DOI: 10.1002/pul2.12363

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

# (18)F-fluorodeoxyglucose uptake by positron emission tomography in patients with IPAH and CTEPH

**Celik Sumer**[1] | **Gulfer Okumus**[1] | **Emine Goknur Isik**[2] | **Cuneyt Turkmen**[2] | **Ahmet Kaya Bilge**[3] | **Murat Inanc**[4]

[1]Department of Pulmonary Diseases, Istanbul University Istanbul Faculty of Medicine, Istanbul, Turkey

[2]Department of Nuclear Medicine, Istanbul University Istanbul Faculty of Medicine, Istanbul, Turkey

[3]Department of Cardiology, Istanbul University Istanbul Faculty of Medicine, Istanbul, Turkey

[4]Department of Rheumatology, Istanbul University Istanbul Faculty of Medicine, Istanbul, Turkey

**Correspondence**
Gulfer Okumus, Department of Pulmonary Diseases, Istanbul University Istanbul Faculty of Medicine, Capa-Fatih, Istanbul, Turkey.
Email: gulferokumus@yahoo.com

**Funding information**
Johnson and Johnson

## Abstract

Pulmonary arterial hypertension (PAH) is driven by pathologies associated with increased metabolism such as pulmonary revascularization, vasoconstriction and smooth muscle cell proliferation in pulmonary artery wall. 18-fluorodeoxyglucose positron emission tomography (18FDG-PET) is an imaging technique sensitive to glucose metabolism and might be considered as a non-invasive method for diagnosis due to significant role of inflammation in idiopathic pulmonary artery hypertension (IPAH) and chronic thromboembolic pulmonary hypertension (CTEPH). The present study aimed to investigate the role of PET/CT imaging of patients with IPAH and CTEPH as an alternative diagnosis method. Demographic characteristics, FDG uptake in lungs, pulmonary artery and right ventricle (RV) of 17 patients (10 IPAH, 7 CTEPH), and 30 controls were evaluated. PET scanning, 6-min walk test, pro-BNP level, right heart catheterization of patients were performed both at the onsert and after 6-month PAH specific treatment. IPAH and CTEPH patients had significantly higher left lung FDG ($p = 0.006$), right lung FDG ($p = 0.004$), right atrial (RA) FDG ($p < 0.001$) and RV FDG ($p < 0.001$) uptakes than controls. Positive correlation was detected between the RV FDG uptake and the mean pulmonary artery pressure (mPAP) ($r = 0.7$, $p = 0.012$) and between the RA FDG uptake and the right atrial pressure (RAP) ($r = 0.5$, $p = 0.02$). Increased RV FDG and RA FDG uptakes predicts the presence of pulmonary hypertension and correlates with mPAP and RAP, respectively, which are important indicators in the prognosis of PAH. Further studies are required whether FDG PET imaging can be used to diagnose or predict the prognosis of pulmonary hypertension.

**KEYWORDS**
CTEPH, IPAH, positron emission tomography, right heart catheterization

## INTRODUCTION

Healthy myocardium gets majority of its energy requirement for oxidative phosphorylation from fatty acids. In pulmonary arterial hyptertension (PAH) resulting from pulmonary revascularization, vasoconstriction and smooth muscle cell proliferation, there exists an expectation of an increase in the glucose metabolism of both pulmonary capillary bed and right heart due to intense cellular metabolism.[1,2]

The past two decades have witnessed advances in imaging techniques that can detect metabolic changes in tissues. Among these techniques, 18-fluorodeoxyglucose positron emission tomography (18FDG-PET), an imaging technique sensitive to cellular activities which metabolize glucose, has a remarkable place. It might be considered an alternative diagnostic method due to pathological role of inflammation in idiopathic pulmonary arterial hypertension (IPAH) and chronic thromboembolic pulmonary hypertension (CTEPH), presence of vascular inflammation.

At present, definitive diagnosis of PAH is made by right heart catheterization (RHC).[3,4] Considerations such as the small number of PAH-specific centers with excessive workload, RHC as an invasive procedure and the need for experienced staff to perform the procedure have resulted in a need to seek for alternative methods for diagnosis in this disease group where early diagnosis and treatment are critical. The present study aimed to investigate the role of 18FDG-PET imaging in right heart evaluation of patients with pulmonary hypertension as an alternative diagnosis method.

