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DISCUSSION PAPER

COPD screening in primary care: who is sick?

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Summary
Current COPD guidelines such as the GOLD workshop report use a fixed FEV_1/FVC value (0.70) to define airway obstruction, and FEV_1 % predicted to classify COPD severity. Evidence is emerging that this approach leads to an unacceptable percentage of false-positive diagnoses of mild and moderate COPD. Expressing FEV_1 as a percent predicted value similarly introduces a bias: small people, elderly people, and especially small elderly people who are in good respiratory health will be incorrectly identified as having an abnormally low FEV_1. More appropriate classification rules for defining the presence and severity of airway obstruction are urgently needed, especially for primary care doctors who have to deal with the early stages of COPD. The use of the lower limit of normal (LLN) for the FEV_1/FVC ratio instead of a fixed ratio value of 0.70 would be a first rational step towards a better classification of airway obstruction.

Introduction

In this issue of the *Primary Care Respiratory Journal*, Tinkelman *et al*. present the results of a very carefully conducted case-finding study of chronic obstructive pulmonary disease (COPD) screening amongst middle-aged smokers.[1] They found that screening of smokers over the age of 40 in general practice, applying GOLD guidelines for the diagnosis and classification of COPD, yielded a pick-up rate of 10-20% undiagnosed COPD cases, many with moderate to severe disease.

As is the same in other diseases such as atherosclerosis and arthrosis, lung damage develops insidiously, and patients often do not perceive or correctly appreciate respiratory symptoms. Smoking cessation is by far the most important intervention for patients found to have COPD; among other health benefits, it leads to a sustained small improvement in the level of forced expiratory volume in 1 second (FEV_1) in smokers[2] and reduces the rate of decline to that of non-smokers.[3] Pharmaceutical intervention is only of some benefit in severe airway obstruction and does not affect the progression of disease to a relevant extent.[4] It is therefore logical and

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laudable that efforts are made to identify cases of airway obstruction at an early stage so as to try and prevent the disease in these patients from progressing to a severe stage.

Screening is only ethically acceptable if a number of conditions are met.[5] In particular, there should be an accepted treatment for patients with recognised disease. However, apart from smoking cessation which occurs successfully only in the minority of COPD patients who smoke, and symptomatic treatment in the small proportion with severe disease, this requirement hardly seems to be met in COPD. Considering the side effects of treatment, some have voiced reservations about screening in primary care practice.[6] A suitable test or examination should be available. Since the current trend is to regard COPD as a clinically silent disease in its earlier stages, the onus rests completely with the diagnostic test, i.e. spirometry, to demonstrate the presence of airway obstruction.

How appropriate are present diagnostic guidelines?

A requirement of any diagnostic test is that it correctly identifies patients with the disease, and has a low rate of false-positive and false-negative test results. Whether or not someone has airway obstruction, and how its severity is assessed, varies with the definition adopted as well as with the selected reference values.[7-11] When the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[8] issued its guidelines in 2001, which were quickly adopted by other organisations, the prevalence of COPD trebled compared to previous definitions (see Table 4 in Tinkelman *et al's* paper).[1] This was due to the change in the definition of airway obstruction — an FEV_1/forced vital capacity (FVC) ratio <0.70 after bronchodilatation — introduced by the GOLD guidelines. The GOLD group ignored the age-dependency of the ratio[8] not because there was evidence that a ratio of less than 0.70 signified obstructive lung disease, but because using a fixed ratio provided a simple rule of thumb. Does ignoring age-dependency of the FEV_1/FVC ratio matter when establishing airway obstruction?

A common way to establish 'abnormality' of an observed value is to compare it to the lower limit of normal (LLN) established in subjects free of the conditions that may affect the index. A survey of the literature yielded 30 reference equations for Caucasians for the lower limit of normal (LLN) for the FEV_1/FVC ratio.[12] Invariably the ratio declined with age, and with very few exceptions it fell to well below 0.70. Figure 1 (upper panel) illustrates this for four prediction equations derived from large European studies, including the widely used ECCS/ERS[13] predicted values. It illustrates that the fixed 0.70 ratio leads to false-negative results in younger adults, and to a considerable proportion of false-positive test results in older adults. The figure also shows that the false-negative and false-positive proportions will differ between men and women. Using the large NHANES III[14] database it was demonstrated that, above the age of 50, about 50% of subjects regarded as having airway obstruction were false-positives.[15] Even if one takes into account the fact that the subjects were not administered a bronchodilator drug, which might have brought some people above the lower limit, the false-positive ratio is staggering. The conventionally-used LLN will identify 5% of healthy nonsmokers as having airway obstruction; a more conservative 1% to 2.5% percentile range would be more appropriate to limit false-positive findings in middle-aged and elderly subjects, and would further widen the gap with the GOLD criteria. The 0.70 cut-off for the FEV_1/FVC ratio, therefore, is not appropriate for diagnosing airway obstruction and is responsible for many recent publications with an unduly high prevalence of airway obstruction among elderly subjects. Similarly it explains the much greater prevalence of obstruction among smokers (50%)[16] than estimated a decade ago (15%).[17]

