Horses for courses: Learning from functional tests of pulmonary health?

1 | HISTORICAL

What was once known as a disease confined to early childhood, cystic fibrosis (CF) now for the first time affects more adults than children in most parts of the world. The primary cause of mortality and morbidity is lung disease; yet, with the introduction of newborn screening, aggressive treatment, and cystic fibrosis transmembrane conductance regulator (CFTR) modulators, there has been a dramatic shift in life expectancy. Despite a notable improvement in quality of life, CF remains a chronic progressive disease. The current "gold standard" for monitoring lung disease in CF is spirometry, its main outcome being forced expired volume in 1 second (FEV₁). Spirometry requires a maximal coordinated effort by the patient and is often not reliably performed until around 8 years of age. Even when patients can perform the maneuver reliably, values are frequently within "normal" ranges up until the mid-teenage years. This is largely due to the maneuver measuring signal from the peripheral airways very poorly; at best they probably contribute only ~10% to FEV₁. A clinically significant change in FEV₁ is thought to be 13 percent predicted (ppFEV₁), suggesting that there can be substantial damage or changes in the peripheral airways before any "meaningful" changes are seen. As CF lung disease progresses, patients with a ppFEV₁ < 30 have a 50% chance of death or transplant (D/T) within 2 years. However, in pediatrics ppFEV₁ 2 years before death was not a good predictor of mortality with a median ppFEV₁ of 53%, ranging from 24% to 102%. With this lack of sensitivity, FEV₁ is not one of the parameters used for the lung allocation score used in the United States, Germany, and the Netherlands as part of the transplant waiting list assessment.

2 | WHAT IS NEEDED?

Sensitive and comprehensive markers of lung disease are essential for the future of CF care. This will ultimately require a move away from a volume-based assessment such as spirometry, instead of concentrating on performance using alternative and more appropriate techniques for a changed population. Recently, Gambaza et al studied the relationship between exercise capacity and multiple breath washout (MBW), which both assess performance and can be used as a measure of ventilation efficiency (when ventilatory gas analysis is assessed). Both measures are being heavily researched in CF and appear to be most useful for different age groups.

3 | MULTIPLE BREATH WASHOUT

MBW is currently being successfully used as a surrogate marker in CF clinical trials. MBW is an attractive technique for clinicians and researchers alike as it can be used across all ages, is a global measure of lung function, and is sensitive in assessing the peripheral airways. The primary outcome of the test is the lung clearance index (LCI), which is a measure of ventilation inhomogeneity, physiological dead-space, and gas mixing efficiency; together, these provide a measure of ventilation efficiency. LCI can be raised in CF compared to healthy populations in infants as young as 3 months, in children and in adults with preserved spirometry. LCI was shown to be the earliest and most predictive measure of disease progression when assessed longitudinally over a 20-year period in 142 children. LCI correlates well with HRCT scores for bronchiectasis, structural changes, and mucus plugging, but somewhat less strongly with trapped air.

4 | LIMITATIONS OF LCI

Although a sensitive marker of lung disease at all ages, LCI is unlikely to be practical in adults, particularly those with advanced lung disease. LCI for an adult CF patient with severe lung disease can take more than 90 minutes to complete, and when shortened, there is a clear trade-off with sensitivity, MBW, in its current form, is limited to only assessing the communicating lung. As well as occluded lung units being overlooked, paradoxical changes with LCI have been seen in severe disease, with those previously occluded lung units contributing to the signal after intervention.

5 | CARDIOPULMONARY EXERCISE TESTING

Cardiopulmonary exercise testing (CPET) with ventilatory gas analysis provides a detailed analysis of the pulmonary and cardiovascular...
systems in addition to the conditioning of the skeletal musculature during exercise. Exercise is most commonly examined using a treadmill or cycle ergometer, with increasing speed and inclination on the treadmill or resistance when cycling. Studies in healthy populations have shown that higher aerobic fitness correlates with increased survival against all-causes of mortality. In CF, the obvious mechanism causative of an abnormal response to exercise would be decreased ventilation efficiency as a result of lung disease; while deconditioning could be present, there is little chance of cardiovascular disease in this population. CPET is currently recommended annually for CF patients older than 12 years of age by the CF Trust (UK) and the European CF Society (ECFS). The ECFS recommends the Cycle ergometer, Godfrey protocol with ventilatory gas analysis as the preferred method of CPET.

