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Dynamic hyperinflation, chronotropic intolerance and abnormal heart rate recovery in non-severe chronic obstructive pulmonary disease patients-reflections in the mirror

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Abstract

Background: The presence of abnormal heart rate recovery (HRR) and chronotropic incompetence (CI) suggests autonomic dysfunction (AD) and is associated with diminished physical activity and increased cardio-vascular (CV) risk.

Aim: Our aim is to analyse the correlation between AD and airflow obstruction - forced expiratory volume in 1 s (FEV1), dynamic hyperinflation (DH) and disease prognosis - the BODE - index (BMI; Obstruction - FEV1;Dyspnea - mMRC;E - exercise capacity) in non-severe COPD patients without overt CV comorbidities.

Methods: We used cardio-pulmonary exercise testing (CPET) with 67 subjects. Inspiratory capacity (IC) manoeuvres were performed for DH assessment. Echocardiography was executed before CPET and 1–2 min after peak exercise. Stress left ventricular diastolic dysfunction (LVDD) was assumed if stress $E/e' > 15$. Wilkoff method calculated the metabolic-chronotropic relationship (MCR). Chronotropic incompetence (CI) and abnormal HR recovery (HRR) were determined.

Main results: CI was detected in 44% of the mild and 65% of the moderate COPD patients. Abnormal HRR was present in 75% of the mild and 78% of the moderate COPD subjects. Multivariate regression analysis showed no association between FEV1, CPET parameters, BODE index, stress LVDD and AD. DH was the only independent predictor for both abnormal HRR and CI.

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Conclusion: Evaluation of AD during incremental CPET unravels lung hyperinflation as a potential mechanism of attenuated HR response and diminished physical activity in non-severe COPD free of overt CV comorbidities. This multifaceted approach to dyspnea may facilitate the discrimination of its pathogenesis and improve its proper clinical management.

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Introduction

Chronotropic incompetence (CI) – the inability to reach the target heart rate (HR) during exercise is believed to represent an impaired sympathetic response and is an independent predictor of cardiovascular diseases.^{1,2} Heart rate recovery (HRR) – the rate of restoration of the heart rate (HR) during the first minute after exercise – the recovery phase, represents the parasympathetic response. Its abnormal delay (a decline of HR < 12 beats/min) implies parasympathetic dysfunction.^{3,4} Abnormal HRR and CI indicate the presence of autonomic dysfunction (AD). Being established as independent predictors of cardiac mortality, these two types of abnormal physiological responses may find application in cardiovascular risk stratification.^{5,6}

Though not systematically investigated, both CI and HRR have been described in either hypoxemic, or normoxemic COPD patients.^{7,8} Their prevalence is variable within the range of 56–86% among studies. Even more controversial is the data regarding the relation between AD and COPD stages.^{8–11} This can be explained by the fact that different COPD stages have been investigated.

Considered a major contributor to exercise intolerance and dyspnea, dynamic hyperinflation (DH) has additional negative consequences in COPD.^{12,13} DH is a result of expiratory airflow limitation and occurs when ventilatory demand increases, leaving less time for expiration. The end-expiratory lung volume (EELV) increases, altering the intrathoracic pressure gradients. Cardio-vascular consequences follow – the right and left ventricle preload diminish, while the left ventricle afterload increases. This impairs LV filling, compliance and cardiac output.^{12,13} DH deters not only the stroke volume, but also blunts HR surge. It has been recently observed that it is associated with AD, and correlates to impaired metabolic-chronotropic relationship (CI) independent of age, static lung volumes and airway obstruction.¹⁴ The autonomic abnormalities, associated with DH are much more constant than the haemodynamic heart-lung effects in the different COPD stages.

Assuming this we set the following aims: (1) to detect the prevalence of CI and abnormal HRR in non-severe COPD patients free of overt CV diseases; (2) to analyse their association with disease severity – forced expiratory volume in 1 s (FEV1), dynamic hyperinflation; (3) and disease prognosis the BODE – index (BMI; Obstruction – FEV1; Dyspnea – mMRC scale; E – exercise capacity).

