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Original Article

Assessing respitatory muscle activity with ^{18}F-FDG-PET/CT in patients with COPD

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Abstract: The purpose of this study was to investigate the metabolic activity of the respiratory muscles in patients with chronic obstructive pulmonary diseases (COPD) and correlate with pulmonary function test results. Thirty-three male patients with a past medical history of smoking and COPD referred to 2-deoxy-2-[^{18}F]-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) because of clinical suspicion of pulmonary cancer were included. The degree of ^{18}F-FDG uptake was visually quantified (grade 0-3) in the respiratory muscles of the neck, intercostal muscles, and abdominal muscles using mediastinal blood pool uptake and liver uptake as references. Visual grade of ^{18}F-FDG uptake was compared to forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) and FEV_1 percent predicted (FEV_1 % pred) by the Wilcoxon-type test for trend. We found significant correlation between the visual grading score and both FEV_1/FVC (P=0.017) and FEV_1 % predicted (P=0.045) for the intercostal muscles. Grade was not significantly associated with pulmonary function tests in either the neck or abdominal muscle groups. ^{18}F-FDG-PET/CT of the respiratory muscles may have potential in characterization of COPD. Future prospective studies with a larger number of subjects should be undertaken to better understand respiratory muscle physiology in patients with COPD.

Keywords: ^{18}F-FDG-PET/CT, COPD, accessory muscles of respiration

Introduction

Emphysema is the one of the chronic obstructive pulmonary diseases (COPD) and is characterized by progressive dilatation of air spaces distal to the terminal bronchiole, along with destruction of alveolar walls [1]. Cigarette smoking is the most common risk factor for development of emphysema, with alpha-1-antitrypsin deficiency being the main documented genetic risk factor [2]. Clinically, COPD can be diagnosed by the presence of forced expiratory volume in the first second (FEV_1) <80% of the predicted postbronchodilator combined with FEV_1/forced vital capacity (FVC) of 0.7 on spirometry [3].

The most significant and disabling symptom of COPD is dyspnea, which is the result of the decreased capacity of respiratory muscles to meet increased mechanical load. In order to increase ventilatory demands, the respiratory center recruits expiratory muscles. Recruitment of expiratory muscles in healthy subjects aids in inspiration by reducing end-expiratory lung volume. In contrast to this, patients with COPD have limited expiratory flow resulting in inability to reduce the lung volume [4]. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), the severity of symptoms as assessed by FEV_1, the number of exacerbations, and the severity of dyspnoea should be used to strategize treatment and management of patients [5].

2-deoxy-2-[^{18}F]-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) has proved its sensitivity in de-

Table 1. Classification of airflow limitation severity in COPD (based on post-bronchodilator FEV_1) as per the GOLD guidelines

In patients with FEV_1/FVC <0.70:		
GOLD 1	Mild	FEV_1 ≥80% predicted
GOLD 2	Moderate	50% predicted ≤ FEV_1 <80% predicted
GOLD 3	Severe	30% predicted ≤ FEV_1 <50% predicted
GOLD 4	Very Severe	FEV_1 <30% predicted

FEV_1: Forced Expiratory Volume in 1 minute; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

tecting various physiological and pathological changes in the metabolism of skeletal muscles and associated soft tissue [6-8]. While imaging modalities as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US) are used to evaluate the structural changes in muscles, ^{18}F-FDG-PET/CT remains the most sensitive functional imaging modality. Through these unique features of ^{18}F-FDG-PET/CT, patients with COPD could receive personalized disease monitoring and treatment based on ^{18}F-FDG-PET/CT combined with spirometry results.

The purpose of this study was to investigate the feasibility of ^{18}F-FDG-PET/CT in assessing respiratory muscles in patients with a known history of clinically diagnosed COPD.

Our hypothesis was that the metabolic activity seen on ^{18}F-FDG-PET/CT in patients with COPD would show correlation with the pulmonary function tests in terms of the severity index.

