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ORIGINAL ARTICLE

Evaluation of Lung Glucose Uptake with Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/CT in Patients with Pulmonary Arterial Hypertension and Pulmonary Hypertension Due to Left Heart Disease

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Abstract

***Aim*: Previous studies have demonstrated increased glucose uptake by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in lung parenchyma in animal models or small pulmonary arterial hypertension (PAH) cohorts. However, it is not well known whether increased FDG uptake in the lung is a unique phenomenon in PAH or whether elevated pulmonary artery pressure (PAP) induces FDG uptake.**

***Methods and results*: Nineteen patients with PAH, 8 patients with pulmonary hypertension due to left heart disease (PH-LHD), and 14 age matched control subjects were included. All PH patients underwent right heart catheterization and FDG-PET. The mean standard uptake value (SUV g/mL) of FDG in each lung was obtained and average values of both lungs were calculated as mean lung FDG SUV. The correlation between hemodynamics and mean lung FDG SUV was also analyzed in PH patients. Mean PAP (mPAP) was not significantly different between PAH and PH-LHD (45 ± 11 vs 43 ± 5 mmHg, p=0.51). PAH patients demonstrated significantly increased mean lung FDG SUV compared with PH-LHD and controls (PAH: 0.76 ± 0.26 vs PH-LHD: 0.51 ± 0.12 vs controls: 0.53 ± 0.16, p=0.0025). The mean lung FDG SUV did not correlate with mPAP either in PAH or PH-LHD.**

***Conclusion*: PAH is associated with increased lung FDG uptake indicating increased glucose utilization in the lung. This may represent metabolic shift to glycolysis and/or active inflammation in the remodeled pulmonary vasculature, and is observed to a greater extent in PAH than in patients with PH secondary to LHD and control subjects without PH.**

Keywords: ^{18}F-fluorodeoxyglucose positron emission tomography, Glucose metabolism, Glycolysis, Pulmonary arterial hypertension, Pulmonary hypertension due to left heart disease, Remodeled pulmonary vasculature
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Pulmonary arterial hypertension (PAH) is a progressive disease characterized by vascular remodeling of the intima and media with proliferation of endothelial and smooth muscle cells leading to narrowing and obliteration of small pulmonary arteries and arterioles, and progressive increases in pulmonary vascular resistance (PVR) (1). A specific morphological feature in advanced PAH is the so-called plexiform lesions which are complex, glomeruloid-like

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vascular structures originating from pulmonary arteries (2, 3). In contrast pulmonary hypertension (PH) secondary to left heart disease (LHD) (PH-LHD, or group 2 PH) occurs secondary to passive transmission of elevated venous pressures due to the underlying LHD, where pulmonary vascular remodeling may not be present, especially in patients with isolated post capillary PH (4–6). Recent studies have shown increased glucose metabolism in the PAH endothelial cell and pulmonary artery smooth muscle cell (PASMC) cultures (7, 8), which may reflect underlying metabolic abnormalities in the remodeled pulmonary vasculature.

This increased glucose uptake can be demonstrated in-vivo with ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging (8–11). Whether the glucose uptake visualized in the lungs of PAH patients (with primary pulmonary vascular remodeling) is different from patients with PH from LHD (and passive venous congestion) has not been previously evaluated. This study was designed to determine whether FDG lung imaging can identify increased glucose uptake in the lungs of patients with PH, and whether differences exist across different pathophysiologic groups of PH (PAH vs PH-LHD).

Methods

Study populations

All study subjects were recruited at the University of Ottawa Heart Institute (UOHI). The study subjects consisted of the following groups; 1) group I PH (PAH), 2) Group 2 PH (PH-LHD) and 3) controls without a diagnosis of PH. We retrospectively recruited patients from 2 different cohorts including an earlier pilot study and ongoing previous prospective study for PAH (12, 13). Patients with PH-LHD were recruited from a registry of subjects who underwent cardiac ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) in Ottawa between September of 2008 and September of 2009, for assessment of myocardial viability in the setting of heart failure due to ischemic heart disease (IHD) and who also had undergone right heart catheterization (RHC) and met criteria for PH. For the control population without PH, we included healthy volunteers from our previous prospective study for PAH, those who had been referred for cardiac sarcoidosis (CS) but not found to have CS, and patients with coronary artery disease (CAD) and no evidence to suggest PH from viability registry. We stratified PAH patient cohorts for subgroup analyses (idiopathic PAH or connective tissue disease associated PAH) (CTD-PAH). We excluded subjects with interstitial lung disease (ILD) since the presence of ILD can increase lung FDG uptake.

All PH patients underwent RHC to obtain pulmonary hemodynamics including pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), mean right atrial pressure (mRAP), and cardiac output (CO) using Swan-Ganz catheter. CO was measured by the thermodilution method. Cardiac index (CI) was calculated as CO divided by body surface area (L/min/m^2). Pulmonary vascular resistance (PVR) was calculated as mean PAP (mPAP) minus PAWP and divided by CO, expressed in woods units. Pulmonary arterial capacitance was estimated by the formula stroke volume/pulmonary artery pulse pressure (14–16). The diagnosis of PAH or PH-LHD was determined based on the 6th World Symposium on Pulmonary Hypertension in 2018 (17). We reclassified PH-LHD into 2 subgroups including isolated post-capillary PH (Ipc-PH) (mPAP >20, PAWP >15 and PVR <3 WU) or combined post-capillary and pre-capillary PH (Cpc-PH) (mPAP >20, PAWP >15 and PVR ≥3 WU) (17).

