Weaning from mechanical ventilation

Streamlining weaning: protocols and weaning units
A K Simonds

Use of weaning protocols and specialised weaning units for patients who fail to wean from mechanical ventilation

Discontinuation of ventilation is estimated to take up to 40% of the total duration of ventilatory support, and around 3–6% of patients admitted to the intensive care unit (ICU) require a prolonged course of mechanical ventilation (MV). Patients being liberated from ventilatory support therefore occupy a significant amount of ICU beds and have a major impact on healthcare resources. There have been several recent key developments in the field of weaning—the use of weaning protocols, ventilatory strategies to reduce the need for invasive ventilation and facilitate successful extubation, and the creation of regional long term ventilator units. All have the potential to affect weaning outcome, but how valuable are they in practice?

WEANING PROTOCOLS

In 1996 Ely and colleagues showed that the implementation of a standardised protocol of daily trials of spontaneous breathing performed by nursing staff reduced the total duration of MV from 6 to 4.5 days, and complications such as need for reintubation, tracheostomy, and mean hospital stay from 37.5 to 24.7 days, and complications such as COPD showed that use of NIV reduced the incidence of nosocomial pneumonia, and improved 60 day survival in COPD patients extubated on to NIV 48 hours after admission with a severe hypercapnic exacerbation compared with continued standard invasive ventilation. In addition, in a heterogeneous group of patients with persistent weaning failure randomised to either NIV or continued invasive ventilation, the NIV group had a shorter hospital stay and improved 60 day survival (odds ratio 6.6, p = 0.035). Indeed, the results were so clear cut the trial was halted after planned interim analysis. These findings suggest that NIV should be considered early in the process of weaning, before a tracheostomy is performed unless there are specific indications for this (such as upper airway obstruction, severe bulbar weakness). By the same token, NIV has increasingly been used in patients who develop post extubation respiratory failure. Here one should apply a note of caution—while a historical case control study in patients with COPD showed that use of NIV reduced the need for reintubation from 67% to 20%, two recent prospective randomised trials have shown no advantage to the use of NIV in post extubation respiratory failure. In fact, Esteban et al showed an increase in mortality in patients treated with NIV compared with those receiving standard management. There are several possible explanations for this discrepancy. Firstly, in the trial by Esteban et al only 10% of patients had COPD while the remainder had a variety of conditions including pneumonia, postoperative respiratory failure, trauma, cardiac failure, and ARDS. Most work suggests that NIV is more effective in patients with COPD than in those with acute hypercapnic normocapnic respiratory failure. Secondly, the median time from extubation until reintubation was longer in the NIV group (12 v 2.5 hours), suggesting that use of NIV may delay reintubation, thereby affecting outcome adversely.

