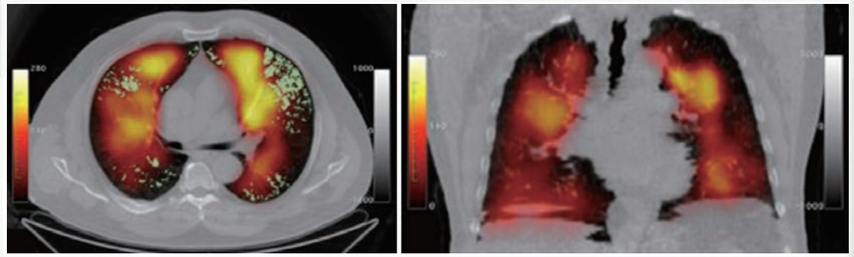
Journal of Thoracic Disease
Volume 6 Number 11 November 2014 Pages 1521-1653

Vol 6, No 11 November 2014 ISSN 2072-1439

JOURNAL of THORACIC DISEASE

www.jthoracdis.com

SPECIAL ISSUE: Chronic Obstructive Pulmonary Disease
Guest Editors: Ian A. Yang and Paul V. Zimmerman



Published by

The Official Publication of

Indexed in PubMed, SCI

Aims and Scope

The *Journal of Thoracic Disease* (JTD, J Thorac Dis, pISSN: 2072-1439; eISSN: 2077-6624) was founded in Dec 2009, indexed in Pubmed/Pubmed Central in Dec 2011, and Science Citation Index (SCI) on Feb 4, 2013. It is published quarterly (Dec 2009- Dec 2011), bimonthly (Jan 2012- Dec 2013), and monthly (Jan 2014-), and openly distributed worldwide. JTD publishes manuscripts that describe new findings in the field to provide current, practical information on the diagnosis and treatment of conditions related to thoracic disease (lung disease, cardiac disease, breast disease and esophagus disease). Original articles are considered most important and will be processed for rapid review by the members of Editorial Board. Clinical trial notes, Cancer genetics reports, Epidemiology notes and Technical notes are also published. Case reports implying new findings that have significant clinical impact are carefully processed for possible publication. Review articles are published in principle at the Editor's request. There is no fee involved throughout the publication process. The acceptance of the article is based on the merit of quality of the manuscripts. All the submission and reviewing are conducted electronically so that rapid review is assured.

The Official Publication of:

- Guangzhou Institute of Respiratory Disease (GIRD)
- China State Key Laboratory of Respiratory Disease
- First Affiliated Hospital of Guangzhou Medical University
- Society for Thoracic Disease (STD)

Endorsed by:

- International COPD Coalition (ICC)

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Cover image:

Technegas ventilation SPECT/CT fusion images of a 68-year-old man with moderately severe COPD. (See P1577 in this issue).

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Preface

Chronic obstructive pulmonary disease (COPD) is a world-wide problem that is increasing in prevalence. COPD is a chronic lung disease characterised by persistent airflow limitation that is not fully reversible. COPD is the third leading cause of death world-wide. It is a heterogeneous disease, with multiple aetiological factors, clinical phenotypes and comorbidities. Acute exacerbations and progressive decline in lung function contribute to symptoms and outcomes. It is vitally important that we develop a deeper understanding of this complex chronic disease, in order to enhance the preventive and therapeutic strategies for patients with COPD, with the ultimate goal of effective management using a "personalised medicine" approach.

This 'Hot Topics in COPD' Supplement of the *Journal of Thoracic Disease* addresses innovative and emerging areas at the leading edge of our understanding of COPD, in the fields of pathogenesis (microbiome, biomarkers, inflammation), diagnosis (spirometry, imaging) and treatment (guidelines, self-management, pulmonary rehabilitation, anxiety and depression, oxygen therapy, lung transplantation and other emerging therapies). We thank the authors who, as leading researchers in these areas, have contributed state-of-the-art reviews and perspectives of these critical topics.

The lung microbiome

The lung was previously thought to be a sterile organ in health; however, this is now known not to be the case. The bacterial communities present in the normal lung, collectively called the lung microbiome, have important implications for patients with COPD. Chambers and colleagues (1), in their invited perspective, alert us to the potential role of the lung microbiome in COPD, particularly in pathophysiology, cellular and molecular biology, and clinical phenotypes. Their article calls for a greater appreciation of the impact of altered microbial diversity in the lung, through the use of novel culture-independent techniques to identify all of the microbes present in COPD lung. In this way, patterns of bacterial diversity can be better understood in COPD, with a view to developing treatment approaches that would rebalance bacterial communities in the lung.

Emerging biomarkers for COPD

Given the complexity of COPD as a chronic disease, the development of biomarkers would be useful for detecting the presence of COPD, characterising COPD phenotypes, and monitoring response to treatment. Shaw and colleagues (2) have catalogued the remarkably large number of biomarkers associated with various aspects of the pathogenesis and clinical manifestations of COPD. When focussing particularly on predicting the rate of disease progression, the numbers of biomarkers are far fewer. Their review appraises the current knowledge about radiological, sputum, blood, exhaled breath and other biomarkers for COPD, including those linked to response to air pollution or ageing.

Insights into chronic lung inflammation

COPD is characterised by persistent and excessive inflammation, both in the lungs and systemically. In their review, Bozinovski and colleagues (3) argue that specific mediators fail to turn off the excessive inflammation that is present in COPD. This has implications for the recruitment and survival of inflammatory cells within the airways, leading to a heightened and prolonged chronic inflammatory response. They provide evidence that multiple mediators converge on a central receptor system (ALX/FPR2) of the N-formyl peptide receptor family. Future non-steroid-based treatments targeting inflammation could therefore be developed (including analogs that stimulate this receptor), to promote resolution of chronic inflammation in the lung.

Advances in spirometry

The spirometric measures of FEV_1 and FVC remain the cornerstone of the diagnosis of well-established COPD. The underutilisation of spirometry in primary care can delay the recognition of COPD. This in turn can delay advice to avoid

aggravating factors such as smoking and can delay commencement of therapy, thereby contributing unnecessarily to the burden of this disease. Extensive small airway disease can develop before traditional spirometric indices become abnormal. An interesting new approach to the early recognition of small airways disease described Johns and colleagues (4) involved measuring indices of curvature of the expiratory limb of the flow-volume loop. It has yet to be shown whether intervention at this early stage can reverse the pathological processes or slow the rate of progression of the airways or parenchymal involvement.

Functional lung imaging

A number of imaging modalities are available to characterise the structure of the lung, to define morphological abnormalities in COPD. However, advancing imaging techniques are now being used to identify physiological consequences of COPD i.e., both structural and functional changes. Stephen Milne and Greg G. King (5) describe CT- and nuclear medicine-based techniques, as well as highly novel approaches such as micro-CT, synchrotron imaging, optical coherence tomography and electrical impedance tomography. As these techniques are developed further and applied clinically, greater accuracy will be available to measure lung mechanics and ventilation/perfusion abnormalities in COPD, to increase our understanding of lung pathophysiology, enable subphenotyping of COPD, and to monitor changes with treatment.

Improving uptake of clinical guidelines for COPD

Adherence to treatment guidelines has been shown to be surprisingly suboptimal by clinicians treating patients with COPD. The production of management guidelines involves an inherent assumption that compliance with the recommendations contained in such guidelines will produce tangibly improved outcomes for individuals with COPD. The evidence for this is well-established as reported in the review by Overington and colleagues (6), and centres mainly on strong engagement with clinicians about guidelines, effective dissemination and integrated systems for their implementation. Hence it is reasonable to expect that enhanced uptake of guideline recommendations into everyday practice would improve clinical outcomes for COPD, through more successful prevention, earlier detection, and better management to slow disease progression and reduce complications.

New developments in self-management of COPD

Self-management is an important element of the chronic disease management of patients with COPD. It is now increasing recognised that the patient's multi-morbidities also impact significantly on self-management strategies. Effing and co-workers (7) describe their efforts to improve on traditional self-management programs, by including action plans for common comorbidities (e.g., heart failure, ischaemic heart disease, metabolic disease, and psychological factors). They outline practical approaches to behavioural change in patients, and highlight safety features such as access to case managers. Ultimately, the goal is a fully integrated, holistic approach that is patient-focused, yet supported by health care professionals in primary and tertiary care.

Improving access to pulmonary rehabilitation

Pulmonary rehabilitation is of proven benefit for symptomatic patients with COPD, with reductions in symptoms, improvements in exercise capacity and quality of life, and decreased rate of hospital admissions. However, access to pulmonary rehabilitation programs is difficult, due to limited resourcing. In their systematic review, Jennifer A. Alison and Zoe J. McKeough (8) provide evidence for the efficacy of exercise training using minimal equipment. Although the number of clinical trials in this specific field was relatively small, the pooled differences showed benefit in terms of improved six minute walk distance and improved St. George's Respiratory Questionnaire for health-related quality of life. This timely systematic review sets the scene for further, large-scale studies of minimal equipment pulmonary rehabilitation programs.

Managing anxiety and depression as comorbidities of COPD

As described in the review by Pumar and co-authors (9), the presence of anxiety and depression in COPD patients has been shown to be associated with increased mortality, exacerbation rates, length of hospital stay, and decreased quality of life and functional status. It is not yet known, however, whether anxiety and depression are independent predictors of outcome. The authors highlight that there is currently no consensus on the most appropriate approach to screening for anxiety and depression. Furthermore, the most effective treatment modalities have not yet been ascertained by rigorous studies. However, it is likely that patients will certainly benefit symptomatically from early recognition and appropriate intervention. Whether COPD-specific outcomes can be enhanced by treating anxiety and depression is still to be determined.

State-of-the-art use of oxygen therapy for COPD

The use of long-term oxygen therapy in COPD patients with resting hypoxaemia is well-established. Nevertheless, the evidence for its use in milder severities of hypoxaemia is not as certain. In her wide-ranging review, Christine F. McDonald (10) re-examines the landmark studies of long-term oxygen therapy in COPD, with critical appraisal of study design and in the context of other advances in management of COPD. The evidence for use of supplemental oxygen in nocturnal or exertional hypoxaemia is not as clear. Other situations for potential use of oxygen therapy in COPD are evaluated, including palliative care, acute exacerbations and during pulmonary rehabilitation. This helpful review ends with a call to action for multicentre data registries and larger prospective trials of oxygen therapy (including placebo arms) for specific subgroups of COPD patients.

Lung transplant and novel bronchoscopic therapies for COPD

Treatment of advanced lung disease has long been a focus of clinicians, clinical researchers and policy-makers. Trotter and co-authors (11) provide an interesting discussion of 'what's on the horizon' for lung volume reduction and lung transplantation for patients with COPD. They provide an insight into emerging bronchoscopic lung volume reduction techniques that have been recently implemented or are emerging. These include endobronchial valve therapy, bronchial thermal vapour ablation and lung volume reduction coils. Advances in lung transplantation selection, surgery and medical management are outlined, including successful reconditioning of marginal donor organs using *ex vivo* lung perfusion. Fortunately, these established and emerging therapies are now increasing the management options for patients living with advanced COPD.

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doi: 10.3978/j.issn.2072-1439.2014.11.28
Disclosure: The authors declare no conflict of interest.
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.11.28

Cite this article as: Yang IA, Zimmerman PV. Preface. J Thorac Dis 2014;6(11):1521-1524. doi: 10.3978/j.issn.2072-1439.2014.11.28

Review Article

JTD special edition 'Hot Topics in COPD'—The microbiome in COPD

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Abstract: The pathogenesis of chronic obstructive pulmonary disease (COPD) and its exacerbations, are intricately linked to colonisation and infection with bacteria and other microbes. Despite their undeniable importance, we have a poor understanding of the complex relationships between COPD phenotypes, physiology, cellular and molecular biology and the roles of colonising microbe or infecting pathogens. The management algorithms for the care of patients with COPD that include microbial influences, have almost exclusively been developed using microbial methods that were entirely dependent on the ability to grow bacteria on suitable media. The shortcomings of this approach are becoming clear now that it is possible to completely and accurately define the microbial ecology of ecosystems using genomic methods, which do not rely on the ability to cultivate the organisms present. Whilst our appreciation of the relationships between some bacterial ecosystems and the organ in which they reside in humans is now relatively advanced, this is not true for lung. This perspective serves to highlight the growing importance of including an accurate description of bacterial ecology in any attempt to decipher the pathobiology of COPD. While this field is in its infancy, there is significant potential to gain new insights which will translate into more rational and effective treatment algorithms for patients with COPD.

Keywords: Chronic obstructive pulmonary disease (COPD); microbiome; metagenomics

Submitted Jun 21, 2014. Accepted for publication Sep 03, 2014.
doi: 10.3978/j.issn.2072-1439.2014.11.08
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.11.08

Introduction

Throughout history many inventions have radically altered the way we are able to perceive the world—the telescope, the microscope, lenses for those with refractive errors and cochlear implants for those with deafness. A similar revolution has recently occurred in the way we are able to observe the microbial world. The genomic methods and biostatical approaches which can now be employed to comprehensively determine the structure of microbial communities have transformed the study of microbial ecology and will have a similar impact on our understanding of human health. What should be self-evident—that we have evolved not in a sterile world, but in one teeming with microbes (our cells are outnumbered 10:1 by our gut bacteria alone) where each species has their own evolutionary agenda, but is also open to collaboration—has been brought into clear focus. The idea that infectious disease is a two-sided battle to the death has been exposed as simplistic, with symbiotic relationships between host and microbe being at least as prevalent and important to human health in some organs (especially the gut, but possibly also the lung). The implications for diseases like COPD where microbial colonisation and infection is central to pathogenesis are obvious and are the subject of this perspective.

What is the microbiome and how can we 'see' it?

The microbiome can be defined as the collective sum of microorganisms (and their genomes) inhabiting a given

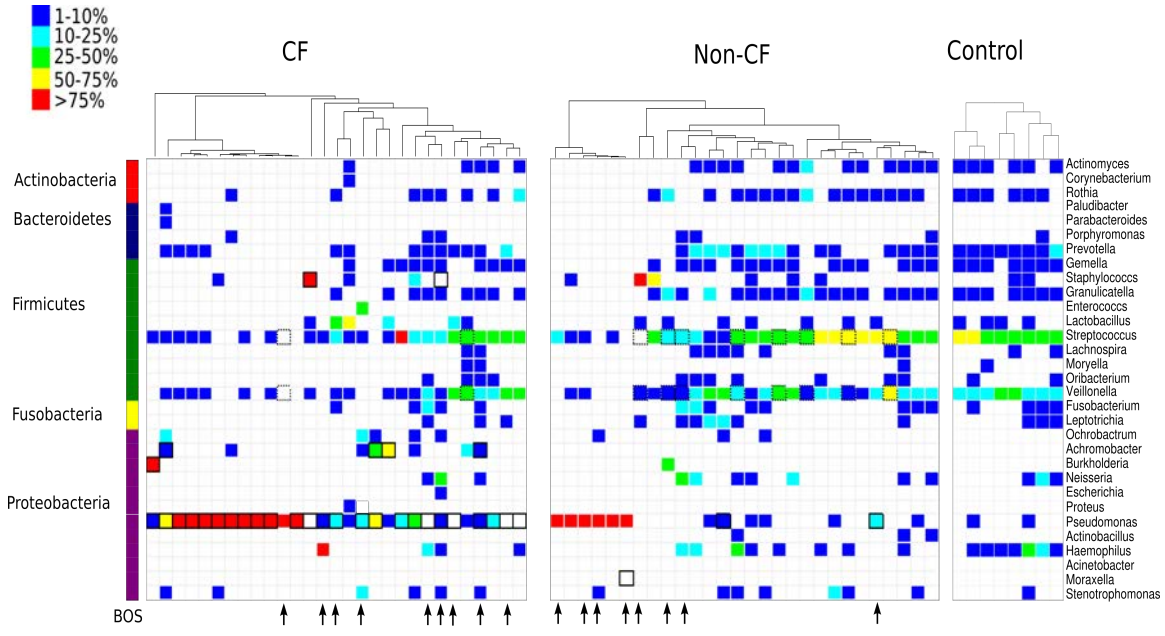

Figure 1 Bacterial community profiling using high throughput DNA sequencing of a highly conserved bacteria-specific gene (*16S rRNA* gene). In this example the microbial community composition in bronchoalveolar lavage samples obtained from lung transplant patients and controls is shown. Samples are clustered based on weighted Unifrac distance. Phylum level taxonomy is presented on the left and genus level taxonomy on the right. Arrows identify samples from individuals with bronchiolitis obliterans syndrome (BOS—the commonest form of chronic rejection). Solid black outlined boxes in the heat map represent organisms identified in pre-transplant sputum culture. In this example, loss of *Pseudomonas* from the allograft microbiome is associated with BOS in cystic fibrosis (CF) ($P<0.01$, exact logistic regression). Reprinted with permission of the American Thoracic Society from Willner DL, Hugenholtz P, Yerkovich ST, *et al.* Reestablishment of recipient-associated microbiota in the lung allograft is linked to reduced risk of bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2013;187:640-7. Copyright © 2014 American Thoracic Society.

ecosystem. In the case of the human microbiome that ecosystem is us. Traditional microbiological methods have been blind to the majority of the microbiome for the simple reason that most microorganisms have not been readily grown in the laboratory and thereby become amenable to manipulation and interrogation at the human-scale. Things began to change in the 1980s when it was recognised that microorganisms could be catalogued by their gene sequences, primarily the highly conserved 16S rRNA marker gene, without the need to grow them (1). This was the birth of culture-independent molecular microbiology. First, bulk nucleic acids are extracted from a biological sample and the target gene is PCR-amplified from the extracted DNA.16S rRNA is so conserved that it is possible to target all cellular lifeforms using "universal" PCR primers, which allows essentially all microorganisms in a given sample to be amplified in one PCR reaction. The mixture of 16S rRNA amplicons were then historically separated by cloning into *E. coli*, but now are sequenced in parallel using cloneless next generation sequencing technologies such as 454 pyrosequencing or Illumina sequencing. The 16S rRNA amplicon sequences are then quality trimmed, compared to each other and typically clustered into operational taxonomic units (OTUs) and finally identified against a reference database. The number of reads assigned to each OTU for a given sample provides relative abundance information to create a community profile, an example of which is provided in *Figure 1*. Through such cataloguing surveys, it quickly became apparent that most microbial (evolutionary) diversity, roughly 85%, was not captured by our collection of domesticated microbial isolates (2). Moreover, in many instances, microorganisms isolated from a given habitat were, at best, bit players in ecosystem function (3). Combining 16S rRNA microbial profiling with 'metadata' such as disease state, physiology, etc., has proven to be a powerful way of identifying statistically significant correlations between the microbiome and disease that can be used for example as diagnostic biomarkers (4).

Today, gene-based surveys are still heavily used in microbiome research, but they have also evolved into genome-based (metagenomic) surveys courtesy of greatly improved sequencing and computational technologies (5). Taking a census of the total genetic inventory of a given ecosystem not only tells us who is there, but also what they are potentially capable of doing. Complementary molecular methods such as metatranscriptomics and metaproteomics, which identify mRNA transcripts and proteins respectively, can tell us which genes and pathways are being expressed under a given set of conditions (5). Consequently our understanding of the microbiome in humans has exploded in recent years (6).

The 'normal pulmonary microbiota'—does it exist?

Even today most medical students are taught that the lung is sterile. This idea was founded on data obtained in an era when non-selective genomic techniques were unavailable, so that microbial identification relied on basic general culture systems that were blind to 99% of bacterial species. Community profiling and metagenomic approaches now facilitate comprehensive characterization of the human microbiota and analysis of its role in health and disease. Given the extraordinary ability of microbes to adapt to even very hostile environments it seems unlikely that complete sterility of the lower respiratory tract that is continually exposed to the environment could be maintained, at a reasonable energy cost, given the enormous microbial load delivered with each breath. Although a number of studies purporting to confirm the presence of a healthy pulmonary microbiome have been published (7-10), all are in some way (as openly acknowledged by the authors) methodologically deficient either due to the acquisition of lower respiratory tract samples bronchoscopically (7-9), where oropharyngeal contamination is impossible to exclude, and/or due to the acquisition of lower respiratory tract material from potential organ donors (10) or lung resections (10). Organ donors will have invariably experienced gastric aspiration and/or ventilator associated bacterial colonization/infection (11), and lung resections from healthy subjects are difficult to obtain. A further difficulty is that the normal pulmonary microbiota, should it exist, will be many log lower than the surrounding human biomass, complicating DNA amplification and sequencing. Despite these deficiencies, the emerging model is that the human respiratory tract is not neatly compartmentalized into upper and lower tracts and hence the question of lung sterility is not a binary one. Intermittent colonisation of the lower respiratory tract occurs, even in healthy individuals, with more persistent or permanent colonisation being common in certain scenarios. Dickson *et al*., recently borrowed the 'adapted island model' from ecology to describe this pulmonary biogeography (12). While beyond the scope of this review, their work provides a convincing and useful framework for understanding lung ecology, and provides an intriguing perspective from which to view pneumonia. In their proposed model pneumonia does not occur as the result of a large inoculum of a pathogenic species overwhelming host defences, but as a small but snowballing disruption in the complex adaptive lung microbial ecosystem (12). A COPD exacerbation could be viewed in the same way. In summary, while these new models provide a more realistic framework for understanding the interactions between the human lung and the respiratory tract microbiota, the fundamental question remains whether this interaction is so intimate as to be classified as mutualistic or symbiotic.

Confirmation of such a relationship would imply benefit for both the microbiota and the host and would carry profound implications for our understanding of lung health. At the most basic level, we would need to reconsider what 'self' means in the context of lung immunology. In the best studied human system—the gut—it is clear that a healthy microbiota is critical to the development of both local and systemic immune responses and the maintenance of epithelial integrity. Perturbations in this symbiotic relationship ('dysbiosis') have been implicated in the pathogenesis of inflammatory bowel disease and the metabolic syndrome (13,14). Much of the literature on COPD microbiology has been written with the idea that the now colonised/infected lung was previously sterile. It is intriguing to think that a normal pulmonary microbiota may exist and that the act of its displacement by other organisms may in itself be detrimental to host health. In the lung, dysbiosis could predispose the host to excessive immune activation and/or loss of epithelial integrity—key features of multiple lung diseases including asthma, COPD and idiopathic pulmonary fibrosis. It could be that cigarette smoke induced dysbiosis, or disruption of lung biology by cigarette smoke, in conjunction with host genetic factors, may be important in COPD pathoegenesis, and, as a corollary, that restoring the microbiome could improve host health, opening the door to more subtle and more nuanced, but potentially highly effective, therapies.

What's known about the microbiome in COPD?

Only a handful of studies have been published exploring

the role of the lung microbiome in COPD and therefore our understanding this interaction remains in its infancy. Due to the heterogeneity of COPD features, particularly as they relate to disease severity, various studies have sought to evaluate the lung microbiome in stable or exacerbating disease states, in healthy patients *vs.* those with COPD, or in COPD compared to unrelated lung diseases such as cystic fibrosis (CF) or asthma. They have assessed the microbiome from differing parts of the airways and via different sampling techniques. As a result of these issues, the data that has resulted are not easily compared with each other and lack consistency.

Nevertheless these studies have produced valuable associative data on the changes in the microbiome in COPD. The major phyla that are associated with the normal lung microbiome appear to be Proteobacteria, Firmicutes, Bacteroidetes, and Actinobacteria, and most studies agree that this is regardless of the presence of COPD, its status or severity (8-10,15,16). These studies have demonstrated no apparent difference in the total bacterial load nor in diversity. However, principle component analyses have revealed that the microbiome of COPD patients clusters separately (and therefore differs) from that of healthy controls. This is partly driven by increases in members of the phylum Firmicutes in patients with stable COPD (8,10,15,16). In severe COPD, however, the microbiome is unlike that of mild disease. In two notable studies using lung explants (2,3) and one using sputum (17) from severely affected COPD lungs compared to healthy controls, a shift was observed to a decrease in lung microbiome diversity driven partly by increases in Proteobacteria. This correlated with a shift towards the dominance of particular bacterial genera, especially *Pseudomonas* although one must consider that this effect could be influenced by bacterial induced exacerbations. Three studies have demonstrated a decrease in diversity during exacerbations and with antibiotic treatment and a further decrease in diversity with increasing severity and persistence of these disease flares (17-19). As a majority of all COPD exacerbations are associated with respiratory infections (20) this finding is not surprising. Nevertheless, no study has definitively shown that a reduction in COPD microbiome diversity in the lung has caused the outgrowth of a particular bacterial genera or an increase in bacterial load. This is difficult to assess in humans but may be investigated using animal models that are representative of the human condition (21-24).

One important issue with investigations thus far is sample collection. Cabrera-Rubio *et al.*, assessed the microbiome from bronchial aspirates, sputum, bronchial lavage (BAL) and bronchial mucosal brushings. They found that the microbial diversity was lower and the load was higher in samples collected from the upper (aspirate and sputum) compared to the lower respiratory tract (BAL and mucosa). Furthermore, Erb-Downward *et al.*, found that the microbial community in tissue from lung explants differed depending on the location from which the sample was taken, even within same patient (8). This indicates that the COPD lung microbiome is not homogeneous.

Recently it has become clear that inhaled corticosteroid use in COPD is associated with an increased risk of pneumonia (25,26). At present this observation, whilst very robust, remains empiric with little understanding of the mechanisms that lead to pneumonia, who may be at highest risk, and how that risk may be mitigated in the face of continued drug exposure. It is likely that answers to these highly relevant and clinically important questions will come through the deeper understanding of bacterial ecology in the COPD lung which is now obtainable with ecogenomic approaches (19).

Host-pathogen interactions in lung disease

Whilst exposure to environmental irritants, particularly cigarette smoke, is obviously central to COPD pathogenesis, airway infection also plays a role both in exacerbations and in disease progression even during the 'stable' phase of the illness (27). However, not all bacteria are created equal in this regard. For the best-studied pathogen, *Haemophilus influenzae*, it is clear that some strains induce more inflammation (particularly IL-8 induced neutrophilic inflammation) than others (16). However, given that most of the literature in this field was developed using traditional microbial techniques, the roles and/or impact of bacterial ecosystem was not incorporated into these studies.

When a host encounters a potential threat, annihilation of the threat is only one of the defence strategies available to ensure survival. In some cases, attempted annihilation may do more harm than good through collateral damage to host tissues. Other than this traditional concept of 'resistance' the other strategies available to the threatened potential host include 'avoidance' of the threat prior to infection as well as 'tolerance' (28). In the lung, the mechanisms of resistance (e.g., the innate and adaptive immune responses) and avoidance (e.g., nasal hairs, the cough reflex and the mucociliary escalator) are well described, but the concept of tolerance is poorly studied. Nevertheless, we see examples of tolerance in our thoracic clinics every day.

For instance, patients with CF live for decades with a

microbial load in the lower respiratory tract that would probably be fatal to most hosts. Tolerance to infection, or so called 'disease tolerance' does not represent a failed eradication effort, but rather a highly specific host defence strategy which minimises the negative health effects of infection, without directly affecting pathogen burden (28). Chronic *Pseudomonas* infection in the CF lung is an example and is associated with classic features of the tolerant state, including tolerance to endotoxin (29) and polarisation of circulating monocytes toward an M2 phenotype. These cells are characterised not only by reduced secretion of pro-inflammatory cytokines like TNFα and secretion of anti-inflammatory cytokines like IL-10, but also an impaired capacity to present antigen despite markedly enhanced phagocytic activity (29). Recently, as would be predicted from the disease tolerance model, multiple investigators have noted that host health is dissociated from *Pseudomonas* biomass in CF (30-32), and similar observations have been made in lung transplant recipients (33). Recently, and again in the setting of lung transplantation, we have demonstrated that tolerance to *Pseudomonas* translates into allograft tolerance (*Figure 1*) (34). It is likely that gaining a better understanding of the tolerogenic mechanisms in operation at the interface of the airway mucosa and the role of commensal bacteria will provide important insights into COPD pathogenesis, and potentially guide the development of new treatments. This will depend heavily on accurately describing commensal microbial ecology in the COPD lung, an aim now achievable through the application of metagenomic techniques.

The microbiome in COPD—is it only about the lung?

Most microbiome studies to date have involved the gastrointestinal (GI) tract and diseases at that site such as colitis. Yet it is increasingly being recognised that changes to the GI microbiome can have profound effects on extraintestinal organs.

One of the earliest observations has been the effect of antibiotics on obesity. It has long been known that antibiotics can lead to increased weight gain in farm animals and have been used as growth factors in standard practice in many countries since the 1950s (35). This observation has been closely investigated and links have been shown between antibiotic use and obesity in mice (36), and with weight gain in malnourished humans (37). Metagenomics of the gut microbiome in murine studies has revealed that antibiotics cause a shift in microbial populations to those capable of producing short chain fatty acids as metabolites. These metabolites have been associated with improvements to colonic and systemic health. Furthermore the antibiotics caused an upregulation of liver enzymes involved in lipogenesis and triglyceride synthesis (36). Other studies have demonstrated gut microbiome effects on diabetes and atherosclerosis through alterations in the metabolites produced by the microbes that mediate communication between the microbiome and its host (38,39).

To date, the involvement of the microbiota in lung health has only been inferred through associative studies. There are no studies that demonstrate a direct effect of changes to the lung microbiome causing a subsequent change to lung health. This is in part due to the field's infancy, and because the microbial load in the lung is low and the potential for contamination with microbes from the oral cavity and/or nasopharynx during sampling is high. However, studies are emerging that highlight the involvement of the gut microbiome in maintaining lung health and in contributing to lung disease. Ichinohe *et al*., demonstrated that mice treated with oral antibiotics had diminished immune responses when subsequently infected with influenza (40). Specifically, treated mice had significant reduced influenza antibody titres and CD4 and CD8 T-cell responses. In another study, Russell *et al*., demonstrated that neonatal mice given oral vancomycin had increased immune responses in the lung when challenged with ovalbumin in a model of allergic asthma. These mice also had increased airway hyperresponsiveness compared to untreated mice (41). Complementary to this, Ong *et al*., were able to demonstrate a strong association in children given antibiotics in the first year of life with the development of both transient and persistent asthma. These associations were strong even when children who received antibiotics for respiratory tract infections were excluded (42).

In regard to COPD, it has been known for many years that smoking impacts intestinal as well as lung health (43). Furthermore, there is a strong association between inflammatory bowel diseases and COPD, with many patients are also affected with Crohn's disease (44,45). Moreover, smoking and smoking cessation have been recently shown to have clear effects on the microbiome of the gut (46). Thus, the evidence suggests that smoking can affect gut microbiota which in turn may induce systemic effects.