All study subjects underwent FDG-PET/CT. The study was approved by Ottawa Health Science Network Research Ethics Board (OHSN-REB) and informed consents were obtained from all patients and volunteers.

FDG-PET/CT imaging protocol

All patients were instructed to fast overnight prior to the PET study. Patients were positioned in the GE Discovery 600 PET/VCT scanner (Waukesha, WI). Following a scout scan to confirm patients positioning, a low dose x-ray CT scan was performed at normal end-expiration to correct for photon attenuation. A static FDG uptake scan was initiated 40 minutes after injection of 5 MBq/kg of FDG. We used FDG-PET/CT protocols; fasting and glucose load. On the glucose load protocol, the tracer was injected at 30 minutes after the glucose load.

Both fasting and glucose loading protocols were used in this analysis. In our earlier pilot study for PAH, we performed FDG-PET/CT with a glucose load protocol as with prior studies (11, 13, 18–20). In our ongoing previous prospective study for PAH (12), we performed FDG-PET/CT under fasting condition in order to investigate both glucose and free fatty acid uptake (PAH and controls). In patients with PH-LHD (group 2 PH) and CAD patients with no PH (controls), a glucose load protocol was used because FDG-PET/CT studies were performed to assess myocardial viability. Patients who investigated for sarcoidosis underwent FDG-PET/CT under fasting condition (controls). In addition, since July 2012, all patients who underwent FDG-PET/CT for the evaluation of suspected CS were prescribed a low-carbohydrate, high-fat and protein-permitted diet as dinner the day before the test. Hence, fasting protocols were classified into fasting-only protocol (fasting) and fasting with dietary modification protocol (fasting with low-carb). Thus, we used three FDG-PET protocols; fasting, fasting with low-carb and glucose load.

Table 1 Patient Characteristics

	PAH (n=19)	PH-LHD (n=8)	Control (n=14)	p-value
Age, yrs	53.6 ± 13.4	59.4 ± 14.5	55.9 ± 17.1	0.65
Gender (M/F)	4/15	8/0	9/5	0.0004
Underlying disease				
IPAH	13	−	−	
CTD	6	−	−	
HFrEF due to IHD	−	8	−	
CAD	−	−	4	
Healthy	−	−	3	
Arrhythmia	−	−	7	
PH medication, yes	17 (89)	−	−	
PAP, mmHg				
Systolic	73 ± 19	66 ± 7	−	0.31
Diastolic	27 ± 9	26 ± 6	−	0.71
Mean	45 ± 11	43 ± 5	−	0.51
PAWP, mmHg	9 ± 3	30 ± 6	−	<0.0001
CI, L/min/m^2	2.1 ± 0.5	1.7 ± 0.3	−	0.05
mRAP, mmHg	9 ± 4	14 ± 6	−	0.007
PVR, wood unit	11 ± 6	4 ± 1	−	0.003
PAC, ml/mmHg	1.2 ± 0.6	1.2 ± 0.5	−	0.95
FDG-PET protocol (fasting/fasting with low-carb/glucose)	12/0/7	0/0/8	4/5/5	

CAD: coronary artery disease, CI: cardiac index, CTD: connective tissue disease,
FDG-PET: ^{18}F-fluorodeoxyglucose positron emission tomography, HFrEF: heart failure with reduced ejection fraction,
IHD: ischemic heart disease, IPAH: idiopathic pulmonary arterial hypertension, LHD: left heart disease,
PAWP: mean pulmonary artery pressure, mRAP: mean right atrial pressure, PAC: pulmonary artery capacitance,
PAH: pulmonary arterial hypertension, PAP: pulmonary arterial pressure, PH: pulmonary hypertension,
PVR: pulmonary vascular resistance

Image processing

PET images of activity concentration (Bq/cc) were reconstructed using an iterative algorithm (VuePoint HD) with 8 mm Hann post-filter. CT image alignment was verified against PET using a fusion display program (ACQC) to ensure accurate attenuation correction. Patient body weight and injected activity were used to convert the PET image units to standardized uptake values (SUV g/cc) according to standard methods (12).

PET imaging data analysis

Regions of interest (ROIs) were drawn to include the lateral one-third of the lungs on the sagittal images to avoid including major blood vessels and airways and fibrotic lesions (appendix). The mean lung FDG SUV was obtained by the following formula: mean lung FDG SUV=[mean SUV (Rt)+ mean SUV (Lt)]/2.

Statistical analysis

PAH (entire PAH, IPAH, or CTD-PAH), PH-LHD and controls were compared using one-way ANOVA. Comparison among 3 subgroups in terms of those different FDG-PET/CT protocols (fasting, fasting with low-carb or glucose load) were performed using one-way ANOVA. Correlations between PET data and hemodynamics were evaluated using Spearman correlation coefficients. Statistical significance was defined as $p<0.05$. Data are described as mean ± SD. All analyses were performed using SAS software version 9.3.

