ON-LINE SUPPLEMENT

MATERIALS AND METHODS

Subjects

We included incremental cardiopulmonary exercise testing data (CPET) from all patients (N= 51) who were prospectively enrolled in studies addressing the pathophysiology of coexisting COPD-HF from March 2015 to December 2018. The specific outcome of the present report (aerobic dysfunction during ramp-incremental CPET) has never been explored in our previous investigations who involved a fraction of these patients (i.e., those assessed up to September 2017); thus, there is no overlap between the current report and the data previously shown in a sub-set of these patients. [3] [4] [5] [6] [7] Patients have an established clinical and functional diagnosis of COPD according to the Global Initiative for COPD (GOLD) guidelines (post-bronchodilator FEV_1/forced vital capacity (FVC) ratio < lower limit of normal and GOLD spirometric stages 2-3)[1] and documented heart failure with reduced left ventricular ejection fraction (LVEF) (≤ 40%) [2].They were recruited from the institutional respiratory and cardiology clinics (Sao Paulo Hospital and Kingston Health Science Center Affiliated Teaching Hospitals in Brazil and Canada, respectively) situated in academic centers (Federal University of Sao Paulo and Queen's University, respectively). Key inclusion criteria were: age 50 years or older and a smoking history of at least 10 pack-years. Study's respirologists (FFA, LEN, DOD, JAN) and cardiologists (AR, MCA) carefully

optimized patient's treatment before study. The patients performed the measurements described below only after an agreement had been reached between respirologists and cardiologists regarding diseases stability for at least 2 months, i.e., they underwent a variable period of clinical stabilization (ranging from 2 to 8 months) in which their treatment was carefully optimized. Main exclusion criteria: COPD and/or heart failure exacerbation in the preceding 2 months; presence of asthma or other respiratory condition that could contribute to dyspnea or exercise limitation; contraindications to exercise testing; use of daytime oxygen; and body mass index less than 18.5 kg/m^{2}or greater than 35 kg/m^2. The original prospective studies which provided the data from the current reported had received ethical approval from the Federal University of Sao Paulo Hospital 's Research Ethics Board (REB) (# 1151/2015) and Queen's University Affiliated Teaching Hospitals REB (DMED-1588-13).

Procedures

Transthoracic echocardiogram

All individuals underwent a comprehensive two-dimensional (2D) echocardiography with a GE Vivid 7 (GE Healthcare, USA) echocardiography system with a 1.5 to 4.3 Mhz phase array transducer under continuous electrocardiographic monitoring. The quantification of the cardiac chambers was performed according to American Society of Echocardiography guidelines.[8] The LVEF was calculated according to a modified Simpson´s rule and the right

ventricular systolic function was assessed by the tricuspid annular plane systolic excursion (TAPSE). [8] The pulmonary artery systolic pressure (PASP) was estimated by continuous wave Doppler assessment of maximal tricuspid velocity and the estimated right atrial pressure by inferior vena cava diameter and its respiratory changes.[9]

Pulmonary function tests

Spirometry, static lung volumes, lung diffusing capacity and maximal static respiratory pressures were performed using automated equipment (1085 ELITE D™, Medical Graphics Corp, St. Paul, MN in Brazil and Vmax229d; SensorMedics, Yorba Linda, CA in Canada) according to current guidelines. Reported values were expressed in absolute and % predicted values.[10][11][12][13]

Cardiopulmonary exercise tests (CPET)

Exercise tests were conducted on an electronically-braked cycle ergometer (Ergoline 800s; SensorMedics, Yorba Linda, CA) using a SensorMedics Vmax229d system in both laboratories. Measurements included: standard breath-by-breath cardiorespiratory and breathing pattern parameters;[14] oxygen saturation by pulse oximetry (SpO_2); heart rate (HR) by 12-lead ECG; arterial blood pressure by auscultation; dynamic operating lung volumes calculated from inspiratory capacity (IC) maneuvers [15] and dyspnea intensity assessed with the modified 10-point Borg scale.

The rate of work rate (WR) increment was individually selected according to reported exercise tolerance (typically 5–10 W). The data were calculated automatically and displayed in descriptive numerical (average of 15 s) and graphical (8 breath moving average) forms. The following data were obtained breath-by-breath: pulmonary oxygen uptake ($\dot{V}O_2$ ml/min); pulmonary carbon dioxide output ($\dot{V}CO_2$, ml/min); respiratory exchange ratio (RER); minute ventilation ($\dot{V}_E$, L/min); tidal volume (V_T, ml); respiratory rate (*f*, breaths/min); ventilatory equivalents for O_2 and CO_2 ($\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$); and end-tidal partial pressures of CO_2 ($P_{ET}CO_2$, mmHg). The following parameters of aerobic function were calculated: [16] [17]

• *Peak $\dot{V}O_2$ (mL/min)*: the average $\dot{V}O_2$ for the last 15 s of the ramp was considered representative of the subject's peak $\dot{V}O_2$. A plateau was established if $\dot{V}O_2$ values did not vary by more than 50 mL/min for at least 2 min despite progressive increase in WR.[18][19]

• *$\dot{V}O_2$ "lag phase" duration (s):* the duration of the initial lag phase was estimated by the difference in time between the onset of the ramp and the intersection of two lines: a) a line through the linear phase of the $\dot{V}O_2$ response and b) a line parallel to the time axis through the $\dot{V}O_2$ response preceding the linear phase (see **Figure 1** in the main text) (adapted from [16] and [17]);

• *$\Delta \dot{V}O_2/\Delta WR$ relationship (mL/min/W).* The slope of the linear region of the $\Delta \dot{V}O_2/\Delta WR$ relationship was calculated for each subject as an index of the overall gain of the $\dot{V}O_2$ response, i.e. normal values would indicate adequate metabolic

cost for the production of a given power output.[16][20][21][22] For the accurate calculation, we discarded from the analysis the initial "lag phase" (as described above) or any eventual plateau. A value below the lower limit of normal for each gender (95% confidence interval around mean predicted value) defined an abnormal test result.[22]

• *$\dot{V}O_2$ at the lactate threshold (LT) (mL/min)*. This parameter was estimated by the gas exchange method, inspecting visually the inflection point of $\dot{V}CO_2$ with regard to $\dot{V}O_2$ (modified V-slope) [23] and by the ventilatory method when $\dot{V}E/\dot{V}O_2$ and $P_{ET}O_2$ increased while $\dot{V}E/\dot{V}CO_2$ and $P_{ET}CO_2$ remained stable. For the accurate determination of the LT, two regions were discarded from the analysis: the initial 2 min—during which R decreases—to account for the effects of transient CO_2 storage, and the points beyond the respiratory compensation point.[23] The reading was performed independently by two experienced observers without knowledge of other results or subject identities.

Statistical Analysis

The statistical software package used was IBM™ SPSS™ Statistics version 24. Unpaired t test (or Mann-Whitney test when appropriated) were used to compare between-subject differences. χ^2 test was used to compare frequencies. Association between selected continuous variables was investigated by Pearson's product-moment correlation test. Two-way ANOVA with repeated measures were used to compare symptoms intensity and cardiorespiratory, metabolic, gas

exchange, and operating lung volumes at rest and iso-WR. A $P<0.05$ level of significance was used for all analyses.

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