Does ^{18}F-FDG Uptake by Respiratory Muscles on PET/CT Correlate with Chronic Obstructive Pulmonary Disease?

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^{18}F-FDG muscle uptake is evident in some benign physiologic processes as seen in the respiratory muscles of patients with chronic obstructive pulmonary disease (COPD) and labored breathing. The purpose of this study was to correlate the presence of COPD with the patterns of ^{18}F-FDG uptake by muscles as demonstrated by PET/CT scans. **Methods:** ^{18}F-FDG PET/CT scans and pulmonary function tests (PFTs) were performed for 63 consecutive patients with newly diagnosed or highly suspected lung cancer. Presurgical pulmonary function tests by way of spirometry examinations were performed as the standard of care. Patients were grouped into those with normal spirometry findings and those with mild to very severe COPD. The guidelines of the Global Initiative for Chronic Obstructive Lung Disease were used for staging COPD and obstructive impairment. A nuclear medicine physician and 2 residents who did not know the COPD status retrospectively reviewed PET/CT scans and kept a log for cases of increased ^{18}F-FDG uptake in the respiratory muscles (diaphragm, intercostal muscles, and scalene muscles). The χ^2 test and Cramer V were used to evaluate the correlation between increased ^{18}F-FDG uptake by muscles and the presence of COPD. **Results:** Sixty-three patients underwent both ^{18}F-FDG PET/CT and PFT within 1 mo of each another without interval therapy. Of the 63 patients, 26 (41%) had no spirometric obstruction and 37 (59%) had spirometric obstruction. Of these, 30 (81%) had a previously established diagnosis of COPD (1 mild, 26 moderate, 9 severe, and 1 very severe). Excessive ^{18}F-FDG uptake was seen in at least 2 of the 3 muscles (diaphragm and intercostal muscles) in 27 (73%) of the 37 patients with COPD and obstructive ventilatory impairment. The severity of COPD and obstruction showed a significant correlation with the presence of abnormal ^{18}F-FDG uptake by any of the 3 muscle types, particularly when 2 groups of muscles were involved (Cramer V = 0.60, χ^2 $P < 0.001$). **Conclusion:** Our study revealed a strong correlation between increased ^{18}F-FDG uptake by respiratory muscles and the presence of COPD.

Key Words: fluorine-18 (^{18}F) fluorodeoxyglucose (FDG); positron emission tomography; PET/CT; chronic obstructive pulmonary disease; COPD; respiratory muscles

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At the beginning of the 21st century, chronic obstructive pulmonary disease (COPD) had replaced tuberculosis as the leading cause of lung-related disease (*1*). COPD is a preventable and treatable lung disease with significant extrapulmonary effects that may contribute to its severity in individual patients. The pulmonary component is characterized by an airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response.

Currently, 16 million Americans have COPD, and an estimated 14 million are underdiagnosed because of a lack of specific signs and symptoms. COPD ranks as the fourth leading cause of morbidity and mortality in the United States, with 96,000 deaths annually (*2*). An estimated 600 million are afflicted by COPD worldwide (*3*). Current trends suggest that it will become the third leading cause of death by 2020 (*4,5*). The use of ^{18}F-FDG PET has been gaining momentum in diagnosing, staging, and restaging many cancers. According to the Academy of Molecular Imaging, there are more than 5,000 PET/CT systems installed worldwide, making it one of the fastest-growing imaging modalities (*6*).

Patients with obstructive pulmonary disease use more of their respiratory muscles to maintain adequate ventilation. Although malignant cells have a higher affinity for ^{18}F-FDG, benign physiologic processes such as muscle inflammation also account for increased uptake due to glycolytic activity (*7*). Artifacts of excessive uptake in the diaphragm,

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intercostal muscles, and scalene muscles have been identified in PET/CT studies (*8*). We hypothesized that such patterns of uptake may be related to an underlying obstructive pulmonary disease. The purpose of this study was to correlate the presence and severity of COPD and obstruction with the pattern of ^{18}F-FDG uptake in patients undergoing PET/CT.

MATERIALS AND METHODS

Patient Selection

This retrospective study was approved by the Institutional Review Board, and the need for informed consent was waived.

