Thorax in focus: chronic obstructive pulmonary disease

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ABSTRACT

Keeping up to date with scientific developments in any field of medicine is challenging, and chronic obstructive pulmonary disease (COPD) is no exception. *Thorax* has played an important part in the communication of key developments to its readership. In this article we review original research published in the journal over the last 2-3 years. We consider scientific and clinical developments in the epidemiology, mechanisms and treatment of COPD, placing these articles in the context of other relevant literature in COPD.

Chronic obstructive pulmonary disease (COPD) continues to challenge clinicians and scientists to address the burden the disease imposes on patients, carers, health services and wider society. It is encouraging that the appreciation of these unsolved problems has resulted in a burgeoning scientific literature in COPD and *Thorax* has played an important part in communicating key developments to its readership. In this article we have reviewed articles relating to COPD that have been published in *Thorax* over the last 2–3 years.

It has recently been highlighted that keeping up with the pace of scientific development even in a relatively narrow field is a Herculean task beyond most doctors and scientists.[1] We cannot claim any special diligence in this respect but have picked out articles that either excited our interest or helped with everyday understanding and management of the disease. We have tried to place articles in context and highlight themes that we believe will be in the forefront of scientific and clinical advances in this debilitating disease.

EPIDEMIOLOGY AND NATURAL HISTORY OF COPD

The British Lung Foundation 'Missing millions' campaign has brought the prevalence and health burden of undiagnosed COPD to our attention. Using a Spanish telephone database, Miravitlles *et al* performed spirometry screening in 3802 adults.[2] The prevalence of COPD was 10.2% (4.4% having Global Initiative for Chronic Obstructive Lung Disease (GOLD) II or worse) with only a quarter having a prior diagnosis. Importantly, health-related quality of life was worse in those with COPD, including those not previously diagnosed. These observations were supported by Jordan *et al*[3] who analysed spirometry and respiratory symptoms from the health survey of England data (1995–1996) and estimated the prevalence of COPD to be in the order of 5%, the majority of which was previously undiagnosed. Interestingly, they went on to test a model of active case findings, suggesting that more patients would be diagnosed using this approach. More recently, similar prevalence rates of diagnosed and undiagnosed COPD estimated from the primary care Quality and Outcomes Framework database were reported.[4] This study of data from over 53 million patients also identified factors predicting COPD-related hospitalization, which included the rate of undiagnosed disease as well as smoking rates and indices of deprivation. Interestingly, the quality of local primary care service provision was also a predictor of hospitalisation, suggesting COPD is a 'primary care sensitive' condition.

COPD prevalence estimates clearly depend on the characteristics of the population screened but will also be determined by criteria used to diagnose COPD, with continuing debate over the fixed spirometric ratio of 0.7 or lower limit of normal method.[5 6]

The traditional view that COPD is caused by smoking in genetically susceptible people has been tempered by the appreciation of the importance of other factors, such as early life influences, preceding symptoms and environmental/occupational exposures. The burden of disease attributable to occupational exposures has been estimated to be as much as 15%.[7] Blanc *et al*[8] estimated the risks attributable to occupational exposures and smoking from a large US managed care organisation (The Function, Living, Outcomes and Work (FLOW) study), which suggested that the attributable risk from self-reported occupational exposure was substantial when adjusted for smoking. Importantly, smoking and occupational exposures acted synergistically, increasing the risk of COPD 14-fold. More recently, Govender *et al* found observed similar attributable risks from a cohort of South African subjects, confirming the importance of occupational exposures even in regions where other factors such as the high prevalence of tuberculosis would be expected to be influential.[9] The importance of air pollution in the development of COPD has always been suspected but difficult to confirm in the absence of reliable pollution data. However, we now have more robust evidence that the population risk of COPD is independently related to the intensity and duration of air pollution.[10] Moreover, Peacock *et al* reported that short-term increases in particulate pollution (PM10), nitrogen dioxide and black smoke adversely affected symptoms in a cohort of patients in London.[11] In developing countries, indoor pollution from biomass solid fuel combustion is a key factor in the development of COPD, reiterated in a recent systematic review.[12]

