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Research Letter

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INCREASED LUNG [^{18}F]-FDG UPTAKE IN CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION WITH DISTAL INVOLVEMENT

Jeisson Osorio[1,2], Olga Tura-Ceide[1,2,3], Javier Pavía[4,5], Ivan Vollmer[4], Isabel Blanco[1,2], Aida Niñerola-Baizán[4,5], Pilar Paredes[4], Francisco Lomeña[4], Jesús Ruiz-Cabello[2,5,6,7], Manel Castellà[8], Victor Ivo Peinado[1,2,9], Joan Albert Barberà[1,2#].

[1]Department of Pulmonary Medicine, Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, Spain.

[2]Biomedical Research Networking Centre on Respiratory Diseases (CIBERES), Madrid, Spain.

[3]Translational Research Group on Cardiovascular Respiratory Diseases (CAREs), Institut d´Investigació Biomèdica de Girona (IDIBGI-CERCA), Salt, Girona, Spain.

[4]Center for Diagnostic Imaging, Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, Spain.

[5]Biomedical Research Networking Centre on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Barcelona, Spain.

[6]CIC biomaGUNE, Basque Research and Technology Alliance (BRTA), Donostia San Sebastián, Spain & Ikerbasque, Basque Foundation for Science, Bilbao, Spain.

[7]MR and Imaging in Biomedicine Group, Department of Chemistry in Pharmaceutical Sciences, Pharmacy School, University Complutense Madrid, Madrid, Spain.

[8]Department of Cardiovascular Surgery, Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, Spain.

[9]Department of Experimental Pathology, Institut d'Investigacions Biomèdiques de Barcelona (IIBB), CSIC-IDIBAPS, Barcelona, Spain

#Corresponding Author: Joan Albert Barberà, MD, PhD. Department of Pulmonary Medicine, Hospital Clinic, Villarroel 170. 08036 Barcelona, Spain. Email: jbarbera@clinic.cat.

Summary (take home message for social media, 250-character max)

Patients with distal chronic thromboembolic pulmonary hypertension (CTEPH) show greater FDG lung uptake on PET scans than those with proximal disease, suggesting a proliferative microvasculopathy. These findings support further investigation on the role of PET/CT in characterising CTEPH.

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To the Editor,

Pulmonary hypertension (PH) is characterised by elevated pulmonary artery pressure and is classified into five groups based on clinical characteristics and therapeutic approaches [1]. Group 4 corresponds to chronic thromboembolic pulmonary hypertension (CTEPH), which is characterised by a combination of thrombotic occlusive disease and peripheral vasculopathy. The balance between these abnormalities determines the therapeutic approach [2].

We have previously demonstrated a proliferative phenotype in endothelial cells of pulmonary endarterectomy (PEA) specimens from patients with CTEPH with predominant proximal disease [3]. Distal vasculopathy involves remodelling of peripheral pulmonary arteries with lesions like those observed in pulmonary arterial hypertension (PAH) [2], namely intimal fibrosis and fibromuscular proliferation. Recent studies have identified a distinct microvasculopathy in CTEPH, involving small pre-capillary vessels, capillaries, and pulmonary venules with widespread cellular proliferative phenomena [4,5].

Positron emission tomography (PET) is a molecular imaging tool that detects and quantifies the metabolic activity associated with various processes, including cellular proliferation. In PAH, significant cellular proliferation has been demonstrated in the right ventricle [6,7], although conclusive data regarding the lung parenchyma is lacking[8,9]. Similarly, PET studies in CTEPH have not yielded conclusive results[9,10]. We hypothesised that patients with CTEPH, depending on whether they have predominant proximal or distal involvement, would exhibit different patterns of [^{18}F]-FDG uptake in PET/CT imaging reflecting differences in cell proliferation. This study aimed to investigate the differences in [^{18}F]-FDG uptake in the lung parenchyma, pulmonary arteries, and right ventricle between CTEPH patients with proximal and distal involvement, comparing them to patients with idiopathic PAH (iPAH) and healthy controls.

We evaluated 15 patients (62±10 years; 33% women) with CTEPH and proximal occlusive lesions (CTEPH-p) eligible for pulmonary endarterectomy, 10 patients (66±6 years; 80% women) with CTEPH with distal lesions (CTEPH-d) unsuitable for surgical removal, 20 patients (51±14 years; 65% women) with iPAH, and 20 healthy volunteer controls with no known underlying medical condition (44±9 years; 65% women). Patients with other lung or systemic diseases that could affect FDG uptake on PET/CT were excluded. The study was approved by the Hospital Clínic Ethics Committee and registered at the EUDRACT database (2016-000347-14).

