Frequency and Causes of Combined Obstruction and Restriction Identified in Pulmonary Function Tests in Adults

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BACKGROUND: The frequency of combined obstruction and restriction identified in pulmonary function tests has not been well described. Moreover, although the causes of combined-obstruction-and-restriction patterns are known, the frequency of the various etiologies has received little attention. METHODS: We retrospectively reviewed medical records and surveyed pulmonologists. RESULTS: 43,212 PFT sessions were evaluated, which yielded 130 patients who satisfied our criteria for spirometry evidence of combined obstruction and restriction. Their demographic features were: mean ± SD age 54 ± 14 y, 51% male, mean ± SD body mass index 28.8 ± 6.7 kg/m^2, mean ± SD height 174 ± 9 cm (men) and 162 ± 7 cm (women). The causes of combined obstruction and restriction were classified as either a pulmonary parenchymal disorder (Group A, $n = 49$, 38%) or a combination of pulmonary parenchymal and non-pulmonary diseases (Group B, $n = 63$, 48%). In 18 patients (14%) no clear etiology of combined obstruction and restriction could be determined. The most common pulmonary disease was chronic obstructive pulmonary disease (45/130, 35%), and the most common non-parenchymal disease was congestive heart failure (27/130, 21%). We electronically sent a survey to 55 pulmonary physicians, of whom 30 (55%) responded. The respondents estimated that combined obstruction and restriction occurs in approximately 20% of all the pulmonary function tests performed in their practices and that pulmonary parenchymal diseases were responsible for 35% of all instances of combined obstruction and restriction. CONCLUSIONS: Combined obstruction and restriction occurs infrequently and is more commonly caused by a combination of pulmonary parenchymal and non-pulmonary disorders. Pulmonologists' impressions regarding the frequency and causes are generally discordant with the observed frequencies.
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Introduction

By providing an objective physiologic assessment, pulmonary function tests (PFTs) allow the clinician to classify patterns of chest disease that may then facilitate diagnosis and therapy decisions. Spirometry is commonly used to identify patients with obstructive airway disease, defined by a decreased forced expiratory volume in the first second (FEV_1) and a decreased ratio of FEV_1 to forced vital capacity (FVC).[1] At the same time, limitations of spirometry include its inability to establish the presence of a concomitant restrictive disorder or a pattern of combined (also called mixed) obstruction and restriction.

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Dr Stoller has disclosed relationships with Boehringer-Ingelheim, Talecris, CSL Behring, Asmatx, Grifols, Baxter, Philips-Respironics. The other authors have disclosed no conflicts of interest.

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In this context and based on American Thoracic Society/European Respiratory Society recommendations that lung volumes should be measured to establish restriction when spirometry indicates a decreased FVC,[2,3] combined measurement of spirometry and static lung volumes is common in clinical practice, though the actual frequency of these tests and the rate of occurrence of combined obstruction and restriction have received little attention. Furthermore, although the differential diagnosis of combined obstruction and restriction is known, information about pulmonary physicians' familiarity with this differential diagnosis and about the frequency of combined obstruction and restriction is also sparse.

To address this gap, we undertook the current study to determine the frequency and causes of combined obstruction and restriction, in the pulmonary function laboratory of a tertiary-care center. We also conducted a survey to assess pulmonologists' perceptions about the frequency and etiologies of combined obstruction and restriction, and we compared the respondents' impressions about the frequencies of the causes to the actual frequencies.

Methods

The study protocol was approved by the institutional review board of The Cleveland Clinic.

