

with bronchiectasis. *Chest* [online ahead of print] 14 Mar 2020; DOI: 10.1016/j.chest.2020.02.048.

11. Cai G, Bossé Y, Xiao F, Kheradmand F, Amos CI. Tobacco smoking increases the lung gene expression of ACE2, the receptor of SARS-CoV-2. *Am J Respir Crit Care Med* 2020;202:1557–1559.
12. Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M, et al.; HCA Lung Biological Network. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med* 2020;26:681–687.

Copyright © 2020 by the American Thoracic Society



## Positron Emission Tomography: A Novel Approach to Detect Pulmonary Artery Hypertension at the Early Stage?

To the Editor:

Pulmonary arterial hypertension (PAH) is a severe disease with a poor prognosis, and both early diagnosis and early treatment are crucial to improve outcomes (1). However, methods for early diagnosis are limited, especially at the stage of PAH development before the onset of elevated pulmonary arterial pressure. Macrophages play an important role in the development and progression of PAH (2). In a recent study published in the *Journal*, Park and colleagues tracked macrophages in the lung using positron emission tomography (PET) with <sup>68</sup>Ga-2-(p-isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid mannoseylated human serum albumin in patients with PAH and animal models (3). Some of the results of these studies were previously reported in the form of an abstract (4).

Via PET scans, Park and colleagues showed that the density of mannose receptor, a marker for macrophages, was significantly higher in patients with PAH and monocrotaline-induced rat PAH models (3). In addition, pulmonary hypertension-targeted therapy with sildenafil or macitentan reduced the density of mannose receptor in the lungs of rats with PAH. These results suggest that the density of lung macrophage infiltration could reflect the severity of PAH. Interestingly, this study also indicates that at the early stage, only 1 week after injection of monocrotaline, a higher density of mannose receptor was found in the rat lungs. This suggests that using PET to monitor lung macrophages may predict the development of PAH even before the onset of high pulmonary arterial pressure, because in the first week after injection of monocrotaline, the rats showed only a mild elevation of pulmonary arterial pressure, which did not meet the standard for PAH diagnosis. Based on these results, Park and colleagues concluded that lung macrophage detection via PET scans

could be used as a diagnostic and monitoring tool for PAH. However, this study raised several concerns. First, PAH is a rare disease, and PET is an expensive diagnostic approach with very limited availability; thus, it may not be realistic to use this technique to diagnose PAH in low-risk populations. However, in individuals at high risk for PAH, such as those with connective tissue disease or HIV infection, PET may be a useful approach for diagnosing PAH, especially at the early stage before the onset of elevated pulmonary arterial pressure. Second, the detection of mannose receptor to monitor macrophage infiltration is questionable because mannose receptor is expressed not only in macrophages but also in other cell types in the lung, especially tracheal smooth muscle cells (5). It would be important to know whether this receptor is upregulated in macrophages in PAH before concluding that macrophage infiltration is increased in the lung during PAH, as the increased PET signal could be a result of increased mannose receptor expression, and not the number of macrophages. Third, the presence of an inflammatory lung disease, such as interstitial lung disease, may affect macrophage infiltration, as shown by Park and colleagues, which may affect diagnostic specificity.

Overall, this study is very interesting in that it demonstrates dynamic changes in mannose receptor in the lung at different time points of PAH development and therapy, and provides solid evidence that macrophage infiltration (mannose receptor elevation) is associated with PAH development and progression. Further studies, especially in humans, are needed to provide more data to evaluate the specificity and sensitivity of lung mannose receptor density for the diagnosis and evaluation of PAH. ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

Ruidi Tang, B.S.\*  
The First Affiliated Hospital of Guangzhou Medical University  
Guangzhou, China

Yingkang Jin, M.D., Ph.D.\*  
Guangzhou Women and Children's Medical Center  
Guangzhou, China

Jing Liao, M.D.\*  
Lingdan Chen, M.D.  
Chunli Liu, M.D., Ph.D.  
Shaoqiang Li, M.D.  
Jian Wang, Ph.D.  
Tao Wang, M.D., Ph.D.  
Wenju Lu, M.D., Ph.D.†  
The First Affiliated Hospital of Guangzhou Medical University  
Guangzhou, China

ORCID ID: 0000-0001-9372-1648 (T.W.).

\*These authors contributed equally to this work.  
†Corresponding author (e-mail: [wlu92@yahoo.com](mailto:wlu92@yahoo.com)).

## References

1. Kiely DG, Lawrie A, Humbert M. Screening strategies for pulmonary arterial hypertension. *Eur Heart J Suppl* 2019;21:K9–K20.
2. Savai R, Pullamsetti SS, Kolbe J, Bieniek E, Voswinckel R, Fink L, et al. Immune and inflammatory cell involvement in the pathology of idiopathic pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2012;186:897–908.
3. Park J-B, Suh M, Park JY, Park JK, Kim Y-I, Kim H, et al. Assessment of inflammation in pulmonary artery hypertension by <sup>68</sup>Ga-mannoseylated human serum albumin. *Am J Respir Crit Care Med* 2020;201:95–106.

§This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern ([dgern@thoracic.org](mailto:dgern@thoracic.org)).

Supported by grants from the National Natural Science Foundation of China (81700426 and 81970046 to T.W.) and the Young Scholar Foundation of the State Key Laboratory of Respiratory Disease (SKLRD-QN-201714 to T.W.).

Originally Published in Press as DOI: 10.1164/rccm.202002-0314LE on April 8, 2020

4. Ashek A, Dubois O, Wilkins M, Zhao L. Kinetic analysis of 3'-deoxy-3'-[18F]-fluorothymidine (FLT) positron emission tomography (PET) in monocrotaline-induced pulmonary hypertension rat [abstract]. *Am J Respir Crit Care Med* 2016;193:A3911.
5. Martinez-Pomares L. The mannose receptor. *J Leukoc Biol* 2012;92:1177–1186.

