Can a normal peak expiratory flow exclude severe chronic obstructive pulmonary disease?

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BACKGROUND: Chronic obstructive pulmonary disease (COPD) is underdiagnosed. One barrier to diagnosis is the limited availability of spirometry testing, but in adults at risk for COPD, a normal pre-bronchodilator (pre-BD) peak expiratory flow (PEF) may rule out clinically significant COPD.

OBJECTIVE: To identify post-BD airway obstruction using data from 13 708 individuals aged ⩾40 years from the PLATINO and BOLD studies.

METHODS: We evaluated different cut-off points of pre-BD. The PEF was obtained from a diagnostic-quality spirometer (not a mechanical PEF meter). At least one of the following COPD risk factors was present in 77% of the subjects: chronic respiratory symptoms; exposure to tobacco smoke, biomass smoke or dust in the workplace; or a previous diagnosis of asthma, COPD, emphysema or chronic bronchitis.

RESULTS: Although the positive predictive value was low as expected, a pre-BD PEF of ⩾70% predicted effectively ruled out Stages III and IV COPD of the Global Initiative for Chronic Obstructive Lung Disease. Among those with at least one risk factor, only 12% would require confirmatory spirometry using this criterion.

CONCLUSIONS: Adding PEF measurement to a screening questionnaire may rule out severe to very severe COPD without the need for pre- and post-BD spirometry testing. Confirmation is needed from a study using inexpensive PEF meters or pocket spirometers with a staged screening protocol.

KEY WORDS: COPD; screening; PEF; PLATINO; BOLD

ALTHOUGH chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide,¹ it is greatly underdiagnosed.² International guidelines now recommend documenting irreversible airflow obstruction, assessed via post-bronchodilator (post-BD) spirometry, as the primary diagnostic test for COPD, before an inhaler prescription is considered.¹ Despite the increasing availability of relatively low-cost, easy to use office spirometers,³,⁴ spirometry is not often available in the primary care setting and economic factors may limit specialty referrals for spirometry testing. This problem is further exacerbated in resource-poor countries for which even the least expensive spirometers may be a luxury for many primary care practitioners and an unaffordable test for many patients. In this context, access to a simple, inexpensive, easy to interpret test to screen patients and identify those most likely to benefit from spirometry is a highly desirable goal.

Measurement of the peak expiratory flow (PEF) requires only a short maximal expiration, and the demands required of the patient and technician to achieve reliable data are fewer than for spirometry. Although previous studies have concluded that PEF is not an adequate substitute for spirometry for the diagnosis of COPD,⁵,⁶ these studies did not evaluate the possible value of PEF as a screening tool to reduce the need for spirometry in adults with COPD risk factors.

The data used for this report are from the Latin American Project for the Investigation of Obstructive Lung Diseases (PLATINO) study⁷ and the ongoing Burden of Obstructive Lung Disease (BOLD) study.⁸ These population-based COPD prevalence studies shared a common protocol and have been carried out to date in over 17 countries around the world. We tested whether PEF, assessed before bronchodilator use and using a diagnostic-quality spirometer with trained technicians, identified spirometrically confirmed post-BD airflow obstruction.

METHODS

Summaries of the rationale and design of the PLATINO and BOLD studies have been published elsewhere⁸,⁹

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and are only summarized here. The two studies differed mainly in the manner in which their target populations were defined and sampled. Both were limited to non-institutionalized adults aged ≥40 years. Approval was obtained from the Ethics Committees of each of the institutions involved in the studies.

**Study population**

PLATINO was a population-based survey of COPD prevalence conducted in five Latin American cities: Sao Paulo, Brazil; Mexico City, Mexico; Montevideo, Uruguay; Santiago de Chile, Chile; and Caracas, Venezuela. In all, 5183 participants provided post-BD spirometry and questionnaire data.

BOLD is an ongoing population-based survey of COPD prevalence for which we present data from 12 sites: Guangzhou, China; Adana, Turkey; Salzburg, Austria; Hannover, Germany; Krakow, Poland; Sydney, Australia; Reykjavik, Iceland; Vancouver, BC, Canada; Lexington, Kentucky, USA; Manila, the Philippines; Cape Town, South Africa; and Bergen, Norway. A total of 8525 participants provided post-BD spirometry and questionnaire data.

We therefore present data on a total of 13,708 subjects from 17 cities in 17 different countries.