Given the possible pathological role of inflammation in idiopathic PAH and CTEPH, the presence of deranged endothelial cell bioenergetics and the recent development of techniques allowing the imaging of vascular inflammation, we hypothesized that increased 18FDG uptake in the pulmonary arteries and right ventricle would be present in subjects with pulmonary hypertension compared with controls.

## METHODS

The study included patients who were recently diagnosed with IPAH or inoperable CTEPH patients presented to the Pulmonary Hypertension Clinic of the Department of Pulmonary Diseases, Istanbul University Medical Faculty. We recorded information on 6-min walk test distances (6MWD), pro-BNP levels, echocardiographic examinations and results of RHC procedure, baseline FDG results for each patient and repeated them all after 6-month PAH specific treatment.

We selected only IPAH patients from a large group of Group I patients and CTEPH patiens from Group IV, and thus we avoided any effect of the pathologies like parenchymal inflammation that may occur due to involvement of connective tissue diseases leading to increased glycolysis metabolism on FDG uptakes and making false inferences.[5]

For control group, we selected 30 patients who underwent 18FDG-PET imaging procedure for prior diagnosis of non-thoracic malignancy, who had no respiratory or cardiac disease, no active malignancy detected and whose echocardiographic evaluation results and pro-BNP levels were reported normal.

All of the patients fasted for at least 6 h before imaging, and their blood glucose levels were less than 200 mg/dL at the time of the tracer injection. PET/CT scans were started 60 min after intravenous administration of 18F-FDG. Whole-body PET scans were performed on a Discovery IQ PET/CT scanner (GE Healthcare). The protocol and quality of chest imaging were same between the controls and the patients. All results were evaluated by two blinded nuclear medicine experts.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the ethics committee of the Istanbul University Istanbul Medical Faculty Institutional Board (Ethics No. :2016/1298).

### Statistical analysis

The data were evaluated using the SPSS 21.0 software program (AMIS, Istanbul, Turkey). Descriptive information was described as mean ± standard deviation (%). Continuous variables were presented as mean ± standard deviation, and categorical variables as numbers (%). Normal distribution of data was assessed by histogram, Q-Q plots and Shapiro–Wilk test. Homogeneity of variance was tested using Levene's test. For independent group comparisons, Student's $t$ test was used when parametric test assumptions were met, and Mann–Whitney $U$ test when parametric test assumptions were not met. For comparisons of more than two groups, we used one-way analysis of variance and Kruskal Wallis test. Pearson $\chi^2$ analysis was used to compare categorical data. For multiple comparisons, we used Tukey's HSD test. The correlation between quantitative data was assessed by Spearman's correlation analysis.

## RESULTS

In the study group, 11 of 17 patients (64%) were female, and 6 (36%) were male, with a mean age of 55.9 ± 15.7 years. Among those with IPAH, 7 out of 10 patients (70%)

were female, and 3 (30%) were male, with a mean age of 61.8 ± 12.1 years while 4 of 7 patients (57%) with CTEPH were female, and 3 (43%) were male, with a mean age of 47.5 ± 17.3 years.

The control group consisted of 21 (70%) females, and 9 (30%) males, with a mean age of 45 ± 14.05 years. A comparison in mean age and gender distribution between the study and control groups showed no statistically significant difference ($p = 0.89$) (Table 1).

After the diagnosis one patient with IPAH received a triple combination treatment including intravenous epoprostenol, and other patients received an oral combination therapy including endothelin receptor blocker and phosphodiesterase-5 inhibitor (1 month until addition of a second medication). All patients with CTEPH were inoperable based on the inclusion criteria. They were initiated on a treatment with oral riociguat, and maintained after titration to a maximum dose of 2.5 mg TID.

The 18FDG-PET results were evaluated by two nuclear medicine experts. A significant difference was found in mean left lung FDG ($p = 0.006$), right lung FDG ($p = 0.004$), thoracic aorta FDG ($p = 0.012$), right atrium (RA) FDG ($p < 0.001$) and right ventricle (RV) FDG ($p < 0.001$) uptakes compared to mean uptake values in the control group. Although left ventricular FDG uptake of patients was lower than left ventricular FDG uptake of subjects in the control group, the difference was not statistically significant ($p = 0.82$) (Table 2). When four patients with a baseline functional class IV were compared to other patients, a statistically significant difference was found between the RV ($p = 0.01$) and RA ($p = 0.02$) FDG uptakes (Table 3).

