_2 utilisation capacities. Future research is needed to determine the benefits of physical training using modalities such as eccentric exercise known for its low exercise-induced hyperventilation, to enhance skeletal muscle peripheral extraction capacity and limit the impact of disease progression.

Strengths and limitations

The study presents several strengths including its large number of participants representative of the COPD population at large, the inclusion of a standardised CPET as well as the concurrent exercise monitoring of gas exchange and of bioimpedance Qc measurements throughout the CPET. As recently positioned,[7] we recognise that a spirometry-based classification is not synonymous with chronological disease progression.

The study is not without limitations. While exercise physiology parameters measured in the ever smokers without COPD are comparable to measurements on healthy adults of similar age from the larger CanCOLD cohort, this group cannot be considered as a 'healthy' control group. Finally, markers of arterial oxygen content or arterial oxygen saturation were not included in the dataset provided for analysis. Our results showed a marked deficit in a-VO_2 in the GOLD 2 COPD group not only at near-peak exercise but also at levels of V'O_2 typical of regular daily recreational activities, for which a significant hypoxaemia would not be expected. It is therefore likely that the impairment in a-vO_2 reflects an impairment in limb muscle O_2 extraction although it could have been compounded by hypoxaemia at severe exercise levels.

Interpretation

This study revealed that peak exercise O_2 delivery and utilisation is compromised in individuals with moderate but not mild COPD or in smokers without COPD. The deficit in O_2 extraction for same V'O_2 and blunting of exercise SV were compatible with greater self-reports of symptoms and exercise intolerance, leading to deconditioning affecting peripheral muscle circulatory and oxidative capacities. These observations reinforce the need for early dyspnoea symptom relief interventions to

enable continued physical activity to preserve O_2 delivery and utilisation capacities.

Author affiliations
[1]Université Clermont Auvergne, Clermont-Ferrand, France
[2]CRNH, CHU Clermont-Ferrand, Clermont-Ferrand, France
[3]CHU Clermont Ferrand, Service de médecine du Sport et des Explorations Fonctionnelles, Université Clermont Auvergne, Clermont Ferrand Cedex 1, France
[4]Kinesiology & Physical Education, McGill University, Montreal, Quebec, Canada
[5]DRCI, CHU Clermont-Ferrand, Clermont-Ferrand, France
[6]Centre Jean Perrin, Clermont-Ferrand, France
[7]Respiratory Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada
[8]Université Laval, Quebec, Québec, Canada
[9]The University of British Columbia, Vancouver, Vancouver, Canada
[10]McGill University, Montreal, Quebec, Canada
[11]University of Ottawa Faculty of Health Sciences, Ottawa, Ontario, Canada