Results

Patient characteristics

Nineteen patients with PAH, 8 patients with PH-LHD and 14 control subjects were enrolled in the study (Table 1). In the PAH group, 13 patients were diagnosed with idiopathic PAH (IPAH) and 6 were PAH associated with connective tissue disease (CTD-PAH). Of the 6 patients with CTD-PAH, five had scleroderma and one had mixed connected disease.

In the PH-LHD group, all patients were diagnosed with heart failure with reduced ejection fraction (HFrEF) due to ischemic heart disease (IHD). All patients had moderately or severely reduced left ventricular ejection fraction. Of these, 3 patients were categorized into Ipc-PH and the remaining 5 patients were categorized into Cpc-PH. In the control group, 4 patients also had coronary artery disease (CAD), 3 were

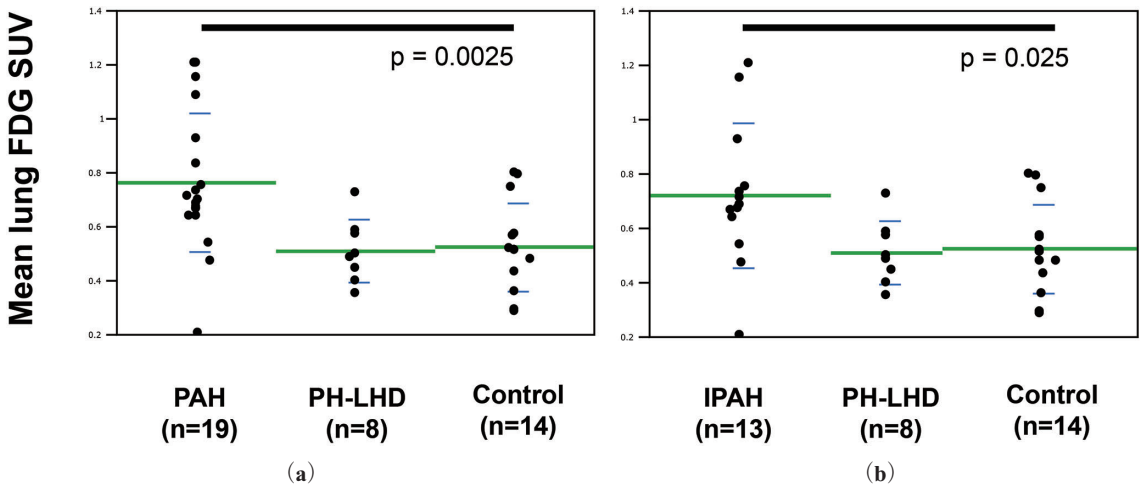

Figure 1　Increased lung FDG uptake in PAH group.
(**a**)　Mean lung FDG uptake in PAH patients (n=19; FDG SUV: 0.76 ± 0.26) was increased compared with PH due to LHD patients (n=8; 0.51 ± 0.12) and control subjects (n=14; 0.53 ± 0.16), p=0.0025.
(**b**)　Patients with IPAH (n=13; FDG SUV: 0.72 ± 0.26) showed higher lung FDG uptake than PH due to LHD patients (n=8; 0.51 ± 0.12) and control subjects (n=14; 0.53 ± 0.16), p=0.025.

healthy subjects, and 7 patients were investigated for CS due to arrhythmia, which was ruled out after the examinations. Control subjects did not any evidence of PH by physical examination, chest X-ray, electrocardiogram and transthoracic echocardiogram.

There were no significant differences in the mean age amongst 3 groups (p=0.65). In the PAH group, patients were predominantly female (p=0.0004).

Seventeen of the 19 PAH patients were treated with PAH specific medications. The mean pulmonary arterial pressure (mPAP) was not significantly different between PAH and PH-LHD groups (45 ± 11 vs 43 ± 5 mmHg, p=0.51). Compared with the PAH group, the PH-LHD group had a significantly higher PAWP (9 ± 3 vs 30 ± 6 mmHg, p<0.0001). There was no significant difference in the mean pulmonary arterial capacitance (PAC) between the PAH cohort and the PH-LHD cohort (1.2 ± 0.6 vs 1.2 ± 0.5 ml/mmHg, p=0.95). In the PAH and control groups, fasting, fasting with low-carb or glucose load protocol was used for FDG-PET/CT studies (PAH: 12/0/7 [fasting/fasting with low-carb/glucose]; control 4/5//5 [fasting/fasting with low-carb/glucose]) (Table 1). All patients with PH-LHD underwent FDG-PET/CT with a glucose load (Table 1).

Lung FDG uptake

The mean lung FDG SUV was greater in the group with PAH when compared to the other groups (entire PAH group vs PH-LHD and control groups; 0.76 ± 0.26 vs 0.51 ± 0.12 vs 0.53 ± 0.16, p=0.0025) (Figure 1). There were no statistically significant differences in mean lung FDG uptake when PAH patients were divided into IPAH and CTD-PAH, but CTD-PAH patients showed slightly higher lung FDG uptake but this doesn't not reach statistical significance (IPAH vs CTD-PAH; 0.72 ± 0.26 vs 0.85 ± 0.24, p=0.31).

