

Resurrection men and the FEF₂₅₋₇₅

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The movement of medicine toward a scientific foundation in the late 18th and early 19th centuries had the unexpected effect of creating a cottage industry called “body snatching.” Corpses were disinterred from graveyards, sold to medical schools and private institutions, and recycled for anatomic dissection.¹ This process was dubbed “resurrectionism,” and the practitioners were called “resurrection men” because they caused the dead to rise again. In a sense, Simon et al² in the current issue of the Journal are also “resurrection men” who are giving a new purpose to a lung function test long considered dead and buried.

The forced expiratory flow at 25% to 75% of forced vital capacity (FEF₂₅₋₇₅) was suggested as an index of peripheral airway obstruction almost 40 years ago.³ Its rise and fall is a story worth reviewing because it offers both a historical and a modern perspective to the work under discussion. In the spirit of complete disclosure, I need to state that I do not treat children, but given that the relevant physiologic and clinical parameters transcend age, I trust that I will not do substantive damage to the subject matter. Further, because the paramount finding in the work of Simon et al² is the FEF₂₅₋₇₅, my remarks will be confined to that parameter.

The concept of peripheral airway obstruction and its detection is tightly related to the manner in which the mammalian lung has evolved. The primary purpose of the respiratory system is to provide oxygen to meet metabolic demands and eliminate carbon dioxide to regulate acid-base balance. The sequential branching pattern of the tracheobronchial tree creates a multitude of parallel pathways of slightly smaller daughters at each bifurcation that produce a progressively increasing cross-sectional area.⁴ Ultimately, the combined airway and alveolar surface area reaches an enormous size that is estimated to be between 100 and 150 m² in an adult. In practical terms, this is about the size of a tennis court.

Such a geometric arrangement greatly facilitates efficient air delivery to the alveoli by both convection and diffusion. However, it is easy to appreciate that significant pathology could potentially exist in many peripheral units and not be easily detected by conventional means. This possibility was confirmed in a dog

Abbreviation used

FEF₂₅₋₇₅: Forced expiratory flow at 25% to 75% of forced vital capacity

model in 1967, thereby ushering in the concept of peripheral airway disease.⁵ In short order, searches began in many laboratories to determine whether this phenomenon also occurred in human beings. The hope was that it was now possible to think of the early detection of a progressive illness like chronic obstructive pulmonary disease at a time when interventions would be most likely to change its natural history.

Because all of the regions of the lung fill and empty synchronously,⁶ and because nonuniform distribution of disease in the periphery disrupts this pattern, the diagnostic tack usually taken was to use tests sensitive to respiratory rate such as frequency dependent compliance or resistance.⁷ Later, other tests were explored like the distribution of alveolar air, increases in alveolar-arterial gradients for oxygen, and dynamic hyperinflation.⁸ The common denominator underlying all of them was that if the lung units filled and emptied asynchronously, such tests would be abnormal, and the discrepancies would worsen as respiratory frequency rose. This is exactly what was found, and proof of concept was established.

For the most part, these early studies investigated smokers and patients with asthma with normal, or near normal, conventional mechanics and deduced that the findings represented peripheral airway obstruction. Although sensitive, these tests were highly invasive, required specialized expertise, and were not suited for clinical use. What was needed was a test that could be widely applied and interpreted and one that patients could easily and reproducibly perform.

From a physiologic standpoint, if parts of the lungs were truly emptying sequentially, then flows in the mid to low vital capacity during a forced exhalation might be the tests of choice to meet the need because they would be selectively dominated by the units with the highest resistance and therefore the lowest emptying rates. One of the earliest indices to be examined was the FEF₂₅₋₇₅, but variations on this theme like maximum flows at 50% of the vital capacity or flows later in exhalation soon followed. Space constraints prohibit an exhaustive review of a voluminous literature, but suffice it to say that it became apparent this genre of pulmonary testing could demonstrate peripheral airway obstruction under appropriate circumstances. Each test had its proponent, and the requisite academic battles ensued. However, in short order, major limitations that materially compromised utility were encountered in all. Like the tests of frequency-dependent behavior, FEF₂₅₋₇₅ and other flows could be used to distinguish the site of obstruction only when standard indices like the FEV₁ and airway resistance were normal. If they were not, then the site of obstruction could not be differentiated. Hence, it was not the test *per se*

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but the circumstances in which it was used that become critical. This concept was frequently overlooked. Equally importantly, there could be considerable variability from trial to trial, and the normal range was poorly defined. Thus, the issue of what constituted an abnormality was often arbitrarily decided by the investigator. Applicability was now deferred while normal ranges were debated. Finally, there were no epidemiologic data to show whether, or how, the FEF_{25-75} measured or predicted disease activity over time. Consequently, enthusiasm dimmed and then died.

One potential that has never been fully explored is how the FEF_{25-75} reflects the natural history of asthma and its management. After an acute exacerbation, the FEF_{25-75} remains depressed long after the FEV_1 and specific conductance normalize and takes weeks to resolve.⁹ It is usually associated with an elevated residual volume, depressed arterial O_2 tension, and increased peripheral airway resistance by direct measure.^{9,10} In fact, it and a high residual volume are the most common abnormalities in pulmonary function in cross-sectional studies in asymptomatic adults and children with asthma.^{11,12} Thus, it is an intimate part of the disease.

The issue has always been what to do with such information, because the waxing and waning of the FEF_{25-75} does not seem to carry any major clinical changes with it. There are some data that the presence of peripheral obstruction heightens airway reactivity¹³ but none showing that it changes attack frequency or materially alters medication requirements or the quality of life. Here, Simon et al² offer some help, albeit indirectly.

Although their study is a retrospective analysis of published data, their elegant statistics show that an FEF_{25-75} of 65% of predicted or less has a 90% sensitivity and a 67% specificity of predicting a bronchodilator response to albuterol. This is believed to be important because the latter implies suboptimal asthma control. By inference, then, the FEF_{25-75} could possibly become a surrogate to assess the overall therapeutic effectiveness of a given regimen. If the FEF_{25-75} is low, patients need more medication for complete control. As interesting as this possibility is, however, it should be pointed out that consistent bronchodilator responsiveness and therefore poor clinical outcomes is a relatively

uncommon phenomenon and for example was seen in just 5% of the children in the Childhood Asthma Management Program.¹⁴ Once again, specific applicability may not be as widespread as wished. As Simon et al² point out, long-term studies will be required to reach definitive conclusions about the ultimate clinical utility of the FEF_{25-75} in asthma management.

As with the dissection of corpses without the benefit of refrigeration, "resurrection" can be short-lived. Let us hope that this is not the case here.

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