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ORIGINAL RESEARCH

Chronotropic incompetence can limit exercise tolerance in COPD patients with lung hyperinflation

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Purpose: Metabolic-chronotropic relationship is the only concept that assesses the entire chronotropic function during exercise, as it takes into account individual fitness. To better understand interrelationships between chronotropic incompetence (CI), dynamic hyperinflation (DH) and exercise limitation among Global initiative for chronic Obstructive Lung Disease (GOLD) stages of chronic obstructive pulmonary disease (COPD) disease severity, we evaluated cardiopulmonary responses to symptom-limited cycle exercise in stable patients.

Patients and methods: We prospectively studied 47 COPD patients classified by GOLD stage severity. Pulmonary function tests and cardiopulmonary responses to symptom-limited incremental exercise were studied. CI was defined by regression line between percent heart rate (HR) reserve and percent oxygen uptake ($V'O_2$) reserve, ie, chronotropic-metabolic index (CMI). DH was defined from the knot resulting from the nonlinear regressions of inspiratory capacity changes from rest to peak (dynamic inspiratory capacity (IC_{dyn})) with percentage of maximal HR and CMI.

Results: Aerobic capacity (median interquartile ranges) peak $V'O_2$, 24.3 (23.6; 25.2), 18.5 (15.5; 21.8), 17.5 (15.4; 19.1) $mL \cdot kg^{-1} \cdot min^{-1}$ and CMI worsened according to GOLD severity. The optimal knot of IC_{dyn} was equal to –0.34 L. The multivariate logistic regression showed a strong relationship between CI (outcome) and DH (odds ratio [confidence interval 95]) 25 (3.5; 191.6).

Conclusion: COPD patients with DH have a poor cardiovascular response to exercise, which may be attributed to CI.

Keywords: COPD, hyperinflation, chronotropic incompetence, exercise

Introduction

Patients with chronic obstructive pulmonary disease (COPD) have limited exercise tolerance, which has been related to reduced maximal voluntary ventilation (MMV), impaired diffusion capacity of the lung and lung hyperinflation.[1–3] The major consequence of lung hyperinflation is the association of increased ventilatory workload and decreased inspiratory muscle pressure generating capacity, which contributes to dyspnea and poor exercise tolerance.[2,4] Beyond the lungs, deleterious cardiovascular consequences of dynamic hyperinflation (DH) have been consistently identified in COPD patients during incremental exercise.[5–7] In these observations, DH was associated with reduced oxygen (O_2) uptake efficiency slope and O_2 pulse, which noninvasively reflect cardiac stroke volume during submaximal exercise.[6,8,9] Interestingly, lung volume reduction surgery has been shown to improve exercise tolerance through cardiac stroke volume increases.[10]

Along with cardiac stroke volume impairment is the concept that a contributing factor of reduced cardiac output leading to poor exercise tolerance might be the

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limitation to increase heart rate (HR), so called chronotropic incompetence (CI).[11] Chronotropic regulation involves cardiac interactions with the autonomic nervous system, which influences HR response to exercise, HR recovery and multiple components of HR variability.[12,13] HR increases upon initiation of exercise are principally mediated by the withdrawal of cardiac parasympathetic activity, with the sympathetic contribution being manifested at a longer latency. Since vagal withdrawal with the initiation of exercise can result to an increase of 30 to 50 beats per minute (BPM) in HR, further increases are thought to be related to sympathetic activation. Recovery involves reactivation of the parasympathetic system and deactivation of sympathetic activity, causing a decline in HR. Interestingly, both impaired HR increases in proportion to the metabolic demand and HR recovery kinetics are associated with poor outcome.[13]

An inability of HR to increase appropriately in proportion to the metabolic demands of exercise has been termed CI, which has been originally defined as an inability to reach 80% of age-predicted maximum HR (HR_{max}) or HR reserve utilization.[11] More adequately, the only concept that allows assessment of the entire chronotropic function is metabolic-chronotropic relationship, which takes into account individual fitness. Indeed, to ensure that reduced peak HR is not solely related to low exercise capacity, CI must be defined by the regression line between percent HR reserve and percent oxygen uptake ($V'O_2$) reserve, ie, chronotropic-metabolic index (CMI).[11,14] Using this approach, reduced CMI has clearly identified subgroups of patients largely dependent upon an increased HR for an increase in cardiac output during incremental exercise (HR becoming the limiting factor).[11] Furthermore, in heart failure patients, CI has been consistently associated with increased mortality, independently of confounding factors, such as age, gender, physical fitness, and traditional cardiovascular risk factors.[15,16]

