Understanding COPD Etiology, Pathophysiology, and Definition

Jeffrey L Curtis

COPD, one of the leading worldwide health problems, currently lacks truly disease-modifying medical therapies applicable to most patients. Developing such novel therapies has been hampered by the marked heterogeneity of phenotypes between individuals with COPD. Such heterogeneity suggests that, rather than a single cause (particularly just direct inhalation of tobacco products), development and progression of COPD likely involve both complex gene-by-environment interactions to multiple inhalational exposures and a variety of molecular pathways. However, there has been considerable recent progress toward understanding how specific pathological processes can lead to discrete COPD phenotypes, particularly that of small airways disease. Advances in imaging techniques that correlate to specific types of histological damage, and in the immunological mechanisms of lung damage in COPD, hold promise for development of personalized therapies. At the same time, there is growing recognition that the current diagnostic criteria for COPD, based solely on spirometry, exclude large numbers of individuals with very similar disease manifestations. This concise review summarizes current understanding of the etiology and pathophysiology of COPD and provides background explaining the increasing calls to expand the diagnostic criteria used to diagnose COPD and some challenges in doing so. *Key words: COPD; pathophysiology; small airways disease; nosology.* [Respir Care 2023;68(7):859–870. © 2023 Daedalus Enterprises]

Introduction

The goals of this review are 2-fold: to summarize succinctly the current understanding of the etiology and pathophysiology of the condition presently recognized as COPD and to explain the increasing calls for an expanded redefinition of COPD not based purely on spirometry.[1-5] The focus is predominately on human data, with selected supplementation on mechanisms from experimental studies. I draw upon a variety of evidence, in particular from 2 ongoing multi-center observational cohort studies, COPDGene[6] and SPIROMICS.[7]

COPD Etiology and Pathology

Multiple Pathways to COPD Status

COPD is a highly prevalent, heterogeneous, variably progressive spectrum of conditions resulting primarily from lung injury and repair following prolonged oxidative inhalational exposures.[4,8-13] COPD has a long latency and is greatly underdiagnosed;[14,15] it can progress even when inciting exposures are removed,[16] suggesting that once its underlying pathological processes attain momentum they become self-sustaining. As a disease currently defined by abnormal lung function, it is unsurprising but important to appreciate that COPD can be reached not only by accelerated loss of lung function, long postulated to be the primary pathway,[17] but also by failure to achieve normal lung function in early adulthood with subsequent normal age-related decline[18] or by both.[19] Accordingly, early childhood exposures[20,21] and genetic causes of impaired lung growth[22] may account for as much of half of COPD cases, based on accepted spirometry criteria, but many of those individuals will not progress to severe disease.[18,20] Inclusion of such individuals with late mild COPD in clinical trials may dilute the effect of potential disease-modifying agents targeting specific molecular pathways.

Exposures Leading to COPD as Currently Defined

In industrialized nations, direct inhalation of tobacco products has been long recognized as the principal causative exposure leading to COPD. In developing nations, by contrast, air pollution (both indoor due to biomass fuel use and outdoor) is a major contributor.[23,24] Unfortunately, almost all data on lung pathology in COPD come from analysis of smoking-related disease in regions of high sociodemographic index (SDI). Far more work is needed on other exposures as potential etiological agents before extrapolation to the Global South can be assured.

However, this etiological dichotomy based on SDI is overly simplistic to explain disease status and outcomes in individuals. Risks of COPD are not uniformly distributed among residents of one high-SDI nation, the United States, but instead reflect a complex mix of differences in race/ethnicity, social class, and geographic location.[25-27] These factors are doubtless applicable worldwide and will probably worsen due to climate change.[28-30] COPD is also common among never smokers in the industrialized world, with apparent sex-based differences; eg, in the population-based Rotterdam study, smoking history was absent in far more females than males with COPD (27.2% vs 7.3%).[31] Importantly, different oxidant inhalation exposures can interact to drive adverse COPD outcomes.[32,33] Collectively, these findings imply the urgent need to reduce or eliminate all toxic inhalational exposures.

Small Airways Disease Is a Prominent Early COPD Pathology Initiated in Part by Loss of Local Innate Immune Defenses

Small airways are defined as those < 2 mm in diameter; in adults, they are stated to be distributed between the fourth–14th (mean eighth)[34] or eighth–22nd (mean 14th)[35] generation of airway branching. This region is distal to the point of maximal airway resistance and is characterized by diminishing individual airway diameters but a rapidly expanding total cross-sectional airway area. These distal airways are uniquely susceptible to damage induced by inhaled oxidative stresses such as smoking and air pollution for several reasons. The small airways are the region where gas transport switches from laminar or turbulent flow to diffusion, which facilitates deposition of fine particles and may enhance time of exposure to gas-phase irritants. Additionally, as considered below, small airways are much more dependent than the proximal airways on innate immune defenses that are altered by smoking.