**Spirometry**

Lung function was measured before and after administration of 200 μg of albuterol/salbutamol using the EasyOne Diagnostic Spirometer with firmware version 2.00.00 (ndd Medical Technologies, Zurich, Switzerland). We chose this spirometer because it is handheld (easily portable), battery-operated, accurate, includes several maneuver quality checks, and automatically grades the quality of test sessions. Spirometry measures used in this analysis included: pre- and post-BD forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), FEV₁/FVC, and pre-BD PEF (measured by the spirometer). FEV₁, FVC and PEF were chosen as the highest value from all acceptable maneuvers.

Tests and calibration data were downloaded to a personal computer using EasyWare version 2.7 (ndd Medical Technologies). Calibration in the EasyOne spirometers was verified each day using a 3.00 liter syringe. Accuracy was sustained much longer than the duration of the field work. Testing followed the 1994 American Thoracic Society (ATS) standards, but the same quality goals recommended by 2005 guidelines were used.

All spirometry results were reviewed either by the PLATINO Pulmonary Function Reading Center (PFRC) or the BOLD PFRC, and assigned an overall quality score (A–F) based on ATS/European Respiratory Society acceptability and reproducibility criteria. To better simulate the conditions of real life testing under busy clinical work, for this analysis we included all test sessions, regardless of quality score.

**Definition of COPD**

We defined COPD as a post-BD FEV₁/FVC < 0.70, with staging based on the per cent predicted FEV₁ (FEV₁ %): FEV₁ % ≥ 80 = Stage I; 50 ≤ FEV₁ % < 80 = Stage II; 30 ≤ FEV₁ % < 50 = Stage III; FEV₁ % < 30 = Stage IV. Spirometry reference equations for Caucasian men and women derived from the third United States National Health and Nutrition Examination Survey were used to define the FEV₁ %. Although we show COPD prevalence by all stages, we focus on Stages III and IV, as this is where the clinical impact of COPD becomes most apparent.

**Statistical methods**

The performance of PEF as a diagnostic test (sensitivity and negative predictive values [NPVs]) was evaluated for pre-BD PEF cut-off points of 60% to 100% of predicted to identify post-BD defined airflow obstruction. As we are proposing the PEF as a screening tool to rule out COPD, the more pertinent of these two measures is the NPV. Odds ratios (ORs) for having Stage II or III–IV COPD, as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, are computed in reference to the ‘no COPD’ group (FEV₁/FVC ≥ 0.70).

For some analyses, we present data separately for those at low and increased a priori risk of having COPD. We considered a subject to be at increased risk if they met any of the following criteria: ‘usually’ coughing or bringing up phlegm, wheezing in the last year, and dyspnea on exertion (Medical Research Council [MRC] Dyspnoea Scale score >1), more than

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Subject characteristics and lung function*</th>
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<tbody>
<tr>
<td></td>
<td>Increased COPD risk</td>
</tr>
<tr>
<td></td>
<td>(n = 10616)</td>
</tr>
<tr>
<td>Age, years</td>
<td>56.3 (11.4)</td>
</tr>
<tr>
<td>Male, %</td>
<td>47.7</td>
</tr>
<tr>
<td>Ever-smoker, %</td>
<td>52.6</td>
</tr>
<tr>
<td>Pack-years</td>
<td>25.0 (26.1)</td>
</tr>
<tr>
<td>PEF, % pred</td>
<td>96.1 (23.4)</td>
</tr>
<tr>
<td>FEV₁, % pred</td>
<td>89.2 (19.2)</td>
</tr>
<tr>
<td>FEV₁/FVC (%×100)</td>
<td>73.4 (9.1)</td>
</tr>
<tr>
<td>FEV₁/FVC &lt; LLN post-BD, %</td>
<td>13.4</td>
</tr>
<tr>
<td>PEF &lt; 80% pred, %</td>
<td>21.6</td>
</tr>
<tr>
<td>PEF &lt; LLN, %</td>
<td>15.8</td>
</tr>
<tr>
<td>GOLD Stage I, n (%)</td>
<td>972 (9.2)</td>
</tr>
<tr>
<td>GOLD Stage II, n (%)</td>
<td>875 (8.2)</td>
</tr>
<tr>
<td>GOLD Stages III–IV, n (%)</td>
<td>223 (2.1)</td>
</tr>
</tbody>
</table>

* Continuous data are expressed as mean (SD).
† The differences in mean values and percentages from subjects at increased risk when compared to low-risk subjects were all statistically significant (P < 0.0001).
‡ Pack-years data are limited to current and former smokers.
§ Spirometry results are pre-BD, unless indicated as post-BD.
¶ COPD = chronic obstructive pulmonary disease; PEF = peak expiratory flow; % pred = percentage of predicted value (NHANES III); FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; LLN = lower limit of normal range (fifth percentile); GOLD = Global Initiative for Chronic Obstructive Lung Disease; NHANES III = Third National Health and Nutrition Examination Survey; BD = bronchodilator.
10 pack-years of smoking, more than 200 hour-years of exposure to biomass smoke or coal smoke, more than 5 years of workplace exposure to dust or smoke, or a previous medical diagnosis of asthma, COPD, chronic bronchitis or emphysema. Receiver operating characteristic (ROC) curves and data analysis were performed using STATA, version 9.0 (Stata Corp, College Station, TX, USA).