Materials and methods

Patients and study protocol

It was a prospective study which was performed in 224 clinically stable outpatients, diagnosed with COPD at the University Hospital for Respiratory Diseases “St. Sophia”, Sofia. Only 163 of them met the inclusion criteria: (1) non-severe COPD (post bronchodilator FEV1/FVC < 70%; FEV1/ > 50%); (2) preserved left ventricular systolic function LVEF > 50%; (3) lack of overt cardiovascular disease; (4) exertional dyspnea. A total of 67 patients were considered eligible, assuming the exclusion criteria. The recruitment period was between April 2018–April 2019, and was approved by the local Ethical Committee (protocol 5/12.03.2018). All the patients signed informed consent before their participation. They were previously acquainted with the aim of the study, its scientific value and the potential presentation of data at different forums. Dyspnea was rated applying the modified Medical Research Council (mMRC) scale. Exercise capacity was assessed using the 6 min walking test (6MWT). Body mass index, airflow Obstruction, Dyspnea and Exercise capacity – (BODE) index was calculated.¹⁵ Inhaled bronchodilators (β_2 agonists and anti-cholinergics) were withdrawn 24 h before investigation.

The following exclusion criteria were considered: (1) LVEF < 50%; (2) LVDD at rest more than first grade; (3) echocardiographic signs of systolic pulmonary arterial hypertension; (4) valvular heart disease; (5) documented cardiomyopathy; (6) severe uncontrolled hypertension (systolic blood pressure > 180 mmHg and diastolic blood pressure > 90 mmHg); (7) atrial fibrillation or malignant ventricular arrhythmia; (8) the intake of β -blockers; (9) ischaemic heart disease; (10) anaemia; (11) diabetes mellitus; (12) cancer; (13) chronic kidney disease; (14) recent chest or abdominal surgery; (15) recent exacerbation (during the last three months); (16) recent change (during the last three months) in medical therapy; (17) none of the subjects had non-invasive positive-pressure ventilation support or long-term ambulatory O2 therapy; (18) previous rehabilitation procedures.

Procedures

Pulmonary function testing and body plethysmography at rest

All subjects underwent preliminary clinical examination which included chest X-ray, spirometry, electrocardiogram,

and echocardiography. Those eligible for the study performed spirometry and exercise stress test. Both tests were performed on Vyntus, Carefusion, Germany following the guidelines. Spirometry was performed after bronchodilatation test – application of (400 μ g) of salbutamol. Following the ERS guidelines a post-bronchodilatation ratio of FEV1/FVC < 70% was assumed for the diagnosis of COPD.¹⁶ Only patients with mild/moderate airway obstruction (FEV1 > 50%) were selected. The severity of COPD was staged according to the GOLD criteria.¹⁷ Static lung volumes – residual volume (RV), total lung capacity (TLC), inspiratory lung volume and inspiratory capacity (IC) were measured by body plethysmography (Vyntus, body plethysmograph, CareFusion, Germany). Static hyperinflation has been assumed if FRC was above the upper lower limit of normal. Static lung volume measurements and interpretation of data has been performed following the guidelines.^{18,19} The ECCS/ERS equations have been used for lung volume analysis.²⁰

Exercise tests

Six-minute walk test (6-MWT)

Six-minute walking test was performed in accordance with ATS guidelines.²¹ It was done on a separate day after the initial visit for study eligibility criteria and after the performance of the exercise stress test and stress echocardiography. Subjects were instructed and encouraged to walk through 30m preliminary measured distance in a hospital corridor. SpO₂, heart rate and arterial blood pressure were obtained before and during the recovery period.

Cardio-pulmonary exercise testing (CPET) – stress test protocol

All the patients underwent symptom limited incremental exercise stress test following the guidelines.²² It was performed in an upright position on a bicycle after the clinical examination and spirometry. Subjects respired through an oro-nasal mask (Hans Rudolf 7450 SeriesV2™ Mask, CareFusion). Breath-by-breath cardiopulmonary data (Vyntus, CareFusion) were measured at rest, warm up and incremental exercise testing. Gas and flow sensors were calibrated before each test. Clinical monitoring of the patients included standard electrocardiography through the whole exercise test; manual blood pressure measurements, and heart rate recordings at the end of every stage.

A continuous ramp protocol was applied. After two minutes of unloaded pedaling (rest phase-0W), a three minute warm-up phase (20W) followed. The test phase included 20W/2min load increments. Patients were instructed to pedal with 60–65 rotations per minute. Patients' effort was considered to be maximal if two of the following criteria emerged: predicted maximal HR is achieved; predicted maximal work is achieved; $\dot{V}E/\dot{V}O_2 > 45$, RER > 1.10, lactate level > 6 mmol L⁻¹, and pH drop > 0.06, as recommended by the ATS/ACCP.²³ Arterial blood (240 μ L) was sampled at rest and at peak exercise and immediately analyzed using a blood gas analyzer/cooximeter (ABL700, Radiometer, France).