Mechanisms of CI are thought to be secondary to chronic overactivation of the sympathetic system and subsequent downregulation of cardiac β-adrenoreceptor densities.[17,18] Consistent studies have shown that acute lung hyperinflation in breath-hold maneuvers can induce pulmonary vessels and heart compression leading to sympathetic activity increase.[19,20] It is thus likely that chronic hyperinflation in COPD patients would lead to chronic sympathetic overactivation and blunted cardiac chronotropic response.[21,22] Recent findings supported that CI is common in patients with severe COPD and may be improved after lung volume reduction surgery.[23,24] CI was also found as an independent and powerful outcome predictor in severe COPD patients.[25] Of note, whether CI as evaluated by CMI was related to lung hyperinflation has not been reported previously. Our aim was thus to test whether CI could be related to lung DH in exercising patients. We also aimed to determine the different factors, such as breathing pattern, DH and CI, which can influence exercise intolerance in COPD patients.

Patients and methods

Patients

This study was conducted in accordance with the amended Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/). The Institutional Review Board of Lille University Hospital (Lille, France) approved this study (2014-0111-b), which only included patients referred to our department for routine functional evaluation. Written informed consent was obtained from all patients. We prospectively enrolled all consecutive patients suffering from COPD, defined according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[26] The diagnosis of COPD was confirmed by forced spirometry, when the patient was considered clinically stable. All the procedures and their risks were explained to the patients, who gave their verbal informed consent to enter the study. Pulmonary function testing as well as exercise studies had been undertaken for clinical reasons at the request of the patients' clinicians.

Inclusion and exclusion criteria

Caucasian subjects, either current or former smokers, with spirometrically confirmed COPD in GOLD stages were included. They had to have been free of COPD exacerbations during the last 3 months prior to inclusion. Patients with a history of left ventricular disease, left ventricular ejection fraction <45%, severe pulmonary hypertension (mean pulmonary artery pressure (PAP) >35 mmHg) were excluded. Patients treated for hypertension with blood pressure >160/90 mmHg, with arrhythmias, with significant coronary artery disease or using β-blockers were also excluded. None of the subjects had noninvasive positive-pressure ventilation support or long-term ambulatory O^2 treatment.

Pulmonary function

Standard forced expiratory spirometry (forced expiratory volume in the first second (FEV_1) and forced expiratory vital capacity (FVC)) and body plethysmography (residual volume (RV), functional residual capacity (FRC), total lung capacity (TLC)), and diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) were performed (MasterScreen™ body plethysmograph, Viasys, France) using European and American Thoracic Society guidelines.[27]

Cardiopulmonary testing

Cardiopulmonary exercise testing was performed according to standardized procedures using an electromagnetic braked cycle ergometer.[28] Exercise protocol involved an initial 2 minutes of rest, followed by 2 minutes of unloaded cycling with a progressive increment every minutes (10 W·m^{-1}) until exhaustion at a pedaling frequency of 60–65 rpm. Subjects were continuously monitored by 12-lead electrocardiogram (Cardiosoft, CareFusion, France). Blood pressure assessed by sphygmomanometry was recorded every 2 minutes. Arterial blood (240 µL) was sampled at rest and at peak exercise and immediately analyzed using a blood gas analyzer/co-oximeter (ABL700, Radiometer, France).

Subjects respired through an oro-nasal mask (Hans Rudolf 7450 SeriesV2™ Mask, CareFusion, France). Breath-by-breath cardiopulmonary data (Vyntus, CareFusion, France) were measured at rest, warm up and incremental exercise testing. Before each test, O_2 and carbon dioxide (CO_2) analyzers and flow mass sensor were calibrated using available precision gas mixture and a 3-L syringe, respectively. Minute ventilation (V'_E), $V'O_2$, carbon dioxide output ($V'CO_2$) were recorded as concurrent 10 seconds moving averages, as was determined ventilation anaerobic threshold (AT) by the V-slope method. Ventilatory reserve was calculated as (MVV – peak V'_E)/MVV * 100 where MVV is maximal voluntary ventilation estimated as FEV_1 multiplied by 35. Peak values were averaged over the last 30 seconds of exercise. Patient effort was considered to be maximal if two of the following occurred: predicted maximal work is achieved, predicted maximal HR is achieved, $V'_E/V'O_2$ >45, lactate level >6 mmol·L^{-1}, RER >1.10 and pH drop >0.06, as recommended by the ATS/ACCP.[28] At peak exercise, subjects assessed Borg-perceived exertion ratings for both respiratory and leg discomfort. During the study period, mean values between qualified replicate tests performed weekly on control subjects were 5.1%±4.2%, 5.4%±3.2%, 6.1%±2.2%, for peak $V'O_2$, $V'CO_2$ and V'_E, respectively.

