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The Vital Capacity Is Vital

Epidemiology and Clinical Significance of the Restrictive Spirometry Pattern

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Epidemiologic research has revealed a substantial portion of the general population with abnormal spirometry results that are characterized by decreased FEV_1 and FVC but a preserved FEV_1/FVC ratio. This restrictive spirometry pattern (RSP) is inconsistently defined in the literature and not well addressed by current guidelines; there is an accumulating body of evidence, however, that RSP is prevalent to a similar degree as airflow obstruction. Genetic and other risk factors for RSP, such as inhalational injuries and early life exposures, continue to be actively described. Although it seems that RSP is closely associated with the metabolic syndrome, diabetes, and systemic inflammation, it is not a simple marker of obesity. RSP is associated with adverse cardiovascular outcomes, as well as mortality, and it may be an underappreciated cause of functional impairments and respiratory symptoms. Improvement in outcomes in this population will require that clinicians have an appreciation for the significance of this spirometry pattern; additional research into the clinical and radiologic phenotype of these subjects is also needed. This article provides an overview of the recent developments in our understanding of this prevalent and highly morbid spirometry pattern. CHEST 2016; 149(1):238-251

KEY WORDS: epidemiology; lung function; pulmonary; spirometry

Spirometry has proven to be a useful tool for assessing the respiratory health of individual patients and populations. Numerous large epidemiologic studies in the United States and elsewhere have incorporated spirometry as part of their examinations, primarily to assess the prevalence of obstructive lung disease. However, these data have also revealed a substantial proportion of the population with nonobstructive abnormal spirometry results that are characterized by matched deficits in FEV_1 and FVC, leading to a preserved FEV_1/FVC ratio. This abnormal spirometry phenotype is referred to alternately as the restrictive spirometry pattern (RSP); "GOLD-unclassified"[1]; preserved ratio-impaired spirometry[2]; or the nonspecific pattern[3] (when accompanied by a normal total lung capacity [TLC]). This spirometry phenotype occurs far more than

ABBREVIATIONS: BOLD = Burden of Obstructive Lung Disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LLN = lower limit of normal; RSP = restrictive spirometry pattern; TLC = total lung capacity

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FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

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DOI: http://dx.doi.org/10.1378/chest.15-1045

what would be expected as a result of interstitial lung disease and has been associated with diabetes,[4,5] the metabolic syndrome,[6-9] increased respiratory symptoms,[2,10-12] functional limitations,[13] and mortality.[10,14-18]

Despite these observations, the mechanisms of disease associated with RSP are poorly understood. In addition, this spirometry pattern was not well addressed in extant American Thoracic Society/European Respiratory Society guidelines.[19] Recognition of RSP is important because it is highly prevalent in the general population and has consistently defined an at-risk population that requires further study and characterization. The present review provides an overview of the epidemiology of RSP; discusses recent research on risk factors, clinical features, radiology, and outcomes related to this pattern of spirometry; and identifies key areas for future study.

Definition of RSP and Guidelines

RSP has been defined in many studies as the absence of airflow obstruction (typically denoted by an $FEV_1/FVC \geq 0.70$) with a reduced FVC $<$ 80% predicted (Table 1).[20-35] Alternative definitions have included a nonobstructive FEV_1/FVC ratio with an FEV_1 $<$ 80% predicted[36] or an FEV_1/FVC higher than or equal to the lower limit of normal (LLN) and FVC below the LLN.[6] In the American Thoracic Society/European Respiratory Society guidelines, this spirometry pattern is attributed to "failure of the patient to inhale or exhale completely" or "may also occur when the flow is so slow that the subject cannot exhale long enough to empty the lungs to RV."[19] However, since those guidelines were published, more data on RSP have become available, and these explanations may require reexamination. For example, in the Tucson Epidemiological Study of Airway Obstructive Disease (TESAOD) trial, 12% of the study population had RSP at baseline. Among the subjects with baseline RSP and follow-up spirometric data, some developed airflow obstruction that resulted in mixed restriction-obstruction on follow-up; the majority of subjects, however, did not develop airflow obstruction, with 33% exhibiting a recurrent restrictive pattern (RSP at enrollment and at ≥50% of follow-up examinations, and never an obstructive pattern) and 29% exhibiting an inconsistent restrictive pattern (RSP at enrollment and at <50% of follow-up examinations, and never an obstructive pattern).[10] In the COPDGene study, subjects with RSP had significantly lower lung volumes according to CT volumetry and less emphysema than subjects with COPD.[12] These data suggest that RSP is unlikely to represent misclassified COPD and that it is a distinctive finding by itself.

Epidemiology

The prevalence of RSP in several large population studies is presented in Table 1. Burden of Obstructive Lung Disease (BOLD) studies have shown a striking geographic variance, with prevalence in the single digits in Canada and Norway and increasing to upward of 60% in the Philippines and India.[14] Interestingly, this research found that a powerful correlate for the presence of restriction was poverty, with the number of restricted patients rising dramatically when the per-capita gross national product was less than $15,000. Studies performed in the United States have shown a relatively stable prevalence of restriction between 8% and 12%. In many of these studies, the prevalence of RSP is comparable to that of airflow obstruction. Assessment of the frequency of interstitial lung disease (a clinical cause of RSP) is problematic because of changing definitions and classifications of disease, as well as a reliance on death certificates for information on causes of death. However, the estimated overall prevalence of interstitial lung disease is < 1% of the adult population,[37] far lower than the prevalence of RSP.

When interpreting the results of the studies in Table 1, several methodologic issues warrant consideration. The study populations are of widely varying ages, which is a variable known to affect spirometric measurements of restriction[38] (and obstruction), although use of percent predicted values would take age into account. In addition, RSP was inconsistently defined, and measurements were not specifically obtained after use of a bronchodilator. However, these studies did include quality control procedures and standards for spirometry that generally met or exceeded contemporary recommendations (e-Table 1).

Finally, different predictive equations to establish RSP were used across studies. For example, the BOLD study investigators chose to use the FEV_1/FVC and FVC LLN criteria for white subjects derived from the Third National Health and Nutrition Examination Survey to define restriction in their study. Use of race- or ethnicity-based predictive equations is controversial, and assumptions that observed variations in lung function are due to race or ethnicity should be avoided.[39] Rather, studies such as BOLD highlight the marked differences