Early life influences in the aetiology of COPD are attracting increasing attention. Data from a US

longitudinal cohort established in 1972 suggested that the presence of chronic bronchitis before the age of 50 years was a predictor of future COPD risk and all-cause mortality, independent of smoking habit and pack years, roughly doubling the risk of subsequent airflow limitation.[13] Meanwhile, other data have suggested the origins of COPD may lie far in early life. Svanes *et al*[14] measured spirometry at two time points approximately 9 years apart in patients recruited to a large European health survey. They observed a higher prevalence of COPD and a more rapid decline in forced expiratory volume in 1 s (FEV_1) in patients with childhood 'disadvantage factors' (a history of personal or parental asthma, maternal smoking or childhood respiratory infections), of a magnitude comparable to heavy smoking. Early life factors might also explain the more recent observation that forced vital capacity (FVC) was a better predictor of mortality than the FEV_1/FVC ratio; in other words, lung size rather than airflow obstruction was of more prognostic significance.[15] The natural history of different phenotypes of COPD is the subject of ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints), a 3-year study which recruited over 2000 patients with COPD across a range of severity of airflow limitation. Hurst *et al*[16] determined exacerbation frequency in the patients with COPD, reporting that although the frequency increased as the airflow limitation worsened, 22% of those with GOLD II still had two or more exacerbations in the first year suggesting a distinct 'frequent exacerbator' phenotype. Vestbo *et al*[17] reported considerable variation in decline in FEV_1 that was more rapid in those who smoked and those with emphysema or a bronchodilator response.

The interaction between COPD and other common comorbidities and their impact on mortality and morbidity is being increasingly recognised. Using a UK-wide validated primary care database (The Health Improvement Network (THIN)), Feary *et al*[18] observed a fivefold increased risk of cardiovascular (CV) disease, threefold of stroke and twofold of diabetes in patients with physician-diagnosed COPD. In keeping with these findings, Calverley *et al*[19] reported a post hoc analysis of CV events in patients recruited to the TORCH study (Towards a Revolution in COPD Health). A high incidence of CV events was seen (20–25% over the 3 years, independent of smoking history), but reassuringly, no adverse effect of the study interventions was observed. Plausible mechanisms to account for this increased risk, over and above smoking, might include increased aortic stiffness and associated impaired LV diastolic dysfunction.[20] Indeed, Barr *et al* reported impaired left ventricular filling was associated with greater emphysema extent and worse airflow obstruction.[21] One further contributory factor might be increased platelet activation reported in 18 patients with stable COPD compared with controls, matched for age and smoking.[22] This activation was greatest at the time of an acute exacerbation (AECOPD) compared with post-exacerbation stability. An AECOPD may be a particular at-risk period for CV events.[23] Biomarkers of cardiac dysfunction, including N-terminal brain natriuretic peptide and troponin T, are often elevated at hospitalisation for AECOPD and two recent observational cohort studies suggested their prognostic utility.[24 25]

The importance of CV mortality and morbidity in COPD has raised the question of whether secondary prevention with β-blockers, statins or anti-platelet agents should be prioritised in this population. β-Blockers have previously been debated in *Thorax*.[26 27] Confirmation of β-blocker efficacy in prospective trials is awaited but their potential benefits have been highlighted more recently in large observational cohorts.[28 29]

The increased risk of cancer in COPD independent from smoking was highlighted in two other cohort studies. Van Gestel *et al* conducted a longitudinal cohort study of patients undergoing vascular surgery[30] and observed a twofold increase in the incidence of lung cancer and extra-pulmonary malignancy. Tantalisingly, the risk of extra-pulmonary malignancy was lower in patients receiving statin therapy. Almagro *et al* compared outcomes in two cohorts of patients with COPD (recruited after hospitalisation for AECOPD) separated by 7 years (1996/1997 and 2003/2004).[31] The poor prognosis of this sub-population of patients was confirmed but reassuringly 3-year mortality was significantly lower in the more recent cohort (38.7% vs 47.4%). Survival in the second cohort was particularly improved in patients with heart disease and lung cancer, suggesting we may be getting better at identifying and managing these comorbidities.