A log of patients who had newly diagnosed or highly suspected lung cancer and had undergone PET/CT between June 2004 and February 2006 was compiled. As part of the standard of care at our institution, patients with a high likelihood of lung cancer also underwent PFT by spirometry. Our patient log recorded the ^{18}F-FDG uptake in the respiratory muscles (diaphragm, intercostals, and scalene muscles), body mass index, history of tobacco use, and number of pack-years. These records were then compared with the database of the Pulmonary Function Department at our institution to extract the pulmonary function reports on these patients. Patients who had PET/CT scans and PFT on the same day or within 30 d of each other without interval therapy were included. Patients with prior lung surgery or radiation therapy or who used medications or a nebulizer before the spirometry were excluded. Patients with diabetes were excluded. Sixty-three patients (38 men and 25 women; mean age, 71.4 y) were included in the study. COPD was assessed in these patients according to the recommendations of the Global Initiative for Chronic Obstructive Lung Disease (*9*). All patients presented with dyspnea, and 89% were current or former smokers, 1% had exposure to asbestos, and 1% had radiographic studies suggesting congestive heart failure. A prior diagnosis of COPD was present in 30 (48%) patients, all with stable disease. Review of available medical records and CT scans of the chest did not yield a diagnosis of other respiratory diseases. Also, there was no known metastasis in the head and neck or in the chest wall. Further patient characteristics are reported in Table 1.

TABLE 1
Patient Demographics

Variable	Data
Total number of patients	63
Sex (*n*)	
Male	38
Female	25
Mean age (y)	71.4
COPD (*n*)	
None, based on spirometry	26
Mild	1
Moderate	26
Severe	9
Very severe	1
BMI (*n*)	
<20 (underweight)	4
20–25 (normal weight)	15
25–30 (overweight)	24
>30 (obese)	20
Tobacco abuse (*n*)	
Yes	56
No	7

PET/CT Procedure

Patients fasted at least 4 h before the PET acquisition and received an intravenous injection of approximately 5.18 MBq (0.14 mCi) of ^{18}F-FDG per kilogram, with a maximum of 444 MBq (12 mCi). Blood glucose level was measured immediately before ^{18}F-FDG injection and was less than 200 mg/dL in all patients. Patients were instructed to sit in a quiet injection room without talking during the subsequent 60 min of the ^{18}F-FDG uptake phase and were allowed to breathe normally, without specific instructions, during image acquisition. All scans were acquired using a PET/CT scanner (Gemini; Philips) with an axial coscan range of 193 cm, enabling true whole-body imaging from the top of the head through the bottom of the feet, which is the standard protocol for all patients in our PET center.

CT Acquisition

The CT component of the PET/CT scanner consisted of a 16-slice multidetector helical CT scanner. The gantry allowed for a patient port of 70 cm. Parameters were as follows for 12 or 13 bed acquisitions (from the top of the head through the bottom of the feet): 120–140 kV and 33–100 mAs (based on body mass index), 0.5 s per CT rotation, pitch of 0.9, and 512 × 512 matrix. CT acquisition was performed before emission acquisition. CT data were used for image fusion and the generation of the CT transmission map. In all patients, the arms were placed above the patient's head for image acquisition. The CT images were obtained without oral or intravenous contrast material according to the usual PET/CT protocol in our institution.

PET Acquisition and Image Reconstruction

Emission data were acquired for 12–13 bed positions (193-cm coverage, identical to the CT protocol). Emission scans were acquired at 3 min per bed position. The field of view was from the top of the head to the bottom of the feet in all patients. The 3-dimensional true whole-body acquisition parameters consisted of a 128 × 128 matrix and an 18-cm field of view with a 50% overlap. Reconstruction was performed using the 3-dimensional row action maximum-likelihood algorithm (*10*).

Image Analysis

PET/CT images were retrospectively evaluated on Syntegra workstations (Philips) by a board-certified nuclear medicine physician and 2 residents who did not know the patients' COPD or obstructive impairment status. Increased uptake in the diaphragm, intercostal muscles, and scalene muscles was recorded in a log. The muscles were consid-

ered positive if the uptake was greater than the intensity of uptake in the mediastinum on visual assessment. Visualization was best in the coronal view for the intercostal and scalene muscles and in the sagittal view for the diaphragm.

Spirometry Procedure

Pulmonary function tests with spirometry were performed on an Elite DX Body Plethysmograph (Medical Graphics). Patients were instructed to discontinue all nebulizers, inhalers, and lung-related oral medications 48 h before the examination unless indicated otherwise by the ordering physician. Albuterol was available during the scan if the patient could not tolerate the examination. However, these patients were excluded from the study. Patients performed various breathing techniques with a mouth piece attached to the spirometer.

