completion rates), it could potentially be cost-effective or even cost-saving in the long run despite higher short-term treatment costs. Unfortunately, such benefits are difficult to estimate at the present time given the uncertainties surrounding the efficacy of rifampin. Aspler *et al* address this issue by assuming that 4 months of treatment with rifampin reduced the risk of active disease by at least 60%, approximately the same as 3 months of rifampin. While this minimum value seems reasonable, the requirement for wide variations in their estimate underscores the need for additional data on rifampin monotherapy.

While unknown efficacy has been an issue, the major concern about use of rifampin for LTBI treatment has been the possibility of inadvertent treatment of active tuberculosis with rifampin monotherapy which would lead to acquired rifampin monoresistance. Rifampin is a vital drug for tuberculosis treatment and, while patients infected with isoniazid-monoresistant isolates can often be successfully treated with 6 months of therapy, patients infected with rifampin-monoresistant isolates usually require 12–18 months of treatment. To date, there has been a single case report of rifampin resistance apparently developing de novo on treatment for LTBI.[8] Nonadherence and poor absorption (due to vomiting) probably played a role in this case and no further cases have been reported in subsequent trials, so the real risk of rifampin resistance developing on therapy may be quite small. Nonetheless, thorough standardised evaluation for active tuberculosis prior to initiation of LTBI treatment and close observation while on treatment will be an essential component of any tuberculosis control programme that initiates large-scale rollout of the 4-month rifampin regimen. Any potential cost savings of this regimen would be quickly offset by the cost of the lengthy treatment for rifampin-monoresistant disease. Furthermore, the pharmacokinetic interactions between rifampin and a number of other medications (which generally are not a significant issue with isoniazid) also pose a challenge to wide-scale implementation of this regimen. In particular, the use of rifampin for LTBI treatment will be limited in patients infected with HIV due to significant drug–drug interactions between rifampin and several classes of antiretroviral drugs.[9]

Regardless of these concerns, shorter better-tolerated regimens with higher completion rates in high-risk populations are needed to make progress towards tuberculosis elimination in the developed world. Given funding constraints for tuberculosis control, the cost-effectiveness of these regimens is of paramount importance to make them viable for public health practice. The study by Aspler *et al* is an important addition to the evidence that the 4-month rifampin regimen may be a less expensive and more effective tool in the fight against tuberculosis. We look forward to a conclusive demonstration of the effectiveness of the regimen in the authors' ongoing clinical trial.

Competing interests None.

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

Provenance and peer review Commissioned; not externally peer reviewed.

Thorax 2010;**65**:572–573.
doi:10.1136/thx.2010.138685

REFERENCES

1. **Sterling TR,** Bethel J, Goldberg S, *et al*. The scope and impact of treatment of latent tuberculosis infection in the United States and Canada. *Am J Respir Crit Care Med* 2006;**173**:927–31.
2. **Horsburgh CR Jr,** Goldberg S, Bethel J, *et al*. Latent TB infection treatment acceptance and completion in the United States and Canada. *Chest* 2010;**137**:401–9.
3. **Aspler A,** Long R, Trajman A, *et al*. Impact of treatment completion, intolerance and adverse events on health system costs in a randomised trial of 4 months rifampin or 9 months isoniazid for latent TB. *Thorax* 2010;**65**:582–7.
4. **Anon.** Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. *MMWR Recomm Rep* 2000;**49**:1–51.
5. **Ziakas PD,** Mylonakis E. 4 months of rifampin compared with 9 months of isoniazid for the management of latent tuberculosis infection: a meta-analysis and cost-effectiveness study that focuses on compliance and liver toxicity. *Clin Infect Dis* 2009;**49**:1883–9.
6. **Holland DP,** Sanders GD, Hamilton CD, *et al*. Costs and cost-effectiveness of four treatment regimens for latent tuberculosis infection. *Am J Respir Crit Care Med* 2009;**179**:1055–60.
7. **Young H,** Wessolossky M, Ellis J, *et al*. A retrospective evaluation of completion rates, total cost, and adverse effects for treatment of latent tuberculosis infection in a public health clinic in central Massachusetts. *Clin Infect Dis* 2009;**49**:424–7.
8. **Livengood JR,** Sigler TG, Foster LR, *et al*. Isoniazid-resistant tuberculosis. A community outbreak and report of a rifampin prophylaxis failure. *JAMA* 1985;**253**:2847–9.
9. **Maartens G,** Decloedt E, Cohen K. Effectiveness and safety of antiretrovirals with rifampicin: crucial issues for high-burden countries. *Antivir Ther* 2009;**14**:1039–43.