Changes in small airways are the best studied pathology in COPD and likely the primary smoking-induced lesion in most of those who progress to significant air flow obstruction.[36] Elegant retrograde catheter studies in the 1960s demonstrated that small airways are the major site air flow obstruction in the human lung, with their contribution to total peripheral resistance increased 4–40-fold in advanced emphysema.[37] A recent study using archival paraffin-embedded lung sections also found damage and loss of terminal and transitional bronchioles in spirometrically mild-moderate COPD. Loss of small airways in Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1–2 patients was significant in regions without emphysema, with a 40% reduction in small airway numbers in those with GOLD stage 1 obstruction.[38] These studies indicate the importance

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Dr Curtis discloses relationships with AstraZeneca PLC, Novartis AG, and CSL Behring LLC.

This work was supported by R01 HL144718, R01 HL144849, and U01 HL137880 from National Institutes of Health, National Heart, Lung, and Blood Institute; and I01 CX002377 and I01 CX001969 from the Department of Veterans Affairs. The opinions expressed are solely those of the author and do not reflect the official positions of the Department of Veterans Affairs or the Department of Health and Human Services.

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DOI: 10.4187/respcare.10873

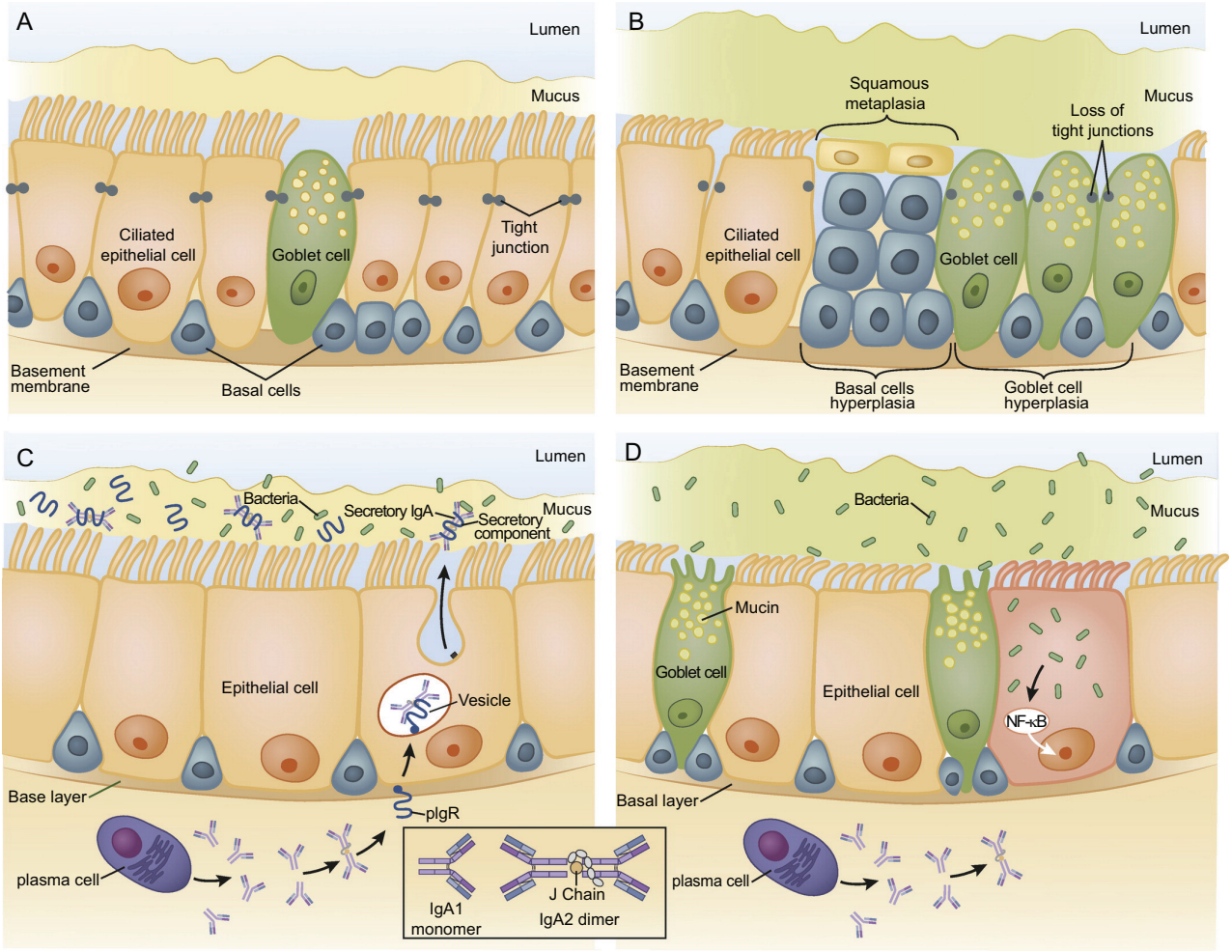

Fig. 1. Epigenetic changes induced by smoking lead to progressive small airway damage and inflammation in early COPD. (A and C) Normal small airways; (B and D) small airways in early COPD. A: Normal distal epithelium contains self-renewing basal cells, which differentiate into ciliated, mucus-producing goblet, and secretory (club) cells, joined by tight junctions that form an impermeable barrier. Mucus is separated from the epithelial surface by a robust aqueous periciliary layer. B: Smoking induces hyperplasia of basal and goblet cells, squamous metaplasia, loss of club and ciliated cells, decrease in the periciliary layer and ciliary damage and crowding, and junctional barrier loss. C: In normal small airways, dimeric immunoglobulin A (IgA) (structure shown in inset) is transcytosed by the polymeric immunoglobulin receptor (pIgR) into the mucosal lumen. pIgR cleavage at the luminal surface liberates secretory IgA, which prevents bacterial invasion. D: Smoking reduces pIgR expression, leading to localized secretory IgA deficiency in small airways, allowing bacteria to invade and induce sustained airway inflammation. Illustration by Patricia Ferrer Beals. From Reference 40, with permission. NF-KB = nuclear factor kappa B; pIgR = polymeric immunoglobulin receptor; IgA = immunoglobulin A.