We retrospectively reviewed PFT results from consecutive adult patients referred to the pulmonary function laboratory of The Cleveland Clinic between January 1, 2000, and December 31, 2003. For patients who underwent more than one PFT session during that interval we considered only the results from the first PFT session. Spirometry (MasterLab Pro, Jaeger, Würzburg, Germany) and plethysmographic lung-volume measurements (MasterScreen Body PFT, Jaeger, Würzburg, Germany) were performed in accordance with the recommendations of the American Thoracic Society/European Respiratory Society.[4,5] We used the post-bronchodilator values in the analysis. The percent-of-predicted values were determined with reference equations for spirometry,[6] lung volumes,[7] and diffusing capacity of the lung for carbon monoxide (D_{LCO}).[8]

A pattern of obstructive airway disease was defined as an FEV_1/FVC below the 5th percentile of the predicted value.[4,9] A restrictive pattern was defined as a plethysmographically measured total lung capacity (TLC) below the 5th percentile of the predicted value.[6,7] A pattern of combined obstruction and restriction satisfied both the latter criteria.

In the majority of subjects the causes of abnormal PFT results were determined by the physician who ordered the PFT and were documented in the medical record. For the remainder of the subjects the causes of the PFT abnormalities were determined by two of the investigators (EDG, AS) after reviewing the text of the electronic medical record and radiology and pathology reports.

We developed a Web-based survey at SurveyMonkey.com, and via e-mail asked all the pulmonary/critical-care attending physicians and fellows in the Department of Pulmonary, Allergy, and Critical Care Medicine of The Cleveland Clinic, and some pulmonologists who had trained at The Cleveland Clinic but were practicing at other institutions, to participate in the survey.

Results

During the study period, 43,212 PFT sessions were performed. Of those, 7,506 (17%) included simultaneous spirometry and body plethysmography. 2,203 (29%) patients satisfied our criteria for a restrictive pattern, and 151 (2%) satisfied our criteria for combined obstruction and restriction. Figure 1 depicts the distribution of PFTs and corresponding number of patients (as some patients underwent more than one PFT session during the study period).

Altogether, 4,767 patients underwent simultaneous spirometry and body plethysmography. Among these, 130 patients (2.7%) met our criteria for combined obstruction and restriction. The remaining 24,723 patients did not complete lung-volume measurements at the same visit as spirometry. Among those 24,273 patients, 11% (2,670 patients) had a low FEV_1/FVC and a low FVC, of whom 319 underwent lung-volume measurements at a later date; 30 (9.4%) of those patients showed restriction (ie, TLC was below the lower limit of normal).

Study subjects' demographic features were as follows: mean ± SD age 54 ± 14 y, 51% male, 87% white, 12% African-American, mean ± SD body mass index 28.8 ± 6.7 kg/m^2, mean ± SD height 174 ± 9 cm (men) and 162 ± 7 cm (women). Fifty-two percent (68/130) had a history of cigarette smoking.

The causes of combined obstruction and restriction were classified as either a pulmonary parenchymal disorder (Group A) or a combination of parenchymal and non-pulmonary diseases (Group B). Approximately half of all instances of combined obstruction and restriction were attributed to a combination of parenchymal and non-pulmonary diseases (Table 1). The most common parenchymal disease was chronic obstructive pulmonary disease (COPD), and the most common non-parenchymal disease was congestive heart failure. In the group with combined conditions, obesity (mean body mass index 42.1 ± 4.9 kg/m^2) and a history of thoracic surgery were the most common features. In 14% (18/130) of the subjects the cause of the combined obstruction and restriction could not be determined from the medical record.

Groups A and B had similar FVC, FEV_1, FEV_1/FVC, and TLC values. Compared to patients in Group B, patients with pulmonary parenchymal disorders had lower