A breath-by-breath analysis was used for expiratory gas evaluation. Oxygen uptake ($\dot{V}O_2$ (mL/kg/min)), carbon dioxide production ($\dot{V}CO_2$ (L/min)), minute ventilation ($\dot{V}E$ (L/min)) and end-tidal CO₂ pressure (PetCO₂ (mm Hg)) were

collected continuously at rest and throughout the exercise test. Peak values of oxygen consumption and carbon dioxide production were presented by the highest 30-second average value, obtained during the last stage of the exercise test. Peak respiratory exchange ratio was the highest 30s averaged value between $\dot{V}O_2$ and $\dot{V}CO_2$ during the last stage of the test. Ten-second averaged $\dot{V}E$ and $\dot{V}CO_2$ data, from the initiation of exercise to peak, were used to calculate the $\dot{V}E/\dot{V}CO_2$ slope via least squares linear regression.²⁴ A dual approach for the measurement of the anaerobic threshold (AT) was applied. Both V-slope method and the ventilatory equivalents method for $\dot{V}O_2$ and $\dot{V}CO_2$ were used. The modified Borg scale was applied for peak dyspnea and leg discomfort.

The maximum HR (MHR) was calculated (MHR = 220 – age). The target HR (THR) was set at 80% of MHR. A cut-off point of 12 beats was taken as an abnormal HRR.⁴ The chronotropic response index was calculated.² The metabolic-chronotropic relationship (MCR) was calculated by Wilkoff's formula.²⁵ CI was assumed if MCR < 0.80. Breathing reserve (BR) was calculated as MVV - peak $\dot{V}E$ /MVV x 100 where MVV is maximal voluntary ventilation estimated as FEV1 multiplied by 35.

Dynamic hyperinflation (DH) during CPET

Changes in operational lung volumes were derived from measurements of dynamic inspiratory capacity (IC), assuming that total lung capacity (TLC) remained constant during exercise.^{26,27} This has been found to be a reliable method of tracking acute changes in lung volumes.^{26,27} IC was measured at the end of a steady-state resting baseline, at 2 min intervals during exercise, and at end exercise. End-expiratory lung volume (EELV) was calculated from IC maneuvers at rest, every 2 min 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.²⁸ Dynamic hyperinflation (DH) was defined as a decrease in IC from rest of more than 150 mL or 4.5% pred at any time during exercise.²⁹

Stress echocardiographic methods and CPET

After exercise cessation patients were put on a bed, near the ergometer. Stress echocardiography was performed in a supine position on a patient lying down 1–2 min after peak exercise.

Routine structural and haemodynamic indices of both chambers at rest were measured following the guidelines.³⁰ The systolic function of the left ventricle was defined by Simpson's modified rule. The diastolic function of both ventricles was evaluated by the E/A ratio at rest.³¹ As a more precise approach for diastolic dysfunction detection, tissue Doppler analysis was used. We used e' value as the average of medial and the lateral measurements for the mitral annulus. The peak of the average E/e' ratio > 15 was considered as a marker for stress induced left ventricular diastolic dysfunction.³⁰

Statistical analysis

Descriptive statistics was used for demographic and clinical data presentation. The Kolmogorov-Smirnov test was used to explore the normality of distribution. Continuous variables were expressed as median and interquartile range when data was not normally distributed and with mean \pm SD if normal distribution was observed. Categorical variables were presented as proportions. Data were compared between patients with GOLD I and GOLD II. An unpaired Student's t test was performed for normally distributed continuous variables. Mann-Whitney-U test was used in other cases. Categorical variables were compared by the χ^2 test or the Fisher exact test. Univariate logistic regression analysis was applied to determine the ventilatory, echocardiographic and CPET parameters, associated with CI and abnormal HRR. Age, FEV1, body mass index, ICdyn, LV E/e' at rest, stress LV E/e' > 15 were taken as covariates in multivariate logistic regression analysis. In all cases a p value of less than 0.05 was considered significant as determined with SPSS® 13.0 Software (SPSS, Inc, Chicago, Ill) statistics.

