References

1. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, *et al*.; AIR2 Trial Study Group. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med* 2010;181:116–124.
2. Wechsler ME, Laviolette M, Rubin AS, Fiterman J, Lapa e Silva JR, Shah PL, *et al*.; Asthma Intervention Research 2 Trial Study Group. Bronchial thermoplasty: long-term safety and effectiveness in patients with severe persistent asthma. *J Allergy Clin Immunol* 2013;132:1295–1302.
3. Global Initiative for Asthma. Update of the Global Strategy for Asthma Management and Prevention. Fontana, WI: Global Initiative for Asthma; 2020 [accessed 2020 Aug 12]. Available from: https://ginasthma.org/gina-reports/#:~:text=The%202020%20update%20of%20the,on%20the%20GINA%20Science%20Committee.
4. Goorsenberg AWM, d'Hooghe JNS, Srikanthan K, ten Hacken NHT, Weersink EJM, Roelofs JTH, *et al*.; TASMA Research Group. Bronchial thermoplasty induced airway smooth muscle reduction and clinical response in severe asthma: the TASMA randomized trial. *Am J Respir Crit Care Med* 2021; 203:175–184.

In Chronic Obstructive Pulmonary Disease Progression, Is It Airway Narrowing or Airway Loss?

First published in *The New England Journal of Medicine* in 1970, Mead's now comprehensively validated hypothesis that the small airways "represent a quiet zone" that offers no resistance to airflow in healthy subjects, but becomes the site of major airflow obstruction in various pulmonary diseases, remains integral to our understanding of airway remodeling in chronic obstructive pulmonary disease (COPD) (1, 2).

Indeed, we now recognize that disease can build up over time in this zone without being detectable by global diagnostic methods such as pulmonary function tests, and therefore it is here that early detection of lung diseases such as COPD must occur (3, 4). This realization has fueled extensive research into new, more sensitive techniques for detecting early signs of disease accumulation in the small airways, leading to the development of numerous nonimaging methods such as forced oscillation (4, 5) and multiple breath washout (6).

Although there is still no clinical imaging technique with high enough resolution to directly visualize the small airways, several sophisticated quantitative imaging methods have produced powerful tools for unmasking small airway disease, such as the parametric response map (PRM), which can indirectly extract regional information about the functional integrity of small airways (7, 8) via the coregistration of computed tomography (CT) images acquired at full expiration and full inspiration.

The low image resolution implies that, like PRM, all CT-based approaches can only evaluate the small airways *indirectly*. In this issue of the *Journal*, however, Bodduluri and colleagues (pp. 185–191) have taken advantage of recent findings (9–11) that, in patients with COPD, more proximal airways display the same features as small airways. These more proximal airways can be visualized directly via CT images obtained at "full inspiration" after bronchodilator administration, and the authors have used such images to evaluate the progression of airway remodeling in patients with COPD (smokers [Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 0–4] plus a small group of nonsmokers) to determine whether airway loss or narrowing is more prominent in a given patient by measuring the airway surface–to–volume ratio (SA/V). Airway trees were first segmented, and surface area and volume were then estimated from the three-dimensional segmented airways. The authors then used a simulation to determine the "relative contribution of airway narrowing and airway loss to SA/V" from the change in longitudinal SA/V (ΔSA/V).

On cross-sectional data, baseline SA/V showed an inverse correlation with all-cause mortality and a direct correlation with FEV_1/FVC, FEV_1% predicted, and 6-minute-walk distance. Lower SA/V was also associated with higher subjective life impact measured by St. George's Respiratory Questionnaire. In their longitudinal study, SA/V was inversely correlated with lung function decline measured by FEV_1 loss. Longitudinal analysis also showed that remodeling because of predominant airway loss was associated with significantly higher functional decline (greater FEV_1 loss) and, perhaps most importantly, significantly worse survival rates than airway narrowing–predominant remodeling. Although no breakdown statistics are presented for either 6-minute-walk distance or St. George's Respiratory Questionnaire, the shift within the predominant airway loss cohort, from 52% to 38% current smokers at study's end, is also interesting.

As expected, imaging data showed a significant decrease in total airway count among airway loss subjects, with no change among airway narrowing subjects. Subjects with predominant airway loss also had more emphysema and thicker segmental airway walls at both baseline and follow-up, as well as more air trapping at follow-up than those with predominant airway narrowing. Among those with mild disease, a higher percentage of subjects with predominant airway narrowing remained in the lower GOLD stages at follow-up.