Throughout the study, a total of 5 patients (29%) died despite maximal therapy. Among four patients with IPAH in the baseline high-risk group, two patients died 1 month after enrollment, and one patient 2 months after enrollment while the patient who were initiated on intravenous epoprostenol died at month 3, and one patient with CTEPH who was in the baseline moderate-risk group died due to ventricular fibrillation 2 months after enrollment. Among remaining 12 patients, 7 (58%) had a baseline functional class III category, which decreased to functional class II after PAH-specific therapy

RHC of survival patients could not be repeated in one patient diagnosed with IPAH due to refusal to consent, and in another patient with CTEPH who had severe

**TABLE 1** Gender and age characteristics of patients.

| | IPAH ($n = 10$) | CTEPH ($n = 7$) | Control group ($n = 30$) | $p$ value |
|---|---|---|---|---|
| Female/male | 7/3 | 4/3 | 21/9 | 0.92 |
| Age, years | 61.8 ± 12.1 | 47.5 ± 17.3 | 44.4 ± 14.3 | 0.47 |

Abbreviations: CTEPH, chronich thromboembolic pulmonary hypertensiyon; IPAH, idiopathic pulmonary arterial hypertensiyon.

**TABLE 2** Comparison of FDG uptake values between the patient and control groups.

| FDG values | Patient group ($n = 17$) | Control group ($n = 30$) | $p$ value |
|---|---|---|---|
| SUV, left lung (mean ± *SD*) | 0.82 ± 0.39 | 0.51 ± 0.15 | 0.006 |
| SUV, right lung (mean ± *SD*) | 0.72 ± 0.39 | 0.48 ± 0.14 | 0.004 |
| SUV, thoracic aorta (mean ± *SD*) | 2.02 ± 0.46 | 1.68 ± 0.40 | 0.012 |
| SUV, right atrium (mean ± *SD*) | 2.25 ± 0.56 | 1.54 ± 0.66 | <0.001 |
| SUV, right ventricle (mean ± *SD*) | 2.37 ± 0.84 | 1.63 ± 0.40 | <0.001 |
| SUV, left ventricle (mean ± *SD*) | 2.90 ± 1.74 | 3.08 ± 1.94 | NA |

Abbreviations: FDG, fluorodeoxyglucose; SUV, standardized uptake value.

**TABLE 3** Comparison between patients with functional class IV and other patients.

| | Patients with FC IV ($n = 4$) | Patients with FC II–III ($n = 13$) | $p$ value |
|---|---|---|---|
| SUV, right atrium (mean ± *SD*) | 2.52 ± 0.42 | 2.17 ± 0.58 | 0.01 |
| SUV, right ventricle (mean ± *SD*) | 2.98 ± 0.39 | 2.21 ± 0.60 | 0.02 |

Abbreviations: FC, functional class; SUV, standardized uptake value.

persistent thrombocytopenia (platelet count <20,000/μL) despite transfusion. Although there was a reduction in the mean walking distance, the systolic pulmonary artery pressure measured by echocardiography and the mean pulmonary artery pressure (mPAP) and right atrial pressures (RAP) measured by RHC of patients, only the difference in 6MWD ($p = 0.006$) and systolic pulmonary artery pressure ($p = 0.003$) was statistically significant (Table 4).

A comparison of baseline and 6-month follow-up FDG uptakes of the patients who survived and benefited from treatment showed that there was non-significant trend between the onset and after treatment FDG value of RA, RV and both lung fields (Table 5).

A regression analysis of FDG uptakes in all patients showed that among all variables, there was a high positive correlation between the RV FDG uptake and the mPAP measured by RHC ($r = 0.7$, $p = 0.012$) and a moderate positive correlation between the RA FDG uptake and the RAP ($r = 0.5$, $p = 0.02$), while no significant correlation was found with pulmonary vascular resistance (PVR).

## DISCUSSION

The present study aimed to evaluate the use of 18-FDG PET imaging as an alternative method for diagnosis of patients with IPAH and CTEPH. Based on literature survey, there are only a limited number of studies are conducted. In a study of 8 patients with IPAH, 6 patients with CTEPH and 6 healthy controls, Hagan et al. found that FDG uptake was higher in lung fields and RV of patients compared to the healthy controls.[6] However, all the patients had been receiving PAH specific therapy before and correlations between RHC or echocardiographic parameters were not examined because of the time interval between hemodynamic investigations and the PET/CT scan. We only included treatment naïve cases and performed RHC 2 days after PET scan both onset and after 6-month PAH specific therapy to analyse the correlation between PET/CT and RHC. In another study with 30 patients with IPAH and 8 healthy controls, the mean uptakes in lung fields and right myocardium were higher in IPAH patients compared to controls.[7] However the results of both studies are based on small