Peak oxygen pulse (O_2 pulse) was calculated and was expressed in mL per beat and as percentage of predicted value by dividing the predicted peak $V'O_2$ by predicted peak HR. $V'_E/V'CO_2$ slope was calculated off-line as a linear regression function using 10-s averaged values and excluding the non-linear part of the relationship after the respiratory compensation point (where nonlinear rise in V'_E occurred relative to $V'CO_2$ in the presence of decrease of end-tidal pressure of CO_2). The $V'O_2$ efficiency slope (OUES) describes the relationship between $V'O_2$ and V'_E during incremental exercise, via a log transformation of V'_E.[29] OUES was expressed as the slope of the linear relationship of $\log_{10} V'_E$ to $V'O_2$ (L·min^{-1}) using $V'O_2$ (L·min^{-1}) = m ($\log_{10} V'E$) + b, where m=OUES. Double-product (mmHg·bpm) was calculated as the product of systolic blood pressure by the HR.

DH

Changes in operational lung volumes were evaluated from measurements of inspiratory capacity (IC).[1–3] End-expiratory lung volume (EELV) was assessed from IC maneuvers at rest, every 2 minutes during exercise and at peak exercise (Vyntus). In these maneuvers, after EELV was observed to be stable over 3–4 breaths, subjects were instructed to inspire maximally to TLC. For each measurement, EELV was calculated as resting TLC minus IC, using the plethysmographic TLC value. Dynamic IC (IC_{dyn}) was defined as resting IC minus IC at peak exercise. DH as dichotomous variable was performed from optimal knot of IC_{dyn} (see section "Statistical analysis", "Results", and Figure 1). An inflection

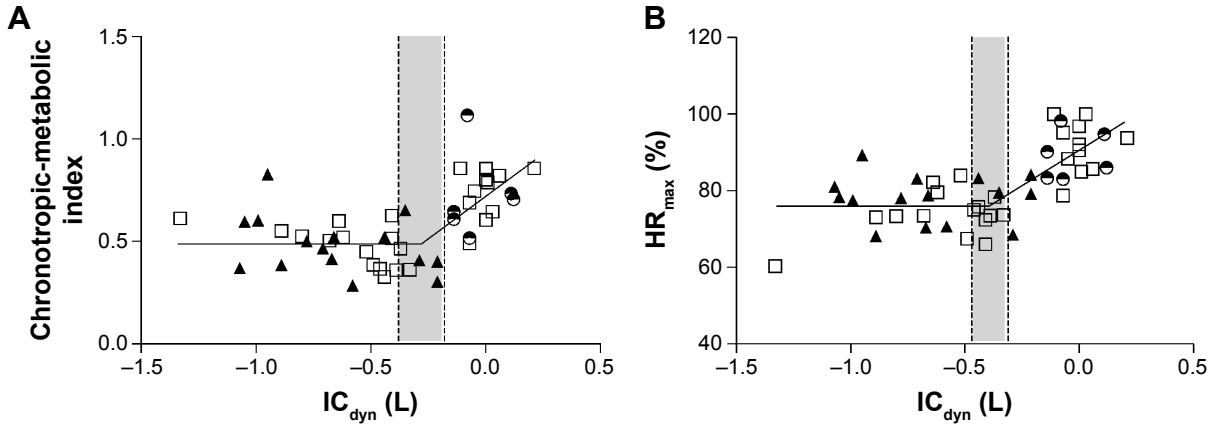

Figure 1 Relationship between dynamic inspiratory capacity (IC_{dyn}) changes from rest to peak with chronotropic-metabolic index and percentage of age-predicted maximum heart rate (HR_{max}), (**A** and **B**), respectively.

Notes: Global Initiative for Chronic Obstructive Lung Disease stages (stage 1: half-full dots; stage 2: empty squares; stage 3 and 4: filled triangles). The broken-line trend is represented by the black solid lines.

in tidal volume (V_T) relative to V'_E (expressed as % peak V'_E) was determined in each patient during exercise.

CMI

Chronotropic index was defined as an index of maximal predicted HR reserve achieved.[11] The percentage of HR reserve used at peak exercise referred to $[(HR_{stage} - HR_{rest})/(220 - \text{age in years} - HR_{rest})] * 100$, where HR is heart rate. For any given stage of exercise, the percentage of $V'O_2$ reserve used referred to $[(V'O_{2\ stage} - V'O_{2\ rest})/(V'O_{2\ peak} - V'O_{2\ rest})] * 100$. CMI was calculated off-line as the regression line slope between percent HR reserve and percent $V'O_2$ reserve. A patient was referred to as having CI if the resulting slope index was <0.75 and $HR_{max} <80\%$.[11,14]

Statistical analysis

The statistical analyses were performed with SAS software (SAS Institute Inc., Cary, NC, USA; version 9.3). A two-sided significance level of 0.05 was chosen for all tests. Descriptive statistics, with tests of normality (Shapiro–Wilk test) for values showed free distributions. Values were expressed as medians with interquartile ranges (IQR). Patients were divided according to GOLD classification.[30] Nonparametric analysis (Kruskal–Wallis test) was used to test for differences between classes. Post hoc comparisons were determined by Wilcoxon test with Bonferroni correction. Relationships between quantitative variables were assessed by the Spearman's correlation coefficient (r). Bivariate comparisons for categorical variables were performed with Chi-squared test (with Fisher correction as appropriate).

