with asthma (14, 15). These findings are pivotal, particularly in the light of sustaining discussions with regard to the role of ambient NO2 concentrations on population health. It emphasizes the need to have strategies that not only reduce exhaust particulate but also scavenge NO2, particularly within congested urban areas, where diesel vehicles make up a significant proportion of the fleet.

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Jenny A. Bosson, M.D., Ph.D.
Department of Public Health and Clinical Medicine
Umeå University
Umeå, Sweden

Ian S. Mudway, Ph.D.
School of Population Health and Environmental Sciences
King’s College London
London, United Kingdom

Thomas Sandström, M.D., Ph.D.
Department of Public Health and Clinical Medicine
Umeå University
Umeå, Sweden

References

1. Holgate S, Grigg J, Agius R, Ashton JR, Cullinan P, Exley K, et al. Every breath we take: the lifelong impact of air pollution, report of a working party. London, United Kingdom: Royal College of Physicians; 2016.

2. Thurston GD, Kipen H, Annesi-Maesano I, Balmes J, Brook RD, Cromar K, et al. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. Eur Respir J 2017;49:1600419.

3. Samoli E, Atkinson RW, Analitis A, Fuller GW, Mudway I, et al. Associations of short-term exposure to traffic-related air pollution with cardiovascular and respiratory hospital admissions in London, UK. Occup Environ Med 2016;73:300–307.

4. Bell ML, Ebisu K, Peng RD, Samet JM, Dominici F. Hospital admissions and chemical composition of fine particle air pollution. Am J Respir Crit Care Med 2009;179:1115–1120.

5. Rich DQ, Zhang W, Lin S, Squizzato S, Thurston SW, van Wijngaarden E, et al. Triggering of cardiovascular hospital admissions by source specific fine particle concentrations in urban centers of New York State. Environ Int 2019;126:387–394.

6. Mills IC, Atkinson RW, Anderson HR, Maynard RL, Strachan DP. Distinguishing the associations between daily mortality and hospital admissions and nitrogen dioxide from those of particulate matter: a systematic review and meta-analysis. BMJ Open 2016;6:e010751.

7. Bai L, Chen H, Hatzopoulou M, Jerrett M, Kwong JC, Burnett RT, et al. Exposure to ambient ultrafine particles and nitrogen dioxide and incident hypertension and diabetes. Epidemiology 2018;29:323–332.

8. Bai L, Weichenthal S, Kwong JC, Burnett RT, Hatzopoulou M, Jerrett M, et al. Associations of long-term exposure to ultrafine particles and nitrogen dioxide with increased incidence of congestive heart failure and acute myocardial infarction. Am J Epidemiol 2019;188:151–159.

9. Wooding DJ, Ryu MH, Hüls A, Lee AD, Lin DTS, Rider CF, et al. Particle depletion does not remEDIATE acute effects of traffic-related air pollution and allergen: a randomized, double-blind crossover study. Am J Respir Crit Care Med 2019;200:565–574.

10. Muranaka M, Suzuki S, Koizumi K, Takafuji S, Miyamoto T, Ikemori R, et al. Adjuvant activity of diesel-exhaust particulates for the production of IgE antibody in mice. J Allergy Clin Immunol 1986;77:616–623.

11. Miyabara Y, Takano H, Ichinose T, Lim HB, Sagai M. Diesel exhaust enhances allergic airway inflammation and hyperresponsiveness in mice. Am J Respir Crit Care Med 1998;157:1138–1144.

12. Diaz-Sanchez D, Tsien A, Fleming J, Saxon A. Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human in vivo nasal ragweed-specific IgE and skews cytokine production to a Th2 helper cell 2-type pattern. J Immunol 1997;158:2406–2413.

13. Diaz-Sanchez D, Jyrala M, Ng D, Nel A, Saxon A. In vivo nasal challenge with diesel exhaust particles enhances expression of the CC chemokines rantes, MIP-1alpha, and MCP-3 in humans. Clin Immunol 2000;97:140–145.

14. Bylin G, Lindvall T, Rehn T, Sundin B. Effects of short-term exposure to ambient nitrogen dioxide concentrations on human bronchial reactivity and lung function. Eur J Respir Dis 1985;66:205–217.

15. Strand V, Rak S, Svartengren M, Bylin G. Nitrogen dioxide exposure enhances asthmatic reaction to inhaled allergen in subjects with asthma. Am J Respir Crit Care Med 1997;155:881–887.

*Validation of Imaging Measures in Chronic Obstructive Pulmonary Disease*

Imaging provides an amazing opportunity to glean in vivo insights into acute and chronic diseases. The imaging community has described many features that can be used to detect disease and stratify its severity, predict outcomes, and even assess disease progression. These typically begin with the identification of a novel structural aspect of an organ, obtaining a range of measures of that feature and then demonstrating that those measures remain statistically significantly associated with an outcome of interest despite exhaustive multivariable adjustment. These approaches are not wrong, but they are often accompanied, appropriately, by disclaimers in the limitations section of the discussion or even a modification of the name of the feature to communicate an appropriate degree of uncertainty as to what is actually being measured. Few of the imaging-based measures reported in the literature are backed by histopathology or knowledge of what is occurring on the microscopic level.
In this issue of the Journal, Vasilescu and colleagues (pp. 575–581) report the results of their investigation linking data collected using both clinical computed tomography (CT) and micro-CT (1). Their features of interest were derived by a technique called parametric response mapping (PRM) (2) and their goal was to demonstrate that the application of their approach to clinical CT scans could noninvasively disambiguate the contributions of emphysema and small airway disease to gas trapping observed on expiratory images. To do so, they collected explanted lungs from 14 subjects, inflated and then froze them before sectioning and taking 1.5-cm core samples. They then performed micro-CT scanning on these core specimens (33 from patients with COPD and 22 from control subjects), and assessed the resultant images for features indicative of emphysema, such as airspace size and alveolar surface area, as well as those suggestive of small airway disease, including wall thickening, decreased circularity, and obstruction of the terminal bronchioles.