Patients with IPAH showed higher lung FDG SUV than the other 2 groups (IPAH group vs PH-LHD and control groups, p=0.025) (Figure 1). There were no significant differences in mean lung FDG SUV between fasting and glucose load protocols in the PAH. Also, no significant differences were present in mean lung FDG SUV among fasting, fasting with low-carb and glucose load in controls (Figure 2).

The mean lung FDG SUV did not correlate with mPAP either PAH or PH-LHD group (r=0.07, p=0.77 for PAH; r=0.08, p=0.85 for PH-LHD) (Figure 3). Mean lung FDG SUV did not correlate with PAP, PVR or mRAP in either the PAH nor the PH-LHD group. PAC was not related to mean lung FDG SUV when the entire population was studied together. There was a nonsignificant trend for decreased PAC to be related to increased lung FDG uptake in the CTD-PAH, entire PH-LHD and Cpc-PH (r=-0.68, p=0.14 for CTD-PAH; r=-0.55, p=0.15 for PH-LDH; r=-0.77, p=0.13 for Cpc-PH). Mean lung FDG-SUV was not significantly different between the IpC-PH and the CpC-PH cohorts from the PH-LHD group (p=0.25). Figure 4 shows a representative case of each group.

Discussion

This study evaluated the relationship between pulmonary hemodynamics, type of PH and lung FDG uptake in patients with PH and controls. We demonstrated that PAH was associated with a significantly higher mean lung FDG SUV than PH-LHD and control groups. The mean lung FDG SUV did not significantly correlate with pulmonary hemodynamics and PVR either in PAH or PH-LHD. There was a nonsignificant trend towards increased lung FDG uptake and

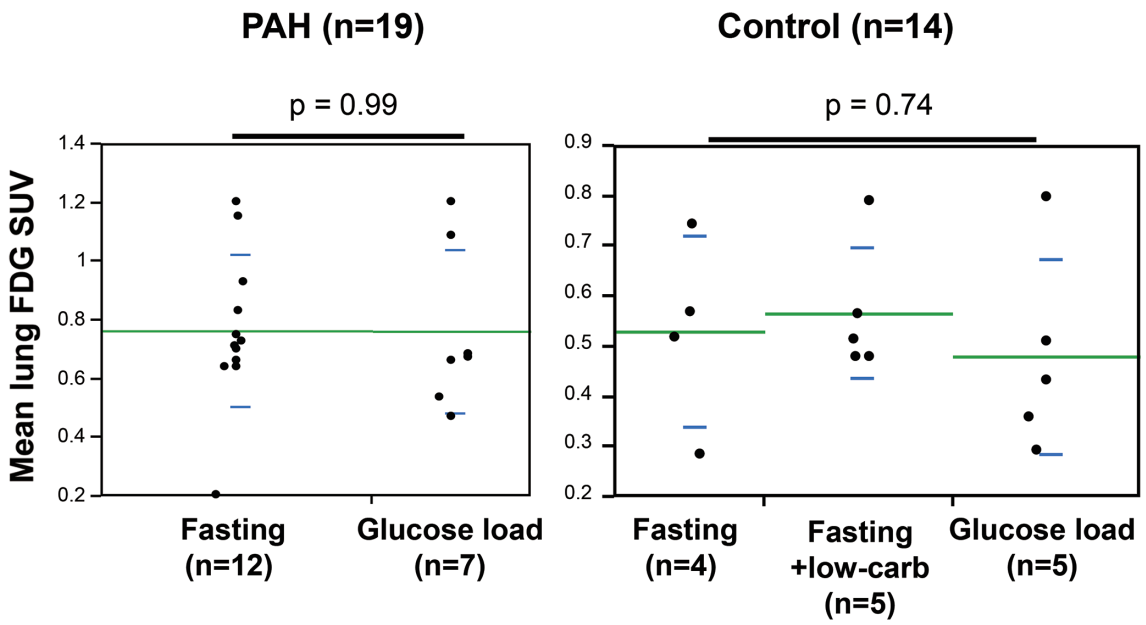

Figure 2 Comparison of lung FDG uptake in the three protocols.
Compared with lung FDG uptake in the fasting and glucose load protocols, no significant differences were shown in PAH group (fasting; n=12; FDG SUV 0.76 ± 0.26 vs glucose load; n=7; 0.76 ± 0.28, p=0.99) and control group (fasting; n=4; 0.53 ± 0.19, fasting with low-carbo; n=5; 0.57 ± 0.13 vs glucose load; n=5; 0.48 ± 0.20, p=0.74).