Locally estimated scatterplot smoother SAS procedure showed a broken-line trend between CMI or HR_{max} and IC_{dyn} changes. Linear mixed model procedure was used to analyze the change of CMI and HR_{max} versus a broken function of IC_{dyn} that took 0 before the knot and subject's IC_{dyn} after the knot; the knot position was fixed by the smallest Akaike information criterion (AIC) using Gauss–Newton method.[31,32] Thus, mean and 95% confidence interval of optimal knot, intercept (no change), and slope (increase) were estimated by nonlinear mixed model. As these two variables are used interchangeably in the literature to define CI, we took the middle of the overlap area of the IC_{dyn} knot from these two relationships. IC_{dyn} converted to DH as dichotomous variables indicating $IC_{dyn} <$ optimal knot (DH=1) or $IC_{dyn} \geq$ optimal knot (DH=0). The association between CI and DH with covariables (age, body mass index (BMI), TLC, IC/TLC, RV/TLC, GOLD stage) was estimated as an odds ratio (OR) and 95% confidence intervals by using multivariate logistic regression analyses.

Results

We included 47 consecutive stable COPD patients (age 55 (49; 61) years, BMI 26 (22; 30), female n=14). All patients were maximally treated with bronchodilators. At study entry, patients were receiving inhaled steroids (75%), long-acting β_2-agonists (75%) and tiotropium (65%); all of them were active or ex-smokers. Overall, a wide range of airflow obstruction (FEV_1/FVC from 26% to 69%; 56 (50; 64) %), static hyperinflation (IC/TLC from 24% to 61% predicted; 40 (36; 46) % predicted), diffusing capacity ($D_{L,CO}$ from 17% to 98% predicted; 73 (49; 85) % predicted) was found. Nine out of 42 patients (21%) suffered from well-controlled arterial hypertension and were on diuretics (72%), ACE-inhibitors (52%), calcium-antagonists (36%) to control the disease.

According to objective ATS/ACCP criteria, exercise was considered maximal in all patients.[28] Mean peak workload and $V'O_2$ was 90 (65; 95) watts (range 55–170 watts) and 18.5 (15.6; 22.6) $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ (67 (61; 78) % predicted), respectively. AT $V'O_2$ was 12.1 (11.0; 14.4) $mL{\cdot}kg^{-1}{\cdot}min^{-1}$. Peak V_T to FEV_1 ratio was 37 (30; 48) % and plateau of V_T increase occurred at 70.8 (61.1; 77.8) % of maximum V'_E. Breathing reserve at peak exercise was reduced (24 (3; 33) %). IC_{dyn} change measured from rest to peak exercise was –0.39 (–0.67; –0.07) L and peak EELV (% TLC) was 64 (56; 72) %. HR_{max} was 134 (119; 150) bpm (80 (73; 88) % predicted) with HR reserve utilization of 60 (43; 76) %. Peak O_2 pulse was 10.2 (8.6; 12.4) $mL{\cdot}bpm^{-1}$ (84 (71; 97) % predicted). Peak systemic arterial partial pressure of O_2 (Pa,O_2) and CO_2 (Pa,CO_2) were 91 (70; 99) and 39 (35; 41) mmHg, respectively. Arterial lactate was 5.6 (4.7; 7.0) $mmol{\cdot}L^{-1}$ at peak exercise.

Functional characteristics of patients classified by GOLD scaling system are shown in Table 1. Static hyperinflation significantly decreased incrementally from stage I to stage III–IV among baseline pulmonary function parameters (Table 1). Tables 2–4 (main features of CPET, ventilatory and cardiovascular response details, respectively) display all results and significant differences of medians of exercise parameters between each group (GOLD stage I, stage II and stage III–IV) after adjustments. Peak $V'O_2$ (% of predicted values) was not significantly different between GOLD stages (Table 2). At peak exercise (Table 3), EELV (% TLC), V_D/V_T(%) and Pa,CO_2 significantly increased incrementally with patient's COPD severity. IC_{dyn} significantly decreased incrementally with patient's COPD severity (Table 3).