The core samples from COPD lungs had increased airspace size, greater airway obstruction, and decreased numbers of terminal bronchioles compared with cores from control lungs. The authors also found that the PRM-based measures of emphysema (PRM\textsubscript{Emph}) were highly significantly associated with the corresponding tissue destruction observed on micro-CT. These findings are not surprising given work by this group linking the loss of small airways to COPD (3, 4), as well as the more extensive body of older literature linking densitometric assessments of the lung parenchyma to airspace dilation observed on direct assessment of the explanted lung tissue (5, 6). Although these findings establish the overall validity of their experiment, the true novelties in this work are the links established between the tissue-based measures of small airway disease and the PRM\textsubscript{fSAD}.

Greater amounts of PRM\textsubscript{fSAD} were associated with lower numbers of terminal bronchioles as well as reduced lumen area, circularity, and more frequent obstruction of those that remained. What is equally compelling but elicited little comment is the lack of association between the fSAD measure and both the mean linear intercept and alveolar surface area. These measures were uniquely associated with the PRM-based measure of emphysema. This lack of association between PRM\textsubscript{fSAD} and measures of emphysema on micro-CT must have elicited relief from the investigative team. This allows them to state that the technique has some degree of specificity and can appropriately classify these processes as either emphysema or airway disease.

Where does this leave us? The first place to look may be back on the increasing body of literature focused on the application of these measures in smokers. One important clinical validation is the increasing body of literature focused on the application of these techniques to clinical CT scans. Unlike those focused on hypothesis-driven approaches that involve segmentation and quantification of anatomic features believed to be related to the condition of interest, deep learning–based efforts may converge on a clinical signal without human input. One thing that is generally common to both is the belief that the validation of these techniques requires a demonstration of clinical association. Although such findings may substantiate the methods being presented, we cannot conflate substantiation with true validation. With imaging, the latter can really only be done with tissue. Vasilescu and colleagues should be congratulated for taking on such a challenging study long after the medical community had accepted PRM, and establishing this link between noninvasive imaging features and pathologic findings in severe COPD. Future work may help establish these measures in early or mild COPD, from which conclusions about pathologic contributions to disease progression in COPD may be better inferred. For now, at the very least, we can drop the word “functional” and embrace this as a metric for small airway disease in smokers.

The imaging community has greatly benefitted from the deployment of software libraries that enable deep learning approaches to image postprocessing. These tools have led to a divergence of efforts surrounding image analytics. Unlike those focused on hypothesis-driven approaches that involve segmentation and quantification of anatomic features believed to be related to the condition of interest, deep learning–based efforts may converge on a clinical signal without human input. One thing that is generally common to both is the belief that the validation of these techniques requires a demonstration of clinical association. Although such findings may substantiate the methods being presented, we cannot conflate substantiation with true validation. With imaging, the latter can really only be done with tissue. Vasilescu and colleagues should be congratulated for taking on such a challenging study long after the medical community had accepted PRM, and establishing this link between noninvasive imaging features and pathologic findings in severe COPD. Future work may help establish these measures in early or mild COPD, from which conclusions about pathologic contributions to disease progression in COPD may be better inferred. For now, at the very least, we can drop the word “functional” and embrace this as a metric for small airway disease in smokers. ■

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Carrie Pistermaa Aaron, M.D.
George R. Washko, M.D.
Department of Medicine
Brigham and Women’s Hospital
Boston, Massachusetts

References

1. Vasilescu DM, Martinez FJ, Marchetti N, Galbán CJ, Hatt C, Meldrum CA, et al. Noninvasive imaging biomarker identifies small airway damage in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2019;200:575–581.
2. Galbán CJ, Han MK, Boes JL, Chughtai KA, Meyer CR, Johnson TD, et al. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. Nat Med 2012;18:1711–1715.
3. McDonough JE, Sanchez PG, Elliott WM, Horng D, Getfer WB, Wright AC, et al. Small airway obstruction in COPD [abstract]. Am J Respir Crit Care Med 2009;179:A2970.
4. Koo HK, Vasilescu DM, Booth S, Hsieh A, Katsamanis OL, Fishbane N, et al. Small airways disease in mild and moderate chronic obstructive pulmonary disease: a cross-sectional study. Lancet Respir Med 2018;6:591–602.
5. Müller NL, Staples CA, Miller RR, Abboud RT. “Density mask”: an objective method to quantitate emphysema using computed tomography. Chest 1988;94:782–787.
6. Gevenois PA, De Vuyst P, de Maertelaer V, Zanen J, Jacobovitz D, Cosio MG, et al. Comparison of computed density and microscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med 1996;154:187–192.
7. Bhatt SP, Soler X, Wang X, Murray S, Anzueto AR, Beatty TH, et al.; COPDGene Investigators. Association between functional small airway disease and FEV\textsubscript{1} decline in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2016;194:178–184.
8. Labaki WW, Gu T, Murray S, Hatt CR, Galbán CJ, Ross BD, et al. Voxel-wise longitudinal parametric response mapping analysis of chest computed tomography in smokers. Acad Radiol 2019;26:217–223.

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