Results

Echocardiographic, ventilatory and cardiovascular parameters of GOLD I and GOLD II patients at rest

Subjects enrolled in the study were Caucasians with a mean age of 62.9 ± 7.5 . Subjects are divided into two groups based on the GOLD stages. The demographic and clinical data of the patients is presented in [Table 1](#). Though not of statistical significance, there is a higher prevalence of DH, CI and abnormal HRR in moderate, as compared to mild, COPD patients. The echocardiographic characteristics ([Table 2](#)) were similar between the patients with GOLD I and GOLD II, but those with moderate disease demonstrated a higher incidence of stress LVDD. The ventilatory, cardiovascular and cardio-pulmonary exercise testing parameters of the two groups at peak exercise are given in [Tables 3 and 4](#).

Cardio-vascular parameters of GOLD I and GOLD II patients at peak exercise

The patients with mild COPD achieved significantly higher peak HR and performed with higher MCR ([Table 4](#)). CI was met in seven (44%) of them with median heart rate reserve utilization – 78.53 (69.61–89.42) Abnormal heart rate recovery was established in 12 (75%) of the mild COPD.

The moderate COPD subjects demonstrated much lower MCR and chronotropic intolerance was met in 33 (65%) of these patients; they reached much lower peak HR and had a lower median heart rate reserve utilization 57.08 (41.74–81.12). Abnormal HRR was present in 40 (78%) of the GOLD II patients.

Ventilatory parameters of GOLD I and GOLD II patients at peak exercise

The analysis of the ventilatory parameters at peak exercise showed that mild COPD patients had higher minute

ventilation and higher breathing reserve in comparison to those with moderate one. None of the patients in the studied group demonstrated static hyperinflation, but 32(46%) showed DH. There is a predominant prevalence of hyperinflators – 27(53)% among the patients with GOLD II in comparison to GOLD I – 5(31)% ([Table 1](#)).

Cardio-respiratory parameters of GOLD I and GOLD II patients at peak exercise

According to the objective ATS/ACCP criteria, exercise was considered maximal in all patients. The mild COPD patients achieved a higher peak load, higher V'O2 at peak and at anaerobic threshold. They performed with higher oxygen pulse and lower VE/VCO2 slope ([Table 4](#)). Dyspnea was the predominant limiting factor in 5 (31%) of GOLD I patients, but exhausted breathing reserve was detected in only 2 (13%) of them; in comparison 46 (90%) of the GOLD II patients complained of dyspnea and exhausted breathing reserve was the limiting factor in 18 (35%) of them. Leg fatigue was the reason for exercise cessation in 11 (69%) of GOLD I subjects, while 5 (10%) of the patients with GOLD II mentioned it ([Table 4](#)).

Association between ventilatory, cardio-pulmonary and echocardiographic parameters and AD

[Table 5](#) demonstrates univariate logistic regression analysis for predictors of AD. Among the studied ventilatory, cardio-pulmonary and echocardiographic parameters only ICdyn and stress E/e' > 15 presented as predictors for both CI and abnormal HRR. Multivariate logistic regression analysis was also performed. The following covariates – age, BMI, FEV1, RV, RV/TLC, IC/TLC were taken in assumption. The multivariate regression analysis did not show association between the CI or abnormal HRR or any of the tested ventilatory, echocardiographic, CPET parameters or the BODE index [Table 5](#). DH is the only independent predictor of CI and HRR in non-severe COPD patients.

Discussion

The major findings of our study are: (1) we demonstrate a high prevalence of abnormal HRR (76.5%) and CI (54.5%) in non-severe COPD patients who complain of exertional dyspnea and are free of overt cardiovascular diseases; (2) DH was the only independent predictor for AD parameters (CI and/or abnormal HRR); (3) the prevalence of HRR and CI are independent from the FEV1, LV cardiac function and the BODE index.

Chronotropic regulation of the cardiac function is responsible for HR response to exercise, HR recovery and HR variability.^{32,33} AD was first reported in advanced COPD with respiratory failure and later in normoxemic patients.^{7,34} Data regarding the prevalence of CI in COPD patients is even more controversial. The reasons for this are different criteria for CI definition, different COPD stages and study protocols.^{35,36} Abnormal HRR has also been demonstrated in COPD independently of exercise intensity, peak and resting

Table 1 Anthropometric, clinical and autonomic dysfunction parameters of the patients with GOLD I and GOLD II.