Conclusions & future directions

Since bacterial colonisation and infection is common in COPD and is central to the pathogenesis of exacerbations, gaining a more comprehensive understanding of lower

respiratory tract bacterial ecology in patients with COPD is likely to be of considerable importance. The tools to achieve this objective are now readily available, but in order to make sense of the findings in stable COPD, the more fundamental question 'do we have a normal lower respiratory tract microbiota?' will need to be answered. It is also apparent that accurate determination of the makeup of the lower respiratory tract microbiome is confounded in studies where access to the lower respiratory tract is gained via the oropharynx where the bacterial biomass is high, even if a protected brush is used (47). Animal studies and approaches to obtaining human material surgically (e.g., at the time of lung resection and transplantation) can circumvent this difficulty. In the future, determining the makeup of the microbiome in healthy smokers and patients with mild COPD will assist in determining whether dysbiosis is a triggering event for COPD progression or whether it is a biomarker of more severe disease. Furthermore, it is likely that non-bacterial microbes will contribute to COPD pathogenesis, so determining the makeup of the viral and fungal microbiomes (the 'virome' and 'mycobiome'), alongside the bacterial microbiome, in COPD will also be key objectives. These studies will complement, and may, in terms of their impact on the practice of medicine, even outshine the findings of the genomic era which began with the sequencing of the human genome (48).

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Chambers DC, Gellatly SL, Hugenholtz P, Hansbro PM. *JTD* special edition 'Hot Topics in COPD'—The microbiome in COPD. J Thorac Dis 2014;6(11):1525-1531. doi: 10.3978/j.issn.2072-1439.2014.11.08

Review Article

Biomarkers of progression of chronic obstructive pulmonary disease (COPD)

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Abstract: Disease progression of chronic obstructive pulmonary disease (COPD) is variable, with some patients having a relatively stable course, while others suffer relentless progression leading to severe breathlessness, frequent acute exacerbations of COPD (AECOPD), respiratory failure and death. Radiological markers such as CT emphysema index, bronchiectasis and coronary artery calcification (CAC) have been linked with increased mortality in COPD patients. Molecular changes in lung tissue reflect alterations in lung pathology that occur with disease progression; however, lung tissue is not routinely accessible. Cell counts (including neutrophils) and mediators in induced sputum have been associated with lung function and risk of exacerbations. Examples of peripheral blood biological markers (biomarkers) include those associated with lung function (reduced CC-16), emphysema severity (increased adiponectin, reduced sRAGE), exacerbations and mortality [increased CRP, fibrinogen, leukocyte count, IL-6, IL-8, and tumor necrosis factor α (TNF-α)] including increased YKL-40 with mortality. Emerging approaches to discovering markers of gene-environment interaction include exhaled breath analysis [volatile organic compounds (VOCs), exhaled breath condensate], cellular and systemic responses to exposure to air pollution, alterations in the lung microbiome, and biomarkers of lung ageing such as telomere length shortening and reduced levels of sirtuins. Overcoming methodological challenges in sampling and quality control will enable more robust yet easily accessible biomarkers to be developed and qualified, in order to optimise personalised medicine in patients with COPD.

Keywords: Pulmonary disease; chronic obstructive; disease progression; biological markers (biomarkers); lung; sputum; blood

Submitted Jul 28 2014. Accepted for publication Nov 21, 2014.
doi: 10.3978/j.issn.2072-1439.2014.11.33
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.11.33

Chronic obstructive pulmonary disease (COPD) is a chronic, inflammatory lung disease that arises from exposure to cigarette smoke and other inhaled toxins, and results from a gene-environment interaction (1). Disease progression of COPD is variable, with some patients having a relatively stable course, while others suffer relentless progression leading to severe breathlessness, frequent acute exacerbations of COPD (AECOPD), respiratory failure and death. This review will initially focus on radiological markers, and biological markers (biomarkers) in lung tissue, sputum and blood, which may be useful in predicting disease progression in COPD. Emerging approaches to discovering markers of gene-environment interaction will then be discussed, including exhaled breath analysis, exposure to air pollution, the lung microbiome, and lung ageing.

Measurements of disease progression in patients with COPD

Decline in lung function has been the classical objective

measure of progression of COPD over time. However, other clinically important measures have been used in epidemiological studies and clinical trials, including symptoms and health status, exacerbations and health care utilisation, and mortality.

Lung function

Lung function, particularly the forced expiratory volume in 1 second (FEV_1), provides an objective, physiological measure of worsening airflow obstruction in COPD. The classic Fletcher and Peto study (2) described variable decline in lung function in a cohort of male workers, with some smokers being more susceptible to accelerated decline. A range of clinical and demographic factors has been shown to influence decline in lung function in COPD, such as environmental and occupational pollutants, cigarette smoking, respiratory infections, exacerbations and comorbidities (3). The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort study of 2,163 patients observed a mean rate of decline in FEV_1 of 33 mL/year, with higher rates of FEV_1 decline in the presence of current smoking, emphysema and bronchodilator reversibility (4).

Symptoms and exacerbations

The Global Initiative for chronic obstructive lung disease (GOLD) guidelines recommend the inclusion of symptom assessment and exacerbation history, together with measurement of the severity of airflow limitation measured by FEV_1 (5). The ECLIPSE study confirmed that patients with 2 or more exacerbations per year (frequent exacerbators) were at higher risk of future exacerbations, and this risk was further increased with more severe airflow limitation (6). Change in health status is also an important measure of disease progression (1).

Mortality

COPD is the third leading cause of death world-wide, after ischaemic heart disease and stroke (7). This high rate of mortality is driven by increased smoking worldwide, reduced mortality from other treatable diseases and an ageing world population (5). Groups at high risk of mortality, as described in the Copenhagen City Heart Study of 10,457 participants, included those with lower baseline FEV_1 and excessive longitudinal decline in FEV_1, even before the point where their lung function becomes abnormal (8).

It is evident that a multitude of relevant clinical phenotypes portrays the disease progression of COPD, which reflects the heterogeneous and complex nature of this chronic disease.

Biomarkers for disease progression of COPD

Biomarkers are any clinical features, imaging quantification or laboratory-based test markers that characterise disease activity, which are useful for diagnosing and monitoring disease processes and response to therapy. Recent excellent reviews have summarised putative biomarkers for detecting the presence of COPD, characterising COPD phenotypes and monitoring response to treatment (9-11). Biomarkers of acute exacerbations have also been reviewed (12).

Identifying individuals with COPD who are at higher risk of progression would enable more personalised management, in order to slow disease progression. Use of biomarkers would potentially add to existing strategies for smoking avoidance, pharmacotherapy, pulmonary rehabilitation and chronic disease management in COPD. Benefits from measuring biomarkers for COPD progression (and not only susceptibility to COPD) include identifying patients who are rapid decliners in the early stages of the disease, predicting disease progression in all severity groups of COPD, and quantifying response to treatment.

The search for reliable biomarkers in COPD, other than FEV_1, is ongoing [e.g., the international efforts by the COPD Biomarker Qualification Consortium (9)]. Providing reliable evidence to validate biomarkers before clinical implementation remains an important challenge. Important issues to be addressed include the accuracy and reliability of biomarkers for the clinical state of interest, evaluation of clinical utility and cost-effectiveness, and real world effectiveness compared to other biomarkers (13). The validation of biomarkers (biomarker qualification) for COPD would be clinically applicable to risk stratification of patients and outcome markers of efficacy and safety in drug development and other clinical trials (9).

Radiological markers for emphysema, airway thickness, bronchiectasis and multi-morbidities

Image biomarkers, especially radiological features of COPD morphology visualised on high resolution computed tomography (CT) chest scans, have been found to be useful

predictors of disease progression.

Emphysema and airway wall thickness

High resolution CT is able to assess emphysema and airway disease using quantitative indices (14). Inspiratory *vs.* expiratory analysis of distribution of parenchymal (emphysema) and functional small airways disease provides information about COPD phenotype (15), and change in lung density over time can itself be measured as an endpoint of COPD progression (16).

Quantitative CT measurements have been associated with outcomes of COPD progression in large cohort studies. Accelerated decline in lung function has been associated with more severe emphysema measured quantitatively by CT (17). The MESA (Multi-Ethnic Study of Atherosclerosis) study found that the presence of centrilobular and panlobular emphysema correlated with increased dyspnoea and reduced exercise capacity (18). Airway wall thickness correlated with reduced lung function and increased symptoms in smokers in a cross-sectional study (19). In the COPDGene study of 1,002 subjects, exacerbations were more frequent in those subjects who had a more severe CT emphysema index, and who displayed increased airway wall thickness (20). A higher CT emphysema index was associated with increased risk of respiratory (21,22) and COPD-specific mortality (23). Airway wall thickness was not independently associated with mortality (22).

Bronchiectasis

Bronchiectasis frequently coexists with COPD. Bronchiectasis is a persistent or progressive condition that is characterised by dilated, thick-walled bronchi that fail to clear airway secretions normally. This leads to bacterial infection and a chronic cough productive of sputum, recurrent infective exacerbations and ultimately, lung destruction and respiratory failure (24). In some COPD patients, bronchiectasis is an incidental finding on CT and may be subclinical, as observed in the ECLIPSE study where the overall prevalence of bronchiectasis was 4% in a highly selected population of milder COPD patients (25). In contrast, studies of moderate to severe COPD have demonstrated a higher prevalence of bronchiectasis of from 30% to 60%, with more extensive bronchiectasis in severe COPD (26-28).

The presence of bronchiectasis influences respiratory infections and other complications of COPD. In a study of patients with moderate to severe COPD, patients with COPD and co-existing bronchiectasis, compared to COPD alone, had more severe airflow obstruction (OR 3.9) and an increased yield of potentially pathogenic microorganisms on sputum culture (OR 3.6) (29). Furthermore, bronchiectasis increased the rate of at least one hospital admission for an AECOPD in the previous year (OR 3.0). In a subsequent study of 201 patients with moderate to severe COPD, the same investigators showed that bronchiectasis was independently associated with increased all-cause mortality (HR 2.5) (30). Conversely, a study of 245 patients with non-cystic fibrosis bronchiectasis in Belgium found that 17% of patients had co-existing COPD (31). Over 5 years of follow-up, patients with both bronchiectasis and COPD had a mortality rate of 55%, which was considerably higher than 13% in patients with bronchiectasis alone (31).

These studies emphasise the clinical impact of coexisting bronchiectasis in patients with COPD, especially in terms of excessive rates of AECOPD and mortality. Detecting bronchiectasis in patients with COPD from their routine HRCT chest scans may therefore be potentially clinically useful, identifying those patients who are predisposed to higher rates of exacerbations and increased mortality.

Coronary artery calcification (CAC)

Cardiovascular multi-morbidity is highly prevalent in patients with COPD, and adversely affects mortality. A high prevalence of coronary artery disease has been associated with emphysema severity (32). CAC is a marker of coronary artery disease (*Figure 1*), and its extent is directly associated with the total burden of coronary atherosclerosis (33). Whilst CAC can be measured using calcium scores on gated, non-contrast CT scans, the use of simple visual scores of CAC has also found utility in lung cancer screening studies (34). In a cross-sectional study of 200 patients with moderate to severe COPD, we observed a high prevalence of CAC (87%) on routine CT chest scans (35). Of prognostic importance, a moderate to high ordinal visual score for CAC (>4 out of a possible 12) was predictive of increased all-cause mortality (HR 2.0) in these patients with COPD (35) (*Figure 2*). This association was independent of duration of cigarette smoking. Similarly in the ECLIPSE study, a higher coronary artery calcium score percentile was associated with increased mortality (HR 1.77) in COPD patients (36). The results of these radiological studies suggest the scoring of CAC severity on CT chest

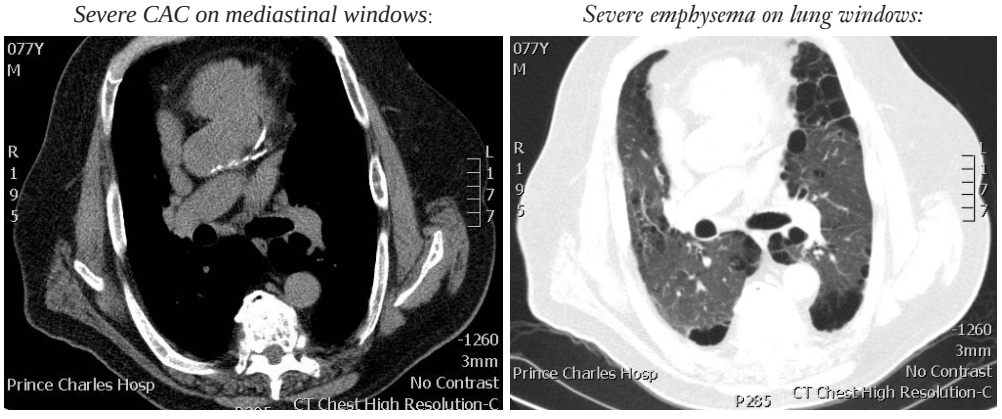

Figure 1 CAC on CT chest scan in a 77-year-old male patient with COPD and emphysema. CAC, coronary artery calcification; CT, computed tomography. Reproduced with permission from (3).

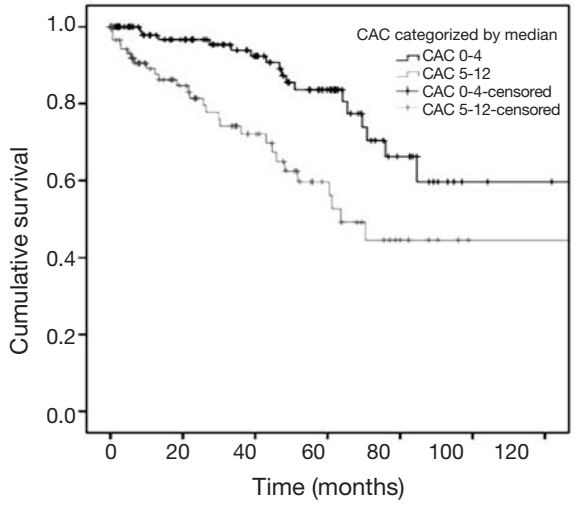

Figure 2 Kaplan-Meier survival curves for all-cause mortality for COPD patients, according to CAC score >4 (CAC 0-4 n=109, CAC 5-12 n=91). The Kaplan-Meier survival curve (censored at 120 months) shows that COPD patients with CAC scores of 5 to 12 (dichotomised by the median of 4) had higher mortality than patients with CAC scores of 0 to 4 (log rank test, P=0.001). CAC, coronary artery calcification. Reproduced with permission from (35).

scans can non-invasively screen for coronary artery disease in patients with COPD with important prognostic implications.

Lung tissue: gene expression markers

Molecular changes in lung parenchyma are a direct reflection of alterations in lung pathology that occur with disease progression in COPD. Routine collection of lung samples is only feasible in patients undergoing lung surgery. Nevertheless, molecular changes in lung tissue provide valuable insight into biomarkers that may be expressed and therefore usefully measured in accessible samples (e.g., sputum, exhaled breath condensate and blood).

A number of studies have used microarrays to examine differences in global mRNA expression between chronic lung disease and normal lung samples (37,38). Other studies have extended this approach by profiling gene expression across different severity stages of COPD. A study of lung tissue from COPD patients (n=21 GOLD stage 0; n=9 stage I; n=10 stage II; n=3 stage III) showed that gene expression correlated with forced expiratory flow between 25% and 75% of forced expiratory volume ($FEF_{25-75\%}$), a measure of small airways function (39). Upregulated genes included those involved in pathways of apoptosis and extracellular matrix synthesis and degradation; down-regulated genes included anti-inflammatory genes. A study of 56 lung tissues (no COPD, to COPD patients from mild to severe) found correlation of FEV_1 % predicted and FEV_1/FVC with functional classes of genes involved in DNA binding and transcription (40).

Studies from our group have also provided evidence for differences in gene expression signatures in the earlier stages of COPD disease progression. We have undertaken a study of lung tissue of 30 smokers with emphysema undergoing lung resection for lung cancer, with biological validation in an independent set of 62 patients (41). All patients had airflow limitation with FEV_1/VC ratio <0.70 and were arbitrarily classed, based on gas transfer, as mild (KCO ≥75% of predicted) or moderate (KCO <75% of predicted) emphysema. Gene expression profiling

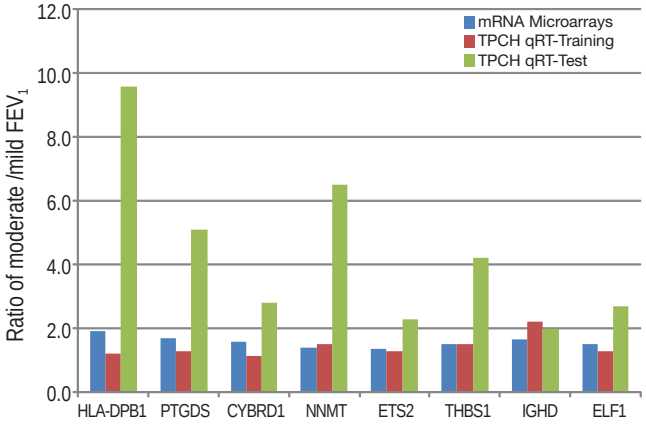

Figure 3 Comparison of mRNA expression differences in non-tumour lung tissue between mild and moderate COPD patients, based on FEV_1 % predicted. Fold-changes are shown for eight candidate genes measured by gene expression microarrays (TPCH training set, n=30), and qRT-PCR (technical replication: TPCH training set, n=30; biological validation: TPCH test set, n=58). NNMT, nicotinamide N-methyltransferase; THBS1, thrombospondin 1; IGHD, immunoglobulin heavy delta chain; HLA-DPB1, major histocompatability complex, class II, DP Beta 1; PTGDS, prostaglandin D2 synthase; CYBRD1, cytochrome B-Reductase 1; ETS2, erythroblastosis virus E26 oncogene homologue 2; ELF1, E74 like factor 1. Reproduced with permission from (42).

and confirmatory PCR identified seven genes that were differentially expressed in moderate emphysema, compared to mild emphysema by more than 1.3-fold: *COL6A3*, *SERPINF1*, *ZNHIT6*, *NEDD4*, *CDKN2A*, *NRN1* and *GSTM3* (41). Our additional study of lung tissue from patients with mild (n=9) or moderate (n=9) COPD, based on FEV_1 % predicted, with validation in an independent set of 58 lung samples, confirmed differential expression of eight genes (*NNMT*, *THBS1*, *HLA-DPB1*, *IGHD*, *ETS2*, *ELF1*, *PTGDS* and *CYRBD1*) by more than 1.8-fold between mild and moderate COPD severity (42) (*Figure 3*). Ontologies represented by these genes were predominantly cell migration, proliferation, angiogenesis and apoptosis (42). Using the same lung tissue, we have also shown that expression of microRNA-34c is associated with emphysema severity, and modulates SERPINE1 expression in COPD lung (43). Genes and pathways associated with severity of COPD, including the early stages of progression, could therefore be tested as lung biomarkers for progression of emphysema and airflow obstruction in COPD.

Gene expression profiling of specific cells or regions of COPD lung provide additional information about distinct gene signatures for disease progression. Expression of repair genes was examined in 136 paired small airways and emphysema lung tissue obtained by laser capture microdissection from 63 patients (44). Genes involved in tissue destruction were more commonly increased in expression in emphysematous lung tissue and correlated with impaired FEV_1, whereas these genes were not as highly expressed in the small airways, thereby promoting bronchiolar remodelling rather than destruction (44). In a study of 238 smokers with or without COPD, gene expression in bronchial brushings was similar to the expression in lung tissue, and this gene expression was regulated in part by activating transcription factor 4 (ATF4) (45). Finally, distinct gene signatures were observed in fibrotic and emphysematous areas of lung, in patients with combined pulmonary fibrosis and emphysema (46). Fibrotic regions expressed genes associated with immune function, and emphysematous areas expressed genes related to cellular fraction, membrane biology, and vascular biology (46), demonstrating that functional differences in gene expression occur with different lung pathologies. Overall, these studies show that specific cells and pathologies in the lung are likely to yield characteristic biomarkers that reflect individual COPD phenotypes of progression.

Sputum: inflammatory cells and mediators

Sputum has been studied as a non-invasive method of sampling biomarkers to assess disease severity and progression in COPD, including exacerbations. Many COPD patients can produce spontaneous sputum samples. However, these often contain a high proportion of non-viable cells which may influence the cell count and mediator profile. To overcome this, sputum can be induced with hypertonic saline in stable patients with COPD, with good safety and reproducibility for cell counts and inflammatory markers (47). Induced sputum also has an adequate safety profile during acute exacerbations, as demonstrated in studies of patients with mild to moderate (48) and moderate to severe COPD (49). Because of many technical and clinical confounding factors (such as interference with assays, smoking status of patients, bacterial infection and concomitant treatment), induced sputum is still undergoing investigation as a source of clinically useful biomarkers (9).

Sputum biomarkers during stability have been associated with severity of COPD. Sputum neutrophil count increased

with GOLD stage but was only weakly associated with lung function in the ECLIPSE study (50). Higher levels of human neutrophil peptides (HNP), neutrophil elastase (NE), interleukin (IL)-8 and matrix metalloproteinase (MMP)-9 in spontaneous sputum of COPD patients were associated with greater decline in lung function (FEV_1) over 2 years (51). In the ECLIPSE study, microarray profiling of gene expression in induced sputum from 148 COPD patients (and validated in 176 patients) found 277 genes differentially expressed between moderate, severe and very severe GOLD classes, and 198 genes that were differentially expressed between severities of emphysema (52). Further validation is required to test the clinical utility of these genes as biomarkers for COPD progression.

During exacerbations, sputum cell and mediator profiles are heterogeneous and can predict response to therapy of the exacerbation (53). The presence of a mixed inflammatory cell profile in the sputum, together with increased concentrations of sputum and serum biomarkers, were found in patients with exacerbations who had lower FEV_1 and increased hospital length of stay (53). Inflammatory mediators in induced sputum during stability may predict future risk of exacerbations. A review by Koutsokera and co-workers found that levels of some mediators in sputum [including in sputum IL-6, IL-8 and myeloperoxidase (MPO)] may be associated with frequency of exacerbations, although more confirmatory studies are needed (12). In a longitudinal study with monthly visits, sputum levels of leukotriene B_4 were found to be elevated prior to an exacerbation, and were suggested as possible biomarkers for exacerbation risk (54).

Blood biomarkers: monitoring the systemic compartment

Blood samples provide a convenient source of biomarkers of lung disease. The relevance of blood biomarkers depends on release of markers from the lung into the bloodstream, or systemic markers present in the blood that reflect active disease processes in the lung.

A range of blood biomarkers has been associated with severity of airflow limitation and emphysema. Reduced levels of serum club (Clara) cell protein 16 (CC-16), a protein produced in the lungs and released to the serum, were weakly associated with accelerated decline in lung function (FEV_1) in both the Lung Health Study (55) and ECLIPSE study (4). In the TESRA (Treatment of Emphysema with a Selective Retinoid Agonist) and ECLIPSE studies, reduced serum levels of soluble receptor for advanced glycation endproducts (sRAGE) were associated with more severe GOLD stage and more extensive emphysema (56). Lower levels of sRAGE were similarly associated with more advanced emphysema or lower FEV_1 in two other studies (57,58). In the ECLIPSE cohort, low levels of vitamin D were correlated with FEV_1 and severity of emphysema and associated with 6-minute walk distance, bronchodilator response and CC-16 levels (59). In a subset of the COPDGene cohort, emphysema quantified on CT was associated with higher plasma levels of the adipokine, adiponectin (60) and lower levels of plasma IL-16 (61). Plasma YKL-40 has been associated with higher all-cause mortality (HR 1.4) in a cohort of 493 COPD patients in Denmark (62). Thus a range of biomarkers detectable in peripheral blood show potentially promising relationships with COPD phenotypes.

Panels of blood biomarkers may provide more accurate modelling of future risk. In the Grosshansdorf COPD cohort of 140 COPD patients, clusters of plasma proteins involved in neutrophil function were associated with parameters related to FEV_1 (63). Furthermore, proteins related to the epidermal growth factor receptor (EGFR) pathway were associated with gas transfer (DLCO) and FEV_1 (63). A panel of three systemic inflammatory markers in peripheral blood (CRP, fibrinogen and leukocyte count) was tested in 6,574 individuals with COPD (defined as FEV_1/VC ratio <0.7) in the Copenhagen City Heart Study and the Copenhagen General Population Study (64). Elevation of all three biomarkers simultaneously was associated with an increased risk (OR 3.7) of having frequent exacerbations. This association was observed even in subjects with milder COPD and those with no history of frequent exacerbations (64). In the ECLIPSE study, adding the full range of studied blood biomarkers [white blood cell counts, fibrinogen, chemokine ligand 18, surfactant protein D, CRP, Clara cell secretory protein-16, IL-6, IL-8, tumor necrosis factor α (TNF-α)] to the model of age, BODE index and previous COPD hospitalisations improved prediction of mortality (65). A refined panel of six systemic inflammatory markers in peripheral blood (white cell count, fibrinogen, CRP, IL-6, IL-8, TNF-α) in the ECLIPSE study was able to predict increased mortality and exacerbation rates in COPD patients with inflammation, compared to patients without inflammation (66). Of these, currently plasma fibrinogen is being considered for regulatory qualification as a prognostic marker by the US Food and Drug Administration and the European Medicines Agency (9,67).

Because of the large number of putative biomarkers, heterogeneity in study design and evaluation, a formal systematic review of this emerging field is beyond the scope of this review.

Emerging gene-environment approaches to biomarkers of disease progression in COPD

In addition to the more traditional sampling of biomarkers described above, emerging approaches to capturing the effects of gene-environment interaction on COPD disease progression are receiving more focus in research studies. Of these, analysing biomarkers in exhaled breath is a potentially useful, non-invasive method of sampling the airways and epithelial lining fluid that is exposed to the environment. In addition to cigarette smoking, exposure to air pollution and infection are important environmental drivers of COPD progression and phenotypes. Finally, lung ageing, whilst an endogenous chronological factor, also brings with it exposure to internal and external factors over many years, and should be integrated into the complex profiling of COPD.

Exhaled breath analysis

Volatile organic compounds (VOCs)

Advances in technology have produced small, portable array type devices (electronic noses) that are highly applicable to the clinical setting. Electronic noses use a variety of technologies to emulate the human nose, with VOCs adsorbing onto sensors to produce a change in conductivity, colour or oscillation of a crystal, leading to readouts that are analysed. These devices approach the problem of detection from an entirely different viewpoint from that of the gas chromatograph: in the same way a human nose can tell the difference between the bouquet of chocolate and a rose without needing to know the chemical constituents of the vapour, so the electronic nose is able to discriminate between two vapour mixtures without needing to characterise the exact molecules responsible.

Exhaled breath analysis using differing technologies, including gas chromatography-mass spectrometry and the electronic nose, can discriminate between a range of pulmonary diseases (68), including COPD and asthma (69,70). Relatively few studies to date have linked VOCs profiling of the exhaled breath with COPD progression. A recent study showed that the VOCs pattern is reasonably reproducible in healthy subjects and patients with severe COPD and has some correlation with tests of small airways disease (71). VOCs pattern was shown to differentiate between some phenotypes of COPD, such as patients with higher sputum eosinophilia or frequent exacerbations (72).

Identifying the neutrophilic and eosinophilic inflammatory phenotypes of COPD would further aid in tailoring effective treatment. A strong association between sputum cell count and exhaled breath compounds has been demonstrated in subjects with mild to moderate COPD (GOLD stages I and II) (73). Moreover, VOCs profiling was able to discriminate between subjects with COPD and α_1-antitrypsin (AAT) deficiency, with very high accuracy, and the VOCs profile of AAT deficiency patients changed with human recombinant AAT therapy, indicating a possible marker of response to treatment (74). However, before widespread application in the clinical setting, methodological issues of VOCs testing need to be overcome, and more extensive validation is required (75).

Exhaled breath condensate (EBC)

Collection of cooled exhaled breath as condensate is a non-invasive method of sampling the airway lining fluid (76). To date, a small number of studies have examined EBC biomarkers and COPD progression. EBC pH was found to be lower in former smokers with GOLD stage III to IV COPD, compared to stage I (77), suggesting that airway acidification could be a marker of airway inflammation and disease severity in COPD, although not all studies have shown a relationship with FEV_1 (78). EBC pH is also reduced during acute exacerbations (79). EBC hydrogen peroxide (H_2O_2), a marker of oxidative stress, has been shown to correlate with COPD health status as measured by the COPD assessment test (CAT) (80). Methodological issues such as dilution and sensitivity of assays, as well as interpretation of clinical factors that impact on EBC analysis, still require to be solved in larger studies (9).

Exposure to air pollution

The predominant sources of particulate matter in the lungs of COPD patients are cigarette smoke and ambient air pollution (81). With up to 25-45% of patients with chronic airflow limitation being never smokers (82), it is evident that non-smoking-related factors (e.g., air pollution) play a role in the progression of COPD (82,83). Exposure to air pollution should therefore be characterised as a factor that influences disease outcomes in COPD.

Vehicle emissions are a major contributor to air pollution

in the urban environment. The main components of vehicle emissions are particulate matter less than 10 μm in diameter (PM_{10}), nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) (84). Recent epidemiological studies have observed strong associations between air pollution exposure and COPD outcomes, including exacerbations, hospital admissions and mortality (*Table 1*). The repetitive nature of the inhalation injury caused by air pollution is considered a major mediator in the COPD progression (81). Chronic exposure to air pollution, specifically vehicle emissions, has been linked to increased hospital admissions of COPD patients, including those who are never smokers (89). Analysis of early evidence showed that long-term exposure to particulate matter can lead to a reduction in lung function and increased COPD incidence and progression (81). These studies and others (86,87) support the notion that exposure to air pollution is a driver of COPD progression in susceptible individuals.

Monitoring of air quality occurs for legislative and public health requirements, as well as epidemiological research. However, real-time monitoring of personal air pollution exposure and biomarkers of the adverse effects of ambient air pollution are still in development (93). *In vitro* studies have elucidated gene and protein expression profiles of human bronchial epithelial cells, in response to air pollutant exposure (3), which could be brought to clinical testing with further validation. EBC levels of nitrite and nitrate (markers of oxidative stress) were associated with concentrations of ambient coarse particles, but not indoor air pollutant levels, in four cities in Europe (94). Systemic responses to air pollutants were studied in 242 stable COPD patients in Spain (95). In this time series analysis, blood levels of CRP, fibrinogen, HGF and IL-8 were associated with increased ambient NO_2 levels, mainly detected in former smokers.

At present, little is known about the molecular mechanisms by which air pollution can promote progression of COPD, and further studies are needed in this field.

