Published in final edited form as:
COPD. 2016 ; 13(2): 125–129. doi:10.3109/15412555.2015.1077506.

EPIDEMIOLOGY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN AGING POPULATIONS

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Abstract

Current epidemiologic practice evaluates COPD based on self-reported symptoms of chronic bronchitis, self-reported physician-diagnosed COPD, spirometry confirmed airflow obstruction, or emphysema diagnosed by volumetric computed chest tomography (CT). Because the highest risk population for having COPD includes a predominance of middle-aged or older persons, aging related changes must also be considered, including: 1) increased multimorbidity, polypharmacy, and severe deconditioning, as these identify mechanisms that underlie respiratory symptoms and can impart a complex differential diagnosis; 2) increased airflow limitation, as this impacts the interpretation of spirometry confirmed airflow obstruction; and 3) “senile” emphysema, as this impacts the specificity of CT-diagnosed emphysema. Accordingly, in an era of rapidly aging populations worldwide, the use of epidemiologic criteria that do not rigorously consider aging related changes will result in increased misidentification of COPD and may, in turn, misinform public health policy and patient care.

Keywords

COPD; epidemiology; aging; GOLD; spirometry

The epidemiologic evaluation of COPD should account for aging related changes in respiratory symptoms and in lung function and structure, because the highest risk population for having COPD includes a predominance of middle-aged or older persons (aged ≥40 years).[1–5] This article highlights aging related considerations specific to the epidemiology of COPD, but may also apply to other diseases of chronic airflow obstruction such as asthma and the asthma-COPD overlap syndrome.

Current Epidemiologic Practice

A longstanding practice in the epidemiologic evaluation of COPD has been to rely on self-reported symptoms of chronic bronchitis (CB) or on self-reported physician-diagnosed

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DECLARATION OF INTEREST

Dr. Vaz Fragoso takes full responsibility for the content of this work. He is a recipient of a Merit Award from the United States Department of Veterans Affairs. The author reports no conflicts of interest, including no commercial support.

COPD.[2–5] Using these criteria and data from a representative sample of Americans aged 40 to 80 years (Third National Health and Nutrition Examination Survey [NHANES III]), the prevalence of COPD was 12.6% and 6.7% when based on self-reported CB (cough or sputum production on most days for at least 3 months during the year) and self-reported physician-diagnosed COPD (CB or emphysema), respectively.[6]

Because a predominant respiratory impairment in COPD is chronic airflow obstruction,[7] an additional longstanding practice has been to evaluate the epidemiology of COPD based on spirometric criteria, most often using diagnostic thresholds from the Global Initiative for Obstructive Lung Disease (GOLD).[8] The spirometric criteria include a decreased ratio of the forced expiratory volume in 1-second (FEV1) to forced vital capacity (FVC), defined by a GOLD threshold of <0.70 that is uniformly applied across all ages. The severity of COPD is then classified by the FEV1 percent predicted (%Pred), calculated as [measured/predicted FEV1] × 100%) and is most often reported in a 3-level stratification of mild (≥80 %Pred), moderate (50–79 %Pred), and severe (<50 %Pred), also applied across all ages. Using data from a representative sample of Americans aged 40 to 80 years (NHANES III), prevalence rates for GOLD-defined COPD were 37.7% in those aged 65–80 years and 22.2% in those aged 40–64 years.[9,10] In both age groups, 49% of those with GOLD-defined COPD had mild severity (FEV1/FVC <0.70 and FEV1 ≥80 %Pred), whereas only 10–13% had a severe classification (FEV1/FVC <0.70 and FEV1 <50 %Pred).[1]

A more recent development in epidemiologic surveys has been the use of volumetric computed chest tomography (CT), in particular an inspiratory scan, to establish a diagnosis of emphysema.[11] This is based on a calculation of percent lung having a low attenuation area of less than −950 HU ($LAA950_{insp}$), with threshold values >5% establishing a diagnosis of emphysema.[11,12] Using data from the Genetic Epidemiology of COPD study (COPDGene), which included 10,131 participants who were aged 45–81 years and had a smoking history averaging 44.3 pack-years, CT-diagnosed emphysema was established in 30.3%.[13]

For reasons discussed below, epidemiologic surveys of COPD that are based on respiratory symptoms, a physician diagnosis, GOLD-based spirometric criteria, and CT-diagnosed emphysema are likely to have potential limitations in aging populations.