	Patients with GOLD I (n, 16)	Patients with GOLD II (n, 51)	p-Value
Demographic data			
Age, year,	57.19 ± 6.13	61.89 ± 5.79	0.769*
Male, n	11	48	0.378 [†]
Duration of COPD	3.78 (2.86–5.12)	9.87 (6.73–11.58)	0.619 [†]
Pack, years	25.98 (23.79–31.81)	29.19 (30.43 ± 38.87)	0.391 [†]
Body mass index, kg/m ²	28.57 (25.49–32.65)	26.31 (20.86–33.48)	0.717 [†]
Discharge medication			
LABA, n (%)	9 (56%)	18 (35%)	0.187 [†]
LAMA, n (%)	7 (44%)	12 (24%)	0.097 [†]
LABA + LAMA, n (%)	–	21 (41%)	0.319 [†]
Angiotensin converting enzyme Inhibitors, n (%)	11 (69%)	32 (63%)	0.762 [†]
Diuretics, n (%)	7 (44%)	29 (57%)	0.224 [†]
mMRC	1.5 (0.8–1.7)	1.8 (1.1–2.0)	0.721
6 MWT			
Distance walked, m	486.05 (451.38–499.21)	465.84 (436.73–481.19)	0.437 [†]
AD prevalence			
Chronotropic incompetence, n (%)	7 (44%)	33 (65%)	0.635 [†]
Abnormal HRR at 1 min, bpm	12 (75%)	40 (78%)	0.721 [†]
Dynamic hyperinflation			
IC _{dyn} > 150 mL	5 (31%)	27 (53%)	0.613 [†]
Stress LVDD			
Stress E/e' > 15	7 (44%)	39 (76%)	0.247 [†]

Abbreviations: GOLD – Global Initiative On Obstructive Lung Disease; LABA – long acting β₂ agonists; LAMA – long acting muscarine antagonist; AD – autonomic dysfunction; HRR – heart rate recovery; bpm – beats per minute; IC_{dyn} = IC_{rest} - IC_{peak}; LVDD – left ventricular diastolic dysfunction; LV – left ventricle; mMRC – modified Medical Research Council; 6MWT – 6 min walking test.

* Unpaired t test.

[†] Mann–Whitney U test.

[‡] Chi square test.

Table 2 Echocardiographic parameters of the patients with GOLD I and GOLD II.

	Patients with GOLD I (n, 16)	Patients with GOLD II (n, 51)	p-Value
LV structural parameters			
LAVI, ml/m ²	28.34 (26.58–31.29)	29.18 (27.61–32.83)	0.286*
Septum, mm	11.00 (10–13)	12.00 (11–13)	0.887*
PW, mm	11.05 (10.75–12)	12.00 (11–13)	0.921*
LV functional parameters at rest			
LVEF, %, Simpson	64.50 (61–66)	61.00 (57–66)	0.653*
E/A ratio	0.89 (0.75–1.25)	0.75 (0.65–0.90)	0.520*
E/e' aver ratio	6.46 (6.05–8.33)	6.97 (5.76–9.15)	0.456*
TR jet velocity, m/s	2.16 (1.98–2.31)	2.34 (2.04–2.42)	0.618*
Dec-E, ms	210.5 (201.32–211.29)	211.8 (212.61–221.83)	0.374*
IVRT, ms	89.6 (82.58–94.29)	91.2 (84.61–96.83)	0.895*
LV functional parameters after exercise stress test			
E/A ratio	1.25 (0.8–1.50)	1.53 (1.25–1.86)	0.043*
E/e' aver	8.07 (6.7–9.6)	17.43 (15.71–19.46)	0.036*
e' aver	10.03 (7.8–12.1)	7.8 (6.32–9.11)	0.012*
TR jet velocity, m/s	2.63 (2.22–2.92)	2.76 (2.50–3.12)	0.709*

Abbreviations: GOLD – Global Initiative On Obstructive Lung Disease; LV – left ventricular; LAVI – left atrium volume index; PW – posterior wall; LVEF – left ventricular ejection fraction; TR – tricuspid; Dec-deceleration; IVRT – isovolumic relaxation time.

* Mann–Whitney U test.