Classifying the severity of airway obstruction

The severity of airway obstruction is gauged from the level of FEV_1. Almost invariably COPD guidelines recommend expressing FEV_1 as a percentage of the predicted value. Yet no author of reference values has ever advocated or justified this usage: instead, authors have invested a lot of effort to compute a LLN, which is conventionally designed so that 5% of a reference population of nonsmokers falls below that limit over the whole age and height range. International expert committees regard these lower limits as scientifically justified cut-off values.[13,18,19] Using 'percent predicted' leads to an age- and height-related bias. This is illustrated in the lower panel of Figure 1, showing the LLN as a percentage of the predicted FEV_1. If the FEV_1/FVC ratio is <0.70 but still above the LLN for that index, which it will frequently be in perfectly healthy lifelong nonsmokers above the age of 50 (Figure 1, upper

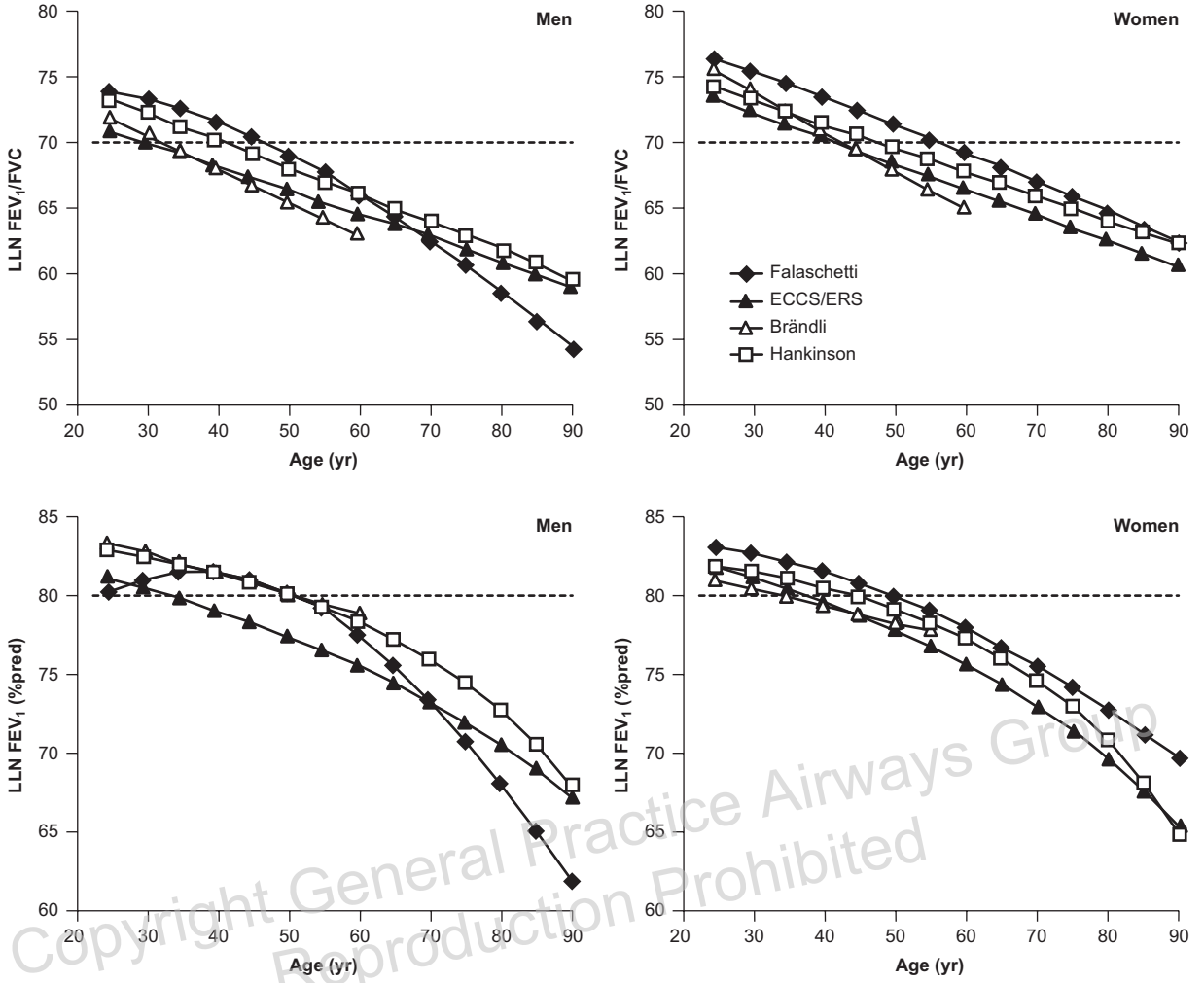

Figure 1 The lower limit of normal (LLN) for FEV_1/FVC (upper panel), and the LLN for FEV_1 expressed as a percentage of the predicted FEV_1 (lower panel) for men and women of average height (178 and 168cm, respectively).[13-14, 23-24] According to GOLD guidelines FEV_1/FVC <70% (i.e. 0.70 x 100%, upper panel) signifies airway obstruction, and FEV_1 % predicted <80% signifies moderate airway obstruction. Note how this often leads to false-positive findings, and how a subject will migrate from 'normal' to GOLD stages I or II simply by tracking in parallel with predicted values but still within the normal range.

panel), it does not take much to have an FEV_1 percent predicted which falls below the arbitrary 80% mark. If so, according to current staging methods[8-11] the subject has moderate airway obstruction, even though both the FEV_1 value and the FEV_1/FVC ratio are in the normal range. During follow-up, someone thus classified as GOLD stage I will in due time progress to GOLD stage II simply by tracking in parallel with the predicted value — but being still within the normal range; this may in part explain findings of disease progression during follow-up.[20] Expressing FEV_1 as a percent predicted value introduces a bias: small people, elderly people, and especially small elderly people who are in good respiratory health will be incorrectly identified as having an abnormally low FEV_1.

Correctly classifying airway obstruction

The correct way to assess the severity of airway obstruction follows from an understanding of how FEV_1 prediction equations are derived. They usually have the general form: $FEV_1 = a + b \cdot Height + c \cdot Age + \varepsilon$, where ε is the standard deviation (SD) of the scatter remaining after differences in height and age between subjects have been taken into account. If the residual scatter has a Gaussian distribution, the 5th percentile is at $-1.64 \cdot SD$.