Methods

Study setting

As part of a prospective study conducted at the Philadelphia VA Medical Center, informed consent was obtained from 67 patients who underwent ^{18}F-FDG-PET/CT scanning for the evaluation of suspected pulmonary cancer. Thirty-three patients were included in our retrospective study if they met the following criteria: 1) past medical history of smoking and COPD, 2) ^{18}F-FDG-PET/CT scans with the accessory muscles of respiration in the field of imaging, and 3) pulmonary function test results with FEV_1/FVC and FEV_1 % pred in accordance with the guidelines established by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (**Table 1**).

Image acquisition

After an overnight fast of at least 4 hours and a confirmed blood glucose concentration below 150 mg/dL, ^{18}F-FDG-PET/CT imaging was performed by a whole-body full-ring PET/CT scanner (Siemens Biograph True Point 64; Siemens Medical Solutions Inc., USA) at 60, 120, and 180 minutes after 5.2 MBq/kg intravenous ^{18}F-FDG administration. Only images acquired after 60 minutes of administration were analyzed. PET images were obtained from mid-skull to mid-thigh in 3D mode and then reconstructed in transverse, coronal, and sagittal views. Low-dose CT imaging was performed for attenuation correction and anatomical orientation.

Image analysis

OsiriX MD software (Pixmeo SARL, Bernex, Switzerland) was used for image analysis. The accessory muscles of respiration, namely, the neck, intercostal and the abdominal muscles were identified on the 3D MIP view of the attenuation corrected (AC) images acquired at 60 minutes after the intravenous administration of the radiotracer.

Statistical analysis

STATA software (Stata/IC Version 10.1, StataCorp, College Station, TX) was used to analyze our results from the visual assessment of the 33 subjects' ^{18}F-FDG-PET/CT in relation to their corresponding PFT results, FEV_1/FVC and FEV_1 % pred. Nonparametric tests for trend of ordered groups were performed, in which the null hypothesis of equality of all medians is tested against the alternative hypothesis of non-decreasing order of medians (with at least one strict increase) across ordered groups [9].

Results

The degree of ^{18}F-FDG uptake was qualitatively assessed in the respiratory muscles of the neck, intercostal muscles, and abdominal muscles (**Figure 1**). We devised a grading system that used blood pool uptake and the liver uptake as reference. Patients were visually graded on a scale of 0: No uptake at all (neck N=4; intercostal N=13; abdominal N=27); 1≤ mediastinal blood pool uptake (SUVmax) (neck

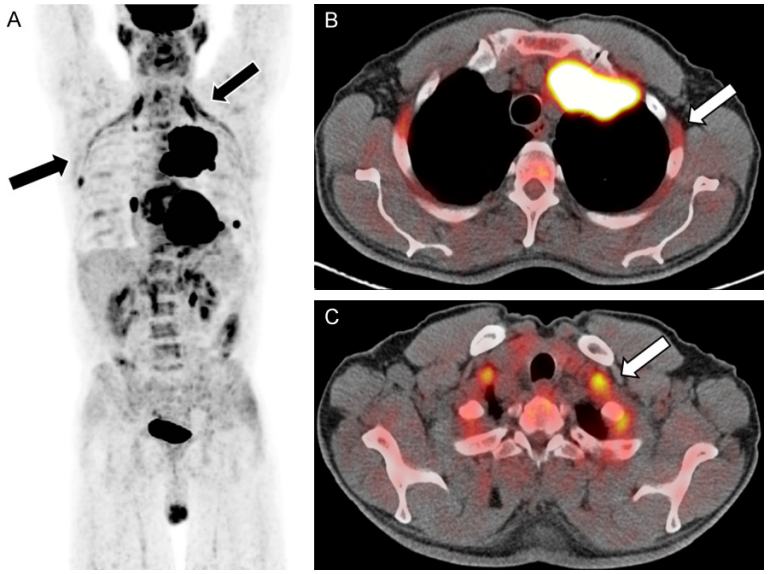

Figure 1. The 3D Maximum Intensity Projection (3D MIP) image showing high metabolic activity in the scalene muscles and the intercostal muscles (A). Fused PET/CT images showing corresponding high intensity uptake in the scalene and the intercostal muscles (B and C). The patient received a scoring of 3, 3 and 0 for the neck, intercostal and abdominal muscles, respectively on the visual assessment of the PET/CT scan. On PFT, the FEV_1/FVC ratio was 0.58 with FEV_1 % pred of 53.1%, correlating with Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2 stage.