HR.^{37,38} It was associated with increased risk of all-cause mortality especially among subjects with FEV₁ < 50%.³⁹

Our data supports previous findings. We observed both abnormal HRR (assuming parasympathetic dysfunction) and

CI (an indicator of impaired sympathetic response) in COPD patients, which implies that both limbs of the autonomic cardiac regulation may be affected in mild/moderate COPD.

Table 3 Cardio-vascular and ventilatory parameters at rest and at peak exercise of the patients with GOLD I and GOLD II.

	Patients with GOLD I (n, 16)	Patients with GOLD II (n, 51)	p-Value
Cardio-vascular parameters			
HR at rest, bpm	78 (72–86)	89 (82–98)	0.502 [†]
Peak HR, bpm	138 (110–143)	117 (103–121)	0.042 [†]
HR max, %	86.7 (82.48–93.69)	77.84 (71.24–88.72)	0.014 [†]
Heart rate reserve use, %	78.53 (69.61–89.42)	57.08 (41.74–81.12)	0.019 [†]
MCR	0.73 (0.61–0.78)	0.54 (0.48–0.72)	0.032 [†]
Post-exercise			
HRR at 1 min, bpm	11 (5–12)	10 (3–12)	0.982 [†]
Blood pressure at rest			
Systolic blood pressure, mmHg	126.73 ± 8.41	128.87 ± 11.32	0.803 [‡]
Diastolic blood pressure, mmHg	80.43 ± 4.14	82.31 ± 6.56	0.451 [‡]
Blood pressure at peak exercise			
Systolic blood pressure, mmHg	161.81 ± 9.18	169.62 ± 10.84	0.219 [†]
Diastolic blood pressure, mmHg	85.37 ± 7.65	87.19 ± 7.32	0.398 [†]
Ventilatory parameters at rest			
FVC, l	4.68 (4.56–5.72)	3.72 (3.09–4.98)	0.021 [†]
FVC, % pred	83.42%	84.11%	0.036 [†]
FEV1, l	3.06 (3.02–3.39)	2.32 (1.56–3.21)	0.033 [†]
FEV1, % pred	81.02 (80.56–89.21)	66.18 (59.21–72.65)	0.040 [†]
FEV1/FVC %	65.38(59.26–66.22)	62.30 (50.48–64.45)	0.046 [†]
IC, l	3.19 (3.02–4.43)	2.87 (2.40–3.32)	0.216 [†]
TLC, l	7.48 (6.72–8.09)	6.14 (5.59–7.28)	0.187 [†]
TLC, % pred	91 (88–102)	94 (86–109)	0.709 [†]
RV, l	2.38 (2.33–2.89)	2.81 (1.82–3.39)	0.283 [†]
RV, % pred	92 (78–102)	94 (87–111)	0.421 [†]
IC/TLC, %	45.62 (41.08–52.88)	41.57 (38.89–47.31)	0.179 [†]
BODE index	1.05 (0.67–1.32)	2.64 (1.47–3.81)	0.016 [†]
Ventilatory parameters at peak exercise			
V _t , l	2.28 (1.79–3.34)	1.79 (1.57–2.02)	0.212 [†]
VE, l/min	72.38 (60.87–84.58)	54.97 (46–62)	0.031 [†]
BR, %	33.89 (21.68–39.83)	27.94 (20.87–33.38)	0.043 [†]
EELV/ TLC, %	53 (50–59)	61 (54–70)	0.047 [†]

Abbreviations: HFpEF – heart failure with preserved ejection fraction; HR – heart rate; HRR – heart rate recovery; CRI – chronotropic response index; bpm – beats per minute; MCR – metabolic-chronotropic relationship; IC – inspiratory capacity; TLC – total lung capacity; FRC – functional residual capacity; RV – residual volume; V_t – tidal volume; VE – minute ventilation; EELV – end expiratory lung volume; BR – breathing reserve.

[†] Mann-Whitney U test.

[‡] Chi square test.