Lung microbiome

Bacteria are strongly associated with AECOPD, with bacteria cultured in ~50% of patients with an AECOPD (96). Chronic airway infection with bacteria (colonisation of the airways by bacteria) is more common in patients with severe COPD (97). Whether chronic infection contributes to the pathogenesis of airway inflammation and increasing frequency and severity of AECOPD is not known. The 'vicious circle' hypothesis outlines the principles that chronic microbial colonisation, alters innate immunity and airway epithelial injury contributes to the progression of both COPD and other chronic lung diseases such as bronchiectasis (28,98). According to this paradigm, the presence of chronic bacterial infection in the airways, (including during stable disease), may drive inflammation and disease outcomes.

The microbiome describes the microbial community that share an environment in a particular body site. Next-generation sequencing is used to identify these microbial populations which include microbes that are unculturable (99). Characterising the microbiome is rapidly emerging as an important approach to unravelling the complex microbiology of chronic lung diseases (100) [outlined in detail in this issue of the Journal by Daniel Chambers and colleagues (101)]. The community composition of microbial communities can be determined by sequencing the variable regions of the 16S gene, which encodes bacterial ribosomal RNA (rRNA) (98). Published studies of the lung microbiome in COPD have recruited relatively small numbers of patients, with a range of methods of sampling the microbiome (*Table 2*). Furthermore, few studies to date have applied study of the lung microbiome to outcomes of COPD progression. In general, tobacco smoking in the absence of COPD does not appear to alter the lung microbiome, but severe COPD is associated with less population diversity of resident bacterial communities, although even this result seems dependent on whether BAL or airway tissue is being sampled (96,103,106).

In COPD, bacterial community profiles in BAL samples from patients using inhaled steroids and long-acting bronchodilators clustered differently from the profiles observed in patients not using these medications (105). Infection with respiratory viruses increases the total bacterial load in patients with COPD, compared to similarly infect healthy controls, but with no obvious difference in bacterial diversity based on analysis of sputum samples (106).

These alterations to the lung microbiome have considerable potential implications for the pathogenesis and progression of COPD. Predominance of one bacterial species in an anatomical lung region (e.g., affected by bronchiectasis) could reduce bacterial diversity, leading to disruption of the balance between mucosal immunity and the bacterial communities present (airway dysbiosis). Alteration of the normal balance of bacterial flora may lead to an excessive inflammatory response, perpetuating the airway inflammation that is characteristic of COPD (98). The microbiome is an emerging source of biomarkers of respiratory infection and possibly COPD progression.

Table 1 Examples of recent studies of air pollution exposure and COPD outcomes

Study	Location	Study design	Main findings
Waked 2012 (85)	Lebanon	◆ Cross-sectional analysis of Lebanese residents over 40 years from October 2009 to September 2010 ◆ Out of 2201 individuals, 732 were never smokers, and 3.4% had COPD ◆ Lung function and exhaled carbon monoxide levels were measured	◆ Correlation between COPD incidence and indoor air pollution from house warming with diesel, as well as childhood respiratory disease and older age
Gan 2013 (86)	Canada	◆ Longitudinal study with a 5-year exposure period and 4 year follow up period ◆ 467,994 participants, with no COPD baseline and an age range between 45-85 years old	◆ Black carbon was strongly associated with risk of COPD hospitalization and mortality (which was attenuated when demographic factors such as age and sex were accounted for) ◆ 6% increased risk of mortality and 7% increased risk of hospitalization with higher levels of exposure
Hansel 2013 (87)	USA	◆ Longitudinal study to investigate the effects of indoor PM and NO_2 concentrations on COPD morbidity in a peri-urban community ◆ Pollutant concentrations measured at baseline, 3 and 6 months ◆ 84 participants with moderate to severe COPD	◆ Indoor pollutant exposure to $PM_{2.5}$ and NO_2 was associated with increased respiratory symptoms and risk of COPD exacerbations
Wang 2013 (88)	Taiwan	◆ Time series analysis of outpatient visits and air pollution in the context of a heavily polluted urban area	◆ NO and NO_2 were positively associated with respiratory disease, but also some association was seen for PM_{10}, $PM_{2.5}$, O_3, CO and SO_2 ◆ COPD outpatients were most sensitive to air pollution and weather
Schikowski 2014 (89)	Europe	◆ Impact of chronic exposure to air pollution on COPD in four cohorts ◆ The annual average of PM_{10}, NO_2 and road traffic exposure was assessed	◆ In meta analyses, NO_2, SO_2, PM_{10} and the traffic indicators were positively associated with COPD ◆ Significant positive association with traffic intensity and COPD incidence in never smokers
Tao 2014 (90)	China	◆ Time series analysis of PM_{10}, SO_2 and NO_2 and respiratory hospitalizations ◆ 28,057 recorded admissions for respiratory disease	◆ Significant positive association between air pollutants and respiratory hospitalizations, and stronger effects were observed for females and persons aged ≥65 years
Zhou 2014 (91)	China	◆ Cohort of 71,431 middle-aged Chinese men from 25 different cities ◆ Annual average particulate matter exposure was estimated and compared to total, cardiovascular and respiratory disease mortality	◆ 1.7% increase in respiratory mortality per 10 μg/m^3 increase in PM_{10}
Vanos 2014 (92)	Canada	◆ Investigation into the relative risk of mortality from all non-accidental, respiratory, and cardiovascular related causes, associated with exposure to four air pollutants, by weather type and season, in ten major Canadian cities	◆ In total, 61% of the respiratory-related mortality relative risk estimates were significantly higher than for cardiovascular-related mortality. The combined effect of weather and air pollution is greatest when tropical-type weather is present in the spring or summer

COPD, chronic obstructive pulmonary disease; PM_{10}, particulate matter less than 10 μm in diameter; NO_2, nitrogen dioxide; SO_2, sulfur dioxide.

Table 2 Microbiome studies of COPD patients and smokers

Study	Population	Main findings
Hilty 2010 (102)	11 asthma, 5 COPD, 8 controls—bronchial brushings	Microbiota present in bronchial tree. Proteobacteria more frequent in COPD and asthma
Huang 2010 (96)	8 COPD, mechanically ventilated—endotracheal aspirates	Presence of diverse bacterial communities in airways of COPD patients with severe exacerbation
Erb-Downward 2011 (103)	4 COPD, 7 smokers, 3 never-smokers—BAL; 6 severe COPD—lung tissue explants	Lung microbiome distinct from oral microbiome. Lower diversity in more severe COPD; Pseudomonas predominance. Differences in bacterial communities within lung sites in severe COPD
Cabrera-Rubio 2012 (104)	6 moderate COPD—sputum, bronchial wash, bronchial biopsy, BAL	High bacterial diversity. Sputum and washings – different microbiota to BAL and biopsies
Pragman 2012 (105)	22 moderate to severe COPD, 22 controls—BAL	Increase in microbial diversity in COPD. No difference with increasing severity. Differences based on inhaler therapy
Sze 2012 (99)	8 severe COPD, 8 CF, 8 smokers, 8 never-smokers—lung tissue	Lower bacterial density and differences in bacterial populations in severe COPD lung tissue
Molyneaux 2013 (106)	14 COPD, 17 controls infected with rhinovirus—induced sputum	Increase in bacterial burden in COPD after RV infection, including Haemophilus influenzae
Morris 2013 (107)	19 smokers, 45 non-smokers—BAL, oral wash	Higher abundance of some bacteria in the lungs. No difference between smoker and non-smoker lung microbiota
Zakharkina 2013 (108)	9 COPD, 9 controls—BAL	Diverse bacteria present in healthy lungs and COPD, different bacterial taxa in COPD
Galiana 2014 (109)	9 mild/moderate COPD, 10 severe COPD—sputum	Increased total bacterial load in severe COPD
Huang 2014 (110)	60 samples from 12 mild/moderate/severe COPD patients in a longitudinal study—sputum	Altered microbial communities with acute exacerbation, and with type of treatment for exacerbation (antibiotics, steroids or both)
Millares 2014 (111)	11 severe COPD; 5 COPD colonised by PA—sputum	Increased biodiversity during exacerbation in PA-infected sputum, to equal non-PA sputum

COPD, chronic obstructive pulmonary disease; PA, Pseudomonas aeruginosa.

Lung ageing

Ageing is an endogenous rather than exogenous factor, representing cumulative exposures to environmental factors over time. A wide range of phenotypes and biomarkers of ageing are currently being investigated in chronic diseases, including COPD (112,113). Examples of potential relevance to COPD progression include telomere shortening and sirtuins.

Telomeres are protective structures of repetitive sequence that stabilise the ends of chromosome by preserving genetic information and preventing DNA degradation (114,115). Telomere length varies between different cell types, tissues and individuals. Shortening of telomere repeats occurs naturally with cell division, with the shortened telomere ends eventually acting as a signal for apoptosis (116,117). For example, the reduction rate of telomere repeats in peripheral blood mononuclear cells is measured at approximately 84 bp per year, with an accompanying progressive decrease in telomerase activity, in healthy individuals under 40 years of age (118). Telomere length is also a predictor of years of healthy life in older persons (119). Because of this relationship with biological age, telomere length has been associated with ageing and age-related diseases such as COPD. Telomeres are shorter in peripheral blood leukocytes of COPD patients (120,121), particularly cigarette smokers (122,123), providing a common risk factor for accelerated ageing and replicative senescence in COPD.

Telomere length has been linked with lung function

in large population studies. A population study of 46,396 subjects (120) found an association between reduced leukocyte telomere length and COPD, and a weak correlation with lung function (FEV_1, FVC, FEV_1/FVC). A second study found circulating leukocyte telomere length was reduced in patients with COPD (n=934) compared to controls (n=15,846), and more strongly correlated with lung function in never smokers than in smokers (122). Telomeres were found to be relatively preserved in patients with AAT deficiency, compared to non-AAT-related, aged-matched COPD subjects, and there was good correlation between blood and lung telomere lengths (with blood being shorter on average) (124). Of prognostic importance, short leukocyte telomere length was associated with increased risk of all-cause mortality (HR 1.29), compared to longer telomeres, in 4,271 subjects with mild to moderate COPD in the Lung Health Study (125).

Sirtuins (SIRTs) are NAD^+-dependent deacetylases and are members of the silent information regulator 2 (Sir2) family (126), with seven homologues in man, SIRT1-7 (127). This family of enzymes is involved in gene silencing and several studies have demonstrated that SIRT1, an anti-inflammatory and anti-ageing protein, is decreased in the lungs of patients with COPD and peripheral blood mononuclear cells in COPD (128-130). Sirtuins also control resistance to oxidative stress and DNA repair (130) and SIRT1 activation reduces cigarette smoke-induced oxidative stress (131). MMP-9 is down regulated by SIRT1 and reduced levels of SIRT1 may cause structural changes in the lung tissue (126,132,133). Sirtuins were shown to be suppressed by cigarette smoking in the large airways of asymptomatic smokers and not in the small airways, whereas in COPD a greater suppression of sirtuin expression was seen in both the large and the small airways (127). Thus there is emerging evidence to suggest that a reduction in sirtuin expression is involved in accelerated lung ageing and pathogenesis of COPD (112).

Conclusions

COPD is a heterogeneous and complex chronic lung disease with extrapulmonary manifestations. Identification of clinically applicable biomarkers would help to screen for and diagnose COPD, monitor disease activity and progression, and guide response to therapy. Similar to other chronic diseases, the search for relevant biomarkers is certainly expanding rapidly in COPD. However, access to samples remains a major issue. Gene expression profiling of lung tissue has identified genes whose expression differs in COPD according to severity, but markers derived from lung tissue are not routinely available for clinical disease monitoring, whereas sputum and blood are readily accessible. Biomarkers in blood, especially inflammatory markers such as fibrinogen, are associated with exacerbations and mortality in larger COPD cohort studies. Much more work is needed to assess blood and sputum biomarkers against disease progression outcomes in COPD. Emerging approaches to studying gene-environment interaction, which impacts on disease pathogenesis and progression in COPD, are providing promising leads for novel biomarkers. These include (I) sampling exhaled breath for VOCs and exhaled breath condensate for protein markers; (II) characterising responses of the lung to inhaled air pollutants; (III) applying knowledge of the lung microbiome to COPD phenotypes; and (IV) determining the significance of biomarkers of ageing such as telomere attrition. Overcoming methodological challenges in sampling and quality control will enable more robust yet easily accessible biomarkers to be developed and applied to optimise personalised medicine in patients with COPD.

Acknowledgements

We thank the patients and staff of The Prince Charles Hospital for their involvement in our research program.
Funding: NHMRC Career Development Fellowship 1026215 (IY), NHMRC Practitioner Fellowship 1019891 (KF), Australian Research Council (ARC) Discovery Grant DP120100126 (IY), Queensland Health and Medical Research project grants (IY, KF, RB), The Prince Charles Hospital Foundation project grants (IY, KF, RB) and PhD scholarship (AV).
Authors' contributions: All authors contributed to preparing the manuscript, and approved the final version.
Disclosure: The authors declare no conflict of interest.

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Cite this article as: Shaw JG, Vaughan A, Dent AG, O'Hare PE, Goh F, Bowman RV, Fong KM, Yang IA. Biomarkers of progression of chronic obstructive pulmonary disease (COPD). J Thorac Dis 2014;6(11):1532-1547. doi: 10.3978/j.issn.2072-1439.2014.11.33

Review Article

Targeting pro-resolution pathways to combat chronic inflammation in COPD

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Abstract: Chronic obstructive pulmonary disease (COPD) is an inflammatory lung condition that is associated with irreversible airflow obstruction as a consequence of small airways disease, excessive mucus production and emphysema. Paradoxically, excessive inflammation fails to control microbial pathogens that not only colonise COPD airways, but also trigger acute exacerbations, which markedly increase inflammation underlying host tissue damage. Excessive production of leukocyte mobilising cytokines such as CXCL8 (IL-8) and leukotriene B4 (LTB_4) in response to environmental stimuli (cigarette smoke and microbial products) are thought to maintain chronic inflammation, in conjunction with inefficient macrophage clearance of microbes and apoptotic neutrophils. In this perspective, we discuss an alternative view on why inflammation persists with a focus on why pro-resolution mediators such as lipoxin A4 (LXA_4), D-series resolving and Annexin A1 fail to effectively switch off inflammation in COPD. These pro-resolving mediators converge on the G-protein coupled receptor, ALX/FPR2. This receptor is particularly relevant to COPD as the complex milieu of exogenous and host-derived mediators within the inflamed airways include agonists that potently activate ALX/FPR2, including Serum Amyloid A (SAA) and the cathelicidin, LL-37. There is emerging evidence to suggest that ALX/FPR2 can exist in alternative receptor conformations in an agonist-biased manner, which facilitates alternate functional receptor behaviors. Hence, the development of more stable pro-resolving analogs provides therapeutic opportunities to address ALX/FPR2 conformations to counteract pathogenic signaling and promote non-phlogistic clearance pathways essential for resolution of inflammation.

Keywords: ALX/FPR2; chronic obstructive pulmonary disease (COPD); inflammation; catabasis; resolution; Serum Amyloid A (SAA)

Submitted Jun 20, 2014. Accepted for publication Jul 18, 2014.
doi: 10.3978/j.issn.2072-1439.2014.08.08
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.08.08

Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health issue and is a leading cause of morbidity and mortality worldwide (1). Cigarette smoke exposure is a primary cause of COPD and as smoking rates continue to rise in South-East Asia, the long disease latency of COPD will impact dramatically on global health care resources for many decades to come. It is also well established that environmental influences such as indoor and outdoor air pollutants contribute to the development of chronic lung disease in individuals with no smoking history (2). Pathologically, COPD manifests into impaired lung function and irreversible airflow obstruction as a consequence of small airways disease, excessive mucus production and the development of emphysema. The mechanisms that drive such deleterious remodelling processes are heterogeneous in nature; however it is evident that chronic inflammation and excessive oxidative stress become central to the progression of COPD (3).

Nature of persistent inflammation in COPD

Innate and adaptive immune cells accumulate with

progression of COPD. CD8+ T cells increase with disease severity and can release proteolytic enzymes that contribute to apoptosis of structural cells (4). CD4+ T cells, B cells and dendritic cells also aggregate into organised tertiary lymphoid organs (TLOs), which are found in COPD lungs and experimental models of chronic cigarette smoke exposure (5). The significance of these lymphoid follicles has yet to be established, where B cell accumulation may prove to be beneficial in terms of antibody production to colonising and invading pathogens, or detrimental through autoantibody production against lung tissue antigens (6). Of note, targeted disruption of TLO formation through neutralisation of CXCL13 does not reduce lung inflammation and alveolar enlargement in a chronic smoke exposure model (7), suggesting that immune cells of the innate system are sufficient to drive pathological changes that occur in COPD. In addition, inflammation does not fully resolve even when individuals with COPD stop smoking. Inflammation persists in bronchial biopsies and in sputum samples from COPD patients when compared to asymptomatic smokers (8-10). In particular, neutrophilic inflammation remained elevated in COPD subjects who had ceased smoking for at least one year (8-10). Given that neutrophils are a relatively short-lived immune cell; their persistence in COPD indicates that there is continual recruitment of leukocytes into the airways even when the primary insult of smoke exposure is removed.

Smoke exposure is particularly deleterious to host immunity against respiratory pathogens. Macrophage function is compromised in a microenvironment where there is excessive oxidative stress, leading to a deficiency in phagocytosis of bacteria (11) and efferocytosis of apoptotic cells (12). Free radicals have been shown to impair clearance mechanisms by directly causing cytoskeletal instability and carbonyl modification of pseudopodia (13-15). Macrophages also interact with carbonyl-adduct modified extracellular matrix proteins, which impair their ability to clear apoptotic neutrophils (16). Reduced macrophage function is consistent with high colonisation rates in COPD, where up to 50% of COPD patients are chronically colonized with microorganisms including Haemophilus influenzae, Streptococcus pneumoniae and Moraxella catarrhalis (17,18). Impaired immunity to respiratory pathogens also contributes to susceptibility to acute exacerbations of COPD (AECOPD), which are predominately caused by a new respiratory pathogen that is different to the colonized pathogen (19). AECOPDs result in a more rapid decline in lung function (20), which adversely affects mortality rates (21) and health related quality of life (22). Viral infections are a common cause of AECOPDs (23,24), as are bacterial infections, which are associated with a marked increase in neutrophilic inflammation (25).

Bacterial colonization and AECOPDs contribute to persistent inflammation of the airways, as neutrophils and monocytes are recruited from the circulation in an attempt to clear the invading pathogens. Since resident airway macrophages in COPD have a reduced capacity to clear efferocytic neutrophils, the emergence of necrotic neutrophils may further facilitate a vicious cycle of inflammation through release of endogenous damage associated molecular patterns (DAMPs). For example, degranulating necrotic bodies release neutrophil elastase, which localize to lung elastic fibers in emphysematic patients and degrades extracellular matrix components (26). Excessive neutrophil elastase activity can also promote the release of mucins through Epidermal Growth Factor Receptor (EGFR)-dependent mechanisms (27). Furthermore, increased EGFR transactivation augments inflammatory responses initiated by rhinovirus infection in bronchial epithelial cells (28). Necrotic neutrophils also release High-Mobility Group Box-1 (HMGB1), which is a DNA binding protein that is elevated in COPD airways (29). HMGB1 can synergize with microbial products and endogenous cytokines to enhance inflammation through Toll Like Receptor (TLR) (30,31) and Receptor for Advanced Glycosylation End (RAGE) (29) dependent mechanisms. Hence, COPD airways represent a highly complex milieu consisting of inhaled irritants, respiratory pathogens and endogenous mediators released from damaged tissue, which collectively drive excessive host immunity and sterile inflammation.

Pro-resolution mediators promote catabasis in the inflamed airway

The ongoing recruitment of leukocytes from the circulation is consistent with increased local production of CXCL chemokines in COPD including IL-8 (CXCL8), ENA78 (CXCL5), GCP-2 (CXCL6) and GRO isoforms (CXCL1-3) (32,33). The CXCR family of G coupled protein receptors (GPCR) binds to these endogenous chemokines, where CXCR2 is the cognate receptor for this family (34). There is also a high degree of redundancy in leukocyte mobilization as alternate mediators such as leukotriene B4 (LTB4) are associated with neutrophilic inflammation in colonized COPD patients (35). These

pathways are essential to lung host immunity and are normally self-limiting through the activation of pro-resolution pathways. Pro-resolving mediators actively counterbalance inflammation by effectively switching off mechanisms that maintain leukocyte recruitment and survival. Eicosanoids such as lipoxins, resolvins and protectins and the protein termed Annexin A1 are integral to resolution of inflammation, [reviewed in (36-38)]; where there is a class switch of eicosanoid production from chemoattractants (such as the leukotriene LTB4) to pro-resolving mediators (such as lipoxin A4, LXA4) (39).

Lipoxins are synthesized in response to cell-cell interactions [reviewed in (40,41)]. In the lung, 15-lipoxygenase is expressed in epithelial cells and converts arachidonic acid to 15S-hydroxyleicosatetraenoic acid (15S-HETE). This metabolite is then taken up by neutrophils and converted to LXA4 by the enzyme 5-lipoxygenase (42). LXA4 opposes leukocyte migration and activation through multiple mechanisms including suppression of transendothelial (43) and transepithelial (44) migration and azurophilic degranulation (45). LXA4 can also directly target activated mucosal epithelial cells by opposing production of inflammatory cytokines (46). *In vivo*, administration of a stable analog of LXA4 reduced pulmonary inflammation and airway hyperreactivity in a murine model of asthma (47). Furthermore, this eicosanoid can directly contribute to tissue repair through the promotion of basal cell proliferation required for wound healing following mucosal injury (46). Another important anti-inflammatory role for LXA4 is its influence on macrophage function. Treatment with nanomolar concentrations of LXA4 stimulated more efficient efferocytosis of apoptotic neutrophils in human monocyte derived macrophages without provoking release of inflammatory mediators (48,49). LXA4-induced uptake of apoptotic neutrophils was reduced in macrophages from Fpr2 deficient mice, which is the mouse ortholog of the human ALX/FPR2 G-protein coupled receptor (GPCR) that potently interacts with lipoxins (50).

ALX/FPR2 is central to resolution of inflammation

In addition to lipoxins, the alternate anti-inflammatory mediators Annexin A1 and Resolvin D1 also interact with ALX/FPR2, implicating this receptor as an integral component of pro-resolution pathways. Accordingly, they display overlapping functions, where both LXA4 (51) and Annexin A1 (52) promote apoptosis of neutrophils as a mechanism of resolving acute inflammatory responses. Unlike lipid mediators derived from cell-cell interactions, Annexin A1 is highly abundant in neutrophils where the 37kDa protein is localized to the cytoplasm and in gelatinase/azurophilic granules. Annexin A1 is a glucocorticoid-induced lipocortin that can be rapidly mobilized through degranulation of neutrophils. Cytoplasmic Annexin A1 is also subjected to post translational modifications such as phosphorylation, which facilitate translocation to the cellular membrane [reviewed in (52)]. In addition to promoting neutrophil apoptosis, Annexin A1 reduces neutrophil endothelial attachment and subsequent transmigration. Like LXA4, Annexin A1 has also been shown to enhance efferocytosis of apoptotic neutrophils by macrophages [reviewed in (52)], thereby facilitating catabasis of the inflamed tissue to homeostasis.

Another family of mediators that target ALX/FPR2 is the D series resolvins derived from the omega-3 fatty acid, docosahexaenoic acid (DHA) [reviewed in (53)]. Although there is relatively less information on the actions of D-series resolvins in lung diseases, there is emerging evidence to support an important role in resolution of lung inflammation. In a murine model of acute lung injury, treatment with stable derivatives of Resolvin D1 improved epithelial and endothelial integrity and reduced neutrophilic inflammation concurrently with reduced inflammatory cytokine secretion in the airways (54). In addition, aspirin-triggered Resolvin D1 (AT-RvD1) significantly reduced airway inflammation and enhanced macrophage phagocytosis in a murine asthma model (55). Furthermore, Resolvin D1 reduced neutrophilic lung inflammation, inflammatory cytokine production and phagocytosis in an acute cigarette smoke exposure model (56).

Is there an imbalance between inflammatory and pro-resolving mediators in COPD?

Given their important role in resolution of acute inflammation, any perturbation in the production of pro-resolving mediators can lead to the generation of pathogenic inflammatory conditions. Indeed, it has been shown that reduced production of LXA4 relative to cysteinyl leukotrienes is associated with the persistence of inflammation in severe asthma (57,58). Reduced levels of LXA4 are also observed in exhaled breath condensate during asthma exacerbations (59) and in the airway fluid of patients with cystic fibrosis (60). Since multiple mediators converge on ALX/FPR2, their relative abundance within the airway milieu of the chronically inflamed lung can profoundly

influence catabasis and restoration of homeostasis.

ALX/FPR2 belongs to the N-formyl peptide receptor (FPR) family, of which there are three human members (FPR1, ALX/FPR2 and FPR3). FPRs demonstrate wide tissue distribution, although ALX/FPR2 expression is particularly prominent on myeloid cells including neutrophils and monocytes (61). Airway mucosal epithelial cells also express ALX/FPR2 in a manner that is increased via COX-2 dependent mechanisms in response to injury (46). Prominent staining is also observed on the apical and basolateral side of the epithelium of COPD airways (62).

ALX/FPR2 is a GPCR superfamily member characterized by seven putative TM domains that displays diverse ligand affinities that extend beyond interactions with lipoxins, series D-resolvins and Annexin A1. Accordingly, ALX/FPR2 can interact with over 30 ligands that can exert opposing biological actions (63). Hence, selective agonists are likely to bind with different affinities and given the diverse conformation of endogenous and synthetic ligands, are likely to bind to alternate regions of the receptor. Numerous receptor conformations can exist where ligand binding alters receptor formation, which facilitates alternate functional behaviors that control multiple downstream signaling pathways (64). This is true for ALX/FPR2, where agonist biased signaling can either promote inflammation or resolution contingent on alternate receptor conformations [reviewed in (65)]. Serum Amyloid A (SAA) and the anti-microbial peptide LL-37 both interact with ALX/FPR2 and in complete contrast to pro-resolving mediators, promote neutrophil transmigration, activation and survival (summarized in *Figure 1*). Another high affinity ligand for ALX/FPR2 includes mitochondrial N-formylated hexapeptides derived from NADH dehydrogenase and cytochrome c oxidase subunits (66). These formylated peptides are released from damaged cells and can interact with FPR1 and ALX/FPR2 (66). Although it is not known whether these ligands are elevated in COPD, there is increased mitochondrial dysfunction and cytochrome c oxidase levels in the skeletal muscle of COPD patients (67-69).

There are multiple mechanisms that may address why ALX/FPR2 receptors modulate cell responsiveness in a ligand-biased fashion. This includes the formation of homologous and/or heterologous receptor dimers and differential conformational ligand activation of specific receptor domains. The molecular nature of how ALX/FPR2 downstream signaling pathways are activated in a ligand-specific manner has yet to be fully characterized. However, there is evidence for conformational ligand activation. LXA4 has been shown to activate ALX/FPR2 by interacting with extracellular loop III and the associated transmembrane region (70), whereas SAA initiates extracellular loops I and II dependent signaling (71). In addition, SAA has recently been shown to promote ALX/FPR2 homodimerisation and activation of pro-survival pathways, which can be counteracted by Annexin A1 that promotes an alternative receptor conformation that engages pro-apoptotic pathways (72).

Conclusions

Since the accurate detection of lipid pro-resolution mediators in human tissue requires LC-LC-MS approaches that have only recently become available, there are currently relatively few studies demonstrating their presence in human tissue (73). Hence, there is a current knowledge gap in terms of whether there is a deficiency in production of pro-resolving mediators in COPD that facilitates a chronic inflammatory state, and advances in detection technology will reveal new insight here. Importantly, this should inform on the development of new classes of drugs to treat COPD away from conventional steroid-like anti-inflammatory approaches that can detrimentally dampen immunity leading to immunosuppression. Specialized pro-resolving mediators offer an alternative approach to switching off chronic inflammation and may concurrently boost beneficial host immunity and tissue repair mechanisms. Whilst the organic synthesis of pro-resolving lipid mediators can be challenging, chemically stable E-class resolvin analogs have been successfully synthesized and are currently in Phase III clinical trial for chronic inflammatory dry eye syndrome (Resolvyx Pharmaceuticals in partnership with Celtic Therapeutics).

