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Detecting early lung disease in cystic fibrosis: are current techniques sufficient?

P D Sly, S Brennan

Use of the multiple breath inert gas washout technique in the early diagnosis of CF

The philosophy underlying treatment at most cystic fibrosis (CF) clinics is essentially preventative—that is, early detection, treatment and hopefully resolutions of problems before they become major clinical issues. The introduction of newborn screening programmes around the world is also based on the idea that early detection and treatment will result in an improved outcome for patients. Progressive lung disease represents the greatest threat to the health and well being of patients with CF. The goal of treatment is to prevent or delay progressive lung disease, so early detection and monitoring of effective treatments would be expected to improve the health and life expectancy of children with CF.

Lung disease in CF is characterised by a progression from bacterial colonisation to mucosal infection and finally invasive infection. This is accompanied by a host inflammatory response characterised by cytokine secretion and influx of neutrophils. The neutrophils appear to be drawn to the lungs largely by a chemotactic protein, interleukin 8 (IL-8), that is found in increased levels in the sputum and lavage of patients with CF.[1 2] Increased numbers of neutrophils result in increased levels of the products of activated neutrophils such as neutrophil elastase (NE). Unbound NE is thought to be responsible for much of the lung damage seen in CF.[3] Breakdown products of elastin found in the urine of patients with CF are thought to originate in the lung,[3] indicating that lung destruction is occurring.

Recent studies provide strong evidence that lung disease begins during early life in most children with CF. Bronchoalveolar lavage (BAL) performed in infants and young children with CF shows evidence of inflammation and infection early in life, even in children who are asymptomatic at the time.[4 5] A significant proportion of children diagnosed by newborn screening have been shown to have inflammation and infection, including *Pseudomonas aeruginosa*, before the onset of any respiratory symptoms.[6] Armstrong *et al* also showed that much of this inflammation could be reduced by antibiotic treatment.[1] These data demonstrate the usefulness of BAL for monitoring patients in the long term and for tailoring treatments to individual patients. However, BAL is invasive, requires general anaesthesia in young children, and cannot be repeated frequently. In addition, the presence of inflammation on BAL may not equate directly to progressive lung disease.

Lung imaging with high resolution computed tomography (HRCT) in children with CF shows that irreversible structural changes can occur long before reliable measurements of lung function can be obtained using conventional techniques at around school age.[7 8] In older children changes on the HRCT scan are more sensitive than changes in pulmonary function.[7 9 10] The use of HRCT in conjunction with lung function has been proposed as a sensitive marker of treatment outcomes.[11] However to have an impact on preventing or delaying progressive lung disease, these assessments must be done before lung disease has become irreversible. No studies to date have investigated the relationships between structural changes (especially in the lower lobes) and inflammatory markers in the initiating stages of lung disease. Likewise, no data have been published investigating the relationships between early structural and physiological changes, despite the fact that abnormal lung function has been demonstrated in infants and preschool children.[12–14]

Lung function measured by standard spirometry in school age children with CF is insensitive to structural damage seen on HRCT scanning. Many children with clinically apparent lung disease (for example, daily cough with sputum production) have normal spirometric indices due to a lack of sensitivity of standard spirometric tests. Reliable measurements of lung function are now available for infants and preschool children. Careful measurements of pulmonary function in infants and young children with CF show detectable abnormalities early in the clinical course.[12 13 15–17] Two recent studies have compared inflammatory indices with lung function measures taken concurrently.[16 17] Nixon *et al* demonstrated lower lung function—as measured by raised volume rapid thoracoabdominal compression—in those with clinically apparent lung disease.[17] In this study lung function did not appear to be related to inflammation per se. In contrast, Dakin *et al*[16] identified significant relationships between specific respiratory system compliance (sCRS), the pathogen load, and the number of neutrophils in the BAL fluid. None of the previous studies has used a technique that is capable of providing separate estimates of the mechanical properties of airway and pulmonary parenchyma. Lung disease in CF begins in the distal parts of the lung and should be reflected in abnormalities of parenchymal mechanics. The low frequency forced oscillation technique (LFOT) allows the measurement of the respiratory system impedance (Zrs) at a range of frequencies and enables lung function to be partitioned into components representing the airways and pulmonary parenchyma. However, no systematic studies aimed at detection of early lung disease in infants with CF using this technique have been published to date.

One of the relatively ignored areas of lung function testing has been that of ventilation distribution. An ''old fashioned'' test that is currently generating considerable interest is the multiple breath inert gas washout (MBW) technique. This can be used to measure lung volume and regional ventilation distribution and has been shown to correlate well with standard spirometric techniques in older children and adults. MBW has recently been applied to early detection of lung disease in CF with very promising preliminary results.[18] When compared with standard spirometry in children old enough to make both measurements, a significantly higher number of children were identified as abnormal by multiple breath gas mixing technique (72%) identified by standard spirometry (23%).[18]

In this issue of *Thorax* Aurora *et al*[19] report the results of MBW performed with sulfur hexafluoride (SF_6) in healthy school age British children and those with CF. The authors compared both volume (FEV_1) and flow (MEF_{25}) parameters obtained by standard spirometry with the lung clearance index (LCI) derived by MBW in 22 children with CF aged 6–16 years and 33 healthy controls. The LCI essentially measures the number of times the lungs need to be flushed out with air to remove the SF_6. Poorly ventilated lung regions take longer to wash out, resulting in a prolongation of LCI. On group mean data, lung function—assessed either from spirometry or from MBW—was abnormal in the children with CF. LCI appeared to be a more sensitive index of lung disease in CF; while approximately half the children had normal spirometric results (as judged by a z-score of more than −1.96), only one child had a normal LCI. These data are very similar to those published earlier by these authors in a Swedish population.[18]

There are several very encouraging implications from the data presented by Aurora *et al*.[19] They show that LCI is repeatable with a very acceptable within-subject coefficient of variation for both CF (6%) and healthy controls (5%). They also show that the normal values for LCI are independent of age, at least for children over the age of 6 years. In addition, they show that the normal data obtained from British children are essentially identical to those obtained from healthy Swedish children, a finding that should encourage the rapid compilation of an international reference data set.