MECHANISMS AND OUTCOME MEASURES

There has been considerable recent effort to understand the mechanisms underpinning the development of COPD and develop more discriminatory outcome measures to assess the impact of the disease.

The potential aetiological influence of vitamin D in COPD has been of recent interest. Janssens *et al*[32] reported direct associations between 25-hydroxyvitamin D (25-OHD) levels and lung function in patients with COPD. The majority of those with more severe airflow obstruction had deficient 25-OHD levels. Those homozygous for rs7041 T allele (a genetic variant in the vitamin D binding gene) had lower 25-OHD levels and had an OR >2 for COPD. Wood *et al*[33] also reported an association between vitamin D binding protein levels, lung function and macrophage activation in patients with α1 antitrypsin deficiency, those with usual COPD and healthy controls, suggesting a potential mechanism for these observations. More recently, however, Shaheen *et al*[34] reported an association between dietary vitamin D intake and lung function in a cross-sectional analysis of people enrolled in the Hertfordshire Cohort Study but no association with serum 25-OHD levels.

The role of matrix metalloproteinases (MMP) in the aetiology of COPD has attracted recent interest with the report from a genome-wide association study linking variations in the MMP-12 gene with lung function and the risk of developing COPD.[35] Haq *et al* extended these observations by showing that a single nucleotide polymorphism (SNP) of the MMP-12 gene was associated with increased MMP-12 levels, together with increased lung macrophage infiltration and greater emphysema.[36]

Previous research has demonstrated high levels of interleukin 6 (IL-6) in both serum and sputum of patients with COPD, associated with a more rapid decline in lung function. He *et al*[37] related IL-6 SNPs to decline in FEV_1 in 1488 patients participating in the Lung Health Study. However, questions remain unanswered, especially as these SNPs did not relate to IL-6 levels.

Though plasma markers of inflammation have been observed in patients with COPD, the temporal relationship remains unclear. Engstrom *et al*[38] examined data from 5247 patients who underwent spirometry and measurement of five plasma proteins associated with inflammation. Follow-up was over 25 years with the endpoint being admission to hospital with COPD. The age-adjusted HR for admission was significantly increased with at least three raised inflammatory plasma proteins regardless of smoking status.

The measurement of physical activity and energy expenditure (EE) in the home setting has been of increasing interest as the relevance of these outcomes to morbidity, healthcare utilisation and nutritional status becomes clear. Hill *et al*[39] studied the

properties of a lightweight portable activity monitor (SenseWear armband, BodyMedia Inc, Pittsburgh, Pennsylvania, USA) compared with indirect calorimetry in 26 patients with COPD. The SenseWear was able to identify small changes in EE associated with daily life with good reliability, and therefore may be a useful device for the measurement of these outcomes in clinical trials.

There has been recent focus on developing more sophisticated techniques for examining airway function. Forced oscillometry can be used to measure the properties of the airway under tidal breathing conditions. Paredi *et al*[40] reported a difference between inspiratory and expiratory reactance during forced oscillometry in COPD that was not observed in patients with asthma. While this might be due to greater dynamic airway narrowing in COPD, the authors recognised that more research is needed to confirm the significance and clinical utility.

Wilkens *et al*[41] used opto-electronic plethysmography (calibrated video cameras recording the movement of reflective markers placed over the torso) to assess the pattern of chest wall movement in patients with chronic respiratory failure due to pulmonary fibrosis, cystic fibrosis and COPD. Perhaps unsurprisingly, different patterns of ventilation were observed, suggesting the diseases impose different physiological burdens to the respiratory system. Interestingly, in a separate cohort of post-transplant patients the ventilatory pattern was similar to a healthy control group, suggesting these adaptations are reversible.

The development of field tests of exercise performance has allowed the assessment of disability in patients with COPD without the need for sophisticated exercise testing equipment. Minimal clinically important differences (MCIDs) for the incremental shuttle walking test and the 6 min walking test have been reported[42 43] but not for the endurance shuttle walking test (ESWT), a potentially more responsive measurement. Pepin *et al* reported that patients were able to perceive an improvement of 45–85 s in ESWT following bronchodilation.[44] Importantly, however, this did not correspond closely to perceptions following pulmonary rehabilitation, suggesting that MCIDs for a given exercise challenge may depend on the intervention being tested.