The nonlinear procedure established between IC_{dyn} change and CMI (Figure 1A) or HR_{max} (Figure 1B) has converged to broken-line models. The best fit, which was defined

Table 1 Subject characteristics

GOLD stage	Stage I	Stage II	Stage III–IV	*P*-value
Sample size	**n=6**	**n=26**	**n=15**	
Age, years	53.5 (49; 56)	60 (54; 64)‡	49 (44; 56)‡	**0.031**
BMI, kg·m^{-2}	26.0 (23.8; 26.4)	27.8 (22.8; 30.7)	21.9 (18.9; 29.1)	0.224
Gender, M/F	4/2	22/4	7/8	**0.028**
Smoking status, % current	50	40	20	0.238
Smoking, pack-year	30 (30; 40)	27.5 (16.5; 40)	42.5 (25; 61)	0.279
Lung function test				
FEV_1, L	3.2 (3.0; 3.4)*,#	2.1 (1.8; 2.6)*,‡	1.4 (1.2; 1.7)#,‡	**<0.001**
FEV_1, % predicted	0.88 (0.83; 0.94)*,#	0.66 (0.59; 0.72)*,‡	0.45 (0.34; 0.48)#,‡	**<0.001**
FVC, L	4.9 (4.4; 5.7)*,#	3.8 (3.1; 4.3)*,‡	3.1 (2.7; 3.6)#,‡	**<0.001**
FEV_1/FVC, %	67.2 (64.8; 68.4)*,#	58.8 (54.1; 63.7)*,‡	47.8 (32.6; 54.5)#,‡	**<0.001**
IC, L	3.2 (3.0; 4.4)#	2.8 (2.4; 3.3)‡	2.1 (1.9; 2.7)#,‡	**0.001**
TLC, L	7.4 (6.7; 8.1)	6.1 (5.6; 7.3)	6.5 (5.8; 7.5)	0.187
FRC, L	3.7 (3.6; 3.9)	3.5 (3.0; 4.6)	4.5 (3.5; 4.8)	0.248
IC/TLC	45.7 (40.8; 53.8)#	41.5 (38.8; 47.1)‡	35.6 (29.4; 39.9)#,‡	**<0.001**
RV, L	2.4 (2.3; 2.9)#	2.8 (1.8; 3.4)	3.4 (2.7; 4.0)#	**0.012**
RV/TLC, %	98 (86; 100)*,#	114.5 (104; 123)*,‡	145 (136; 160)#,‡	**<0.001**
D_{LCO}, mL·min^{-1}·mmHg^{-1}	23.0 (15.2; 26.7)	19.8 (14.4; 24.3)	11.6 (9.6; 15.5)	**0.032**
D_{LCO}, % predicted	81.5 (59; 88)	75 (51; 85)	48 (38; 62)	**0.033**

Notes: Data are presented as median (interquartile range). *,#,‡Significant difference between groups. Bold values represent the significant results.
Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; BMI, body mass index; FEV_1, forced expiratory volume in the first second; FVC, forced expiratory vital capacity; IC, inspiratory capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; D_{LCO}, diffusing capacity of the lung for carbon monoxide; M, male; F, female.

by the smallest AIC, allowed us to obtain the values of the following knots IC_{dyn} (mean ± standard error): −0.28±0.1 L and −0.39±0.08 L, respectively. The middle of the overlap area allowed us to determine the DH threshold with IC_{dyn} change equal to −0.34 L.

The prevalence of DH was higher in GOLD III–IV patients than in GOLD I–II patients (Table 5). Patients with lung hyperinflation had more CI than patients without DH (Table 5). CI status was not related to GOLD score (*P*=0.1).

The logistic regression that analyzed the association between CI (outcome) and DH showed a strong relationship (OR [confidence interval 95%]) 20 [4.4–91.9] that was confirmed by multivariate analysis taking into account the following covariates: age, BMI, TLC, CI/TLC, RV/TLC and GOLD stage (Table 6).

Discussion

A new finding of this study is that lung hyperinflation in COPD patients is associated with impaired metabolic-chronotropic relationship, so-called CI, which may present as a limiting factor of exercise tolerance.

In our study, both static and dynamic lung volume measurements were performed to assess lung hyperinflation in COPD patients. Among baseline pulmonary function parameters, we used IC/TLC ratio as a static hyperinflation-derived variable

Table 2 Cardiopulmonary exercise testing (peak values, except AT)