Of interest, two human phenotypes have been described in response to cantharidin-induced skin blisters in male healthy volunteers involving distinct production of LXA4, which controlled the longevity and severity of the inflammation (74). The relative abundance of alternative ALX/FPR2 ligands may also directly influence the functional behavior of this complex receptor in COPD airways, where there is a rich milieu of microbial derived products and endogenous mediators. LL-37 (or hCAP-18) is a breakdown product of cathelicidin that promotes microbial killing through pore formation. LL-37 is also a chemoattractant for neutrophils, monocytes and lymphocytes via its actions on ALX/FPR2 (75). Since LL-37 levels are elevated in sputum samples from stable COPD patients (76) and are further increased during

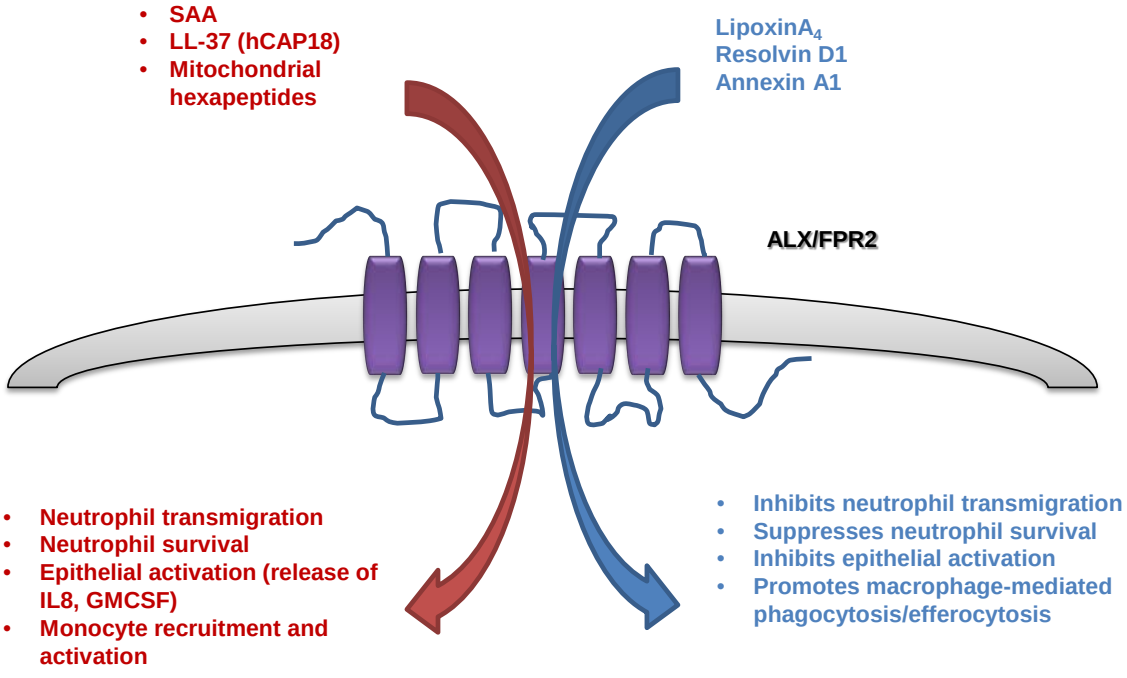

Figure 1 ALX/FPR2 and chronic inflammation in COPD. The ALX/FPR2 complex is expressed on leukocytes and the respiratory mucosa, where expression is particularly prominent on injured epithelial cells. The expression of two known ligands for ALX/FPR2, Serum Amyloid A (SAA) and LL-37 (hCAP-18) are known to be elevated in COPD and acute exacerbations of COPD. Mitochondrial hexapeptides released from damaged tissue also activate ALX/FPR2. SAA and LL-37 have been shown to initiate a pro-inflammatory response involving recruitment of neutrophils and monocytes. SAA can also promote neutrophil survival and release of inflammatory mediators from epithelial cells. In contrast, alternate ligands can bind to a different receptor region and promote distinct receptor conformations that translate to an opposing biological action. When the pro-resolving mediators LipoxinA4, Resolvin D1 and Annexin A1 interact with this receptor, they can actively initiate processes to reduce the influx of leukocytes and stimulate macrophages to clear exhausted immune cells and damaged tissue. SAA is disproportionally expressed relative to LXA4 in circulation during exacerbations and with the recent advance in technology to detect pro-resolving mediators in human tissue; it will be possible to explore this putative imbalance in COPD airways. With the ongoing development of more stable pro-resolving analogs, their therapeutic application may provide an opportunity to suppress chronic inflammation and clear damaged tissue to promote catabasis in the lung.

bacterial AECOPDs (77), this normally protective molecule may contribute to persistent inflammation. Likewise, SAA, which has previously been characterized as a systemic biomarker for AECOPD severity (78), is prominently expressed in lung resection tissue from COPD patients (62). Using the same lung resection tissue, SAA transcript expression was also detected and found to be positively associated with the number of tissue neutrophils (79).

In addition to promoting neutrophil survival via ALX/FPR2, SAA is a potent chemotactic factor that mediates migration of leukocytes (80) and can also stimulate expression of pro- inflammatory mediators under *in vitro* (81) and *in vivo* conditions (62). More recently, SAA was shown to promote the differentiation of monocyte derived macrophages into a pro-inflammatory phenotype that expresses higher levels of the TH17 polarizing cytokines, IL-6 and IL-1β in a manner that was dependent on CSF-1R signaling (82). Hence, the relative abundance and persistence of pro-inflammatory agonists such as SAA and LL-37 in COPD airways is likely to facilitate agonist biased signaling that favors leukocyte recruitment, activation and survival. The nature of this receptor also provides therapeutic opportunities to address ALX/FPR2 conformations that may lead to pathogenic functions through the development of more stable analogs of lipoxins, D-series resolvins and cleavage resistant Annexin A1 mimetics, which can override pro-inflammatory signals to initiate resolution of inflammation.

Acknowledgements

This work was supported by the National Health & Medical Research Council (NHMRC) of Australia and an Australian Research Council (ARC) Future Fellowship to Steven Bozinovski. The authors declare no conflict of interest.

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Bozinovski S, Anthony D, Vlahos R. Targeting pro-resolution pathways to combat chronic inflammation in COPD. J Thorac Dis 2014;6(11):1548-1556. doi: 10.3978/j.issn.2072-1439.2014.08.08

Review Article

Diagnosis and early detection of COPD using spirometry

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Abstract: The standard respiratory function test for case detection of chronic obstructive pulmonary disease (COPD) is spirometry. The criterion for diagnosis defined in guidelines is based on the FEV_1/FVC ratio forced expiratory ratio (FER) and its severity is based on forced expiratory volume in one second (FEV_1) from measurements obtained during maximal forced expiratory manoeuvres. Spirometry is a safe and practical procedure, and when conducted by a trained operator using a spirometer that provides quality feedback, the majority of patients can be coached to provide acceptable and repeatable results. This allows potentially wide application of testing to improve recognition and diagnosis of COPD, such as for case finding in primary care. However, COPD remains substantially under diagnosed in primary care and a major reason for this is underuse of spirometry. The presence of symptoms is not a reliable indicator of disease and diagnosis is often delayed until more severe airflow obstruction is present. Early diagnosis is worthwhile, as it allows risk factors for COPD such as smoking to be addressed promptly and treatment optimised. Paradoxically, investigation of the patho-physiology in COPD has shown that extensive small airway disease exists before it is detectable with conventional spirometric indices, and methods to detect airway disease earlier using the flow-volume curve are discussed.

Keywords: Spirometry; chronic obstructive pulmonary disease (COPD); case finding; flow-volume curve

Submitted Jun 11, 2014. Accepted for publication Aug 12, 2014.
doi: 10.3978/j.issn.2072-1439.2014.08.18
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.08.18

Pathology of chronic obstructive pulmonary disease (COPD)

Relatively early research in the 1950s and 1960s into what was by then recognized as a smoking-related disease (1) focused on pathology, and especially tissue remodeling changes in the airways and lungs. It was observed that throughout the airways there was some element of inflammation, but sub-mucosal mucous gland hyperplasia, epithelial goblet cell hyperplasia and epithelial squamous metaplasia were prominent. The characteristic lung lesion was usually peri-bronchial, centri-lobular parenchymal destruction, termed emphysema (2-4). An important conclusion from the detailed pathological analysis of this epoch was that the airway pathological component in COPD was universal and generalized, while emphysema usually developed later, perhaps as a secondary phenomenon, and only in some individuals but by no means all. This is different from the diffuse primary pan-acinar emphysema that occurs in the younger-onset alpha-1 anti-trypsin (anti-proteinase) deficiency lung disease, for example (5).

The next research epoch involved innovative physiological laboratory work in the late 1960s into the 1970s, which defined the obstructive consequences of smoking-related airway disease and the anatomical site of increased airway resistance that ultimately lead to symptoms (6,7). From this work, construction of a series of iso-volume pressure-flow curves gave rise to development of the now widely used flow-volume curve, but then without the sophisticated, sensitive and computerized equipment now available, and which we will be discussing later in some detail. However, even by that time and using the relatively crude bellows-based spirometer, the standard measure for defining airway obstruction had been specified as a reduction in the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC), the forced expiratory ratio

(FER); indeed in that regard little has changed over the last fifty years or so, in spite of improved understanding of physiology. Paradoxically, the seminal work of Macklem and others in clinical physiology showed that the first change in spirometry in COPD was actually a reduction in FVC due to air trapping, rather than a change in FEV_1 (8). Importantly, they showed that this in turn is caused by fixed small airway narrowing, in airways less than 2 mm internal diameter. To demonstrate this, they used flow-volume studies in patients and volunteers with gases of different densities, and also measured flow resistance in different parts of the airway with retrograde catheters in resected lungs. Normal small airways have low resistance to air flow but this is markedly increased in COPD (9-11). In contrast, in asthma the main pattern is one of non-uniformly distributed larger airways obstruction, except in older asthmatics and those that smoke in whom a peripheral distribution of resistive change was common, similar to COPD.

Notably, it was shown in this epoch of physiological research, that there could be a great deal of peripheral increase in flow resistance before there was any indication on traditional spirometric measures. Patho-physiological correlation studies followed, indicating that in small airways in COPD there is indeed narrowing due to wall thickening, fibrosis and indeed airway obliteration (10,12,13). This was a new and startling insight, which is now confirmed by more sophisticated methodology (14), that there can be extensive small airway disease, damage and obliteration before it is detectable with conventional spirometric tests.

Over the years, new physiologic methods were developed to try and pick up these early small airway changes in smokers before overt COPD, defined by the FER emerged. However none was robust or practical enough at the concurrent stage of technological development to be suitable for clinical laboratory or medical office use. Such attempts continue with increasingly sophisticated techniques, and this is dealt with in a separate article in this volume; the FER remains the standard. In this article, we will review and discuss how useful in clinical practice this standard measure is, what we know about its pitfalls in clinical application and especially in primary care practice. We will also look anew at how the use of all the information available in the current standard flow-volume curve, which is now routinely obtained at the time of FER measurement but largely ignored, can potentially be harnessed and give a better overview of the status of the airways. This might contribute to recognizing early physiological impairment in smokers, perhaps as an alternative to the need to develop more expensive and complex tests.

Epidemiology and prevalence of COPD

The prevalence of COPD varies across countries; accurate estimates based on standardised population-based sampling of adults aged 40 and over in 12 sites in the burden of obstructive lung disease (BOLD) survey indicated an overall COPD prevalence (GOLD stage II or higher, FEV_1 <80% predicted) (15) of 10.1% (SE 4.8) (16). Prevalence increased with age and smoking history, but other factors were also thought to be important in explaining the variation. In the Australian BOLD survey conducted in six centres, prevalence was 7.5% (95% CI, 5.7-9.4%) overall, but was greater among those aged above 75 years at 29.2% (95% CI, 18.1-40.2%) (17). The Australian survey showed large variations between centres the causes of which are being investigated (unpublished data).

Estimates of the population attributable fraction of tobacco smoking as a cause of COPD vary by age and population setting (18), although more recent estimates in those aged 30-69 years, 54% for men and 24% for women, are probably accurate and less than the widely quoted 80-90% in the 1984 US Surgeon General Report (19). Attributable fractions are higher in industrialized countries than developing countries (18), and other risk factors are also important, including exposure to biomass smoke, occupational exposures to dust and fumes, history of pulmonary tuberculosis, outdoor air pollution, and poor socioeconomic status (20) or chronic asthma (21). However smoking remains the most important cause of COPD in western countries. Around 50% of smokers eventually develop COPD, although the risk falls by about half following smoking cessation (19).

Diagnosis of COPD

As discussed previously, spirometry is accepted as the diagnostic test to assess airflow obstruction and classify severity of disease, based on specific cut points for FER (FEV_1/FVC <0.7 after bronchodilator) and FEV_1 (mild ≥80% predicted, moderate 50-80%, severe 30-49% predicted, very severe <30% predicted) (15). FEV_1 normally decreases with age, and the rate of fall is an important spirometric indicator of disease progression in COPD. In healthy non-smoking adults the decrease is about 30 mL/year with an upper limit of about 50 mL/year (22-24); a decrease greater than this is considered abnormally rapid. There is

debate on the use of a single fixed cut-off for FER to confirm the presence of airflow obstruction in COPD, because the lower limit of normal for FER decreases with age (25). Thus, this may misclassify some older patients as having COPD (26). Similarly, basing the classification of COPD on FEV_1 as percentage predicted may misclassify patients especially the elderly and those in global initiative for chronic obstructive lung disease (GOLD) stages I and II (27). It has been proposed that classification should be based on a lower limit of normal (LLN) i.e., more than 1.64·SD below the predicted level (5^{th} percentile) (28), although international guidelines still recommend use of the fixed FER for diagnosis (15).

Maximum flow achieved during forced expiration decreases progressively as lung volume falls and is most evident in the expiratory flow-volume curve where flow is plotted as a function of volume. Although flow and volume are complex biological signals, the curve is highly repeatable in both healthy and obstructed individuals and the shape of the curve can be helpful as it reflects the underlying mechanics limiting maximal flow. In healthy younger adults the shape of the flow-volume curve usually approximates a straight-sided triangle with maximum flows decreasing linearly with lung volume. In people with obstructive lung disease key physiologic features of the flow-volume curve are reduced expiratory flows in proportion to disease severity and the presence of a concavity in the descending limb; the latter indicating an abnormal decrease in maximal flow as lung volume falls.

Flow measurements derived from spirometry such as the forced expiratory flow over the middle half of the FVC ($FEF_{25-75\%}$) and forced expiratory flow at 75% of the FVC ($FEF_{75\%}$) may be more specific to small airway function, particularly in the presence of a normal FEV_1, but they have not proved particularly helpful because they are dependent on the measurement of FVC, lack the repeatability of FEV_1, have a wide normal range, and are reduced in the presence of narrowing occurring in proximal airways (29,30).

COPD recognition and detection

However, in spite of spirometric standards for diagnosis, a high proportion of COPD in the community remains undiagnosed; estimates of non-diagnosis in the 1990's were 66% in the US (31) to 78% in Spain (32). Under-recognition is related to the severity of airflow obstruction; 50% of those with FEV_1 <40% predicted reported a physician diagnosis of COPD, but only 19% of those with FEV_1 between 60-79% predicted in the Obstructive Lung Disease in Northern Sweden study (33). More recently, only 5.2% of BOLD population survey participants in Australia reported having been diagnosed with COPD compared to the 7.5% prevalence detected (17). Undetected COPD or asthma is common in primary care; over half those aged between 25-70 years in general practices in the Netherlands had symptoms or signs (34). There is also consistent evidence of misclassification of COPD in general practice. Substantial misclassification (31% and 42%) based on practice records COPD diagnosis was found in two studies in Australia (35,36). This probably relates to the diagnosis not being based on objective spirometry testing criteria.

Increased detection of COPD may result from a community-based screening programme; 27% of participants aged over 40 years had airflow obstruction based on FER <85% predicted in outpatient clinics in Poland (37). However such screening has not been widely implemented; a US Preventive Services Task Force assessment of the evidence did not recommend screening with spirometry and concluded with moderate certainty that there was no net benefit (38).

A more cost effective strategy using opportunistic case finding in primary care based on the presence of risk factors (age and smoking) and symptoms is recommended in the UK Update Guideline on COPD (39). A substantial amount of undiagnosed clinically significant COPD was demonstrated in the Health Survey for England 1995-6 (40). In over half these cases of unrecognized COPD management guidelines recommend treatment, either with combination inhaled corticosteroid/long-acting beta agonist or anticholinergic inhaler to reduce hospitalisation and mortality, or pulmonary rehabilitation to improve quality of life (40). Case finding can be effective when conducted opportunistically for patients attending general practice for any reason (41), compared with only a small improvement for 'targeted' case finding using pre-attendance practice register searches and mail out invitations to selected patients (42).

In many health systems, primary care provides the most accessible and most frequently accessed health care and efforts to increase recognition and diagnosis of COPD have mainly focussed on general practice (43,44). Spirometry testing should focus on those at risk particularly from smoking; thus spirometry was able to detect unrecognised airflow obstruction (FEV_1 <80% predicted) in 22% of current smokers aged 35 to 70 years with at least one typical COPD symptom in the Netherlands (41). The proportion of COPD of at least GOLD grade II (FEV_1 <80% predicted) in smokers aged over 40 in general practices

varies, from 25% in a Canadian study (45) to 47% in a study in Belgium (46), with only around a third in both already having a COPD diagnosis.

An alternative approach is to base spirometry testing on respiratory-relevant symptom screening using a questionnaire (47), with the cut-off score for subsequent spirometry chosen to maximise sensitivity and specificity (48). In this way, using a COPD screening questionnaire (48) and a cut-off score of 17 or above (range, 0-40) in patients over 40 years attending general practice in Greece, the sensitivity for new COPD diagnosis was 93% but specificity was only 39% (49). Simple inexpensive hand-held spirometers are available for use in general practice; they display FEV_1, forced expiratory volume in 6 seconds (FEV_6) as a surrogate for FVC, and the ratio FEV_1/FEV_6. Applying a cut off ratio FEV_1/FEV_6 <0.7 after bronchodilator in the same study in Greek general practices, increased the specificity to 94% with sensitivity of 80% for COPD diagnosis (49).

A further refinement for identifying COPD in general practice is to combine a COPD symptom questionnaire with measurement of FEV_1/FEV_6 ratio. In the Greek study quoted above, the combination of the questionnaire with its high negative predictive value and the hand-held spirometer with its high positive predictive value had a sensitivity of 74% and specificity of 97% for COPD diagnosis, while the negative predictive value was 95% and positive predictive value was 82% (49). In a scenario when individuals at risk of COPD in primary care were screened with a hand-held spirometer before full spirometry testing, a cut off point corresponding to FEV_1/FEV_6 <0.75 was found to offer optimal sensitivity (81%) and specificity (71%) for diagnosis in current and former smokers aged over 50 years (50). Linking symptom screening to case finding for COPD is ideal if the intention is to commence treatment in symptomatic individuals, but this approach is less suitable if the aim is to reduce end-organ disease.

Symptoms and a diagnosis of COPD

The place of symptoms in the diagnostic criteria for COPD has been debated (51) and there is some inconsistency between GOLD (15) and NICE (39) guidelines, with NICE advising not diagnosing COPD in the absence of symptoms in patients with mild airflow obstruction (FER <0.7, FEV_1 >80% predicted) (52). However, there is substantial evidence that reported symptoms are unreliable for diagnosis, although in general the symptom burden in COPD increases with severity of airflow obstruction. There is wide variation in the degree of breathlessness, health status and exercise capacity within GOLD stages; thus even when airflow obstruction is severe in COPD, some people do not report symptoms or exercise limitation (53). There is also under-presentation by patients with potential chronic respiratory disease who do not raise respiratory symptoms with their general practitioner; 46% of patients with spirometrically confirmed COPD had not paid a single visit for respiratory health problems during a 10-year observational study in the Netherlands (54). Patients may attribute their symptoms to ageing and attribute multi-casual explanations that lessen the importance of obtaining a diagnosis (55). On the other hand, respiratory symptoms typical of COPD may be noted in practice records for long periods prior to diagnosis (56), with varying attitudes and degrees of vigilance among general practitioners to early diagnosis (56,57). Thus diagnosis of COPD may be delayed and indeed often does not occur until an acute exacerbation results in admission and hospital-based diagnosis (57).

Early diagnosis

Early diagnosis is a contentious issue, but it optimises the opportunities to prevent worsening of disease and prevention of comorbidities. Guidelines for COPD emphasise that it is a multi-system disease requiring a multidimensional approach to treatment (52). There is a strong emphasis on smoking cessation in both NICE (39) and GOLD (15) guidelines as the intervention with the greatest capacity to influence the natural history of COPD (58). Although a review in 2007 of randomised controlled studies on the value of spirometry itself as a motivational tool to increase smoking cessation was inconclusive (59), telling smokers their 'lung age' based on spirometry testing increased 12 months sustained quitting by over 7%, irrespective of the actual deficit in 'lung age' (60).

An increased risk of lung cancer in COPD was found in a long term US observational study in moderate or severe COPD (61) and in a case control study in lung cancer (62). The increased risk with COPD is present even when allowance is made for cigarette smoking history.

Similarly, the association of reduced FEV_1 with increased overall mortality has been recognized in studies in non-smokers (63) and smokers, with the effect of reduced FEV_1 independent of smoking history (64). The potential importance of the FVC was highlighted in a USA general population cohort without chronic respiratory diagnoses or persistent respiratory symptoms, in which survival was associated with

higher FVC in both men and women after adjustment for smoking and demographic factors (65). Such associations underlie the need for an earlier awareness of abnormality on spirometry as a part of a general health screening approach, such as was taken in cardiovascular disease to reduce the high burden of mortality that existed 40 years ago (66).

Value of current diagnostic tools for COPD: spirometry

Spirometry is a safe, practical and reproducible maximum breathing test that can be used in primary care to objectively determine the ventilatory capacity of the lungs. As already emphasised earlier in this article, it is the 'gold standard' for detecting and quantifying airflow obstruction (15) and as discussed, is the core component of clinical guidelines for the diagnosis and management of COPD (67). The test is relatively quick to perform, well tolerated by most patients and the results are immediately available to clinician. It is important to appreciate that the clinical value of spirometry is critically dependent on the correct operation and accuracy of the spirometer, performance of the correct maximal breathing manoeuvre, selection of the best test results to use and correct interpretation. When a trained and experienced operator using modern equipment conducts the test, at least 90% of adults are able to provide acceptable and repeatable results (68). In the primary care setting the rate is lower but can still be reasonable at about 80%, especially when the spirometer grades each test and provides feedback relating to test quality (69).

Development of spirometry

A spirometer is a medical device that allows measurement of how much air is expelled and how quickly the lungs can be emptied, in a maximal expiration from full inflation. Modern spirometry has its origins in the 1840's when the English surgeon, John Hutchinson, developed the spirometer and described the measurement of slow vital capacity as a means of detecting lung disease (70). One hundred years later Tiffeneau and Pinelli from France revolutionised spirometry by describing the forced expiratory timed spirogram and introducing an obstructive index, the ratio FEV_1/inspiratory vital capacity (IVC) which is still used today, albeit with IVC most commonly replaced with FVC (71) or expiratory vital capacity (72). It was only a few years later in 1960 that the American physiologists, Fry and Hyatt, in a landmark study of lung mechanics, replotted the data contained in the timed spirogram in the form of the flow-volume curve (73) which is now universally accepted as the preferred method of graphically displaying spirometric data. The flow-volume curve is now available in almost all commercially available spirometers and is displayed in real-time as the patient performs the test.

Modern spirometers

Almost all modern spirometers utilise a sensitive real-time flow sensor to directly measure respired flow and obtain volume by electronic or numerical integration. Manual volume-displacement spirometers are still in limited use, especially in primary care (74), such as the iconic wedge bellows Vitalograph which over many decades has played a very significant role in popularising the measurement and application of spirometry beyond the expert laboratory, but this genre of spirometer usually lacks portability, is difficult to clean and disinfect, can be difficult to calibrate and requires spirometric variables to be calculated manually and does not produce the flow-volume curve.

There are many spirometers on the market today and most are robust, portable, accurate and reliable and specifically designed for use in either a lung function laboratory or a physician's office (74). Most, if not all, modern spirometers meet minimum international performance standards and validation procedures that were developed jointly by the American Thoracic Society and European Respiratory Society (75). These include meeting accuracy requirements for volume, flow and time signals using specifically developed test signals, and applying the back-extrapolation technique to identify both sluggish starts to the blow and the zero time point from which timed volumes such as FEV_1 are calculated. Modern spirometers also have the added advantages of infection control, automatic calculation of all lung function indices including correction for temperature, pressure and water-saturation conditions. Many will also provide immediate computer-generated feedback to the operator on the test quality and repeatability as well as real-time graphical display of the spirogram and flow-volume curve, will select the best results to report, calculate normal reference values including the lower limit of normal, and can automatically upload results to medical records.

Primary care spirometry

Spirometry is commonly performed outside the lung function laboratory. A survey of primary care practices in

Australia found that 64% owned a spirometer with almost 70% performing at least one test per week mainly for the diagnosis and management of asthma and COPD (76). The high spirometer ownership was not surprising given that a large number of patients with lung disease are first seen and subsequently managed in primary care.

Opinion is divided as to whether the quality of spirometry performed outside expert laboratories meets adequate minimum standards (75) with the potential for high rates of misclassification, especially when the results are near the lower limit of normal (69,77-79). The measurement of spirometry requires a motivated and enthusiastic operator to coach the patient to perform a number of very rigorous maximally forced and sustained breathing manoeuvres (80). It is not surprising therefore that unlike most other medical tests such as the measurement of blood pressure and the electrocardiogram, the quality of spirometry tests are crucially dependent on the operator and cooperation of the patient and thus spirometry performed in primary care is often of poor quality (81). Although the key to obtaining quality spirometry is attending a comprehensive training course, the importance of testing experience cannot be overstated and may well be the most important factor.

The concave pattern on flow-volume curve

Current guideline criteria for airway obstruction and its severity essentially rely on just two variables FEV_1 and FVC, and their ratio the FER. Although these variables have played an important role in developing our understanding of the mechanisms and functional effects of COPD, we have emphasised that they are relatively insensitive to early obstructive small airway pathology, because these cause FVC to fall first (8) with initial preservation of the FER. Spirometry has thus been of limited use as a screening tool for early disease; this is disappointing as it is the most practical and widely performed test of lung health and should therefore be ideal to screen for early disease. We present a case that relying solely on the FEV_1 and FER potentially misses information contained in the whole flow-volume curve, particularly the concave pattern, which may provide greater sensitivity in detecting and monitoring early disease.

The development of concavity in the descending limb of the maximum expiratory flow-volume curve is a recognised feature of airflow obstruction, with greater concavity reflecting increased obstruction, and the first indication of a concavity is frequently seen in the tail of the curve (30,72). This is explicitly acknowledged in the ATS/ERS statement on the interpretation of lung function (82), but has largely been ignored in practice because none of the measurements taken currently to reflect this concavity are robust enough.

The functional information provided by the FEV_1 is necessarily limited to the first second of the forced expiratory manoeuvre when the lung is relatively fully inflated and the small airways exposed to significant distending forces. This means that in older people with a normal FER, as much as 40% of the flow-volume curve is not assessed, all in the terminal portion of the curve, and a greater proportion in people with airflow obstruction. In contrast, the concave pattern seen in people with airflow obstruction is not limited to the first second but often extends over most of the curve, reflecting a global pattern of airway dysfunction. In early airflow obstruction, when the FEV_1 is normal, a concavity is often present and may well be mostly confined to the terminal portion of the curve where lung volume is relatively low and the distending forces on the small airways are significantly reduced, resulting in a higher peripheral airway resistance and non-uniform emptying in peripheral lung regions. It is notable that the latter may well be the major spirometric defect signalling early disease, and requires better quantitative assessment.

The concave pattern develops when lung compartments have widely differing expiratory time constants causing regional inhomogeneity (83) as is certainly the case in obstructive lung disease with peripheral increase in airway resistances, with the slowest emptying compartments contributing disproportionally to flows near residual volume, resulting in a curve with the familiar exaggerated 'tail'. It is not surprising, therefore, that even though the underlying mechanics determining FEV_1 and the concave pattern overlap, they are not necessarily equivalently strong physiological signals at different disease stages. They may however be quite complementary, not only in assessing airflow obstruction overall but especially in detecting early obstructive small airway disease (84).

It seems reasonable that to detect and assess early disease we need a method that is sensitive to inhomogeneous airway emptying because this almost certainly precedes the development of the more advanced obstruction for which we use currently the standard FER. Highly sophisticated technology is currently being developed to measure this inhomogeneous lung emptying, but it could well be that much of this information is already available in the expiratory flow-volume curve if only it can be harnessed.

Strong evidence that a concavity confined in the terminal portion of the curve is most likely to be associated with

small airways dysfunction came from further studies that compared flow-volume curves obtained breathing gases of widely differing gas density which showed that maximal flows near the terminal portion of the flow-volume curve predominantly reflect small airway function (85). This is also consistent with studies using wave speed mechanics (86) and the equal pressure point theory (72) which predicts that the flow-limiting segment developed during forced expiration moves peripherally into progressively smaller airways as lung volume falls and especially when peripheral airway resistance increases.

The clinical value of quantifying concavity has been under-appreciated although demonstrated spirometrically in different populations (84,87-92). The study by Kraan *et al.* (89) was of particular interest as it provided strong evidence that although the reduction in FEV_1 and the degree of concavity are related, they do not necessarily measure the same things; for example they were differentially affected by bronchodilator and anti-inflammatory treatment. Schachter *et al.* (87) showed that although cotton workers had abnormal spirometry, the concave pattern was only present in current cigarette smokers. Another study showed the degree of concavity was greater in those with a smoking history and people with breathlessness and wheezes (88).

New indices to quantify concavity

Visual assessment of concavity in the flow-volume curve is highly subjective and cannot reliably be used to assess an abnormal degree of concavity. What is needed is a practical and easily understood numerical index to quantify concavity with clearly defined limits of normal. Although a number of methods have been described (83,87,93) they are complex or difficult to apply routinely and none has been incorporated into commercial spirometry software or clinical guidelines.

However, we describe two indices for estimating concavity (global and peripheral) with preliminary data comparing these with conventional spirometric variables, in a randomly selected population of adults aged >40 years in Australia. The *global index* is based on $FEF_{50\%}$ and quantifies concavity that usually involves the entire descending limb, whilst the *peripheral index* is based on the $FEF_{75\%}$ and independently quantifies concavity present near the terminal portion of the curve. The degree of concavity is obtained by calculating the percentage decrease of the measured flows from the corresponding idealised reference flows (*Figure 1*).

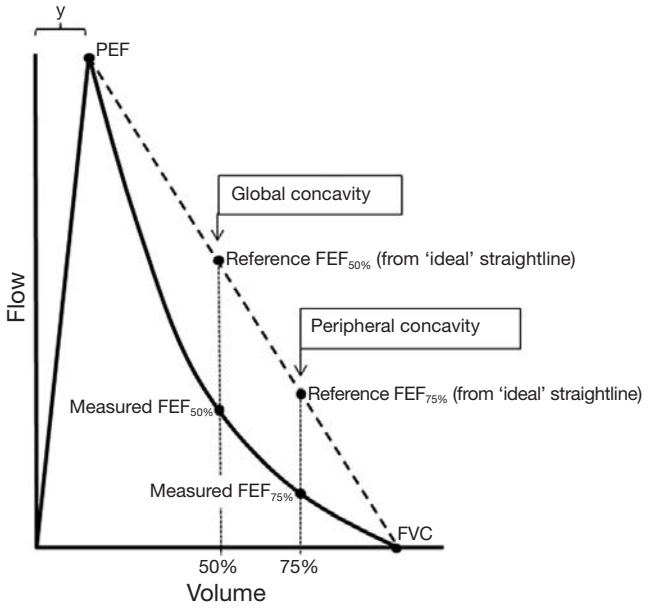

Figure 1 Variables used to quantify global and peripheral concavity (see text). Measured $FEF_{50\%}$ and measured $FEF_{75\%}$ are the forced expired flows when 50% and 75% of the FVC has been expired. Reference $FEF_{50\%}$ and Reference $FEF_{75\%}$ are the reference flows that would be obtained if the flow-volume curve had zero curvature i.e., a linear descending limb (dotted line). The variable, y, is the volume to peak expiratory flow (PEF); a value of 0.6 L can be assumed for this. In this example, global concavity is approximately 50 Units and peripheral concavity is approximately 65 Units.