NEW VENTILATORY AND EXTUBATION STRATEGIES

There is now a substantial body of evidence confirming that the application of non-invasive ventilation (NIV) in acute exacerbations of COPD can prevent the need for intubation, such that NIV should be available on a 24 hour basis in units managing patients with acute respiratory failure. For intubated patients who have failed a spontaneous breathing trial for 30 minutes to 2 hours, there is little point in repeating the trial before 24 hours has elapsed. During this period patients should receive optimum ventilatory support in assist mode to allow some muscle activity and patient control over the ventilation delivered. Brochard et al have shown that gradually reducing pressure support ventilation is superior to intermittent mandatory ventilation or progressive spontaneous breathing trials in reducing weaning time. Early extubation onto NIV has been shown to be effective in patients with COPD. Nava et al found that non-invasive pressure support ventilation reduced weaning time, shortened ICU stay, decreased the incidence of nosocomial pneumonia, and improved 60 day survival in COPD patients extubated on to NIV 48 hours after admission with a severe hypercapnic exacerbation compared with continued standard invasive ventilation. In addition, in a heterogeneous group of patients with persistent weaning failure randomised to either NIV or continued invasive ventilation, the NIV group had a shorter total period of ventilation, reduced ICU stay (14.1 v 25 days), and reduced hospital stay (27.8 v 40.8 days) (p = 0.026). The need for a tracheostomy was markedly reduced (1.5% v 13.5%) and the conventional (invasive) weaning approach proved to be an independent risk factor for decreased ICU and 90 day survival (odds ratio 6.6, p = 0.035). Indeed, the results were so clear cut the trial was halted after planned interim analysis. These findings suggest that NIV should be considered early in the process of weaning, before a tracheostomy is performed unless there are specific indications for this (such as upper airway obstruction, severe bulbar weakness). By the same token, NIV has increasingly been used in patients who develop post extubation respiratory failure. Here one should apply a note of caution—while a historical case control study in patients with COPD showed that use of NIV reduced the need for reintubation from 67% to 20%, two recent prospective randomised trials have shown no advantage to the use of NIV in post extubation respiratory failure. In fact, Esteban et al showed an increase in mortality in patients treated with NIV compared with those receiving standard management. There are several possible explanations for this discrepancy. Firstly, in the trial by Esteban et al only 10% of patients had COPD while the remainder had a variety of conditions including pneumonia, postoperative respiratory failure, trauma, cardiac failure, and ARDS. Most work suggests that NIV is more effective in patients with COPD than in those with acute hypercapnic normocapnic respiratory failure. Secondly, the median time from extubation until reintubation was longer in the NIV group (12 v 2.5 hours), suggesting that use of NIV may delay reintubation, thereby affecting outcome adversely.
Furthermore, spontaneous breathing trials provide an overall guide to ventilatory capacity but signify little regarding cough efficacy and the ability to clear bronchial secretions if an endotracheal tube or tracheostomy is in situ. Salam et al.20 evaluated the extent to which cough efficiency (measured by cough peak flow), neurological function, and the volume of endotracheal secretions affect the outcome of extubation in patients who had passed a spontaneous breathing trial. A cough peak flow of 40 L/min increased the likelihood of extubation failure nearly fivefold, and the combination of low cough peak flow, volume of secretions >2.5 ml/hour, and failure to respond to simple commands produced an extubation failure rate of 100% compared with only 3% in those without these risk factors. This study21 was performed in 88 routine ICU admissions with diagnoses including pneumonia, COPD, congestive heart failure, asthma and sepsis, and there was no particular emphasis on neurologi- cal or neuromuscular patients. Cough efficiency with a normal physiological status, and the ability to clear secretions are likely to assume even greater importance in patients with neuromuscular weakness, and the results suggest these assessments (including evaluation of bulbar and swallowing function) should be added to spontaneous breathing trials in neuro- muscular and neurological groups. Additional strategies such as a combination of NIV and cough insufflator/exsufflator devices22-25 may be valuable in these patients and reduce the need for tracheostomy ventilation.26 Clearly, in neuromuscular patients with a history of gradual decline before acute ventilatory decompensation, or a progressive condition such as amyotrophic lateral sclerosis/motor neurone disease, failed trials of spontaneous breathing should not be fruitlessly and demoralisingly repeated but should prompt early referral for consideration of long term ventilatory support.