Aging Related Considerations

By 2050, the World Health Organization projects 400 million people worldwide will be aged ≥80 years.[14] The aging shift is most pronounced in low- and middle-income countries, wherein the population aged ≥65 years is expected to double over the next 20 years.[14] Developed countries also demonstrate rapidly aging populations. For example, in the United States, the percent of those aged ≥65 years will have increased from 12.9% in 2009 to 20% in 2030.[15]

Advancing age is characterized by a high burden of respiratory symptoms, such as dyspnea on exertion (DOE), chronic bronchitis (CB), and wheezing.[6] Using data from a representative sample of Americans aged 40 to 80 years (NHANES III), prevalence rates

were 28.6% for DOE, 12.6% for CB, and 12.9% for wheezing.[6] The mechanisms underlying respiratory symptoms in aging populations are likely to be multifactorial, given age-related increases in multimorbidity (62% of Americans aged ≥65 years have ≥2 chronic conditions), adverse effects related to polypharmacy (20% to 30% of Americans aged ≥65 years use medications listed in drugs-to-avoid lists), and high rates of severe deconditioning (dual effect of increased sarcopenia and a highly sedentary status).[16–19] Accordingly, establishing a diagnosis or staging the severity of COPD based on respiratory symptoms[20] will have limited diagnostic specificity in aging populations.

It is also imperative to consider the effects of advancing age on lung function and structure.[21–24] The aging lung is characterized by a progressive reduction in physiologic capacity, starting in the 3rd decade of life.[21–24] The most pronounced age-related physiologic impairment is in respiratory mechanics, including increased rigidity of the chest wall, decreased elastic recoil of the lung, decreased diameter of the small airways, and “senile” emphysema.[21] The latter relates to degeneration of elastic fibers around the alveolar duct (in the absence of alveolar wall destruction), resulting in homogeneous airspace enlargement and reduced alveolar surface area.[21] These impairments in respiratory mechanics present as: 1) airflow limitation: defined by a decreased FEV1/FVC; 2) air trapping and hyperinflation: defined by an increased residual volume and functional residual capacity; 3) reduced maximum breathing capacity: defined by a decline in the maximal attainable minute ventilation, correlating with a decrease in FEV_1; and 4) ventilation-perfusion mismatch: defined by an increased closing volume that approaches the FRC by age 65 years and subsequently leads to premature closure of the small airways and a widened alveolar-arterial oxygen gradient.[21] Other age-related physiologic impairments include reductions in pulmonary capillary density, mucociliary clearance efficiency, respiratory muscle strength, and cerebrovascular responsiveness to carbon dioxide (CO_2) (tightly linked to the CO_2 ventilatory response).[21]

Because of progressive airways disease and emphysematous destruction of the alveolar-capillary interface, the respiratory impairments of COPD overlap with physiologic impairments of the aging lung, although occurring to a more severe extent.[7] The most important of these COPD-based respiratory impairments include 1) mucus hypersecretion, 2) chronic airflow obstruction, 3) air trapping and hyperinflation, and 4) gas exchange abnormalities. Hence, physiologic and anatomic criteria that establish COPD, including spirometric measures and chest CT imaging, must account for aging related changes in lung function and structure.[7,21–24]

Epidemiologic Concerns

Prior work has shown that two-thirds of middle-aged or older persons who have self-reported CB do not have spirometry-confirmed COPD.[6] This may be explained by age-related increases in factors other than COPD that contribute to CB (particularly the cough component), including chronic rhinosinusitis, gastroesophageal reflux, and medications (e.g. angiotensin converting enzyme inhibitors). Prior work has also shown that more than half of middle-aged or older persons who have self-reported, physician-diagnosed COPD do not

have spirometry-confirmed COPD.[25] This may relate to a low spirometric utilization in primary care settings.[26,27]