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All participants underwent a six-minute walk test and measurement of B-type natriuretic peptide (BNP) levels at the time of study inclusion. Plasma levels of angiogenic factors were measured in 28 subjects using a commercially available ELISA kit (QAH-ANG-3, Raybiotech). Diagnostic right heart catheterisation (RHC) was performed in all patients with pulmonary hypertension (PH), and the measurement closest to the FDG-PET/CT assessment (mean 114±114 days) was considered for the analysis in patients with multiple RHCs.

PET/CT imaging was performed using a Siemens Biograph mCT system after at least 6 hours of fasting. Approximately 281 MBq (181-395 MBq) of [^{18}F]-FDG was injected intravenously[11]. Low-dose chest CT was performed before PET for anatomical placement and attenuation correction. Dynamic PET acquisition over 90 minutes captured mediastinum, pulmonary parenchyma, pulmonary arteries, right ventricle (RV), and left ventricle (LV). Average standardised uptake values (SUV) of [^{18}F]-FDG were computed from PET images summed over the final 30 minutes of acquisition for regions of interest (ROIs) within these anatomical areas. Five ROIs of the pulmonary parenchyma in axial, coronal and sagittal planes were obtained for each lung. Pulmonary artery ROIs were placed at the level of the pulmonary artery trunk. The RV/LV FDG uptake ratio was computed. The analysis of [^{18}F]-FDG uptake in ROIs was conducted using GIMIAS 1.8 program and expressed as the average value (SUVmean). Statistical analyses involved ANOVA, post hoc tests, and Pearson's or Spearman's correlation tests.

Patients with CTEPH-d and CTEPH-p were older than controls ($P<0.05$), whereas age in the iPAH group was comparable. Females predominated in the CTEPH-d, iPAH, and control groups, whereas CTEPH-p patients were predominantly males. BMI was significantly higher in CTEPH-d patients (35±9 kg/m^2) than in controls (25±4 kg/m^2; $P<0.05$); while in the CTEPH-d and IPAH groups (27±5 kg/m^2, each) BMI was similar.

At the time of study inclusion, 95% patients with IPAH, 100% with CTEPH-d, and 67% with CTEPH-p were receiving PAH therapies. Six-minute walk distance (6MWD) was significantly shorter in all patient groups (413±76, 416±110 and 508±124 m; CTEPH-p, CTEPH-d and IPAH, respectively) compared to controls (654±79 m; $P<0.05$). BNP levels were highest in CTEPH-p (207±201 vs. 13±12 pg/ml in controls; $P<0.05$) and elevated in CTEPH-d (35±26 pg/ml) and IPAH (93±145 pg/ml). At the closest RHC, mean pulmonary artery pressure was higher in CTEPH-p (48±11 mmHg) than in CTEPH-d (39±12 mmHg) and similar to IPAH (44±10 mmHg). Cardiac index was significantly lower in CTEPH-p than in CTEPH-d (2.04±0.3 and 2.65±0.3 L/min/m^2, respectively; $P<0.05$) and similar to iPAH (2.32±0.5 L/min/m^2). Pulmonary vascular resistance was higher in both CTEPH-p and iPAH (794±197

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and 780±340 dyn·s·cm^{-5}, respectively) than in CTEPH-d (490±176 dyn·s·cm^{-5}; P<0.05 compared to IPAH).

The [^{18}F]-FDG uptake in the lung parenchyma was higher in the CTEPH-d group than in the CTEPH-p, iPAH and control groups (Figure 1b). Patients with CTEPH-d also showed greater FDG uptake in the pulmonary arteries than healthy controls, which did not differ from patients with CTEPH-p or iPAH (Figure 1c). In contrast, FDG uptake by the RV, as assessed by the RV/LV ratio, was significantly higher in the CTEPH-p and iPAH groups than in the CTEPH-d and control groups (Figure 1e).

The [^{18}F]-FDG uptake in lung parenchyma correlated with that in pulmonary arteries (r=0.71; p<0.001), but not with the RV uptake. The RV/LV FDG uptake ratio correlated with the CI (r=-0.35 p=0.018), 6MWD (r=-0.25; p=0.04), and BNP (r=0.53; p<0.001).