of identifying small airway disease (SAD) early to develop therapies to stop its progression. Clinical detection of SAD by pulmonary function testing has been difficult, as the process has minimal effect on FEV_1, and even sensitive techniques such as forced expiratory flow during the middle half of the FVC maneuver ($FEF_{25–75\%}$) are highly variable. Nevertheless, use of spirometry on large populations can overcome that limitation, and results demonstrate the high global prevalence of SAD.[39] Alternative physiological methods to determine SAD include oscillometry, determination of residual volume, profiling the washout of inert gases, and machine learning approaches to analyze expiratory flow patterns.

The proximate cause of SAD is smoking-induced reprograming of airway epithelium in multiple ways that collectively reduce small airway immune defenses.[40,41] Healthy airway epithelium comprises a diverse community of cell types that all derive from basal progenitor cells (Fig. 1A). Smoking epigenetically reprograms these progenitors, causing them to undergo not only hyperplasia but also skewed maturation, with goblet cell expansion and loss of club cells and ciliated cells.[42,43] Hyperplastic goblet cells produce mucus in greater amounts and with altered physical properties, which the reduced numbers of ciliated cells have difficulty clearing[44] (Fig. 1B). The adverse effect of this change is shown by the association of total sputum mucin concentrations

with multiple adverse COPD outcomes, including annualized exacerbation rates, and with imaging or spirometric measures of SAD.[45] Visual scoring of mucus plugs detectable by computed tomography (CT), predominately in subsegmental airways, is associated with FEV_1 and hypoxemia, independently of emphysema and with a similar effect size.[43] Hence, reversing mucus hypersecretion could be one means of halting COPD progression.

Equally or perhaps more important to SAD pathogenesis is the local loss of host defenses resulting from epithelial reprograming. CC16, a secretoglobin family member that is the most abundant product of club cells, is reduced in smokers and to even a greater degree in mild and severe COPD.[46] In a transgenic murine cigarette smoke exposure model, CC16 protected lungs by reducing lung nuclear factor kappa B (NF-KB) activation.[46] Reprogramming also causes loss of translocation of dimeric secretory immunoglobulin A (sIgA) into small airway lumens.[47,48] In health, sIgA binds bacteria and their products, leading to their elimination without inducing inflammation. In small airways, sIgA must be translocated by the polymeric Ig receptor (pIgR), which is specifically downregulated by smoking[48,49] (Fig. 1C). This process is crucial, as it is now well recognized that even healthy lungs are not sterile but instead are repeatedly exposed to oropharyngeal bacteria.[50] In the absence of luminal sIgA, these bacteria can adhere and invade the epithelium, inducing NF-KB activation, which generates chemotactic molecules that attract inflammatory cells[49,51] (Fig. 1D). Bacterial clearance from the lungs is further compromised by smoking and, to a greater degree, COPD development due to reduced host defense capabilities of the principal resident lung phagocytes,[52-54] lung macrophages.[55]