Spirometry Analysis

The 2 values extracted from the spirometry reports were the actual forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) and the predicted FEV1. The patients' obstructive impairment was staged according to the Global Initiative for Obstructive Lung Disease criteria, which use the actual FEV1/FVC and the predicted FEV1. Patients were staged according to the spirometry results as having normal function (actual FEV1/FVC $\geq$ 70%), mild obstruction (actual FEV1/FVC $<$ 70% and predictive FEV1 $\geq$ 80%), moderate obstruction (actual FEV1/FVC $<$ 70% and predictive FEV1 $\geq$ 50% but $<$ 80%), severe obstruction (actual FEV1/FVC $<$ 70% and predictive FEV1 $\geq$ 30% but $<$ 50%), or very severe obstruction (actual FEV1/FVC $<$ 70% and predictive FEV1 $<$ 30%) (*11*). Patients were then categorized into 2 groups: those with normal spirometry results (no obstruction) and those with mild to very severe obstruction.

Statistical Analysis

Data were analyzed using the χ^2 test to evaluate the correlation between patients' obstruction status and the excessive ^{18}F-FDG uptake in the 3 groups of muscles. Cramer V was calculated to show the strength of association between obstructive impairment and ^{18}F-FDG uptake in the respiratory muscles.

RESULTS

Of the 63 studied patients, 26 (41%) had no spirometric obstruction (Figs. 1A, 2A, and 3A), and 37 (59%) were diagnosed with COPD (established diagnosis in 30 subjects) and obstructive impairment. The most likely attributable cause of obstruction in the small minority without a previously established diagnosis was COPD, given the preponderance of smokers in the populations studied and the referral bias for an established or suspected diagnosis of lung cancer. Further, review of available medical records and radiologic studies did not point to an alternate diagnosis of obstructive impairment. Thus, available clinical history and spirometry essentially confirmed that the patients included 1 with mild, 26 with moderate, 9 with severe, and with 1 with very severe COPD.

The PET/CT scans revealed increased ^{18}F-FDG uptake in both the diaphragm and the intercostal muscles in 27 (73%) of the 37 COPD patients. Uptake for the 37 COPD and obstructive impairment patients had the following frequencies: 9 (24%) had increased uptake in the scalene muscles (Fig. 1B), 29 (78%) had increased uptake in the intercostal muscles (Fig. 2B), and 31 (84%) had increased uptake in the diaphragm (Fig. 3B). By comparison, only 1 patient (4%) of the 26 patients with no spirometric obstruction (non-COPD) showed uptake in both the diaphragm and the intercostal muscles. Increased ^{18}F-FDG uptake was present in the scalene muscles in 6 (67%) of 9 patients with severe COPD. No ^{18}F-FDG uptake was present in the scalene muscles in the mild COPD or non-COPD groups.

The χ^2 test demonstrated a significant correlation between the excessive ^{18}F-FDG uptake and the presence of COPD, with a P value of less than 0.001. A Cramer V of 0.60 satisfied the correlation between uptake and obstructive impairment status.

DISCUSSION

Airflow obstruction in COPD may be identified by checking for the presence of wheezes on auscultation or by timing the end of expiration while auscultating over the trachea to measure forced vital time. However, forced expiratory spirometry is the gold standard for diagnosing and quantifying the presence of airflow obstruction (*12*).

Despite a handful of case reports, to our knowledge this was the first study to correlate increased ^{18}F-FDG uptake by muscles and the presence of obstruction in COPD with spirometry (*13–15*). One study discussed similar findings but used only non–attenuation-corrected PET images, not PET/CT (*16*). Another study assessed both obstructive and restric-

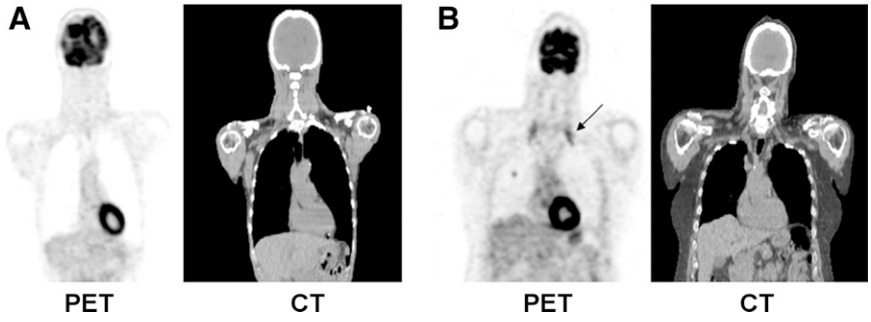

FIGURE 1. (A) Patient with no COPD showing no uptake in scalene muscles. (B) Patient with COPD showing intense ^{18}F-FDG uptake in scalene muscles bilaterally (arrow).