Global Concavity =100* (reference $FEF_{50\%}$—measured $FEF_{50\%}$)/reference $FEF_{50\%}$

Peripheral Concavity =100* (reference $FEF_{75\%}$—measured $FEF_{75\%}$)/reference $FEF_{75\%}$

The measured $FEF_{50\%}$ and measured $FEF_{75\%}$ are obtained from the subject's flow-volume curve. The two corresponding reference flows are calculated assuming that the descending limb is a straight line from PEF to end-expiration (*Figure 1*) and therefore has no curvature:

Reference $FEF_{50\%}$ = PEF*(FVC/2)/(FVC-y)

Reference $FEF_{75\%}$ = PEF*(FVC/4)/(FVC-y)

The variable, y, is the volume expired to PEF (*Figure 1*) and although ideally should be measured from the curve, assuming a fixed value of 0.6 litres leads to little error. The calculated indices are dimensionless with units ranging from zero (no concavity) to a theoretical limiting value

Table 1 Spirometry and concavity data mean and standard deviation (SD) from the Tasmanian BOLD population (17)

	Males (n=164); mean (SD)		Females (n=223); mean (SD)	
	Never smoked (n=66)	Ever smoked (n=98)	Never smoked (n=115)	Ever smoked (n=108)
Post-BD spirometry				
FEV_1, % predicted	101.5 (13.2)	93.3 (15.5)	98.8 (16.6)	99.0 (16.3)
FVC, % predicted	101.3 (12.4)	97.5 (14.1)	99.5 (15.2)	99.4 (13.2)
FER, absolute %	76.0 (6.8)	72.5 (9.3)	77.2 (8.0)	73.8 (9.5)
Acute reversibility				
FEV_1, % change	4.4 (4.1)	3.7 (6.6)	3.2 (7.0)	3.6 (5.8)
FER, absolute change	2.3 (4.2)	2.8 (4.5)	2.4 (4.2)	2.2 (4.5)
Global concavity units				
Pre-BD	32.7 (21.6)	40.4 (22.3)	22.9 (24.2)	32.0 (26.9)
Post-BD	27.5 (22.6)	35.2 (23.6)	13.4 (26.4)	25.6 (29.4)
Peripheral concavity units				
Pre-BD	67.1 (19.0)	74.0 (14.0)	63.9 (19.4)	69.5 (18.5)
Post-BD	59.1 (24.1)	68.3 (18.0)	56.9 (21.6)	63.3 (21.4)

BD, bronchodilator; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FER, forced expiratory ratio.

approaching 100 (maximum concavity). Negative values are possible and indicate that that the curvature of the descending limb is convex (no concavity). These indices (Concavity Units) are easily incorporated into spirometry software, are independent of the size of the flow-volume curve and closely mirror the intuitive way many clinicians visually assess the degree of concavity, mentally adding the straight line, but with more objectivity.

Our exploratory analysis of global and peripheral concavity involved 387 (223 females, 164 males) randomly selected subjects from Tasmania who had participated in the BOLD Australia study (17). Spirometry and the degree of concavity were obtained from baseline and post-bronchodilator flow-volume curves measured using the Easyone ultrasonic spirometer (ndd Medizintechnik) that met ATS/ERS acceptability and repeatability criteria (75). The age range of subjects was 42-87 years, with mean age 59.4 years for males and 58.3 for females. A higher proportion of males had ever smoked (60%) compared with females (48%) and males had substantially higher lifetime tobacco consumption (median 24 versus 11 pack years). Overall subjects who had ever smoked, especially males with the highest lifetime tobacco consumption, had a greater degree of global and peripheral concavity compared with never smokers (*Table 1*). The degree of global and peripheral concavity decreased after the administration of a bronchodilator, in both the male and female subjects who had ever smoked or had never smoked. Of note, even in people who had never smoked the presence of both patterns of concavity was a common finding in this older population.

The limits of normal for concavity were estimated separately for males and females using post-BD data from subjects who had never smoked, with FER >0.7 and reversibility of FEV_1 <10%. Thus, an abnormal degree of concavity was defined as present in males if global concavity >34.8 Units or peripheral concavity >61.2 Units, and in females if global concavity >26.3 Units and peripheral concavity >63.1 Units. The LLN for $FEF_{25-75\%}$ was based on reference values from Hankinson *et al.* (25).

In this Tasmanian population, the prevalence of abnormal global and peripheral concavity was far higher than estimated based on either GOLD criteria or $FEF_{25-75\%}$ (*Table 2*). It is of interest that the presence of an abnormal degree of concavity confined solely to the terminal portion of the curve (global > ULN plus peripheral < ULN) was not uncommon. This pattern was present in 73 (19%) of participants overall of whom only four had abnormal FER (<0.7).

Both the FER and degree of concavity are independent of the size of the flow-volume curve. *Figure 2* shows that there is a strong non-linear relationship between FER and our measures of concavity. The horizontal and vertical lines are the limits of normal for FER (GOLD) and concavity, respectively. According to clinical guidelines, subjects falling to the right of the vertical line have a normal FER

Table 2 Comparison of prevalence rates of abnormal conventional spirometry indices and abnormal concavity for the Tasmanian BOLD population (17)

Index	Criterion for abnormal	n, prevalence (%)	
		Males (n=164)	Females (n=223)
FER (± FEV_1 % pred.)	FER <0.7 (GOLD any stage)	46 (28.0)	47 (21.1)
	FER <0.7 + FEV_1 ≥80% pred. (GOLD stage I)	31 (18.9)	27 (12.1)
	FER <0.7 + FEV_1 ≥50% to <80% pred. (GOLD stage II)	14 (8.5)	17 (7.6)
$FEF_{25-75\%}$	$FEF_{25-75\%}$ < LLN (25)	11 (6.7)	20 (9.0)
Global Concavity Units	> ULN	76 (46.3)	89 (39.9)
Peripheral Concavity Units	> ULN	108 (65.9)	110 (49.3)
Pure peripheral Concavity	Global < ULN + peripheral > ULN	37 (22.6)	36 (16.1)

GOLD, global initiative for chronic obstructive lung disease (15).

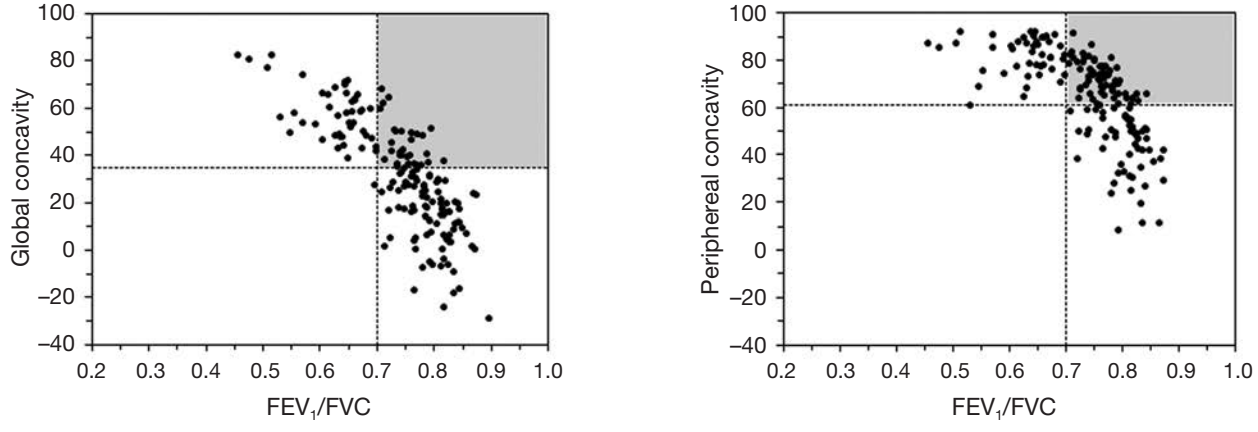

Figure 2 Post-bronchodilator forced expiratory ratio (FER) of FEV_1/FVC plotted against global and peripheral concavity in male participants. The horizontal and vertical lines are the limits of normal for FER (15) and concavity, respectively. The shaded quadrant identifies subjects with normal FER but an abnormal degree of concavity (see text).

(no airflow obstruction) and from our data those above the horizontal line have an abnormal degree of concavity. The upper right quadrant (shaded area in *Figure 2*) is of special interest because it identifies subjects without airflow obstruction defined by the FER but who have an abnormal degree of concavity. This may be useful in detecting airflow obstruction that is unseen by conventional analysis of spirometric data. This requires further investigation as does the relationship between concavity and symptom scores, and whether the association is stronger than between symptoms and FEV_1. The ability to fully utilize the large amount of information obtained in modern spirometry could have great potential, opening a way to introduce the insights about early small airway dysfunction from classical physiology into the clinic without a need for additional complex equipment.

Conclusions

The standard respiratory function test for case detection of COPD is spirometry, with the criterion for diagnosis defined in guidelines being based on FER and the severity being based on FEV_1. However, using this approach is poor at detecting early disease in the small airways. Improved, although more complex, tests are being developed to recognise such early cases but we have shown that by using all the information available from the spirometric expiratory flow-volume curve, and especially by quantifying the degree of concavity, that this may be in itself more sensitive and specific for small airways disease. However, even the current means of diagnosing relatively more severe disease that is detectable by the FER threshold is poorly taken up in primary care, despite the benefits that could be

achieved with smoking cessation and pharmacological and non-pharmacological interventions to improve patients' well-being. The reasons are not completely understood but include attitudes of both doctors and patients to COPD. The potential importance of detecting early fixed airway obstruction for prevention of lung cancer and non-respiratory end-organ disease also needs to be better highlighted in public health campaigns.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Johns DP, Walters JA, Walters EH. Diagnosis and early detection of COPD using spirometry. J Thorac Dis 2014;6(11):1557-1569. doi: 10.3978/j.issn.2072-1439.2014.08.18

Review Article

Advanced imaging in COPD: insights into pulmonary pathophysiology

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Abstract: Chronic obstructive pulmonary disease (COPD) involves a complex interaction of structural and functional abnormalities. The two have long been studied in isolation. However, advanced imaging techniques allow us to simultaneously assess pathological processes and their physiological consequences. This review gives a comprehensive account of the various advanced imaging modalities used to study COPD, including computed tomography (CT), magnetic resonance imaging (MRI), and the nuclear medicine techniques positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Some more recent developments in imaging technology, including micro-CT, synchrotron imaging, optical coherence tomography (OCT) and electrical impedance tomography (EIT), are also described. The authors identify the pathophysiological insights gained from these techniques, and speculate on the future role of advanced imaging in both clinical and research settings.

Keywords: Chronic obstructive pulmonary disease (COPD); respiratory physiology; medical imaging; pulmonary ventilation; respiratory function tests

Submitted Oct 08, 2014. Accepted for publication Nov 10, 2014.
doi: 10.3978/j.issn.2072-1439.2014.11.30
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.11.30

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality world-wide. Its impact is significant and increasing: COPD is predicted to be the 4th leading cause of death and the 7th leading contributor to the global burden of disease by 2030 (1). A better understanding of its pathophysiology, early detection and effective treatments is therefore imperative.

COPD involves at least two well-defined pathological features, namely parenchymal lung destruction (emphysema) and the loss or narrowing of airways (termed airways disease). The measureable physiological correlate of these changes is airflow obstruction, as indicated by a reduced spirometric ratio [forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC)]. Until recently, these structural and physiological components have been studied in isolation, with inferences made about their relationship.

Advanced imaging techniques allow detailed anatomical and structural data to be acquired *in vivo*. Functional data can also be acquired, often in real-time, and co-registered with the anatomical images. In combination, these imaging data expose a remarkable degree of regional variation in lung function. Depending on the resolution of the images, information can be obtained down to the alveolar level (2). The different modalities vary greatly in terms of temporal and spatial resolution, and each has its own advantages and disadvantages.

In this review, we will describe advanced imaging modalities that are currently in use, either clinically or in a research setting, at varying stages of development. A large focus will be on their role in furthering our understanding of pathophysiology, clinical phenotyping and response to treatment. We will also speculate on the future place of

these techniques among the assortment of tools available to clinicians for managing COPD.

High-resolution computed tomography (HRCT)

X-ray computed tomography (CT) has been in commercial use since 1972 (3), and has been revolutionary in providing insight into pulmonary structure and function *in vivo*. The technology involves an X-ray beam source with a row of detectors positioned opposite—the source and detectors are assembled in a circular arrangement that rotates around the patient through 180 degrees. Measuring the attenuation of narrow X-ray beams as they pass through tissues of varying densities allows the construction of a 2-dimensional (x,y) axial 'slice' through the body. The digitised image slices are comprised of pixels with relative 'densities' [measured in Hounsfield Units (HU)] that are representative of the tissue density in that location. Early scanners used relatively thick, contiguous slices that were obtained along the cranio-caudal (z) axis as the patient was moved stepwise through the scanner.

High-resolution CT achieves its increased spatial resolution by the use of thinner detectors, which allows the effective thickness of the axial slices to be reduced, usually to around 1 mm. The physical size of the X-ray detectors is therefore one of the determinants of resolution, while scanning technique is the other and more dominant determinant of spatial resolution. The high-resolution technique traditionally involves axial or 2-dimensional scanning, i.e., subjects are stationary during a single tube rotation to acquire a single cross-sectional slice. Because of the increased time and radiation required to perform contiguous thin slices, the slices are typically separated along the z axis by an interval of around 10 mm, which minimises total radiation exposure but images only 10 percent of the lung. It is therefore suitable for imaging the lung parenchyma but not for detecting, for example, mass lesions.

These days, almost all CT scans are performed in 'helical' or 'spiral' mode, rather than the older axial technique. That is, the patient is moved continuously through the scanner during tube rotation, effectively producing a 'cork-screw' motion. In this way, 3-dimensional or volumetric data is obtained; the faster the patient is moved through the rotating tube (pitch), the faster the acquisition time and the lower the radiation exposure. However, this effectively produces greater blurring of the images and reduces spatial resolution. Hence imaging technique, including tube current and voltage, once again has a large effect on spatial resolution.

Post-processing of the raw image data produces reconstructions in three orthogonal planes, which are most commonly displayed as axial images. Reconstruction also involves algorithms to produce images that are optimised for diagnostic viewing, such as 'high-resolution reconstruction algorithms'. These produce sharper but noisier images. Advances in CT technology have led to faster tube rotation, greater detector sensitivity and more rows of detectors – now up to 128 rows. This has greatly reduced acquisition time and reduced breath artifact; computer algorithms are able to correct for artifacts related to image inconsistency and motion (4). Axial slices of any thickness can be reconstructed, down to around 0.5 mm thickness (see *Figure 1*). However, at this level, spatial resolution is determined more by scanning technique (e.g., table speed) than by reconstructed slice thickness. There may therefore be no major advantage in such thin reconstructions. Modern post-processing techniques also allow true 3-dimensional reconstruction of the entire lung, airways and vasculature. Whether these are clinically useful is arguable.

Assessment of emphysema

HRCT is ideal for the detection and characterisation of emphysema (5). Moreover, it is very straightforward to use HRCT images to quantify the extent of emphysema. Older, standardised visual scoring systems to quantify emphysema (6) were subject to a high degree of inter- and intra-rater variability (7). More recent computer-automated quantification tools have removed the subjectivity of scoring (7). Emphysematous lung is represented by image voxels (the unit of a 3-dimensional image dataset) of density less than around –900 HU, which equates to a density of around 0.1 g/mL (water has a density of 1 g/mL). Identification of all voxels of density less than this threshold is a process commonly known as 'density masking', and the volume of the emphysematous lung can be calculated by multiplying the voxel numbers by the known volume of the voxels (8). A commonly used index is the percentage of low-attenuation areas (LAA%), which expresses the emphysema volume as a proportion of total lung volume measured by CT. The LAA% has been shown to correlate with FEV_1 (9-11), diffusing capacity for carbon monoxide (DLCO) (9), the frequency of COPD exacerbations (12), BODE index and quality of life scores (13). These relationships

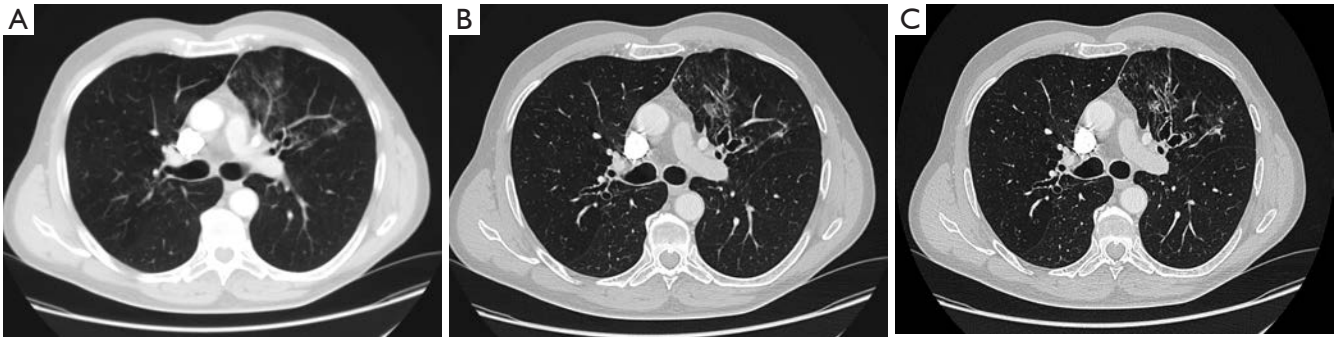

Figure 1 High-resolution CT scan of a 69-year-old man with allergic bronchopulmonary aspergillosis. Three axial reconstructions of (A) 6 mm, (B) 2.0 mm and (C) 0.625 mm thickness. Note the increasing spatial resolution with decreasing slice thickness. (Helical acquisition with the following settings to maximize spatial resolution: 120 kVp, 548 mAs, tube rotation time 0.5 s, collimator width 0.625 mm, pitch 1.375, voxel dimensions 0.76 mm × 0.76 mm × 0.625 mm).

confirm that the severity of emphysema is a determinant of the severity of airflow limitation as well as the clinical expression of disease.

A proposed clinical application of quantitative CT is in the longitudinal monitoring of emphysema progression. In the ECLIPSE study, which was a 3-year prospective, multi-centre observational study of COPD patients, emphysema progressed and became more extensive over the study period (14). The observations also confirmed that the extent of emphysema predicted the rate of decline of FEV_1 (15). Although it may be useful in identifying the so-called 'emphysematous phenotype', the ECLIPSE study also re-emphasised the marked clinical heterogeneity among COPD patients (16). More work is therefore needed to determine precisely how changes in CT emphysema over time translate into clinically important outcomes.

The LAA% gives an estimate of emphysema quantity, but not its distribution. The importance of emphysema distribution was demonstrated in the NETT (National Emphysema Treatment Trial) study of patients undergoing lung volume reduction surgery (LVRS). In this study, patients who had predominantly upper lobe emphysema (i.e., localised or heterogeneous emphysema, so-named because of the obvious differences in emphysematous and relatively preserved regions in the same lung) had improved survival following LVRS compared to the control group. In contrast, those in whom emphysema was not localised but rather spread out over a large proportion of the lung had poorer clinical outcomes (17).

In addition to this spatial heterogeneity, emphysematous lesions also exhibit so-called 'fractal geometry'. This is measured by identifying emphysematous clusters, i.e., a discreet and isolated zone of emphysema. In COPD, there is a large number of small emphysematous lesions but only a small number of large lesions or cysts. Plotting a cumulative frequency of emphysematous lesion size in log-log space results in a linear relationship with a negative slope (18). The slope of that relationship is the 'fractal dimension', with a more negative slope indicating a more heterogeneous distribution of emphysema zone sizes. As an example of its clinical significance, Coxson *et al*. (19) showed that the fractal dimension derived from the pre-operative CT predicted the change in exercise capacity following LVRS. Although this complex CT assessment of emphysema appears to have some clinical significance, its potential role in routine clinical practice remains unclear.

Assessment of airways

Airways are also visible in HRCT image data, down to approximately generation 6 or 7. In COPD, changes in small airways (terminal and respiratory bronchioles) are considered to be the among the earliest signs of disease (20) and precede the development of emphysema (21). However, CT airway measurement is much more difficult than measurement of emphysema for a number of reasons. Firstly, airway branching is asymmetrical (in terms of length and calibre of bronchi) and hence 'functional' classification of individual airways cannot be made by simple counting of generations (22). Indeed, the small airways (0-2 mm in diameter) can be found anywhere between the 4^{th} and 14^{th} generations (22). Secondly, the measurable parameters of airway geometry (such as airway wall thickness and luminal area) vary greatly by anatomical location (23). Finally, since

the major site of airflow obstruction in COPD is in airways with dimensions less than 2 mm (20,21), the primary area of pathology is generally below the resolution of conventional HRCT.

Early attempts at quantitative analysis of visualised (generally large to medium sized) airways involved manual tracing of internal luminal area (Ai), outer area (Ao) and the calculation of wall area (Aw). Computer algorithms using a density mask have been used to automate this process, whereby circles surrounding the airway lumen are progressively 'eroded' based on density measures until the airway wall and lumen are identified (24). Another method known as the full-width-half-maximum method has been used to identify internal and external wall edges. This principle uses density analysis along radial 'spokes' from the centroid of the lumen, and identifies the wall edge as the point where density is half way between the local minimum and local maximum along each spoke (10). A well-documented problem is that CT measurement systematically over-estimates Aw and underestimates Ai, a feature that alters with airway angle and becomes more pronounced with decreasing airway calibre (24); mathematical corrections can be applied to overcome this error. Automated airway measurements have been validated for larger airways (down to the 6th generation) (25,26), but concerns regarding accuracy continue to limit their use.

Measurement of the small airways is even more problematic. Although large airway wall thickness correlates with symptoms (27) and lung function (10,25) in COPD, and may be predictive of small airway abnormalities (28), direct measurement of small airway geometry by CT has remained elusive. 'Air trapping' is an indirect HRCT measurement of small airway dysfunction, where lung lobules remain inflated due to airway obstruction and hence show a less-than-normal increase in attenuation during expiration, creating a mosaic pattern of attenuation. However, this phenomenon is observed to a degree even in healthy, non-smoking individuals without airflow obstruction (29,30). In COPD, this method is further complicated by the presence of emphysema, which itself shows low-attenuation during expiration (31). Although attempts at quantifying air trapping in the presence of COPD have been made (31,32), more validation studies are needed to determine the best method. For now, at least in the clinical setting, it seems that air trapping on CT will remain a more qualitative marker of small airways disease, and probably adds little to the diagnosis or monitoring in COPD.

Ventilation CT

Although anatomical information from CT is of value for diagnosis and assessment of disease severity, there is likely added benefit when it is combined with imaging-derived measurement of lung function. For example, the distribution of inhaled xenon (Xe) gas (which is radiopaque, and distributes into the airways and alveoli on inhalation) can be measured by its CT attenuation. The CT density of these Xe-containing airspaces increases linearly with Xe concentration (33). In this way, specific ventilation (i.e., ventilation per unit lung volume) can be measured and the regional distribution of ventilation explored. New dual-energy (i.e., two X-ray sources) CT allows both dynamic and static evaluation of regional ventilation, and simultaneous acquisition of anatomical and ventilation images (34). This eliminates the problems of serial scanning, such as differences in breath-hold volume affecting density, and spatial misregistration of the two scans (35). Dual-energy Xe gas ventilation scanning has been shown to reliably quantify both emphysema and airways disease (36).

Limitations of CT

In addition to problems with spatial resolution, CT has other important limitations. For example, there are minimal data regarding normal ranges for airway dimensions (37) and currently no consensus standards for validation and quality control of CT airway measurement—a prerequisite for high-quality, longitudinal studies. Perhaps the most important limitation of CT is the risk posed by ionising radiation, particularly with serial scanning (38). Quantitative measurements using current-generation detectors with low-dose protocols may be acceptable for certain applications (39) but the reduced signal-to-noise ratio poses an additional challenge when assessing small airways (40,41).

Ultra-high-resolution imaging

Like all diagnostic tools, imaging techniques need to be verified against a gold standard test. In the case of COPD, this would be histopathological evaluation of lung tissue. However, even as a gold standard, histopathology itself has problems: tissue changes from fixation, cutting and drying as the specimen is processed cause measurement error; the small size of specimens may introduce sampling error; and analysis is generally performed in two (or even single) dimensions, giving only estimates of the 3-dimensional

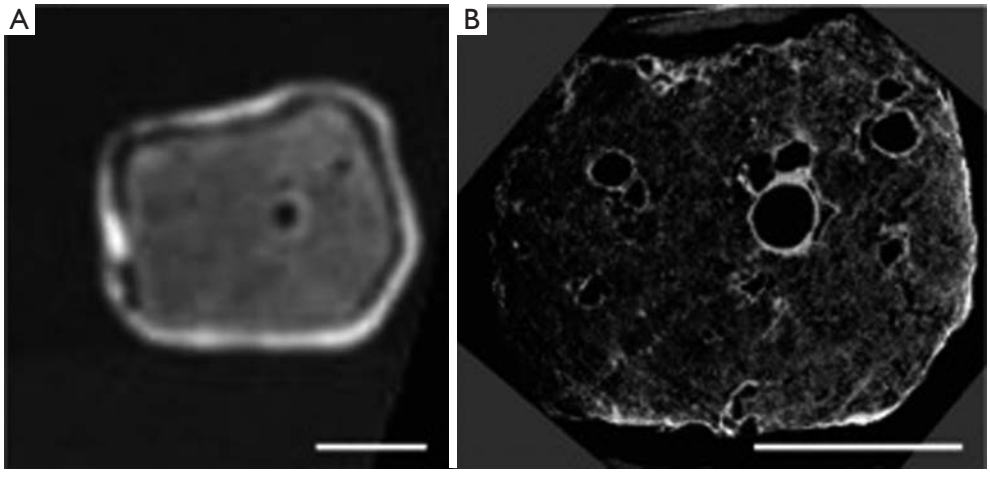

Figure 2 Micro-computed tomography (micro-CT) of a 2 cm pig lung cube. Lungs were inflation-fixed in formalin steam prior to scanning. (A) Cross-sectional high-resolution CT image and (B) corresponding micro-CT image of the same region of interest. Exquisite detail is seen with micro-CT. Scale bars =1 cm.

structure (42). The use of ultra-high-resolution imaging techniques is aimed at countering these problems.

Micro-computed tomography (micro-CT)

Micro-CT is similar to conventional CT in that it uses an X-ray source and detectors that are arranged around the study object. Like conventional CT, full volumetric data is captured. However, the source and detectors are brought much closer to the specimen, and the specimen itself is rotated while the X-ray source and detectors stay stationary. This allows exceptionally higher resolution (down to 1 μm per voxel), which is ideal for studying the lung microstructure including that of the small airways. The trade-offs are that only small specimens, i.e., excised tissue or small animals, can be imaged. Furthermore, the samples are exposed to high radiation doses that are damaging to living tissue.

Micro-CT was first used to image lung parenchyma by Watz *et al*. (43), who used a hot formalin vapour fixation technique and silver nitrate staining to provide the necessary contrast. This provided spectacular images of alveoli and terminal airways, and even allowed a "virtual bronchoscopy" through an alveolar duct (43). The technique has subsequently been validated against light microscopy in mouse lungs (44). It has also been used to generate gold-standard airway measurements from explanted lung to calibrate 3-dimensional airway measurements made by whole body HRCT (45). *Figure 2* demonstrates the spectacular detail obtained using micro-CT of the lung. In COPD, micro-CT has been used to demonstrate the loss of terminal bronchioles in early-stage disease, which has been suggested to precede the microscopic emphysematous destruction of the alveoli (21).

Although living, *in vivo* human studies are precluded (due to both specimen size and the radiation dose), micro-CT has provided fascinating insights into the structural changes in COPD. The technology, in its currently form, will likely remain limited to research. It may play a future role in, for example, developing disease-modifying therapies in animal models.

Synchrotron imaging

This form of imaging utilises the properties of particle beams, e.g., electrons, in a particle accelerator. The particles are in continuous motion at near the speed of light, held in line by electromagnetic fields. When the particles are accelerated further they emit X-rays with a wide energy range, allowing a wide range of samples to be imaged, and a high photon flux, which allows fast acquisition times. The result is an image with resolution in the 1-10 μm range (46), which is ideally suited to studying the microstructure of fine tissues such as the lung.

The technique has been used to define the structure of both mouse (47) and human (48) lung acini *ex vivo*, as well as *in vivo* whole mouse lungs (49). The high temporal resolution also makes functional imaging possible,

including pulmonary acinar mechanics (50) and regional ventilation (51,52). In COPD mouse models, it has been used to identify early emphysematous changes (53,54). While the anatomical detail is impressive, synchrotron imaging is yet to provide significant functional information on human lungs, being hampered by the limitations of specimen size (necessitating excised tissue or small animals only), radiation damage to tissues, and the need for a particle accelerator.

Nuclear medicine imaging

Unlike CT imaging methods, which are based on the relative absorbance of radiation transmitted through the tissues from an external source, nuclear medicine techniques utilise tracers that emit radiation and are introduced into the organs. This has been used to image a variety of body tissues and organs, including bone, the heart and the brain. Nuclear medicine scanners are in routine clinical use for the diagnosis and staging of malignancy. They have also long been used for the diagnosis of pulmonary embolism (PE)—this involves intravenous injection of radioisotopes to the pulmonary vasculature and inhalation to the peripheral airspaces, thus giving functional images of ventilation and perfusion.

Positron emission tomography (PET)

PET is a 3-dimensional nuclear imaging technique, which utilises radioisotopes that emit positrons as they decay. A positron is a sub-atomic particle found in the nucleus, with the same molecular weight as an electron. As the positron makes its way out of the nucleus, it encounters a free electron—these two oppositely-charged particles combine and 'annihilate' each other. In the process, two identical beams of gamma-radiation are emitted at 180 degrees to each other—beams detected at or very near the same time are considered to be 'coincident' i.e., from the same source. The location of the source particle can therefore be determined geometrically from coincident beams, being located on a straight line between the two detectors. However, this localisation is affected by beam scatter, the presence of random coincidences, and by attenuation as the beams travel through tissues of different densities. Corrections for this image noise can be made during image processing, which includes the use of a tissue density map i.e., a CT scan. Many scanners incorporate multi-detector CT (PET-CT) so that, in addition to providing a tissue density map for attenuation correction, organ function can be superimposed onto the CT images. This image co-registration has an obvious application in oncology for localisation of active tumour cells for targeted treatment.

The most commonly used PET radioisotope is fluorine-18, which has a half-life of approximately 110 minutes. This isotope is attached to fluorodeoxyglucose (FDG, a glucose analogue) to form the radiotracer 18F-FDG. The radiotracer is taken up by metabolically active tissue—a property used to identify cancerous tissue in the lungs and surrounding structures. In COPD, 18F-FDG has been used to demonstrate an increase in neutrophilic inflammation in the lungs compared to controls and to those with alpha-1 antitrypsin deficiency-associated emphysema (55). This provides interesting insights into COPD pathophysiology and is a non-invasive, *in vivo* measurement. However, it is also potentially useful in studies of new therapies targeting neutrophils, given their role in the pathogenesis and pathophysiology of COPD (56).

