Using Targeted Spirometry to Reduce Non-Diagnosed Chronic Obstructive Pulmonary Disease

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Key Words

Airway obstruction · Chronic obstructive pulmonary disease · Non-diagnosed airway obstruction · Spirometry

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is increasing worldwide and thus its associated morbidity and mortality. However, COPD often goes undiagnosed. **Objectives:** We evaluated the rate of non-diagnosed irreversible airway obstruction (AO) and characterized this patient group. We further assessed the possible effects of conducting targeted spirometry in a population sample in Salzburg, Austria, as part of the Burden of Obstructive Lung Disease (BOLD) study. **Methods:** 1,258 adults ≥ 40 years of age completed a questionnaire and performed spirometry before and after bronchodilator therapy (post-BD). Irreversible AO was defined as post-BD FEV₁/FVC below the lower limit of normal; we used the FEV₁% predicted (pred.) to further grade the disease. Participants without a physician diagnosis of COPD who reported respiratory symptoms and a history of risk factors (ever smoking or occupational risk) were defined as eligible for targeted spirometry. **Results:** 85.9% (171/199) of the participants with irreversible AO did not re-

port a prior diagnosis of COPD. Non-diagnosed AO was inversely related to severity, age, self-reported prior respiratory diseases and cough as a respiratory symptom. 343 participants were eligible for targeted spirometry and irreversible AO was present in 86 (25.1%) participants. Therefore, targeted spirometry could reduce the underdiagnosis of irreversible AO of any severity by 50.3% (86 of 171). The diagnosis of 1 person with FEV₁ <80% pred. would require spirometry in 8.4 subjects (95% confidence interval 6.2–11.1). **Conclusion:** Although several factors are associated with non-diagnosed AO, spirometry in individuals with respiratory symptoms and exposure to risk factors could reduce undiagnosed irreversible AO by half.

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Introduction

In patients with chronic obstructive pulmonary disease (COPD) diagnosed at an early stage, the accelerated lung function decline seems largely reversible. Thus, current therapies for COPD are focusing on prevention and early detection [1]. This is important because COPD is now the fourth leading cause of mortality in Europe and

is projected to be the third leading cause of death globally by 2020 [2].

In addition to its social burden, the economic burden of COPD is huge. Medical care for patients with advanced COPD, for example, is associated with a fourfold increase in health care costs compared to costs of care for people without the disease [3]. If unrecognized and untreated, COPD often results in impaired quality of life, substantial morbidity and eventually premature death [4].

The PLATINO study (the Latin American Project for Investigation of Obstructive Lung Disease), carried out in five Latin American countries, showed that 88.7% of persons with airway obstruction (AO) after bronchodilator therapy (post-BD) had escaped diagnosis [5]. Based on data from the NHANES III (the Third National Health and Nutrition Examination Survey), which used spirometry before bronchodilator therapy, Coultas et al. [6] reported that 74.9% of patients with AO were not diagnosed. Similarly, in a multicenter, population-based study conducted in Spain [7], COPD diagnosis was missed in 78.2%. In a meta-analysis including 15 studies with spirometrically confirmed AO, Halbert et al. [8] estimated the range of missed diagnoses to be 47–97%. Different diagnostic criteria for COPD explain part, but not all, of the variability in estimates of non-diagnosed COPD.

Until recently, most population-based studies of COPD did not include post-BD spirometry. The BOLD initiative (Burden of Obstructive Lung Disease) was designed to allow countries at all levels of economic development to estimate COPD prevalence using simple standardized methods with strict quality control [9]. For the first 12 countries reported, 5.1–12.4% of adults aged 40 years and older had stage II–IV disease based on GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria [10], which is about twice as high as previously reported [8]. However, the practice of using a fixed forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <70% to determine AO, as recommended by GOLD, has been criticized because it can lead to overdiagnosis in the elderly [11, 12]. To avoid this possible bias we analyzed our data according to the proposed sex- and age-specific lower limit of normal (LLN) criteria recommended by the American Thoracic Society (ATS) and the European Respiratory Society [13]. Non-diagnosed AO was investigated for different grades of severity. Since we did not want to neglect patients with mild COPD [13], we decided not to limit severity criteria to <80% predicted (pred.). Our study provides estimates for non-diagnosed irreversible AO at the beginning of the 21st century, a time when smoking rates of men and women in high-

income countries are equal. Estimates from the mid-1990s do not reflect this because men smoked at higher rates than women.