The clinical importance of weight loss and muscle wasting in COPD is now well recognised[45–47] and has resulted in further efforts to understand underlying mechanisms and develop reliable outcome measurements. Doucet *et al* previously reported differences in the expression of genes and proteins thought to regulate muscle growth and atrophy in COPD compared with healthy controls.[48] The same group compared the expression of these pathways in the diaphragm and the quadriceps muscles in patients with COPD undergoing thoracic surgery.[49] Differences in the expression anabolic and catabolic signalling targets was observed between these muscle groups, suggesting local factors, particularly muscle disuse, were key regulators of muscle wasting in COPD. Studies exploring the intramuscular response to an intervention such as physical training will shed further light on these issues. Along these lines, a maladaptive oxidant/antioxidant response in the quadriceps to aerobic training in COPD was observed by Barreiro[50] compared with controls. In keeping with this finding, a more recent study reported a significant reduction in quadriceps muscle mitochondrial DNA content after high-intensity exercise in patients with COPD,[51] which was associated with evidence of increased oxidant stress compared with the response in healthy controls. The importance of these observations for exercise and training prescription during pulmonary rehabilitation remains to be determined. The relationship between skeletal muscle function and pulmonary mechanics during exercise in COPD was studied using near-infrared spectroscopy to measure skeletal muscle microvascular oxygen delivery during exercise following the administration of short-acting bronchodilators.[52] The authors surmised that these agents may reduce muscle metabolic demands imposed by exercise-related dynamic hyperinflation.

Seymour *et al* demonstrated the potential of ultrasound to detect reduced quadriceps muscle mass in patients with COPD compared with controls.[53] The portability and lack of radiation of ultrasound are clear advantages but its responsiveness to an intervention requires further evaluation. More recently, van den Borst *et al* analysed longitudinal muscle mass and lung function data from the Health ABC study.[54] They observed lower muscle mass in patients with evidence of airway obstruction compared with healthy controls who had never smoked. Intriguingly, muscle mass in patients with COPD was comparable at baseline with those without COPD who smoked. In addition, trajectories of reductions in muscle mass with ageing (sarcopenia) did not differ between the groups, suggesting an interaction early in life among smoking, lung function impairment and sarcopenia.

Data from longitudinal studies have shed light on the relationships between structural and functional abnormalities in the lungs of patients with COPD.[17 55] Hoesein *et al*[56] reported data from a European lung cancer screening study confirming that CT evidence of emphysema was associated with poorer lung function but also, importantly, that early emphysema in the absence of impairment was a predictor of subsequent decline.

The recognition of the importance of a global assessment of the impact of COPD on the patient has led to the evaluation of patient-reported outcome measures aimed at capturing additional symptomatology. Al-shair *et al*[57] reported the development and validation of the Manchester Fatigue score in a cohort of patients with COPD, demonstrating that the scale was able to discriminate patients with depression and those with poor exercise performance. The COPD Assessment Test (CAT) has been developed to enable a rapid, broad assessment of the symptom burden of COPD.[58] In a pragmatic observational, multicentre study, Dodd *et al* demonstrated that the CAT is sensitive to pulmonary rehabilitation and correlates with other measures of health status, such as the St George's respiratory questionnaire (SGRQ).[59]

Breathlessness is a key symptom in COPD and Murphy *et al* reported the development of a novel method for assessing neural respiratory drive[60] using parasternal electromyogram activity. This index correlated well with Borg score and predicted improvement in a cohort of patients hospitalised for AECOPD and suggested it may have clinical utility. Taking a different approach, Smith *et al*[61] assessed the subjective quality of breathlessness reported by patients with COPD compared with those from patients with asthma and pulmonary fibrosis. 'Air hunger' was a common descriptor of exertional breathlessness regardless of the mechanical behaviour of the lungs. Are there common mechanisms that operate in the subjective meaning of breathlessness across a range of respiratory pathologies?

