Total volume/week of physical activity: an underused variable of physical activity in daily life in patients with copd and its association with exercise capacity

Subjects with chronic obstructive pulmonary disease (COPD) may be characterized by muscle dysfunction and symptoms such as dyspnea and fatigue, which may lead to reduced physical activity (PA) levels.[1]

In COPD, functional exercise capacity as measured by the 6-minute walking test (6MWT) is known to be significantly associated with different PA variables such as walking time/day,[2] number of steps/day and time spent/day in different PA intensities, mainly moderate-to-vigorous (MVPA).[3] However, a large systematic analysis concluded that the quality of the evidence for these associations is still relatively low.[4] Furthermore, Mesquita et al.[5] corroborated these findings by showing that changes in the 6MWT are very weakly related to changes in time spent/day in different PA intensities (sedentary: $r = -0.26$, light: $r = 0.25$ and moderate-to-vigorous [MVPA]: $r = 0.24$).

Total volume is a composite variable that corresponds to the product of duration versus intensity of a given effort. It is often used in the context of exercise training, including in patients with COPD.[6] However, it is rarely considered in the context of the total volume of PA in daily life (PADL), especially in the literature of patients with COPD. One can reach the same total PA volume in a certain period through many combinations of time spent in different intensities of PADL, i.e., sedentary, light and MVPA. Moreover, the association of the 6MWT with total PA volume/week has not yet been investigated. Therefore, the aim of this study was to investigate the independent association of functional exercise capacity (assessed by the 6MWT) with total PA volume/week in patients with COPD, as well as to compare this association with those concerning 6MWT and time spent/day in different PA intensities.

A retrospective study was conducted comprising baseline data from subjects with COPD assessed for admission in a pulmonary rehabilitation program performed at the University Hospital of Londrina, Brazil. The present sample concerns the combination of patients from a previously published study[7] and an ongoing study (ClinicalTrials.gov number, NCT03127878). Both studies were approved by the institutional Research Ethics Committee and all participants signed an informed consent term prior to inclusion. Data collection occurred from 2010 to 2019, and the initial assessments, inclusion and exclusion criteria from the two abovementioned studies were similar. Inclusion criteria were: diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[1]; absence of any regular physical training in the preceding year; clinical stability defined as absence of exacerbations within the last month; and absence of severe comorbidities that could interfere with the assessment protocol (e.g., orthopedic, rheumatological, neurological or cardiovascular). Concerning the analysis of the present study, individuals were excluded in cases of unavailable data from the 6MWT or incomplete data from the PADL assessment, i.e., not achieving the pre-established minimum wearing time for a valid day (see below).

Objective assessment of PADL was performed using a validated PA monitor (SenseWear® Armband, BodyMedia, USA).[8] Subjects were instructed to wear the monitor during daytime for 7 consecutive days. A valid day was considered as containing at least 8 h/day of wearing time, excluding sleep periods during the day.[9] Total energy spent during the week was defined as the ''total PA volume/week''. Time spent/day in PA performed at specific intensities (i.e., sedentary [<1.5 metabolic equivalents of task, METs], light [1.5–3 METs], and MVPA [>3 METs]) was also quantified, both in absolute values and adjusted as a percentage of the respective wearing time. Functional exercise capacity was assessed by the best of two 6MWT, performed according to international standards.[10]

Normality in data distribution was evaluated using the Shapiro–Wilk test and results were described as mean ± standard deviation or median [interquartile range 25–75%], accordingly. Correlations were evaluated by the Spearman's coefficient. Multiple regression model was performed to investigate the associations between 6MWT and total PA volume/week, with adjustments for sex, age and FEV_1 %predicted.

The statistical softwares used were SPSS 22.0 (IBM, USA) and GraphPad Prism 6.0 (GraphPad Software Inc., USA). Significance level was defined as $P < 0.05$.

Data from 125 subjects with COPD were screened but 33 of them were excluded due to incomplete assessments. Therefore, 92 subjects were analyzed (46 male; 66 ± 8 years; FEV_1 50 ± 16%predicted; 6MWT 472 ± 73 m; wearing time of the PA monitor 14.4 ± 1.5 h/day; mean ± SD). Median [interquartile range] of total PA volume/week was 1281[1089–1585] MET.min, whereas time spent/day in sedentarism, light activities and MVPA were 569[465–641], 254[147–338] and 32[12–72] min/day, respectively.

There was positive correlation between total PA volume/week and 6MWT ($r = 0.30$; $P = 0.004$). In the multiple regression analysis, total PA volume/week explained 26% of the variation in the 6MWT (independently of sex, age and FEV_1%pred) (Table 1). Time spent/day in each specific intensity (sedentary, light and MVPA) both in absolute values and in percentage of the wearing time, was more weakly correlated with the 6MWT ($0.06 < r < 0.27$), corroborating the previous literature.[4] Furthermore, total PA volume/week was strongly correlated with time spent/day in sedentarism, light activities and MVPA ($r = -0.59$, $r = 0.84$ and $r = 0.79$, respectively; $P < 0.0001$ for all).

This was the first study to show a significant and independent association between functional exercise capacity (i.e., 6MWT) and PADL assessed from a different perspective in COPD: total PA volume/week. This association is welcome in the sense that improvements in exercise capacity may be necessary to make patients more active and less sedentary.[5] Moreover, it was highly correlated with traditional PADL outcomes (time spent/day at different PA intensities). The ''PA volume/week'' perspective reflects

Table 1 Summary of the multiple regression analysis.