Considering the burden of COPD, reducing the rate of non-diagnosed cases remains a major aim to accomplish. The benefits of universal screening versus targeted case finding will continue to be a matter of debate until effective interventions (apart from smoking cessation) aiming to change the natural history of COPD have been established. In the meantime, case finding may be preferred to screening. However, for the same reason, the criteria for case finding also arouse controversy [13, 15–18]. To help clarify this important question, as well as to define characteristics of those with non-diagnosed COPD, we analyzed the Austrian BOLD data in order to estimate the yield of case finding for irreversible AO in a population-based sample of adults ≥ 40 years.

Patients and Methods

Study Population

The study population consisted of participants in the Austrian BOLD study [18]. A gender-stratified random sample of 2,200 individuals (1,100 men and 1,100 women) from Salzburg County, Austria, who were aged ≥ 40 years, were selected and invited to participate. We followed the BOLD protocol reported previously [9]. Data were collected between October 2004 and May 2005. Out of 2,082 eligible participants, 1,258 completed the full protocol, including pre- and post-BD spirometry, and met the quality control criteria. The study was approved by the local ethics committee and all participants gave written informed consent.

Methods

Spirometry was done according to ATS criteria [19] by trained and certified technicians using the ndd Easy One™ spirometer (ndd Medizintechnik, Zurich, Switzerland) with participants in a seated position. Separate measurements were made before and at least 15 min after two puffs of salbutamol (200 μ g) administered via metered-dose inhaler with a spacer (Volumatic; GlaxoSmith-Kline; Research Triangle Park, N.C., USA). Spirometry data were submitted electronically to the Pulmonary Function Quality Control Center in Salt Lake City, Utah, USA, where each spirogram was reviewed using ATS guidelines [19]. Only spiograms that met acceptability and reproducibility criteria were included; at least three trials and two acceptable (free from artifact, sudden stops and back-extrapolated volumes >5.0% of FVC) and reproducible (difference between largest and second largest values is <200 ml) tests for both FEV_1 and FVC. Study technicians were continuously monitored. When a technician's quality scores dropped below a preset level, he/she had to stop testing and be retrained.

Study Questionnaire

The BOLD questionnaire was administered by trained and certified staff, and included information on respiratory symp-

toms, risk factors for COPD, reported diagnoses, medication use, health care utilization, co-morbidities and health status. For its use in Salzburg, Austria, the English version of the questionnaire was translated into German and then back-translated to ensure validity.

Definitions

AO was defined as post-BD FEV_1/FVC below the LLN using the NHANES III reference equations to calculate predicted values [20]. The severity of AO was graded as follows: $FEV_1 >80\%$ pred.; $FEV_1 70\text{--}79\%$ pred., $FEV_1 60\text{--}69\%$ pred., $FEV_1 50\text{--}59\%$ pred. and $FEV_1 <50\%$ pred. Physician-diagnosed COPD was defined as a self-reported physician's diagnosis of chronic bronchitis, emphysema or COPD. Self-reported physician's diagnoses of asthma, tuberculosis, heart disease, hypertension and diabetes were assessed (Has a doctor or health care provider ever told you that you had heart disease, hypertension, asthma, tuberculosis or diabetes?). Ever spirometry use was also recorded [Has a doctor or other health care provider ever had you blow into a machine or device in order to measure your lungs (i.e. a spirometer or peak flow meter)?], as well as spirometry during the last year (Have you used such a machine in the past 12 months?).