Acknowledgements The authors acknowledge the contribution of the CanCOLD Collaborative Research Group and the Canadian Respiratory Research Network. Authors recognise and are grateful to S Cambier, L Boudieu for their support related to the validation of Physioflow tracing, data extraction and digital capture, data organisation and statistical analyses. The authors thank the men and women who participated in the study and the many members of the CanCOLD Collaborative Research Group: executive committee: Jean Bourbeau (McGill University, Montreal, QC, Canada); Wan C Tan, J Mark FitzGerald, Don D Sin (University of British Columbia, Vancouver, BC, Canada); Darcy D Marciniuk (University of Saskatoon, Saskatoon, SK, Canada); Denis E O'Donnell (Queen's University, Kingston, ON, Canada); Paul Hernandez (Dalhousie University, Halifax, NS, Canada); Kenneth R Chapman (University of Toronto, Toronto, ON, Canada); Brandie Walker (University of Calgary, Calgary, AB, Canada); Shawn Aaron (University of Ottawa, Ottawa, ON, Canada); François Maltais (University of Laval, Quebec City, QC, Canada). International advisory board: Jonathon Samet (the Keck School of Medicine of USC, California, USA); Milo Puhan (John Hopkins School of Public Health, Baltimore, USA); Qutayba Hamid (McGill University, Montreal, QC, Canada); James C Hogg (University of British Columbia, Vancouver, BC, Canada). Operations centre: Jean Bourbeau (Principal Investigator), Dany Doiron, Palmina Mancino, Pei Zhi Li, Dennis Jensen, Carolyn Baglole (McGill University, Montreal, QC, Canada); Yvan Fortier (Laboratoire telematique, Quebec Respiratory Health Network, Fonds de la recherche en santé du Québec (FRQS)); Wan C Tan (co-principal investigator), Don Sin, Julia Yang, Jeremy Road, Joe Comeau, Adrian Png, Kyle Johnson, Harvey Coxson, Jonathon Leipsic, Cameron Hague (University of British Columbia, Vancouver, BC, Canada), Miranda Kirby (Ryerson University, Toronto, ON, Canada). Economic core: Mohsen Sadatsafavi (University of British Columbia, Vancouver, BC, Canada). Public health core: Teresa To, Andrea Gershon (University of Toronto, Toronto, ON, Canada). Data management and quality control: Wan C Tan, Harvey Coxson (University of British Columbia, Vancouver, BC, Canada); Jean Bourbeau, Pei-Zhi Li, Zhi Song, Andrea Benedetti, Dennis Jensen (McGill University, Montreal, QC, Canada); Yvan Fortier (Laboratoire telematique, Quebec Respiratory Health Network, FRQS); Miranda Kirby (Ryerson University, Toronto, ON, Canada). Field centres: Wan C Tan (principal investigator), Christine Lo, Sarah Cheng, Elena Un, Cynthia Fung, Wen Tiang Wang, Liyun Zheng, Faize Faroon, Olga Radivojevic, Sally Chung, Carl Zou (University of British Columbia, Vancouver, BC, Canada); Jean Bourbeau (principal investigator), Palmina Mancino, Jacinthe Baril, Laura Labonte (McGill University, Montreal, QC, Canada); Kenneth Chapman (principal investigator), Patricia McClean, Nadeen Audisho (University of Toronto, Toronto, ON, Canada); Brandie Walker (principal investigator), Curtis Dumonceaux, Lisette Machado (University of Calgary, Calgary, AB, Canada); Paul Hernandez (principal investigator), Scott Fulton, Kristen Osterling, Denise Wigerius (University of Halifax, Halifax, NS, Canada); Shawn Aaron (principal investigator), Kathy Vandemheen, Gay Pratt, Amanda Bergeron (University of Ottawa, Ottawa, ON, Canada); Denis O'Donnell (principal investigator), Matthew McNeil, Kate Whelan (Queen's University, Kingston, ON, Canada); François Maltais (principal investigator), Cynthia Brouillard (University of Laval, Quebec City, QC, Canada); Darcy Marciniuk (principal investigator), Ron Clemens, Janet Baran, Candice Leuschen (University of Saskatoon, Saskatoon, SK, Canada).

Contributors RR, DJ, JT, CF, AM, BP, LF, DM, FM, WC, JB, HP are coauthors of this work and have contributed significantly. RR, DJ, JT, CF, LF, HP: data analysis, formatting of results. RR, AM, BP, HP: statistical analyses. RR, DJ, CF, DM, FM, WC, JB, HP: study protocol, execution and monitoring of evaluations. RR, HP: coordination of publication work, writing of the manuscript. DM, FM, WT, JB, HP: coordination and monitoring of the CanCOLD project for the centres involved in the tests and evaluations of the study. RR is the author responsible for the overall content as the guarantor.