It is clear that Bodduluri and colleagues have produced an important new technique for the structural evaluation of small airways (disease) based on the number of novel insights it provides as well as its potential clinical impact as a diagnostic and prognostic tool, which, if validated, could also be used to identify appropriate treatment

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strategies. However, its ultimate clinical utility will be determined by how well its limitations can be addressed moving forward.

First, given the inherent resolution limitations of CT imaging, the SA/V measure developed here is based on the direct evaluation of airways in the higher imageable generations. Thus, in the same way that the multiple inert gas elimination technique, multiple breath washout, and other global measures of lung structure and function have been validated with histology, the authors' use of these larger airways as a surrogate for lung structures beyond the achievable image resolution requires histological validation.

Second, because of the extended time between baseline and follow-up imaging in this longitudinal study, ΔSA/V's true predictive value remains unclear. The authors claim that their clustering technique is sensitive enough to differentiate between subjects with predominant airway loss and those with predominant airway narrowing based on a 5% change in airway volume, a change which they assert is likely achieved within a year of baseline imaging in most patients with COPD. However, as no such time point exists in the current study, the true timeline of this change will need to be validated in future studies.

Third, the authors suggest that airway loss and airway narrowing represent stable subgroups with characteristic declines over time, rather than two stages of the same condition, based on the comparable distributions of the two airway remodeling categories in each GOLD stage and the differences in pathology, functional decline, and prognosis indicated by their imaging markers. However, given the absence of further supporting evidence or casual corroboration, the authors' own acknowledgment that both processes can coexist in the same patient and the ΔSA/V distribution around zero—which does not show obvious clustering to either side of the zero-mean—this contention remains largely speculative at present. Nevertheless, this in no way undermines the authors' claim for the predictive significance of detecting the dominant trajectory of disease progression.

Finally, future studies should also address the mounting evidence that body height is an independent risk factor for patients with COPD. It has been shown, for instance, that the odds of developing emphysema increased by 5% with a 1-cm increase in height (12). Because an individual's lung size is more directly associated with their height than their body mass index, only the latter of which was corrected for in this analysis, the possibility that body height could substantially affect SA/V should be investigated.

Future research on airway remodeling in COPD should also investigate *1*) whether remodeling caused by airway luminal narrowing or airway loss is more responsive to treatment; *2*) what processes are responsible for the first 5% reduction in airway volume and whether early intervention can shift this remodeling from one regime to another; *3*) the relationship between each of these two phenotypes and a multiomics approach to COPD-related airway remodeling; and *4*) sensitivity comparisons to other methods, such as CT PRM, that may be able to offer similar subclassifications. ■

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References

1. Mead J. The lung's "quiet zone". *N Engl J Med* 1970;282:1318–1319.
2. Hogg JC, McDonough JE, Suzuki M. Small airway obstruction in COPD: new insights based on micro-CT imaging and MRI imaging. *Chest* 2013;143:1436–1443.
3. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, *et al*. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:2645–2653.
4. Bhatt SP, Soler X, Wang X, Murray S, Anzueto AR, Beaty TH, *et al*.; COPDGene Investigators. Association between functional small airway disease and FEV1 decline in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2016;194:178–184.
5. Oostveen E, MacLeod D, Lorino H, Farré R, Hantos Z, Desager K, *et al*.; ERS Task Force on Respiratory Impedance Measurements. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J* 2003;22: 1026–1041.
6. Robinson PD, Goldman MD, Gustafsson PM. Inert gas washout: theoretical background and clinical utility in respiratory disease. *Respiration* 2009;78:339–355.
7. 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.
8. Boes JL, Hoff BA, Bule M, Johnson TD, Rehemtulla A, Chamberlain R, *et al*. Parametric response mapping monitors temporal changes on lung CT scans in the subpopulations and intermediate outcome measures in COPD Study (SPIROMICS). *Acad Radiol* 2015;22:186–194.
9. Bodduluri S, Puliyakote AK, Nakhmani A, Charbonnier J-P, Reinhardt JM, Bhatt SP. Computed tomography–based airway surface area–to-volume ratio for phenotyping airway remodeling in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2021;203:185–191.
10. Washko GR, Diaz AA, Kim V, Barr RG, Dransfield MT, Schroeder J, *et al*. Computed tomographic measures of airway morphology in smokers and never-smoking normals. *J Appl Physiol (1985)* 2014; 116:668–673.
11. Bodduluri S, Reinhardt JM, Hoffman EA, Newell JD Jr, Bhatt SP. Recent advances in computed tomography imaging in chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2018;15: 281–289.
12. Miniati M, Bottai M, Pavlickova I, Monti S. Body height as risk factor for emphysema in COPD. *Sci Rep* 2016;6:36896.