6 | CPET AS A PROGNOSTIC MARKER FOR CF

While it still may be debatable whether FEV1 or CPET-derived measures are more sensitive at predicting D/T in CF, there is little argument that CPET measures provide additional prognostic value. The prognostic value of CPET in CF has been researched since 1992, with higher aerobic exercise capacity being associated with a lower risk of D/T over an 8-year period. Recently an expert group provided cluster analysis for high-risk phenotypes for D/T, and despite its insensitivity to the peripheral airways, FEV1 was shown to be the most important variable. The subsequent best variable for clustering was respiratory equivalent for oxygen at peak exercise (VE/VO2peak). The authors determined a high-risk phenotypic group, which, perhaps unsurprisingly, included people with poor FEV1, low BMI and substantially reduced exercise capacity.

7 | VENTILATION EFFICIENCY COMPARISONS

Only a few studies have compared LCI with the Godfrey cycle CPET (with ventilatory gas analysis) and the discordant results have been disappointing, as physiological theory should dictate that these measures correlate strongly. However, LCI and VO2peak derived from the Bruce treadmill CPET act similarly to a subject symptom score. In the report from Gambazza et al., the Godfrey cycle ergometer protocol was used without ventilatory gas analysis, which does not allow for direct measurement of ventilation efficiency and the primary measure is peak work capacity (Wpeak) which translates to the resistance level when exercise is terminated. LCI had a far greater discriminatory power than Wpeak with many patients having a severe LCI score, but a normal Wpeak. However, there were multiple patients with a normal Wpeak, but an abnormal exercise response. Another small study assessed the sensitivity of LCI for predicting abnormalities in exercise tolerance, which only showed a significant difference in oxygen saturation and inspiratory capacity.

8 | WHY THE WEAK RELATIONSHIP?

Various reasons could explain this weak relationship between the methods of measuring ventilation efficiency. Firstly, the relationship could depend on which exercise modality is used to assess ventilation efficiency. CPET has been performed using a cycle ergometer in 88% of studies when testing chronic respiratory patients. There are several advantages to using this method, including safety, the number of staff needed, and the assessment of Wpeak. However, if exercise testing is used mainly as an assessment of lung function, there are several important reasons why using a treadmill ramped protocol might be a more thorough examination. Humans have the ability to run long distances using aerobic metabolism, which has shaped their evolutionary path as well as anatomical composition. However, unlike walking and running, cycling is a learned skill, and a conclusive set of studies has demonstrated that cycling alters ventilatory pattern and pulmonary diffusion. When cycling is used for CPET, leg fatigue often causes the termination of the test rather than dyspnea. VO2peak can be between 7% and 13% higher in healthy individuals when the treadmill is used rather than a cycle ergometer. Potentially these higher VO2peak values derived from treadmill CPET could provide a greater discriminatory power, but further research is needed.

Another main reason for the poor alignment could be due to the limitations with LCI in advanced disease, particularly the lack of signal being derived from occluded airways. As well as CPET is not just a measure of ventilation efficiency, other pathophysiological changes outside of ventilation deficits (most likely deconditioning) will, of course, provide an abnormal exercise response.

9 | FUTURE WORK AND CONSIDERATIONS

We echo the recent call for more studies comparing cycle ergometer and treadmill CPETs in chronic respiratory diseases, but specifically for CF. It will be interesting to see how the relationship between LCI and CPET variables, particularly VE/VO2peak, develops with further research. While Wpeak may be a surrogate for VO2 peak and VE/VO2peak it is rather insensitive and therefore if CPET is used as a measure of lung function, ventilatory gas analysis must be employed. There may be little value in determining the relationship for adults with advanced disease. However, work should be done for children above 12 years of age and with moderate/severe disease when a successful MBW testing session takes considerable time. With the void left by body plethysmography and gas transfer at annual assessment because of their inability to provide short- or long-term utility, it is important to assess if exercise capacity and LCI can be used as sensitive alternatives. It will also be important to establish when there is a moderately/severely elevated LCI, what mechanisms can be adapted to ensure a normal exercise tolerance. With LCI being a sensitive marker of early lung disease and the additional prognostic information of CPET, future work should assess whether (and which method of) CPET can take over from LCI as a sensitive measure of ventilation efficiency when MBW is no longer feasible.
CONFlict of Interests
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