Pulmonary 2-deoxy-2-[^{18}F]-fluoro-D-glucose uptake is low in treated patients with idiopathic pulmonary arterial hypertension

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Abstract: Glucose metabolism measurement using 2-deoxy-2-[^{18}F]-fluoro-D-glucose (^{18}FDG) positron emission tomography (PET) could provide in vivo information about pulmonary vascular remodeling. The purpose of this study was to assess whether pulmonary ^{18}FDG uptake in idiopathic pulmonary arterial hypertension (IPAH) patients changes and, if so, to determine whether the change is related to disease severity and survival. Sixteen IPAH patients who were treated with IPAH-specific therapy and 7 patients who had a myocardial infarction (MI) without pulmonary hypertension were included. IPAH disease severity was determined using the 6-minute walk test and right heart catheterization 2 days before ^{18}FDG PET. Regions of interest were defined for left and right lungs, and standardized uptake values (SUVs), normalized to body weight, injected dose, and plasma glucose level, were derived. Mean SUVs for IPAH left and right lungs were 0.40 ± 0.26 and 0.44 ± 0.18 ($P = 0.32$), respectively. In MI patients, SUVs were 0.38 ± 0.13 and 0.35 ± 0.10 ($P = 0.24$) in left and right lungs, respectively. Total lung SUVs were similar in IPAH and MI patients (0.41 ± 0.19 vs. 0.37 ± 0.11; $P = 0.56$). There was no correlation between SUV and IPAH disease severity parameters. In addition, lung SUV did not predict survival in IPAH patients (hazard ratio, 1.155; 95% confidence interval, 0.16–8.26; $P = 0.88$). In conclusion, pulmonary ^{18}FDG uptake in treated IPAH patients is low and is not associated with disease severity and survival, thereby limiting its clinical use in patient care.

Keywords: positron emission tomography, glycolysis, pulmonary hypertension, glucose analogue, nuclear medicine.

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INTRODUCTION

To date, treatment of pulmonary arterial hypertension (PAH) has been directed toward reduction of pulmonary vascular remodeling, i.e., vasoconstriction and proliferation of pulmonary artery smooth muscle cells (PASMCs).[1] Treatment effects can be monitored using the 6-minute walk test, right heart catheterization, cardiopulmonary exercise testing, and serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels.[2] Many of these parameters, however, are measures of right ventricular function and are rather indirect indicators of changes in lung vasculature. In pulmonary vascular remodeling, cellular (glucose) metabolism and mitochondrial function are abnormal,[3,4] but methods to noninvasively measure abnormal remodeling and metabolism of the pulmonary vasculature are not available in the clinic yet.

Glucose metabolism can be measured using 2-deoxy-2-[^{18}F]-fluoro-D-glucose (^{18}FDG) positron emission tomography (PET). ^{18}FDG is an analogue of glucose that cannot be catabolized after phosphorylation to ^{18}FDG-6-PO_4, and therefore it is essentially trapped in cells. This accumulating signal can be visualized and measured using PET.[4,5] Recently, Marsboom et al.[3] reported increased in vivo pulmonary ^{18}FDG uptake in two rat models of PAH, which subsequently decreased after PAH treatment. These data suggest that ^{18}FDG PET may be a useful tool for evaluating response to treatment in patients. In addition, two pilot studies have reported increased ^{18}FDG uptake in the lungs of patients with idiopathic PAH (IPAH), but no relationship between ^{18}FDG uptake and disease severity has been shown.[6,7] Therefore, the purpose of the present study is twofold: (1) to measure ^{18}FDG uptake in the lungs of IPAH patients and (2) to relate these measurements to PAH disease severity and survival.