GOLD stage	Stage I	Stage II	Stage III–IV	*P*-value
Sample size	**n=6**	**n=26**	**n=15**	
Workload, W	97.5 (95; 150)#	90 (80; 100)‡	65 (60; 85)#,‡	**<0.001**
$V'O_2$, mL·kg^{-1}·min^{-1}	24.3 (23.6; 25.2)#	18.5 (15.5; 21.8)	17.5 (15.4; 19.1)#	**0.035**
$V'O_2$, % predicted	77.4 (62.8; 80.9)	70.0 (55.0; 80.0)	64.0 (61.0; 68.0)	0.215
AT $V'O_2$, mL·kg^{-1}·min^{-1}	16.0 (15.0; 16.6)*,#	12.1 (10.6; 14.1)*	12.0 (11.0; 13.4)#	**0.033**
RER	1.2 (1.0; 1.3)	1.2 (1.1; 1.2)	1.2 (1.1; 1.2)	0.859
Arterial lactate, mmol·L^{-1}	7.6 (5.7; 9.2)	5.7 (4.8; 7.3)	5.5 (4.3; 6.4)	**0.036**
Borg dyspnea score	4 (3; 7)	4 (3; 5)	3 (3; 5)	0.865
Borg leg effort score	4 (4; 7)	4 (3; 5)	3 (2; 5)	0.314

Notes: Data are presented as median (interquartile range). *,#,‡Significant difference between groups. Bold values represent the significant results.
Abbreviations: AT, anaerobic threshold; GOLD, Global Initiative for Chronic Obstructive Lung Disease; $V'O_2$, oxygen uptake; RER, respiratory exchange ratio.

Table 3 Ventilatory response during submaximal exercise (peak values, except V_T/V'_E inflexion point)

GOLD stage	Stage I	Stage II	Stage III–IV	*P*-value
Sample size	**n=6**	**n=26**	**n=15**	
f_R, breaths·min^{-1}	31 (23; 41)	31 (27; 38)	34 (30; 38)	0.655
V_T, L	2.3 (1.8; 3.3)$^{\#}$	1.8 (1.6; 2.0)‡	1.5 (1.1; 1.6)$^{\#,\ddagger}$	**0.001**
V_T/FEV_1, %	74.9 (59.5; 91.0)$^{\#}$	83.6 (74.6; 91.0)‡	105.0 (85.6; 117.2)$^{\#,\ddagger}$	**0.003**
V_T/FVC, %	49.5 (40.7; 57.3)	48.4 (45.2; 51.1)	46.3 (38.5; 50.2)	0.649
V'_E, L·min^{-1}	76.5 (64; 88)$^{*,\#}$	54.5 (48; 64)*,‡	48 (37; 53)$^{\#,\ddagger}$	<**0.001**
V'_E reserve, % predicted	33.9 (11.7; 44.9)$^{\#}$	28.0 (21.8; 34.4)‡	2.7 (−10.5; 16.6)$^{\#,\ddagger}$	<**0.001**
V_T/V'_E inflection point, % peak V'_E	52.5 (46; 61)$^{*,\#}$	40 (32; 50)*,‡	30 (26; 32)$^{\#,\ddagger}$	<**0.001**
IC_{dyn}, L	−0.08 (−0.14; 0.11)$^{\#}$	−0.38 (−0.52; 0)‡	−0.67 (−0.95; −0.35)$^{\#,\ddagger}$	<**0.001**
EELV/TLC, %	53 (49; 58)$^{\#}$	61 (54; 70)‡	70 (68; 79)$^{\#,\ddagger}$	<**0.001**
Gas exchange				
V_D/V_T, %	32 (31; 35)$^{\#}$	37 (31; 40)‡	45 (38; 51)$^{\#,\ddagger}$	**0.004**
Pa,O_2, mmHg	99.8 (98; 101)	93.5 (80.7; 99)	86 (60; 93)	0.065
Pa,CO_2, mmHg	33.1 (27.0; 35.0)$^{*,\#}$	38.5 (36.0; 40.6)*,‡	41.4 (40.7; 45.0)$^{\#,\ddagger}$	<**0.001**

Notes: Data are presented as median (interquartile range). $^{*,\#,\ddagger}$Significant difference between groups. Bold values represent the significant results.
Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; f_R, breathing frequency; V_T, tidal volume; FEV_1, forced expiratory volume in the first second; FVC, forced expiratory vital capacity; V'_E, minute ventilation; IC_{dyn}, dynamic inspiratory capacity; EELV, end-expiratory lung volume; TLC, total lung capacity; V_D, dead volume; *Pa*,O_2, arterial partial pressure of oxygen; *Pa*,CO_2, arterial partial pressure of carbon dioxide.

reflecting mechanical inspiratory constraint.[1–3] We found that over a wide range of airflow, IC/TLC decreased incrementally with FEV_1/FVC obstruction. Such relationship was also observed with RV/TLC, which increased incrementally with FEV_1/FVC. Next, we established exercise-induced DH by measuring IC_{dyn}.[1–3] IC_{dyn} significantly decreased incrementally with patient's GOLD score severity. DH was associated with increased V_T constraint as V_T/V'_E inflection point expressed as peak V'_E percent was decreased incrementally with patient's COPD severity. DH was accompanied with poor cardiovascular response, which was evaluated in our study by noninvasive surrogate markers, such as OUES and O_2 pulse.[5–7] O_2 pulse, a noninvasive measure of stroke volume, requires assumption that the arteriovenous O_2 content difference remains constant during exercise. Physiologically, arterial O_2 content can be altered by hemoglobin availability, arterial blood oxygenation and peripheral O_2 extraction.[33] In our series of COPD patients, hemoglobin concentration and calculated arterial content were within the normal ranges. Furthermore, whether O_2 extraction was normal or reduced in our patients, these changes may not account for O_2 pulse reduction, since a lower O_2 extraction would actually increase O_2 pulse.[6,10]