**WEANING/LONG TERM VENTILATOR UNITS**

Having applied strategies to optimise the probability of weaning success, what can be done for patients who fail to wean simply or who are likely to need long term ventilatory support, and how many individuals fall into this category? Various definitions have been used, but weaning delay can be considered to be the need for ventilatory support for more than 2 weeks in the absence of any non-respiratory factor preventing weaning, and the term weaning failure is used if this persists for 3 weeks or more. In the USA it has been estimated that there are over 11 000 ventilator dependent patients in acute care facilities, costing over $9 million a day.21 A 1 year survey24 in the Northern region of England identified 161 patients with weaning delay; these patients comprised 2.5% of ICU admissions and occupied 6% of ICU beds in the region. A subsequent NHS Modernisation Agency point prevalence survey of critical care facilities in England published in 2002 showed that approximately 8% of ICU patients had weaning delay and 7% weaning failure.7 The most common reasons for weaning failure were chronic lung disease, cardiaic impairment, endocrine or neuromuscular disease. As a result of these findings, the NHS Modernisation Agency has recommended the creation of a specialist NIV service integrated into the critical care network and the provi- sion of a UK-wide service for long term invasive and non-invasive respiratory support for patients who have failed to wean.7 The activity of one such unit is described comprehensively in this issue of Thorax by Pilcher et al.25 who present the outcome from a specialised weaning programme over 4 years. Of approxi- mately 150 weaning delay patients who had received MV for around 20 days before transfer to the unit, 38% were weaned completely from ventilatory sup- port, 35% required home ventilation, and 27% died before leaving hospital. Survival was best in patients with neuromuscular disease (who, conversely, were most likely to remain ventilator dependent) and worst in postoperative patients. Length of ICU stay before transfer, age, and APACHE II score on admission were key predictors of outcome. Female sex was associated with an increased prob- ability of weaning, but this finding may be partly a consequence of the high likelihood of Duchenne patients (male) requiring home ventilation. The eco- nomic analysis is helpful, but further detailed work is required in this area.

In an earlier study, Smith and collea- gues26 found a survival rate of 90% compared with a predicted survival from APACHE II score of 53% in 40 consecu- tive admissions to a regional weaning unit. Nearly 30% of these patients required home ventilation—but only three via tracheostomy. To set this within a European perspective, outcome data from a German regional unit accepting patients with weaning delay showed 60% of referrals had COPD, mortality was 24%, and 31% were discharged using NIV. Here, too, the survival rate was related to the under- lying diagnosis—patients with thoracic cage and neuromuscular disorders far- ing better than those with COPD.

In the USA there is a longer tradition of post ICU care delivered in long term facilities, and this has been substantially finance driven. A growing number of case series reports of patients with weaning failure has shown a common pattern—average age on admission of around 70 years, predominant diagnoses of COPD or postoperative cases, with approximately 60% surviving to discharge from the facility, 30% surviv- ing at 1 year, and around half weaned completely from ventilatory support.26-31 A multicentre study of 23 units commis- sioned by the US National Association of Long Term Hospitals has recently been set up to identify characteristics of the population at risk, extent of post ICU care delivered in long term hospitals, and estimate costs of care.

The advantages and disadvantages of weaning/long term ventilator units should be considered. Results from the European and US case series would suggest that patients whose primary problem is ventilatory dependence can be managed in a less intensive step down unit, thereby reducing costs and facilitating a focus on ventilatory care and rehabilitation. ICU facilities are freed up for patients requiring more complex care such as those with multi- system failure. Survival improves and favourable 1 and 3 year results can be obtained in some subgroups, parti- cularly patients with neuromuscular disease, although outcome remains relatively poor in the elderly and those with COPD, and families have to travel longer distances to visit patients. These centres tend to have greater familiarity with NIV techniques and are able to provide families and carers with compen- tency training in tracheostomy and ventilator care, and to develop compre- hensive home care packages to speed discharge. However, the outcome from weaning units critically depends on the selection criteria used for admission and can be biased if high risk admissions are refused. In many reports acceptance cri- teria are not made explicit. In addition, results may be influenced by the fact that, as in the study by Pilcher et al, long term units are likely to accept patients from their own or local ICUs more swiftly, thereby improving outcome.

Assuming, however, that targeting resources in this manner is rational, how many long term ventilatory places are required? The Northern region of England survey24 included 112 ICU (level 3) beds and suggested that a seven-bed weaning unit would be able to cater for 93% of patients with weaning delay, while a five-bedded unit would cope with 75% of cases of weaning delay—that is, a ratio of around one bed per 20 ICU beds. When planning the allocation of beds it should be recognised that in some countries many weaning failure patients are colonised or infected with methicillin resistant Staphylococcus aureus (MRSA) as a result of prolonged hospital stay and so
Asthma consultations

Consultations for asthma: will greater patient involvement deliver better health?