The wider behavioural and psychological consequences of COPD were explored in two articles that analysed longitudinal data from the FLOW study.[62 63] The authors observed that extra-pulmonary indices of impairment (such as muscle strength and body composition) made a greater contribution to the development of functional disability than measurements of lung function impairment. They also reported a high prevalence of anxiety in patients with COPD enrolled in this study (in keeping with previous data) but further observed that the presence of anxiety predicted poorer health outcomes, including exercise limitation and hospitalisation for AECOPD.

TREATMENT OF COPD

Pharmacological therapy

The paucity of novel molecules for the treatment of COPD in recent years has highlighted the substantial challenges to drug development facing the pharmaceutical and academic communities.[64] Two studies in *Thorax* evaluated the efficacy of indacaterol, a newly developed once daily long-acting β2 agonist (LABA). Dahl *et al*[65] confirmed the safety and bronchodilator efficacy of indacaterol over 1 year compared with placebo and twice daily formoterol. In a smaller study, van Noord *et al*[66] reported greater bronchodilation over 7 days in patients receiving a new combination device containing indacaterol and a LAMA compared with indacaterol alone and placebo, though there were no significant differences in reliever use between active groups. The benefits of a once-daily LABA may reside in improved treatment adherence. The importance of this issue was highlighted by Vestbo *et al*[67] in a post hoc analysis of the TORCH study, in which 20% of patients failed to meet their pre-specified criterion for satisfactory adherence (80% adherence) and 8% took less than 60% of their prescribed medication. This is particularly concerning given that participation in a prospective clinical trial is likely to pre-select patients who will be more adherent to treatment. The potential adverse effects of therapy were highlighted in a meta-analysis of observational and controlled trials which suggested a modest but statistically significant increase in fractures in patients receiving inhaled corticosteroids.[68]

Non-pharmacological treatment

The clinical efficacy of pulmonary rehabilitation is now well established but questions remain about the optimum clinical setting and stage of disease for the delivery of pulmonary rehabilitation. Van Wetering *et al*[69] demonstrated significant and lasting improvements in dyspnoea, quality of life and functional outcomes in 200 patients with milder disease (GOLD II–III) who were randomised to receive community-based pulmonary rehabilitation compared with standard care. The programme included supervised physical training with a maintenance phase for 2 years. The health costs of AECOPD have intensified efforts to reduce the burden of unscheduled hospitalisation. Previous reports[70 71] demonstrated that habitual physical activity is an independent predictor of re-hospitalisation providing a rationale for administering pulmonary rehabilitation in the immediate aftermath of an admission for AECOPD. This was tested by Seymour *et al* who conducted a randomised controlled trial of outpatient pulmonary rehabilitation initiated within a week of discharge in 60 patients with COPD. A significant reduction in readmission to hospital at 3 months was observed in the treatment group compared with those receiving usual care. The routine provision of pulmonary rehabilitation following admission for AECOPD is now supported by the revised NICE guidelines.[72] The central role of progressive exercise training as a component of pulmonary rehabilitation is accepted but debate remains about the optimum mode of training. A systematic review surmised that interval training (intermittent bouts of high-intensity exercise) was an equally effective alternative to conventional continuous aerobic training, despite heterogeneity between studies.[73]

Weight loss is an important systemic feature of COPD; it is common and associated with a poor prognosis. Weekes *et al*[74] assigned patients with COPD who were at risk of malnutrition to receive dietary counselling or an information sheet about food fortification. Compared with the control group, the intervention group gained weight, which was maintained over 6 months of follow-up and was associated with improvements in SGRQ score and dyspnoea. The efficacy of nutritional supplementation in underweight patients continues to be debated,[75] but this study suggests that dietary counselling and food fortification could be a useful approach. Pison *et al* addressed this problem in a cohort of underweight patients with chronic respiratory failure by providing a multimodal intervention comprising pulmonary rehabilitation, nutritional support and testosterone supplementation.[76] Improvements in exercise performance and health status were seen in the treatment group. Tantalisingly, although not statistically significant in the intention to treat analysis, the intervention improved survival when patients who completed the protocol were considered.