Among the 30 angiogenic biomarkers analysed, plasma levels of vascular endothelial growth factor receptor 2 (VEGFR2) were elevated in CTEPH-d and iPAH, while levels of urokinase-type plasminogen activator receptor (uPAR) were increased in CTEPH-p and iPAH, compared to controls.

Our study shows increased [^{18}F]-FDG uptake in the lung parenchyma in patients with CTEPH with distal involvement compared to those with proximal involvement and iPAH. In contrast, [^{18}F]-FDG uptake by the right ventricle was increased in both patients with proximal CTEPH and those with iPAH, the groups exhibiting greater haemodynamic impairment.

Increased [^{18}F]-FDG uptake reflects greater glycolytic metabolism in pulmonary arteries and lung parenchyma of patients with distal CTEPH. A potential explanation would be increased cell proliferation activity in small-sized vessels, consistent with the observation that these patients exhibit prominent microvasculopathy in their lungs [4,12]. Peripheral vasculopathy is also present in patients with proximal CTEPH, downstream of occluded vessels, with anastomoses between bronchial arteries, precapillary arterioles and pulmonary venules[5]. Presumably, the increased FDG uptake by the lung parenchyma in CTEPH-d likely reflects a greater sensitivity in capturing microvasculopathy in "open" arteries than in occluded vessels, although we cannot exclude other sources of increased metabolic activity, like inflammation[13,14]. Future studies utilising radiotracers specific for hyperproliferation may help to clarify this hypothesis [15–17]. Differences in lung perfusion blood volume (PBV) could also explain the differences in FDG uptake between groups. Although PBV has not been directly compared between proximal and distal CTEPH, it inversely correlates with hemodynamic severity[18]. Since patients with CTEPH-p had greater hemodynamic impairment, we cannot exclude that the higher lung FDG uptake in

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CTEPH-d might be attributable to differences in PBV. This hypothesis warrants further investigation employing advanced imaging. Patients with CTEPH-d had higher BMI than those with CTEPH-p. While BMI may influence FDG uptake in pulmonary arteries[19], it does not affect uptake by lung parenchyma[20]. Thus, the increased parenchymal uptake in CTEPH-d, unaffected by BMI, supports a primary role of microvascular pathology on our findings. Interestingly, patients with distal CTEPH also showed higher plasma levels of VEGFR2, which promotes endothelial cell proliferation and is involved in the pathogenesis of pulmonary hypertension [21].

Notably, our study did not find differences in pulmonary FDG uptake between iPAH patients and healthy controls or patients with CTEPH. Other studies have also failed to demonstrate increased FDG uptake in iPAH, despite cell proliferation is a hallmark of PAH vasculopathy [22]. We found elevated plasma levels of VEGFR2 and uPAR in iPAH patients, consistent with previous research[21]. Although iPAH and CTEPH share similarities in the pulmonary microvasculopathy, differences in lung FDG uptake may reflect subtle differences in the underlying pathophysiological processes, with distal CTEPH potentially involving more active proliferative or inflammatory processes.

FDG uptake by the RV was greater in patients with CTEPH-p and iPAH compared with healthy controls, consistent with previous reports [8,10,22,23], and also greater than in patients with CTEPH-d, likely due to less severe haemodynamic compromise in the latter group. Indeed, RV uptake was inversely related to CI and the 6MWD, while it was directly correlated with BNP levels. Overall, this suggests that increased RV metabolism represents an adaptive response to increased afterload rather than a distinct feature distinguishing proximal from distal CTEPH [25].

Our study has limitations, including uncertainty regarding the interpretation of the FDG uptake signal, a small sample size, and differences in PAH therapy between the PH groups. Although PH treatment may contribute to differences in pulmonary hemodynamics and BNP levels, their potential effect on FDG uptake in lung parenchyma or pulmonary vessels remains uncertain.

In conclusion, our study shows a different metabolic profile, assessed by FDG-uptake on PET/CT, in patients with CTEPH, with increased glycolytic activity in the lung parenchyma and pulmonary vessels in those with distal involvement. The potential clinical utility of FDG PET/CT uptake in assessing peripheral vasculopathy in CTEPH warrants further investigation.

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References

1 Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022 Oct 11;43(38): p. 3618–3731.

2 Kim NH, D'Armini AM, Delcroix M, et al. Chronic thromboembolic pulmonary disease. Eur Respir J. 2024 Oct 31;64(4):2401294.