Pack-years of cigarette smoking was defined as the average number of cigarettes smoked per day divided by 20 (i.e. packs/day) times the duration of smoking in years. Ever smoking was defined as smoking >20 packs of cigarettes in a lifetime or >1 cigarette/day for a year. To assess occupational exposure we asked: 'Have you ever worked for three months or more at any of the following occupations: Hard-rock mining, coal mining, sandblasting, working with asbestos, chemical or plastics manufacturing, flour, feed or grain milling, cotton or steel milling, welding, fire fighting or farming?'

Respiratory symptoms, e.g. cough (Do you usually cough when you don't have a cold?), phlegm (Do you usually bring up phlegm from your chest, or do you usually have phlegm in your chest that is difficult to bring up when you don't have a cold?), wheeze (Have you had wheezing or whistling in your chest at any time in the last 12 months?) and dyspnea (Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?) were investigated. The presence of any respiratory symptom was defined as self-reported cough, phlegm, wheeze or dyspnea. When ever smoking, smoking or an occupational exposure relevant to respiratory disease was reported, a history of exposure to risk factors was assumed. All individuals who reported any respiratory symptoms and a history of exposure to risk factors but did not report a physician diagnosis of COPD were considered eligible for targeted spirometry.

Statistical Analysis

We analyzed the frequency of irreversible AO in patients with and without a report of a prior physician diagnosis of COPD. Odds ratios (ORs) for a correct COPD diagnosis with regard to symptoms, smoking status, co-morbidities and the reported prior use of spirometry were calculated. For the group that reported respiratory symptoms and exposure to risk factors but did not have a physician diagnosis of COPD, the yield of targeted spirometry to detect AO at different grades of severity was calculated. Confidence intervals (CIs) to accompany point estimates for the number of subjects needed to have spirometry were calculated. SAS 8.2 (SAS Institute, Cary, N.C., USA) was used for all statistical analyses.

Fig. 1. Proportion of subjects eligible for targeted spirometry among subjects with non-diagnosed AO by severity (n = 199).

Results

Detailed descriptions of participation rates and sample characteristics have been published previously [19]. In summary, from a total of 2,200 eligible individuals, complete interviews and valid pre- and post-BD spirometry data were obtained from 1,258 participants (table 1). Current smoking was 21.5% in women and 17.4% in men, while former smoking was more prevalent in men (42.5%) than in women (22.7%).

Non-Diagnosed Irreversible Airway Obstruction. The overall prevalence of irreversible AO, using the LLN criteria for FEV_1/FVC , was 15.8%. Of these, only 14.1% (28/199) reported a prior physician-diagnosed COPD (table 1). In addition, 32 subjects with a prior physician-diagnosed COPD had no AO (post-BD $FEV_1/FVC < LLN$) and are to be considered false-positive. There was no significant difference between men and women in the proportion with no diagnosis (84.1 vs. 87.4%). There was a clear correlation with the severity of AO, with diagnosis being missed significantly more often in mild compared to more severe disease ($p < 0.001$; table 1, fig. 1). When 10-year age categories were considered, the 40- to 49-year age group had the highest rate of non-diagnosed AO (93.2%). Never smokers (90.5%) escaped more often diagnosis than smokers or ex-smokers, and rates of non-diagnosed AO were similar between current smokers (84.3%) and ex-smokers (83.3%).

Table 1. Prevalence of irreversible AO ($FEV_1/FVC < LLN$), proportion of undiagnosed AO and ORs associated with reported doctor's diagnosis of COPD (n = 1,258)