Funding The study was funded through Ottawa HP-Research Support Operating funds. The Canadian Cohort Obstructive Lung Disease (CanCOLD; NCT00920348) study is currently funded by the Canadian Respiratory Research Network, the Canadian Institutes of Health Research (CIHR; CIHR/Rx&D Collaborative Research Programme Operating Grants: 93326), and the following industry partners: AstraZeneca Canada Ltd; Boehringer Ingelheim Canada Ltd; GlaxoSmithKline (GSK) Canada Ltd; and Novartis. Investigators at Research Institute of the McGill University Health Centre Montreal and iCAPTURE Centre Vancouver led the project. Previous funding partners were the Respiratory Health Network of the Fonds de la recherche en santé du Québec (FRQS), the Foundation of the McGill University Health Centre, and industry partners: Almirall; Merck, Nycomed; Pfizer Canada Ltd; and Theratechnologies. The funders had no role in the study design, data collection, and analysis, or preparation of the manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study protocol was approved by Research Ethics Boards of each institution of the CanCOLD project: more particularly university ethics committees: McGill University and McGill University Health Center, Montreal, QC, Canada; University of Saskatchewan, Saskatoon, Saskatchewan, Canada; Laval University, Quebec, QC, Canada; University of British Columbia, Vancouver, BC, Canada. Participants provided a signed consent before inclusion.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iDs
Ruddy Richard http://orcid.org/0000-0002-9061-2953
Laura Filaire http://orcid.org/0000-0003-1433-9390
Jean Bourbeau http://orcid.org/0000-0002-7649-038X

REFERENCES

1 Barr RG, Bluemke DA, Ahmed FS, *et al*. Percent emphysema, airflow obstruction, and impaired left ventricular filling. *N Engl J Med* 2010;362:217–27.
2 Baum C, Ojeda FM, Wild PS, *et al*. Subclinical impairment of lung function is related to mild cardiac dysfunction and manifest heart failure in the general population. *Int J Cardiol* 2016;218:298–304.
3 Leung C, Bourbeau J, Sin DD, *et al*. The prevalence of chronic obstructive pulmonary disease (COPD) and the heterogeneity of risk factors in the Canadian population: results from the Canadian obstructive lung disease (COLD) study. *Int J Chron Obstruct Pulmon Dis* 2021;16:305–20.
4 Terzikhan N, Verhamme KMC, Hofman A, *et al*. Prevalence and incidence of COPD in Smokers and non-Smokers: the Rotterdam study. *Eur J Epidemiol* 2016;31:785–92.
5 James MD, Milne KM, Phillips DB, *et al*. n.d. Dyspnea and exercise limitation in mild COPD: the value of CPET. *Front Med*;7.
6 Fazleen A, Wilkinson T. Early COPD: Current evidence for diagnosis and management. *Ther Adv Respir Dis* 2020;14:1753466620942128.
7 Rossi A, Butorac-Petanjek B, Chilosi M, *et al*. Chronic obstructive pulmonary disease with mild airflow limitation: current knowledge and proposal for future research - a consensus document from six scientific societies. *Int J Chron Obstruct Pulmon Dis* 2017;12:2593–610.
8 Cherian M, Jensen D, Tan WC, *et al*. Dyspnoea and symptom burden in mild-moderate COPD: the Canadian cohort obstructive lung disease study. *ERJ Open Res* 2021;7:00960-2020.
9 Woodruff PG, van den Berge M, Boucher RC, *et al*. American thoracic society/national heart, lung, and blood Institute asthma-chronic obstructive pulmonary disease overlap workshop report. *Am J Respir Crit Care Med* 2017;196:375–81.

