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

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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

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patients presenting with an unclear CF diagnosis (***see page 594***). The use of biopsied tissue from the distal rectum to examine CFTR and supplement CF diagnostic testing has many advantages, including access to high levels of CFTR expression in 'undamaged' epithelia, the ability to isolate CFTR in living (patient-specific) tissue, the use of CFTR reagents ex vivo that are not suitable for in vivo testing, the ability to perform testing in very young patients (even in the newborn period) and the potential to define other features of CFTR expression that may contribute to reduced CFTR function (such as quantification of mRNA and protein levels and CFTR maturation). The authors' institution serves as a centralised referral area for evaluation of patients with an unclear diagnosis, allowing for the development of standardised testing methodology and diagnostic criteria.

So how is ICM performed? Tiny bits of rectal epithelia (typically 2–3 mm in diameter) are obtained via suction biopsy apparatus from the rectal vault (~5 cm from the anal verge). This biopsy procedure is a commonly used method to evaluate gastrointestinal pathology in the neonatal period (such as obtaining tissue to diagnose Hirschsprung's disease). The procedure, while perhaps a bit uncomfortable (as one might expect from a rectal examination), does not produce biopsy-related pain as the rectal tissue is devoid of pain fibres. Obtaining tissue is rapid (<5 min) and typically does not require sedation. The rectal tissues are mounted in Ussing chambers (which allow measurement of ion conductance in the still living tissue) and are then exposed to a series of stimuli and blockers that isolate and quantify CFTR activity. The procedure is not completely devoid of risk as suction biopsies are performed in a blinded fashion and could in theory produce bleeding or perforation in diseased tissue but, in appropriate patients, experienced hands and in appropriate medical facilities, it can be done with very low risk to the patient. The procedure has been used in European CF care and research centres for nearly 20 years, and over this time some differences have arisen in technique and assay performance that are site-specific. That being said, the general technique has been shown clearly to discriminate between CF and non-CF patients and demonstrates a clear relationship between measured CFTR function and predicted CFTR activity (based on mechanistic understanding of disease-causing mutations).[7 8]

Derichs and colleagues used this technique to define rectal ion transport features in pancreatic-insufficient CF ('severe' CF), pancreatic-sufficient CF ('milder' CF) and non-CF subjects, determining what aspects of ICM segregate these known patient populations with varying amounts of CFTR activity. The data were accumulated over approximately 10 years at their referral centre and were coupled with extensive genetic and sweat chloride information. Their results show that they were able to define CFTR functional ranges (based on stimulation with cAMP agonists, carbachol and histamine) that segregate the known CF from the non-CF groups, and that applying these CF diagnostic ICM criteria to the large group of 'unclear' patients (n=61) helped to classify ~10% in the CF range and 90% out of the CF range. They also demonstrated moderate correlations of ICM values with sweat chloride values in the CF groups, providing further validation of the assay for CF diagnostic testing. While there are some limitations to the study, such as relatively small numbers of pancreatic-sufficient CF patients in the sample, a continuing subpopulation of subjects with borderline sweat and/or ICM data and lack of long-term follow-up clinical information, the study is an important step in defining the utility of ICM in the diagnostic algorithm for challenging 'CF-like' cases. It does confirm that the assay can isolate CFTR function for use in CF diagnostic testing, and it opens the door to use exciting new CFTR modulators to better define CF disease in a patient-specific 'personalised medicine' fashion.

While ICM is likely to remain a research tool and a diagnostic assay in a limited number of CF care and research centres (due to the technical expertise needed to work with these small pieces of tissue, the limited timeframe of tissue viability and the specialised equipment needed for ICM), its role in defining CFTR-related disease should continue to grow. We as a research community need to continue to work towards common ICM methodology across centres (allowing us 'to compare apples with apples') and to collect clinical data in these borderline patients with specialised functional testing of CFTR to define how ICM results (or other specialised tests such as nasal potential difference) change over time and whether they predict long-term clinical outcomes. We also need to think about CFTR gastrointestinal outcome measures as novel biomarkers, with potential utility in the therapeutic development of future CFTR modulators.[9] ICM can be of clear clinical benefit today and has the potential to help shape CF care tomorrow.

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REFERENCES

1. **Rowe SM,** Miller S, Sorscher EJ. Cystic fibrosis. *N Engl J Med* 2005;**352**:1992–2001.
2. **Farrell PM,** Rosenstein BJ, White TB, *et al*. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr* 2008;**153**:S4–14.
3. **Borowitz D,** Parad RB, Sharp JK, *et al*. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. *J Pediatr* 2009;**155**(6 Suppl): S106–16.
4. **Wilschanski M,** Dupuis A, Ellis L, *et al*. Mutations in the cystic fibrosis transmembrane regulator gene and in vivo transepithelial potentials. *Am J Respir Crit Care Med* 2006;**174**:787–94.
5. **De Boeck K,** Wilschanski M, Castellani C, *et al*. Cystic fibrosis: terminology and diagnostic algorithms. *Thorax* 2006;**61**:627–35.
6. **Derichs N,** Sanz J, Von Kanel T. Intestinal current measurement for diagnostic classification of patients with questionable cystic fibrosis: validation and reference data. *Thorax* 2010;**65**:594–9.
7. **Mall M,** Hirtz S, Gonska T, Kunzelmann K. Assessment of CFTR function in rectal biopsies for the diagnosis of cystic fibrosis. *J Cyst Fibros* 2004;**3**(Suppl 2):165–9.
8. **Mall M,** Kreda SM, Mengos A, *et al*. The deltaF508 mutation results in loss of CFTR function and mature protein in native human colon. *Gastroenterology* 2004;**126**:32–41.
9. **Van Goor F,** Hadida S, Grootenhuis PD, *et al*. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. *Proc Natl Acad Sci U S A* 2009;**106**:18825–30.