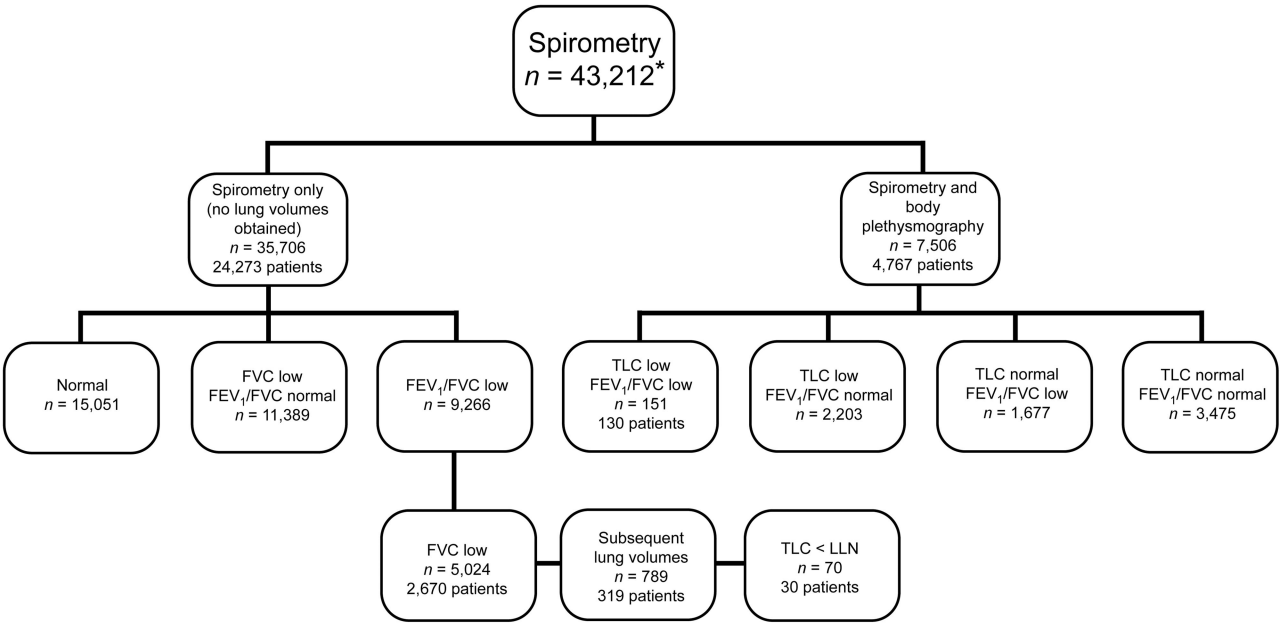

Fig. 1. Distribution of pulmonary function test results. The *n* values represent spirometry sessions. FVC = forced vital capacity. FEV_1 = forced expiratory volume in the first second. TLC = total lung capacity. LLN = lower limit of normal.

D_{LCO} and a lower ratio of residual volume to TLC (Table 2).

We e-mailed the survey invitation to 55 pulmonary/critical-care physicians and past and current fellows of The Cleveland Clinic, of whom 30 (55%) responded. Approximately 75% of the respondents were pulmonary/critical-care attending physicians, with an average of 6 years in practice.

A pattern of combined obstruction and restriction was believed to occur "very frequently" by 4%, "frequently" by 32%, "sometimes" by 54%, and "rarely" by 10% of the respondents. The respondents estimated that combined obstruction and restriction occurs in approximately 20% of all the PFTs performed in their practice, and that pulmonary parenchymal diseases account for 35% of all instances of combined obstruction and restriction. Most respondents (90%) reported feeling "comfortable" or "very comfortable" establishing a differential diagnosis for a combined obstruction and restriction pattern.

Table 3 presents the survey responses regarding the etiologies of combined obstruction and restriction. Figure 2 compares the survey responses to the actual frequencies of causes of combined obstruction and restriction. The respondents perceived the frequency of combined obstruction and restriction (20%) to be much higher than the observed frequency (2%, $P = .003$). Also, the perceived frequencies significantly exceeded the observed frequencies ($P = .001$) for several of the causes of combined obstruction and restriction, including asthma + other, obesity + other, and COPD + other.

Discussion

The main findings of this study are:

1. Although combined obstruction and restriction was perceived by the surveyed pulmonary physicians to be common in clinical practice, combined obstruction and restriction was infrequent in our sample.
2. Combined obstruction and restriction is more commonly caused by a mixture of parenchymal and non-parenchymal diseases than by a single pulmonary entity.
3. Congestive heart failure, obesity, and a history of thoracic surgery compose the majority of non-pulmonary conditions associated with combined obstruction and restriction.
4. Physicians' impressions of the frequency and causes of combined obstruction and restriction appear to be different than the etiologies observed in this series of consecutively tested subjects.