These factors are directly relevant to the issue of why only some individuals with identical oxidant inhalational exposures develop COPD and why its manifestations are heterogeneous in those who do. One plausible explanation is focally stochastic interactions between epithelial-invasive bacteria and weakened local immunity. In other words, regional variation in host defenses, typified by focal loss of CC16 and pIgR and exaggerated production of abnormal mucus, sets the stage for variability in airway damage, both between individuals and between different lung regions in the same individual.[56-58] Inheritable differences in bronchial anatomy that affect deposition of inhaled or aspirated microparticles are also likely a component of variability.[59,60] That differences between individuals in the community composition of their oropharyngeal bacterial microbiome, the source of microaspirated organisms, are another factor is plausible but not entirely confirmed.[61-64] It is clear that advanced COPD is characterized by substantial changes in the community composition of the lung bacterial microbiome. However, whether changes in that community structure precede and drive the development of lower respiratory tract damage remains controversial.[61-65]

Immune Inflammation Can Drive SAD Progression to Emphysema

The Hogg lab recently provided additional evidence on how inflammation in terminal airways could lead to adjacent emphysema.[66] Using micro-CT, they demonstrated that loss of terminal bronchioles in COPD occurs in regions of microscopic emphysematous destruction (average air space size between 500–1,000 μm). Analysis of gene expression there showed enrichment for interferon-gamma and for the chemokines CXL9-11 that it induces. By the CIBERSORT technique,[67] they also identified enrichment of CD8+ and CD4+ T cells and B cells.[66]

These findings extend a significant body of studies collectively implying that adaptive immune mechanisms amplify lung damage initiated by defective lung host defense.[10,68-71] Evidence is particularly strong for a role for B cells in emphysema pathogenesis,[69,72-83] possibly facilitated by appearance within distal lung parenchyma of organized lymphoid follicles,[84,85] which contain germinal centers that permit production of high-affinity antibodies. This process is even seen in panlobular emphysema due to alpha-1 anti-protease deficiency (AA1PD), the quintessential evidence for the protease–anti-protease imbalance hypothesis of COPD pathology. Explants from patients with AA1PD had notable CD4+ and CD8+ T cell infiltration and lymphoid follicles that were even more prominent that those from patients with usual emphysema.[86] Thus, auto-aggressive adaptive immune mechanisms likely amplify distal lung damage initiated as SAD into frank emphysema.

SAD Can Be Detected by Imaging Abnormalities That Correlate to Histopathological Changes

Noninvasive detection of SAD in living individuals has become possible by the imaging technique known as parametric response mapping (PRM)[87] and related techniques.[88,89] Detailed cryo-CT analyses of human lung tissue frozen in standardized inflation after resection confirm that, at least in advanced COPD, the metric of functional small airways disease, PRM^{fSAD} (ie, persistently hyperinflated, non-emphysematous lung regions), actually denotes small airway pathology.[90] This work has been extended by analyzing longitudinal change in PRM^{fSAD} and emphysema over time in the COPDGene cohort.[91] Results showed evolution of initial areas of SAD into later centrilobular emphysema (Fig. 2). These findings suggest that imaging might be used as the outcome in clinical trials of agents designed to arrest SAD, as has been used successfully to prevent emphysema in AA1PD by augmentation therapy.[92] Abnormal PRM^{fSAD} is not specific for the SAD of smokers, as it has also been observed in never smokers with histologically confirmed constrictive bronchiolitis resulting from exposures during military deployment to Southwest Asia.[93]