**TABLE 4** Comparison of follow-up parameters before and after the treatment.

| Parameters | Pre-treatment (mean ± *SD*) (*n* = 17) | Post-treatment (mean ± *SD*) (*n* = 10) | *p* value |
|---|---|---|---|
| pro-BNP, pg/mL | 943.41 ± 2370.07 | 957.50 ± 2447.28 | 0.78 |
| 6MWD, m | 302.50 ± 119.15 | 378.50 ± 124.23 | 0.006 |
| sPAP by ECHO, mmHg | 75.90 ± 21.86 | 50.08 ± 15.90 | 0.003 |
| Mean PAP by RHC, mmHg | 40.71 ± 16.45 | 36.86 ± 19.23 | 0.29 |
| RAP, mmHg | 9.00 ± 5.6 | 8.00 ± 4.39 | 0.65 |
| Cardiac index, L/min/$m^2$ | 2.90 ± 0.78 | 2.57 ± 0.73 | 0.23 |
| PVR, Wood units | 5.57 ± 2.22 | 6.00 ± 3.6 | 0.77 |

Abbreviations: 6MWD, 6 min walk test; PAP, pulmonary arterial pressure; pro-BNP, pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure.

**TABLE 5** A comparison of baseline and 6-month standardized uptake values.

| | Pre-treatment (mean ± *SD*) (n = 17) | Post-treatment (mean ± *SD*) (n = 12) | *p* value |
|---|---|---|---|
| SUV, left lung (mean ± *SD*) | 0.74 ± 0.40 | 0.66 ± 0.80 | 0.35 |
| SUV, right lung (mean ± *SD*) | 0.70 ± 0.23 | 0.62 ± 0.40 | 0.53 |
| SUV, thoracic aorta (mean ± *SD*) | 2.07 ± 0.11 | 1.91 ± 0.09 | 0.16 |
| SUV, right atrium (mean ± *SD*) | 2.13 ± 0.60 | 1.91 ± 0.15 | 0.18 |
| SUV, right ventricle (mean ± *SD*) | 2.28 ± 0.90 | 2.22 ± 0.14 | 0.65 |
| SUV, left ventricle (mean ± *SD*) | 2.65 ± 0.31 | 3.33 ± 0.43 | 0.14 |

Abbreviation: SUV, standardized uptake value.

number of controls. At present study the number of control subjects was sufficient, and there were no differences in race, age and gender between the groups. In our study, the FDG uptake in the right and left lung fields ($p = 0.004$ and $p = 0.006$, respectively) and FDG uptake in RA and RV ($p < 0.001$) was higher compared to the control group, which was consistent with the literature.

We also found that there was no difference between the left ventricular FDG uptakes. Even though it was not significant, FDG uptake in the left ventricles of the PAH group was lower. The reduction in the left ventricular glucose uptake could be explained by reduced cardiac output.[8]

The etiology of increased right ventricular glucose metabolism in IPAH patients has not been fully understood yet. The reason for this is indicated as transition of myocardial metabolism from catabolism of fatty acids to the glycolytic pathway in cases where heart failure develops. Studies with PAH animal models and IPAH patients showed that glycolysis-related genes and proteins such as pyruvate dehydrogenase kinase of the right ventricle are upregulated.[9,10] Furthermore, reduced right coronary artery perfusion pressure or decreased coronary flow reserve and reduction in capillary and small intramyocardial arterioles density in PAH may contribute to right ventricular ischemia.[9,10] The underlying ischemia may explain the switch to the glycolytic pathway in the right ventricle. FDG uptake in lung fields mainly occurs with an increase in metabolic activity due to proliferation in the pulmonary arteries, while hypoxia has been considered as the leading cause of the increase in glycolysis in the right heart.

When we compared the right and left ventricular FDG uptakes of the subjects among themselves, the RV FDG uptakes were significantly higher ($p = 0.003$). Although the left ventricular myocardial layer has more volume because of its anatomy and it is exposed to a higher pressure, inflammatory and hypoxic conditions which induce right ventricle in PAH are not available for the left ventricle.

During the study, 5 patients died, and remaining patients had an increased 6MWD following 6-month PAH-specific treatment ($p = 0.006$), and a reduced systolic blood pressure as measured by echocardiography ($p = 0.003$). The mPAP and RAP decreased numerically, but it was not significant. It may be associated with small number of patients who underwent a secondary RHC (in addition to those died, a secondary RHC was not performed since one patient had severe thrombocytopenia and another patient did not provide consent). In surviving patients, although FDG uptakes in the right lung, left lung, right atrium and right ventricle decreased numerically compared to baseline PET images, the difference was not statistically different.

