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Causes of Death in Smokers

Implications for Chronic Obstructive Pulmonary Disease Management across Disease Severity

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder caused predominantly by exposure to tobacco smoke and characterized by progressive lung function impairment leading to disability and death. There has been much interest in reducing mortality in this condition with a wide array of interventions, including pharmacological and nonpharmacological therapies. Large COPD pharmacological trials have addressed mortality, specifically causes of death. In the TORCH (Toward a Revolution in COPD Health) study with subjects at a mean FEV_1 of 44% predicted, 35% of the deaths with adjudication were of respiratory causes (1), but a sizable proportion was of other causes, including cardiovascular disease (27%) and lung cancer (21%) (2).

In a complex disease, however, deaths will occur by varying mechanisms at different severity stages, and specific interventions are required at different points in the natural history of the condition. We now also have more information on factors associated with mortality in COPD, such as frequent exacerbations (3) and respiratory symptoms, that can help us to understand the type of intervention required.

In this issue of the *Journal*, Labaki and coauthors (pp. 451–460) address this issue by presenting data on causes of death related to lung function impairment in former or current smokers from the COPDgene (Genetic Epidemiology of COPD) study, which has recruited subjects with COPD of all severities (4). A total of 10,132 subjects were included, among whom 2,200 deaths occurred; they were followed for 10.1 years and divided into those with normal spirometry, a group with preserved ratio impaired spirometry (PRISm), and then Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1 and 2 and GOLD 3 and 4 groups. Data on causes of death were available on just over 75% of the deaths, and these were adjudicated after review of death certificates, medical records, and next-of-kin interviews. Analysis of the missing mortality data suggested that those subjects had clinical features similar to those of subjects with mortality causes documented. A number of clinical and imaging variables were available in the COPDgene cohort, allowing detailed analysis of associations between these parameters and mortality.

The results show that in the GOLD 1 and 2 group, deaths caused by lung cancer were common at 18%, and in the GOLD 3 and 4 group, deaths of respiratory causes were highest at 61%. Low-dose lung cancer screening reduces mortality of lung cancer and needs to

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be targeted in COPD in the GOLD 1 and 2 subjects. However, in subjects with GOLD stages 3 and 4 COPD, and especially in those with a BODE index (body mass index, airflow obstruction, dyspnea, and exercise) $\geqslant$7, the data in this paper suggest that the risk of respiratory death in these subjects outweighs the risk of other causes of death. This also confirms previous data showing that lung cancer screening does not reduce mortality in the GOLD 3 and 4 group (5).

Symptomatic COPD patients with poor health status are at greater risk of exacerbations (6) and disease progression, and, in this study, a St. George's Respiratory Questionnaire score of 25 or above was related to mortality in all the groups studied, including PRISm. Subjects with two or more exacerbations in the year before enrollment were at higher risk of death across the GOLD 1 and 2 and GOLD 3 and 4 groups, which emphasizes the importance of exacerbation prevention across the COPD severity spectrum. There have been relatively few exacerbation prevention studies performed in subjects with GOLD 1 and 2 severity. Interestingly, in this study, even one exacerbation was associated with mortality, although at a lower hazard ratio, and this emphasizes the importance of effective prevention of all exacerbations and not waiting until a patient with COPD develops frequent exacerbations. Other factors associated with mortality included the presence of chronic bronchitis, which was statistically significant in the GOLD 1 and 2 and GOLD 3 and 4 groups, and the presence of dyspnea using the modified Medical Research Council scale in all groups except those with normal spirometry. The computed tomography data showed only associations with emphysema and mortality in the GOLD 1 and 2 groups, and Pi10, a standardized measure of the square root of the wall area for a hypothetical airway with an internal perimeter of 10 mm, a measure of airway thickness, was associated with mortality in PRISm and only in the GOLD 3 and 4 group.

The main cause of death in PRISm was cardiovascular disease at 31%, which highlights the importance of screening this group for cardiovascular and metabolic disease. Interestingly, women with PRISm had a higher incidence of lung cancer deaths than men with PRISm, which may reflect metabolic and hormonal factors. Self-reported coronary artery disease and congestive heart failure were also related to mortality.

There are, of course, a number of limitations of this type of study, and the authors cover these well in the Discussion section, especially the limitation that therapy over the 10 years was not accounted for in the analysis. The computed tomography scans were performed a considerable time ago at recruitment, and imaging techniques have improved. I would have expected a relationship with airway wall thickness and mortality in mild or moderate disease, but the relationship missed statistical significance in the group with normal spirometry, and further studies are now needed. However, the authors need to be congratulated on providing the most detailed analysis to date of deaths in smokers with varying lung function severities.