Hence, if the FEV_1 of a tall and young man, and of a middle-aged woman of average standing height, are both 1 standard deviation below predicted, they have a normal and comparable FEV_1, even though the FEV_1 is numerically quite different when expressed in litres or as percent predicted. It follows from the above that the proper index expresses how many standard deviations the measured value differs from the predicted one.[13,18,21] This index is either called the standard deviation score (SDS), z-score, or standardised residual (SR).

Obviously, the same procedure should be applied when assessing the FEV_1/FVC ratio, the FVC, or any other lung function index. The simple rule of thumb, therefore, is that if the observed value is more than 1.64·SD below its predicted level, it is below the conventional LLN (5th percentile). But the LLN should be tweaked for specific purposes, such as for screening, where one needs to balance the consequences of false-positive and false-negative test results. If one wants to limit the number of false-positives, the 2.5th percentile (-1.96·SD), 2nd percentile (-2.05·SD) or 1st percentile (-2.33·SD) may be more appropriate. In Tinkelman *et al's* screening study this approach would have led to different results.

A predicament

In our efforts to identify subjects with airway obstruction at an early stage we unfortunately cannot rely on the absence or presence of respiratory symptoms. Disregarding symptoms, the only prior risk factors for potential airway obstruction are therefore age and known exposure to substances that lead to airway obstruction, such as tobacco smoke. But we still need a crystal ball: who does and who does not have airway obstruction? Current recommendations[8-11] are not based on evidence that lung disease is identified, they lead to an unacceptable percentage of false-positives classified as mild and moderate airway obstruction, and are therefore less than helpful. In the great majority of middle-aged or elderly subjects with mild or moderate airway obstruction it is mainly the co-morbidity that is life threatening — few develop severe airway obstruction. One wonders, therefore, whether at this stage, instead of screening and case-finding, "community programmes on prevention of COPD should focus on anti-smoking, nutritional aspects, and socio-economic conditions".[22] GOLD stages III and IV are not affected by the age and height bias alluded to above, and certainly require medical intervention.

If general practitioners elect to stick with the GOLD guidelines, they should be aware of the fact that a large proportion of subjects in GOLD stages I and II have no airway obstruction at all. More appropriate classification rules for the presence and severity of airway obstruction are needed. Acknowledging the shortcomings of its own spirometric classification in the most recent update of the GOLD guideline (November 2006), and the notion that it would be more appropriate to use the lower limit of normal for the FEV_1/FVC ratio rather than the fixed cut-off of 0.70,[8] is therefore a promising step in the right direction.

Conflicts of interest

There were no conflicts of interest for the authors in the preparation of this paper.

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