10 O'Donnell DE, Laveneziana P, Webb K, *et al*. Chronic obstructive pulmonary disease: clinical integrative physiology. *Clin Chest Med* 2014;35:51–69.
11 Holverda S, Rietema H, Westerhof N, *et al*. Stroke volume increase to exercise in chronic obstructive pulmonary disease is limited by increased pulmonary artery pressure. *Heart* 2009;95:137–41.
12 O'Donnell DE, Milne KM, James MD, *et al*. Dyspnea in COPD: new mechanistic insights and management implications. *Adv Ther* 2020;37:41–60.
13 Bourbeau J, Tan WC, Benedetti A, *et al*. Canadian cohort obstructive lung disease (Cancold): fulfilling the need for longitudinal observational studies in COPD. *COPD* 2014;11:125–32.
14 Stewart AL, Mills KM, King AC, *et al*. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med Sci Sports Exerc* 2001;33:1126–41.
15 Jones PW, Quirk FH, Baveystock CM, *et al*. A self-complete measure of health status for chronic airflow limitation the St. George's respiratory questionnaire. *Am Rev Respir Dis* 1992;145:1321–7.
16 Charloux A, Lonsdorfer-Wolf E, Richard R, *et al*. A new impedance cardiograph device for the non-invasive evaluation of cardiac output at rest and during exercise: comparison with the « direct » Fick method. *Eur J Appl Physiol* 2000;82:313–20.
17 Richard R, Lonsdorfer-Wolf E, Charloux A, *et al*. Non-invasive cardiac output evaluation during a maximal progressive exercise test, using a new impedance Cardiograph device. *Eur J Appl Physiol* 2001;85:202–7.
18 Lewthwaite H, Benedetti A, Stickland MK, *et al*. Normative peak cardiopulmonary exercise test responses in Canadian adults aged ≥40 years. *Chest* 2020;158:2532–45.
19 Galera R, Casitas R, Martínez E, *et al*. Exercise oxygen flow titration methods in COPD patients with respiratory failure. *Respir Med* 2012;106:1544–50.
20 Vogiatzis I, Louvaris Z, Wagner PD. Respiratory and locomotor muscle blood flow during exercise in health and chronic obstructive pulmonary disease. *Exp Physiol* 2020;105:1990–6.
21 Louvaris Z, Spetsioti S, Andrianopoulos V, *et al*. Cardiac output measurement during exercise in COPD: a comparison of dye dilution and impedance Cardiography. *Clin Respir J* 2019;13:222–31.
22 Vasilopoulou MK, Vogiatzis I, Nasis I, *et al*. On- and off-exercise kinetics of cardiac output in response to cycling and walking in COPD patients with GOLD stages I-IV. *Respir Physiol Neurobiol* 2012;181:351–8.
23 Mazzuco A, Souza AS, Medeiros WM, *et al*. Effects of high- and moderate-intensity exercise on central hemodynamic and oxygen uptake recovery Kinetics in CHF-COPD overlap. *Braz J Med Biol Res* 2020;53:e9391.
24 Rocha A, Arbex FF, Sperandio PA, *et al*. Exercise intolerance in comorbid COPD and heart failure: the role of impaired aerobic function. *Eur Respir J* 2019;53:1802386.
25 Oelberg DA, Kacmarek RM, Pappagianopoulos PP, *et al*. Ventilatory and cardiovascular responses to inspired he-O2 during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:1876–82.
26 Light RW, Mintz HM, Linden GS, *et al*. Hemodynamics of patients with severe chronic obstructive pulmonary disease during progressive upright exercise. *Am Rev Respir Dis* 1984;130:391–5.
27 Morrison DA, Adcock K, Collins CM, *et al*. Right ventricular dysfunction and the exercise limitation of chronic obstructive pulmonary disease. *J Am Coll Cardiol* 1987;9:1219–29.
28 Mahler DA, Matthay RA, Snyder PE, *et al*. Determination of cardiac output at rest and during exercise by carbon dioxide Rebreathing method in obstructive airway disease. *Am Rev Respir Dis* 1985;131:73–8.
29 Smith JR. Impaired central hemodynamics in chronic obstructive pulmonary disease during submaximal exercise. *J Appl Physiol* 2019;127:691–7.
30 Ribeiro F, Oueslati F, Saey D, *et al*. Cardiorespiratory and muscle oxygenation responses to Isokinetic exercise in chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 2019;51:841–9.
31 Marklund S, Bui KL, Nyberg A. Measuring and monitoring skeletal muscle function in COPD: current perspectives. *Int J Chron Obstruct Pulmon Dis* 2019;14:1825–38.
32 Fonseca J, Nellessen AG, Pitta F. Muscle dysfunction in smokers and patients with mild COPD: A SYSTEMATIC REVIEW. *J Cardiopulm Rehabil Prev* 2019;39:241–52.
33 Degens H, Gayan-Ramirez G, van Hees HWH. Smoking-induced skeletal muscle dysfunction: from evidence to mechanisms. *Am J Respir Crit Care Med* 2015;191:620–5.