So, what are the implications for COPD management? Exacerbations need to be prevented at all stages of COPD, and further research is needed in the less severe groups regarding the appropriate intervention. Patients with COPD who report exacerbations at diagnosis have been shown to be at higher risk of subsequent events (7). Targeting chronic bronchitis is important in early disease (8), and recently mucus plugs have been shown to be related to mortality in COPD (9). The recent study of inhaled bronchodilators in smokers was disappointing (10). Further studies are now needed in subjects with preserved spirometry or mild impairment with high symptom burden (11) and maybe concomitant exacerbations to understand the mechanisms involved, thus leading to the development of novel interventions. At all stages, patients with COPD need to be assessed for cardiovascular comorbidity, and smokers need to be targeted for lung cancer screening, especially in the mild and moderate severity groups. By targeting smokers and patients with COPD as early as possible in the natural history of their disease, we will be more successful in reducing mortality. ■

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Postbronchodilator Reference Values: Should They Be the Norm?

When spirometry is used to identify the presence and severity of chronic obstructive pulmonary disease (COPD), pre- and postbronchodilator testing is typically performed. In normal populations, there is at most only a small bronchodilator response (1). As a result, prebronchodilator reference values have been used and compared with postbronchodilator results. The Global Lung Function Initiative (GLI) noted that lung function test results can be interpreted using only robust, relevant, and reliable reference values (2). Using data from nearly 100,000 nonsmokers (55% female subjects) aged 3–95 years from 72 centers and 33 countries, the GLI study showed that the FEV_1:FVC ratio is essentially independent of ethnic group and serves as a reliable, although imperfect, indicator of lung function. However, 9-year follow-up of another multicenter study, PLATINO (Projeto Latino-Americano de Investigação em Obstrução Pulmonar), which used prebronchodilator reference values, identified a substantial underdiagnosis of COPD (3). The subjects in that study who did not receive diagnoses of COPD until they returned after 9 years presented with similar clinical characteristics as those who were not diagnosed in the initial phase. For some time, there has been debate as to whether postbronchodilator reference values would be better than prebronchodilator reference values to identify individuals with COPD or at risk for developing COPD. The landmark GLI study did not explore the effect of using postbronchodilator reference values for interpreting spirometry results. Furthermore, there is limited information as to whether the use of postbronchodilator reference values has a significant impact in the clinical interpretation of spirometry results (4, 5).

In this issue of the *Journal*, Malinovschi and colleagues (pp. 461–471) report the results of the study (6). They set out to determine whether postbronchodilator reference values were more successful than prebronchodilator reference values to identify individuals with mild COPD. To do this, they used pre- and postbronchodilator reference values generated from SCAPIS (Swedish Cardiopulmonary Bioimage Study) (7) and assessed the value of using postbronchodilator reference values as opposed to prebronchodilator reference values in a random population sample. The authors also compared pre- and postbronchodilator reference values from SCAPIS with reference values from the GLI and PLATINO studies.

The study included 30,154 middle-aged adults, 50–64 years of age, evenly distributed between men and women, at six academic medical centers in Sweden. The SCAPIS postbronchodilator reference values were obtained from 10,156 nonsmokers without respiratory symptoms or respiratory disease, after inhaling 400 μg of salbutamol. The SCAPIS prebronchodilator reference values were derived from 1,498 individuals at one of the six centers. In addition to pulmonary function testing, participants underwent high-resolution computed tomography to identify emphysema and completed several questionnaires. Participants were divided into three groups: *1*) postbronchodilator FEV_1:FVC ratio greater than the lower limit of normal (LLN) using both the prebronchodilator and postbronchodilator reference values; *2*) postbronchodilator FEV_1:FVC ratio greater than the LLN using the prebronchodilator reference value but lower than the LLN using the postbronchodilator reference values; and *3*) postbronchodilator FEV_1:FVC ratio less than the LLN using both pre- and postbronchodilator reference values.

The authors report that using postbronchodilator reference values resulted in higher predicted median values and LLN values for the FEV_1:FVC ratio. When the higher predicted median and LLN values were used, the prevalence of postbronchodilator FEV_1:FVC ratio less than the prebronchodilator LLN was 4.8%, while that of postbronchodilator FEV_1:FVC ratio less than the postbronchodilator LLN was 9.9% in this general population. Importantly, the additional 5.1% of participants who had abnormal postbronchodilator FEV_1:FVC ratios only when using postbronchodilator reference values had more respiratory symptoms, more computed tomography–diagnosed emphysema (13.5% vs. 4.1%; $P < 0.001$), and more instances of self-reported physician-diagnosed COPD (2.8% vs. 0.5%; $P < 0.001$) than subjects with postbronchodilator FEV_1:FVC ratio greater than the LLN for both pre- and postbronchodilator reference values. Similar results were seen for FEV_1, but not for FVC.

The study has both strengths and weaknesses. Strengths include the large number of individuals recruited from SCAPIS, the age range of 50–64 years (a population most likely to have early or mild COPD), the even distribution of men and women, and the accompanying clinical data, including respiratory symptoms, diagnosis of emphysema, and physician diagnosis of COPD. These clinical findings demonstrate the clinical relevance of postbronchodilator reference values in this population. Weaknesses include the relatively homogeneous population regarding race, ethnicity, and geographic location (although this may also be a strength by increasing the ability to identify an effect in this population) and the fact that prebronchodilator reference values were obtained from only one of the six research sites. In addition, there were some differences with data compared with other studies, such as PLATINO. However, as noted by the authors, the lower dose of salbutamol (200 μg) used

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