To the best of our knowledge, we first to describe AD in mild/moderate COPD patients who complain of exertional dyspnea and are free of overt cardio-vascular diseases. The design of the study takes into consideration the intake of medication that may influence the autonomic nervous system response. The intake of β -blockers was an exclusion criteria, and patients had β 2-agonists and anticholinergic medication withdrawn 24 h before CPET. Though HRR and CI grew with the increase of BODE index and FEV1, none of the respiratory or CPET parameters correlated with them. Remembering that AD is associated with increased cardio-vascular mortality in the general population, HRR and CI may be useful independent markers for cardio-vascular risk stratification in COPD.⁴⁰

Data regarding the relation between AD and FEV1 is controversial among studies. Chick et al., demonstrate delayed HRR in COPD patients, independently of their FEV1.⁹ In contrast, Schedira et al., claim a higher prevalence of HRR as

FEV1 decreases.¹⁰ Hulo et al., find similar trends regarding CRI.¹⁴ Gupta et al., describe that both HRR and CRI are becoming more prevalent in advanced COPD stages.⁸ The controversies regarding the association between AD and COPD progression is probably due to the different study designs and protocol performance.

It is routinely assumed that AD is secondary to chronic sympathetic system overactivation.^{41,42} Lung hyperinflation induces compression of the pulmonary vessels and the heart; the stroke volume and HR decrease.^{43,44} It is therefore likely that lung hyperinflation in COPD blunts the cardiac chronotropic response and increases the sympathetic overactivation.^{45,46} In normal subjects, sympathetic nerve activity is generally synchronized with the central inspiratory motor activity. The degree of lung volume inflation during inspiration activates pulmonary vagal afferents that in turn inhibits sympathetic nerve discharge.⁴⁷ The balance between these mechanisms determines the effect of respi-

Table 4 Cardio-pulmonary exercise testing parameters at peak exercise of the patients with GOLD I and GOLD II.

	Patients with GOLD I (n, 16)	Patients with GOLD II (n, 51)	p-Value
Peak Load, W	98 (100–140)	90 (80–100)	0.018 [†]
Peak Load, % pred	89.4 (78.56–97.14)	83.18 (58.54–88.34)	0.044 [†]
Exercise duration	525.8 + 136.8	484.3 + 129.1	0.312 [†]
Peak VE, l/min	72.38 (60.87–84.58)	54.97 (46–62)	0.031 [†]
Peak V'O ₂ , ml/kg/min	23.81 (22.06–25.18)	18.46 (15.86–19.98)	0.028 [†]
Peak V'O ₂ , % pred	77.4 (62.8–80.9)	70.0 (55.0–80.0)	0.036 [†]
V'O ₂ at AT, ml/kg/min	16.0 (15.0–16.6)	12.1 (10.6–14.1)	0.047 [†]
O ₂ pulse, ml/beat	11.80 (10.15–12.19)	10.90 (10.00–13.04)	0.076 [†]
Peak RER	1.2 (1.1–1.3)	1.2 (1.1–1.3)	0.758 [†]
VE/VCO ₂ slope	26.76 (24.02–30.58)	31.17 (27.15–34.68)	0.035 [†]
Peak Sat%	95.00 (94.02–95.67)	94.9 (94.4–95.25)	0.089 [†]
Borg dyspnea score	4 (3–7)	4 (3–5)	0.621 [†]
Borg leg discomfort score	4 (4–7)	4 (3–5)	0.098 [†]

Abbreviations: HFpEF- heart failure with preserved ejection fraction; RER – respiratory exchange ratio; AT anaerobic threshold; VE – minute ventilation; V'O₂ – oxygen uptake.

[†]Chi square test.

[†] Mann–Whitney U test.

Table 5 Univariate and multivariate logistic regression analysis between respiratory, cardio-pulmonary and echocardiographic parameters and AD parameters.