RESULTS

The mean age of the participants was 56 years (range 40–98); 45% were men and 45% were ever-smokers (Table 1). The a priori ‘increased COPD risk’ group, which comprised 77% of the sample, clearly had worse lung function outcomes. They accounted for 97.4% of GOLD Stage III–IV cases and 93.5% of GOLD Stage II cases. Corresponding ORs for these disease categories, relative to the low risk for the COPD group, were 11.0 (95% confidence interval [CI] 4.9–24.9) for Stages III–IV and 4.5 (3.4–5.8) for Stage II.

As an index of the quality of the test sessions, the mean (± standard deviation [SD]) difference between the two largest values of pre-BD FEV₁ (also known as repeatability) was 62 ± 77 ml (2.6 ± 3.1%), and the 90th percentile was 123 ml (5.3%). The mean difference between the two largest values of pre-BD PEF was 0.45 ± 0.47 l/s (6.5 ± 6.5%) and the 90th percentile was 1.01 l/s (14.4%). The mean difference between per cent predicted PEF and per cent predicted FEV₁ in the subset of subjects with pre-BD airflow obstruction (FEV₁/FVC < 5th percentile) was only −3.3 percentage points. However, variation in this difference was large, as demonstrated by a 95% CI of −30 to +22 percentage points.

A PEF screening cut-off point of 70% predicted (70%P) correctly identified 95.6% (i.e., sensitivity = 95.6%) of those individuals with post-BD confirmed severe airflow obstruction (i.e., GOLD Stages III–IV) and 53.5% of those with moderate airflow obstruction (i.e., GOLD Stage II) (Table 2, Figure 1). At the same time, this cut-off point, if used as a screening tool to rule out severe airflow obstruction, would have triggered confirmatory spirometry in only 12.3% of those with increased risk of COPD. A PEF screening cut-off point of 100%P correctly identified 88.7% of subjects with Stage II COPD, but at the cost of requiring confirmatory spirometry in 55.8% of those screened. Besides, a PEF < 70%P effectively ruled out GOLD Stages III–IV (NPV = 99.9%), while a PEF < 100%P had a NPV of 98.6% for GOLD Stage II.

Among individuals at increased a priori risk, PEF

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Sensitivity and NPV of a screening strategy for COPD based on PEF*</th>
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<tbody>
<tr>
<td>PEF cut-off point</td>
<td>&lt;100%P†</td>
</tr>
<tr>
<td>Gold standard = GOLD Stages III–IV</td>
<td></td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>96.9</td>
</tr>
<tr>
<td>95%CI</td>
<td>95.7–97.2</td>
</tr>
<tr>
<td>NPV</td>
<td>99.9</td>
</tr>
<tr>
<td>95%CI</td>
<td>99.9–99.9</td>
</tr>
<tr>
<td>Gold standard = GOLD Stage II</td>
<td></td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>88.7</td>
</tr>
<tr>
<td>95%CI</td>
<td>88.1–89.2</td>
</tr>
<tr>
<td>NPV</td>
<td>98.6</td>
</tr>
<tr>
<td>95%CI</td>
<td>98.4–98.8</td>
</tr>
<tr>
<td>% of subjects below the PEF cut-off point in the group at increased risk for COPD (requiring spirometry to confirm GOLD Stages III–IV)</td>
<td>55.8</td>
</tr>
</tbody>
</table>

* Only participants at increased risk of COPD (n = 10 616, see Table 1) were included in this analysis.
† %P refers to the PEF cut-off point, expressed as percentage of predicted by NHANES III.
NPV = negative predictive value; COPD = chronic obstructive pulmonary disease; PEF = peak expiratory flow; GOLD = Global Initiative for Chronic Obstructive Lung Disease; CI = confidence interval; NHANES III = Third National Health and Nutrition Examination Survey.
Table 3  Prevalence of respiratory symptoms in the whole cohort below each PEF cut-off point