While the study by Aurora *et al*[19] and the earlier study by these authors[18] are very encouraging, neither really addresses the issue of whether MBW can be used to detect lung disease early enough in the course of CF to prevent the onset of lung destruction. Most of the children in both studies had abnormal lung function and presumably already had lung destruction. Little of the work to date with MBW in CF has been done in infants and preschool children, and no systematic examination has been undertaken comparing MBW with markers of inflammation, HRCT or measurements of peripheral lung mechanics. A series of systematic studies in younger children will be required to understand whether any of our current tests have the ability to detect the onset of lung destruction, whether they are suitable as outcome variables for new treatments aimed specifically at preventing lung damage, and whether they will be useful for predicting the long term outcome. MBW is a technique that is potentially useful from infancy to adulthood, even in the difficult preschool years. Time will tell whether MBW—used either alone or in combination with other tests—will be the answer.

Thorax 2004;**59**:1008–1010.
doi: 10.1136/thx.2004.025924

Authors' affiliations
P D Sly, S Brennan, TVW Telethon Institute for Child Health Research, Subiaco, Western Australia 6008, Australia

Correspondence to: Professor P D Sly, TVW Telethon Institute for Child Health Research, Subiaco, Western Australia 6008, Australia; peters@ichr.uwa.edu.au

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Funding of grant applications

Getting grant applications funded: lessons from the past and advice for the future

G J Laurent

Respiratory research deserves more funding. This editorial proposes ways this can be achieved

Throughout the world respiratory research is underfunded with a large discrepancy between the proportion of patients suffering from lung diseases and the amount of research funds awarded by our national agencies.[1–4] In fact, many governments—including the current British government—acknowledge this and are committed to directing more resources into an area where the diseases often affect the most vulnerable in our society. In this editorial I have attempted to analyse how we have got into this ''Cinderella'' state, and try to propose practical approaches to help us get more funding into respiratory research. The discussion focuses on Britain, but it is hoped that some of the suggestions might resonate with respiratory colleagues in other countries where similar underfunding is in danger of undermining valuable clinical strengths that have been nurtured over many years.

This article predominantly assesses the state of affairs in the more basic science, but it is hoped that it will also promote debate around more clinical and translational research which is so central to progress in patient care. In this area it is my sense that the respiratory community still has a strong reputation. However, whereas in the past these studies were predominantly supported by government agencies, the recent trend is for more and more dependency on pharmaceutical companies. This may be inevitable—and even desirable—as we seek new drugs and refine old ones, but at the very least the trend requires analysis.

WHY IS RESPIRATORY RESEARCH CURRENTLY UNDERFUNDED?

There has, for as long as I can remember, been a feeling that respiratory research is poorly funded compared with other disciplines where patient numbers are comparable. This feeling is also borne out by the numbers provided by the major funding bodies such as the Wellcome Trust and the Medical Research Council. For example, while deaths from respiratory disease accounted for 13% of all deaths in England and Wales in 2002, funding for respiratory research claimed only 2.8% (£11.4 million) of the MRC's total expenditure in 2001–2 (£412.9 million).[5–7] Why should this be the case? When you challenge the leaders of the funding bodies their response is almost always that ''we need to look at ourselves, not them''. They point out that all their grants are peer reviewed in the same way and that, if grants in respiratory medicine were as highly rated as grants in other areas, they would also get funded. Let's accept this for a moment and try to analyse why. One possible answer lies in history. In the late 1970s, in Britain at least, respiratory research was confined to a few centres and was largely of the ''measure and correlate it'' type, with the main aim to monitor response to treatment rather than elucidate mechanisms of disease. At this time, research in other areas (cardiology, neuroscience and oncology, for example) was already embracing the new opportunities provided by progress in cell and molecular biology. This yielded strong progress that laid the foundations to establish many centres throughout Britain where the next generation of people are now benefiting. The respiratory world needed to catch up and, to a great extent, it has now done so.

My sense is that this discrepancy between respiratory medicine and other disciplines applies to most countries, although the time scales are different. In the US, for example, there was a concerted move to embrace molecular biology at least a decade before this occurred in Europe. However, even in the US it could be argued that we let our colleagues in other areas of medical research get the jump on us, and this may partly explain why the impact factors of specialist journals in many other areas are often higher than those in respiratory medicine.[8]

The last 25 years has seen unprecedented growth in basic respiratory research, particularly in key centres. This growth explains the current status of the many groups who are now recognised as world leaders in medical research. Nevertheless, not all of these centres are well supported by the established funding bodies. One possible reason for this is that we are, despite progress, still not writing grant applications of the highest calibre. I will return to this later. Another possibility is that the peer review process in the respiratory world is leading to lower rating not based purely on the quality of the science. In other words, as a community we set the bar higher than our colleagues in other medical disciplines and look for reasons not to fund. This is hard to assess objectively but it is certainly my sense that, in Britain at least, we are a very critical community. For example, there is no doubt that in some areas such as asthma research we are worldwide leaders by any standards, but this may work against us as competing asthma researchers sense (often incorrectly) that there is a limited cake to be portioned among their peers.

THE WAY FORWARD

Lobby the funding agencies

All of us leading research need to coordinate with each other and provide a strong lobby for government support, both at national and international