N=12; intercostal N=18; abdominal N=4); 2> mediastinal blood pool uptake, ≤ liver uptake (SUVmean) (neck N=26; intercostal N=1; abdominal N=1); and 3> liver uptake (neck N=4; intercostal N=1; abdominal N=1) (**Table 2**). Semi-quantitative measures were also obtained in physiological areas corresponding to reference organs, liver, and blood mediastinal pool structures using a circular region of interest (ROI) with radius of approximately 3 cm away from the edge of the liver and excluding central ducts and vessels (**Figure 2A**), and a ROI within the aorta lumen but with a lower diameter of the vessel, avoiding the vessel wall or areas of calcification for blood mediastinal pool structure (**Figure 2B**). The mentioned semi-quantitative parameters were only used to reinforce the visual analysis interpretation in borderline cases. Visual assessment of ^{18}F-FDG-PET/CT images was correlated with PFT results in 33 male patients with COPD and suspicion of pulmonary cancer (**Figures 3**, **4**). In the intercostal muscles, the visual grading of metabolic activity was significantly associated with both FEV_1/FVC (P=0.017) and FEV_1 % pred (P=0.045) (**Table 3**). This relationship was not significant in either the neck or abdominal muscle groups.

Discussion

To our knowledge, this is the first study to compare visually-assessed ^{18}F-FDG uptake within the accessory muscles of respiration of COPD patients with disease severity. In the present study, metabolic activity within the intercostal muscles was significantly correlated with decreased FEV_1/FVC and FEV_1 % pred values. This adds evidence to support the feasibility of ^{18}F-FDG-PET/CT in the clinical assessment of COPD patients.

The pathophysiology of COPD is multifactorial, involving pro-inflammatory cells, the generation of autoantibodies, and the reduction of antioxidants. Oxidative stress in COPD could be attributed to inhalation of cigarette smoke and air pollutants. The imbalance between oxidants and antioxidants results in further proinflammatory gene expression. All these factors initiate apoptosis, which ultimately leads to alveolar destruction [10]. Clinically, COPD is characterized by lung hyperinflation, which is either static or dynamic. Static hyperinflation is due to loss of elastic recoil whereas dynamic hyperinflation is due to more air being trapped with successive breath as the patient initiates inspiration even before completion exhalation. This results in an “obstructive” pattern on the pulmonary function test (PFT). Hence, the work of breathing is significantly increased in these patients during inhalation in order to overcome elastic recoil of both, chest wall and lung. In these patients, tidal breathing occurs at higher volumes closer to the total lung capacity (TLC). Also, the elastic work increases as inspiration progresses, so that even though it is high initially, it continues to increase as the volume of the lung increases during inspiration [11]. This increased respiratory work in COPD may result in macroscopic and cellular changes to meet the increased ventilatory demands [12]. Sanchez *et al.* demonstrated that COPD patients demonstrated increased glycolytic enzymes (lactate dehydro-

Table 2. Visual grading of metabolic uptake of the respiratory muscles using blood pool and liver uptake as reference, and counts for each grade in the neck, intercostal muscles, and abdominal muscles across 33 subjects

Grade	Visual assessment of metabolic uptake	Counts of each grade		
		Neck	Intercostal	Abdominal
0	No uptake at all	4	13	17
1	≤ mediastinal blood pool uptake (SUVmax)	12	18	4
2	> mediastinal blood pool uptake, ≤ liver uptake (SUVmean)	13	1	1
3	> liver uptake	4	1	1

SUV: Standardized uptake value.