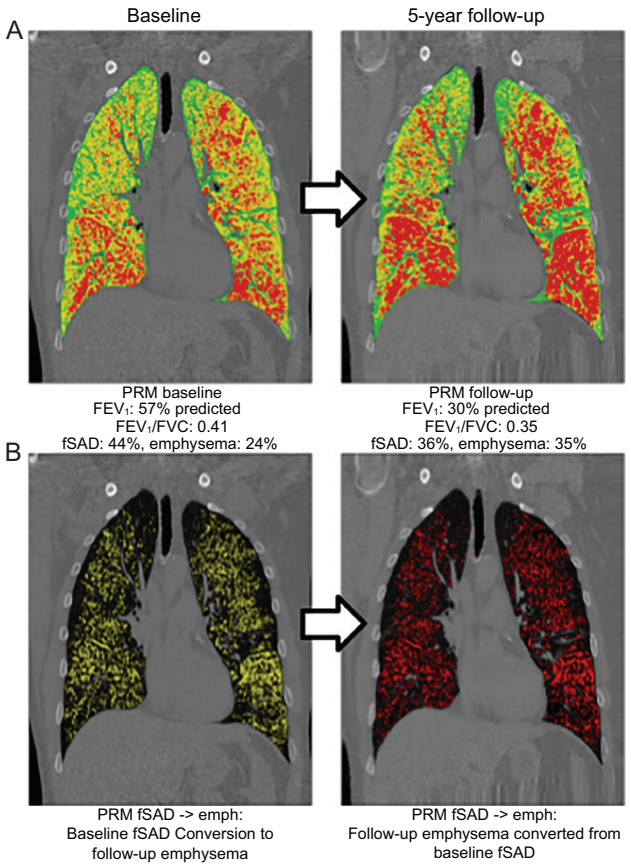

Fig. 2. Illustration of changes in parametric response mapping (PRM) metrics in a representative male patient with COPD. (A, B) Representative coronal computed tomography sections of the same individual at baseline (left) and after 5-y follow-up (right). A: All PRM metric values are depicted as normal lung parenchyma (green), functional small airway disease (fSAD, yellow) and emphysema (red). B: Only those individual voxels that were classified as fSAD at baseline (yellow) and which became emphysematous are shown. From Reference 91, with permission. PRM = parametric response mapping; fSAD = functional small airway disease; emph = emphysema.

Additional Pathologic Processes Leading to COPD

Thus, the processes leading to SAD are sufficient to induce centrilobular emphysema and may be the major pathway in many individuals. However, SAD cannot explain the complete heterogeneity of COPD phenotypes and is unlikely even to be the only pathway to centrilobular emphysema (Table 1). An alternative, not mutually exclusive, process is loss of pulmonary microcirculation, which is supported by evidence from both human pathological specimens[94] and in vitro and experimental animal models.[95-100] Using dynamic contrast-enhanced magnetic resonance imaging, the Multi-Ethnic Study of Atherosclerosis COPD Study found 30% reductions in pulmonary microvascular blood flow even in mild COPD; correlations were strongest with emphysema and were independent of measures of SAD.[101]

Table 1. Pathological Processes Leading to Emphysema

SAD
Loss of pulmonary microvasculature
Direct apoptosis of airway epithelial cells
Epithelial cell death deriving from loss of matrix attachments

SAD = small airway disease

Additionally, alveolar destruction might result from induction of epithelial cell apoptosis, either following loss of matrix attachments due to remodeling[102] or from the direct action of natural killer cells, which show enhanced cytotoxicity of autologous epithelial cells, relative to never smokers or non-obstructed smokers both in vitro[103,104] and in situ.[105] Hence, the ultimate phenotype of any individual with COPD almost certainly results from one or more pathological processes that will require tailored interventions.

Rationale for a Revised Definition of COPD

Is Airway Narrowing or Air Flow Limitation Universal in Those With COPD Risk Factors?

Given this diversity of lung pathologies associated with smoking and spirometrically mild COPD, the question arises: do such exposures always induce airway narrowing or air flow limitation? The answer is a resounding no, as demonstrated in several groups of individuals with smoking histories. The first is those with emphysema despite normal spirometry. An analysis of the COPDGene cohort using visual reads according to Fleischner Society criteria identified some degree of emphysema in 44% of GOLD 0 participants.[106] In a 5-y follow-up study from a larger group in the same cohort, those who initially exhibited visually evident emphysema had significantly greater changes in multiple parameters characteristic of COPD, including FEV_1/FVC.[107] Nevertheless, these individuals would not currently be classified as having COPD based on spirometric criteria. In addition to radiographic detection of emphysema, considerable data support the detrimental effect of low values of diffusing capacity for carbon monoxide (D_{LCO}), which is a risk factor for death independent of the degree of air flow limitation.[108,109] The recent availability of reliable portable systems to measure both spirometry and D_{LCO}[110] should permit broader use of this technique in cohort studies. These findings collectively argue strongly for including in the spectrum of COPD those with significant emphysema regardless of spirometry.

Additionally, in those with sufficient lifetime smoking history (10–20 or more pack-years), absence of air flow obstruction can still be associated with significant respiratory symptoms characteristic of COPD, including respiratory events compatible with exacerbations and empiric treatment using bronchodilators, as described in both the SPIROMICS[110] and COPDGene[112] cohorts.