3 Tura-Ceide O, Smolders VFED, Aventin N, et al. Derivation and characterisation of endothelial cells from patients with chronic thromboembolic pulmonary hypertension. Sci Rep. 2021 Sep 22;11(1):18797

4 Gerges C, Gerges M, Friewald R, et al. Microvascular Disease in Chronic Thromboembolic Pulmonary Hypertension: Hemodynamic Phenotyping and Histomorphometric Assessment. Circulation. 2020 Feb 4;141(5):376-386.

5 Dorfmüller P, Günther S, Ghigna MR, et al. Microvascular disease in chronic thromboembolic pulmonary hypertension: A role for pulmonary veins and systemic vasculature. Eur Respir J. 2014 Nov;44(5):1275-88.

6 Tatebe S, Fukumoto Y, Oikawa-Wakayama M, et al. Enhanced [18F]fluorodeoxyglucose accumulation in the right ventricular free wall predicts long-term prognosis of patients with pulmonary hypertension: A preliminary observational study. Eur Heart J Cardiovasc Imaging. 2014 Jun;15(6):666-72.

7 Oikawa M, Kagaya Y, Otani H, et al. Increased [18F]fluorodeoxyglucose accumulation in right ventricular free wall in patients with pulmonary hypertension and the effect of epoprostenol. J Am Coll Cardiol. 2005 Jun 7;45(11):1849-55.

8 Saygin D, Highland KB, Farha S, et al. Metabolic and functional evaluation of the heart and lungs in pulmonary hypertension by gated 2-[18F]-Fluoro-2-deoxy-D-glucose positron emission tomography. Pulm Circ. 2017 Apr-Jun;7(2):428-438.

9 Kluge R, Barthel H, Pankau H, et al. Different Mechanisms for Changes in Glucose Uptake of the Right and Left Ventricular Myocardium in Pulmonary Hypertension. J Nucl Med. 2005 Jan;46(1):25-31.

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10 Hagan G, Southwood M, Treacy C, et al. 18FDG PET imaging can quantify increased cellular metabolism in pulmonary arterial hypertension: A proof-of-principle study. Pulm Circ. 2011 Oct-Dec;1(4):448-55.

11 Boellaard R. Standards for PET image acquisition and quantitative data analysis. J Nucl Med. 2009 May:50 Suppl 1:11S-20S.

12 Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest. 1993; 103: 685–692.

13 Zabini D, Heinemann A, Foris V, et al. Comprehensive analysis of inflammatory markers in chronic thromboembolic pulmonary hypertension patients. Eur Respir J. 2014 Oct;44(4):951-62.

14 Willems L, Kurakula K, Verhaegen J, et al. Angiogenesis in Chronic Thromboembolic Pulmonary Hypertension: A Janus-Faced Player? Arterioscler Thromb Vasc Biol. 2024 Apr;44(4):794-806.

15 Park JB, Suh M, Park JY, et al. Assessment of inflammation in pulmonary artery hypertension by 68Ga-mannosylated human serum albumin. Am Am J Respir Crit Care Med. 2020 Jan 1;201(1):95-106.

16 Botros L, Jansen SMA, Ashek A, et al. Application of [18F]FLT-PET in pulmonary arterial hypertension: a clinical study in pulmonary arterial hypertension patients and unaffected bone morphogenetic protein receptor type 2 mutation carriers. Pulm Circ. 2021 Jun 1;11(3):20458940211028017.

17 Ashek A, Spruijt OA, Harms HJ, et al. 3'-Deoxy-3'-[18F]Fluorothymidine Positron Emission Tomography Depicts Heterogeneous Proliferation Pathology in Idiopathic Pulmonary Arterial Hypertension Patient Lung. Circ Cardiovasc Imaging. 2018;11(8):e007402.

18 Takagi H, Ota H, Sugimura K, Otani K, Tominaga J, Aoki T, et al. Dual-energy CT to estimate clinical severity of chronic thromboembolic pulmonary hypertension: Comparison with invasive right heart catheterization. Eur J Radiol. 2016;85:1574–1580.

19 Bang JI, Moon CM, Kim HO, Kang SY, Yoon HJ, Kim BS. Blood pool activity on F-18 FDG PET/CT as a possible imaging biomarker of metabolic syndrome. Sci Rep. 2020;10(1):17367.

