

# PostScript

## LETTERS

### Sweat testing in CF

The European Diagnostic Working Group presented comprehensive diagnostic algorithms for cystic fibrosis (CF) and confirmed the fundamental role of the sweat test for the diagnosis of CF.<sup>1</sup> However, several important differences between well-accepted guidelines for sweat testing<sup>2,3</sup> and the recommendations of the Working Group need to be discussed.

An adequate sweat sampling volume depends on the sampling area and not on the body surface area of the patient.<sup>2,3</sup> The unit therefore has to be cited as "g/m<sup>2</sup> sampling surface area/min sweat sampling time"<sup>2,3</sup> instead of "g/m<sup>2</sup> body surface area/min".<sup>1</sup>

For stimulation and sampling of sweat the authors recommend only the Gibson and Cooke technique and do not even mention the widely used Macroduct collection method which is well accepted by the National Committee for Clinical Laboratory Standards (NCCLS) and UK guidelines.<sup>2,3</sup> The authors do not give any reason for this limitation. Mastella *et al*<sup>4</sup> have shown an acceptable agreement between both collection systems with a mean (SD) difference for chloride of 1.205 (6.47) mmol/l,<sup>4</sup> comparable to Denning's results which showed a mean (SD) difference between sequential Gibson-Cooke tests of -0.05 (8.6) mmol/l.<sup>5</sup> Different failure rates, especially in patients under 4 months of age, should not be misused to condemn the Macroduct collection system<sup>4</sup> because this problem can be overcome by experience.

The most important difference is the extension of the intermediate sweat chloride range up to 30-60 mmol/l from 40-60 mmol/l. This recommendation is based on the work of Lebecque and co-workers<sup>6</sup> who investigated patients with sweat chloride levels of 30-60 mmol/l by extensive genetic testing and nasal potential difference measurements. Adults accounted for 30% of all patients with intermediate sweat chloride levels but were excluded from the analysis. Lebecque *et al* presented 10 children with intermediate sweat chloride levels and a diagnosis of CF. However, only 2 of the 10 patients (sweat chloride levels of 34 and 45 mmol/l) fulfilled the clinical criteria and laboratory evidence of CFTR dysfunction, according to the diagnostic criteria of the Cystic Fibrosis Consensus Panel.<sup>7</sup> The other 8 patients had no clinical features of CF and/or no laboratory evidence of CFTR dysfunction in accordance with the diagnostic criteria of the Cystic Fibrosis Consensus Panel.<sup>7</sup> As shown by Lebecque<sup>6</sup> and Denning,<sup>5</sup> the extension of the intermediate range can more than double the number of patients who will need further diagnostic investigations. Before such a far-reaching recommendation of the expansion of the intermediate chloride range is implemented in daily routine, prospective (not only retrospective) studies are urgently needed to define the specificity and sensitivity of this modification. As we all know, even a chloride level of <30 mmol/l cannot exclude the diagnosis of CF.

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### Previously undiagnosed obesity hypoventilation syndrome

There are approximately 300 million obese individuals (body mass index (BMI) 30 kg/m<sup>2</sup> or higher) worldwide,<sup>1</sup> and in the UK nearly one quarter of all adults are classified as clinically obese.<sup>2</sup> Obesity hypoventilation syndrome (OHS) describes a subgroup of obese individuals who develop chronic daytime hypercapnia (arterial carbon dioxide tension (Paco<sub>2</sub>) >6 kPa) and hypoxia (arterial oxygen tension (PaO<sub>2</sub>) <8 kPa) in the absence of chronic obstructive pulmonary disease (COPD).<sup>3,4</sup> Presentation is usually indolent, with symptoms arising due to hypercapnia and sustained hypoventilation (hypersomnolence, alterations in cognitive function, headache, peripheral oedema, hypertension, congestive cardiac failure).<sup>5</sup> At Southend Hospital we have noticed an increase in acute admissions in obese individuals with type II respiratory failure of initially unknown cause in whom a diagnosis of OHS was eventually made.

We collected data on 11 patients (seven men) diagnosed with OHS from 1996 to 2005 from the respiratory disease register. Patients with possible overlap syndrome were excluded (smokers with forced expiratory volume in 1 s/forced vital capacity (FEV<sub>1</sub>/FVC) ratio <70%). Patient demographics, lung function and Epworth sleep score (ESS) were documented. The results of initial sleep studies on air were analysed. Initial management was recorded and follow-up data were reviewed regarding ESS, blood gases, long-term use of continuous

positive airway pressure (CPAP) or non-invasive ventilation (NIV, using bi-level pressure support ventilation).

The mean (SD) age of the 11 patients was 59 (12) years and the mean (SD) BMI was 52.7 (16.6) kg/m<sup>2</sup> (range 37-102). Two patients were current smokers, one an ex-smoker and eight were never smokers. Seven patients were hypertensive, three were known to have hypothyroidism (two on treatment) and two had asthma. Only two cases presented before 2002 and nine after 2002. Eight presented to the A&E with type II respiratory failure of unknown cause, with a mean (SD) pH of 7.25 (0.15), mean PaO<sub>2</sub> 11.6 (4.0) kPa and mean (SD) HCO<sub>3</sub><sup>-</sup> 34.9 mmol/l (4.5). Three patients presented to respiratory outpatients.