<table>
<thead>
<tr>
<th>PEF cut-off point</th>
<th>&lt;100%P*</th>
<th>&lt;90%P*</th>
<th>&lt;80%P*</th>
<th>&lt;70%P*</th>
<th>&lt;65%P*</th>
<th>&lt;60%P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheezing in last 12 months†</td>
<td>29.5</td>
<td>33.2</td>
<td>38.7</td>
<td>45.3</td>
<td>49.4</td>
<td>52.4</td>
</tr>
<tr>
<td>Dyspnea on exertion (MRC &gt;1)†</td>
<td>8.3</td>
<td>10.3</td>
<td>13.0</td>
<td>16.4</td>
<td>18.4</td>
<td>19.8</td>
</tr>
<tr>
<td>Chronic cough or phlegm†</td>
<td>34.4</td>
<td>37.9</td>
<td>42.2</td>
<td>49.0</td>
<td>51.4</td>
<td>54.8</td>
</tr>
<tr>
<td>Cough, phlegm, wheezing or dyspnea†</td>
<td>58.9</td>
<td>63.7</td>
<td>70.1</td>
<td>77.2</td>
<td>79.8</td>
<td>81.7</td>
</tr>
</tbody>
</table>

* %P refers to the PEF cut-off point expressed as percentage of predicted by NHANES III.
† Prevalences in the group at increased risk for COPD are slightly higher than those shown in the table.

**Figure 2** ROC curves. Diagnostic characteristics of questionnaire (see text for symptoms and risk factors) and pre-bronchodilator PEF% vs. several gold standards. Curve a = performance of questionnaire alone in the whole population (a priori classification used in the manuscript) to identify GOLD Stages I–IV; Curve b = performance of PEF in the low risk for COPD group to identify GOLD stages I–IV; Curves c, d and e for GOLD Stages I–IV, II–IV and III–IV, respectively. PEF alone adds to the diagnosis of mild airflow obstruction in the whole population, or even in the low risk for COPD subjects (curve b) significantly more than questionnaire alone (curve a).

**DISCUSSION**

We found that the measurement of pre-BD PEF as a COPD screening tool in adults with high priori risk substantially reduced the number of individuals who subsequently required confirmatory spirometry, while minimizing false-negative diagnoses. The addition of a quick, inexpensive PEF test to a simple questionnaire has the potential to make widespread screening for severe COPD more cost-effective when compared to a spirometry test for all adults aged >40 years.

There is controversy regarding the definition of the ‘target group’ for which COPD screening should be applied. Some guidelines suggest that all current and former smokers aged >45 years should have a spirometry test to detect COPD,14 but never-smoking women who have been chronically exposed to smoke from biomass fuel represent a considerable proportion of COPD patients seen in resource-poor countries.15 Some guidelines suggest that all adults with respiratory symptoms, regardless of smoking or other exposures, should be screened for COPD,1 while other guidelines suggest that only adult smokers who complain to a physician about shortness of breath on exertion should receive spirometry for COPD case-finding.16 The definition of ‘increased’ COPD risk used for this analysis was broad (not just including those at high risk), and thereby included 77% of the adults from these population-based samples. A short screening questionnaire designed and validated to identify a smaller population with high risk for COPD (for example, relative risk >5.0) would likely provide greater efficiency.17

Controversy also exists regarding the definition of ‘clinically significant’ COPD. There is no question that patients with airway obstruction and a post-BD FEV1 <50% predicted post-BD have COPD.18–22 Detection of people with moderate airway obstruction (GOLD Stage II, with FEV1 between 50%P and 80%P) may be worthwhile, as their exercise capacity is reduced,18 but no medication has been demonstrated to reduce their subsequently rapid loss of lung function,22,23 and confronting them with their abnormal spirometry results does not prompt them to be more successful with smoking cessation.24 All smokers, regardless of spirometry results, should be advised and helped to quit smoking.
We have provided separate analyses for detecting only severe COPD (GOLD Stages III and IV) and for detecting mild and moderate COPD (GOLD Stages I and II) that may be applicable to different needs and priorities. The use of PEF greatly improved efficiency (due to a very high NPV) when the goal was to detect the 1.7% of adults in the PLATINO and BOLD surveys with severe COPD (GOLD Stages III–IV), and moderately improved efficiency when detecting the 6.8% of adults with moderate COPD (GOLD Stage II).25 Thirteen per cent of those individuals with respiratory symptoms had moderate to severe airflow obstruction compared to 56% of those with symptoms and a PEF <70%P, considerably increasing the justification for a trial of bronchodilator therapy instead of prescribing it based only on respiratory symptoms.