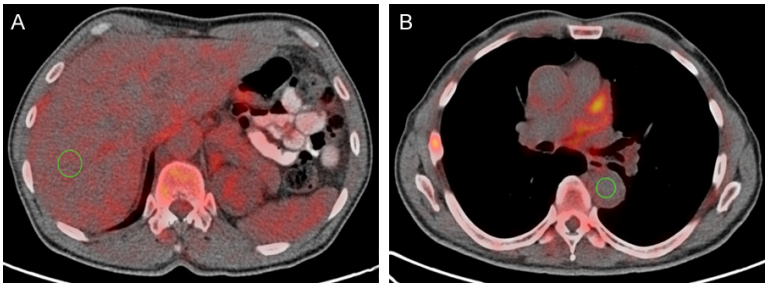

Figure 2. Semi-quantitative assessment was done to reinforce the visual assessment in doubtful cases. A circular region of interest (ROI) with an approximate area of 3 cm^2 was placed away from the edge of the liver. A similar ROI of approximately 2 cm^2 was placed in the lumen of the thoracic aorta to measure the blood pool activity.

genase, hexokinase, citrate synthase, and 3-hydroxyacyl-CoA dehydrogenase) within the fifth internal and external intercostal muscles compared to healthy controls, suggesting that COPD patients have increased intercostal muscle metabolism [13]. Other studies have concluded that COPD patients consistently display strong scalene inspiratory contractions, but not sternocleidomastoid or trapezius [14, 15]. Duiverman *et al.* also concluded that, during an incremental cycle exercise test, the scalene muscles and intercostal muscles display increased activity as measured by electromyography (EMG) in COPD patients relative to controls [16]. On the other hand, Ninane *et al.* demonstrated that patients with COPD contract the rectus abdominis during expiration [17]. In the current study, we found that metabolic activity in intercostal muscles in patients with COPD correlated significantly with PFT results.

^{18}F-FDG is a radioactive glucose analog which, much like conventional glucose, enters the cells via facilitative GLUT (glucose transporters). The GLUT4 isoform is present in the skeletal muscles, apart from other tissues, and is insulin responsive. ^{18}F-FDG-PET/CT presently demonstrates varying degrees of utility in the assessment of physiologic and pathological skeletal muscle activity [18, 19]. The uptake of ^{18}F-FDG in skeletal muscle depends on the number of GLUTs and activity of glucose-6-phosphate, which traps ^{18}F-FDG and varies with the metabolic activity of the muscle; the uptake is high with increased metabolic activity of the muscle [20-23]. Lin *et al.* reported that ^{18}F-FDG-PET/CT was increased in the accessory muscles of respiration in a patient with history of COPD and small-cell lung cancer [24]. This physiologic feature was observed as increased ^{18}F-FDG uptake in the accessory respiratory patients with COPD in the current study.

Other studies have utilized ^{18}F-FDG-PET/CT to assess muscle glucose metabolism in obstructive pulmonary disease. Aydin *et al.* similarly found that glucose metabolism is increased in the chest and abdominal muscles for patients with COPD [24]. This result was reproduced by Osman *et al.*, who showed that excessive ^{18}F-FDG uptake within the diaphragm and intercostal muscles was observed in patients with COPD and obstructive ventilatory impairment [25]. Our study further expands on these studies by directly comparing ^{18}F-FDG activity in COPD patients with clinical PFT results.

Given the utility of ^{18}F-FDG-PET/CT in detection of inflammatory processes, this imaging modality may also be clinical useful in the detection and quantification of the inflammatory course of COPD as well as in the evaluation of respon-