Case selection for ambulatory oxygen continues to be an important issue for clinicians. Though ambulatory oxygen is often prescribed for patients with exertional dyspnoea who are not hypoxic at rest but desaturate during exercise, this does not have a robust evidence base outside a laboratory setting.[77] The study by Moore *et al*[78] helps to clarify the situation. A total of 143 patients with stable COPD and no resting hypoxia were randomised in double-blind fashion to receive either high flow ambulatory oxygen or air over 12 weeks. Though there were within-group improvements in dyspnoea and depression scores, these were small in magnitude and there were no differences between the two groups. Importantly there was no difference in the response of patients who did and did not desaturate on exertion. The results suggest a substantial placebo effect from the administration of intranasal gas. This is supported by the work of Abernethy *et al*,[79] who observed no short-term effect of supplemental oxygen on refractory dyspnoea in a population of patients with a variety of long-term cardiopulmonary conditions (predominantly COPD) or lung malignancy.

Although long-term home nocturnal non-invasive ventilation (NIV) is clearly beneficial in hypercapnic respiratory failure in restrictive chest wall or neuromuscular disease, its use in COPD continues to be debated. McEvoy *et al*[80] conducted an open-label clinical trial of NIV plus long-term oxygen therapy (LTOT) compared with LTOT alone in 144 patients with hypercapnic COPD. Nocturnal NIV improved survival, but did not affect daytime gases or rates of hospitalisation. Importantly, health status was lower in the treatment group, suggesting the intervention may have been burdensome to patients. The inspiratory pressure was low in this study and this issue was further explored by Dreher *et al*[81] in a small open-label randomised controlled trial comparing low-pressure and high-pressure NIV for patients with stable hypercapnic COPD over 6 weeks. High-pressure support was better tolerated and was associated with physiological improvements. Impacts on longer-term outcomes including survival require further evaluation.

The role of NIV in the management of de-compensated hypercapnic respiratory failure during AECOPD is much clearer. The UK national COPD 2008 audit[82] highlights the high mortality in this group compared with clinical/controlled trials, which had not improved from the 2003 audit. This may in part be due to the substantial use of NIV in more severely ill patients (initial pH <7.26) in whom evidence for a survival benefit is weaker. An additional concern from the audit was evidence that many patients were receiving high flow oxygen during ambulance transfer, which was associated with increased mortality. Pre-hospital titration of oxygen flow rates to a target saturation (88–92%) by ambulance staff can improve survival in patients presenting with AECOPD.[83]

Organisation of care

The increasing health burden of COPD has intensified efforts to improve integration of care for patients with COPD, particularly in the management of AECOPD for which costs are highest. Three studies in *Thorax* explored the impact of self-management treatment plans for AECOPD. Advice on self-management of AECOPD in addition to a broader self-management plan increased medication use but reduced the number of patient-reported exacerbation days.[84] This was supported by a randomised trial of a written exacerbation action plan compared with usual care in 233 patients,[85] with those receiving the action plan showing a more rapid recovery of health status following an exacerbation, although healthcare utilisation was unaffected. In a third study, adherence to written exacerbation self-management plans was low at approximately 40%, with adherence associated with improvement in exacerbation recovery times but no difference in unscheduled healthcare utilisation.[86] The benefits of helping patients manage their disease themselves are starting to emerge but reductions in health costs may not be realised unless they are incorporated into broader, integrated disease management programmes.[87] The problem of hospitalisation for AECOPD is not going to disappear fast! Hopkinson *et al* developed a discharge care bundle for patients who have been hospitalised for AECOPD which was delivered by hospital staff.[88] Compared with historical controls, there was a trend to a reduction in 30-day readmission. Discharge should present an important opportunity to deliver evidence-based interventions and patient education.

Smoking cessation

Smoking cessation in COPD is clearly a high priority. Hoogendoorn *et al*[89] conducted a systematic review of smoking cessation strategies in COPD and concluded that pharmacotherapy combined with 'intensive' counselling (≥90 min) was the most effective and economical overall.

SUMMARY

Thorax has played a key part in understanding the enormity of COPD and its impact on the patient as well as exploring risk factors and appreciating mechanisms. The recognition of the systemic manifestations of COPD supports the current multidisciplinary approach to care. The paucity of new treatments which have substantial impact on disease progression is a concern, and highlights the importance of identifying those at risk, understanding mechanisms and employing early preventive strategies.

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