Based on spirometry results, respiratory disorders are commonly classified as demonstrating obstructive or restrictive physiology.[1] Also, when lung volumes are measured, a mixed pattern of obstruction and restriction pattern can be identified.[10] Despite common knowledge among pulmonary physicians of what a mixed pattern is, the available literature on the causes and prevalence of mixed patterns is scant. Furthermore, the issue is given sparse attention in commonly used learning resources such as reference pulmonary textbooks.[11-15] For example, in the

Table 1. Observed Etiologies of Combined Obstruction and Restriction ($N = 130$)

Diagnosis	Patients *n* (%)*
Pulmonary Parenchymal Disease + Obstruction (Group A)	49 (38)
Sarcoidosis	12 (9)
COPD + other parenchymal disease	10 (8)
COPD + interstitial lung disease (systemic lupus erythematosus)	1
COPD + interstitial lung disease (rheumatoid arthritis)	1
COPD + unspecified interstitial lung disease	4
COPD + idiopathic pulmonary fibrosis	4
Pneumoconiosis	8 (6)
Silicosis	5
Coal worker's lung	1
Berylliosis	2
Interstitial lung diseases (all causes)	6 (5)
Unspecified connective tissue disease	2
Non-specific interstitial pneumonitis	1
Constrictive bronchiolitis	1
Cryptogenic organizing pneumonia	2
Langerhans cell histiocytosis	4
Idiopathic pulmonary fibrosis	4
Pulmonary alveolar proteinosis	3
Lymphangioleiomyomatosis	1
Bronchiolitis obliterans syndrome	1
Combined Parenchymal + Non-parenchymal Disorders (Group B)	63 (48)
COPD + other non-parenchymal diseases (all causes)	35 (27)
COPD + CHF	11
COPD + obesity	6
COPD + thoracic surgery	13
COPD + diaphragm paralysis	2
COPD + scoliosis	2
COPD + pleurodesis	1
CHF + other non-pulmonary disease (all causes)	12 (9)
CHF	4
CHF + scoliosis	3
CHF + lung resection	2
CHF + obesity	3
Asthma + other	9 (7)
Asthma + obesity	3
Asthma + lung resection	2
Asthma + radiation fibrosis	1
Asthma + trapped lung	1
Asthma + CHF	2
Unspecified interstitial lung disease + obesity	4
Unspecified interstitial lung disease + CHF	2
Lung hypoplasia + scoliosis	1
Unknown	18 (4)
Asthma + unknown	3
COPD + unknown	9
No information available	6

* Percent values given only for relevant subcategories.
COPD = chronic obstructive pulmonary disease
CHF = congestive heart failure

Table 2. Pulmonary Function Test Results

	Group A*	Group B	*P*
FVC (mean ± SD L)	2.1 ± 0.1	2.1 ± 0.7	.60
FVC (mean ± SD % predicted)	51 ± 13	51 ± 15	.80
FEV_1 (mean ± SD L)	1.3 ± 0.5	1.2 ± 0.4	.60
FEV_1 (mean ± SD % predicted)	43 ± 15	42 ± 14	.90
FEV_1/FVC (mean ± SD)	61 ± 10	60 ± 8	.70
TLC (mean ± SD L)	3.7 ± 0.9	4.1 ± 0.9	.07
Residual volume/TLC (mean ± SD %)†	57 ± 35	82 ± 44	.001
D_{LCO} (mean ± SD % predicted)	42 ± 17	53 ± 24	.04
D_{LCO}/V_A (mean ± SD % predicted)	61 ± 21	70 ± 22	.04