Univariate analysis	CI			Abnormal HRR		
	p-Value	OR	95% CI	p-Value	OR	95% CI
FEV 1, l/min	0.079	1.008	0.990–1.623	0.651	0.924	0.626–1.397
FRC,l	0.064	0.617	0.327–1.324	0.231	0.712	0.478–0.909
RV,l	0.073	1.562	0.998–2.864	0.097	1.023	0.096–1.241
IC/TLC,%	0.082	0.911	0.614–1.206	0.457	0.876	0.418–1.259
RV/TLC,%	0.301	0.921	0.689–1.223	0.793	0.658	0.395–0.968
V _t , l	0.090	1.002	0.831–1.948	0.151	0.918	0.549–1.328
VE, l	0.319	0.954	0.788–1.923	0.421	0.683	0.264–1.014
BR, %	0.065	0.958	0.779–1.561	0.059	0.917	0.692–1.218
ICdyn > 150 mL	0.036	18.9	4.521–32.418	0.027	19.3	3.804–27.613
Peak Load, W	0.071	1.107	0.604–1.221	0.109	2.401	1.013–5.411
Peak V'O ₂ , mL/min/kg	0.623	0.769	0.412–0.965	0.398	1.023	0.587–3.102
Peak O ₂ pulse mL/min/kg	0.126	0.989	0.674–1.003	0.812	0.911	0.634–2.121
VE/VCO ₂ slope	0.074	0.830	0.987–1.871	0.231	1.076	0.754–3.812
BODE index	0.152	0.013	0.000–0.938	0.473	0.811	0.432–3.089
LV E/e' at rest	0.078	0.542	0.423–0.897	0.067	1.241	0.932–1.968
Stress LV E/e' >15	0.023	3.673	1.418–6.924	0.048	2.037	1.806–5.473
Multivariate analysis						
ICdyn	0.042	11.21	3.862–27.851	0.039	12.06	2.653–19.087

Abbreviations: FEV1 – forced expiratory volume in 1 s; IC – inspiratory capacity; TLC – total lung capacity; RV – residual volume; FRC – functional residual capacity; V_t – tidal volume; VE – minute ventilation; BR – breathing reserve; EELV – end expiratory lung volume; HRR – heart rate recovery; CI – chronotropic incompetence.

ratory modulation on the autonomic nervous system, which in COPD patients is likely to become in favor of sympathetic activation.^{45,46} Although hyperinflation correlates to sympathetic overactivation in COPD, in most of the studies its role has been overlooked. It is unclear whether DH is associated with AD. CI has been most commonly diagnosed when HR fails to reach 80%–85% of the HRmax.³³

In order to objectively evaluate CI in COPD, we, for the first time, employed the Wilkoff formula – the relationship between HR and V'O₂ during exercise.²⁵ The advantage of

using the formula and the metabolic-chronotropic relationship as a marker for CI, is that MCR is adjusted for age, physical fitness, functional capacity and is unaffected by the exercise testing mode or protocol.^{48,49} This metabolic-chronotropic relationship approach allowed us to define an association between AD and DH. 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 let us determine DH as a

potential mechanism of attenuated HR response even in mild/moderate COPD. The results of the study are strengthened by the fact that none of the patients had LV systolic dysfunction.

In summary, abnormal HRR and CI are prevalent in non-severe COPD even in the absence of overt CV comorbidities. Neither abnormal HRR, nor CI are associated with the degree of airflow limitation (FEV1), LV cardiac function or the BODE index. DH is the only independent predictor for them. Evaluation of AD during incremental CPET unravels lung hyperinflation as a potential mechanism of attenuated HR response and diminished physical activity in non-severe COPD free of overt CV comorbidities. This multifaceted approach to dyspnea may facilitate the discrimination of its pathogenesis and improve its proper clinical management.

Our study confirms the versatile clinical presentation of a disease, affecting the lungs and going beyond them in its pathophysiological sequelae. The contemporary phenotype/endotype approach in COPD is undoubtedly demanding.⁵⁰ It is unfortunately obvious that the signs and symptoms, the CT and spirometry parameters, are insufficient to cluster the patients and to facilitate the establishment of biomarkers, useful for precise pharmacotherapy.⁵⁰ The pathophysiological phenotypisation may propel the laborious ambition of understanding the heterogeneous multimorbidity of COPD.

Study limitations

The main limitations of this study are: (1) the relatively small sample size and the multiple tests may lead to false commission or omission results (type I/type II error); (2) coronary artery disease may not be excluded as neither invasive (coronary angiography), nor sophisticated imaging modalities (exercise single photon emission computed tomography (SPECT) – myocardial perfusion imaging (MPI)) were performed; (3) most of our patients had arterial hypertension, but it was controlled by optimal medical treatment, not clinically overt; (4) COPD patients experience enhanced pressure swings during the respiratory cycle and measurements were performed at the end of expiration, which may have influenced the results; (5) we do not have invasive measurement of sPAP; (6) measurements were acquired in the early recovery period (approximately 2 min) after symptom-limited exercise. The timeline of changes in the pulmonary and intrathoracic pressures during the brief time interval from peak exercise to their measurement in early recovery is not well known and underestimation is possible.

Conflicts of interest

The authors have no conflicts of interest to declare.

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