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 \(^{68}\text{Ga}\)-2-(p-isothiocyanato)benzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid mannosylated 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.

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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 in macrophages in patients with 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 68Ga-2-(p-isothiocyanatobenzyl)-1,4,7-triazacyclononane1,4,7-triacetic acid mannosylated human serum albumin (68Ga-NOTA-MSA) PET in two patients with systemic sclerosis and no evidence of PAH on right heart catheterization, the lung-to-reference ratio of 68Ga-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 68Ga-NOTA-MSA PET for predicting possible PAH.

Another important issue is the diagnostic specificity of 68Ga-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 68Ga-NOTA-MSA is not necessarily equal to the increased infiltration of macrophages into the pulmonary vessels. As the authors mentioned, the expression of mannos 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 68Ga-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 mannos 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 mannos 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 68Ga-NOTA-MSA uptake. Further studies are definitely needed to address the diagnostic specificity of 68Ga-NOTA-MSA PET for PAH. If these issues are resolved, the next step will be to demonstrate whether the use of 68Ga-NOTA-MSA PET can complement echocardiography or even right heart catheterization, hopefully to overcome the uncertainties of PAH diagnosis or prognosis in the future. ■

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