20 Sprinz C, Altmayer S, Zanon M, et al. Effects of blood glucose level on 18F-FDG uptake for PET/CT in normal organs: A systematic review. PLoS One. 2018;13(2):e0193140.

21 Kurakula K, Smolders VFED, Tura-Ceide O, Jukema JW, Quax PHA, Goumans MJ. Endothelial Dysfunction in Pulmonary Hypertension: Cause or Consequence?. Biomedicines. 2021;9(1):57.

22 Tobal R, Potjewijd J, van Empel VPM, et al. Vascular Remodeling in Pulmonary Arterial Hypertension: The Potential Involvement of Innate and Adaptive Immunity. Front Med (Lausanne). 2021;8:806899.

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23 Sakao S, Daimon M, Voelkel NF, et al. Right ventricular sugars and fats in chronic thromboembolic pulmonary hypertension. Int J Cardiol. 2016;219:143-149.

24 Bokhari S, Raina A, Rosenweig EB, 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(6):641-647.

25 Can MM, Kaymaz C, Tanboga IH, et al. Increased right ventricular glucose metabolism in patients with pulmonary arterial hypertension. Clin Nucl Med. 2011;36(9):743-748.

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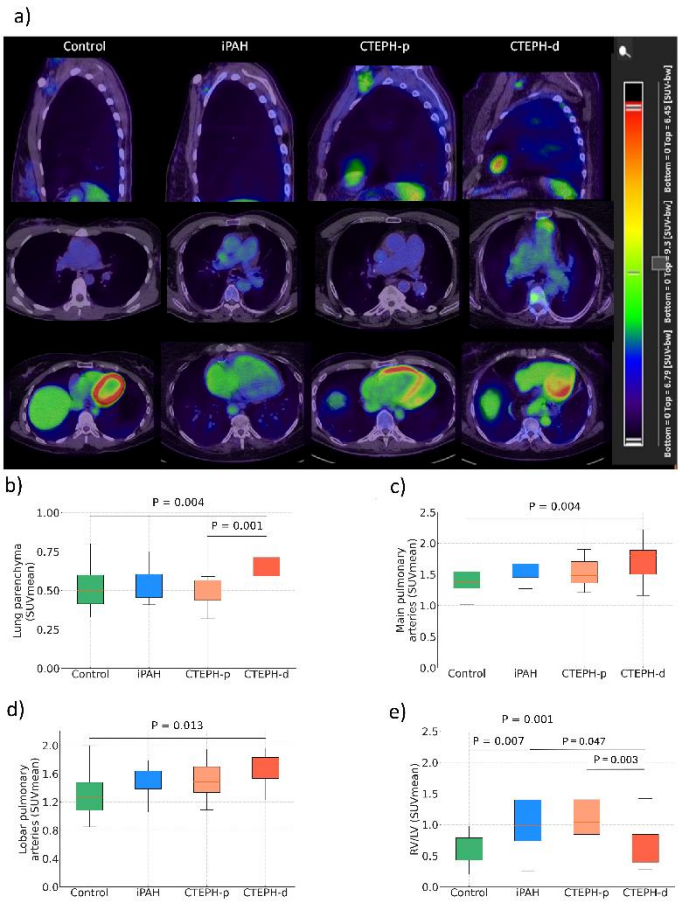
FIGURE LEGENDS

Figure 1: **a)** Representative PET/CT fusion images illustrating [18F]-fluorodeoxyglucose (FDG) uptake patterns in control subjects and patients with idiopathic pulmonary arterial hypertension (iPAH), chronic thromboembolic pulmonary hypertension with proximal (CTEPH-p) and distal involvement (CTEPH-d). Top row: sagittal views of the left lung; middle row: pulmonary arteries; and bottom row: right and left ventricles. Control subjects showed negligible FDG uptake in lung parenchyma and pulmonary vasculature. FDG uptake was increased in the lung parenchyma and pulmonary arteries in patients with CTEPH-d. Conversely, FDG uptake in right ventricle (RV) relative to the left ventricle (LV) was increased in patients with CTEPH-p and iPAH. **b-e)** Bar diagrams showing mean standardised FDG uptake values (SUVmean) in: **b)** lung parenchyma, **c)** main pulmonary arteries, **d)** lobar pulmonary arteries, and **e)** RV/LV ratio in control subjects and patient groups. Statistical significance (P values) between groups is indicated where applicable.



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