C J Griffiths

Self-management of asthma is a complicated activity, perhaps more demanding for asthma than for any other chronic illness. People with asthma are faced with an illness whose causes and fluctuations are poorly understood (witness the pages of this journal), to be controlled with an often mysterious collection of inhalers. Our increasingly high expectations of patients' abilities to self-care are fuelled by trials in selected populations and politicians with visions of reduced healthcare costs. The realities of asthma self-management are often scepticism and low uptake. The consultation remains the most important opportunity for helping patients to develop the ability to manage their asthma. Rightly, the consultation continues to be subject to a range of critical perspectives. Social scientists offer a number of deficiencies that hinder success in promoting self-care: the infrequency with which doctors seek and patients air fears about medication and side effects, lack of opportunity for patient involvement in treatment decisions, lack of recognition of the coexistence of lay and popular remedies. We stand accused of an enthusiasm for authoritarian, positivist, illness centred medicine. Ethicists show how clinicians can undermine trust by failing to discuss how rationing affects their prescribing or referral decisions; any patient who says their doctor "prescribes the cheapest of the cheap medicines" is unlikely to value advice. Educationalists and psychologists argue that, while knowledge about asthma is inadequate and that the key skills needed are goal setting, problem solving, and development of confidence—a view backed by empirical research in the USA. These perspectives can be grouped together under the general heading of a failure to involve patients sufficiently in their care. Patient centred care is not
about destructive consumerism and deprofessionalisation,\textsuperscript{13} but acknowledgment of the complementary expertise and knowledge that patients and professionals bring to the consultation.\textsuperscript{17} It incorporates the notion of promoting shared decision making in consultations.\textsuperscript{18} It is an explicit goal of healthcare reform.\textsuperscript{19} From an ethical standpoint, there is no doubt that patients should exercise autonomy and control over their care. However, while reviews of interventions suggest the goals of increased patient involvement, satisfaction and adherence are often met, improved health and reduced costs have been more elusive.\textsuperscript{20} Providing convincing evidence of these benefits remains a most important challenge.

In this issue of Thorax Caress and colleagues bring a useful contribution to this debate.\textsuperscript{21} In a study of asthmatic subjects drawn from primary and secondary care they show that most want to be more involved in decisions about their asthma care. They show that few people live at the extremes of wanting to make decisions without advice or having them made for them. The study is strengthened by combining qualitative data from interviews with patients to illuminate their positions on decision making.

Very similar findings were reported in hypertensive patients in the USA by Strull and colleagues 20 years ago, which suggests that this is a persistent and generalisable finding.\textsuperscript{22} Using a similar questionnaire design, patients reported higher preferences for involvement than they experienced across five categories. A higher percentage of patients reported a fully passive role in 2004 compared to 1984 (14% v 47%). It is difficult to predict individual preferences, but previous work shows that the desire for involvement broadly relates to condition, context and demographic factors. For instance, patients wish for greater involvement in decisions for benign versus malignant breast disease, for routine versus emergency care,\textsuperscript{23} and for emotional compared with physical problems.\textsuperscript{24} In general, younger, more educated people prefer greater involvement.

So what remains concerning patient involvement and respiratory care? Research priorities are to find ways to enhance involvement of patients in consultations (particularly where care is increasingly driven by data collection and contract targets), and then to evaluate these in trials, testing their effects on health status and health care use. Promising work in this area needs to be tested in settings outside the USA.\textsuperscript{25} People with asthma from minority ethnic groups have poorer outcomes for asthma and are rarely involved in treatment decisions, even when language barriers are absent.\textsuperscript{26} Interventions may be of particular benefit in such groups. Layed education programmes for people with chronic disease are becoming integral to modern health care, but with little evaluation.\textsuperscript{27} We need to find out how effective these are in promoting more effective consultations and better health, and whether integration with more traditional professionally led education creates benefits or new problems.

Patients were asking for more involvement in 1984 and continue to do so 20 years later. Our response might improve the health of people with asthma.