	Prevalence of irreversible AO	Proportion of non-diagnosed irreversible AO	OR (95% CI) for reported doctor's diagnosed COPD
All	15.8% (199/1,258)	85.9% (171/199)	
Sex			
Female	19.4% (111/573)	87.4% (97/111)	1
Male	12.9% (88/685)	84.1% (74/88)	1.31 (0.59–2.92)
Age			
40–49 years	12.2% (44/362)	93.2% (41/44)	1
50–59 years	16.5% (60/364)	86.7% (52/60)	2.10 (0.52–8.43)
60–69 years	12.2% (40/328)	87.5% (35/40)	1.95 (0.44–8.76)
≥70 years	27.0% (55/204)	78.2% (43/55)	3.81 (1.00–14.50)
Education			
<12 years	16.8% (180/1071)	86.1% (155/180)	1
≥12 years	10.2% (19/187)	84.2% (16/19)	1.16 (0.32–4.28)
Smoking status			
Never	10.6% (63/595)	90.5% (57/63)	1
Former	15.7% (66/421)	83.3% (55/66)	1.90 (0.66–5.49)
Current	28.9% (70/242)	84.3% (59/70)	1.77 (0.62–5.11)
Occupational risk			
No	14.6% (123/840)	83.7% (103/123)	1
Yes	18.2% (76/418)	89.5% (68/76)	0.61 (0.25–1.45)
AO severity			
$FEV_1 \geq 80\%$ pred.	9.9% (105/1064)	90.5% (95/105)	1
$FEV_1 \geq 70\text{--}79\%$ pred.	36.4% (39/107)	94.9% (37/39)	0.51 (0.11–2.47)
$FEV_1 \geq 60\text{--}69\%$ pred.	51.0% (26/51)	80.8% (21/26)	2.26 (0.70–7.31)
$FEV_1 \geq 50\text{--}59\%$ pred.	68.2% (15/22)	66.7% (10/15)	4.75 (1.35–16.68)
$FEV_1 < 50\%$ pred.	100% (14/14)	57.1% (8/14)	7.13 (2.06–24.70)
Reported diagnosis			
Asthma	32.2% (29/90)	72.4% (21/29)	2.86 (1.12–7.30)
Heart disease	22.2% (32/144)	88.5% (28/32)	0.85 (0.27–2.64)
Hypertension	18.1% (66/364)	81.8% (54/66)	1.63 (0.72–3.67)
Tuberculosis	29.4% (10/34)	60.0% (6/10)	4.58 (1.21–17.43)
Respiratory symptoms			
Phlegm	26.3% (82/312)	80.5% (66/82)	2.12 (0.94–4.77)
Cough	28.7% (64/223)	78.1% (50/64)	2.42 (1.08–5.44)
Dyspnea	25.5% (56/220)	80.4% (45/56)	1.81 (0.80–4.16)
Wheeze	33.9% (56/165)	83.9% (47/56)	1.25 (0.53–3.00)
Prior spirometry			
Ever	19.3% (100/518)	80.0% (80/100)	2.84 (1.19–6.81)
Last 12 months	26.1% (40/153)	75.0% (30/40)	2.61 (1.10–6.22)

Participants with self-reported asthma or tuberculosis were appreciably less likely to have non-diagnosed AO. This trend was not seen for self-reported non-respiratory co-morbidities such as hypertension or heart disease.

Presence of the self-reported respiratory symptoms phlegm, cough and dyspnea increased the likelihood of having a physician diagnosis of COPD. However, only the presence of cough was significant (OR 2.42, 95% CI 1.08–

5.44). A prior spirometry test was reported by 518 subjects, and this was a significant predictor for COPD being diagnosed by a physician (OR 2.84, 95% CI 1.19–6.81); however, even in this group, 80% were not diagnosed (table 1).

Targeted Spirometry. One or more respiratory symptoms were reported by 491 participants, and 865 participants revealed a history of exposure to risk factors. Of

Table 2. Study population according to severity of irreversible AO and eligibility for targeted spirometry (n = 1,258)

