function decline in patients with moderate chronic obstructive pulmonary disease and heightened cardiovascular risk. *Am J Respir Crit Care Med* 2018;197:47–55.

6. Vestbo J, Anderson JA, Brook RD, Calverley PM, Celli BR, Crim C, *et al*; SUMMIT Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016;387:1817–1826.
7. Vestbo J, Anderson JA, Calverley PM, Celli B, Ferguson GT, Jenkins C, *et al*. Bias due to withdrawal in long-term randomised trials in COPD: evidence from the TORCH study. *Clin Respir J* 2011;5:44–49.
8. Gonzalez AV, Coulombe J, Ernst P, Suissa S. Long-term use of inhaled corticosteroids in COPD and the risk of fracture. *Chest* 2017;pii: S0012-3692(17)31243-6.
9. Nannini LJ, Poole P, Milan SJ, Kesterton A. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013;(8):CD006826.
10. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, *et al*; TORCH Investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775–789.
11. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, *et al*; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543–1554.

Copyright © 2018 by the American Thoracic Society

The Case of Missing Airways in Chronic Obstructive Pulmonary Disease

Cigarette smoking is the main cause of chronic obstructive pulmonary disease (COPD) in the developed world. Emphysematous destruction as well as mural thickening and luminal occlusion of the small airways have long been recognized as pathologic markers of COPD (1). Less recognized is that smokers with COPD also have a paucity of small airways, the loss of which might precede the development of emphysema. McDonough and colleagues demonstrated a striking loss of terminal bronchioles on micro-computed tomography (CT) in lung tissue from patients with moderate to very severe COPD compared with control patients (2). This loss of distal parallel pathways is thought to explain the increased (4–40×) resistance to airflow in COPD, a central physiologic feature of the disease. Interestingly, the loss of airways seems to extend to proximal airways (i.e., large to medium-sized airways; those that can be visualized on clinical CT scans) as well, as we demonstrated in patients with significant emphysema (3). Until recently, it was unclear whether airway loss was only a feature of advanced COPD or whether the phenomenon was also present in those with more mild disease.

In this issue of the *Journal*, Kirby and colleagues (pp. 56–65) examined CT airway measures in 286 never-smokers, 298 ever-smokers without COPD, and 600 ever-smokers with COPD (Global Initiative for Obstructive Lung Disease [GOLD] grade I–II airflow limitation) from the CanCOLD study, a Canadian, multicenter, population-based study (4). Using software to segment and count branches of the bronchial tree, Kirby and colleagues found that compared with never-smokers and ever-smokers without COPD, those with mild to moderate COPD had a 19% and 17% decrease in the total airway count (TAC), respectively. In addition, the parent airways with missing daughter branches (vs. those without missing branches) had both smaller lumens and

thinner walls. Furthermore, those participants with lower TAC at baseline had a greater decline in lung function, independent of baseline emphysema degree, during approximately 6 years of follow-up. Although the study has some limitations, including lack of longitudinal lung function data in all study subjects and lack of software validation against other methods, it provides important information about tobacco-induced structural damage to the proximal airways.

Histologic and imaging studies of proximal airway morphology have yielded conflicting results. Although histopathologic studies and some CT studies in smokers have demonstrated mural thickening of the proximal airways, particularly in mild COPD (5, 6), larger imaging studies, including subjects with a wide spectrum of airflow obstruction, have found thinner-walled, smaller proximal airways in patients with COPD versus control patients (7, 8). These discrepancies might be a result of differences in populations, airway sampling, and technical aspects including software, CT protocols, and scanner brands. When measuring airways, it is important to remember that they are distensible tubes, the morphologies of which are influenced by the properties of the elastic parenchyma in which they reside (9). For example, when connections between the airways and parenchyma are disrupted by emphysema, the airways cannot dilate completely. It has been demonstrated that patients with COPD with greater burdens of CT emphysema have smaller total bronchial area (i.e., lumen area plus wall area), a finding that may be a result of loss of airway tethering (10). This altered airway–parenchymal interdependence is further illustrated by observations that patients with COPD with an emphysema-predominant phenotype are less able to distend their airways with lung inflation (11). Beyond proximal airway size and mural thickness, Kirby and colleagues demonstrated a smaller number of distal airways in patients with mild to moderate COPD and minimal emphysema (4). The finding that parent airways with missing daughter branches had smaller lumens and thinner walls compared with parent airways without missing branches raises the possibility that airways might shrink and undergo further distortion en route to disappearance (Figure 1). Interestingly, Kirby and colleagues

A.A.D. is supported by U.S. National Institutes of Health grants HL118714 and HL133137 and the Brigham and Women's Hospital Minority Faculty Career Development Award.