The sociologist Talcott Parsons wrote in 1951: "By the same institutional definition the sick person is not, of course, competent to help himself, or what he can do is, except for trivial illness, not adequate. But in our culture there is a special definition of the kind of help he needs, namely, professional, technically competent help. The nature of this help imposes a further disability or handicap upon him. He is not only generally not in a position to do what needs to be done, but does not ‘know’ what needs to be done or how to do it. It is not merely that he, being bedridden, cannot go down to the drug store to get what is needed, but that he would, even if well, not be qualified to do what is needed and to judge what needs to be done..."\textsuperscript{28} Thorax 2005; 60:177–178. doi: 10.1136/thx.2004.033506

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The exhaled biomarker puzzle: bacteria play their card in the exhaled nitric oxide–exhaled breath condensate nitrite game

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Exhaled NO and nitrite as potential biomarkers in asthma

The measurement of exhaled biomarkers has gained increasing interest in recent years, mainly driven by the unmet clinical need to monitor airway inflammation and the response to anti-inflammatory treatment. The current issue of Thorax contains two important publications in this rapidly growing field. The study by Pijnenburg et al shows how exhaled nitric oxide (NO) measurement can serve clinical practice,1 while the investigation by Marteus et al draws attention to the potential pitfalls of measuring nitrite in exhaled breath condensate (EBC).2

It was hardly more than a decade between the discovery by Gustafsson et al in 1991 that the exhaled breath contains NO and the approval of such a measurement for clinical practice to monitor the effect of anti-inflammatory treatment in asthma.1,4 The road has been paved by approximately 2000 publications on the measurement of the fractional concentration of exhaled nitric oxide (FeNO) in health and disease, including three guidelines which provide methodological recommendations for internationally known experts in the field and endorsed by the European Respiratory Society (ERS) and/or the American Thoracic Society (ATS).5–7 By using these recommendations, exhaled NO can be measured reproducibly and data from different laboratories can be compared.

Exhaled NO has been extensively studied as a marker of airway inflammation in asthma and it serves as a prototype for the application of biomarkers to the management of the inflammatory component of asthma. Can monitoring FeNO in addition to symptoms and spirometry contribute to asthma control? The paper by Pijnenburg et al in this issue of Thorax provides a positive answer to this question.1 In a longitudinal study the authors determined whether FeNO predicted asthma exacerbation (positive predictive value of 80–90%) at a time when symptoms were stable.

Although as yet we do not know whether using exhaled NO measurements to guide anti-inflammatory treatment in asthma in addition to traditional means of monitoring would improve asthma control, both studies indicate that exhaled NO can serve as a marker of loss of asthma control and may be useful in clinical decision making.

While a decade was enough for exhaled NO measurement to enter clinical practice, the same decade was only good enough to give a boom to research for measurement of biomarkers in EBC. It is easy to collect, requiring only the non-invasive collection of exhaled breath for 10–20 minutes in a cold trap. The fluid obtained is a complex diluted solution of diverse biomarkers with various chemical stabilities including a number of constant nitrite.8,9 Because of the complexity of EBC and the fact that it is a much diluted sample, there are still a number of uncertainties surrounding it. Although there is an expectation that this sampling method will be clinically useful, there are still several unresolved issues, many of which are highlighted in the report by the ERS/ATS Task Force entitled “Exhaled Breath Condensate” which is awaiting ATS approval for publication.

