Positron emission tomography in chronic obstructive pulmonary disease

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Abstract

The purpose of this paper was to systematically search the literature on ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) in the management of chronic obstructive pulmonary disease (COPD) and to provide a concise review of the reported results. *Papers were searched* through PubMed, EMBASE and Cochrane Library using the MESH terms "pulmonary disease, chronic obstructive", "pulmonary emphysema", and "positron-emission tomography". Of the 38 citations from the search and from browsing the literature lists of selected articles, seven relevant reports were identified. The sparse and heterogeneous literature available *provide some indication that* ^{18}F-FDG-PET could prove useful in COPD by a) differentiating COPD from chronic asthma and alpha-1-antitrypsin deficiency, b) measuring pulmonary and systemic inflammation to guide treatment and estimate prognosis, c) quantifying respiratory muscle use, and d) diagnosing cor pulmonale. *In conclusion*, the role of ^{18}F-FDG-PET in diagnosing and managing COPD patients seems to be promising and deserves to be further studied.

Introduction

Chronic obstructive pulmonary disease (COPD) is the number four leading cause of death worldwide and hereby constitutes a major burden for patients and society. To a large extent, however, the disease is preventable, and, when correctly diagnosed, treatment options are available [1].

Diagnosis of COPD is based primarily on spirometry which typically demonstrates fixed bronchial obstruction. However, this pathophysiological measurement reflects a very broad disease spectrum ranging from predominant emphysema with destruction of alveolar septa, diffusion impairment and loss of elastic recoil to mainly bronchial inflammation with mucus production and remodeling of the airways. In addition, chronic asthma may present with fixed bronchial obstruction and constitutes a diagnostic challenge. Rarely, COPD is caused by alpha-1-antitrypsin deficiency (AATD). A common feature of all obstructive pulmonary diseases is dynamic hyperinflation, which results in excessive use of respiratory muscles to overcome the increased work of breathing. In addition, cor pulmonale is a consequence of COPD in more advanced stages. Bronchial inflammation, bronchoconstriction and dynamic hyperinflation are all important pathophysiologic components of COPD, but recently focus has been on systemic inflammation as a consequence of COPD, and patients with COPD is found to have higher levels of systemic biomarkers of inflammation [2, 3]. These patients probably have a worse cardiovascular risk profile and prognosis [4].

Basic treatment modalities in stable COPD are smoking cessation, various vaccinations, pharmacotherapy, long-term oxygen therapy and pulmonary rehabilitation. According to the latest strategy from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), treatment should be based on grading the disease severity, primarily by means of the measured forced expiratory volume in the first second (FEV_1), number of exacerbations, and by the severity of dyspnea [1]. However, an even more individually based treatment could prove valuable due to the heterogeneity of COPD. Positron emission tomography with fluorine-18-fluorodeoxyglucose (^{18}F-FDG-PET) depicting increased glucose metabolism has been studied to some degree during the last decade to demonstrate both pulmonary and systemic inflammation in COPD, to visualize respiratory muscle activity and right heart function. This paper reviews these reports.

Material and methods

We searched PubMed on March 29 2013 using the combination of the MESH terms "pulmonary disease, chronic obstructive", "pulmonary emphysema" and "positron-emission tomography". This search resulted in 34 articles, and similar searches in the EMBASE database and Cochrane Library resulted in four additional papers. We did not include ongoing studies in this review.

Of these 38 articles, 33 papers did not meet the pre-specified criteria for further review due to the following: a) topic of article was not relevant for this review (23 articles) [5-27], b) article was not an original paper (3 reviews, 3 case reports, 1 editorial) [28-34], c) only conference abstract was available (1 paper) [35], and finally d) language was non-English (2 papers) [36, 37]. Some papers fulfilled more than one exclusion criteria (e.g. non-English and not relevant).

Left for review were five articles [38-42], and a thorough search of their reference lists revealed two additional papers [43, 44].

Results

COPD and pulmonary inflammation

Jones and co-workers performed ^{18}F-FDG-PET in 6 patients with COPD (inclusion criteria FEV_1 <60% and reduced diffusion capacity), 6 patients with chronic asthma (defined by at least partially reversible airflow limitation and normal/supranormal diffusion capacity) and 5 never-smoking controls. The pulmonary ^{18}F-FDG uptake in COPD patients was significantly higher than in asthmatic and normal subjects [44]. Recently, other researchers examined 10 patients with AATD (mean FEV_1 1.7L), 10 patients with non-AATD-COPD (30%≤FEV_1<80%, mean FEV_1 1.7L), and 9 normal subjects, with ^{18}F-FDG-PET. Patients with AATD had pulmonary ^{18}F-FDG uptake comparable to normal subjects, but patients with non-AATD-COPD had a higher pulmonary ^{18}F-FDG uptake which correlated to both the level of FEV_1 and the distribution of emphysema on computed tomography [38]. Other researchers reported a study of 49 patients which were examined by diagnostic chest computed tomography and ^{18}F-FDG-PET. When corrected for the partial volume effect, they found that the degree of pulmonary inflammation (visualized by ^{18}F-FDG-PET) was correlated to the severity of emphysema, much like previous study [38], but the more recent group of researchers [42] only found this when data were corrected for partial volume effect emphasizing the importance of valid quantification strategies.

