agents for soft tissue injury have demonstrated parallel findings. Although non-steroidal anti-inflammatory drugs can reduce a particular marker of inflammation, their overall benefit towards healing of tendon and muscle injury is questionable.[16]

Skeletal muscle dysfunction is a major contributor of morbidity and mortality in COPD. Its pathogenesis, although multifactorial, is not clearly defined. The findings of Barreiro and colleagues[7] challenge the prevailing notion that local inflammation contributes to the decline in muscle function. Like any good research, they have made us think outside the box and to approach this growing problem in a new and refreshing way. Only well designed clinical and animal studies in the future can answer the question: is inflammation good, bad or irrelevant for skeletal muscles in COPD? Or perhaps the more pressing question should be: what aspects of the inflammatory response should be adjusted during the various degenerative and regenerative phases of skeletal muscle as this tissue responds to physical activity, exercise and disuse in COPD? Inflammation is a complicated tangled web of intertwining cascades that are carefully controlled by numerous positive and negative feedback and feed-forward mechanisms. Until we develop a better understanding of the influence of inflammation on muscle injury, regeneration and healing in COPD, clinicians should strongly encourage their COPD patients to stop smoking, exercise regularly and engage in pulmonary rehabilitation, which are proven ways to enhance muscle performance in COPD patients.

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# Lung clearance index in CF: a sensitive marker of lung disease severity

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Despite airways which are thought to be normal at birth, 90% of patients with cystic fibrosis (CF) ultimately die from respiratory complications of the disease. The steps involved in the progressive destruction of the airways, and strategies aimed at limiting these processes, are therefore major areas of research. For both research and clinical purposes, measures of lung involvement should ideally be (1) sensitive enough to detect abnormalities early and directly reflect changes in disease severity, either naturally occurring or in response to interventions; (2) feasible and reproducible in all age groups; and (3) repeatable over time.

With regard to the first of these criteria, there is increasing concern that conventional measures such as spirometry and chest radiography are insufficiently sensitive, particularly at the mild and moderate stages of disease. Use of these investigations has enabled a generation of clinicians to improve pulmonary status significantly, but these clinical improvements themselves serve to highlight the inadequacy of the tools we have available to assess them. In contrast to the situation several decades ago, forced expiratory volume in 1 s ($FEV_1$) now falls too late and too slowly to be accepted unquestioningly as the gold standard. From bronchoscopic studies there is growing concern that, by the time routine spirometry is abnormal, a self-perpetuating infective and inflammatory process has taken hold within the lung that may be difficult to reverse.[1 2] Furthermore, reports of annual falls in $FEV_1$ as low as 1%[3 4] mean that any new intervention aimed, early in the course of the disease, at slowing this decline will require huge numbers of patients and long duration studies to achieve sufficient power. Similarly, plain radiographs fail to detect early changes, although reflect relatively well the gross anatomical abnormalities of end-stage disease. With regard to the second criterion (applicability across the age range), infant lung function is being pioneered by an increasing number of

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dedicated laboratories although reproducible measurements in the preschool years—possibly a key window for monitoring and intervention—are more difficult to obtain. Finally, with regard to the third criterion, one of the benefits of conventional spirometry is repeatability, in contrast to other assays such as CT scans or invasive bronchoscopic measurements which may be more sensitive but pose other problems. To date, no other measure of pulmonary function has been as readily repeatable as spirometry.

The paper by Gustafsson and colleagues in this issue of *Thorax*[5] (***see page 129***) highlights a potential clinical measurement of CF airway involvement that may fulfil all the criteria described above. Lung clearance index (LCI) measured by multiple breath washout is a sensitive measure of ventilation inhomogeneity. Whereas $FEV_1$ in health and early disease mostly reflects proximal airways, LCI is considered to reflect abnormalities of the smaller airways which are considered the site of early lung injury in CF. LCI will be increased in the presence of airway narrowing caused by either inflammation or mucus plugging. It has previously been described as being more sensitive than spirometry in the early stages of CF lung disease.[6] It reflects disease progression, correlating well with $FEV_1$, although it is abnormal at an earlier stage in the disease. The technique is harmless, easy for patients to perform and reproducible, even in infants[7] and small children.[8] Being non-invasive, it is repeatable on multiple occasions, increasing its longitudinal applicability.

In their paper Gustafsson *et al*[5] provide an important bridge between structural and physiological measures of pulmonary injury, comparing high-resolution CT (HRCT) scanning with both LCI and conventional spirometric measurements. HRCT provides a detailed structural overview of the CF lung and airways. Abnormalities such as mucus plugging, airway wall thickening, air trapping, consolidation and bronchiectasis can be clearly visualised and sensitive scoring systems have been developed and validated. However, the radiation burden inherent in this investigation, albeit with new scanners and protocols, means that even clinics advocating this as a routine clinical test do not perform scans more than once every 2 or 3 years. In this study, involving cross-sectional data from children and young adults aged 5–19 years, there was no significant agreement between abnormalities in $FEV_1$ (predicted mean −1.96 SD) and the presence on the HRCT scan of bronchiectasis, significant (>30%) air trapping or overall CT severity score. Maximal expiratory flow when 75% of forced vital capacity was expired ($FEF_{75}$), considered to be a better reflection of small airways disease, did perform rather better. However, LCI correlated best with all CT parameters measured and possessed the greatest sensitivity for detecting structural CT abnormalities. A normal LCI almost ruled out the presence of CT abnormalities, although LCI was abnormal in some patients with a normal HRCT scan. However, as the authors themselves highlight, their HRCT protocol was designed specifically to limit the dose of radiation and this compromise may have reduced its sensitivity for early changes. Alternatively, LCI may genuinely detect milder lung disease than is possible with HRCT scanning.

Studies reporting LCI in CF are few, in part because of the complex and expensive mass spectrometer-based technology used by most groups. Cross-sectional studies have demonstrated abnormal LCI values in both children[8] and adults[9] with CF, and longitudinal studies have suggested that it may be a sensitive technique to track the decline in pulmonary status and the detrimental effects of bacterial infection.[10] Newer technologies are becoming available, such as ultrasonic devices[11] and miniature highly sensitive gas analysers using the photoacoustic principle,[9] which may increase the ease with which these measurements can be obtained. As the authors discuss, what is needed now is further well-designed longitudinal studies assessing the ability of techniques such as LCI to reflect both the natural history of CF and responses to interventions. We need to better understand the relationship over time between LCI and symptoms, acquisition and eradication of infection, markers of inflammation, structural abnormalities and other physiological tests. We need to establish whether LCI can be useful across the spectrum of severity of CF or whether certain subgroups—such as those with the earliest stages of lung disease—are those for whom this technique shows most promise. Such data will help us to understand whether LCI can be used in routine clinical monitoring and as a valid clinical surrogate for responses to therapeutic interventions in clinical trials.

The UK Cystic Fibrosis Gene Therapy Consortium[12] is working towards a multidose clinical trial of *CFTR* gene therapy designed to demonstrate whether this intervention can lead to clinical benefit. Both the trial and a preceding non-interventional period of longitudinal data collection will incorporate serial LCI measurements as, for the reasons outlined above, we consider that many conventional outcome measures will be insufficiently sensitive to be useful in this context. The study reported by Gustafsson and colleagues adds to the body of accumulating evidence that measurement of LCI may represent a significant improvement in our ability to monitor distal small airways disease sensitively, safely and non-invasively.

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