In this issue of Thorax an important study by Marteus et al10 addresses the relation between exhaled NO and EBC nitrite/nitrate concentration. The authors performed a carefully designed study which assessed the source of nitrite in orally collected EBC, compared nitrite levels between oral and tracheal EBC samples, and investigated the influence of nitrate intake and antibacterial mouthwash on the nitrite concentration in oral EBC samples, nasal air condensates, and on FeNO. Their findings can be summarised as follows: (1) nitrate levels in EBC are influenced by dietary intake; (2) nitrate is reduced to nitrite primarily by bacterial activity which takes place mainly in the oropharyngeal tract in healthy subjects; and (3) there is a substantial contribution of nitrite from the oropharyngeal tract during oral EBC collection. The findings of this study draw attention to the acknowledged pitfall of oral EBC sampling—namely, the potential nasooropharyngeal influence on mediator levels. They also question, to some extent, the reliability of oral EBC nitrite in reflecting lower airway NO production and its ability to serve as a marker of airway inflammation.11–15 The study also highlights the importance of potential external contamination (the authors covered the condensing surface with a specific plasma layer to minimise nitrite contamination) and emphasises the need for great care when measuring mediators which occur in such a low concentration in the EBC.


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Exhaled biomarkers in asthma

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Interventional bronchoscopy

Brave new world for interventional bronchoscopy

T P Toma, D M Geddes, P L Shah

New applications for interventional bronchoscopy

Until recently, interventional bronchoscopy was limited to foreign body removal, debulking endobronchial tumours, or insertion of stents for the palliation of lung cancer. Most of these procedures are performed with a rigid bronchoscope under general anaesthesia by thoracic surgeons. As a result, only a few respiratory physicians developed an interest in interventional bronchoscopy. The small range of interventions that has meant that, up to now, interventional bronchoscopy has been less glamorous than, for example, interventional cardiology.

Will this situation change? Firstly, there is an increased interest in transbronchial fine needle aspiration (TBNA) for staging lung cancer and in endobronchial ultrasound guided TBNA. The latter technique samples suspicious lymph nodes as small as 5 mm and has the potential for replacing mediastinoscopy. Secondly, tumours can be debulked with electrocautery, photodynamic therapy or lasers, and stents can be inserted under local anaesthesia with flexible bronoscopes.

Recent research has driven an expansion of interventional bronchoscopy for some of the more common non-malignant respiratory diseases. Bronchial thermoplasty for the treatment of asthma is close to receiving FDA approval. This procedure, performed under local anaesthesia, involves the obliteration of smooth muscle in airways larger than 3 mm by applying radiofrequency energy. An endobronchial probe is passed through the working channel of the bronchoscope and applied to the airway wall. A controlled amount of energy is delivered which heats and destroys the muscle. Smooth muscle ablation causes a reduction in bronchial hyperreactivity and early studies suggest an improvement in asthma control. Pilot human trials have shown that the method is safe and can decrease airway hyperreactivity in patients with moderate asthma. Studies on patients with more severe or steroid dependent asthma are currently underway.

A number of procedures are being developed to improve breathlessness in severe emphysema. These aim to achieve volume reduction by bronchoscopy rather than surgery. The basic idea is to induce collapse of the worst affected lobe or segments by blocking the relevant airways with one-way valves. A number of such valves are available and have been designed to block inspiration while allowing drainage of expired air and secretions. This results in controlled deflation of the target segment or lobe. The valves are inserted directly through the working channel of the fibroscope or over a guide wire using the Seldinger technique.

More than 100 patients have been treated in this way and the safety record to date is encouraging. The valves remain in place and have only seldom been implicated in cough or distal infection. Worthwhile improvements in lung function and quality of life have been reported in up to a third of patients and failure is probably due to collateral ventilation from surrounding lung units. This is not surprising since only patients with very severe emphysema have so far been treated and more work needs to be done to define the most suitable patients. A pivotal randomised trial is now underway.

While bronchoscopic valve placement has been proposed for patchy (heterogeneous) emphysema, an alternative intervention has been suggested for diffuse (homogeneous) emphysema. This involves the creation of extra-anatomical airways to bypass the flow-limiting segment airways in expiration. A needle catheter is used to make fenestrations connecting emphysematous lung to nearby cartilaginous airways, and these holes are held open by “spiracles” (similar to small vascular stents). Pilot studies have shown that these fenestrations can be created safely and have a beneficial effect on lung function. There is, however, a tendency for the fenestrations to become blocked by granulation tissue.

