complete observation, analysis, and interpretation. They acknowledge that while some studies have shown that a shorter regimen may be effective, the evidence is not yet conclusive and that further research is needed. They also raise concerns about patient adherence and the potential for drug resistance to develop.

One of the key issues highlighted is the possibility of inadvertent treatment of LTBI, which could be a less expensive and more effective tool against tuberculosis. They support the ongoing clinical trial and call for a conclusive demonstration of the effectiveness of these regimens.

Competing interests: None.

Contributors: Both authors drafted the article and take full responsibility for its content.

Better lungs for better legs: novel bronchodilator effects in COPD

Peter Calverley

Limitation of exercise capacity plays a central role in the life of the patient with chronic obstructive pulmonary disease (COPD), both as a marker of well-being and as an indicator of a poor prognosis. Our ability to characterise this crucial aspect of disease has grown rapidly in the last decade and with this so has our understanding of the many complex reasons for exercise impairment. It has long been recognised that the maximum ventilation during exercise is related to the initial FEV₁ (forced expiratory volume in 1 s), with several formulae being developed to predict this. It was accepted that an inability to sustain a high level of ventilation would limit exercise performance in COPD, although exactly why this happened was uncertain. In the last decade there has been compelling evidence that changes in the operating lung volumes during exercise lead to mechanical limitation of inspiration and hence of tidal volume, which is associated with the sensation of breathlessness.

Dynamic hyperinflation is a very consistent finding in COPD and can even occur early in the natural history of COPD, at least in symptomatic people. However, not all patients are limited exclusively by breathlessness on exertion, and data from the McMaster group in the 1990s pointed out that many patients were limited by a feeling of heaviness or fatigue in their legs, either along with breathlessness or dominating this sensation. As a result, attention

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began to turn to other factors, such as co-morbid cardiac disease and the possibility that skeletal muscle itself was not normal in COPD.7

One way of exploring the impact of lung disease on exercise performance is to study people before and after treatments designed to improve lung mechanics in some way. Bronchodilators improve operating lung volumes in subjects at rest and have been shown to increase exercise performance measured in a variety of ways in COPD. In a series of studies, Professor O’Donnell has shown that bronchodilators, both anticholinergics and β-agonists, improve exercise capacity and that this is best related to falls in the end-expiratory lung volume—that is, an increase in inspiratory capacity at rest and during exercise.8–10 Not all people benefit from this treatment, and we have previously described paradoxical responses where lung function appears to improve at rest but the response of the patient is abnormal and exercise tolerance worsens.11 How widespread such effects are has not been documented so far. Other groups found that bronchodilators were less effective when patients’ exercise performance was limited by the development of quadiceps muscle fatigue.12 These studies, and many others, have contributed to an active debate about the mechanisms limiting exercise performance in COPD which has recently been summarised.13

One important issue is the potential interaction between the effort made during respiration in patients with COPD and the cardiac output. Patients with COPD develop marked intrathoracic pressure swings which relate to some degree to the extent of abdominal muscle activation at rest and during exercise.14 There are now data suggesting that patients who show paradoxical movement of the lower ribcage are more likely to develop breathlessness on exercise, while those without this feature are limited when they exercise, and recognise that developing tiredness in the legs is a direct effect of lung disease on their cardiac output and peripheral muscle oxygenation. Despite these issues the data here represent a considerable technical achievement and point to a clinically relevant effect of bronchodilators on tissue oxygen delivery as well as lung function. How important these effects are in the overall limitation of exercise performance and why oxygen delivery is limited will be debated, although a direct effect of hyperinflation on cardiac function output seems increasingly likely. Whatever the mechanisms are, these data have implications for the way we view the symptomatic treatment in COPD. The effects of bronchodilators on cardiac function represent an additional potentially beneficial effect which could explain why in some circumstances, far from increasing cardiac mortality, use of long-acting inhaled bronchodilators is associated with a lower cardiac event rate.21 It is also relevant to ask our patients why they are limited when they exercise, and recognise that developing tiredness in the legs is not just a sign of being unfit but may be a direct effect of lung disease on their muscle function. We should no longer be surprised when they tell us their legs are less tired after taking their inhalers because, as usual, the patient has got it right before the doctor can explain why this happens.

Competing interests None.

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REFERENCES
Diagnosing cystic fibrosis in patients with non-diagnostic results: the case for intestinal current measurements

J P Clancy

Cystic fibrosis (CF) is a well-described genetic disease with characteristic defects in ion transport in disease-affected tissues. CF results from dysfunction of the cystic fibrosis transmembrane conductance regulator protein (CFTR) which is an ATP binding cassette protein that, in addition to chloride channel function, regulates other ion transport pathways such as sodium channels, other chloride channels and bicarbonate transport.1 Diagnosis of CF is generally straightforward in patients with classic disease and builds upon these basic ion transport features, with well-defined clinical manifestations combined with elevated sweat chloride values, nasal ion transport abnormalities and/or common CFTR mutations.2 Newborn screening algorithms have added elevated serum immunoreactive trypsinogen levels to the diagnostic pathway (typically prior to symptoms), and together allow healthcare providers to confidently provide diagnostic and prognostic information to the majority of families and patients with CF.3

Unfortunately, there is a spectrum of disorders that have been linked to CFTR dysfunction which may not fulfil the diagnostic criteria for CF. In general, these milder manifestations of CFTR dysfunction can present in numerous ways such as recurrent upper and lower airway respiratory symptoms, pancreatic disease, male infertility, liver disease and vague gastrointestinal symptoms.4–5 Standard CF diagnostic testing may provide information that is conflicting or sits squarely in the ‘grey zone’, with intermediate sweat chloride values (above the normal range but below the CF diagnostic cutoff), nasal potential difference measurements with both CF and non-CF features, inconclusive genetic testing and additional (less specific) clinical measurements that may support a CF diagnosis but are not able to define the disease (such as abnormal stool elastase measurements, intermittent detection of CF respiratory pathogens or evidence of obstructive airway disease but without clearcut bronchiectasis). These patients are difficult to counsel and care for, as the absence of a clear diagnosis can undermine adherence to treatments and long-term prognostic information is insufficient. Carrying an erroneous CF diagnosis can have detrimental emotional, financial and quality of life implications for the patient and family, while failing to secure a diagnosis of CF puts patients at risk of permanent organ damage and premature death. Thus, for these diagnostic dilemmas, there remains a need to isolate and define CFTR function (or dysfunction) in patient-derived tissue. All available clinical tests of CFTR function are performed in vivo, which limits the available reagents and assays to those that can be performed safely in patients.

In this issue of Thorax, Derichs and colleagues6 describe the use of intestinal current measurements (ICM) to diagnose CF, examining this assay in subjects with classic pancreatic-insufficient CF, pancreatic-sufficient CF, non-CF participants and

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