Severity of irreversible AO according to FEV ₁ % pred.	n	Presence of any reported respiratory symptom(s)	Presence of any reported risk factor(s)	Presence of any reported respiratory symptom(s) and any reported risk factor(s)	Reported doctor's diagnosis of COPD and FEV ₁ /FVC < LLN	Eligible for targeted spirometry	Targeted spirometry population and FEV ₁ /FVC < LLN	Additional spirometries necessary to detect 1 AO case, n
>80% pred.	1,064	377/1,064	709/1,064	273/1,064	10/105	265/1,064	45/265	5.9
70–79% pred.	107	53/107	87/107	44/107	2/39	42/107	18/42	2.3
60–69% pred.	51	31/51	41/51	25/51	5/26	21/51	10/21	2.1
50–59% pred.	22	19/22	15/22	12/22	5/15	9/22	7/9	1.3
<50% pred.	14	11/14	13/14	11/14	6/14	6/14	6/6	1.0
All	1,258	491/1,258	865/1,258	365/1,56	28/199	343/1,258	86/343	3.9

Fig. 2. Hypothetical number of subjects requiring spirometry to detect 1 additional case of irreversible AO [according to severity (FEV₁% predicted)] in subjects eligible for targeted spirometry (n = 343).

these, 365 participants reported respiratory symptoms as well as exposure to risk factors. Of those, 28 also reported a prior physician diagnosis of COPD. Therefore, 343 participants were considered eligible for targeted spirometry and 86 (25.1%) of those presented with irreversible AO (table 2).

Among those eligible for targeted spirometry, the potential yield of detectable COPD paralleled the severity of AO. To diagnose 1 additional case of COPD within the group with least severe AO (FEV₁ >80% pred.), 5.9 (95% CI 4.6–7.7) subjects would have to have spirometry. However, only 2.3 (95% CI 1.7–3.4) subjects with FEV₁ 70–79% pred., 2.1 (95% CI 1.5–3.5) subjects with FEV₁ 60–69% pred., 1.3 (95% CI 1.1–2.3) subjects with FEV₁ 50–59% pred. and only 1.0 subject (95% CI 1.0–1.7) in the group of FEV₁ <50% pred. would need spirometry to detect 1 additional case with irreversible AO (table 2, fig. 2).

To detect 1 case of moderate-to-severe AO (FEV₁/FVC < LLN and FEV₁ <80% pred.) in the total population of

343 subjects eligible for targeted spirometry, a mean of 8.4 (95% CI 6.2–11.1) spirometry tests would have to be conducted. Targeted spirometry for this population would detect 41 cases of moderate-to-severe disease, and 45 individuals with mild functional impairment (FEV₁/FVC < LLN and FEV₁ >80% pred.; fig. 2).

Discussion

In a population-based survey in Salzburg, we found that 85.9% of men and women aged ≥40 years with irreversible AO according to the LLN criteria did not report a prior physician diagnosis of COPD. Lack of a diagnosis is associated with severity of AO, age, prior respiratory disease and cough as a respiratory symptom. We further demonstrated that targeted spirometry in subjects with respiratory symptoms and a history of risk factors for COPD could reduce underdiagnosis by 50.3%.

The PLATINO group recently reported a similar finding from population-based surveys in five Latin American countries, using the same methods as the BOLD study: 88.7% of their participants had not been diagnosed previously [5]. With respect to the NHANES III data set, using only pre-BD spirometry, Coultas et al. [6] found 74.9% of subjects with non-diagnosed AO. Individuals with mild AO were less likely to receive a diagnosis than those with more severe disease [6, 22]. These findings indicate that approximately 90% of patients with mild and >50% with severe AO are not diagnosed with COPD. This finding holds true for countries with a range of economic development.

With respect to gender, no significant association with diagnosed AO was seen, a finding in agreement with results from PLATINO [5]. However, our data in-

dicating that non-diagnosed patients with COPD were likely to be younger. Coultas et al. [6] reported a higher occurrence of non-diagnosed AO among males (14.2%) than females (9.9%) but no difference by age. For the data from Spain reported by Pena et al. [7], gender played no role, a finding similar to ours, but lack of a diagnosis was more prevalent in patients aged <60 years. Taken together, our data and observations made by others indicate that gender does not significantly affect COPD diagnosis but that younger age [7] is associated with COPD underdiagnosis.