COPD and systemic inflammation

Other investigators prospectively studied aortic inflammation (as a measure of systemic inflammation) with ^{18}F-FDG-PET in 19 patients of whom 7 were ex-smokers with COPD with a mean FEV_1 of 1.2L and 7 ex-smokers without COPD (mean FEV_1 3.1). Despite similar systemic blood pressure and slightly lower mean age, the mean target-to-background ratio in the aorta was significantly higher in COPD patients than in ex-smoking patients without COPD (1.60 vs. 1.34, P=0.001). No other potential explanation for this difference was found than COPD [40].

COPD and respiratory muscle activity

One paper reported a retrospective study comprising 25 patients with COPD and 25 without COPD who had undergone ^{18}F-FDG-PET for other reasons than COPD, e.g. malignancy. The authors demonstrated a significantly increased ^{18}F-FDG uptake in respiratory muscles in all patients with COPD compared to the non-COPD patients [41]. This finding was confirmed by other researchers who retrospectively studied 26 patients without COPD and 37 with COPD in a population referred to ^{18}F-FDG-PET imaging for evaluation of lung cancer. They found increased ^{18}F-FDG uptake in both the diaphragm and intercostal muscles in 73% of the COPD patients compared to only 4% in the non-COPD group. There was no significant correlation between lung function and ^{18}F-FDG accumulation in the respiratory muscles [39].

COPD and right heart function

Other researchers reported results of a retrospective study of 14 patients with increased ^{18}F-FDG uptake in the intercostal musculature. These patients had undergone ^{18}F-FDG-PET due to various malignant diseases, but had, in addition, multiple underlying cardiorespiratory diseases including COPD. Ten had increased ^{18}F-FDG uptake in their intercostal musculature only, while 4 had also a prominent right ventricular uptake and these 4 had pulmonary hypertension confirmed by echocardiography [43].

Discussion

None of the studies described in this review were sufficiently sized to allow more general judgments on the use of ^{18}F-FDG-PET in COPD, the role of which has yet to be defined. All studies were descriptive or exploratory in nature, and, thus, their results cannot be implemented into clinical practice. Therefore, this discussion should also be considered as preliminary. However, important suggestions could be retracted from the available literature.

The first important finding was that patients with AATD and chronic asthma do not exhibit increased pulmonary ^{18}F-FDG accumulation in contrast to non-AATD-COPD patients. If confirmed by future studies, ^{18}F-FDG-PET could become valuable in distinguishing between these conditions.

The second point was that ^{18}F-FDG accumulation is highest in areas of emphysema and probably correlated to FEV_1. This could turn out important, e.g. in the planning of lung volume reduction (surgical or bronchoscopic) and for grading of disease severity.

The third important aspect was that increased systemic vascular inflammation in COPD (in the shape of enhanced aortic ^{18}F-FDG uptake) appears to be quantifiable with ^{18}F-FDG-PET. This is essential, as systemic inflammation is correlated to increased cardiovascular risk and a worse prognosis, in particular in COPD patients [4].

The fourth information from these studies was that some COPD patients exhibit increased ^{18}F-FDG accumulation in respiratory muscles as a sign of increased muscular activity. This could turn out to be useful for the triage of patients suitable for pulmonary rehabilitation and for monitoring of treatment response.

The fifth suggestive finding was that patients with cor pulmonale in COPD had a two-fold increased uptake of ^{18}F-FDG in the right ventricular wall. These patients have a worse prognosis, and the presence of cor pulmonale alters treatment strategy including the threshold for long-term oxygen therapy [1]. Whether an increased ^{18}F-FDG uptake can

be used for the diagnosis of cor pulmonale remains to be shown, but in itself it is interesting as this finding suggests a shift in right ventricular substrate preference from free fatty acids to glucose [45].

The ^{18}F-FDG-PET scan allows for a multitude of quantitative measurements. All studies in this review used quantification to some extent, some emphasizing the importance of quantifying data as compared to simple visual assessment of images. Thus, along with a clear need for further and more comprehensive studies to elucidate the role of ^{18}F-FDG-PET in the management of COPD, there is a call for an enhanced use of internationally more standardized and better validated quantitative image analysis tools [46].

In conclusion, the role of ^{18}F-FDG-PET in the management of COPD is still to be established. However, some evidence exists that a) pulmonary ^{18}F-FDG accumulation appears different in chronic asthma, AATD, and COPD, b) pulmonary ^{18}F-FDG accumulation is likely correlated to emphysema distribution and severity, c) systemic inflammation in COPD can probably be visualized and quantified by ^{18}F-FDG-PET, d) respiratory muscle use in COPD is presumably quantifiable by ^{18}F-FDG-PET, and finally e) ^{18}F-FDG-PET appears able to detect cor pulmonale.

The authors declare that they have no conflicts of interest.

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