Regional ventilation can also be measured by PET using the PET isotope nitrogen-13 (13NN) gas dissolved in saline. A peripheral venous injection of this tracer enters the lung via the pulmonary arterial circulation. Due to its low tissue solubility, the 13NN then rapidly diffuses across the alveolar membrane. An initial breath-hold during injection allows the 13NN to enter the lung in direct proportion to blood flow, which allows measurement of regional perfusion. Regional ventilation can subsequently be measured by the decrease in 13NN activity over time as the subject breathes, clearing the 13NN in direct proportion to ventilation (57). Combining this information thus produces the regional distribution of lung ventilation/perfusion ratios (V/Q). Quantification of regional V/Q by PET has been shown to correlate closely with global measures of gas exchange such as arterial partial pressure of oxygen (PaO_2) (58). Using this 13NN technique in COPD, Brudin and colleagues (59) reported that high V/Q tended to be more common in subjects with an emphysematous phenotype, whereas low V/Q was more common in those with a small airways disease phenotype. This is consistent with the archetypal concept of 'pink puffers' and 'blue bloaters'.

While much of the focus in COPD is on airways disease and changes in regional ventilation, there has been an increasing focus on the role of the pulmonary vasculature in this disease. Vidal Melo *et al*. (60) found that regional heterogeneity in Q was increased in patients with mild COPD compared to healthy controls, in a manner that was independent of changes in regional tissue density. This very interesting finding suggests that regional changes in

pulmonary blood flow, perhaps due to inflammation, may precede lung parenchymal changes in COPD. This may have utility as a biomarker for early disease.

One limitation of PET, with its short half-life radioisotopes, is the need for a cyclotron and radiopharmaceutical formulation often on-site. Additionally, for repeated studies, the radioisotope has to decay enough to avoid signal contamination. Adjustments following a 'baseline' scan prior to repeat administration help overcome this problem, however rapid, repeat testing is generally not possible. The spatial resolution of PET does not allow imaging of individual gas exchange units, although it is probably sufficient to separate physiologically meaningful differences in regional ventilation.

In spite of these limitations, and its relatively recent inception, PET may have a significant future in the study of COPD. The recent findings regarding regional distribution of blood flow may provide insight into the role of vascular remodeling, especially with regard to longitudinal changes and therapies targeted at this process.

Single-photon emission computed tomography (SPECT)

SPECT is similar to PET in that a radiotracer is introduced to the body, and the radiation it emits is detected externally. However there are several key differences. SPECT radioisotopes emit a single gamma-beam as they decay, as opposed to the two gamma beams emitted simultaneously from PET isotopes. This results in a lower radiation exposure to the patient, at the expense of an increased acquisition time per image. Increased scanning time may decrease resolution due to movement artifact, although there have been attempts to overcome this with breath hold/respiratory gating (61). The spatial resolution of SPECT is less than that of PET, however it is more widely available, and SPECT radiotracers are easier and cheaper to manufacture. SPECT has been a major advance in nuclear imaging for suspected PE (62), as opposed to the traditional planar lung scintigraphy. The more recent appearance of SPECT-CT fusion has helped overcome a lot of the resolution and anatomical registration problems, and can provide true 3D assessment of regional lung function (63,64).

In addition to its diagnostic role for PE, SPECT can give us insights into pulmonary physiology, both with respect to ventilation and perfusion. Perfusion scanning is generally performed using 99m-technecium labeled macro-aggregated albumin (^{99m}Tc-MAA), which lodges in the pulmonary circulation after peripheral injection. Ventilation scanning requires inhalation of gaseous radioisotopes or radiolabeled particulate aerosols. A true gas distributes throughout the whole lung, and differences in its regional distribution reflect differences in regional ventilation. Dynamic SPECT could therefore potentially give information on the time course of ventilation in different lung regions. Both ^{81m}Kr (65) and ^{133}Xe (66) have been used to demonstrate ventilation heterogeneity in COPD.

Unlike true gases, particulate aerosol tracers are 'deposited' in the lung and have the advantage that imaging can be performed without the tracer continuously redistributing. Also, aerosols will not distribute by collateral ventilation between lung units, which is increased in COPD compared with healthy lungs. However, aerosol particles of a diameter 0.5-1 μm are 1,000 times larger than gas molecules and are therefore transported by convective ventilation only (67). The distribution of radioaerosols therefore neglects diffusive ventilation, which is the predominant mode of gas transport within acini beyond the terminal bronchiole (68). In COPD, airway narrowing and emphysematous destruction likely brings the convection-diffusion front more centrally so that a larger volume of the lung ventilates by diffusion compared with healthy lungs. Therefore, the interpretation of inhaled radioaerosols distributions in COPD should take these physiological changes into account (69).

A commonly used aerosol tracer is 99m-technecium-labelled diethylene triamine pentaacetic acid (^{99m}Tc-DTPA). The generated particle size is around 1 μm but this increases on entry into the airways due to agglomeration. These larger particles deposit onto large airways, particularly at airway branch points, causing 'hot-spots' on the ventilation image (70). Technegas is a ^{99m}Tc-labelled, aerosolised ultra-fine carbon particle of approximately 200 nm diameter. It is used routinely in Australia (where it was invented) and other countries in V/Q scanning for the diagnosis of PE. Due to its small particle size, the distribution of Technegas approximates that of a true gas (71), even in the presence of severe airflow obstruction (72) (*Figure 3*). Technegas deposits more homogenously, and is less susceptible to central airway deposition or movement after inhalation, than ^{99m}Tc-DTPA (73).

Regional V/Q ratios are heterogeneous in COPD due to the variable effects of inflammation and tissue destruction on lung parenchyma, small airways and blood vessels. Jogi *et al*. (74) reported significant relationships between SPECT-derived V/Q ratios and both airflow obstruction measured by spirometry and emphysema severity on CT. In

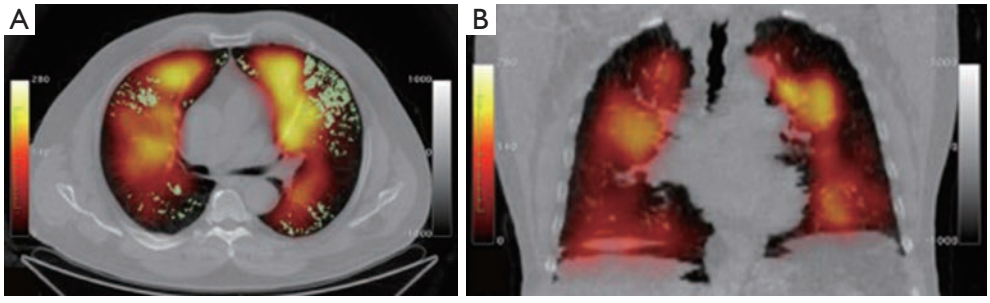

Figure 3 Technegas ventilation SPECT/CT fusion images of a 68-year-old man with moderately severe COPD. (A) Axial dimension, with well-ventilated areas (bright yellow), less ventilated areas (red) and non-ventilated areas (black). Green indicates emphysema determined by a CT density mask, with pixel density less than –910 HU. Note that poorly ventilated areas tend to correspond to areas of emphysema. Some non-ventilated areas are not associated with emphysema, suggesting airway obstruction without macroscopic parenchymal destruction in these areas; (B) coronal reconstruction of ventilation map.

patients with COPD, Suga *et al*. (75) found that automated, quantitative analysis of V/Q distribution by SPECT was more sensitive at detecting early emphysema than the corresponding CT density mask. The standard deviation of the V/Q profile (i.e., dispersion of V/Q ratios) could differentiate the GOLD spirometric classes of severity, and also correlated well with the measured alveolar-arterial oxygen gradient (A-aDO2), a global measure of V/Q inequality (75).

There have been a number of intervention studies in COPD patients using nuclear scintigraphy techniques, including SPECT, to predict and measure clinical success. For example, SPECT imaging has been shown to predict post-operative lung function following surgery for lung cancer. Sudoh *et al*. (76) demonstrated that perfusion SPECT/CT was as accurate as the segment-counting technique (77) but was less affected by the presence of severe emphysema (76). In emphysematous patients undergoing LVRS, Inmai and colleagues (78) found that LVRS improved ventilation distribution as measured by Technegas SPECT, not only in the surgical field but also in the contralateral lung. Recently, Argula *et al*. (79) performed a retrospective analysis of data from the VENT endobronchial valve study (80) to investigate the effects of baseline lobar perfusion on outcomes following endobronchial valve placement. In this analysis, target lobe perfusion was quantified from ^{99m}Tc-MAA perfusion images taken prior to stent insertion. The patients were dichotomised as 'high' or 'low' baseline lobar perfusion. Post-procedure, the low perfusion group were found to have a significantly greater increased in 6-minute walk distance at 6 months, which was independent of the degree of emphysematous destruction in that lobe. The authors postulate that the redistribution of blood flow seen in the 'high' baseline perfusion group may explain their poorer exercise performance (79). This study used planar scintigraphy, and it is possible that similar studies using the more sophisticated SPECT/CT may shed further light on this interesting finding. To date, there are no published studies using SPECT ventilation imaging to assess the effects of treatments aimed at improving the ventilation patterns in COPD, including bronchodilators, inhaled corticosteroid therapy, bronchial stents or intrapulmonary thermal treatment.

In summary, there have been many technical advances in SPECT imaging of lung ventilation and perfusion. There are potentially many research questions in COPD to which SPECT imaging could be applied, particularly because of its relative wide availability in large centres. Future studies will inform eventual clinical applications in COPD. Although PET ventilation imaging could eventually be preferred over SPECT, the current availability and cost of PET may limit its use.

Magnetic resonance imaging (MRI)

MRI has the advantage of not requiring ionising radiation. Its usefulness for lung imaging has traditionally been limited by technical factors and, consequently, there has been much less MRI lung imaging in research and clinical practice compared with the modalities already discussed. The technique employs large magnetic fields, which alter the behavior of individual atoms. Conventional MRI utilises the nuclear spin properties of hydrogen atoms, found in

abundance in water. In their natural state, hydrogen ions (or protons) spin on an axis in random orientations. The application of a strong and uniform magnetic field causes them to align parallel or anti-parallel to the field. When the magnetic field is switched off, the spinning protons return to their natural state and in the process release a burst of radiofrequency energy. It is this energy that is detected by the MRI scanner, and is used to construct the image. MRI has excellent anatomical resolution in tissues of high water content, such as the brain. However the lung, being mostly air, has a low density of hydrogen ions, meaning low signal intensity and poor signal-to-noise ratio. Conventional proton MRI images of the lung therefore have low contrast and contain little meaningful information. Additionally, being comprised of air-filled alveolar sacs, the lung has millions of air-tissue interfaces. Each of these causes decay of the radiofrequency signal as it travels through the lung, known as 'susceptibility artifact', which contributes to poor signal intensity (81). Such inherent limitations have left the lung relatively unexplored by MRI. However, the large potential for MRI imaging of the lung has been recognised for decades (82) and thus many attempts have been made to overcome these barriers.

Inhaled noble gas MRI

Inhaled noble gases have been used to overcome the aforementioned limitations (83). Unlike particulate aerosols, gases undergo 'self-diffusion' by random Brownian motion, where the gas molecules continually move further apart until stopped by a physical boundary. The speed and direction of movement is determined by the physical properties of the gas, and the likelihood of colliding with a neighbouring gas particle i.e., the local concentration of the gas. An example of a noble gas ventilation agent is hyperpolarised helium-3 which, unlike air, is highly excitable by a magnetic field and thus provides excellent MRI contrast. It diffuses freely in air at a rate of 0.88 cm^2/s, which means that, over a timecourse of 2 ms, an individual molecule will travel 0.59 mm. Given that the typical acinar size is 0.3 mm, the diffusive movement of a molecule of ^3He in an acinus will be limited by the alveolar boundaries within the 2 ms timeframe—that is, its diffusion will be 'restricted' from 0.88 to 0.2 cm^2/s. The restricted gas molecule movement is measurable by MRI, and is known as the 'apparent diffusion coefficient (ADC)'. A high ADC indicates that the alveolar walls are further apart, i.e., there is alveolar destruction or acinar expansion, which is an early sign of emphysema (84). The technique has been validated against histological specimens (2). It is increased in smokers who still have a normal FEV_1, suggest that alveolar expansion and early emphysema are present even without clinical manifestation of disease (85). The ADC also correlates very closely with standard lung function measures including FEV_1/FVC ratio, TLC and RV (85). In more advanced disease, the mean ADC correlates strongly with FEV_1 (86) and DLCO (87), in fact more strongly than HRCT measures of emphysema (86,87).

From a functional perspective, ventilation can also be assessed using the properties of inhaled noble gases. Inhalation of the hyperpolarised gas distributes reasonably homogeneously in healthy young adults, but is heterogeneous in otherwise healthy elderly subjects (81). Regions of absent MRI signal, which indicate non- or poorly-ventilated lung units, have been shown to correlate with emphysema that is detectable by CT or the ADC (88). Ventilation defects may also be observed even in the absence of anatomically gross emphysema visible by CT (89,90). In this case, small airways disease, mucous plugging or a combination of both small airways diseases and microscopic emphysema are possible explanations for absent ventilation. This suggests that, like PET and SPECT, functional disturbances measured by MRI may be more sensitive markers of early abnormalities in COPD, compared with anatomical imaging by HRCT.

The ability of hyperpolarised ^{129}Xe to diffuse across the alveolar membrane into the circulation allows gas exchange to be measured. There is a large chemical shift of ^{129}Xe between the gas compartment, the dissolved (tissue and plasma) compartment and the red blood cells (91). By detecting the change in resonance frequency between these compartments, measures of the alveolar membrane thickness (91) and blood uptake (92) can be made. This technique has been used to demonstrate the influence of posture on regional perfusion heterogeneity (93) as well as ventilation heterogeneity (94) in COPD.

Oxygen-enhanced MRI

Although the use of hyperpolarised noble gases has greatly advanced the use of MRI for lung imaging, these gases are expensive to use, requiring specialised laser polarising equipment and dedicated detectors. ^3He in particular is in limited and restrictive supply. There is therefore a need for simpler and less expensive contrast agents. Oxygen was suggested as a MRI contrast agent by Edelman (95) over 15 years ago as a way of overcoming the inherent

limitations of conventional proton MRI and avoiding the problems of hyperpolarised gases. Ohno and Hatabu (96) have written a detailed review of the theory and application of oxygen-enhanced MRI. In basic terms, molecular oxygen is weakly paramagnetic and, in the concentrations found in air and in blood, provides little MR signal. The inhalation of 100% oxygen produces a high concentration of oxygen in alveolar tissue and in blood, where is it predominantly dissolved in plasma. The result is an increase in the signal intensity, which then allows visualisation of the pulmonary parenchyma. The difference between room-air and oxygen-enhanced images represents ventilation to that area. Edelman's original publication (95) clearly showed ventilation defects in a patient with emphysema. Ohno and colleagues (97) showed that oxygen-enhanced MRI was as good as CT at quantifying pulmonary emphysema across a wide range of severities, and correlated reasonably well with FEV_1 and DLCO. Recent work in subjects with COPD has shown increased heterogeneity of V/Q distribution measured by oxygen-enhanced MRI even in those without CT-defined emphysema (98), which varies with the severity of COPD (99).

The advantages of oxygen-enhanced MRI (OE-MRI) are that it is a simple, low-cost and safe alternative to hyperpolarised gas MRI. One of the limitations is that the gas itself is not directly visualised, but rather the tissue and blood, so that OE-MRI is only an indirect measure of ventilation. Another limitation is that the absorption of oxygen by circulating blood removes it from the lung unit, meaning there would inevitably be a difference between the wash-in and wash-out phases if they were measured. Additionally, the administration of 100% oxygen to patients, particularly those with advanced COPD, may alter the fundamental pulmonary physiology that we are attempting to measure (96).

In summary, MRI is increasing our current understanding of regional ventilation in COPD, whilst overcoming the limitations of ionising radiation associated with other functional imaging modalities. Cost and availability of the gases, polarisers and research scanning time will likely remain major constraints. Therefore, OE-MRI may be more practical in terms of clinical application. More studies are needed to build on the limited treatment (100,101) and longitudinal (102) data available to date.

Emerging imaging modalities

Optical coherence tomography (OCT)

OCT has emerged from the field of interventional pulmonology. It involves the measurement of lung structure from an endobronchial approach. Analogous to B-mode ultrasound but utilising light waves rather than sound waves, OCT involves the insertion of a near-infrared optical probe into the airway, with a sensor to detect back-scattered and reflected light waves. A detailed description of the physics of OCT is present in Huang's seminal review of the topic (103). OCT images have sufficient resolution to distinguish between different tissue types within the airways, i.e., mucosa, sub-mucosa, lamina propria, cartilage, airway smooth muscle and alveoli. This ability of OCT can therefore potentially identify malignant tissue at the time of bronchoscopy, where the structural components of tissues are altered in their organisation, content and reflective properties (104).

Although there are few studies in subjects with COPD, OCT is ideally placed to measure the anatomical properties of small airways, being limited only by the physical reach of the probe and by the need for repeated measurements in different areas to obtain representative sampling. Miniaturised probes can be introduced down to the level of the terminal bronchiole (105,106). Coxson and colleagues demonstrated an excellent correlation between airway dimension measured by OCT and by CT (107). OCT may give more accurate measurement of airways size since, in this study, CT-measured dimensions tended to be larger than the OCT measurements. Furthermore, OCT airway dimensions measured at the 5^{th} generation bronchi showed a strong negative correlation with the subject's FEV_1, and had greater discriminatory power for airflow obstruction than CT measurements (107). There was also an increase in %wall area and an increase the density of subepithelial structures in subjects with a lower FEV_1 (107). Kirby *et al*. (108) reported a strong negative correlation between airway wall area and FEV_1 in males COPD subjects but not in females, which is an interesting observation that may be relevant to the observed differences in disease behavior between the sexes (109,110).

OCT shows promise as a very useful tool for relating structural and functional changes in COPD *in vivo*. There are very important advantages of high resolution, the ability to measure small airways and the lack of ionising radiation, but it is nevertheless an invasive procedure requiring at least conscious sedation. The potentially important and novel information on small airways means that it will likely be increasingly used in research and clinical practice as the technology improves and becomes more accessible.

Electrical impedance tomography (EIT)

As its name suggests, EIT measures differences in impedance to the flow of an electrical current through different tissues. A typical setup involves a set of surface electrodes, usually 16 to 32, positioned around a body structure. Through a pair of electrodes (the 'drive pair') a small current is applied. The potential difference between each pair of adjacent electrodes is then recorded, and hence the resistivity or impedance at that location can be determined. The process is repeated with each pair of electrodes acting as the drive pair, and a spatial map of resistivity is developed. This technique is ideally suited to pulmonary monitoring for several reasons. Firstly, the lungs, being filled with air, have naturally high impedance and are subject to large changes in volume during respiration. This gives a relatively large 'swing' in impedance that can be used to monitor breathing patterns and interventions. The change in electrical lung impedance is proportional to the change in gas content, which has been validated against other imaging modalities (111-113). Secondly, a decrease in impedance from initially high values could be used to detect focal consolidation/collapse or more diffuse changes in, for example, acute respiratory distress syndrome (ARDS). Thirdly, the short acquisition time provides enough temporal resolution for real-time monitoring of the lungs over long periods, as opposed to quasi-dynamic imaging of ventilation CT or nuclear medicine. Finally, being small and portable, EIT can be used in a variety of physical settings.

Even though the potential clinical utility of EIT respiratory monitoring has been recognised for many years (114), the pulmonary application of EIT has so far been largely limited to the intensive care setting. For example, EIT has been used to develop protective ventilation strategies by optimising positive end-expiratory pressure (PEEP) to minimise regional hyperinflation and collapse (115). In a case report of a patient with COPD undergoing mechanical ventilation, Mauri *et al*. (116) could optimise ventilator settings to overcome intrinsic PEEP and decrease gas trapping measured with OCT. More recently, the technique has been used to explore other obstructive airways diseases. Zhao and colleagues (117) showed that, in patients with cystic fibrosis, regional airway obstruction measured by OCT correlated with a CT composite index of bronchiectasis severity, mucous plugging, parenchymal opacity and hyperinflation in the same lung region.

The most detailed physiological study using EIT in subjects with COPD was recently published by Vogt *et al*. (118). EIT was used to measure the regional distribution of tidal volume, inspiratory vital capacity and FEV_1 during a forced expiratory manoeuvre. Ventilation heterogeneity between regions was quantified as the coefficient of variation. COPD subjects showed greater ventilation heterogeneity than either young or older healthy subjects. Importantly, the measurements were able to discriminate between healthy and COPD subjects even during quiet tidal breathing.

EIT therefore represents an exciting new technique for assessing regional ventilation in COPD. It is a simple, portable, radiation-free, real-time measurement that would be well suited to dynamic physiological studies. More work is needed to determine its role in, for example, the early detection of disease and for treatment/intervention studies.

Conclusions

Our understanding of the pathophysiological mechanisms in COPD is increasing with the new era of imaging tools that are available. There is a greater recognition of the complexity of lung mechanics and regional ventilatory abnormalities in this clinically heterogeneous disease, and advanced imaging techniques are at the forefront of this investigation. As older techniques are refined, and new techniques are developed, the information we gain from advanced imaging in COPD is likely to expand exponentially. The major limitation of ionising radiation exposure is being overcome by advances in technology, which minimise radiation dose while increasing image quality. These modalities are likely to become increasingly important in drug design and delivery, and offer the chance to monitor the impact of such therapies over time. Ultimately, the aims of COPD research should be directed towards modifying the natural history of the disease. We believe the role of advanced imaging techniques in detecting disease in its earliest stage is paramount, as this is the stage at which potentially disease-modifying interventions are likely to have the greatest impact.

Acknowledgements

Dr. Milne is supported by NHMRC Postgraduate Research Scholarship; A/Prof. King is supported by NHMRC Practitioner Fellowship #632916.

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Milne S, King GG. Advanced imaging in COPD: insights into pulmonary pathophysiology. J Thorac Dis 2014;6(11):1570-1585. doi: 10.3978/j.issn.2072-1439.2014.11.30

Review Article

Implementing clinical guidelines for chronic obstructive pulmonary disease: barriers and solutions

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Abstract: Chronic obstructive pulmonary disease (COPD) is a complex chronic lung disease characterised by progressive fixed airflow limitation and acute exacerbations that frequently require hospitalisation. Evidence-based clinical guidelines for the diagnosis and management of COPD are now widely available. However, the uptake of these COPD guidelines in clinical practice is highly variable, as is the case for many other chronic disease guidelines. Studies have identified many barriers to implementation of COPD and other guidelines, including factors such as lack of familiarity with guidelines amongst clinicians and inadequate implementation programs. Several methods for enhancing adherence to clinical practice guidelines have been evaluated, including distribution methods, professional education sessions, electronic health records (EHR), point of care reminders and computer decision support systems (CDSS). Results of these studies are mixed to date, and the most effective ways to implement clinical practice guidelines remain unclear. Given the significant resources dedicated to evidence-based medicine, effective dissemination and implementation of best practice at the patient level is an important final step in the process of guideline development. Future efforts should focus on identifying optimal methods for translating the evidence into everyday clinical practice to ensure that patients receive the best care.

Keywords: Pulmonary disease; chronic obstructive; clinical practice guidelines; health services; evidence-based practice

Submitted Sep 16, 2014. Accepted for publication Nov 20, 2014.
doi: 10.3978/j.issn.2072-1439.2014.11.25
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.11.25

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex lung disease that is characterised by progressive worsening of airflow limitation, punctuated with acute exacerbations that if severe, frequently require hospitalisation (1). COPD is the third leading cause of mortality worldwide (2). Several evidence-based guidelines for the diagnosis and management of COPD are available to clinicians, including the GOLD guidelines internationally and the COPD-X Plan: Australian and New Zealand Guidelines for the management of COPD. Although they are widely available, the knowledge and implementation of these guidelines are highly variable in actual clinical practice. Many barriers to the implementation of management guidelines by clinicians have been identified (3), but relatively few studies have investigated methods for enhancing the use of guidelines. This review explores these critical issues, gaining insight from efforts in clinical guidelines for other chronic diseases, and applying these principles to improving uptake of the COPD guidelines amongst clinicians.

Benefits of adhering to clinical recommendations contained in guidelines for COPD

The goals of therapy in COPD are to reduce symptoms

and improve quality of life, and reduce future risk of adverse outcomes including exacerbations, hospitalisations and mortality. The evidence base for achieving these goals are encapsulated in international (1) and national clinical guidelines available throughout the world. By following these guidelines, clinicians will ensure that they are translating the best available evidence into their everyday clinical practice.

Spirometry is the gold standard diagnostic test to confirm fixed airflow limitation in individuals with dyspnoea, chronic cough or sputum production, and risk factors for COPD (1). Spirometric diagnosis of COPD at any stage is an essential step to ensure an accurate diagnosis and to guide therapy (4). The benefits from using non-pharmacological therapies in COPD are substantial—smoking cessation reduces lung function decline (5), influenza and pneumococcal vaccination decrease the risks of these infections (6,7), and pulmonary rehabilitation improves quality of life, increases exercise tolerance and reduces frequency of hospitalisations (8,9). In addition, pharmacological therapies provide benefit for patients, with long-acting bronchodilators (10-15) and inhaled corticosteroids (16) acting to reduce dyspnoea, improve quality of life and lung function, decrease risk of exacerbations and possibly reduce mortality (17). Early recognition and appropriate treatment of acute exacerbations with bronchodilators, systemic corticosteroids and antibiotics, where appropriate, reduce symptoms, shorten time to recovery and reduce risk of relapse (18,19).

Preparation of evidence-based clinical guidelines: the Australian COPD-X guidelines as an example

Many national guidelines have been written and adapted for use in specific countries. In the process of evidence-based guideline development, it is particularly important that the developers regularly review and critically appraise the evidence, to ensure that the guidelines are up-to-date, high quality, clinically relevant and beneficial to healthcare professionals and patients (20). As an example, many of us have been involved in the Australian COPD-X clinical guidelines developed by Lung Foundation Australia. COPD-X stands for Case detection and Confirm diagnosis, Optimise function, Prevent deterioration, Develop management plan of care, and manage eXacerbations. These guidelines were initially published in 2003 in the *Medical Journal of Australia* (21) and an update was published in 2006 (22). Since then, regular updates have been available on a dedicated website administered by the Lung Foundation (www.copdx.org.au), with the latest version (2.37) recently published online.

The guidelines are prepared by the Lung Foundation Australia's COPD Guidelines Committee, which consists of eight clinical members plus executive administrative support. Conflict of interest statements from each Committee member are recorded on an annual basis and published on the COPD-X website. The Committee meets quarterly to appraise the latest published evidence and make recommendations on updating the guidelines. Prior to each meeting, searches are carried out in the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and PubMed, using detailed search strategies (available on request) which include COPD and emphysema as key words.

At each meeting, search results are discussed to decide whether full papers should be obtained for review. At the subsequent meeting, committee members discuss their appraisal of the papers reviewed and recommend whether the papers should be cited in the guidelines, with any additional form of wording included. After an approval process, Lung Foundation Australia publishes online updates of COPD-X (typically two updates per year) to include the changes agreed at recent meetings of the Committee. An email is sent to all the registered users of the COPD-X website informing them when an update has been made and what changes have occurred. A COPD-X Concise Guide for Primary Care, based on the full guidelines, will be released by Lung Foundation Australia in November 2014 (www.copdx.org.au).

Low concordance with guideline recommendations

A major issue is low awareness of clinical guidelines, which may subsequently translate into low adherence to guideline recommendations, and potentially suboptimal clinical care for patients in primary, secondary and tertiary care. Even with detailed processes for preparation and implementation of guidelines, such as the Australian COPD-X guidelines above, observational studies suggest that clinician knowledge of management guidelines is relatively low world-wide, both for chronic diseases generally and specifically for COPD.

Chronic disease guidelines

Many lessons can be learned from use of clinical guidelines in chronic diseases other than COPD, and applied in principle to COPD guidelines. As examples, comparison of

studies examining chronic disease management reveals that many cardiovascular-related guidelines are largely adhered to; however, lower adherence has been generally observed to guidelines for metabolic diseases such as diabetes and osteoporosis (23-28).

Cardiovascular disease

In general, good adherence has been observed for cardiovascular disease guidelines (23,24). For hypertension, a study of 410 physicians in Finland found an 89% adherence rate to the guidelines, and that implementation improved in larger centres with more structured health care systems (24). Another study of general practitioners (GPs) in Austria found 83% adherence to cardiovascular disease and diabetes guidelines (23). However, when non-adherence occurred, factors included lack of familiarity with guidelines, even after education, and disagreement with guideline treatment recommendations (23,26,28,29).

Metabolic diseases

In general, rates of adherence to guidelines in the management of metabolic diseases have been observed to be relatively low. Studies of adherence to guidelines for screening of gestational diabetes found very low rates of adherence in obstetric units in France (25) and Canada (26). Factors identified included lack of familiarity with new guidelines, unfamiliar screening measures, poor acceptance and feasibility, difficulty with administration of recommendations, patient non-adherence, and ambiguity in guideline recommendations (25,26). Additionally, a retrospective survey of 200 GP referral letters to a hospital in Scotland showed that the introduction of local type 2 diabetes guidelines had no significant effect on screening for patient complications, or on GP referral letter content about complications of diabetes (27). In a survey of Canadian GPs, 35% of respondents had not read or been aware of the latest osteoporosis guidelines (28).

Though many guidelines for chronic diseases have been carefully developed, relatively low adherence to guideline recommendations—particularly for metabolic disease but less so for cardiovascular diseases—may result in suboptimal healthcare. Many barriers to adherence with chronic disease guidelines have been identified, as outlined for the examples above. Hence to improve adherence to guidelines, research has focused on strategies to target health professional education, decision-making algorithms (including electronic systems), and reminders at the time of consultation, and continuous quality assurance programmes.

COPD guidelines

Correct diagnosis and subsequent appropriate treatment selection have been the most common areas of deficiency identified in adherence to COPD guidelines. Most studies have focused on outpatient management of COPD, particularly primary care. A cross-sectional study of 455 primary care physicians and 243 physicians practicing in a hospital system, published in 2004, found that only 55% of Swiss physicians used spirometry in the diagnosis of COPD, and only one-third knew the GOLD criteria for COPD (30). Knowledge of the indications for use of inhaled steroids and referral to pulmonary rehabilitation were also low. A recent cross-sectional study of 593 GPs in Shanghai found that whilst 55% of GPs recognized the different severity classifications, only 8% of patients with COPD received prescriptions in accordance with GOLD guidelines (31). Thus, although COPD guidelines are widely available and accessible in print and online, studies suggest that clinician awareness of their specific recommendations is generally low, despite many efforts for their implementation and dissemination.