SUBJECTS AND METHODS

Patients

Patients with IPAH who had undergone ^{18}FDG PET for cardiac research purposes, as described elsewhere by Wong et al.,[8] were retrospectively included in the current analysis. Briefly, 16 patients with IPAH who had been receiving IPAH treatment and were clinically stable for at least 3 months were included. To assess clinical and hemodynamic characteristics, they underwent a 6-minute walk test and right heart catheterization 2 days prior to the PET study.[8] In addition, ^{18}FDG scans from 7 patients who had a myocardial infarction (MI) were included as a comparison group. Pulmonary hypertension secondary to pulmonary venous congestion after MI was excluded by echocardiography in these patients. The study was approved by the Medical Ethics Review Committee of the VU University Medical Center, and each patient provided written informed consent prior to inclusion.

Data acquisition

The scanning protocol has been described in detail elsewhere.[8] Briefly, patients had to fast overnight, and 2 and 1 hours prior to ^{18}FDG injection they received a single oral dose of 250 mg of acipimox (Nycomed, Hoofddorp, Netherlands) and a carbohydrate- and protein-enriched meal for glucose loading.[9] All scans were performed using an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN) in 3D acquisition mode. Before intravenous injection of ^{18}FDG, a 10-minute transmission scan was performed to correct the subsequent emission scan for tissue attenuation. Starting at the time of ^{18}FDG injection, a dynamic emission scan was acquired for 60 minutes (39 frames with increasing frame duration). Venous blood samples were drawn to measure serum glucose and free fatty acid levels at 30, 40, and 50 minutes after the beginning of the scan in IPAH patients. MI patients were prepared in the exact same way and underwent static imaging 45–60 minutes after ^{18}FDG injection, with serum glucose level measurement at the beginning of the scan.

Data analysis

Sinograms were reconstructed and processed as described elsewhere.[10,11] In addition, for pulmonary ^{18}FDG measurements, two regions of interest (comprising entire left and right lungs) were drawn on transaxial planes (Fig. 1). The number of planes used for analysis ranged from 8 to 13 per patient (mean, 9.4 ± 1.8 planes), with a mean total volume of interest for left and right lungs, respectively, of 54 ± 28 and 78 ± 23 mL in IPAH patients and 180 ± 113 and 264 ± 87 mL in MI patients. In addition, in IPAH patients, four separate regions of interest were drawn

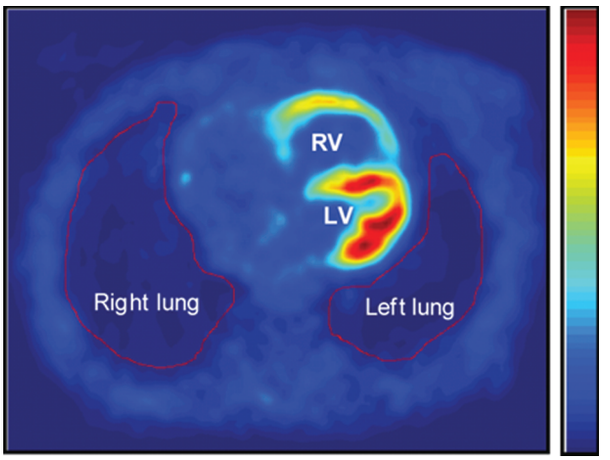

Figure 1. Typical example of a transaxial 2-deoxy-2-[^{18}F]-fluoro-D-glucose (^{18}FDG) positron emission tomography image from an idiopathic pulmonary arterial hypertension (IPAH) patient, acquired 55–60 minutes after ^{18}FDG administration. The color scale represents ^{18}FDG uptake, ranging from dark blue (lowest uptake) to dark red (highest uptake). LV: left ventricle; RV: right ventricle. Red lines indicate total lung regions of interest.

in the anterior or posterior parts of the left and right lungs (mean volume of interest, 11 mL).

Standardized uptake values (SUVs) were calculated by normalizing obtained tissue radioactivity concentrations to body weight and injected dose and by correcting for plasma glucose levels, the latter normalized to a (normal) glucose level of 5 mmol L^{-1}.[12] SUV was determined 50–60 minutes after ^{18}FDG administration in IPAH patients. Patlak analysis was performed to calculate the metabolic rate of glucose uptake, which is the product of the influx rate constant (K_i) and serum glucose concentration.[13] To obtain K_i, an image-derived input function from the ascending aorta blood pool was used.