Variable	*B*	SE_B	β	95 %CI (LB; UP)
6MWT (m)				
Constant	411.647	65.842		(280.774; 542.510)
Total PA volume/week (MET.min)	0.059	0.021	0.260*	(0.018; 0.100)
Sex	45.593	13.540	0.312*	(18.679; 72.506)
Age (years)	−1.727	0.850	−0.193*	(-3.417; −0.037)
FEV_1 (%pred)	1.478	0.420	0.322*	(0.644; 2.313)

* $P < 0.05$; *B* = unstandardized regression coefficient; SE_B = standard error of the coefficient; β = standardized coefficient; 95% CI = 95% Confidence Interval; LB = Lower Bound; UB = Upper Bound; 6MWT = 6-minute walking test; PA = physical activity; FEV_1 = forced expiratory volume in the first second.

PA guidelines' recommendations and incorporates different intensities of PA into a single and comprehensive outcome. Therefore, this preliminary report suggests that this is a reasonable and promising approach, since increasing total PA volume/week (regardless of whether this increase occurred at any intensity) may be a more realistic way of achieving PADL improvements in severely debilitated patients. Further investigation of its measurement properties (i.e., sensitivity to changes due to interventions such as pulmonary rehabilitation) may advance the understanding of its usefulness. In conclusion, total PA volume/week in daily life is significantly and independently associated with functional exercise capacity in patients with COPD.

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Conflict of interest

The authors have no conflict of interest to disclose.

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Rhodococcus equi infection as inaugural manifestation of idiopathic CD4⁺ lymphopenia: A rare entity and a therapeutic challenge

Introduction

Rhodococcus equi (R. equi) is a facultative intracelular gram-positive coccobacillus which primarily causes zoonotic infection.[1,2] This bacteria is becoming an emerging opportunistic agent in humans.[3] As far as we know, we present the first case of *R. equi* infection in a patient with idiopathic T-CD4⁺ lymphopenia (ICL), a rare condition defined by the repeated presence of a T-CD4⁺ lymphocyte count <300 cells/mm^3 or less than 20% of total T cells without evidence of human immunodeficiency virus (HIV) infection or other condition that might lead to decreased T-CD4⁺ counts.[4]

Case description

In April 2017, a 69-year-old never smoker male presented to the emergency department with cough, left pleuritic thoracalgia and fever during the previous month. He was a retired driver who owned a farm with several animals. Past medical history included hypothyroidism treated with levothyroxine and chronic hepatitis B under entecavir. He had undergone lower left lobectomy in 2004 for a pulmonary mass, but histology of the operative specimen suggested an infectious etiology and the patient received no further treatment or follow-up.

On admission, he had peripheral oxygen saturation of 97% on room air and decreased respiratory sounds in the left pulmonary field.

Blood test revealed white blood cells count of 10 030/μL (83.3% neutrophils and 7.5% lymphocytes) and C-reactive protein of 14.7 mg/dL. Chest X-ray revealed a pleural-based consolidation in the left pulmonary field (Fig. 1A) which was characterized by contrast-enhanced chest computed tomography (CT) showing a 67 × 41 × 24 mm mass on the periphery of the left upper lobe (LUL) with heterogeneous contrast uptake and hypodense areas suggestive of necrosis (Fig. 1B).

The diagnosis of necrotizing pneumonia was established and the patient was hospitalized. Urine was negative for pneumococcal and *Legionella* antigens. Blood cultures were collected. Intravenous amoxicillin/clavulanic acid and azithromycin were started. Bronchofibroscopy and bronchoalveolar lavage (BAL) were conducted without endobronchial lesions. *R. equi* was isolated in both blood cultures and BAL. Antimicrobial susceptibility test (AST) showed sensitivity to imipenem and levofloxacin and intermediate sensitivity to ceftriaxone and ciprofloxacin. Treatment was adjusted for a combination of rifampicin and levofloxacin. Although sensitivity to rifampicin could not be tested, it was included due to its intracellular action and because it is a first choice drug.[3,5] The patient underwent transthoracic aspiration biopsy of the LUL lesion that excluded malignancy and showed signs of *R. equi* infection, namely, histiocyte foci with granulomatous configuration, necrosis and coccoid elements in the macrophage cytoplasm. The diagnosis of necrotizing pneumonia by *R. equi* with hematogenous dissemination was established. Central nervous system, cardiac, abdominal and cutaneous involvement were excluded. HIV and human T-lymphotropic infections were ruled out. Further extensive work-up to detect any other immunodeficiency condition was made leading to the diagnosis of ICL with an initial T-CD4⁺ lymphocyte count of 28 cells/μL.

The patient was discharged after two weeks of intravenous treatment with rifampicin and levofloxacin and instructed to continue oral antibiotic treatment at home.

After one month, blood cultures were negative and radiological improvement was documented with a significant reduction in the LUL mass. After six months of treatment, bronchofibroscopy revealed persistence of *R. equi* in BAL, albeit with significant reduction in the number of colonies.

In April 2018, nearly one year after starting treatment, the patient developed stridor. Rigid bronchoscopy showed obstruction of the lumen of the lower third of the trachea in about 50% due to a protruding lesion (Fig. 1C) in which endoscopic treatment was conducted. Tracheal lesion biopsy revealed chronic inflammation with intracellular bacteria, malakoplakia and no signs of malignancy. Relapse of *R. equi* infection was assumed based on these histopathological findings, but since microbiological isolation was not obtained it was not possible to determine AST. Other potential recurrence sites were investigated leading to the diagnosis of an asymptomatic small brain abscess in magnetic resonance without indication for surgical treatment (Fig. 1D). A new antibiotic regimen was started with ertapenem, gentamycin and linezolide according to the literature.[3,5] One-year treatment was proposed and a central line was placed allowing outpatient parenteral treatment.