* Group A had parenchymal pulmonary diseases. Group B had both parenchymal pulmonary and non-parenchymal disorders.
† Predicted ratio of residual volume to total lung capacity (TLC).
FVC = forced vital capacity
FEV_1 = forced expiratory volume in the first second
D_{LCO} = diffusing capacity of the lung for carbon monoxide
V_A = alveolar volume

latest edition of *Murray and Nadel's Textbook of Respiratory Medicine,* no specific section or paragraph discusses a mixed pattern of combined obstruction and restriction[13]; similarly, in the textbook *Fishman's Pulmonary Diseases and Disorders,* only 2 paragraphs describe combined obstruction and restriction, which is said to occur occasionally and is associated with sarcoidosis, interstitial fibrosis, or a combination of other pathologic processes.[11]

Although isolated reports have suggested a low prevalence,[10-12] the frequency of combined obstruction and restriction in clinical practice has not been studied systematically. The prevalence estimate in the present study (2.7% of patients) accords with the few other estimates of which we are aware. For example, in a review of more than 20,000 PFTs, Balfe et al reported a prevalence of 5.6%,[16] and reports of smaller series (ie, < 300 patients) estimated the prevalence of a combined obstruction and restriction pattern as 3.5–4%.[17,18]

Compared to these observed frequencies, the perceived occurrence of combined obstruction and restriction that is diagnosed by pulmonary physicians appears to be higher. For example, Hong et al reported that physicians diagnosed combined obstruction and restriction in 11% of a sample of 681 patients.[19] In keeping with that report, our study suggests that the perceived frequency of combined obstruction and restriction by pulmonary physicians is higher than the actual prevalence observed in our consecutive series of patients who underwent PFTs. Possible reasons for this discordance include non-generalizability of our sample, though large, to the respondent physicians' experience, and personal prevalence estimates that are conditioned by one's training and/or practice environment. For example, pulmonologists practicing in areas where smoking and obesity are prevalent may understandably

Table 3. Survey Responses Regarding the Causes of Combined Obstruction and Restriction

Pulmonary Condition	Respondents* (%)
Sarcoidosis	95
Hypersensitivity pneumonitis	85
Respiratory bronchiolitis-interstitial lung disease	81
Lymphangioleiomyomatosis	76
Cystic fibrosis	71
Langerhans cell histiocytosis	71
Cryptogenic organizing pneumonia	61
Idiopathic pulmonary fibrosis	33
Pulmonary alveolar proteinosis	23
Combined Obstruction Plus Restriction (all causes)	Percent of Diseases Responsible†
COPD + 2nd diagnosis (all causes)	45
COPD + obesity	21
COPD + CHF	11
COPD + interstitial lung disease	10
COPD + scoliosis	3
CHF + 2nd diagnosis (all causes)	24
CHF + obesity	7
CHF + interstitial lung disease	5
CHF + asthma	10
CHF + scoliosis	2
Asthma + 2nd diagnosis (all causes)	16
Asthma + obesity	10
Asthma + interstitial lung disease	3
Asthma + scoliosis	3
Pulmonary parenchymal diseases (only one diagnosis)	15
Sarcoidosis	5
Hypersensitivity pneumonitis	4
Cryptogenic organizing pneumonia	3
Bronchiolitis interstitial lung disease	2
Langerhans cell histiocytosis	1

* Percent of respondents who indicated the given condition causes combined obstruction plus restriction.
† Percent of combined-obstruction-plus-restriction cases the respondents thought were caused by the given condition.
COPD = chronic obstructive pulmonary disease
CHF = congestive heart failure

have the impression that combined obstruction and restriction related to COPD and obesity is very common.