Similarly, GOLD-based spirometric criteria lack diagnostic accuracy when establishing COPD in aging populations, a consequence of two fundamental flaws. First, GOLD defines a reduced FEV_1/FVC by a fixed ratio of 0.70 across all ages, thus failing to distinguish between age-related airflow limitation and COPD-related airflow obstruction.[21–24] In particular, an $FEV_1/FVC < 0.70$ is frequently seen in otherwise healthy, asymptomatic never-smokers starting at age ≥45–50 years.[21–24,28] Second, GOLD expresses FEV_1 as %Pred, which assumes incorrectly the equivalence of spirometric variability across the lifespan.[22,23,29] To illustrate the effect of age on spirometric performance, the FEV1 in a white male of average height at the 5th percentile as calculated in a reference population of healthy never-smokers is equal to 74%Pred at age 30 years but only 63%Pred at age 70 years.[29] Importantly, these age-related flaws limit the diagnostic accuracy of GOLD in establishing both the prevalence of COPD and the development of COPD over time (incident COPD). For example, in a population of healthy lifelong non-smokers, at the 5th percentile of distribution (lower limit of normal), a white male of average height has an FEV1/FVC of 0.75 at age 40 years, thereafter declining to an FEV1/FVC of 0.65 by age 80 years — this is interpreted by GOLD as incident COPD, but simply reflects normal aging.[22] Similar comments apply when evaluating COPD severity over time based on FEV1 %Pred.[22,23,29]

GOLD recommendations also state that spirometry should be performed before and after administration of an inhaled bronchodilator (BD), in order to establish reversibility (pre- vs. post-BD values) and a diagnosis of COPD (using post-BD values). Among older persons, this approach has three disadvantages. First, older persons have limited capacity to perform multiple FVC maneuvers (pre- and post-BD), and may have an adverse response to a BD.[30,31] Second, post-BD values have limited clinical relevance in distinguishing COPD from asthma, and low reproducibility over time.[32–34] Third, the diagnostic thresholds for spirometric interpretation are based on reference populations that only recorded pre-BD values (a BD was not given).[22,23]

Lastly, emphysema established by a CT-measured $LAA950_{insp}$ value >5% may also have aging related limitations. As discussed earlier, normal aging is associated with “senile” emphysema and prior work has shown that values for CT-measured $LAA950_{insp}$ may be as high as 30% in otherwise healthy persons with normal lung function.[21,35] Unfortunately, age-specific reference equations for $LAA950_{insp}$ as determined in healthy populations of asymptomatic lifelong nonsmokers are currently unavailable.[36]

Alternative Approach

Because respiratory symptoms lack diagnostic specificity and because the application of chest CT imaging on a large scale is impractical (radiation exposure, cost, potential for further testing of false positive findings [pulmonary nodules]),[37] spirometry remains the preferred approach to evaluate the epidemiology of COPD. In addition, as discussed earlier, chronic airflow obstruction is a predominant respiratory impairment in COPD.

To better distinguish aging related airflow limitation from COPD related chronic airflow obstruction, investigators have suggested that spirometric measures be expressed as a Z-score, which converts a raw measurement on a test to a standardized score in units of standard deviations.[21–23] More recently, a method for calculating spirometric Z-scores has been developed, termed Lambda-Mu-Sigma (LMS).[22] This strategy uses all three elements of the distribution, including: median (Mu) — representing how spirometric measures change based on predictor variables (age, height, sex, and ethnicity); coefficient-of-variation (Sigma) — representing the spread of reference values (variability in spirometric performance) and adjusting for non-uniform dispersion; and skewness (Lambda) — representing the departure from normality.[22] The LMS-derived Z-score is then calculated as follows: [(measured ÷ predicted median)^{Lambda} minus 1] ÷ (Lambda × Sigma).[22] Clinically, Z-scores are already routinely used to diagnose osteopenia and osteoporosis based on bone mineral density testing, and the LMS method is widely applied to growth charts in children.[22,38]

In late 2012, the Global Lung Function Initiative (GLI) expanded the availability of LMS-calculated spirometric Z-scores by publishing reference equations that include ages up to 95 years and multiple ethnic groups.[23] Using GLI equations, Z-scores are calculated for FEV_1, FVC, and FEV_1/FVC. The diagnostic algorithm then applies a single threshold, namely a Z-score of −1.645, corresponding to the lower limit of normal at the 5th percentile of distribution (LLN), as follows: normal spirometry by an FEV_1/FVC ≥LLN and FVC ≥LLN, restrictive-pattern by an FEV_1/FVC ≥LLN and FVC <LLN, and COPD (airflow obstruction) by FEV_1/FVC <LLN.[21,39] COPD severity is next evaluated as a 3-level stratification, based on a diagnostic algorithm that applies two thresholds for FEV1 Z-scores, as follows: FEV1 Z-scores ≥−1.64 (mild), <−1.64 but ≥−2.55 (moderate), and <−2.55 (severe), respectively. The Z-score threshold of −1.64 corresponds to the 5th percentile (LLN), while −2.55 corresponds to the 0.5th percentile of distribution; these thresholds are associated with adverse health outcomes.[40,41] Other FEV1 Z-score thresholds for staging COPD are available, using instead a 5-level severity.[42] Methodology regarding GLI-calculated spirometric Z-scores and the spirometers that include GLI software can be found at http://www.lungfunction.org/