Whether respiratory symptoms alone could define early COPD has been long debated. Some longitudinal observations indicate that symptoms per se cannot predict the development of AO [23]. In our cross-sectional study, COPD diagnosis was two times more frequent in the presence of symptoms. However, even in the presence of any symptom (cough, phlegm, dyspnea or wheeze), the proportion of non-diagnosed AO was still about 80%. Also, there was a higher percentage of non-diagnosed AO in never smokers compared with former and current smokers. In comparison to data published by Pena et al [7], this difference did not show a significant effect on diagnosed AO in our study. COPD diagnosis was less frequently missed when either a prior diagnosis of tuberculosis or asthma was present. Co-morbidities not related to the respiratory system, such as heart disease or hypertension, had no influence on COPD diagnosis, a finding also observed by others [8]. A likely explanation is that the presence of respiratory disease increases the likelihood of being seen by a respiratory physician, who then performs spirometry and diagnoses AO. Conversely, the presence of cardiovascular comorbidities does not appear to alert health care providers to consider a diagnosis of COPD, which suggests a potentially fertile opportunity for education.

According to our data, non-diagnosed AO is less frequent when subjects report a prior lung function test. Surprisingly, in 80% of subjects with a previous lung function test presenting with non-reversible AO COPD was not diagnosed. Considering only subjects who reported having had spirometry in the last 12 months, 75% were still not diagnosed with COPD. These findings may indicate that either the performance or the interpretation of spirometry was unreliable. Other explanations for the observed discrepancy may relate to variable spirometric criteria to define COPD, or the inherent intertest variability of lung function tests. We are not able to differentiate between spirometry being carried out in primary or respiratory care practices. Primary care physi-

cians might not have time to do high-quality spirometry [24, 25].

There is currently an intense debate about who should be targeted for spirometry. The recent clinical practice guidelines of the American College of Physicians recommend against screening for COPD with spirometry [18]. According to GOLD, subjects who are at risk for COPD but asymptomatic should not receive spirometry testing [26]. It is well known that spirometry, when used as an indiscriminate screening tool, is associated with high opportunity costs, i.e. time, effort and expenses impose a burden on patients and the health care system.

Given the high prevalence of non-diagnosed AO, recommendations differ with regard to the use of spirometry for COPD case finding [13, 15–17]. Our data indicate that a large number of patients with non-diagnosed AO have identified risk factors. Since performing spirometry in all of these cases is expensive and could restrict resources for the treatment of symptomatic COPD patients, we have chosen a more restrictive way. Therefore, we analyzed whether a subgroup of subjects with any respiratory symptom and a history of risk factors would benefit from targeted spirometry.

Using this definition, we calculated that among subjects eligible for targeted spirometry, 8–9 tests would detect 1 case of moderate-to-severe COPD ($FEV_1/FVC < LLN$ and $FEV_1 < 80\%$ pred.). This effort would also identify approximately the same number of symptomatic subjects with a history of risk factors but only mild AO. Applying this method of case finding limits the opportunity costs of targeted spirometry, while maximizing the ability to identify patients with non-diagnosed AO. Data from the Lung Health Study indicate that smoking cessation in mild AO might be more beneficial than quitting when AO is at a more advanced stage [1]. Since these patients are at risk for developing more severe AO, this finding suggests that interventions require implementation early in the disease process. To fully assess the potential impact of targeted case finding in COPD, an intervention study testing the efficiency and feasibility of such an approach is needed.

As this study was population-based, undersampling of less severe AO was avoided, while very severe disease might have been underrepresented. Another limitation arises from reported 'doctor-diagnosed' COPD, which was ascertained only by questionnaire and might have been subject to selective recall. Incomplete recall might have also been present when asking for a prior lung function test. In addition, we cannot be sure if the prior lung function tests reported included post-BD measurements.

Dealing with the COPD epidemic requires major efforts both in terms of detection and treatment. Our strategy of targeting subjects with respiratory symptoms and a history of risk factors would reduce non-diagnosed AO by half.

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