Question everything

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A large study concludes that FEF25–75% and FEF75% do not provide a clinical advantage over FEV1 and FEV1/FVC http://ow.ly/tnB7D

Advances through scientific endeavour have delivered many benefits to the human race and overall these benefits have outweighed any associated problems. Not uncommonly apparent improvements in our knowledge are eventually shown to be incorrect or misguided in the light of subsequent knowledge. This might arise because a different perspective was taken on a problem so that a new understanding was achieved or it might arise because technological advances revealed imperfections in previous studies.

In the early 1960s a view became common practice that expressing results as a percentage of the predicted value was the best way to look at lung function and that 80% of predicted was "as a rule of thumb" the lower limit of normality [1]. This view was immediately challenged [2] but the practice persisted, despite the fact it retains age, sex and height biases [3], and is not true for all lung function indices. In 1972 the forced expiratory flow between 25% and 75% ($FEF_{25–75\%}$) of forced vital capacity (FVC) was proposed as a more sensitive test of small airways disease [4], with evidence presented from 53 heavy smokers who did not have asthma and had normal forced expiratory volume in 1 s (FEV_1), FVC and their ratio, but with $FEF_{25–75\%}$ that was deemed abnormal (below 80% of predicted). The scatter of results in a normal population for $FEF_{25–75\%}$ is very wide [5], so the normal range includes values as low as 40% when expressed as a percentage of the predicted value. This contributed to misleading these authors into thinking this index was a sensitive test for smoking-related small airways disease when they incorrectly used 80% of predicted as their criterion for normal cut-off. Over the years, $FEF_{25–75\%}$ has been quite widely used, especially in paediatric practice, although it has not been recommended for use in a clinical setting because the values obtained are very dependent on the achieved FVC [6].

In this issue of the *European Respiratory Journal*, QUANJER *et al.* [7] report a study to determine whether $FEF_{25–75\%}$ and $FEF_{75\%}$ can add any information to the FEV_1 and its ratio to FVC with regard to early diagnosis of obstructive airway disease. They used the correct methodology of lower limits of normality [8] and found that in most cases the FEV_1, FEV_1/FVC, $FEF_{25–75\%}$ and $FEF_{75\%}$ agreed upon the diagnosis of airflow obstruction. In only 2.75% of the cases the $FEF_{25–75\%}$, and in 1.29% the $FEF_{75\%}$, were below predicted values as opposed to normal or near normal FEV_1, FVC and FEV_1/FVC. This is not surprising if one considers that in a person with a normal FEV_1/FVC of 0.75 the $FEF_{25–75\%}$ represents the same effort-independent part of the FVC. Conversely, in 2.9% of the cases the $FEF_{25–75\%}$, and in 12.3% the $FEF_{75\%}$, were within the normal range despite a reduced FEV_1/FVC. These findings led the authors to conclude that $FEF_{25–75\%}$ and $FEF_{75\%}$ do not add substantial information with respect to the diagnosis of airflow obstruction. The strengths of the study are the statistical approach and the impressive number of subjects studied (22 767) with a life span ranging from 3 through 94 years.

The idea of flow at low lung volumes being more sensitive to peripheral airway obstruction than classical spirometric indices stems from a theory that the flow-limiting segment moves towards the periphery as the

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lung empties [9]. In this model, flows at low and high lung volumes are considered to be independent of each other, which may not be true for some physiological mechanisms. First, any increase in peripheral resistance may reduce flow, not only at low but also high lung volumes, because it also causes a reduction of transmural pressure downstream from the flow-limiting segment [9–11]. Secondly, central airway narrowing causes a decrease in flow at high lung volume but also a downstream shift of the choke point, which may counterbalance the effects of peripheral airway narrowing on flow at low lung volumes [9, 10]. Thirdly, in obstructive lung diseases airway narrowing is non-homogeneously distributed across the lungs [12]. Thus, at any lung volume forced expiratory flow is the average of the contributions from flow-limited and non-flow-limited regions. For these reasons, it seems unlikely that peripheral airway obstruction may affect flows at low lung volumes only. QUANJER *et al.* [7] rightly emphasise the critical dependence of $FEF_{25–75\%}$ and $FEF_{75\%}$ on FVC. If the latter does not match the predicted value, then $FEF_{25–75\%}$ and $FEF_{75\%}$ will be over or underestimated simply because they were measured at a different lung volume and elastic recoil pressure, which is the driving force for expiratory flow. In addition, because forced expiratory flow measured at the mouth is affected by thoracic gas compression, discrepancies between classic spirometric parameters (FEV_1 and FEV_1/FVC) and $FEF_{25–75\%}$ or $FEF_{75\%}$ may also arise from differences in the effort of the manoeuvers from which values are derived.

A decrease in flow at low lung volume is often regarded as a marker of intrinsic airway disease. However, some young healthy males exhibit a decrease in forced expiratory flow at low lung volume for a given pressure, a finding consistent with compression of intrathoracic airways rather than intrinsic airway disease [13]. Moreover, a reduction in forced expiratory flow at low lung volumes may equally result from an increased peripheral pressure loss or a decrease in lung elastic recoil [12].

With all these potential artefacts able to affect instantaneous flows more than the FEV_1, we support the conclusion of QUANJER *et al.* [7] that flows at low and mid lung volumes do not have any practical clinical advantage over FEV_1 and FEV_1/FVC. In scientific research we must continually keep formulating questions and then carry out the relevant studies and experiments to help answer them, but it is equally important to challenge established apparent truths rigorously, as done by QUANJER *et al.* [7]. The bottom line is that there is not much more we can learn from looking at spirometric recordings from different angles. Rather, we should focus on the search for new tests of lung function that are more sensitive to peripheral airways physiology than those currently available.

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