All patients had increasing shortness of breath; in two the breathlessness was gradual (over 4-6 months), in six cases the breathlessness was only present in the preceding 3-4 weeks, and in three the symptoms were acute, starting only days before admission. These three patients also had evidence of a respiratory infection. All patients had a normal chest radiograph on admission. None of the patients had a diagnosis of OHS made until reviewed by a respiratory physician.

Sleep studies showed a mean (SD) apnoea/hypopnoea index score of 33 (22)/h and oxygen desaturations 39 (37)/h. The range of the mean nocturnal oxygen saturation was 66-89.9%. The mean ESS was 15 on presentation (range 5-22), mean (SD) FEV<sub>1</sub> was 1.53 (0.52) l and mean (SD) FEV<sub>1</sub>/FVC ratio was 77 (6)%. In the eight patients presenting to A&E, six required NIV, one CPAP and one did not require intervention acutely. One patient has required treatment with NIV long-term and eight others were managed on CPAP. One patient died due to non-compliance with treatment. One has improved with weight loss alone. Only the patient with asthma has subsequently decompensated and developed acute type II respiratory failure.

At follow up the mean ESS was 3 (range 0-10). Blood gases on air had improved with a mean (SD) pH of 7.46 (0.10), mean (SD) Paco<sub>2</sub> 5.94 (1.15) kPa, mean PaO<sub>2</sub> 8.59 (1.38) kPa, and mean HCO<sub>3</sub><sup>-</sup> 28.6 (4.1).

Decompensated OHS is often not recognised in A&E. In our study a diagnosis of OHS as the cause of respiratory failure was not appreciated until referral to a respiratory physician had been made. The presentation of OHS is very non-specific, but should be considered in obese patients who have increasing shortness of breath, have never smoked, and have type II respiratory failure and a normal chest radiograph.

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### Authors' reply

We thank Dr Naehrlich for commenting on the Cystic Fibrosis Diagnostic Network consensus.<sup>1</sup> The first comment is correct. Adequacy of sweat collection is dealt with clearly in the guidance for performing sweat tests for investigating cystic fibrosis (CF) in the UK. The Multidisciplinary Working Group gives calculations for assessing the adequacy of collection (<http://www.acb.org.uk>). A minimum sweat rate of 1 g/m<sup>2</sup>/min is required. This does indeed relate to the sampling surface and an error occurred in the published paper.

With regard to the method of sampling, the members of the Diagnostic Network Group did discuss this in detail. There is increasing evidence that the Macroduct system gives an acceptable collection, but direct comparison with the method of Gibson and Cooke shows that an inadequate sweat collection is more likely with the Macroduct system (6.1% vs 0.7%). Also, where the Macroduct collection is linked to analysis using conductivity (which measures total ionic concentration rather than chloride), there is a higher rate of false positivity (results falling within the borderline range) than with the traditional Gibson and Cooke method, and this is a particular concern when investigating non-classic disease. However, there is no increased likelihood of false negative results with the Macroduct technique.

In the UK even laboratories currently using the Macroduct system continue to analyse chloride conductivity to comply with the National Quality Control regulations. Two large studies using capillary collections linked with

conductivity showed good correlation between this methodology and iontophoresis with determination of chloride concentration.<sup>2</sup> However, the technique has not been examined critically in patients with non-classic disease and, because of this and the increased likelihood of obtaining an inadequate sweat collection, the Diagnostic Network Group continues to advocate the Gibson and Cooke method in combination with direct measurements of chloride.

The evidence that a proportion of CF patients with chloride concentrations of 30–60 mmol/l will be found to have two CFTR mutations is recent and has evolved following CFTR mutation testing. These data would not have been available before the development of mutation testing, and this information supersedes previous data on the limits of sweat test chloride concentrations. As shown by Lebecque *et al*,<sup>3</sup> sweat test results between 30 and 60 mmol/l are uncommon—about 4% of more than 2300 sweat tests performed. It is the only paper in which mutation scanning was done using the range 30–60 mmol/l. Indeed, most studies have focused on a chloride range of 40–60 mmol/l and cannot state any conclusion about the range 30–60 mmol/l.<sup>4</sup> But when one reads the papers carefully, it is obvious that others also regularly report and diagnose CF by detection of two CFTR mutations in patients with sweat chloride values below 40 mmol/l.

Josserand *et al*<sup>5</sup> studied 50 men with congenital bilateral absence of the vas deferens. Three of the 11 patients in whom two CFTR mutations were detected had a sweat chloride level below 40 mmol/l. Highsmith *et al*<sup>6</sup> reported a novel mutation in patients with pulmonary disease and “normal” sweat chloride concentrations. Again, 3 of the 13 patients had a sweat chloride level of 30–39 mmol/l and 7 had levels between 40 and 59 mmol/l.

In the UK guidelines on sweat testing, 40 mmol/l is considered as the lower limit but the data supporting this were only graded B evidence level 2b and 3. The majority of the studies referred to in the UK document date from the time before genotype analysis and—as stated in the document—“the normals could include some persons with CF or CF-related

disorders”. Only two papers report CF mutations and sweat chloride levels.<sup>7,8</sup> The study by Farrell and Kosciak<sup>7</sup> only concerns newborns, while the study by the CF Genotype-Phenotype Consortium<sup>8</sup> only explores specific genotypes and does not report values for healthy individuals. Furthermore, we do not state that patients with a sweat chloride level above 30 mmol/l suffer from CF. We simply state that, in symptomatic individuals with a sweat chloride level of, for example, 35 mmol/l, further investigation is warranted.

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