Statistical analysis

SUVs for left and right lungs were compared using the paired Student *t* test. Differences in SUVs at different regions of interest were tested by one-way analysis of variance with Bonferroni post hoc analysis. IPAH and MI patients were compared using the unpaired Student *t* test. Correlations between SUV and clinical parameters were determined by Pearson linear regression. Kaplan-Meier survival was stratified by the median value of total lung SUV for all patients and compared by the log-rank test. Survival was measured from time of PET until cardiopulmonary death or the time of analysis (interquartile range, 24–50 months). Data are shown as mean ± standard deviation. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical and hemodynamic characteristics of all patients are listed in Table 1. Figure 1 shows a typical example of an ^{18}FDG scan in an IPAH patient, demonstrating low ^{18}FDG uptake in the lungs compared with that in the heart. The mean injected dose of ^{18}FDG was 181 ± 16 MBq in IPAH patients and 382 ± 20 MBq in MI patients. The mean left and right lung SUV was 0.40 ± 0.26 and 0.44 ± 0.18 ($P = 0.32$), respectively, in IPAH patients and 0.38 ± 0.13 and 0.35 ± 0.10 ($P = 0.24$), respectively, in MI patients (Fig. 2*a*). Total lung SUV was also similar in IPAH and MI patients (0.41 ± 0.19 vs. 0.37 ± 0.11; $P = 0.56$). Analysis of four separate regions of interest in the lung fields of IPAH patients did not show regional differences in SUV ($P = 0.51$; Fig. 2*b*). There was no correlation between mean total lung SUV and any of the following PAH parameters: 6-minute walk distance ($r^2 = 0.008$, $P = 0.74$), mean pulmonary artery pressure ($r^2 = 0.115$, $P = 0.20$), pulmonary vascular resistance ($r^2 = 0.095$, $P = 0.25$), and NT-proBNP ($r^2 = 0.021$, $P = 0.59$; Fig. 3). Patlak analysis to calculate the metabolic rate of glucose uptake gave negative results and therefore could not be performed. Four IPAH patients did not survive until the current analysis. Figure 4 shows that SUV did not predict survival in this cohort of IPAH patients (hazard ratio, 1.155; 95% confidence interval, 0.16–8.26; $P = 0.88$).

DISCUSSION

This study is a first attempt to correlate pulmonary ^{18}FDG uptake in IPAH patients with disease severity. The main results of this study show that pulmonary ^{18}FDG uptake in treated IPAH patients is similar to that in MI patients without pulmonary hypertension and is not associated with severity of IPAH or survival.

Our data do not confirm the results of Xu et al.,[6] who demonstrated higher ^{18}FDG SUV in 4 IPAH patients compared with 3 healthy controls at 1.5 hours (0.50 ± 0.03 vs. 0.40 ± 0.01; $P < 0.01$) and 3 hours (0.51 ± 0.02 vs. 0.37 ± 0.02; $P < 0.01$) after ^{18}FDG injection. In addition, Hagan et al.[7] also observed a higher ^{18}FDG lung parenchymal target-to-background

Table 1. Patient characteristics at the time of 2-deoxy-2-[^{18}F]-fluoro-D-glucose (^{18}FDG) positron emission tomography

Characteristic	IPAH patients	MI patients
Sex, no.		
Male	1	7
Female	15	0
NYHA functional class, no.		
II	9	. . .
III	7	. . .
Age, years	46.1 ± 11.9	66.5 ± 12.2
6-minute walk distance, m	466 ± 141	. . .
Cardiac output, L min^{-1}	4.9 ± 1.2	. . .
Mean pulmonary arterial pressure, mmHg	49 ± 13	. . .
Mean right atrial pressure, mmHg	6 ± 5	. . .
Pulmonary vascular resistance, dyn s cm^{-5}	628 ± 301	. . .
Mixed venous saturation, %	66 ± 8	. . .
NT-proBNP, ng L^{-1}	1,048 ± 1,644	. . .
Serum glucose, mmol L^{-1}	5.2 ± 0.8	5.6 ± 1.0
Serum free fatty acids, mmol L^{-1}	0.07 ± 0.02	. . .