Copyright © 2020 by the American Thoracic Society



## Reply to Tang *et al.*

From the Authors:

We thank Dr. Tang and colleagues for their interest in our paper (1). We agree that positron emission tomography (PET) may be able to detect pulmonary artery hypertension (PAH) at an early stage, before overt hemodynamic changes become evident. Our study demonstrated that infiltration of macrophages into the lung precedes the onset of any increase in pulmonary artery pressure, which is in line with several previous animal studies suggesting that inflammation is an early driver of PAH pathogenesis (2). Although there are no conclusive data regarding whether inflammation occurs earlier than the increase of pulmonary artery pressure in human PAH, several lines of evidence support the concept that inflammation plays a pivotal role in the pathobiology of human PAH as well (3), suggesting that PET has a great potential to detect possible subclinical changes in the lungs of patients with PAH. However, as the authors sharply pointed out, PET may not be an adequate modality to screen for rare disorders such as PAH, considering the limited accessibility to PET. Exposure to radiation is another important issue that should be taken into account when considering PET as a screening tool for early detection of PAH.

We completely agree with the suggestion by Dr. Tang and colleagues that a more clinically realistic target population for PAH screening using PET would be individuals at high risk of developing this devastating disease, particularly those with chronic inflammatory conditions, such as certain connective tissue diseases (4), sickle cell anemia (5), and HIV infection (6). In particular, considering that the prevalence of PAH is ~10% in patients with systemic sclerosis, with a 50% mortality rate within 3 years of a PAH diagnosis (7, 8), these patients may represent a population in which PAH screening with PET would provide the greatest benefit and could be justified. Indeed, when we preliminarily performed <sup>68</sup>Ga-2-(p-isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid mannosylated human serum albumin (<sup>68</sup>Ga-NOTA-MSA) PET in two patients with systemic sclerosis and no evidence of PAH on right heart catheterization, the lung-to-reference ratio of <sup>68</sup>Ga-NOTA-MSA uptake was 0.215 and 0.221, respectively, which was higher than that observed in the normal subjects or those with pulmonary hypertension by left heart disease, but lower than that in the patients with primary PAH. We are enrolling more patients

with systemic sclerosis and serial echocardiographic assessments to address this issue, aiming to explore the clinical value of <sup>68</sup>Ga-NOTA-MSA PET for predicting possible PAH.

Another important issue is the diagnostic specificity of <sup>68</sup>Ga-NOTA-MSA PET for PAH, which was also raised by Dr. Tang and colleagues. It is crucial to keep in mind that the increased lung uptake of <sup>68</sup>Ga-NOTA-MSA is not necessarily equal to the increased infiltration of macrophages into the pulmonary vessels. As the authors mentioned, the expression of mannose receptor is not confined to macrophages. Because it is also expressed by smooth muscle cells in the trachea (9), as well as in the lymphatic endothelium (10), it is unclear whether the increased uptake of <sup>68</sup>Ga-NOTA-MSA is derived from macrophages or other cells, or both. Although we do not have direct evidence for this, it has been reported that the expression of mannose receptor is increased in peripheral blood mononuclear cells from patients with systemic sclerosis and PAH but not in patients with systemic sclerosis and no PAH (11), implying that the upregulation of mannose receptor in macrophages may contribute to PAH development. In the hope of developing imaging methods to distinguish between PAH and lung parenchymal diseases, such as interstitial lung disease, we are seeking to investigate the difference in the distribution patterns or the heterogeneity of lung <sup>68</sup>Ga-NOTA-MSA uptake. Further studies are definitely needed to address the diagnostic specificity of <sup>68</sup>Ga-NOTA-MSA PET for PAH. If these issues are resolved, the next step will be to demonstrate whether the use of <sup>68</sup>Ga-NOTA-MSA PET can complement echocardiography or even right heart catheterization, hopefully to overcome the uncertainties of PAH diagnosis or prognosis in the future. ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

Jun-Bean Park, M.D., Ph.D.  
Jin Chul Paeng, M.D., Ph.D.\*  
Seung-Pyo Lee, M.D., Ph.D.\*<sup>†</sup>  
Seoul National University Hospital  
Seoul, Republic of Korea

and

Seoul National University College of Medicine  
Seoul, Republic of Korea

On behalf of all the authors

ORCID ID: 0000-0002-5502-3977 (S.-P.L.).

\*These authors contributed equally to this work as co-senior authors.

<sup>†</sup>Corresponding author (e-mail: [sprll1@snu.ac.kr](mailto:sprll1@snu.ac.kr)).

## References

1. Park J-B, Suh M, Park JY, Park JK, Kim Y-I, Kim H, *et al.* Assessment of inflammation in pulmonary artery hypertension by <sup>68</sup>Ga-mannosylated human serum albumin. *Am J Respir Crit Care Med* 2020;201:95–106.
2. Rabinovitch M, Guignabert C, Humbert M, Nicolls MR. Inflammation and immunity in the pathogenesis of pulmonary arterial hypertension. *Circ Res* 2014;115:165–175.
3. Perros F, Dorfmueller P, Montani D, Hammad H, Waelput W, Girerd B, *et al.* Pulmonary lymphoid neogenesis in idiopathic pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2012;185:311–321.
4. Rhee RL, Gabler NB, Sangani S, Praestgaard A, Merkel PA, Kawut SM. Comparison of treatment response in idiopathic and connective tissue

§This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern ([dgem@thoracic.org](mailto:dgem@thoracic.org)).

Originally Published in Press as DOI: 10.1164/rccm.202003-0557LE on April 30, 2020