Bronchoscopic instillation of delivery systems for slow release of drugs may open up new perspectives in the localised treatment of lung conditions. Some polymers have thermotropic properties and so behave as liquids at room temperature but form gels at body temperature. These can be injected into a part of the lung where they are cleared slowly and act as a drug efflux reservoir. These polymers also have a number of influences on cells ranging from effects on drug efflux channels to energy depletion in mitochondria. One such
effect is to improve the sensitivity of drug resistant cells to chemotherapy. The natural development of this technology would be directly instil specific drug eluting gels into the lung via a bronchoscope. For example, a polymer and chemotherapy drug combination could be injected into the target segment of the lung where it forms a gel and gradually elutes the chemotherapeutic drug and also improves the sensitivity of the cells to the treatment. The development of this technology is speculative at present but may have widespread applications in respiratory medicine—ranging from chemotherapy for lung cancer through to gene therapy for cystic fibrosis and regenerative treatments in emphysema.7

These interventions stimulate the future of interventional bronchoscopy. Some may fail to become a clinical reality, but this is likely to be a fertile area of research in years to come. It is clear that interventional bronchoscopy is evolving and will have an impact on a greater number of patients with respiratory diseases in the future.

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Remodelling of CF airways

Muscling into cystic fibrosis airways

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Remodelling of the airway smooth muscle layer is not confined to patients with severe CF but occurs also in those with mild to moderate disease

Most patients with cystic fibrosis (CF) develop progressive airflow obstruction. A subgroup of these patients also have airway hyperresponsiveness to inhaled bronchoconstricting agents1,2 and reversibility of airflow obstruction in response to bronchodilators.3 Parallels have been drawn between these observations and other airway diseases manifesting with airflow obstruction and bronchial hyperresponsiveness such as asthma and chronic obstructive pulmonary disease (COPD). This led to speculation that remodelling of the airway smooth muscle (ASM) layer may contribute to bronchial hyperresponsiveness in CF. Studies in the past have been restricted to patients with severe CF. Pathological studies of the lungs of these patients obtained either at necropsy or following transplantation or lobectomy showed an increase in smooth muscle area compared with healthy controls or patients with COPD.4,5 In this issue of Thorax Hays et al6 have, for the first time, studied the ASM layer in patients with mild to moderate CF using bronchoscopy and design based stereology. They found that the volume of smooth muscle in the airway submucosa in subjects with CF was higher than in normal controls and, furthermore, that this difference was attributable to smooth muscle cell hyperplasia rather than hypertrophy. This study raises several interesting questions. 1. Is this increase in the volume of the smooth muscle layer responsible for the airway hyperresponsiveness seen in many CF patients? 2. What factors are produced in the CF airway that could promote ASM hypertrophy? 3. Is there a relationship between the defective ion transport underlying CF pathophysiology and smooth muscle function in the CF airway?

Is the smooth muscle cell hyperplasia demonstrated by Hays et al sufficient to explain airway hyperresponsiveness in CF patients? Mathematical modelling approaches suggest that changes in airway dimensions in CF, including an increase in the smooth muscle area, probably contribute to airflow obstruction and bronchial hyperresponsiveness in these patients.7 Interestingly, tumour necrosis factor α (TNF-α), a cytokine found in increased amounts in the CF airway, has been shown to potentiate ASM contraction in response to cholinergic stimulation in vitro,8 and there is evidence that TNF-α induces a hypercontractile phenotype by enhancing agonist induced calcium signals, as well as agonist induced force generation.9 Thus, it may be that factors other than ASM hyperplasia alone contribute to bronchial hyperresponsiveness in CF. It would be interesting to investigate whether the presence and degree of airway hyperresponsiveness correlates with smooth muscle hyperplasia in these patients. The difficulty is that it is not possible to study the small airways—which collectively make the greater contribution to airflow obstruction—in the subgroup of patients with mild to moderate disease.