Beside the negative effects of abnormal ventilatory mechanics on cardiac stroke volume, CI can also prevent the

Table 4 Cardiovascular response during submaximal exercise (peak values, except recovery)

GOLD stage	Stage I	Stage II	Stage III–IV	*P*-value
Sample size	**n=6**	**n=26**	**n=15**	
HR, beat·min^{-1}	149 (142; 162)	130 (113; 150)	133 (122; 140)	0.074
HR peak-rest, beat·min^{-1}	60 (54; 71)	42.5 (32; 67)	42 (28; 61)	0.102
HR_{max}, %	88.2 (83.3; 94.7)$^{\#}$	79.2 (73.4; 90.6)	78.8 (70.7; 83.2)$^{\#}$	**0.042**
HR reserve use, %	76.3 (67.5; 87.3)$^{\#}$	55.0 (41.3; 80.6)	52.5 (42.6; 63.8)$^{\#}$	**0.032**
Chronotropic-metabolic index	0.68 (0.61; 0.73)$^{\#}$	0.58 (0.47; 0.75)	0.47 (0.39; 0.60)$^{\#}$	**0.027**
O_2 pulse, mL·beat^{-1}	11.7 (10.5; 12.4)$^{\#}$	10.8 (10.1; 13.9)‡	8.3 (7.3; 9.7)$^{\#,\ddagger}$	<**0.001**
O_2 pulse, % predicted	95.5 (88.0; 104.0)$^{\#}$	86.0 (74.0; 99.0)‡	77.0 (65.0; 82.0)$^{\#,\ddagger}$	**0.005**
OUES, mL·min^{-1}	1 548 (1 344; 1 988)	1 701 (1 467; 1 988)	1 321 (1 138; 1 937)	0.188
$V'_E/V'CO_2$ slope	26.1 (23.8; 30.3)	30.2 (26.9; 33.5)	32.0 (29.0; 37.4)	0.079
Mean arterial pressure, mmHg	125.3 (120.0; 133.0)	123.7 (103.5; 135.2)	117.0 (111.7; 125.0)	0.537
Double product, mmHg·beat·min^{-1}	29 523 (28 120; 31 266)$^{\#}$	25 619 (23 471; 29 539)‡	20 295 (19 380; 24 024)$^{\#,\ddagger}$	<**0.001**
Post-exercise heart rate recovery				
HR recovery at 1 min, beat·min^{-1}	17.5 (13; 18)	10 (3; 19)	13 (6; 20)	0.636
HR recovery at 3 min, beat·min^{-1}	41 (31; 49)	28.5 (20; 35)	27 (19; 36)	0.262

Notes: Data are presented as median (interquartile range). $^{\#,\ddagger}$Significant difference between groups. Bold values represent the significant results.
Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, heart rate; HR_{max}, age predicated maximum heart rate; min, minute; O_2, oxygen; OUES, oxygen uptake efficiency slope; V'_E, minute ventilation; $V'CO_2$, carbon dioxide output.

Table 5 Relationships between dynamic hyperinflation, GOLD stage and chronotropic incompetence

Group patients	No hyperinflation*	Hyperinflation*	*P*-value**
GOLD			**0.019**
I–II	18	14	
III–IV	3	12	
Chronotropic incompetence, %	14.3	76.9	**<0.0001**

Notes: *Defined by an IC_{dyn} <–0.34 L; **P-values obtained by Fisher exact test. Bold values represent the significant results.
Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; IC_{dyn}, dynamic inspiratory capacity.

cardiovascular system from reaching its physiological limits before maximal exercise.[11] In healthy humans, HR increases virtually instantaneously upon the initiation of exercise. Involvement of a reduction in cardiac parasympathetic activity has been demonstrated in human studies showing that atropine can significantly attenuate the initial increase in HR in a variety of exercise conditions. In contrast, the magnitude of HR increase at the onset of exercise is not diminished by prior β-adrenergic blockade, implying a minimal influence of sympathetic activity at this time.[34,35] Thereafter, there is an approximately linear relationship between HR and $\dot{V}O_2$ during incremental dynamic exercise. At moderate-to-elevated exercise intensities β-adrenergic blockade significantly attenuates the size of the HR response, thus suggesting a key role for heightened sympathetic nervous system and elevated catecholamine levels in the circulation.[34–36] At immediate cessation of exercise, HR abruptly declines, which is typically followed by a more gradual decline of HR over minutes depending on exercise conditions. Initial HR recovery is related to rapid restoration of cardiac parasympathetic activity, since it is virtually abolished by atropine administration, but unaffected by β-adrenergic blockade.[37]