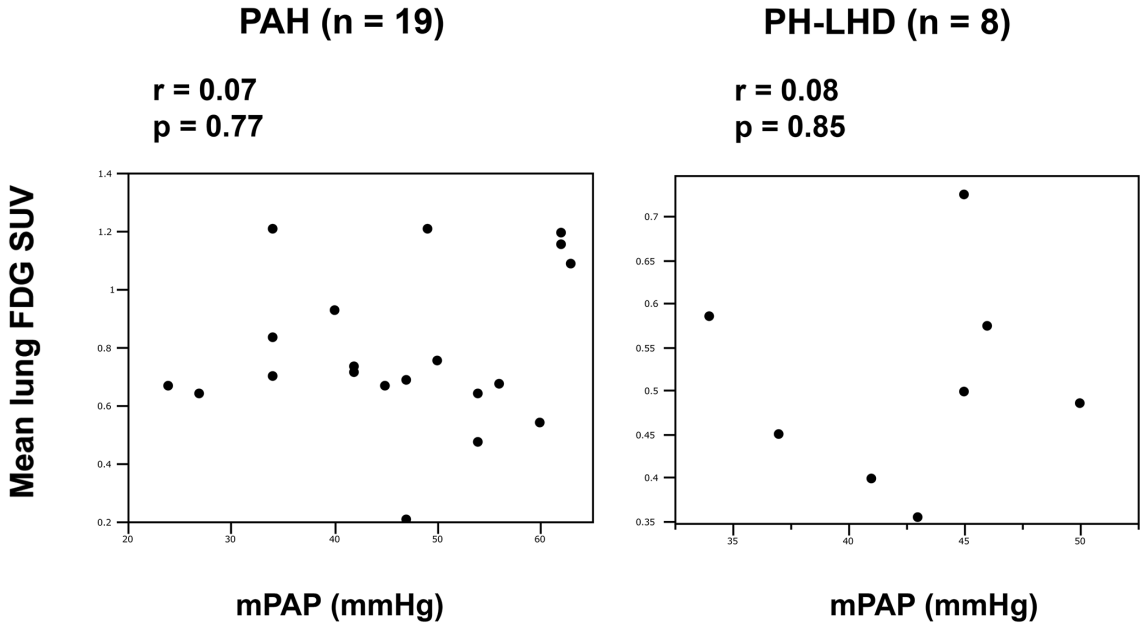

Figure 3 Relationship between mPAP and lung FDG uptake.
Correlation analyses demonstrated no relationship between lung FDG SUV and mean pulmonary artery pressure either in PAH (n=19) (r=0.07, p=0.77) or group 2 PH (n=8) (r=0.08, p=0.85).

decreased PAC in patients with PH-LHD.

In the pathobiology of PAH, disordered metabolism and mitochondrial structure, inflammation, and dysregulation of growth factors have been reported to induce the vascular remodeling (21–23). Several studies have demonstrated that PAH pulmonary artery smooth muscle cells (PASMCs) mitochondria have increased glycolysis as a result of suppressed glucose oxidation, which has been considered to be similar behavior to a cancer cell in order to compensate ATP synthesis in the cytoplasm (7, 8, 24–27). Also this increased glucose uptake could be visualized using FDG-PET (8–10, 28). Xu et al. reported that the elevated aerobic glycolysis was observed in pulmonary endothelial cells derived from IPAH patients and demonstrated increased FDG uptake in the lungs of IPAH patients compared to controls (7). Marsboom et al. demonstrated increased lung FDG uptake in 2 experimental