The RV ($p = 0.012$) and RA ($p = 0.02$) FDG uptakes of four patients who had functional class IV at baseline and died during the first 3 months were significantly higher compared to other patients. Poor functional class and survival of the patients with high right atrial and ventricular FDG uptakes suggest that these values may help predicting prognosis of the disease.

Ruiter et al.[11] performed a study investigating the correlation between pulmonary FDG uptake and PH severity, and no correlation was found between lung FDG uptake and 6MWD, mPAP, PVR, and plasma NT-proBNP levels, similar to our results. Oikawa et al.[12] demonstrated that RV SUV was significantly correlated with mPAP, RAP, PVR, RV wall stress, and plasma BNP levels, but not with RV wall thickness and mass. We have studied the correlation of RV FDG uptake with 6MWD, RAP, PVR, pro-BNP, and sPAP which are used for follow-up of the PAH patients. High positive correlation between the RV FDG uptake and the mPAP ($r = 0.7$, $p = 0.012$) and a moderate positive correlation between the RA FDG uptake and the RAP ($r = 0.5$, $p = 0.02$) were found. These results are confirming prior results in the literature.

As limitations of our study 30% of our patient group died during the study; and there was a lack of definite information about the right heart FDG threshold values due to limited number of studies in the literature. In addition, many pulmonary hypertension groups (e.g., rheumatology-associated pulmonary hypertension, pulmonary hypertension with left-heart disease) were excluded from the study. However previous studies have showed that patients with diffuse parenchymal interstitial lung diseases have increased lung FDG uptake which may cause false inferences.[13,14] Also Ohira et al.[15] have reported that PAH patients demonstrated significantly increased mean lung FDG SUV compared with left heart diseases.

## CONCLUSION

In conclusion, considering the small number of centers experienced in RHC to make a diagnosis for a disease where an early treatment would be lifesaving, it appears that there is a need for non-invasive diagnostic methods that provide results in a short period of time.[16] In the present study, increased right atrial and ventricular FDG uptake was associated with presence of pulmonary hypertension and correlates with mPAP and RAP, respectively, which are important indicators in the prognosis of IPAH and CTEPH. While FDG PET is an

unique method to show inflammatory pathologies related to pulmonary hypertension, it is not yet a sufficient test to make a definitive diagnosis. Accordingly, this test can be used for screening in patients with high suspicion of pulmonary hypertension but who cannot undergo right heart catheterization for various reasons. In those patients pulmonary hypertension should be kept in mind in case of FDG increase in the right heart or lungs of patients while there is no other pathological image that explains these increases. Since there are not enough studies in the literature, we do not yet have enough data to determine the exact diagnosis or subgroup of pulmonary hypertension. Along with the available results in the literature, larger prospective studies are required whether FDG PET imaging can be used to diagnose or predict the prognosis of pulmonary hypertension.

## AUTHOR CONTRIBUTIONS

**Celik Sumer**: Data curation; investigation; writing—original draft, reviewing and editing. **Gulfer Okumus**: Supervision; conceptualization; data curation; investigation; methodology; validation; writing—original draft; reviewing and editing; guarantor. **Emine Goknur Isik**: Data curation; visualization; investigation; reviewing and editing. **Cuneyt Turkmen**: Investigation; reviewing and editing. **Ahmet Kaya Bilge**: Investigation; reviewing and editing. **Murat Inanc**: Investigation; reviewing and editing.

## ACKNOWLEDGMENTS

This work was funded by grants from Johnson & Johnson.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## ETHICS STATEMENT

The study was carried out according to the principles of the Declaration of Helsinki and approved by the ethics committee of the Istanbul University Istanbul Medical Faculty Institutional Board (Ethics No.: 2016/1298).

## ORCID

*Celik Sumer* http://orcid.org/0000-0001-7557-1869
*Emine Goknur Isik* https://orcid.org/0000-0002-3786-8052

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**How to cite this article:** Sumer C, Okumus G, Isik EG, Turkmen C, Bilge AK, Inanc M. (18)F-fluorodeoxyglucose uptake by positron emission tomography in patients with IPAH and CTEPH. Pulm Circ. 2024;14:e12363. https://doi.org/10.1002/pul2.12363