Several studies in COPD have demonstrated that actual clinical practice may deviate significantly from guideline recommendations (*Table 1*). A retrospective study of 450 outpatients with stable COPD in the US (33) found that 56% of patients received guideline-concordant pharmacotherapy, based on the 2007 GOLD guidelines available at that time (35). There was a significant relationship between suboptimal treatment and adverse outcomes: patients who received guideline-discordant treatment had nearly twice the number of exacerbations as those who received guideline-concordant care. A cross-sectional study of 1,517 primary care patients with COPD in the US found that 27% of patients had spirometry documented within the previous year, 25% had comorbid conditions appropriately managed, and 32% had appropriate measures in place for risk reduction (34). In a Swiss study, GP prescription of long-acting bronchodilators or inhaled steroids was guideline-concordant in only 20% of patients with GOLD spirometry stage I and II COPD, whereas 64% of patients with more severe stage III and IV COPD received guideline-concordant treatment (32). Finally, a retrospective study of 1,185 patients with moderate to severe COPD in Slovenia found that those who died during follow-up were more often found to have experienced suboptimal management according to guidelines when compared to patients who were alive at the end of the

Table 1 Examples of studies of actual clinical practice compared to COPD guidelines

Study	Methods	Outcomes
Jochmann, 2010 (32)	Prospective study of 139 GPs and 615 patients with COPD. GPs completed survey of management of each patient. The authors compared actual management with recommended management based on disease severity	➢ 44% of patients did not fulfill GOLD diagnostic criteria for COPD ➢ Only 5% of patients received pulmonary rehabilitation ➢ 36% of all patients with COPD were prescribed a minimum of a short acting bronchodilator ➢ Prescription of long-acting bronchodilators or inhaled corticosteroids was guideline-concordant in 20% of patients with GOLD stage I or II disease and 64% of patients with stage III or IV disease ➢ 6% of patients with stable disease received inappropriate systemic steroids
Sharif, 2013 (33)	Retrospective study of the management of 450 patients with COPD treated in an academic medical centre in the USA. Actual treatment was compared with indicated treatment based on GOLD guidelines	➢ 56% of patients received treatment concordant with GOLD guidelines ➢ Patients co-managed by a primary care physician and respiratory specialist were most likely to receive guideline-concordant treatment ➢ Patients who received guideline-discordant treatment had nearly twice the number of exacerbations as those who received guideline-concordant care in the year following spirometry
Belletti, 2013 (34)	Cross-sectional study of management of 1,517 patients with COPD in US primary care centres with retrospective chart review of medical records	➢ 27% of patients underwent spirometry in previous year ➢ 25% were having comorbid conditions appropriately managed ➢ 32% had appropriate measures in place for risk reduction ➢ 3% of patients met all three guidelines components for (I) spirometry; (II) management of comorbid conditions; and (III) risk reduction measures

GP, general practitioner.

follow up period (including less long-acting inhaled medicine prescribed by their medical practitioners) (36). Overall, these findings support the value of guideline-based care in improving patient outcomes in COPD, and clearly demonstrate areas of practice that can be enhanced.

Barriers to guideline adherence

Specific barriers to adherence to COPD guidelines have been identified in observational studies. In one study of 154 general internists in the US, factors associated with reduced concordance with clinical guideline recommendations included low familiarity with COPD guidelines, perceived low self-efficacy for use of guidelines, and time constraints (37). In another US study, only 32% of 500 primary care physicians reported high familiarity with the GOLD COPD guidelines (38). In comparison, a larger proportion (76%) of the same group of physicians rated themselves as very familiar with guidelines for management of hypertension, indicating a relative disparity in awareness of guidelines for these two common chronic conditions. A qualitative Australian study, using semi-structured interviews of nine hospital-based registrars or interns, and seven GPs, found that barriers to implementation of evidence-based recommendations for COPD included lack of supportive enablers and complexity of the behavioural change needed in their patients (39).

Approaches to improving adherence to guidelines

Improving adherence to chronic disease guidelines

A number of methods of improving guideline implementation have been investigated in chronic diseases other than COPD that could feasibly be applied to COPD guidelines.

Distribution of guidelines

Having knowledge itself does not necessarily translate to clinical practice; therefore implementation and distribution strategies must be utilised. Use of brief summaries or storyboards of guidelines posted in clinical areas are associated with a positive impact on provider knowledge (40). Other distribution methods include mailing guidelines directly to clinicians or generating publicity prior to guideline publication (41). The act of voluntarily downloading guidelines also demonstrated active participation and greater

likelihood that the guidelines would be considered useful.

Clinician professional development

Continuing medical development is another commonly used method with the aim to increase clinician adherence to guidelines. A study of infection management found a significant improvement in compliance with infection control protocols after active education when compared to no intervention (42). A third arm, the passive intervention group where education material was offered but not actively made available, resulted in only 34% of participants engaging in education, compared to the 91% in the active group. However, studies of diabetes care and lower back pain management showed no significant difference in guideline adherence after an educational program (43,44). A Cochrane review of 81 studies found that continuing medical development meetings can lead to a small improvement in practice and patient outcomes (45). Factors associated with effective educational meetings were higher attendance rates and a mix of didactic and interactive sessions.

Electronic health records (EHR)

EHR usage has been associated with improved provider knowledge (40). However, in a 2-year study comparing the EHR to non-EHR primary care practices, there was no significant difference in adherence to diabetes management guidelines between these two groups. In other studies of diabetes management before and after implementation of EHRs, EHRs have been demonstrated to improve attainment of healthcare management standards. For example, EHR implementation increased rates of patients with diabetes having their glycated haemoglobin (HbA_{1c}) level checked at the appropriate intervals, being prescribed antihypertensive medication when indicated, and receiving pneumococcal vaccination (46). EHRs have also been shown to improve treatment intensification following abnormal HbA_{1c} levels (47), and reduce both emergency department (ED) visits and hospitalisations in patients with diabetes (48).

The cost efficiency of EHRs is still controversial, and there are many factors to consider regarding their use. Ultimately, EHRs will be most successful when they can meet the needs of physicians and their patients, promote quality care, and maximise efficiency (49).

Reminders about guideline recommendations

Having guidelines in a readily accessible manner, when they are required at point-of-care, has been shown to improve guideline adherence (50). Similarly, establishing checkpoints, deadlines or cues during a consultation has been associated with improved provider knowledge (40). This has been found to be effective in increasing guideline adherence, which could then be translated into significantly improved patient quality of life (51,52). Reminders have been associated with positive clinician behavioural change, since relevant information is being presented during the clinical decision-making process (28,53). A Cochrane review of 32 studies found that computer-generated reminders for tasks such as ordering screening tests or giving vaccinations provided to clinicians on paper resulted in a median 11% improvement in process of care measures compared to usual care (54).

Though the reminder system has proven to be effective, it has been suggested that physician perception of the benefit of the reminder may also influence their usage. One study has shown that prompts perceived to be regulatory and for enforcement will be used less than prompts perceived to be for guidance (55). A Cochrane review of audit and feedback systems for clinicians found that the success of such programs depends on several factors (56). Characteristics associated with behavioural change in response to these programs include poor baseline performance, feedback from colleagues, repeated feedback, multimodal communication of feedback, and tangible goals with a clear process to achieve them.

Decision support systems

CDSS are software programs that can assist clinician decision-making. One randomised study published in 1999 utilising a CDSS on hypertension management showed no clinically significant improvement (57), possibly attributed to less than expected use of the CDSS. In contrast, a Cochrane review of 42 trials found that point-of-care computerised advice for drug dosing improved objective parameters for several drugs, including anticoagulants, insulin, and antibiotics, although this did not translate to improvements in mortality (58).

Multifaceted health care systems

Evidence is mixed on whether combining implementation techniques have a synergistic effect on adherence to guidelines. A multifaceted approach to gestational diabetes, using pamphlets, reminders and meetings, showed significantly increased guideline adherence in the prescription of screening tests after 2 years of implementation (25). A study of cervical cancer screening showed significant improvements in most of the clinical

Table 2 Examples of studies of methods to improve adherence to clinical guidelines for COPD management

Study	Methods	Outcomes
Ulrik, 2010 (63)	Cross-sectional surveys of 124 GPs in Denmark at baseline and 12 months after completion of an educational program. The management of 1,716 and 1,342 patients with COPD was assessed in the first and second surveys, respectively. The educational program consisted of individual meetings with specialists, expert symposia, individual review of audit data, and included GPs and their staff	➢ Significant improvements were observed in recording of disease severity, smoking status, BMI, dyspnoea severity, and FEV_1/FVC ratio ➢ Significant increases were observed in smoking cessation counseling, teaching of correct inhaler technique, promoting exercise, and pulmonary rehabilitation referrals ➢ Inappropriate prescription of inhaled corticosteroids in patients with mild disease decreased (pre-education 76% *vs*. post-education 45%)
Bertella, 2013 (64)	Retrospective review of 12 GPs in Italy caring for 328 patients with COPD at baseline and 12 months after completion of an educational program for GPs. Educational program involved lectures, spirometry training, and specialty phone consultation service	➢ The educational program did not significantly affect use of spirometry or chest X-rays ➢ A small increase in recording of smoking status was observed with the educational program

recommendations, with use of software modules which facilitated selection, attendance monitoring, follow up and also provided reminders (59). A study conducted of beta-blocker usage in patients with heart failure observed little improvement in prescription after using provider education alone and provider/patient notification, but significant improvements with the use of a nurse facilitator (60). However in diabetes management, implementation methods such as chart audits, performance feedback, reminders and computerized supports improved only 4 of 9 criteria in the first year of use, with effectiveness falling to 2 of the 9 criteria after the second year of implementation (61).

In summary for chronic disease guidelines, numerous methods for improving the implementation of guidelines have been studied, however the results are mixed. Professional education, EHRs and multifaceted implementation programs have shown benefit in some studies, but not in others. Programs that distribute guidelines in a way that promotes active participation by clinicians are more likely to have a positive effect, and interactive reminder systems at the point of care provide an effective solution for guidelines when they are most needed. Further work is needed to identify the aspects of these implementation programs that are beneficial.

Improving adherence to COPD guidelines

There is increasing recognition of the importance of independent research to further clarify the most effective methods for developing and implementing evidence-based guidelines (20). The publication of clinical practice guidelines is only the first step in a process that ends with an actual change in clinician behaviour. The importance of effective guideline dissemination methods cannot be overlooked. Grimshaw *et al.* (62) reviewed the studies of guideline dissemination methods and the role of guideline developers in this process. They concluded that developers must take an active role in including methods for disseminating and implementing their guidelines.

Most research to date on enhancing uptake of COPD guidelines has focused on improving clinician knowledge and awareness of guidelines through education sessions (*Table 2*). Studies have shown mixed results, with some suggesting minor improvements in management following the intervention, and others showing no effect.

Two observational studies have evaluated the effect of an education program for GPs on COPD guideline uptake. A study of GPs in Denmark found that several guideline-related indices of diagnosis and management improved 12 months after a comprehensive education program (63). Better use of spirometry to classify disease severity and a reduction in inappropriate use of inhaled corticosteroids were observed. In contrast, a small study of GPs in Italy found no significant change in management following an educational program that consisted of lectures, spirometry training, and specialty phone consultation service (64). The discrepancy between these study results may be due to pre-existing levels of guideline uptake, contrasting styles of educational programs, different health system contexts or

inadequate sample size.

Point-of care checklists may also be useful in hospital clinical practice. Previously, members of our group have undertaken a prospective pilot study of the use of an inpatient checklist to promote evidence-based recommendations (unpublished data, presented at the Thoracic Society of Australia and New Zealand Annual Scientific Meeting 2012) (65). Focus groups, statewide stakeholder consultation and a literature review were used to develop a paper-based, one page Inpatient Checklist for acute exacerbations of COPD (AECOPD), based on the Australian COPD-X guidelines. Demographic, process of care and patient outcome data for AECOPD admissions were collected in pre-checklist [2010] and checklist-implementation [2011] phases at one tertiary referral hospital. Two groups of admissions were studied in pre-checklist (n=42) and checklist-implementation (n=68) groups. Adherence to checklist use by ward medical staff in a respiratory ward was 51% (35 of the 68 checklist-implementation admissions).

Concordance with COPD-X Plan recommendations was high overall for patient assessment (e.g., admission chest X-ray 100%) and initial treatment (e.g., inhaled bronchodilators 100%, systemic corticosteroids 79%, and antibiotic therapy 91%). Concordance was lower for inpatient consideration of longer-term issues such as referral to pulmonary rehabilitation (36%). Checklist use was associated with significantly increased rates of arterial blood gas analysis (86% *vs.* 61%, P=0.02), sputum microbiology testing (83% *vs.* 58%, P=0.02) and influenza vaccination assessment (71% *vs.* 51%, P=0.04), compared with admissions without checklist use. Median length of stay did not change significantly with checklist use. In this pilot study, checklist use was associated with increased rates of several recommended strategies for management of inpatients with an AECOPD. This study has shown that there is opportunity to improve aspects of inpatient care for COPD and to refine methods of guideline dissemination (65). There may be even better uptake with electronic checklists for COPD, which could be used in both inpatient and outpatient settings to improve guideline adherence.

Lessons from implementation of COPD, asthma and pneumonia guidelines

While the individual interventions recommended by clinical practice guidelines are evidence-based, there are relatively few studies assessing patient outcomes following the implementation of COPD guidelines per se (66). Most studies of guideline implementation to date have focused on healthcare process rather than patient outcome measures. One small randomised controlled trial assessed change in mean peak expiratory flow rate (PEFR) in patients in general practice patients following a comprehensive guideline implementation program (67). Patients in the intervention group experienced a statistically significant improvement in mean PEFR, as well as respiratory symptoms and pain scores. However this improvement was small when compared to the control group receiving usual care. A large RCT of primary care practices in the US has been planned, which will incorporate systems such as computerised patient activation tools and web-based COPD guidelines to improve guideline uptake (68).

Beyond COPD, there are several examples of guideline implementation leading to improved patient outcomes, in particular in the treatment of pneumonia and asthma. A US study found that implementing pneumonia treatment guidelines significantly reduced 30-day mortality of elderly patients (69). The authors hypothesised that the improved patient outcomes were due to earlier and more accurate identification of high-risk cases, with a significant improvement in utilisation of appropriate antibiotics during the same time period.

In Australia, a multi-faceted approach to improving awareness and management of asthma was implemented with success in the early 1990s, in the form of new clinical guidelines published as an initiative of the National Asthma Council (originally the National Asthma Campaign). These guidelines were published in the Asthma Management Handbook, and now the Australian Asthma Handbook (70). The campaign involved promoting the best practice management for asthma to healthcare professionals, especially in primary care, and the general public (71). This highly effective approach likely played a role in improved asthma management and reduced asthma mortality (by 70% since the 1980s) after implementation (72,73).

Conclusions and future studies

COPD is a major cause of morbidity and mortality worldwide. Guidelines for the diagnosis and treatment of COPD are widely available, however, concordance with these guidelines remains sub-optimal. Numerous barriers to guideline adherence have been identified, but studies assessing methods for improving the uptake of guidelines in COPD management are limited to small-scale non-randomised studies. Given the significant resources

invested in guideline development and the cost of management of COPD in general, there is a need for better strategies to ensure effective guideline implementation and optimise their use. Future studies should evaluate implementation strategies used in the management of other diseases for COPD. These studies could assess a combination of techniques to ascertain whether a synergistic response exists and to find the most efficient model with greatest marginal benefit for each different disease. This could allow the development of an optimal protocol that can assist with implementation of guidelines. There are many interventions that have a proven mortality or symptom benefit for patients with COPD. Given the benefits of these treatments, it would be logical to assume that guidelines comprising these interventions would lead to better patient outcomes. There are, however, very few studies assessing the effect of COPD guideline implementation on patient outcomes, and this is an area that requires further research. Clinical guidelines are an important modality for communicating evidence-based recommendations to clinicians at the point of care. The development of guidelines is an important early step, but more research is needed to determine the most effective ways to translate the evidence into everyday clinical practice.

Acknowledgements

We thank the patients and staff involved in our research projects, and the Lung Foundation Australia staff and health professionals in the COPD Evaluation Committee who are involved in the writing of the Australian COPD-X guidelines. We thank John Serginson, Lisa McCarthy and Rina Waller for their assistance with the inpatient COPD checklist study.

Funding: The University of Queensland Research Scholarship (JO), The Prince Charles Hospital Foundation New Investigator Grant (JO), NHMRC Career Development Fellowship 1026215 (IY), NHMRC Practitioner Fellowship 1019891 (KF), AusHSI Stimulus Grant (IY).

Disclaimer: this review article represents the views of the individual contributing authors, and should not necessarily be taken as representing the views of Lung Foundation Australia.

Disclosure: Michael Abramson holds investigator-initiated grants for unrelated research from Pfizer and Boehringer Ingelheim, has received conference support from BI and has undertaken an unrelated consultancy for AstraZeneca. The other authors have no financial conflicts of interest to declare. MA (Chair), IY (Deputy Chair) and JB (Executive Officer) are members of Lung Foundation Australia's COPD Guidelines Committee which updates the Australian COPD-X clinical guidelines. Lung Foundation Australia receives some funding support from a number of pharmaceutical industry partners towards the COPD National Program. The authors declare no conflict of interest.

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Cite this article as: Overington JD, Huang YC, Abramson MJ, Brown JL, Goddard JR, Bowman RV, Fong KM, Yang IA. Implementing clinical guidelines for chronic obstructive pulmonary disease: barriers and solutions. J Thorac Dis 2014;6(11):1586-1596. doi: 10.3978/j.issn.2072-1439.2014.11.25

Review Article

Development of a self-treatment approach for patients with COPD and comorbidities: an ongoing learning process

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Background: Patient-initiated action plans are an important component of COPD self-management (SM) interventions. When integrated into SM interventions, these action plans have proven to be effective in reducing exacerbation severity, hospitalisations, and costs and in improving health status in patients with COPD without severe comorbidities. Because of overlap in symptoms, a self-treatment (ST) approach that focuses solely on traditional symptoms of COPD is inadequate for patients with COPD and comorbidities. The COPE-III SM intervention combines (I) patient-initiated action plans that are tailored to the individual's co-morbid disease(s), and (II) ongoing nurse support. In this paper we provide information regarding the integration of information from two previous COPD SM studies (COPE I and II) in the development of the current COPE-III ST approach.

Materials and methods: COPE-III ST materials include daily symptom diaries and action plans that take patient's common comorbidities [chronic heart failure (CHF), anxiety, depression, ischaemic heart disease (IHD), and diabetes] into account. The comorbid diary and action plans components were developed in collaboration with multiple disease-experts.

Results: Previous SM studies have highlighted some essential topics that need to be considered when developing a SM or ST approach: 'when to initiate ST', 'how to optimize materials and safety', and 'how to achieve behavioural change'. In the COPE-III study, ST is initiated after a significant change in symptoms. This is consistent with the COPE-II approach and was implemented because disease symptoms are often present even when patients are stable. We have tried to ensure patient safety by providing an easily accessible case-manager to patients throughout their involvement in the study. Furthermore, a psychologist has ensured the use of behavioural change techniques throughout the intervention.

Conclusions: We should continue to learn from our experiences with SM interventions to further optimize future SM and ST interventions. The use of materials that are suitable for different levels of patient literacy and the training of health care providers are other points of improvement.

Keywords: Pulmonary disease; chronic obstructive; self-care; comorbidity

Submitted Jun 05, 2014. Accepted for publication Oct 21, 2014.
doi: 10.3978/j.issn.2072-1439.2014.11.14
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.11.14

Introduction

COPD is a leading cause of death and disability internationally (1) that affects approximately 1:10 adults in the developed world and is increasing in prevalence globally (2). High financial and social burdens have been associated with COPD in general (3,4) and COPD exacerbations in particular (5,6). COPD exacerbations, defined by episodes of acute deterioration in respiratory health (7), are also a major contributor to a step-wise worsening of quality of life in patients (7).

The latest Cochrane systematic review of COPD self-management (SM) has documented that COPD-specific SM interventions are associated with a reduction in hospital admissions (8). Patient-initiated action plans are an important component of SM interventions (8,9). When used appropriately, they can lead to accelerated initiation of appropriate treatment (10) and therefore reduce the exacerbation severity (11). When integrated into SM interventions, these action plans have proven to effectively reduce exacerbation severity, hospitalisations, and costs and improve health status (11-13).

Comorbidities are the rule rather than the exception in COPD (14,15). Over two-thirds of COPD patients (68.4%) suffer from at least one comorbidity, about 16% have at least two comorbid conditions (15), and one third of the COPD patients admitted to hospital have at least four coded comorbidities (16-18).

Because the symptoms of COPD and common co-occurring diseases overlap, a "one size fits all" approach that focuses solely on traditional symptoms of COPD is inadequate. For example, increased dyspnoea could relate to either a COPD exacerbation or a sudden deterioration of cardiovascular disease (e.g., heart failure) (19,20). Reliance on specifically designed for COPD symptoms and actions/ treatments could therefore lead to the initiation of incorrect or delayed treatment.

The latter is highlighted by a recent study evaluating COPD-specific action plans in a COPD population with comorbidities (21). The study was terminated because of significantly higher mortality rates in the intervention group. No definite reason for this has emerged and the findings contrast positive outcomes of a comparable SM study (22). Nevertheless, the study (21) has resulted in controversy regarding the effectiveness of SM interventions, especially in patients with high burden of disease and co-morbidities (23). In these patients, SM interventions may be more challenging and not without risk of serious adverse events (23). It underlines the need for further evaluation of action plans in COPD patients with comorbidities.

In this paper we provide an insight into how we have used our experiences with our previous SM studies to develop a novel COPD self-treatment (ST) approach for patients with COPD and co-morbidities.

The COPE studies

During the last 15 years we have performed three large randomized controlled trials to explore effects of SM: the COPE-I (24), COPE-II (11,25), and COPE-III study (26). COPE stands for 'COPD study at Department of Pulmonology Enschede. Whereas the COPE-I and COPE-II study were performed in the Netherlands, COPE-III is a joint Dutch - Australian research project. Experiences from COPE-I and COPE-II have been used to develop the design for the COPE-III study. Details of all three COPE studies have been summarized in *Table 1*.

COPE-I

In the COPE-I study the effects of a comprehensive SM intervention were evaluated in 248 patients with moderate to severe COPD and no severe comorbidities (24). The intervention involved an individualized treatment plan that incorporated smoking cessation, optimisation of pulmonary status by pharmacotherapy, a standardised low-intensity exercise program, and a written ST action plan for COPD exacerbations that was based on symptom perception. If patients experienced an increase of respiratory symptoms and normally would have called their physician, they could start with a short course of oral prednisolone, and with onset of purulent sputum a course of antibiotics for which prescriptions were supplied (24). The study results showed no effects on quality of life and exercise capacity, and an increased number of exacerbations, defined as an increase of respiratory symptoms treated with prednisolone and/or antibiotics in the intervention group. However, because daily symptoms were not recorded in either study groups, it could not be clarified whether this meant that there was an over-treatment in the intervention group or an under-treatment in the control group (24).

COPE-II

In the COPE-II study (11), the extra value of a COPD SM component was evaluated. A group of patients who received

Table 1 Characteristics of the COPE-I, COPE-II, and COPE-III study

COPE study	Methods				Participants			SM intervention group			Primary outcome	Secondary outcomes
	Design	Intervention	Control	Follow-up (months)	Numbers	Major inclusion criteria	Major exclusion criteria	Setting	Session frequency and duration	Key topics		
I	RCT	SM, ST and non-standardized low-intensity exercise	Usual care	12	127 intervention; 121 control	COPD diagnosis; (ex) smoker; age: 40-75	Medical condition with low survival, serious psychiatric morbidity; other serious lung and cardiac disease	Outpatient clinic, exercise in private practices	4 weekly 2-hour group sessions and 1 follow-up 2-hour group session given 3 months after the 4th session. Professionals: respiratory nurse, physiotherapist	COPD knowledge, symptom recognition, COPD ST action plan, inhalation technique, exercise, relaxation, nutrition, breathlessness, energy conservation, communication and social relationships	HRQoL (SGRQ)	Symptoms and exacerbation frequency of COPD, self-confidence, 6MWT, lung function, doctor consultations, hospital admissions, days lost from work
II	RCT (2-by-2 factorial design)	SM, ST and standardized exercise	SM intervention and standardized exercise	24 (published: 12 months)	70 intervention; 72 control	COPD diagnosis; ≥3 exacerbations, and/or 1 respiratory hospitalization in previous 2 years; (ex) smoker; age 40-75	Medical condition with low survival or serious psychiatric morbidity; other serious lung or cardiac disease	Outpatient clinic, exercise in private practices	4 weekly 2-hour group sessions and 5 follow-up phone calls. Professionals: respiratory nurse, physiotherapist	COPD knowledge, symptom recognition, COPD ST action plan, inhalation technique, exercise, relaxation, nutrition, breathlessness, energy conservation, communication and social relationships	Exacerbation severity—daily symptom diary (exacerbation days and severity scores)	Exacerbation frequency, hospital admissions and days, courses of oral steroids and antibiotics, lung function, CRQ, CCQ, HADS, HR-QoL, health care utilisation, costs
III	RCT (international-multisite)	SM and ST	Usual care	12	Recruitment in progress	COPD diagnosis; ≥1 comorbidity: IHD, CHF, AD, DM; ≥3 exacerbations, and/or 1 respiratory hospitalisation in previous 2 years; age ≥40	Medical condition with low survival or serious psychiatric morbidity; other serious lung disease; low cognitive functions	Outpatient clinic	4 or 5 weekly sessions (2 individual 1-hour sessions; 2 or 3 two-hour group sessions) and 3 follow-up phone calls. Professionals: respiratory, cardiac, mental health and/or diabetes nurse	COPD and comorbidity knowledge, symptom recognition, ST action plan for COPD and comorbidities, inhalation technique, exercise, relaxation, nutrition, breathlessness, energy conservation	Number of COPD exacerbation days—daily symptom diaries	Exacerbation severity (symptom score), hospital admissions and days, number of CHF exacerbation days, comorbid symptom scores, courses of oral steroids and antibiotics, lung function, CRQ, ICFS, HADS, CSES, HR-QoL, SM behaviour and knowledge, self-confidence, satisfaction, adherence with ST protocol, health care utilisation, costs

6MWT, 6-minute walking test; AD, anxiety and/or depression; ATS, American Thoracic Society; CCQ, clinical COPD questionnaire; CHF, chronic heart failure; CRQ, chronic respiratory questionnaire; CSES, COPD self-efficacy scale; DM, diabetes mellitus; ER, emergency room; FEV_1, forced expiratory volume in one second; FVC, forced (expiratory) vital capacity; GOLD, global initiative for chronic obstructive lung disease; GP, general practitioner; HADS, hospital anxiety and depression scale; HR-QoL, health related quality of life; ICFS, identity-consequence fatigue score; IHD, ischaemic heart disease; RCT, randomised controlled trial; SGRQ, St George's respiratory questionnaire; SM, self-management; ST, self-treatment.

a SM intervention that included specific training in ST (intervention group; n=70) was compared to a group of patients who received a similar SM intervention without this specific training (control group; n=72). The ST training component incorporated training in COPD symptom recognition (with the help of a daily symptom diary) and use of an action plan. The concerns from the COPE-I study regarding over-treatment in the intervention group were taken into consideration and the start of a COPD exacerbation was defined as 'a clear negative change in two major symptoms or one major and one minor symptom from baseline, for at least two consecutive days' [major symptoms: breathlessness, sputum production, sputum color; and minor symptoms: cough, wheeze, running nose, sore throat, and fever (>38.5 ℃) (27)] (11). This meant ST was only initiated 48 hours after an initial change in symptoms. Similar to the COPE-I study (24), COPE-II data showed a significantly higher use of courses of prednisolone and antibiotics in the ST group. However, the number of reported courses in the ST group was still lower than the actual number of exacerbations reported in the diaries, meaning that prednisolone was not used during every exacerbation. The final COPE-II study results therefore indicated that this approach did not lead to overtreatment, and indeed less COPD exacerbation days and lower costs occurred in the intervention group (11). In summary, the COPE-II study demonstrated that specific COPD ST training within a more general COPD SM training intervention leads to less exacerbation days and lower costs (11). However, these study results cannot be generalized to the large population of COPD patients with comorbidities.

COPE-III

The COPE-III SM intervention incorporates (I) patient-initiated action plans that are tailored to the individual's co-morbid disease(s) as well as their COPD, and (II) phone support from case-managers. The design of the COPE-III study, an international randomised controlled multi-centre trial, has previously been published and the intervention is currently under evaluation in both the Netherlands and Australia (26). Patient recruitment takes place in five hospitals [Netherlands: Enschede (Medisch Spectrum Twente) and Nijmegen (Canisius-Wilhelmina Ziekenhuis); Australia (Adelaide: Repatriation General Hospital, Flinders Medical Centre, Royal Adelaide Hospital)]. We expect that data collection will be completed by the end of 2015.

In the COPE-III study, we have incorporated at similar COPD ST component to that evaluated in the COPE-II study and combined this with action plans for common comorbidities [chronic heart failure (CHF), anxiety, depression, ischemic heart disease (IHD), and diabetes]. The comorbid action plan components have been developed in collaboration with multiple disease-experts (Cardiologist, Cardiac Nurse Practitioner, Endocrinologist, Psychiatrist, and Psychologist). In COPE-III, extensive patient training directed towards individualized materials is provided.

COPE-III ST approach

The COPE-III intervention involves a total of 8-9 hours of SM session time and several additional follow-up phone calls. A more specific description of the intervention has been provided in a previous paper (26). Because of the adjustment of intervention materials for comorbidities, materials are more complex than the ones used in previous two studies. It has therefore become necessary to deliver half the COPE-III training sessions individually instead of in a group and to allocate relatively more session time towards specific ST training compared to previous interventions. ST materials include a 'what are my usual symptoms' card, a daily symptom diary, and an action plan. During training in the use of these materials, hypothetical scenarios were incorporated to engage the patient in practicing the completion of the diaries and understanding appropriate use of the action plans.

As in previous studies, SM training is provided by case-managers (respiratory nurses). Patients are provided with information on how to contact the case-manager if they have any doubts or questions. Access to case-managers is available during office hours and patients are advised to contact their GP or Emergency Department during out of office hours. The case-manager also acts as a triage nurse when the cause of the change in symptoms is unclear and additional advice is necessary (26).