Air flow obstruction is commonly observed on PFTs and is associated with a wide spectrum of diseases.[20] The co-occurrence of a restrictive process narrows the differential diagnosis and should prompt consideration of additional comorbid conditions or less common lung disorders[21] with a distinctive combined obstruction and restriction profile, such as sarcoidosis,[11] cryptogenic organizing pneumonia, lymphangioleiomyomatosis, and Langerhans cell histiocytosis, among others.[21]

A combination of a parenchymal disorder and a non-parenchymal disease was the most common etiology of combined obstruction and restriction in our sample. Not unexpectedly, we also found that the percent of predicted D_{LCO} was lower among patients with parenchymal disorders. This finding probably represents more advanced disease among patients with parenchymal disorders, although selection bias in this small cohort is possible. Nevertheless, a normal percent of predicted D_{LCO} may favor the possibility that the cause of the restrictive component of combined obstruction and restriction relates to a "non-parenchymal" cause (eg, extrathoracic restriction).

Among the parenchymal lung diseases that contribute to combined obstruction and restriction, COPD was the most common cause in this series, accounting for 35% of the cases. Similarly, in the smaller series by Hong et al,[19] of 77 patients with combined obstruction and restriction, the obstructive component was ascribed to COPD in 58 (75%). In keeping with that observation, our respondent physicians' perceptions were that COPD accounted for 45% of all patients with combined obstruction and restriction.

Depending on the duration and severity of the disease, congestive heart failure can be associated with respiratory muscle weakness, obstructive (eg, "cardiac asthma") or restrictive physiology, and impaired D_{LCO}.[22,23] In our series, congestive heart failure was the second most common comorbid condition associated with combined obstruction and restriction, and, in combination with COPD and a history of thoracic surgery, represented the majority of the cases of non-parenchymal disease. Notably, although most patients in this subgroup had a combination of diseases (eg, obesity, scoliosis) explaining their restrictive physiology, the retrospective nature of the study precluded establishing whether obstructive lung disease was caused solely by congestive heart failure or if other comorbidities (such as tobacco use) went unnoticed. Thoracic surgical procedures have also been implicated in causing restrictive or a mixed obstructive and restrictive pattern.[24-26] The obstructive defect may be due to airway deformation or occult airway disease. For example, Bredin suggested that a smoking history may partially explain the obstructive physiology in patients with a history of thoracoplasty.[25] In our cohort, 52% of the patients had smoked, which probably contributed to obstructive physiology in patients with congestive heart failure and a history of thoracic surgery.

Obesity decreases overall respiratory-system compliance, FVC, and FEV_1, and increases the ratio of residual volume to TLC.[27] Approximately 25% of patients in Group B had evidence of obesity contributing to combined obstruction and restriction. Accordingly, these patients had higher ratios of D_{LCO} to alveolar volume, and residual volume to TLC.