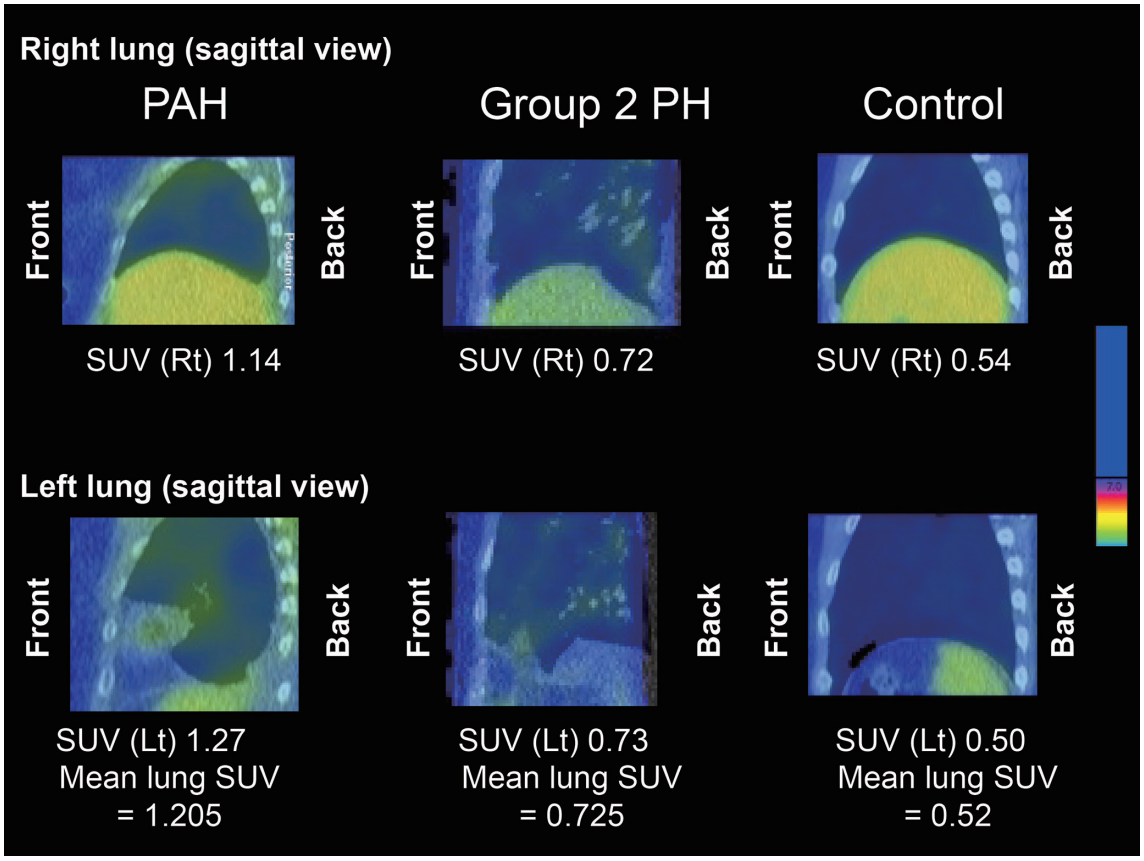

Figure 4　A representative case of each group.
FDG-PET imaging of a representative case of PAH, PH due to LHD and control.
The PAH patient shows higher mean lung SUV compared with the other groups. The images of the cases presented has been adjusted in the same color scale on the right.

small animal models (monocrotaline or SU5416/hypoxia rat) (8). They found that the lung FDG uptake was increased in the early stage of PAH, and the effective therapies (dichloroacetate and imatinib) decreased the increased FDG intensity. Furthermore, they also showed that the glucose transporter 1 (Glut 1) mRNA was upregulated in both endothelium and PASMCs, however, not airway cells or macrophages. They successfully revealed the origins of FDG-PET signal intensity. Zhao et al. reported that mean lung FDG uptake was increased in patients with IPAH (n=18) compared with healthy controls (n=5) and found heterogeneity in lung FDG signal intensity both in the lungs of individual patient and among patients (9). More, recently, Michelakis et al. performed a 4-month phase I clinical trial and demonstrated that dichloroacetate administration led to improvement in hemodynamics and exercise capacity in IPAH patients. However, the response to DCA varied. The patients who showed a hemodynamic response showed an overall decrease in lung FDG uptake, whereas those without a response had an increase in lung FDG uptake (29).

The mechanism of the development of group 2 PH is mainly a passive backward transmission of LV filling pressures (passive PH) (30, 31). However, some group 2 PH patients have disproportionally high PVR. In these patients, the venous congestion may trigger PAH like vascular remodeling (30, 31). The precise characterization of this cohort has been a challenge and has changed over time. Historically, transpulmonary pressure gradient (TPG=mPAP–PAWP) was used to distinguish between ‘passive PH’ and ‘reactive PH’ (32). The 2015 ESC guidelines proposed the use of the diastolic pressure gradient (DPG=diastolic PAP-PAWP) in order to distinguish “Ipc-PH” from “Cpc-PH” (6, 30). However, the latest hemodynamic definitions proposed to distinguish between Ipc-PH and Cpc-PH based on PVR (17). Hemodynamic-biomarker correlates can help to further the understanding of the pathobiology of this complex disease.

We hypothesized that patients with Cpc-PH may have more advanced remodeling of the arterioles, thus they may have higher lung FDG SUV than those with Ipc-PH. In our patient cohorts, patients with Cpc-PH did not have higher mean lung FDG SUV. There was a trend observed between increased lung FDG uptake and decreased PAC in patients with PAH-LHD, and the finding remained a trend even after limiting Cpc-PH. But these findings may have been limited by the small sample size. Previous studies have suggested that PAC is an important predictor of mortality in patients with PH-

LHD, and may be a better marker of RV afterload than PVR (14).

Several studies have reported increased lung FDG uptake in patients with idiopathic pulmonary fibrosis (IPF) and other diffuse parenchymal pulmonary diseases (33–35). Interestingly, Win et al. showed that patients with IPF had increased lung FDG uptake on FDG-PET/CT in normal areas on high resolution computed tomography (HRCT) (36). These results indicate that increased FDG uptake in the lung reflects the inflammatory activity in the lung parenchyma. The spatial resolution of the current PET/CT system is not enough to distinguish between lung vasculature and airways, thus excluding patients with significant parenchymal lung disease helped to confirm that the increased lung FDG uptake seen in patients with PAH was originating from lung vasculature.

There are limitations to the current study. First, the sample size is relatively small, especially in patients with PH-LHD. Additionally, we included 3 different FDG-PET protocols such as fasting, fasting with low-carb and glucose load. FDG is taken up by glucose transporter 1 (GLUT-1) in the endothelial cells and PASMCs. In theory, GLUT-1 is insulin independent, thus insulin secretion induced by oral glucose intake might not affect FDG uptake in the pulmonary vasculature. Despite this, the results were consistent when the data were stratified by study protocol. Lastly, we currently cannot identify if the origin of the increased FDG uptake is in the vascular tissue or the airway. However, animal studies have demonstrated that GLUT-1 mRNA was up-regulated in both endothelium and PASMCs, but not in the airway cells or macrophages, and the results of this study are consistent whether patients with concomitant lung disease are included in the analysis or not.

