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. However, several important differences between well-accepted guidelines for sweat testing 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. The unit therefore has to be cited as “g/m² sampling surface area/min sweat sampling time” instead of “g/m² body surface area/min.” 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. The authors do not give any reason for this limitation. Mastella et al. have shown an acceptable agreement between both collection systems with a mean (SD) difference of 1.205 (6.47) mmol/l, comparable to Denning's results which showed a mean (SD) difference between sequential Gibson-Cooke tests of 0.05 (8.6) mmol/l. Different failure rates, especially in patients under 4 months of age, should not be misused to condemn the Macroduct collection system 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 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. The other 8 patients had no clinical features of CF and no laboratory evidence of CFTR dysfunction in accordance with the diagnostic criteria of the Cystic Fibrosis Consensus Panel. As shown by Lebecque and Denning, 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.

Previously undiagnosed obesity hypoventilation syndrome

There are approximately 300 million obese individuals (body mass index (BMI) 30 kg/m² or higher) worldwide, and in the UK nearly one quarter of all adults are classified as clinically obese. Obesity hypoventilation syndrome (OHS) describes a subgroup of obese individuals who develop chronic daytime hypercapnia (arterial carbon dioxide tension (PaCO₂) >6 kPa) and hypoxia (arterial oxygen tension (PaO₂) <8 kPa) in the absence of chronic obstructive pulmonary disease (COPD). Presentation is usually indolent, with symptoms arising due to hypercapnia and sustained hypoventilation (hypomnolence, alterations in cognitive function, headache, peripheral oedema, hypertension, congestive cardiac failure). 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 (FEV₁/FVC) ratio <70%, Patient demographics, lung function and Epworth sleep score (ESS) were documented. The results of initial sleep studies on air were reviewed by a respiratory physician. 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) PaCO₂ 5.94 (1.15) kPa, mean PaO₂ 8.59 (1.38) kPa and mean HCO₃⁻ 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 breathlessness, have never smoked, and have type II respiratory failure and a normal chest radiograph.

References

conductivity showed good correlation between this methodology and iontophoresis with determination of chloride concentration. 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., 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. 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. 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. 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. The study by Farrell and Kosicki only concerns newborns, while the study by the CF Genotype-Phenotype Consortium 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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