Although PEF has not been well accepted for COPD diagnosis, it has been described as a good indicator of mortality risk in hospitalized COPD patients26 and of diagnosis, it has been described as a good indicator of mortality risk in hospitalized COPD patients. Instead of prescribing it based only on respiratory symptoms and a PEF measurement of PEF in those with a high risk of COPD, using inexpensive PEF meters or electronic pocket spirometers in the clinic setting. These findings need to be confirmed using PEF measurements obtained by a peak flow meter in the clinic setting.

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21. Mannino D M, Doherty D E, Sonia Buist A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease, asthma, and emphysema or of bronchitis chronic.

RESULTADOS: El PEF se utiliza con mayor frecuencia para el diagnóstico y el seguimiento de la enfermedad de vías respiratorias. Se ha utilizado para establecer límites de normalidad y patología, y para el seguimiento de la evolución y la eficacia de tratamientos. El PEF se utiliza también como medida de la función pulmonar en estudios clínicos.

CONCLUSIONES: El PEF es una herramienta útil para el diagnóstico y seguimiento de la enfermedad pulmonar obstructiva crónica (EPOC) y otras enfermedades respiratorias. Su uso en el diagnóstico y seguimiento clínico es recomendado.

RÉSUMÉ

LE DIAGNOSTIC DE BRONCHOPNEUMOPATHIE CHRONIQUE OBSTRUCTIVE PEUCO (BPCO) EST PORTÉ TROP PEU SOUVENT. UNE BARRIÈRE AU DIAGNOSTIC EST CONSTITUÉE PAR LA DISPONIBILITÉ LIMITÉE DES TESTS DE SPIROMÉTRIE, MAIS CHEZ LES ADULTES ENCOURAN UN RISQUE DE BPCO, UN DÉBIT EXPIRATOIRE DE POINTE (PEF) AVANT BRONCHODILATATEUR (PRÉ-BD) PEUT EXCLURE UNE BPCO CLINIQUEMENT SIGNIFICATIVE.

OBJECTIF: Identifier l’obstruction des voies aériennes après bronchodilatateur (post-BD) en utilisant les données sur 13 708 adultes de ≥ 40 ans provenant des études PLATINO y BOLD.

MÉTHODES: Nous avons évalué différentes valeurs seuil des PEF pré-BD. Le PEF a été obtenu à partir d’un spiro-mètre de qualité diagnostique (et non d’un débitmètre de pointe mécanique). Au moins un des facteurs de risque suivants de BPCO était présent chez 77% des sujets: symptômes respiratoires chroniques, exposition à la fumée de tabac, à la fumée de la biomasse ou aux poussières sur le lieu de travail, ou encore un diagnostic antérieur d’asthme, de BPCO, d’emphysème ou de bronchite chronique.

RESULTATS: Plus le PEF pré-BD est élevé, et moindre est le risque d’une obstruction post-BD des voies aériennes. Un PEF de >70% des valeurs prédites exclut pratiquement les Stades III et IV du Global Initiative for Chronic Obstructive Lung Disease (GOLD) de la BPCO. Chez les sujets dépistés par un questionnaire et par le PEF avec une valeur-seuil de 70% des valeurs prédites, une spirométrie complète n’est nécessaire que dans 12% des cas pour détecter les Stades III et IV de GOLD.

CONCLUSIONS: L’addition d’une mesure du PEF à un questionnaire de dépistage peut exclure les BPCO graves à très graves sans nécessiter un test spirométrique pré et post-BD. Une confirmation s’impose provenant d’une étude utilisant des débits de pointe peu coûteux ou des spiro-mètres de poche parallèlement à un protocole de dépistage par étapes.
exposición al humo de tabaco o biomasa o a polvos en el trabajo, diagnóstico previo de asma, EPOC, enfisema o bronquitis crónica.

RESULTADOS: A mayor PEF pre-BD, menos probable la obstrucción post-BD. El PEF $\geq 70\%$ esperado descartó para fines prácticos los Estadios III–IV de EPOC de acuerdo a los criterios del Global Initiative for Chronic Obstructive Lung Disease (GOLD). Solo 12% de los sujetos filtrados por cuestionario y PEF requirieron una espirometría confirmatoria si el objetivo fue detectar los Estadios GOLD III–IV usando como punto de corte un PEF de 70%P.

CONCLUSIONES: Añadiendo la medición de PEF a un cuestionario se puede descartar EPOC grave y muy grave sin necesidad de espirometría pre- y post-BD. Se requiere confirmar la información utilizando flujómetros de bajo costo o espirómetros de bolsillo en un protocolo escalonado de detección.