FDG-PET cannot be used for the diagnosis of PH as it does not have specificity. As shown in the animal studies by Marsboom et al. (8) and Zhao et al. (9), it is expected that FDG-PET may be a tool to investigate the molecular pathology of PAH and may also be able to monitor therapeutic changes in the vasculature. In the current clinical setting, the disease severity of PAH is evaluated by exercise capacity such as WHO functional class or cardiopulmonary exercise tests, pulmonary hemodynamics, cardiac morphology and RV function. FDG-PET may be a complementary imaging test to evaluate the pathologic metabolic changes in PAH, and further studies are needed to evaluate whether FDG PET imaging can be used to assess therapeutic response or guide prognosis in the evaluation of patients with PH.

In conclusion, increased FDG uptake is a unique phenomenon in patients with PAH in our study cohorts. This may reflect underlying metabolic abnormalities in the remodeled pulmonary vasculature itself not by passive elevation of pulmonary arterial pressure. Further prospective studies are needed to evaluate the assessment of lung FDG uptake in PAH.

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Conflicts of interest

L. M. has research grants and advisory board fees from Actelion and Bayer; R. B. is a consultant and has received grant funding from Lantheus Medical Imaging, Jubilant DRAX Image (JDI) and GE Healthcare; R.d.K. and R.K are consultants for and receive research funding from JDI. R.d.K., R. K., and J. R. receive royalty revenues from rubidium generator technology and from FlowQuan tsoftware licenses; D. J. S. has equity with Northern Therapeutics and research funding from United Therapeutics; C.P.has speakers fees from Actelion and Pfizer; R. A. D. has unrestricted educational grants from Actelion and Bayer and speakers fees from Actelion; G.C. has participated in advisory board meetings for Bayer and Actelion.

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References

1. Hassoun PM, Mouthon L, Barberà JA, Eddahibi S, Flores SC, Grimminger F, et al. Inflammation, growth factors, and pulmonary vascular remodeling. J Am Coll Cardiol 2009; 54: S10–9.
2. Fishman AP. Changing concepts of the pulmonary plexiform lesion. Physiol Res 2000; 49: 485–92.