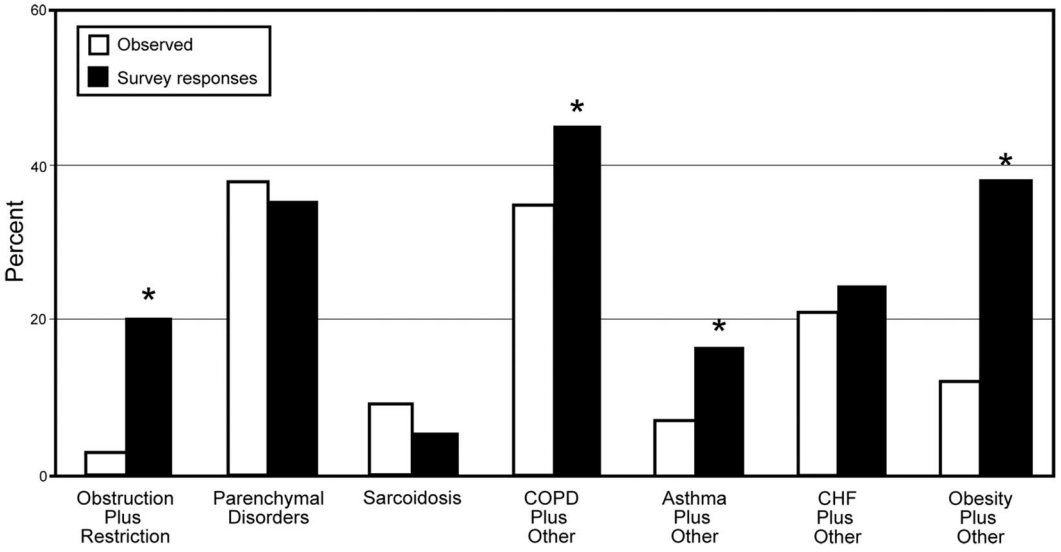

Fig. 2. Pulmonologists' survey responses versus observed prevalence of pulmonary function test patterns that indicated obstruction plus restriction. Obesity was defined as a body mass index > 35 kg/m^2. * For obstruction plus restriction, $P = .003$. For chronic obstructive pulmonary disease (COPD) plus other, $P = .001$. For asthma plus other, $P = .001$. For obesity plus other, $P = .001$.CHF = congestive heart failure.

Interstitial lung diseases are a common indication for PFT, and several publications discuss a broad spectrum of interstitial lung diseases that cause combined obstruction and restriction.[28] In the present series, sarcoidosis was the most frequent parenchymal disorder associated with combined obstruction and restriction. While sarcoidosis is widely recognized as a cause of restriction, the estimated frequency of obstructive airway disease among individuals with this disorder is 2–19%.[29-31] In keeping with the frequency of sarcoidosis and widespread familiarity with the disease among pulmonary physicians, 95% of our survey respondents identified sarcoidosis as a cause of combined obstruction and restriction.

Limitations

Our selection of a cohort of patients who underwent PFT surely introduces ascertainment bias, by overlooking affected individuals who did not undergo PFT or who underwent spirometry without lung-volume measurements. Indeed, in identifying the 30 patients with low FVC measurements whose subsequent (non-concurrent) lung-volume measurements supported the diagnosis of restriction, we attempted to clarify the extent to which our prevalence estimate could underestimate the frequency of combined obstruction and restriction (ie, the number of patients with combined obstruction and restriction might increase by 30 (to 160), which would change our combined obstruction and restriction prevalence estimate to:

$$160/(4{,}767 + 319) = 3.1\%$$

in which 319 is the number of non-concurrent lung-volume measurements. Of course, the lack of lung-volume measurements in the remaining 2,351 subjects whose FVC was low, but for whom lung-volume measurements were not ordered, precludes a precise estimate of the degree to which our estimate of 2.7% may deviate from the true prevalence. Taken together, we recognize that analyses that are predicated on characterizing subjects by their pulmonary physiologic profiles will necessarily be biased by including only individuals who underwent such testing. In addition, because the prevalence and distribution of causes of combined obstruction and restriction are expectedly affected by the referral patterns to the PFT laboratory, our estimates best generalize to similar institutions.

Another potential source of bias relates to the retrospective nature of the study; we cannot discount the possibility that the diagnoses that were deemed responsible for the physiologic pattern were incorrect, and that other unrecognized diseases were present. More specifically, it is possible that some patients with low FVC values but no lung-volume measurements had restrictive chest disease that went unrecognized because no lung-volume measurements were taken. To that extent, our estimate of the prevalence of restrictive disease in the sample (2.7% of patients) may be an underestimate. Also, in 14% of the study subjects no specific cause of combined obstruction and restriction was determined, which opens the possibility that underlying conditions went unnoticed and may have affected our prevalence estimates of the various etiologies of combined obstruction and restriction.

Finally, the small sample size in our survey, and the fact that all respondents were connected with a single institution may limit the generalizability of our survey findings. This bias compounds the observation from Hong et al[19] that clinicians' clinical impressions regarding the presence of obstruction and restriction are frequently discordant with the results of PFTs.

Conclusions

The results of this single institutional analysis comparing actual causes of combined obstruction and restriction with clinicians' impressions regarding the frequency and causes of this pattern indicate that combined obstruction and restriction is relatively uncommon, and that our respondent clinicians' impressions regarding the frequency and causes were discordant with the observed frequencies. Our findings suggest the need for greater attention to this issue in training and educational resources.

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