Using data from a representative sample of Americans aged 40–80 years (NHANES III) and LMS calculated spirometric Z-scores, COPD was established in 15.7% of those aged 40–64 years and 13.2% of those aged 65–80 years.[9,10] As described earlier, also in the same study population, GOLD criteria established a COPD prevalence of 22.2% and 37.7% in those aged 40–64 and 65–80 years, respectively.[9,10] Relative to the LMS approach, GOLD had false positive rates for COPD of 27.9% and 57.1% in those aged 40–64 and 65–80 years, respectively.[9,10]

The high false positive rate for GOLD-defined COPD relates to misidentification of normal spirometry as a respiratory impairment, including COPD or restrictive-pattern.[13] Using the most recent GLI equations for the calculation of spirometric Z-scores (pre-BD values) and data on 10,131 participants from COPDGene (aged 45–81 years), we found that the phenotype of the 5,100 participants with GLI-defined normal spirometry included adjusted mean values and 95% confidence intervals (CIs) that were within the normal range for

dyspnea grade (Modified Medical Research Council grade <2), respiratory health related quality of life (St. George's Respiratory Questionnaire (SGRQ) total score <25), exercise capacity (6-minute walk maximal distance (6MWD) > 1282 feet), BD reversibility (FEV1 change ≤12%), and CT-measured percent emphysema (≤5%) and gas trapping (≤15%).[13] In addition, the phenotype of the 1,146 participants who had the discordant classification of GLI-defined normal spirometry, but GOLD-defined respiratory impairment (COPD or restrictive-pattern), included adjusted mean values and 95% CIs that were within the normal range for corresponding measures.[13] Based on these results, it is likely that the phenotype of GLI-defined normal spirometry suggested the absence of clinically-meaningful COPD, even when classified as COPD by GOLD. The results of this study[13] are consistent with—and provides a mechanistic explanation for2015prior work showing that the GOLD misclassification of normal spirometry as respiratory impairment, including COPD and restrictive-pattern, was not associated longitudinally with adverse health outcomes, such as impaired mobility, COPD hospitalization, or mortality.[28,40,43]

Key Points

When evaluating the epidemiology of COPD in middle-aged or older persons, it is imperative to consider aging related changes, including: 1) increased multimorbidity, polypharmacy, and severe deconditioning, as these identify alternate mechanisms that may underlie respiratory symptoms and can impart a complex differential diagnosis; 2) increased airflow limitation, as this impacts the interpretation of spirometry confirmed airflow obstruction; and 3) "senile" emphysema, as this impacts the specificity of CT-diagnosed emphysema. Hence, the current practice of establishing the epidemiology of COPD based on respiratory symptoms, a physician diagnosis, and GOLD-based spirometric criteria lacks diagnostic accuracy in aging populations. Moreover, the recent use of CT-diagnosed emphysema as an epidemiologic tool has limitations, given the lack of reference equations for $LAA950_{insp}$ and concerns raised by radiation exposure, cost, and a potential high rate of further testing for false positive findings (pulmonary nodules).

Alternatively, an epidemiologic approach based on spirometric Z-scores provides a rigorous distinction between aging related airflow limitation and COPD related airflow obstruction. To further support such an epidemiologic approach, particularly in developing countries, the World Health Organization and professional respiratory societies should embark on a program that provides reference equations for calculating spirometric Z-scores in ethnic groups currently not included in GLI, using methodology as described by GLI investigators. Otherwise, in an era of rapidly aging populations worldwide, the continued use of epidemiologic criteria that do not adequately consider aging effects will lead to increased misidentification of COPD and may, in turn, misinform public health policy and patient care, including inappropriate respiratory therapies and delays in considering other more likely diagnoses.[16,17,44]

ACKNOWLEDGMENTS

Special thanks to the Yale Program on Aging and the Veterans Affairs Clinical Epidemiology Research Center, including Drs. Gail McAvay, Peter H Van Ness, John Concato, H. Klar Yaggi, and Thomas M. Gill. The current work is inspired by the many research contributions of Drs. Philip Quanjer and Paul Enright.

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