3. Pietra GG, Capron F, Stewart S, Leone O, Humbert M, Robbins IM, et al. Pathologic assessment of vasculopathies in pulmonary hypertension. J Am Coll Cardiol 2004; 43: 25S–32S.
4. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013; 62: D34–41.
5. Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, et al. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest 2013; 143: 758–66.
6. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016; 37: 67–119.
7. Xu W, Koeck T, Lara AR, Neumann D, DiFilippo FP, Koo M, et al. Alterations of cellular bioenergetics in pulmonary artery endothelial cells. Proc Natl Acad Sci USA 2007; 104: 1342–7.
8. Marsboom G, Wietholt C, Haney CR, Tosh PT, Ryan JJ, Morrow E, et al. Lung ^{18}F-fluorodeoxyglucose positron emission tomography for diagnosis and monitoring of pulmonary arterial hypertension. Am J Respir Crit Care Med 2012; 185: 670–9.
9. Zhao L, Ashek A, Wang L, Fang W, Dabral S, Dubois O, et al. Heterogeneity in lung ^{18}FDG uptake in pulmonary arterial hypertension: potential of dynamic ^{18}FDG positron emission tomography with kinetic analysis as a bridging biomarker for pulmonary vascular remodeling targeted treatments. Circulation 2013; 128: 1214–24.
10. Hagan G, Southwood M, Treacy C, Ross RM, Soon E, Coulson J, et al. ^{18}FDG PET imaging can quantify increased cellular metabolism in pulmonary arterial hypertension: A proof-of-principle study. Pulm Circ 2011; 1: 448–55.
11. Ruiter G, Wong YY, Raijmakers P, Huisman MC, Lammertsma AA, Knaapen P, et al. Pulmonary 2-deoxy-2-[^{18}F]-fluoro-d-glucose uptake is low in treated patients with idiopathic pulmonary arterial hypertension. Pulm Circ 2013; 3: 647–53.
12. Ohira H, deKemp R, Pena E, Davies RA, Stewart DJ, Chandy G, et al. Shifts in myocardial fatty acid and glucose metabolism in pulmonary arterial hypertension: a potential mechanism for a maladaptive right ventricular response. Eur Heart J Cardiovasc Imaging 2016; 17: 1424–31.
13. Mielniczuk LM, Birnie D, Ziadi MC, deKemp RA, DaSilva JN, Burwash I, et al. Relation between right ventricular function and increased right ventricular [^{18}F]fluorodeoxyglucose accumulation in patients with heart failure. Circ Cardiovasc Imaging 2011; 4: 59–66.
14. Al-Naamani N, Preston IR, Paulus JK, Hill NS, Roberts KE. Pulmonary arterial capacitance is an important predictor of mortality in heart failure with a preserved ejection fraction. JACC Heart Fail 2015; 3: 467–74.
15. Dupont M, Mullens W, Skouri HN, Abrahams Z, Wu Y, Taylor DO, et al. Prognostic role of pulmonary arterial capacitance in advanced heart failure. Circ Heart Fail 2012; 5: 778–85.
16. Pellegrini P, Rossi A, Pasotti M, Raineri C, Cicoira M, Bonapace S, et al. Prognostic relevance of pulmonary arterial compliance in patients with chronic heart failure. Chest 2014; 145: 1064–70.
17. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53: 1801913.
18. Kluge R, Barthel H, Pankau H, Seese A, Schauer J, Wirtz H, et al. Different mechanisms for changes in glucose uptake of the right and left ventricular myocardium in pulmonary hypertension. J Nucl Med 2005; 46: 25–31.
19. Oikawa M, Kagaya Y, Otani H, Sakuma M, Demachi J, Suzuki J, et al. Increased [^{18}F] fluorodeoxyglucose accumulation in right ventricular free wall in patients with pulmonary hypertension and the effect of epoprostenol. J Am Coll Cardiol 2005; 45: 1849–55.
20. Bokhari S, Raina A, Rosenweig EB, Schulze PC, Bokhari J, Einstein AJ, et al. PET imaging may provide a novel biomarker and understanding of right ventricular dysfunction in patients with idiopathic pulmonary arterial hypertension. Circ Cardiovasc Imaging 2011; 4: 641–7.
21. Fartoukh M, Emilie D, Le Gall C, Monti G, Simonneau G, Humbert M. Chemokine macrophage inflammatory protein-1α mRNA expression in lung biopsy specimens of primary pulmonary hypertension. Chest 1998; 114: 50S–51S.
22. Nicolls MR, Taraseviciene-Stewart L, Rai PR, Badesch DB, Voelkel NF. Autoimmunity and pulmonary hypertension: a perspective. Eur Respir J 2005; 26: 1110–8.
23. Humbert M, Monti G, Brenot F, Sitbon O, Portier A, Grangeot-Keros L, et al. Increased interleukin-1 and interleukin-6 serum concentrations in severe primary pulmonary hypertension. Am J Respir Crit Care Med 1995; 151: 1628–31.
24. Sutendra G, Bonnet S, Rochefort G, Haromy A, Folmes KD, Lopaschuk GD, et al. Fatty acid oxidation and malonyl-CoA decarboxylase in the vascular remodeling of pulmonary hypertension. Sci Transl Med 2010; 2: 44ra58.
25. Sutendra G, Dromparis P, Bonnet S, Haromy A, Mcmurtry MS, Bleackley RC, et al. Pyruvate dehydrogenase inhibition by the inflammatory cytokine TNFα contributes to the pathogenesis of pulmonary arterial hypertension. J Mol Med (Berl) 2011; 89: 771–83.
26. Sutendra G, Dromparis P, Wright P, Bonnet S, Haromy A, Hao Z, et al. The role of Nogo and the mitochondria-endoplasmic reticulum unit in pulmonary hypertension. Sci Transl Med 2011; 3: 88ra55.
27. Sutendra G, Dromparis P, Paulin R, Zervopoulos S, Haromy A, Nagendran J, et al. A metabolic remodeling in right ventricular hypertrophy is associated with decreased angiogenesis and a transition from a compensated to a decompensated state in pulmonary hypertension. J Mol Med (Berl) 2013; 91: 1315–27.
28. Saygin D, Highland KB, Farha S, Park M, Sharp J, Roach EC, et al. Metabolic and functional evaluation of the heart and lungs in pulmonary hypertension by gated 2-[^{18}F]-Fluoro-2-deoxy-D-glucose positron emission tomography. Pulm Circ

2017; 7: 428–38.
29. Michelakis ED, Gurtu V, Webster L, Barnes G, Watson G, Howard L, et al. Inhibition of pyruvate dehydrogenase kinase improves pulmonary arterial hypertension in genetically susceptible patients. Sci Transl Med 2017; 9: eaao4583.
30. Vachiéry JL, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, et al. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol 2013; 62: D100–8.
31. Delgado JF, Conde E, Sánchez V, López-Ríos F, Gómez-Sánchez MA, Escribano P, et al. Pulmonary vascular remodeling in pulmonary hypertension due to chronic heart failure. Eur J Heart Fail 2005; 7: 1011–6.
32. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009; 34: 1219–63.
33. Nusair S, Rubinstein R, Freedman NM, Amir G, Bogot NR, Izhar U, et al. Positron emission tomography in interstitial lung disease. Respirology 2007; 12: 843–7.
34. Umeda Y, Demura Y, Ishizaki T, Ameshima S, Miyamori I, Saito Y, et al. Dual-time-point ^{18}F-FDG PET imaging for diagnosis of disease type and disease activity in patients with idiopathic interstitial pneumonia. Eur J Nucl Med Mol Imaging 2009; 36: 1121–30.
35. Groves AM, Win T, Screaton NJ, Berovic M, Endozo R, Booth H, et al. Idiopathic pulmonary fibrosis and diffuse parenchymal lung disease: implications from initial experience with ^{18}F-FDG PET/CT. J Nucl Med 2009; 50: 538–45.
36. Win T, Thomas BA, Lambrou T, Hutton BF, Screaton NJ, Porter JC, et al. Areas of normal pulmonary parenchyma on HRCT exhibit increased FDG PET signal in IPF patients. Eur J Nucl Med Mol Imaging 2014; 41: 337–42.