Originally Published in Press as DOI: 10.1164/rccm.201708-1585ED on September 20, 2017

Figure 1. Schematic of airway remodeling in smoking-related chronic obstructive pulmonary disease. (A–G) A normal airway (A) going through progressive remodeling (B–G). The airway becomes thinner, distorted, and obliterated (E–G) en route to disappearance.

also observed that those subjects with fewer airways at baseline had a more rapid decline in lung function. Although the proximal airways visualized on CT scans are not the site of airflow obstruction in COPD, the decrease in CT TAC might be a surrogate for the profound loss of small airways observed in histological studies, and thus a marker of disease progression. The study was not designed to determine the reason for the “missing” airways, but the authors provide several possible explanations, including “excessive bronchoconstriction,” “mucus occlusion,” and “degradation of the walls,” with the latter possibly being a result of intense inflammation and failed repair processes in smoking-induced airway remodeling. It is important to note that the proximal airways might not actually be missing but, rather, obliterated to the point they are no longer visible on CT. Assuming a dichotomous branching model, it is expected that the airway count exponentially increases with movement to the periphery of the bronchial tree (12). As shown in this work, however, the TAC in all groups (even the never-smoking control patients) decreased in the more distal airway generations (beyond the eighth airway generation), pointing to the limitations of the current methodology/CT resolution (i.e., the inability to accurately perform branch counting of more distal airways). However, an *in vivo* imaging method such as CT scanning is relatively easy to perform, noninvasive, and applicable to large studies, attributes that should be considered when weighing the pros and cons of this tool. The contributions of Kirby and colleagues will hopefully encourage further work to improve our current methodology for assessing the airways and studies to better understand the airway remodeling process in COPD. If airways disappear, how do the remaining proximal airways connect to more distal small airways? Is fibrotic/inflamed tissue filling this space? Is this space just air that looks like emphysematous destruction? If the airways disappear, how does it affect the response to inhaled therapy? Is TAC a potential biomarker to select subjects for inhaled therapy? I envision that in the next few years, we will have answers to some of these questions, and more important, we will have innovative therapies to tackle the effects of smoking on the airways. ■

Alejandro A. Díaz, M.D., M.P.H.
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

References

1. 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.
2. McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, *et al.* Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med* 2011;365: 1567–1575.
3. Diaz AA, Valim C, Yamashiro T, Estépar RS, Ross JC, Matsuoaka S, *et al.* Airway count and emphysema assessed by chest CT imaging predicts clinical outcome in smokers. *Chest* 2010; 138:880–887.
4. Kirby M, Tanabe N, Tan WC, Zhou G, Obeidat M, Hague CJ, *et al.* Total airway count on computed tomography and the risk of chronic obstructive pulmonary disease progression: findings from a population-based study. *Am J Respir Crit Care Med* 2018;197:56–65.
5. Tiddens HA, Paré PD, Hogg JC, Hop WC, Lambert R, de Jongste JC. Cartilaginous airway dimensions and airflow obstruction in human lungs. *Am J Respir Crit Care Med* 1995;152: 260–266.
6. Grydeland TB, Dirksen A, Coxson HO, Eagan TM, Thorsen E, Pillai SG, *et al.* Quantitative computed tomography measures of emphysema and airway wall thickness are related to respiratory symptoms. *Am J Respir Crit Care Med* 2010;181:353–359.
7. 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: 668–673.
8. Smith BM, Hoffman EA, Rabinowitz D, Bleecker E, Christenson S, Couper D, *et al.*; The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study and the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS). Comparison of spatially matched airways reveals thinner airway walls in COPD. *Thorax* 2014;69: 987–996.
9. Diaz AA, Estépar RS, Washko GR. Computed tomographic airway morphology in chronic obstructive pulmonary disease. remodeling or innate anatomy? *Ann Am Thorac Soc* 2016;13:4–9.
10. Diaz AA, Han MK, Come CE, San José Estépar R, Ross JC, Kim V, *et al.* Effect of emphysema on CT scan measures of airway dimensions in smokers. *Chest* 2013;143:687–693.
11. Diaz AA, Come CE, Ross JC, San José Estépar R, Han MK, Loring SH, *et al.*; COPDGene Investigators. Association between airway caliber changes with lung inflation and emphysema

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

assessed by volumetric CT scan in subjects with COPD. *Chest* 2012;141:736–744.