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[1] and as an indicator of a poor prognosis.[2] 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 FEV_1 (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.[3 4] 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.[5] 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.[6] As a result, attention

Correspondence to Peter Calverley, Unit of Inflammation Research, Clinical Sciences Centre, University Hospital Aintree, Lower Lane, Liverpool L9 7AL, UK; pmacal@liverpool.ac.uk

began to turn to other factors, such as comorbid 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 quadriceps 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 show a different pattern of chest wall hyperinflation and may be limited by leg fatigue.[15] Thus the behaviour of the respiratory muscles and hence the intrathoracic pressures may be relevant to exercise performance. Direct measurements of cardiac output and peripheral muscle performance are inevitably difficult in these circumstances. The group from Brazil who report new findings in this issue of *Thorax* (***see page 588***)[16] have previously established that there is a mismatch between oxygen uptake in the body in general and the rate at which oxygen in consumed within exercising skeletal muscle.[17] Moreover, when subjects were breathing heliox, a gas mixture which reduces the mechanical work of breathing and also improves exercise performance in COPD,[18] then the matching of oxygen delivery and oxygen uptake to the leg muscles of the patient with COPD was improved.[19] Similar findings were seen when patients exercised while using proportional assist ventilation to decrease respiratory muscle work.[20] Now Berton and colleagues have extended these observations to the clinically more relevant area of bronchodilator treatment.

They studied 12 patients with severe COPD (FEV_1 38.5% predicted) without resting arterial hypoxaemia in a series of constant work-rate cycle ergometer exercise tests conducted at 70–80% of a previously determined peak exercise performance. They did so before and after the patients had received the combination of ipratropium bromide and salbutamol by inhalation or an identical placebo. Their main outcomes were the speed with which whole body oxygen uptake changed during exercise and how this related to the change in oxygenation within the vastus lateralis muscle using near-infrared spectroscopy and in cardiac output measured by impedance cardiography. This comprehensive analysis allowed them to look at metabolic and cardiac output changes during exercise in COPD as well as the kinetics of peripheral muscle de-oxygenation. These complex studies produced some interesting results. As expected, the bronchodilators increased the exercise endurance time in constant work-rate exercise by almost 40% of the baseline performance, and the authors showed that there was less dynamic hyperinflation which they measured by the change in inspiratory capacity during exercise. The bronchodilators produced small but statistically significant improvements in both FEV_1 and resting inspiratory capacity (130 and 390 ml, respectively), although only 7 of the 12 subjects would have met the conventional criteria for bronchodilator responsiveness. When the bronchodilators were administered there was an improvement in the speed with which the oxygen uptake and cardiac output reached the steady state, and there was a slowing of the desaturation which occurred in the exercising muscle measured as a change in the ratio of deoxygenated haemoglobin to myoglobin. Mismatch between delivery and oxygen consumption was improved by the bronchodilator drugs, and the greatest improvements in cardiac output kinetics were seen in the patients who showed the biggest reduction in dynamic hyperinflation postbronchodilator.

These elegant physiological studies have applied new methodologies which directly measure key variables that determine exercise performance in COPD. Inevitably the number of participants is small and the data apply to those with relatively severe disease. There is continuing controversy about the use of impedance cardiography to monitor cardiac output in patients with hyperinflated lungs, although the group from Sao Paulo have provided further evidence for its appropriateness in these studies. In practical terms, more direct and invasive methods of measuring cardiac output would pose formidable challenges even for determined investigators and patient volunteers, although data such as these may emerge in due course. Similarly, there has been some uncertainty about exactly what near-infrared spectroscopy is recording and how representative it is of overall 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.