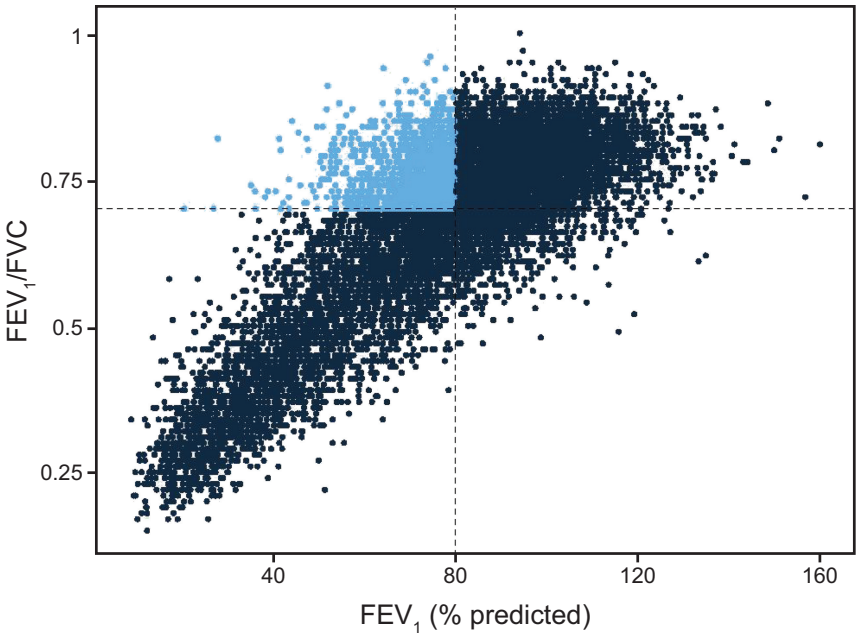

Fig. 3. Distribution of spirometry in the COPDGene cohort, which led to description of the preserved ratio but impaired spirometry (PRISm) phenotype. FEV_1% predicted is plotted on the x axis while FEV_1/FVC is plotted on the y axis. Dashed lines represent fixed-threshold criteria used to delineate PRISm individuals (highlighted in blue upper-left quadrant), individuals with normal lung function (upper-right quadrant), those with mild (lower-right quadrant), and moderate to severe COPD (lower-left quadrant). From Reference 112, with permission.

A third group currently excluded from the definition of COPD merits consideration: those with preserved ratio but impaired spirometry (PRISm)[113] also termed restrictive spirometry.[114] This group is typically defined as $FEV_1/FVC > 0.7$ and FEV_1% predicted $< 80\%$ (Fig. 3, upper left quadrant), although results are similar using lower limit of normal criteria. This graph also illustrates how rigid cutoffs based on spirometric values can misclassify; eg, some individuals with disproportionally high FVC values relative to their FEV_1 (also still in the normal range) will be diagnosed by GOLD criteria as having mild COPD (Fig. 3, lower right quadrant) rather than being normal variants. This issue is related strongly to age. Relative to the fixed-ratio definition, a cutoff based on lower limit of normal values for FEV_1/FVC diagnoses COPD less frequently in the elderly[115,116] and more frequently in those ≤ 45 y old.[115]

PRISm was common at enrollment in the COPDGene cohort (12.3%); many in this category initially appeared to have a clinical phenotype similar to COPD, and many do transition over time to frank COPD, frequently at GOLD stage 2 or greater. Survival in those with PRISm was less than that of GOLD 0 subjects, that is, smokers without air flow obstruction.[117] Congruent results were recently published from the Rotterdam cohort,[118] which showed that the survival of a similarly defined PRISm group was much closer to that of patients with COPD on average and worse than that of GOLD 1 subjects. Some individuals with PRISm in a separate cohort also showed significant emphysema.[119] Because the presence of significant interstitial lung abnormalities was exclusionary in most analysis of PRISm, the risk of it progressing to frank interstitial lung disease remains uncertain to my knowledge and worthy of

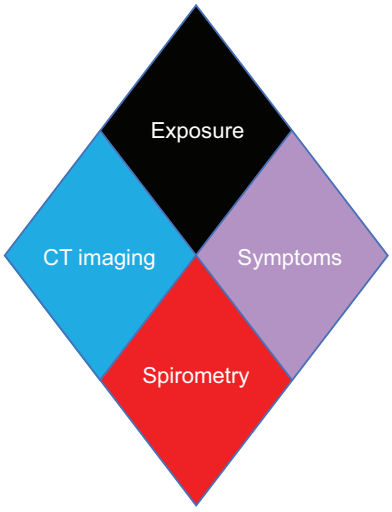

Fig. 4. Features used to define COPD in the COPD Genetic Epidemiology Study (COPDGene). Exposure in the COPDGene study includes individuals with a total of ≥ 10 pack-years smoking. Computed tomography (CT) imaging includes individuals with quantitative assessment showing $\geq 5\%$ emphysema, a square root of airway wall area for a standardized airway of 10 mm internal diameter ≥ 2.5 mm, or $\geq 15\%$ gas trapping. Symptoms include individuals with a Modified Medical Research Council dyspnea scale ≥ 2 or chronic bronchitis. Spirometry includes individuals with $FEV_1 < 80\%$ predicted or $FEV_1/FVC < 0.7$. From Reference 2, with permission. CT = computed tomography.