12. Diaz AA, Rahaghi FN, Ross JC, Harmouche R, Tschirren J, San José Estépar R, et al; COPD Gene investigators. Understanding the contribution of native

tracheobronchial structure to lung function: CT assessment of airway morphology in never smokers. *Respir Res* 2015;16:23.

Copyright © 2018 by the American Thoracic Society

Psychological Outcomes after Critical Illness

Is It Time to Rethink Our Paradigm?

A growing body of literature has documented the consequences of critical illness, delineating the ways in which an ICU stay may constitute a life-altering event. Survivors of critical illness go on to suffer from functional disability, cognitive impairment, and psychological symptomatology, with resultant decrements in quality of life (1–3). Although this constellation of symptoms has received due attention and recognition as a postintensive care syndrome (4), thus far, interventions to improve these long-term outcomes have not been successful (5–8).

In this issue of the *Journal*, Cox and colleagues (pp. 66–78) present results from a randomized multicenter clinical trial conducted in survivors of critical illness and their family members, aimed at improving psychological symptomatology measured at 3 and 6 months (9). Patients who received mechanical ventilation for at least 48 hours (and their family member) were randomly assigned to either a telephone and web-based coping skills training (CST) intervention or an educational program. The CST intervention consisted of two psychologists who aimed to provide six weekly 30-minute telephone sessions intended to teach participants coping skills (e.g., relaxation, cognitive restructuring), in addition to the availability of web-based content. The educational program consisted of six videos containing information about critical illness (without discussing its psychological effect), as well as two phone calls to address participants' questions. Layperson stakeholders contributed to the trial's design and were influential in the decision to have this "active" control. The primary outcome was the change in the Hospital Anxiety and Depression Scale (HADS) summary score between baseline and 3 months. Secondary outcomes included the HADS score at 6 months and posttraumatic stress disorder symptoms, as well as assessments examining quality of life, overall health, coping, and self-efficacy.

Despite more than 6,000 attempted contacts to participants, adherence (defined as completion of at least one phone call) was only moderate (63% for CST vs. 65% for education), with a mean of 2.7 sessions completed for the CST group and 0.8 for the education group. At 3 months, there was no difference in the HADS score between groups; there also were no significant differences in any secondary outcomes at either point. However, in prespecified subgroup analyses, education was superior to CST at 3 months for patients mechanically ventilated for more than 7 days, whereas CST was superior to education at 6 months for patients with a high baseline HADS summary score (>14). Thus, the main findings

of the trial are negative, although there was a hypothesis-generating subgroup finding with some face validity.

In relation to the trial itself, there are several possible explanations for the negative result. First, the "active" control may have blunted the ability to identify a positive effect of the CST intervention. However, observed estimates of the HADS score were similar to those from other nonintervention studies (10, 11), which may indicate that neither intervention was effective. Second, separation between the experimental groups may not have been achieved because of inadequate delivery of the intervention, as there were no measured differences in adaptive coping and self-efficacy. Third, the study population may have been too heterogeneous. As the authors intimate, perhaps the intervention would have demonstrated efficacy in the subgroup of patients with high baseline levels of distress. As with all subgroup analyses, this positive finding may represent a type 1 error, but these patients also demonstrated improvements in measures of self-efficacy and overall global health. Last, the intervention may simply not be effective.

Considering that this study follows several others that failed to improve psychological outcomes after critical illness (or resulted in a signal for harm), we must ask: Is the current model of how we approach this problem correct? At this time, we view the presence of psychological symptomatology after critical illness as pathologic. However, it is not entirely surprising that we see elevated levels of depression and anxiety as people deal with the stress of a potentially traumatic and life-altering event. In particular, the sooner after the event outcomes are measured, the more likely we may be to capture fluctuations in normal grief and adjustment. At this juncture, it may be informative to examine the approach to treating grief (after the death of a loved one) in psychiatry. Interventions to enhance adaptation to grief in this setting have also had mixed results, with studies showing signals for harm and smaller-than-expected treatment effects (12), leading to some concern that intervening on "normal" grief may actually interfere with natural coping processes (13). Also, negative symptoms of grief peak by 6 months, suggesting that the timeframe of diagnosis, intervention, and follow-up for problematic grief should be appropriately shifted (14). These findings have led to a consensus approach that focuses more on secondary or tertiary prevention, offering interventions to patients either who seek them out or who have demonstrated persistent and disruptive symptomatology, as opposed to a primary prevention strategy of administering interventions to all comers (12, 13). However, an important caveat to drawing these parallels is that the loss of a loved one is a singular event, and survivors of critical illness are more likely to have continued stressors, as evidenced by the fact that many