Provenance and peer review Commissioned; not externally peer reviewed.

Thorax 2010;**65**:573–575.
doi:10.1136/thx.2010.135129

REFERENCES

1. **Jones PW.** Health status measurement in chronic obstructive pulmonary disease. *Thorax* 2001;**56**:880–7.

2. **Oga T,** Nishimura K, Tsukino M, *et al*. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med* 2003;**167**:544–9.
3. **O'Donnell DE,** Bertley JC, Chau LK, *et al*. Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms. *Am J Respir Crit Care Med* 1997;**155**:109–15.
4. **O'Donnell DE,** Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**164**:770–7.
5. **O'Donnell DE,** Laveneziana P, Ora J, *et al*. Evaluation of acute bronchodilator reversibility in patients with symptoms of GOLD stage I COPD. *Thorax* 2009;**64**:216–23.
6. **Killian KJ,** LeBlanc P, Martin DH, *et al*. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *Am Rev Respir Dis* 1992;**146**:935–40.
7. **Agusti AG,** Noguera A, Sauleda J, *et al*. Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J* 2003;**21**:347–60.
8. **O'Donnell DE,** Voduc N, Fitzpatrick M, *et al*. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. *Eur Respir J* 2004;**24**:86–94.
9. **O'Donnell DE,** Fluge T, Gerken F, *et al*. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;**23**:832–40.
10. **O'Donnell DE,** Sciurba F, Celli B, *et al*. Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. *Chest* 2006;**130**:647–56.
11. **Aliverti A,** Rodger K, Dellaca RL, *et al*. Effect of salbutamol on lung function and chest wall volumes at rest and during exercise in COPD. *Thorax* 2005;**60**:916–24.
12. **Pepin V,** Brodeur J, Lacasse Y, *et al*. Six-minute walking versus shuttle walking: responsiveness to bronchodilation in chronic obstructive pulmonary disease. *Thorax* 2007;**62**:291–8.
13. **Aliverti AP,** Macklem PT, Debigare R, *et al*. Point: counterpoint—the major limitations to exercise performance in COPD. *J Appl Physiol* 2008;**105**:749–51.
14. **Aliverti A,** Stevenson N, Dellaca RL, *et al*. Regional chest wall volumes during exercise in chronic obstructive pulmonary disease. *Thorax* 2004;**59**:210–16.
15. **Aliverti A,** Quaranta M, Chakrabarti B, *et al*. Paradoxical movement of the lower ribcage at rest and during exercise in COPD patients. *Eur Respir J* 2009;**33**:49–60.
16. **Berton D,** Barbosa P, Takara L, *et al*. Bronchodilators accelerate the dynamics of muscle O2 delivery and utilisation during exercise in COPD. *Thorax* 2010;**65**:588–93.
17. **Chiappa GR,** Borghi-Silva A, Ferreira LF, *et al*. Kinetics of muscle deoxygenation are accelerated at the onset of heavy-intensity exercise in patients with COPD: relationship to central cardiovascular dynamics. *J Appl Physiol* 2008; **104**:1341–50.
18. **Laude EA,** Duffy NC, Baveystock C, *et al*. The effect of helium and oxygen on exercise performance in COPD: a randomised crossover trial. *Am J Respir Crit Care Med* 2006;**173**: 865–70.
19. **Chiappa GR,** Queiroga F Jr, Meda E, *et al*. Heliox improves oxygen delivery and utilization during dynamic exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;**179**:1004–10.
20. **Borghi-Silva A,** Oliveira CC, Carrascosa C, *et al*. Respiratory muscle unloading improves leg muscle oxygenation during exercise in patients with COPD. *Thorax* 2008;**63**:910–15.
21. **Calverley PM,** Anderson JA, Celli B, *et al*. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;**356**:775–89.

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] Diagnosing 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.[3–5] 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 cut-off), 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 bronchiectiasis). 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 colleagues[6] 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

Correspondence to J P Clancy, Department of Pediatrics, University of Alabama at Birmingham and the Children's Hospital of Alabama, 620 ACC, 1600 7th Ave South, Birmingham, AL 35233, USA; jpclancy@peds.uab.edu