	Category	Odds of Change >350 mL in FEV_1 (95% CI)[a]	Hazard Ratio for All-Cause Mortality (95% CI)[b]	COPDGene 2019 Classification
	A	1.0 (ref.)	1.0 (ref.)	No COPD
	B	1.31 (1.04-1.65)	1.05 (0.76-1.44)	Possible COPD
	C	1.42 (1.07-1.88)	1.55 (1.09-2.19)	
	D	0.92 (0.64-1.30)	1.48 (1.03-2.12)	
	E	1.74 (1.28-2.36)	1.90 (1.33-2.71)	Probable COPD
	F	1.02 (0.66-1.60)	2.62 (1.84-3.72)	
	G	2.11 (1.66-2.68)	1.76 (1.36-2.27)	
	H	2.82 (2.18-3.66)	5.18 (4.15-6.48)	Definite COPD

Fig. 5. Logistic regression and Cox regression models for FEV1 progression and all-cause mortality, respectively, with the proposed COPDGene 2019 classification of categories. (A) Change in FEV_1 assessment was done on $n = 4,925$ participants who returned for phase 2 clinical follow-up. Adjusted for age at first visit, sex, race, pack-years, and current smoking. Bolded numbers indicate categories where the 95% CI did not include 1.0. Symbols as in Figure 4. From Reference 2, with permission.

investigation. PRISm has always been recognized to be a highly heterogeneous group, but recent follow-up in COPDGene[120] indicates that it is a highly fluid category, with subsequent changes either to normal spirometry or obstruction. The usefulness of the PRISm category has been questioned,[121] but it does appear to be a prevalent group at risk for poor outcomes and with largely unstudied responses to standard COPD treatments.

Importantly, all 3 of these common groups with lifetime smoking exposures (emphysema with little to no obstruction, symptomatic individuals with preserved spirometry, and PRISm) highlight the shortcomings of basing the diagnosis of COPD on spirometric cutoffs, whether fixed ratio or lower limit of normal based. Based on these groups who might fit under an expanded definition of the chronic lung conditions resulting from the multitude of oxidative inhalational exposures, it might be tempting to drop the "O" from the acronym. However, such a move would lose the name recognition that this long-neglected condition is finally gaining. It is recognized that the current spirometric diagnosis of COPD has considerable specificity, but low sensitivity, which has led to the proposal to recognize a broader group of exposed individuals as having pre-COPD.[122]

The Dilemma of Redefining COPD

Thus, the current definition of COPD is increasingly recognized to be inadequate. The dilemma is how to replace it. An analysis of the COPDGene cohort attempted to capture COPD heterogeneity using spirometry and combinations of CT imaging and symptoms. Based on logistic and Cox regression models of actual outcomes, the classification proposes a range of categories, including possible and probable COPD (Figs. 4, 5).[2] Efforts are already underway to update and expand this classification.

However, one can imagine devising very different definitions, depending on whether the goal is to define homogeneous endotypic groups for clinical trials versus an easy-to-apply algorithm to aid disease management in primary care. Similar tweaks would be needed for disability determination and potentially other uses. Hence, an all-encompassing redefinition appears elusive in the present state of pathological understanding. An alternative viewpoint is to cease considering COPD a unitary disease and instead accept it as a clinical syndrome.[4,123,124] In the meanwhile, every effort should be made to continue to dissect the heterogeneity of this syndrome to identify true biological mechanism–defined endotypes that will be susceptible to precision therapies.

Summary

Understanding of the biological and molecular pathways leading to lung damage in COPD has increased greatly in the last decade, but there is still much to be learned. Research is urgently needed on the pathological correlates of inhalational

exposures other than tobacco smoking that lead to impaired lung function and respiratory symptoms. Research on smokers should embrace the diversity of lifetime lung function trajectories and the heterogeneity of COPD by focusing on subgroups with chronologically early disease and those at increased risk of rapid loss of lung function. Advanced thoracic imaging[125] and the combination of genetic and multi-omics risk scores[126,127] promise to be the most efficient means to define targetable pathological pathways for personalized therapies. Finally, the current purely spirometric definition of COPD is inadequate, but revisions will likely require different definitions for disparate use cases.

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Discussion

MacIntyre: I thought that was a wonderful overview. I find it fascinating that in 2022 we are, for the most part, still defining COPD by spirometry, a test first described in the mid-19th century, and we are rigidly adhering to that definition despite this enormous amount of literature showing us that the FEV_1 is missing an awful lot of chronic small airways inflammation and emphysema. I think this is of particular interest to our pharma friends who manufacture and market bronchodilators, drugs of only limited value in small airway disease and of no value in emphysema. We need a whole new array of therapeutics aimed at these different phenotypes. That wasn't really a question, more of a comment. I also find it interesting, as long as we're discussing FEV_1, that the FEV_1 still remains in the FDA as the standard for approving drugs for COPD. And again, as Jeff has shown us very nicely, there's an awful lot of COPD out there that is not bronchodilator responsive. Any other thoughts?