Note: Data are mean ± standard deviation, unless otherwise indicated. IPAH: idiopathic pulmonary arterial hypertension; MI: myocardial infarction; NYHA: New York Heart Association; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

ratio in a pilot study of 8 IPAH patients (7 treated, 1 untreated) compared with 6 chronic thromboembolic pulmonary hypertensive patients and healthy controls. A direct comparison to the present results is difficult because of differences in patient preparation, scanning time, and analysis of the PET data.[5] However, comparing the present SUVs with those of Xu and colleagues shows that the quantitative differences are small. In addition, reported disease severity parameters in the previous pilot studies are limited. Although New York Heart Association functional class and NT-proBNP values are similar in the current population and the IPAH patients from the study of Hagan et al.,[7] we cannot exclude that patients in the previous studies either had more severe PAH or were not receiving optimal treatment, explaining the higher pulmonary ^{18}FDG uptake. More importantly, in the present study pulmonary ^{18}FDG uptake was correlated directly with clinical and hemodynamic PAH parameters at the time of PET, which has not been done before. Unfortunately, although patients with variable IPAH severity were included, pulmo-

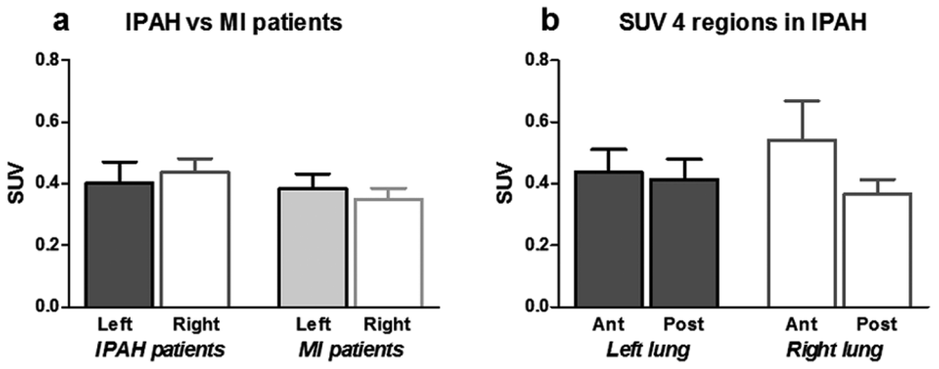

Figure 2. Standardized uptake values (SUVs) normalized to body weight, injected dose, and blood glucose level in left and right lungs of idiopathic pulmonary arterial hypertension (IPAH) and myocardial infarction (MI) patients (*a*) and in four separate regions of interest in lungs of IPAH patients (*b*). No differences were observed between the IPAH and MI patients or between different lung regions within IPAH patients. Ant: anterior part of the lung; post: posterior part of the lung. Data are shown as mean ± standard error of the mean.

