

Spirometric definition of COPD: exercise in futility or factual debate?

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The current international guidelines for the diagnosis and management of COPD recognise spirometry as a major criterion to confirm a clinical diagnosis of COPD.^{1–3} The specific role of spirometry for the diagnosis of COPD is to identify the presence of airflow obstruction, which is the essential requirement for the definition of the disease. Although a reduction of the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) has been consistently adopted as an unquestionable sign of airflow obstruction, no consensus has been achieved regarding the cut-off to separate healthy from obstructed subjects.

In 1986 the American Thoracic Society (ATS) suggested an obstructive abnormality be present when $FEV_1/FVC < 0.75$ independent of age and sex.⁴ By contrast, the European Respiratory Society (ERS) recommended the use of the ratio of FEV_1 to slow vital capacity (VC) with cut-off values as percentage of predicted for age and sex (88% for males and 89% for females).⁵ These values, which roughly correspond to the lower 5th percentiles of a healthy population, take into account the physiological age-related decrease of lung elastic recoil. In line with this statistics-based approach, the recent joint document ATS/ERS on standardisation of lung function testing⁶ indicated an FEV_1/VC or FEV_1/FVC below the lower 5th percentile as the lower limit of normality (LLN) to define airflow obstruction. At variance with this recommendation, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) defined COPD by an opinion-based fixed $FEV_1/FVC < 0.70$,⁷ which was subsequently adopted also by the British National Institute for Health and Clinical Excellence (NICE)² and the Canadian Thoracic Society.³

Since then, the appropriateness of a fixed FEV_1/FVC cut-off for diagnosis of COPD has been long debated without coming to a consensus, mainly because of the lack of consensus on the gold-standard for diagnosis of COPD. Therefore, the recommendation of any given spirometric criterion for diagnosis of COPD can be only based on the balance between pros and cons. Although one may consider this debate as an endless speculation, the choice of different spirometric criteria for COPD may have profound impact on both epidemiologic and clinical studies, as well as on daily clinical practice.

The major problem of the fixed ratio was clearly highlighted in population studies showing that it carries the risk of over-diagnosis in elderly non-smokers^{8–10} and under-diagnosis in young smokers.¹¹ Moreover, the chance of misclassification is expected to be sex dependent, because FEV_1/FVC declines with age faster in males than females.¹² In epidemiological studies, when a pre-test clinical diagnosis is not available, the use of the FEV_1/FVC fixed ratio may thus lead to the conclusion that COPD occurs in a large proportion of never-smokers, with ageing and male sex being inevitable risk factors. An ill message that may arise from this is that smoking avoidance may not be the main step for prevention of COPD.

Jordan *et al*¹³ further show how critical may be the choice of criteria to define airflow obstruction in epidemiological studies. They analysed three cross-sectional data sets to compare the prevalence of COPD as defined by criteria based on fixed FEV_1/FVC (GOLD and NICE) or LLN. The risk of COPD using either GOLD or NICE criteria was, as expected, larger in males than females but the latter resulted more susceptible to COPD for the same smoking level. These contrasting differences in risk and susceptibility to smoking between sexes disappeared when LLN criterion was used. Without a clear definition of COPD and because of its cross-sectional nature, this study cannot tell which one is the most

appropriate spirometric definition of COPD but points to the fact that this is a non-negligible question barely needing consensus, at least for epidemiological purposes. In this scenario, it is noteworthy that a recent ERS Task Force for epidemiological studies on COPD made a position on this issue recommending the use of LLN.¹⁴

Although the pitfalls of the fixed ratio have been recognised even by GOLD committee, the recommendation to use it was maintained, despite a plea to abandon it made by a large international group of scientists.¹⁵ The arguments in favour of the fixed $FEV_1/FVC < 0.7$ are that (1) it is easy to remember, (2) it is not dependent on the choice of predicting equations and (3) the risk of misdiagnosis and overtreatment of individual patients is limited because spirometry is not the only parameter for the clinical diagnosis of COPD. Opposing arguments may be that (1) although a single number is unquestionably easy to remember, this was probably necessary in the old times when computerised spiroimeters with built-in predicting equations were not yet available, (2) LLN, unlike the fixed ratio, is dependent on the choice of reference values but so are the cutoffs for FEV_1 (per cent of predicted) recommended for severity classification^{1–3} or even for diagnosis,² and (3) it is true that using spirometry to confirm a clinical diagnosis reduces the chance of over-diagnosis in elderly subjects, but the risk remains of excluding COPD in symptomatic younger subject with $FEV_1/FVC \geq 0.7$ but $< LLN$.¹¹ The NICE criterion ($FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ of predicted) would reduce the risk of over-diagnosis only in part, because 80% of predicted in elderly subjects may also be $> LLN$,¹⁶ at the cost of an increased risk of under-diagnosis. In regard to this, it should be kept in mind that any spirometric criteria may not be sensitive enough for an early diagnosis of COPD, when the disease is limited to peripheral airways and an increase in residual volume is likely to be the only abnormality present.¹⁷

Another argument brought forth by the advocates of $FEV_1/FVC < 0.7$ is that it may help predict the risks of death even in patients with an $FEV_1/FVC > LLN$.^{18,19} However, one may argue that this does not imply that the diagnosis of COPD with the fixed ratio is more correct than with LLN. This argument is confirmed by a more recent population study showing that subjects with $FEV_1/FVC < 0.7$ but $\geq LLN$ were significantly older, more likely

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to be male, but with less active smoking, less respiratory symptoms and more likely to have other diseases.²⁰

Another question is whether the choice of spirometric definition of COPD might have affected the results of large clinical trials. Patients were generally included according to GOLD criteria, which may have caused enrolment of elderly subjects with borderline or even normal lung function. However, the majority of clinical trials published so far included patients with moderate-to-severe disease, thus with a number of subjects with $\text{FEV}_1/\text{FVC} < 0.7$ but $\geq \text{LLN}$ that was likely too small to have a significant effect on results and conclusions.²¹ This may not be the case in clinical trials specifically designed to study the effects of treatment in mild COPD. In any case, using the less specific GOLD criteria, the power of studies may be reduced due to inclusion of subjects without well documented COPD. This may cause some significant effects to be missed but would strengthen any significant effect of treatment.

In summary, as also shown by Jordan *et al*,¹³ an agreement on the spirometric definition of COPD is needed. The fixed FEV_1/FVC is arbitrary and has no obvious pro but several cons, particularly for epidemiological studies, though it may be acceptable for clinical trials; the LLN is also arbitrary, but it gives an estimate of the chance (5%) of falsely positive results. In any case, clinicians should not forget that other pulmonary function tests in addition to simple spirometry may considerably help make a correct diagnosis of COPD.

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