Haynes: I would extend that to say that not only do we have this love affair with FEV_1 for diagnosis but also determining whether therapy works. There are a lot of data that show that bronchodilators do work even if it's not reflected in the FEV_1.[1]

Mike Hess: I think that really hits it on the head, the love affair with FEV_1. And I say this as a fellow registered pulmonary function technologist, not only is it an old test, it can be inaccurate; it is highly dependent on technique and coaching. When I've spoken with a few different clinicians who are relatively new to the COPD world they said, "Well what do we do, then?"; and I say, "this is the best we've got. We don't have a blood marker; we don't have a lab test. We can look at some of the imaging and use that, but we are legally and regulatorily bound by this FEV_1 idea." I definitely think it's time for an expanded definition. It also reminds me that everything old is new again because in some reading I've done on chronic nonspecific lung disease back in the 1960s Dutch definition, are we going back to that and then developing phenotypes?

Carlin: I agree with everyone else here in the room that I think the definition certainly needs to be changed, but how can we make it simple enough for a care provider to make an accurate diagnosis given the extreme limitations of time for the patient-physician interactions? I liken it back to what Tom Petty MD as part of the National Lung Health Education Program (which he founded) said years ago, that in order to diagnose an illness some type of "numerical" foundation should be made. For example, no one would diagnose hypertension without a blood pressure measurement or diagnose hyperlipidemia without a

lipid or cholesterol measurement. While spirometry may not be the absolute best way to diagnose COPD, it still stands as a cornerstone of the diagnosis.

Haynes: I would suggest that artificial intelligence (AI) is the way we get there. Expecting a primary care physician to calculate all this and consider all of these factors in the limited time they have is unrealistic, but we certainly have AI, and it would be easy to write software to *help* make that diagnosis.

MacIntyre: I assume we'll hear more about this later on with COPD assessment discussions, but it's obviously terribly impractical to require sophisticated imaging (eg, CT scanning) to detect emphysema. We need something simpler. Some things that come to mind is using AI or something like that to analyze the flows as the lung gets smaller and the airways get smaller. The $FEF_{25–75}$ is way too crude, but looking at the shape of the curve could yield valuable information. This is the so-called silent area of the spirometry tracing. Impulse oscillometry is perhaps another way of delving into the small airways in the lung. And then I'll put in a plug for one of my personal favorites, D_{LCO}. We think of diffusion capacity as a simple measurement of gas transport across the alveolar capillary membrane. However, ventilation distribution, intrapulmonary gas mixing, and the properties of the alveolar capillary membrane might all be things impacting D_{LCO} we could use to look for emphysema. Indeed, one of my favorite projects in COPDGene is looking at the relationship of D_{LCO} and CT to determine emphysema. There's clearly a relationship there; the r value is not huge, but it's real. So there may be tools that are a little simpler than going into the CT scanner to get at these small airway abnormalities and emphysema.

Orr: I'd like to make a quick comment on PFTs and diagnosis and share a little concern about liberalizing the diagnostic criteria. What I tend to see clinically is that patients come to me without spirometry and they're already on triple therapy. And I think that as long as the PFT results are a reflex to bronchodilators, and that dyspnea symptoms that are uncontrolled are a reflex to more bronchodilators, we're in a difficult situation. I think there's a lot of medication overuse for things that aren't really responsive to these bronchodilator medications.

Mike Hess: That also crossed my mind. We'll have to thread that needle. We already see people where, "ok, you coughed, you smoked 20 years ago, ergo you have COPD," and now you're tagged with this forever, and you're going to be on this particular medication regimen, and that's it. There is, I think, a danger in oversimplifying.

Criner: I think one of the things, as Brian [Carlin] mentioned, it's not only the primary care physicians but the majority of patients with COPD, and it's probably going to increase in people who are in low- or middle-income countries. And you know, there are more radiologists on Longwood Avenue in Boston than there are on the whole continent of Africa. So some of these tools that we use like CT scans or other elite measurements are useful in characterizing the extent of the disease but are not practical for the clinical diagnosis or to be used in definitions. I think one of the challenges is to be able, with an increasing worldwide prevalence of chronic obstructive lung diseases related to environmental changes and changes in the climate, is to be able to come up with a diagnosis that's established on physiological and clinical principles that are tied to mechanistic things that broaden the diagnostic abilities that we have and be able to triage patients to receive care based on that. Some of the papers that Jeff went through were SPIROMICS papers by Prescott Woodruff.[2,3] Those subjects were treated because they were symptomatic. And for the most part, in any clinical trial, the clinicians get it right. So, there's much more to be gained by milking the clinical history and physical examination than we currently use, and I think we can do a better job of trying to hone those skills.

MacIntyre: I think this is a great beginning. These comments and questions are likely going to keep coming up over the next day and a half, and we'll be referring back to this first talk.

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