There are interesting similarities and contrasts between the inflammatory milieu found in the asthmatic and CF airways. Inflammation in CF is primarily neutrophil driven whereas, in asthma, T lymphocytes, eosinophils and mast cells are of greater importance although neutrophils may play a role in severe asthma. This has consequences for the range of cytokines and mediators that predominate in the inflamed airway. Airway inflammation and remodelling involves not just inflammatory cells but also structural cells such as fibroblasts, epithelial cells, and ASM cells. Inflammatory and structural cells...
produce cytokines, mediators, matrix modifying enzymes, chemokines, and growth factors that initiate and perpetuate inflammation and remodelling. The interplay between these cells and the multitude of biologically active molecules that they secrete is complex and not fully understood. However, those factors that promote proliferation of ASM cells in vitro include growth factors (such as basic fibroblast growth factor, transforming growth factor-β, platelet derived growth factor, epidermal growth factor and insulin-like growth factor), mediators including endothelin-1 and cysteinyl leukotrienes, proteolytic enzymes such as thrombin and mast cell derived tryptase, and cytokines including interleukin (IL)-1β. Many of these factors are found in increased amounts in the asthmatic airway and their influence on ASM function and airway remodelling has been the subject of intense study over the last decade. Some of these factors are also present in inflamed airways in CF.

It remains a matter of debate whether inflammation in the CF lung is driven by the opportunistic infections characteristic of this disease or whether it begins early in the disease, independent of lung infection. However, what is clear is that a chain of events occurs leading to a vicious cycle of infection, inflammation, lung tissue damage and further vulnerability to infection. Bacteria stimulate macrophages to produce IL-1β and TNF-α which, in turn, stimulate epithelial cells to produce chemokines such as IL-8, cytokines such as IL-1 and, growth factors such as GM-CSF. IL-8 attracts neutrophils to the inflammatory site where they release LTβ4, reactive oxygen species, and proteases such as elastase which damage airway structural proteins and further stimulate cytokine production by epithelial cells. Since ASM mitogenesis can be stimulated in vitro by the actions of proteolytic enzymes including thrombin and tryptase, it is interesting to speculate whether proteases in the CF airway may have a similar effect. Other mediators and cytokines found in increased amounts in the CF airway which could promote ASM proliferation include the cysteinyl leukotrienes which augment growth factor induced ASM proliferation, and the potent smooth muscle mitogen and bronchconstrictor endothelin-1.

In CF a number of different mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) lead to defective chloride secretion by epithelial cells and disordered ion transport. This alters the composition of the airway surface liquid, predisposing to pulmonary infection. In the intestine the myofibroblast layer contributes to chloride secretion by intestinal epithelial cells through the production of prostaglandin E2 (PGE2) mediated by cyclooxygenase in response to inflammatory cytokines and thrombin. It is possible that ASM derived factors in the CF airway can modify airway epithelial ion transport. Indeed, it is known that a number of inflammatory cytokines and mediators increase PGE2 production by ASM cells in vitro and, furthermore, that PGE2—the dominant prostanooid produced by ASM under inflammatory conditions—stimulates chloride secretion by airway epithelial cells. It may be that ASM hyperplasia in CF is an adaptive response which compensates, in part, for defective chloride secretion.

Is it possible that the defect in the CFTR itself contributes to ASM hyperplasia in CF? Interestingly, recently published data show that inhibition of the Na+–K+–2Cl− co-transporter by diuretics inhibits ASM proliferation in vitro, suggesting that alterations in ion flux may modify hypertrophic or hyperplastic processes in these cells.

The findings of Hays et al add an important contribution to our knowledge about airway remodelling in CF—specifically that changes in the ASM layer are not confined to patients with severe disease but are present in those with mild to moderate disease. This is of particular importance as it suggests a possible mechanism underlying the airway obstruction and hyperresponsiveness observed in these patients in the clinic. The biological mechanisms underlying ASM hyperplasia in CF warrant further study which will enhance our understanding of the pathophysiology of this disease and may lead to novel approaches to treatment.

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Brave new world for interventional bronchoscopy

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