Blunted HR response is the primary cause of or a significant contributor to severe, symptomatic exercise intolerance in heart failure patients.[15,16] Mechanisms of CI have been related to overstimulation of the sympathetic system, which induces downregulation of β-receptors and their desensitization in the presence of increased circulating catecholamine levels.[17,18] In COPD patients, a striking elevation of sympathetic tone has been demonstrated and might thus provide a link between COPD and CI. Hypoxemia, chemoreflexes, impaired baroreflex sensitivity, muscle ergoreflex and lung hyperinflation are important factors contributing to neurohumoral activation in COPD.[20,38] In normal subjects, sympathetic nerve firings are synchronized with central inspiratory motor activity and increase in lung volume during inspiration activates pulmonary vagal afferents that in turn inhibit sympathetic nerve discharge.[20,38] The relative magnitude of these two opposing mechanisms determines the net effect of respiratory modulation of sympathetic nerve activity, which is in favor of sympathetic activation in COPD patients.[21,22]

Table 6 Multivariate analysis of chronotropic incompetence

Variables	OR (95% confidence interval)
Dynamic hyperinflation status	**25 (3.5–191.6)***
Age	**1.094 (1.008–1.187)***
BMI	0.952 (0.826–1.098)
TLC	0.676 (0.342–1.336)
IC/TLC	0.956 (0.849–1.076)
RV/TLC	1.004 (0.970–1.039)
GOLD stage	1.056 (0.088–12.634)

Notes: *P-values <0.05. Bold values represent the significant results.
Abbreviations: OR, odds ratio; BMI, body mass index; TLC, total lung capacity; IC, inspiratory capacity; RV, residual volume; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Although lung hyperinflation may induce sympathetic overactivation in COPD patients, whether DH would lead to CI during submaximal exercise has not been previously tested. In normal subjects, CI has been most commonly diagnosed when HR fails to reach 80%–85% of the HR_{max}.[11] However, before one concludes that a patient has CI, it is important to consider the patient's level of effort.[14] Whether attenuated HR in response to incremental exercise is related to low effort level or CI represents a major issue in this context. Hence, in order to more objectively evaluate CI, the relationship between HR and $\dot{V}O_2$ during exercise should be measured.[11,14] In this approach, the metabolic-chronotropic relationship is calculated from the ratio of the HR reserve to the metabolic reserve during submaximal exercise.[39,40] If the assumption on which percentage of HR reserve equal $\dot{V}O_2$ reserve is achieved in normal adults, a relationship slope less than 0.75–0.8 is considered indicative of CI in chronic heart disease patients.[39,40] In our study, this metabolic-chronotropic relationship approach allowed us to define an association between CI and DH, which was further characterized by broken-line trend analysis with a reduced IC_{dyn} of 0.34 L as a threshold level for CI.

In conclusion, we have shown that CI evaluated by the metabolic-chronotropic relationship is highly prevalent in a cohort of COPD patients. Adding evaluation of CI to standard pulmonary function parameters at rest and during incremental exercise allows to determine the level of lung hyperinflation as a potential mechanism of attenuated HR response.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Abbreviations

ACE inhibitor, angiotensin-converting-enzyme inhibitor; AIC, Akaike information criterion; AT, anaerobic threshold; ATS/ACCP, American Thoracic Society/American College of Chest Physicians; BMI, body mass index; CI, chronotropic incompetence; CMI, chronotropic-metabolic index; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; DH, dynamic hyperinflation; $D_{L,CO}$, diffusing capacity of the lung for carbon monoxide; EELV, end-expiratory lung volume; FEV_1, forced expiratory volume in the first second; FRC, functional residual capacity; FVC, forced expiratory vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, heart rate; HR_{max}, age predicted maximum heart rate; IC, inspiratory capacity; IC_{dyn}, dynamic inspiratory capacity; IQR, interquartile ranges; MVV, maximal voluntary ventilation; O_2 pulse, peak oxygen pulse; OUES, oxygen uptake efficiency slope; *Pa*, arterial partial pressure; PAP, pulmonary artery pressure; RER, respiratory exchange ratio; RV, residual volume; TLC, total lung capacity; $V'CO_2$, carbon dioxide output; V'_E, minute ventilation; $V'O_2$, oxygen uptake; V_D, death volume; V_T, tidal volume.

Disclosure

The authors report no conflicts of interest in this work.

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