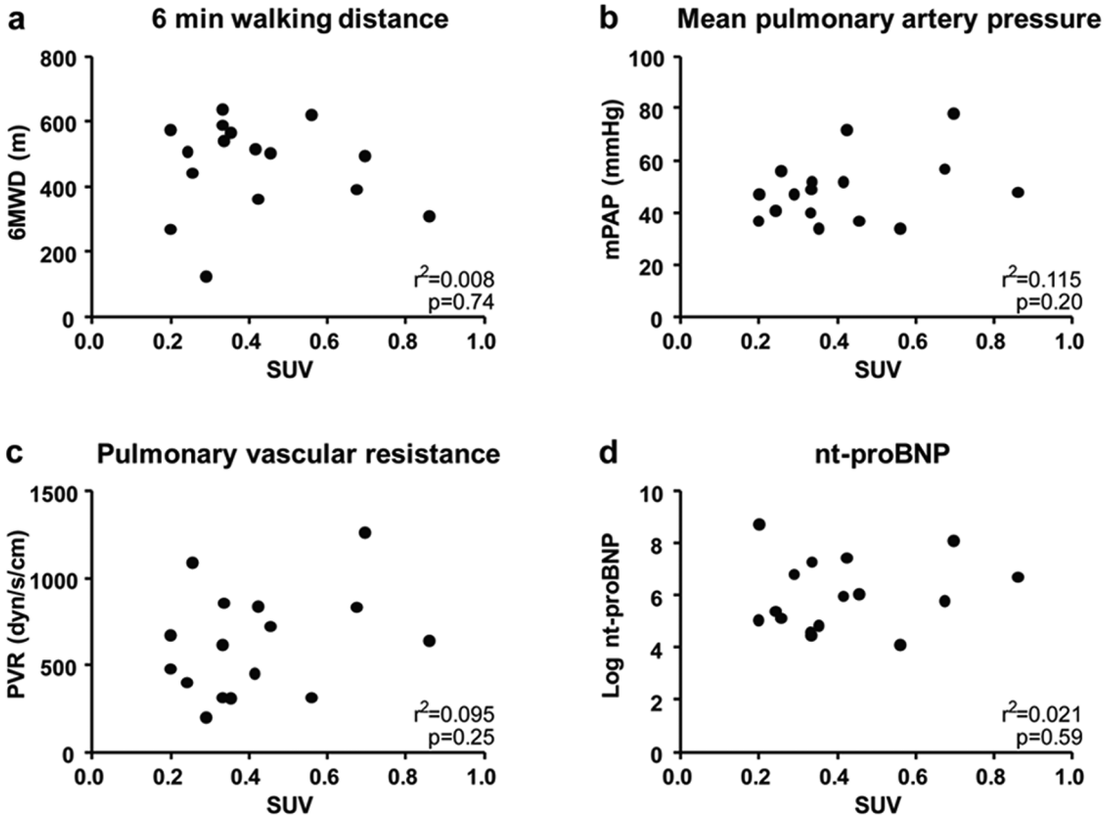

Figure 3. Scatterplots of standardized uptake values (SUVs) from idiopathic pulmonary arterial hypertension (IPAH) patients normalized to body weight, injected dose, and blood glucose level of both left and right lungs versus various PAH clinical parameters: 6-minute walk distance (6MWD; *a*), mean pulmonary artery pressure (mPAP; *b*), pulmonary vascular resistance (PVR; *c*), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP; *d*). Every dot represents a patient. No statistically significant correlations were found.

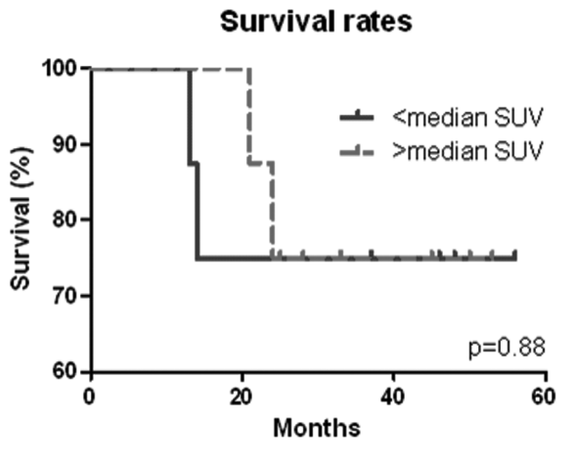

Figure 4. Kaplan-Meier survival plot of all idiopathic pulmonary arterial hypertension (IPAH) patients. Patients were divided on the basis of the median value of total lung standardized uptake value (SUV; 0.34). Four patients died during the time between the positron emission tomography scan and the current analysis (2 patients with SUVs less than the median, and 2 patients with SUVs more than the median). When patients were clinically stable, total lung SUV did not predict survival in this cohort. A color version of this figure is available online.

nary ^{18}FDG uptake was not associated with any clinical IPAH parameter or with survival.