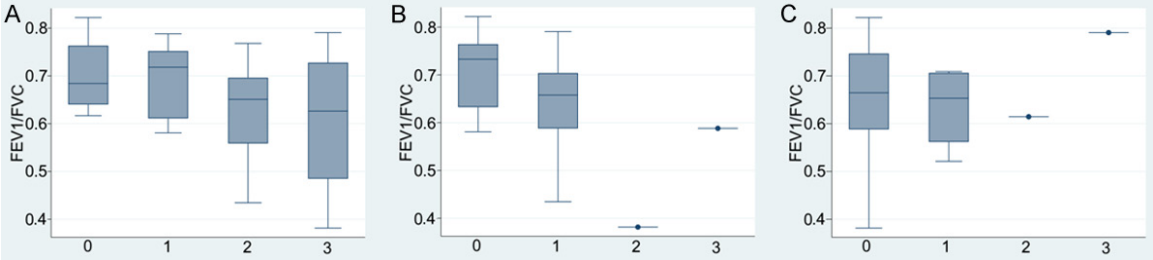

Figure 3. Box-and-whisker plots demonstrating forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) values for subjects with visual grading of (A) neck, (B) intercostal, and (C) abdominal metabolic activity (0: No uptake at all; 1≤ mediastinal blood pool uptake (SUVmax); 2> mediastinal blood pool uptake, ≤ liver uptake (SUVmean); 3> liver uptake).

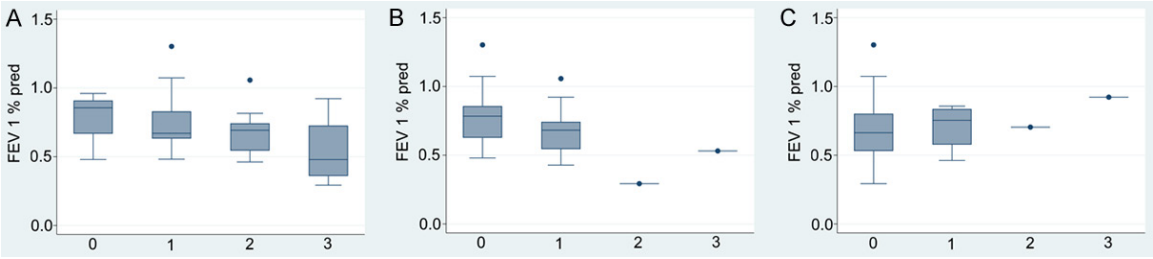

Figure 4. Box-and-whisker plots demonstrating forced expiratory volume in 1 second percent predicted (FEV_1 % pred) for subjects with visual grading of (A) neck, (B) intercostal, and (C) abdominal metabolic activity (0: No uptake at all; 1≤ mediastinal blood pool uptake (SUVmax); 2> mediastinal blood pool uptake, ≤ liver uptake (SUVmean); 3> liver uptake).

Table 3. *P*-values of nonparametric test for trend across ordered groups of 33 subjects' visual grading of metabolic activity and pulmonary function test

Visual grading of metabolic activity	Pulmonary function test	
	FEV_1/FVC	FEV_1 % predicted
Neck	0.15	0.068
Intercostal	0.017	0.045
Abdominal	0.55	0.22

FEV_1/FVC: forced expiratory volume in 1 second/forced vital capacity.

se to treatment. However, this was not the aim of our study.

^{18}F-FDG-PET/CT is a sensitive modality and could have future implications in the diagnostic and therapeutic interventions for the COPD patient population. Among the limitations of our current study is the use of a visually qualitative method to grade ^{18}F-FDG activity within the muscles. However, semi-quantitative measures were also obtained in reference organs in borderline cases making the method more robust and reproducible. Moreover, the patients in the current study were recruited from a prospective study conducted at the Philadelphia VA Medical Center for patients with suspected pulmonary cancer. As most of the patients from VA hospitals are men, only men were included. COPD has been alleged to be a disease of older men, but a recently review have shown support of an increase of COPD in women [26]. Examination of only male subjects limited gender variabilities that are known to exist in pulmonary function [27]. Improved methodology for better muscle characterization is required considering the implications of the neck and abdominal muscle in COPD and the non-significant correlation between the neck and the abdominal and the PFT results in our study.

Conclusion

This study has demonstrated the feasibility of ^{18}F-FDG-PET/CT in assessing metabolic activity of the accessory muscles of respiration in patients with COPD severity ranging from mild to very severe disease as diagnosed by PFT. This observation is consistent with the known pathophysiology that patients with COPD use their accessory respiratory muscles excessively to compensate for airway obstruction. Future

prospective studies with a larger number of subjects are warranted to assess the correlation between COPD severity and metabolic activity in respiratory muscles assessed by ^{18}F-FDG-PET/CT.

Disclosure of conflict of interest

None.

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