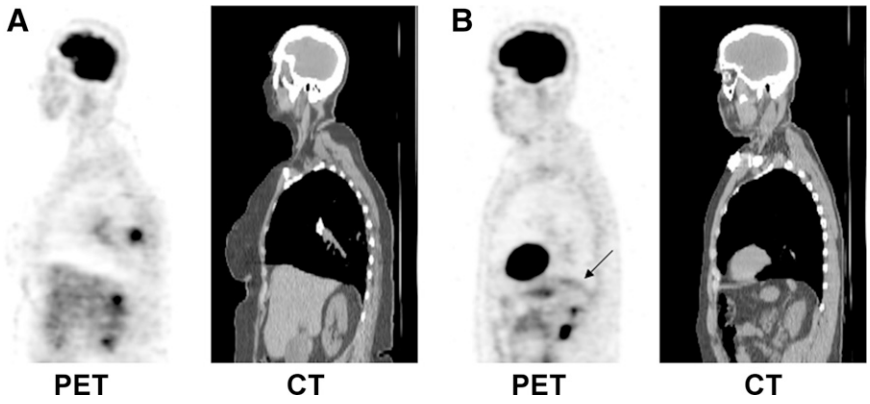

FIGURE 2. (A) Patient with no COPD showing no uptake in diaphragm. (B) Patient with COPD showing intense ^{18}F-FDG uptake in diaphragm (arrow).

tive lung diseases (*17*). Both studies had a smaller sample size, and neither correlated with spirometry. To the best of our knowledge and after an extensive literature review, our study had a relatively larger sample size than other studies, was the only study to use PET/CT for increased localization of the muscles involved, and was the only study to incorporate the gold standard spirometry results.

In our study, we observed increased ^{18}F-FDG uptake in the diaphragm, the intercostal muscles, and the scalene muscles. In 73% of patients, increased ^{18}F-FDG uptake in at least 2 of the 3 muscle groups was present. For severe to very severe cases of COPD, the intensity of uptake in these 2 muscle groups was markedly increased. In addition, the frequency of increased uptake in the scalene muscles was higher in severe cases of COPD. In contrast, the non-COPD patients showed only 1 case of unusual uptake in both muscle groups and no uptake in the scalene muscles.

COPD patients have abnormal respiratory dynamics. Functional lung volume decreases while the dead air space increases, causing an overall increase in lung volume compared with healthy subjects (*18*). The dead air spaces are caused by scarring from damaged alveoli, inflammation from smoking, and abnormal cell growth found in our study population of lung cancer patients. Because of this pathologic increase in nonfunctional volume, the workload increases for both the respiratory muscles and the accessory muscles of breathing (*19*).

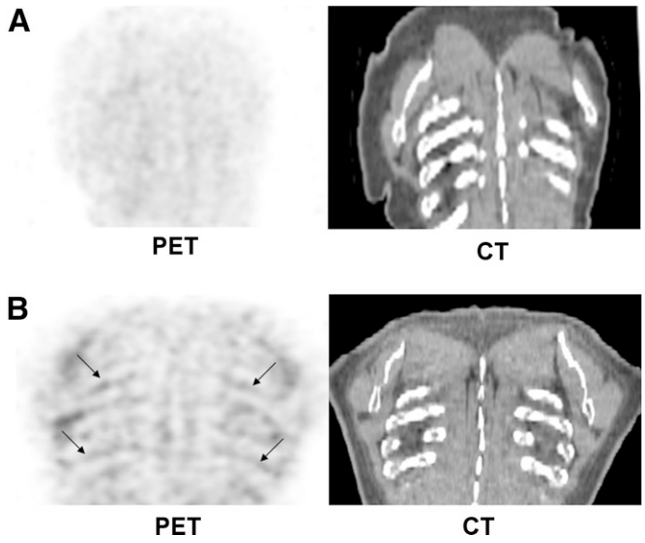

FIGURE 3. (A) Patient with no COPD showing no uptake in intercostal muscles. (B) Patient with COPD showing intense ^{18}F-FDG uptake in intercostal muscles (arrows).