In the present study, patients who had a MI were used as a comparison group. Because patient preparation was the same in IPAH and MI patients, a direct comparison of pulmonary SUV could be made. More importantly, we showed similar SUVs in IPAH and MI lungs, indicating that pulmonary glucose uptake in treated IPAH is indeed low. In addition, comparing the present results with data from the literature shows that the IPAH lung SUVs are comparable to those of healthy controls in the literature.[6,12]

A recent report showed that in vivo pulmonary ^{18}FDG uptake was higher in a rat model of PAH than in control rats.[3] These in vivo data were supported by increased glucose uptake in cultured rat PASMCs and increased glucose transporter 1 expression in both rat PASMCs and pulmonary artery endothelial cells (PAECs).[3,14] In addition, previous reports have

shown increased glycolytic rates in human PAH and IPAH PAECs.[6] Increased ^{18}FDG uptake in rat PAH may in part be due to the choice of the experimental model. Sugen-hypoxia and monocrotaline-injected rats used in the in vivo pulmonary ^{18}FDG measurements are known to exhibit systemic vascular inflammation.[3] Marsboom et al.[3] carefully investigated the role played by inflammation in the lungs of these rats and did not observe an increase in pulmonary macrophages or glucose transporter 1 activity. However, these data did not exclude increased glycolytic rates of inflammatory cells or an increased number of inflammatory cells in the in vivo situation, accounting for higher ^{18}FDG uptake.[3] Interestingly, Hagan et al.[7] did not find a correlation between inflammatory cytokines and lung parenchymal target-to-background ratio in IPAH patients, thereby showing that increased inflammation in human IPAH does not necessarily result in increased pulmonary ^{18}FDG uptake. In light of these results from the literature, one might have expected increased pulmonary ^{18}FDG uptake. However, results of the present study do not confirm this prediction. It should be noted, however, that PET provides a macroscopic measure of pulmonary ^{18}FDG uptake, which in itself does not exclude the possibility that glycolytic rates at the cellular level are indeed increased.[6] Another explanation for the present low pulmonary ^{18}FDG uptake could be that pulmonary glycolytic rates are low because of optimal PAH treatment.

Limitations

First, the comparison group consisted of patients who had a MI and were thereby not completely healthy. Second, only parts of the lungs around the mediastinum were measured, although PAH is considered to be homogeneous throughout the lungs and the middle regions of the lungs should therefore be representative of the entire lungs. To underline this, separate regions of interest in both lungs did not show any differences in SUV. Third, a more accurate way to measure ^{18}FDG uptake would be to calculate the metabolic rate of glucose uptake.[15,16] However, in this study calculation of the metabolic rate of glucose uptake by Patlak analysis resulted in negative values and therefore could not be used. In addition, an image-derived input function from regions of interest over the ascending aorta was used to analyze the data. Because pulmonary blood supply comes from the right ventricle, blood values from the aorta may not be the best input function. However, it is technically challenging to obtain reliable regions of interest from the right ventricular blood pool because of spillover from the myocardium, movement of the heart, and the shape of the right ventricle. Consequently, it was not possible to generate reproducible results with the right ventricular blood pool as input function. Finally, it should be emphasized that the present results may not apply to untreated patients.

Conclusions

Pulmonary ^{18}FDG uptake in treated IPAH patients is low and is not associated with disease severity or survival. Whether uptake is also low in untreated patients remains unknown; however, it is unlikely that ^{18}FDG PET can be used as a tool for follow-up of these patients.

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