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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 ^{68}Ga-2-(p-isothiocyanatobenzyl)-1,4,7-triazacyclononane1,4,7-triacetic acid mannosylated human serum albumin (^{68}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 ^{68}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 ^{68}Ga-NOTA-MSA PET for predicting possible PAH.

Another important issue is the diagnostic specificity of ^{68}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 ^{68}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 ^{68}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 ^{68}Ga-NOTA-MSA uptake. Further studies are definitely needed to address the diagnostic specificity of ^{68}Ga-NOTA-MSA PET for PAH. If these issues are resolved, the next step will be to demonstrate whether the use of ^{68}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.

Jun-Bean Park, M.D., Ph.D.
Jin Chul Paeng, M.D., Ph.D.*
Seung-Pyo Lee, M.D., Ph.D.*‡
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.
‡Corresponding author (e-mail: sproll1@snu.ac.kr).

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

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Limitations of Nasal Nitric Oxide Testing in Primary Ciliary Dyskinesia

To the Editor:

Primary ciliary dyskinesia (PCD), a rare, genetically heterogeneous disease associated with mutations in >45 different genes, (1) is clinically characterized by neonatal respiratory distress, organ laterality defects, persistent rhinosinusitis, chronic bronchitis, and, ultimately, bronchiectasis. Historically, PCD has been difficult to diagnose because no single test identifies all cases. Published in 2018, the American Thoracic Society Clinical Practice Guideline recommended several PCD diagnostic tools, including extended genetic panel testing, transmission electron microscopy (TEM) assessment of the ciliary axoneme, and nasal nitric oxide measurement (nNO) (2). Although the mechanism is unknown, nNO levels are reproducibly reduced in most cases of PCD. When compared with a reference standard of TEM and/or genetic testing, nNO levels <77 nl/min are >95% sensitive and specific in identifying PCD in cooperative patients 5 years and older, who have compatible clinical phenotypes, after excluding cystic fibrosis (2, 3).

Recent editorials have misinterpreted the American Thoracic Society guideline recommendations, stating that nNO levels >77 nl/min exclude PCD (4). Before publication of the guideline, it was well established that limited individuals with certain PCD-associated genes (e.g., *RSPH1*, *GAS8*, *RPGR*, or *CCNO*) had nNO results >77 nl/min. Ten additional PCD-causing genes (e.g., *CCDC103*, *CFAP221*, *DNAH9*, *FOXJ1*, *GAS2L2*, *LRRC56*, *NEK10*, *SPEF2*, *STK36*, or *TTC12*) associated with nNO values >77 nl/min have been discovered since guideline development. Nonetheless, the proportion of affected individuals with higher nNO levels still accounts for <5% of known PCD cases (1). Thus, nNO concentrations >77 nl/min do not exclude the diagnosis of PCD, analogous to a normal sweat chloride measurement not excluding cystic fibrosis.

Moreover, a reduced nNO level alone is not diagnostic for PCD. When using established, standardized protocols (5), meta-analysis shows that low nNO measurements are "comparable to that of TEM and/or genetic testing"; however, the guideline states that "patients should still progress to further corroborative PCD diagnostic studies" (2). This recommendation is underscored by recent observations that some patients with primary immunodeficiency, a heterogeneous group of disorders sharing clinical features with PCD, can also have reduced nNO levels (6). In these cases, misdiagnosis may have serious consequences. Several individuals with chronic suppurative respiratory disease and low nNO values, evaluated in the Genetic Disorders of Mucociliary Clearance Consortium, were ultimately diagnosed with primary immunodeficiency, and some developed secondary malignancies or required stem cell transplantation. Though relatively uncommon, the risk of life-threatening complications in clinically overlapping diseases should give pause to using nNO levels as a single diagnostic test for PCD.

Given this, repeatedly low nNO values with a compatible phenotype can be presumptively diagnostic for PCD, but additional studies are absolutely required for corroboration. In patients who have persistently low nNO levels, if TEM or genetic testing fail to confirm the diagnosis of PCD, an immunology consultation should be considered while initiating PCD therapies. This approach is shown in a revised diagnostic algorithm (Figure 1), which has been reviewed and agreed upon by the entire guideline committee. Subsequent iterations of the guideline will reflect these changes and strive to further improve diagnostic accuracy in patients with PCD. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Adam J. Shapiro, M.D.*
Montreal Children's Hospital
Montreal, Quebec, Canada

Stephanie D. Davis, M.D.
University of North Carolina
Chapel Hill, North Carolina

Margaret W. Leigh, M.D.
Michael R. Knowles, M.D.
University of North Carolina School of Medicine
Chapel Hill, North Carolina

Author Contributions: All authors assisted with drafting of this letter and agree with the contents.

Originally Published in Press as DOI: 10.1164/rccm.202003-0835LE on April 24, 2020