In healthy subjects, the main inspiratory muscles are the diaphragm and external intercostal muscles. In subjects breathing at rest, the diaphragm does most of the work necessary to expand the lung, chest, and abdominal cavity. Of the 26 patients with no COPD, 19 (73%) were ^{18}F-FDG–negative in the diaphragm, 24 (91%) in the intercostal muscles, and 26 (100%) in the scalene muscles. Scalene uptake was present in 6 (67%) of 9 patients with severe COPD and 4 (15%) of 26 patients with moderate COPD. Interestingly, uptake in the scalene muscles was not seen in patients with mild COPD or no COPD. Therefore, increased uptake in the scalene muscles may indicate severe underlying COPD.

In COPD patients, the normal respiratory muscles have difficulty maintaining the minimum required level of alveolar ventilation. These muscles must work harder to maintain adequate ventilation at all times. At times, the body uses additional neck muscles, such as the scalene, to compensate for the increased workload (*20*).

Inflammatory processes of the diaphragm, the intercostal muscles, and the scalene muscles occur as a result of the higher muscle use. The injected ^{18}F-FDG accumulates chiefly in pathologic lesions, creating high contrast between the tumors and surrounding tissues, thus forming the basis for the success of ^{18}F-FDG PET in oncology. ^{18}F-FDG also accumulates in muscles because of their use of ^{18}F-FDG. Under fasting conditions, normal muscles accumulate little ^{18}F-FDG unless they are exercised heavily before the injection and uptake. Benign physiologic ^{18}F-FDG uptake in respiratory muscles is frequently noted in patients with COPD and labored breathing. Such uptake was noted in the diaphragm, the intercostal muscles, and the scalene muscles. Fast twitch muscle fibers are used at higher frequencies in these groups of muscles. These fast twitch

fibers have a high level of glycolytic demands, thus contributing to the increased uptake pattern seen in our study (*21*).

Our study was not without limitations. We hypothesized that the uptake pattern as seen in the 3 muscles would correlate with different stages of COPD and thus reviewed only the subjects with obstructive ventilatory impairment, most of whom had an established diagnosis of COPD. The few who had obstructive impairment but no previous established diagnosis did not have an alternate diagnosis either radiographically or on review of available medical information. Therefore, we cannot exclude a remote possibility of another diagnosis leading to obstructive impairment. The study showed a trend toward the association of severe COPD and increased uptake in the scalene muscles. However, this study did not demonstrate a significant association between patterns of muscle uptake and various stages of COPD. Our study included too few mild and very severe cases of COPD to allow us to draw statistically valid conclusions. Also, an inclusion bias was present in our study because healthy volunteers and patients with other obstructive diseases were not included. However, ^{18}F-FDG PET/CT is not approved for the evaluation of COPD for this population and would result in a large financial burden if both PET/CT and spirometry were performed. Furthermore, quantitative analysis of muscle uptake was not used in our study. Given the diffuse uptake in large muscles, we elected not to do quantitative analysis, believing that qualitative visual analysis was sufficient. Several studies on various types of cancers have shown the qualitative method of evaluation to be as accurate as quantitative evaluation (*22,23*). In addition, the issue of radiation exposure would have been a problem in both these groups. An ^{18}F-FDG PET/CT scan exposes a person to 18 mSv of radiation. This is equivalent to 6 times the annual background radiation limits (3 mSv/y). Therefore, we selected patients with newly diagnosed or suspected lung cancer to overcome these obstacles.

CONCLUSION

Our study revealed a strong correlation between increased ^{18}F-FDG uptake by muscles and the presence of COPD. COPD causes distinctive patterns of excessive ^{18}F-FDG uptake secondary to labored breathing that can be detected by PET/CT. We continue to acquire data and increase our sample size to further elucidate the role of ^{18}F-FDG PET/CT in grading and staging COPD, as well as in evaluating response to medications for COPD.

Although spirometry remains the preferred method of determining COPD, the results of our study suggest that patterns of ^{18}F-FDG muscle uptake may help identify, at least qualitatively, the presence of COPD and may be useful for follow-up. When present, increased ^{18}F-FDG uptake in the diaphragm, intercostal muscles, or scalene muscles should raise the possibility of COPD and not be dismissed as a mere artifact or normal variant, particularly if findings on the lung window of the CT portion of PET/CT support such a diagnosis. COPD is a controllable condition; with the correct therapeutic regimen, COPD patients' quality of life can dramatically improve. Furthermore, the presence of COPD may play a major role in determining patient's candidacy for lung surgery.

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