COPE-III ST materials

Even when stable, many patients with COPD experience symptoms of their respiratory disease and comorbidities, especially patients with moderate to severe disease (19). In the COPE-III intervention, the nurse and patient define together the patient's symptoms during a stable health state and summarize these findings in the patients' 'what are my usual symptoms' card. The patient is advised to use this card while completing the daily symptom diary and to

indicate whether symptoms have changed compared with their stable health state. So as in COPE-II (11), ST actions are linked to changes in symptoms rather than to existing symptoms. This approach requires that patients have skills and knowledge to recognize deterioration in their symptoms (28).

Patients are asked to complete the symptom diary that includes respiratory symptoms and relevant comorbid symptoms, every day. When patients do not experience deterioration in any of the predetermined symptoms listed in the diary during the last 24 hours, they are instructed to tick the box 'no change in symptoms' (indicating no further actions are required). Whenever they experience deterioration in any symptom listed in the diary, they are asked to report the level of change for each of the listed symptoms and if this change is of sufficient magnitude, consult their tailored action plan (26).

Besides the COPD component, all daily symptom diaries and action plans include one or more comorbid components in a pre-defined order: (I) CHF; (II) anxiety and/or depression (AD); (III) IHD; and (IV) diabetes. Diabetes action plans differ for patients with type 1, type 2 and prednisolone-induced diabetes. As such, there are 21 possible action plans that can be instigated.

Cardiac component

Similar action plans are provided for two cardiac comorbidities, IHD and CHF, in both Australia and the Netherlands.

For CHF three questions are included in the daily symptom diary regarding fluid retention (weight, swelling of ankles and abdomen, and waking up at night short of breath). According to the action plan, patients should increase/start their diuretic medication when they record 'a significant change' for two consecutive days for at least one of these questions. The expert team agreed that a change in weight of at least one kilogram in 24 hours should be considered a significant change. Patients are asked to contact the case-manager if symptoms do not decrease with diuretic therapy, or if they think they need more than the 3-day diuretic course as directed in the action plan. In the Netherlands patients are asked to contact their cardiac nurse directly.

A second CHF action plan component is included for safety reasons. Patients are asked to contact the case-manager (or cardiac nurse for Dutch patients) if they become more light-headed and/or dizzy. Consequently, the case-manager contacts the cardiac nurse to see if further actions are required (possible causes for these symptoms include rhythm disorder, over diuresis or a side effect of medication).

The existing action plan for IHD, developed by the 'National Heart Foundation of Australia', is being used with minor adjustments in lay-out (29).

Anxiety and depression

The action plan for anxiety and depression advises patients to commence relaxation exercises (which are practiced during the SM courses) if they experience increased AD. If symptoms do not improve after 5 days patients are asked to contact the case-manager (Dutch patients could directly contact the mental health worker). When necessary, their predefined 'plan' (e.g., seeing their GP to discuss their symptoms and management) is activated and/or a consult with a psychologist arranged.

Prior to inclusion patients are screened with the Hospital Anxiety and Depression Scale (HADS) (30). Patients with scores meeting recognized clinical cut-off points (exceeding 10 per subscale) of the HADS (30) are offered psychological counseling prior to the baseline measurement.

Although experiencing suicidal ideation is an exclusion criterion for the COPE-III study, standardised action plans are used if patients develop suicidal ideation during the study. For example, patients may contact nurses who conduct a risk assessment and patients are also provided with an emergency 24-hour phone number for specialised counselling for suicidal ideation.

Diabetes

Prednisolone treatment of COPD exacerbations increases blood glucose levels (BGLs), especially in patients with pre-existing diabetes. Hyperglycaemia in patients treated with prednisolone predominantly occurs between midday and midnight (31). Higher glucose concentrations are associated with increased mortality, morbidity and length of hospital stay during a COPD exacerbation (32,33).

Separate diabetes action plan components were developed for type 1, type 2 and prednisolone-induced diabetes. In contrast with the other comorbidities, the diabetes action plans are not linked to a change in 'diabetes' symptoms, but to the start of a COPD exacerbation. When taking prednisolone, patients are advised to check their BGL four times per day (before breakfast, lunch, dinner, and bed time). Extra training on blood glucose monitoring and insulin injections is then arranged with a diabetes nurse if required.

There are differences in the action plans for diabetes used in Australia and the Netherlands, in order to mimic as

much as possible usual care in both countries and simplify possible future implementation.

In Australia, patient management plans have been developed for two main groups of patients: (I) patients with diet-controlled diabetes or taking oral hypoglycaemic agents; and (II) patients already taking insulin. If patients record one BGL above 15 mmol/liter or two measurements above 10 mmol/liter, the action plan directs them to contact the case-manager who then contacts an endocrinologist. Patients who are not already taking insulin are taught to administer insulin isophane during COPD exacerbations, with dosing adjustments by an endocrinologist based on ongoing BGL recordings. Patients who are already taking insulin have their current insulin regimen doses adjusted by the endocrinologist.

In the Netherlands, patients with diet-controlled diabetes or taking oral hypoglycaemic agents are instructed to use insulin injections temporarily if they experience a high BGL (one BGL measurement above 15 mmol/liter or three measurements above 10 mmol/liter during a 24-hour period). Insulin dosing schedules are patient-fitted by the diabetes nurse and discussed during SM training. Patients have a tailored insulin dosing schedule (as advised by the diabetes nurse) or they are instructed to administer short-acting subcutaneous insulin using a sliding scale regimen.

Optimising of the COPE-III ST intervention

Prior to the start of the randomized controlled trial, the COPE-III ST intervention was tested in six patients with severe COPD to further optimize the intervention. Recruited patients were already included in an intensive nurse-led case-management program to which the COPE-III ST intervention was added. During the pilot, study nurses and patients were asked to provide frank feedback on the materials. During and after the pilot, significant adjustments were made to the ST materials. We have summarized an overview of these adjustments in *Table 2*. The intervention materials were adjusted to ensure that the intervention could be easily implemented in different health care systems.

Training of the health care providers

Both the COPE-I and COPE-II studies were extensively piloted (by groups of health care providers and patients). Besides optimising the intervention, the goal of these pilots was to train all health care providers in 'SM'. In addition, all involved health care providers in the COPE-III study attended a half day course regarding the guidance of group sessions. The content of this course included discussion of behavioural change techniques that were embedded in the SM sessions: components of education, training, modelling, and enablement, which target desirable and specific behaviours including individualised diary use, patient recognition of deterioration in symptoms, and the correct and timely use of an action plan (26). Ongoing, regular follow-up meetings (approximately once a month) were planned with the health care providers involved.

The COPE-III study was also extensively piloted by patients and health care providers. The education in comorbidities was provided by disease experts in both countries (approximately 2-3 hours per comorbidity) and predominantly directed towards triaging of problems that could occur in these complicated COPD patients. Overlap in disease symptoms was discussed intensively. The training in SM and behaviour change principles was provided by an Australian psychologist during a 2-hour group meeting. This meeting was recorded, so it could also be viewed by the study nurse in the Netherlands.

Separate training in the diaries and action plans was provided by the study investigators in both countries (approximately 4 hours), with frequent follow-up meetings, that were especially important during the first year of the study.

Discussion

The COPE-III study is focused on treatment of COPD and common comorbid diseases. The intervention was developed and adjusted by using experiences and knowledge learnt from two previous COPE studies and by a pilot study. Although the action plans used in COPE-III are established and cannot be changed during evaluation, we are aware that we can continue learning from our experiences with COPD ST.

In the COPE-III study, we are attempting to deal with two of the most important lingering issues within ST, namely dealing with comorbidities and ensuring patient safety. We believe that a 'one size fits all' approach that focuses solely on traditional symptoms of COPD is inadequate and in fact, potentially dangerous in patients with (numerous and severe) comorbidities. This was the rationale underpinning the COPE-III approach. We have tried to optimize patient safety by ensuring a case-manager who is accessible to patients throughout the study. This is emphasized during patient training and highlighted on all ST materials. We also incorporated fallback procedures into the action plans, such as contacting usual health care

Table 2 Summary of adjustments of self-treatment materials (usual symptom cards, symptom diary, action plan, course material) as a result of the pilot study

Aims	Documents	Adjustments
Simplification of education material	All materials	Comorbidity components are colour coded and numbered
	Symptom diary	Reduction of numbers of items by combining the 'minor respiratory symptoms' in one question
	All materials	Remove medical jargon and simplify text
	Symptom diary	Make more clear that the action plan needs to be consulted by using red 'marked' boxes for a change that is 'significantly more than usual'
	All materials	Consistency in wording
	All materials	Consistency in the order in which comorbidities are addressed
Better discrimination between breathlessness due to COPD or due to IHD and CHF	Usual symptom cards	IHD item: record what patients normally use as IHD medication (e.g., a spray or a tablet)
	Symptom diary	IHD item: use of 'sudden change in your breathing' instead of just 'short of breath'
	Action plan	Inclusion of a final box with the comment: 'If you have been significantly more breathless than usual (marked red boxes) for at least 2 days in a row but you did not tick any red boxes for other symptoms: please contact the study office'
	Course material	Extensively discussion of breathlessness by working through scenarios
Stimulating patients to go through the complete action plan	Action plan	Insert a clear message after every box in the action plan to go to the next part of the action plan
	Course material	Practising with the action plan and underlining to read through the complete action plan
Increasing of safety of the ST approach	Symptom diary, action plan, course material	Making clear that patients can always contact the study nurse if uncertain or having questions
	Action plan	Adding a final box to the action plan with the following messages: ➢ Contact the study office if you have been significantly more breathless than usual (ticked red boxes) for at least two days in a row but you did not tick any red boxes for other symptoms ➢ Contact your GP if you have a fever (more than 38.5 ℃) for at least 2 days in a row but you did not tick any red boxes for other symptoms ➢ Please check the action plan tomorrow again and remember: you can always contact the study office during office hours if you have any doubts or questions 'phone number' (Monday-Friday: 8.00 am-4.30 pm; excluding Public Holidays) ➢ If you require assistance during out of office hours: please contact your GP or Emergency Department

IHD, ischemic heart disease; CHF, chronic heart failure; ST, self-treatment; GP, general practitioner.

providers for unresolved or worsening breathlessness or fever (see *Table 2*). The safety of the study is monitored by a Data and Safety Monitoring Board.

Another recommendation is that ST approaches have to be included in a formal SM training intervention (10) that includes behavioural change techniques (9) and is tailored to the patient's individual needs (9). The COPE-III intervention meets all of these criteria. Behavioural change techniques are included in an extensive patient training intervention (e.g., education, training, modeling, individualised action plans, behavioural enablement, individualised goal setting, and feedback on behaviour). Although ST of co-morbidities is patient-tailored, the content of the SM training is part of an intervention with set components (e.g., disease education, relaxation, and breathing techniques). In COPE-III we have utilised a ST approach that provides appropriate tools, training in necessary skills, and the possibility to incorporate the approach in existing health care support systems (9).

Additionally, health literacy of patients should also be taken into account. Literature suggests that only a third of patients with low literacy are able to comply with simple written instruction such as 'Take two tablets by mouth twice daily' (34). We are acutely aware that our ST materials are much more complicated than this instruction, and we concede that SM is not an approach that would be suitable

for all patients with chronic diseases like COPD. However, lessons were learnt during the pilot study and the patient materials were simplified. Although we exclude patients who are non-literate and those assessed as having an impaired cognitive function (26), we have not excluded people with low health literacy in any of the COPE studies.

For ST of COPD exacerbations it is also important to keep in mind that patients should be able to use their action plans regularly. If their symptoms are not varying with some frequency, amounting to repeated exacerbations, there are no opportunities for them to refer to their action plan and therefore learn from or receive feedback on their actions. In COPE-II and COPE-III it was therefore decided to include only frequently exacerbating COPD patients (patients who had at least three exacerbations or one respiratory related hospitalization in 2-year previous to inclusion).

At present there is no general agreement on the specifics of training health care providers to deliver optimal SM interventions, although experts agree that training of health care providers is crucial. In preparation for COPE-III, a psychologist was asked to provide a discussion session regarding behavioural change techniques that could be included in the COPE-III intervention. As this is an important aspect of SM, additional follow-up meetings were organized to discuss behavioural change techniques.

Finally, little is known about the factors influencing the success and failure of SM interventions, although understanding is growing as we acknowledge the intricacies of human behaviour and what drives behaviour change. Perhaps even less is known of the factors influencing the success and failure of ST interventions, and further studies will hopefully shed more light on this in the near future.

Acknowledgements

We would like to thank all disease-experts in respiratory and cardiovascular disease, diabetes, and anxiety and depression for their expertise regarding the development and adjustments of the action plans: Robert Minson, Malcolm Battersby, Marie-Jose Pouwels, Elly Wajon, Hermien ten Bolscher, Anneke van Veen, Janneke Roukema, Anna Weierink and Astrid Brilleman. Finally we would like to thank the data managers Betty Rinsma, Petra Meerlo, Sylvia Punte and Anne Southwell, and the nurses Chantal Bergman, Kim Klieverik, Marin Bilgic, Judith Grooters, Alice Grooten-Nijkamp, Saskia van Diepenbeek, Diana Verstralen, Jacqueline Kloek-Verweij, Ilse Bosman, Marijke van de Pavert, Adrienne Beverley, Cheryl Parton for their support in running the current study and previous studies. Funding from the Netherlands Lung Foundation, the Lung Foundation Australia, and the Repat Foundationhas made it possible to develop and perform this study.
Disclosure: The authors declare no conflict of interest.

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Cite this article as: Effing TW, Lenferink A, Buckman J, Spicer D, Cafarella PA, Burt MG, Bassett KL, van Ommeren C, Anesbury S, van der Valk PD, Frith PA, van der Palen J. Development of a self-treatment approach for patients with COPD and comorbidities: an ongoing learning process. J Thorac Dis 2014;6(11):1597-1605. doi: 10.3978/j.issn.2072-1439.2014.11.14

Review Article

Pulmonary rehabilitation for COPD: are programs with minimal exercise equipment effective?

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Abstract: Pulmonary rehabilitation is an essential component of chronic obstructive pulmonary disease (COPD) management with strong evidence supporting the efficacy of pulmonary rehabilitation to improve exercise capacity and quality of life, as well as reduce hospital admissions. However, it is estimated that only 2-5% of people with COPD who could benefit from pulmonary rehabilitation have access to programs. Most research on the benefits of pulmonary rehabilitation has used equipment such as cycle ergometers and treadmills for endurance training and weight machines for resistance training. To enable greater availability of pulmonary rehabilitation, the efficacy of exercise training using minimal equipment needs to be evaluated. Randomised controlled trials that used minimal, low cost equipment for endurance (eight trials) and strength training (three trials) compared to no training in people with COPD were evaluated. Statistically and clinically significant differences in functional exercise capacity and quality of life, as well as improvements in strength were demonstrated when exercise training with minimal equipment was compared to no training [six-minute walk test: mean difference 40 (95% CI: 13 to 67) metres; St George's Respiratory Questionnaire: mean difference -7 (95% CI: -12 to -3) points]. While the number of studies is relatively small and of variable quality, there is growing evidence that exercise training using minimal, low cost equipment may be an alternative to equipment-intensive pulmonary rehabilitation programs.

Keywords: Chronic obstructive pulmonary disease (COPD); pulmonary rehabilitation; exercise training; walking training; elastic resistance bands

Submitted Jun 06, 2014. Accepted for publication Jul 21, 2014.
doi: 10.3978/j.issn.2072-1439.2014.07.45
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.07.45

Introduction

Pulmonary rehabilitation is an essential component of chronic obstructive pulmonary disease (COPD) management with strong evidence supporting its efficacy (1). Clinically significant improvements in exercise capacity, symptoms of dyspnoea and fatigue, quality of life and reductions in hospital readmission have been documented in Cochrane reviews of randomized controlled trials of pulmonary rehabilitation (1,2).

Recent guidelines (3,4) and statements (5) from major respiratory organisations have outlined the key elements of pulmonary rehabilitation which include supervised exercise training programs of at least 2-3 sessions per week for 6-8 weeks in duration. Guidelines recommend that the exercise session include endurance exercise training and resistance training (3,4).

Endurance training

Physiological studies have demonstrated that lower limb endurance training in people with COPD can decrease ventilatory demand at a given level of exercise due to changes at the muscle level that include increased muscle fibre capillarisation (6,7), mitochondrial density and muscle oxidative capacity (8-10). Such training adaptations improve the aerobic capacity of the muscle, delaying the

onset of lactic acidosis and, as such, reduce the ventilatory requirements for exercise at equivalent pre-training work rates (11). This is reflected in the ability of people with COPD to perform equivalent work rates for longer after training as well as achieving higher peak work rates (11).

In addition to lower limb endurance training, endurance training of the upper limb using either supported arm exercise (arm cranking) or unsupported arm exercise (free weights) has been shown to reduce ventilatory demand and improve arm exercise capacity (12-14). Such improvements are task specific (15), therefore exercise mimicking daily activities may be of greater functional relevance for people with COPD (16,17).

Resistance training

Reductions in skeletal muscle strength are evident in people with COPD (18,19) and may affect the ability to perform functional activities. Resistance training improves strength in people with COPD (20-22). Importantly, gains in strength may improve the performance of functional tasks, such as stair climbing and standing from a chair (21). Resistance training may also improve endurance capacity. Significant improvements in cycle endurance capacity were demonstrated in studies comparing strength training with no intervention (20,22). However, the gains in endurance capacity from resistance training were small compared to those that could be elicited from endurance training (20,22).

Besides improved exercise capacity, pulmonary rehabilitation programs have been shown to significantly improve health-related quality of life (1). It should be noted that while exercise training is considered the key component to achieve changes in exercise capacity and quality of life, exercise training often occurs as part of a comprehensive pulmonary rehabilitation program which includes education, anxiety and dyspnoea management, smoking cessation support, and nutritional advice. These additional components of pulmonary rehabilitation may enhance the outcomes of an exercise training regimen. However, a recent large randomised controlled trial of the addition of education to an exercise training program compared to exercise training alone showed no between group differences in exercise capacity, quality of life, physician visits, medication use or hospital admissions (23).

Access to pulmonary rehabilitation

Despite the high level evidence of the effectiveness of pulmonary rehabilitation, access to pulmonary rehabilitation programs worldwide is low. While reliable data on access to pulmonary rehabilitation programs for people with symptomatic COPD is not easily available, a number of studies have estimated that only 2-5% of people with COPD who could benefit from pulmonary rehabilitation have access to programs (24-26).

Most studies of the effectiveness of pulmonary rehabilitation have been performed in large metropolitan centres with well-equipped gymnasiums. There is a need to evaluate whether low cost programs with minimal equipment can achieve similar benefits. If programs providing pulmonary rehabilitation with minimal equipment are shown to be effective, the availability of pulmonary rehabilitation may be improved.

Exercise programs using minimal equipment

There have been a number of randomised controlled trials of endurance exercise training compared to standard care (no exercise training) in people with COPD in which the training mode required only minimal equipment [for example walking exercise (27-33), sit-to-stand (34), stepping (28,34)]. These trials were identified either from the most recent Cochrane review of pulmonary rehabilitation (1) or new trials published (in English) since that review based on a systematic search of Medline and Physiotherapy Evidence Database (PEDro) databases to identify randomised controlled trials of pulmonary rehabilitation where low resources were used. *Table 1* provides a description of the interventions in these trials.

The methodological quality of the trials was determined by the PEDro score (35). The PEDro score is a valid (36) and reliable (37) measure of the methodological quality of a clinical trial. The PEDro score out of ten is based on a criterion that considers the internal validity of the trial and whether the trial has adequate statistical data to make it interpretable (35). If there was sufficient data for common outcome measures from a number of trials, a meta-analysis was performed. For any meta-analysis, the weighted mean differences (WMD) were determined from the difference between the pre- and post-intervention changes in the intervention and control groups. If change scores had not been presented in the study they were determined by subtracting the post-intervention means from the baseline means. If the standard deviation of change scores was missing, the standard deviations (SD) of the baseline and post-intervention means were pooled according to the equation: SD of mean change scores $=\sqrt{((SD^2\text{post} + SD^2\text{baseline})/2)}$ (38).

Table 1 Randomised-controlled trials using minimal equipment for endurance training

Study [year]	PEDro score/10	Participants (n) intervention/control	Intervention	Outcome measures
Hernández [2000] (27)	4	20/17	M: walking; I: 70% ISWT speed; D: 1 hour; F: 6 days/week; L: 12 weeks; S: every 2 weeks	ICT; ISWT; CRQ; MRC Dyspnoea
Ringbaek [2000] (28)	3	17/19	M:Walk/Jogging, stair climbing, resistance; I: dyspnoea 4-5; D: 1 hour; F: 2×/week; L: 8 weeks; S: 2×/week (physio); Other: Home training with elastic resistance bands	6MWT; SGRQ
Singh [2003] (30)	4	20/20	M: Walking; I: 'sub-maximal speed'; D: 30 minutes; F: 2×/day; L: 4 weeks; S: 1×/week at home; Other: ACT and pursed lip breathing	6MWT; CRQ
Murphy [2005] (34)	4	13/13	M: stepping, sit-to-stand; upper limb elastic band resistance; I: dyspnoea 3-5; D: 30-40 min; F: 2×/week; L: 6 weeks; S: 2×/week; Other: exercise 15 min on other days	ISWT; 3 min step test; Strength: knee ext & hand grip; MRC dyspnoea; SGRQ
Boxall [2005] (33)	5	23/23	M: walking; I: based on 6MWT dyspnoea and desaturation; D: 2-30 min; F: daily; L: 12 weeks; S: 1×/week for 6 weeks; then 1× every 2 weeks for 6 weeks; Other: arm exercises	6MWT; SGRQ, Hospital admissions
Breyer [2010] (29)	5	30/30	M: outdoor nordic walking; I: 75% HRmax; D: 1 hour; F: 3×/week; L: 12 weeks; S: 3×/week; Other: education 1×/week	Physical activity (triaxial accelerometer); 6MWT; SF-36; HADS
Ho [2012] (31)	7	19/20	M: paced walking to music; I: 80% VO_2peak from ISWT; D: 30 minutes; F: 5×/week; L: 12 weeks; S: 1×/month when tempo adjusted; Other: control group 'usual exercise' 5x/wk. Daily exercise diary for both groups.	ISWT; SGRQ; Hospital admissions
Casey [2013] (32)	7	143/134	M: walk; I: dyspnoea or fatigue 3-4; D: 20 minutes; F: 2-3×/week; L: 8 weeks; S: weekly diary review; Other: arm and leg exercises; weekly education	CRQ; ISWT

Intervention, intervention group; Control, control Group; M, mode; I, intensity; D, duration; F, frequency; L, length; S, supervised; 6MWT, six-minute walk test; ISWT, incremental shuttle walk test; ICT, incremental cycle test; CRQ, Chronic Respiratory Disease Questionnaire; SGRQ, St George's Respiratory Questionnaire; HADS, Hospital Anxiety and Depression Scale; ×/, times per; MRC, Medical Research Council; SF-36, Short-Form 36 quality of life questionnaire; ACT, airway clearance techniques; HR, heart rate; VO_2, oxygen consumption.

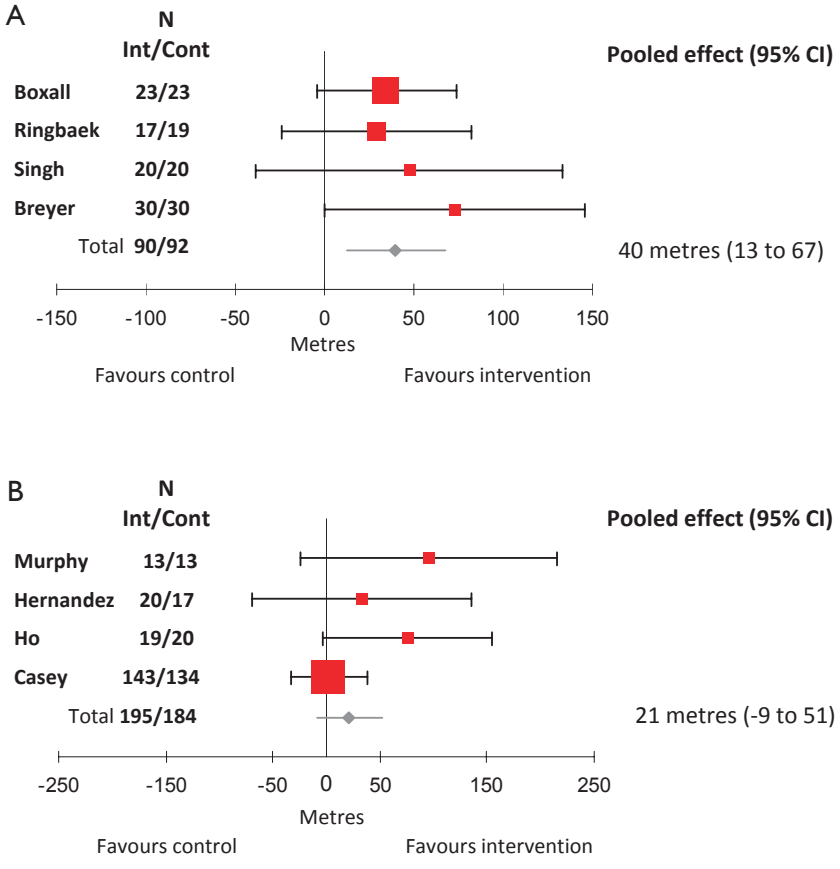

Figure 1 Mean difference (95% confidence interval) for the effect of exercise training using minimal equipment (intervention) compare to no exercise (control) by pooling data from (A) four studies (n=182) that used the six-minute walk test as an outcome and (B) four studies (n=379) that used the incremental shuttle walk test as an outcome. N, number; Int, intervention; Cont, control.

Exercise capacity

The studies of supervised lower limb endurance training in which minimal equipment has been used have mostly prescribed walking training (27-33). Four of these studies used the six-minute walk test (6MWT) to evaluate whether these training modes improved functional exercise capacity (28-30,33).

For the 6MWT, a meta-analysis included 90 participants in the exercise training group and 92 in the control group and showed a mean difference of 40 (95% CI: 13 to 67) metres in favour of the exercise group (*Figure 1A*). This difference in 6MWT distance was greater than the minimal important difference (MID) for the 6MWT which has been reported as 25 (95% CI: 20 to 61) metres (39). These combined studies suggest that walking training is adequate to improve functional exercise capacity.

Four studies used the incremental shuttle walk test as a measure of change in peak exercise capacity (27,31,32,34). For the ISWT, a meta-analysis included 195 participants in the exercise training group and 194 in the control group and showed no significant difference between the exercise group and the control group [mean difference 21 (95% CI: –9 to 51) metres] (*Figure 1B*). The ISWT is a measure of peak exercise capacity and an improvement requires the ability to walk faster. It may be that people with COPD who trained with minimal equipment can walk for longer after exercise training but may not be able to increase walking speed. None of these studies used the endurance shuttle walk test (40) as an outcome measure, which has been shown to be more sensitive to change following pulmonary rehabilitation (41).

The physiological changes induced by walking training have not been well studied. One study of predominately high intensity walking training in 25 participants with COPD demonstrated a significant reduction in lactate and

ventilation at isotime on an incremental cycle test after walking training (42). These data provide some evidence of physiological responses in skeletal muscle due to walking training. In contrast, 20 participants in an eight-week, self-monitored, 5 days/week, home walking training program showed no reduction in lactate or ventilation on a constant work rate treadmill test after training (43). Randomised controlled trials with larger sample sizes are required to demonstrate whether physiological changes during a walking test are elicited after walking training.

Quality of life

Quality of life is an important outcome measure for pulmonary rehabilitation. The most commonly used health-related quality of life questionnaires in the included studies were the Chronic Respiratory Disease Questionnaire (CRQ) (44) and the St George's Respiratory Questionnaire (SGRQ) (45). Three studies reported the dyspnoea and fatigue domains of CRQ (27,30,32). A meta-analysis of these studies which included 183 participants in the exercise group and 171 in the control group showed a significant difference in dyspnoea of 0.48 (95% CI: 0.2 to 0.7) points (*Figure 2A*) and fatigue of 0.42 (0.2 to 0.7) points (*Figure 2B*) in favour of the exercise group. While these improvements were statistically significant, the MID for dyspnoea and fatigue is 0.5 points (46). Therefore, it could be considered that exercise training with minimal equipment resulted in a borderline clinically important improvement in the dyspnoea domain of the CRQ, however did not quite reach the MID for the fatigue domain. These mean differences are also less than those reported for studies that included training with exercise equipment (1).

The SGRQ gives a total score for quality of life and four of the included studies used this as an outcome measure (28,31,33,34). A meta-analysis which included 72 participants in the exercise group and 75 in the control group showed a mean difference in quality of life of –7 (95% CI: –12 to –3) points in favour of the exercise group (*Figure 2C*). A lower score in the SGRQ indicates better quality of life and the MID for SGRQ total score is –4 points (47), indicating that exercise training with minimal equipment is adequate to achieve clinically relevant improvements in health-related quality of life.

Prescribing walking training

A number of the studies in *Table 1* prescribed walking intensity based on symptoms of dyspnoea (28,32,33). However, intensity of walking training can be prescribed from the initial field walking tests of either the 6MWT or the ISWT. Walking at 80% of the average 6MWT speed has been shown to elicit a mean (± SD) oxygen uptake (VO_2) of 77% (±13) of VO_2peak (48), whereas walking at 70% peak ISWT speed has been has been shown to elicit an oxygen uptake (VO_2) of 76% (±11) of VO_2peak (49). Exercise training above 50% VO_2peak is recommended, as exercise above this intensity is usually sufficient to achieve physiological training effects (50), with higher intensities possibly achieving greater training responses (11,51).

Resistance training

Three randomised controlled trials were identified that used minimal equipment for resistance training (52-54). One study compared a 12-week program of once a week supervised and twice a week home-based resistance training exercises such as sit-to-stand, seated row, lunges, simulated lifting, chest press using elasticised resistance bands, compared to no training (53). The trial quality was a PEDro score of 7. Results showed a small mean difference in knee extensor strength in favour of the exercise group with no differences in other outcomes such as 6MWT or health-related quality of life. More recently a high quality randomised controlled trial (PEDro score 8) of supervised elastic band resistance training plus patient education three times per week for eight weeks compared to patient education alone reported significant mean differences in 6MWT, unsupported arm exercise, and muscle strength in favour of the exercise group (52). Interestingly, a study that compared elastic resistance band training to conventional equipment-based resistance training demonstrated that both groups improved strength with no differences between groups (PEDro score 6) (54). Although these studies only equate to limited evidence, the findings suggest that supervised training with resistance bands may be an appropriate substitute for equipment-based resistance training in people with COPD.

Other less conventional training modes using minimal equipment

Tai Chi

Tai Chi is an ancient Chinese martial art which incorporates elements of strengthening, balance, postural alignment and concentration. It represents a mode of training which does

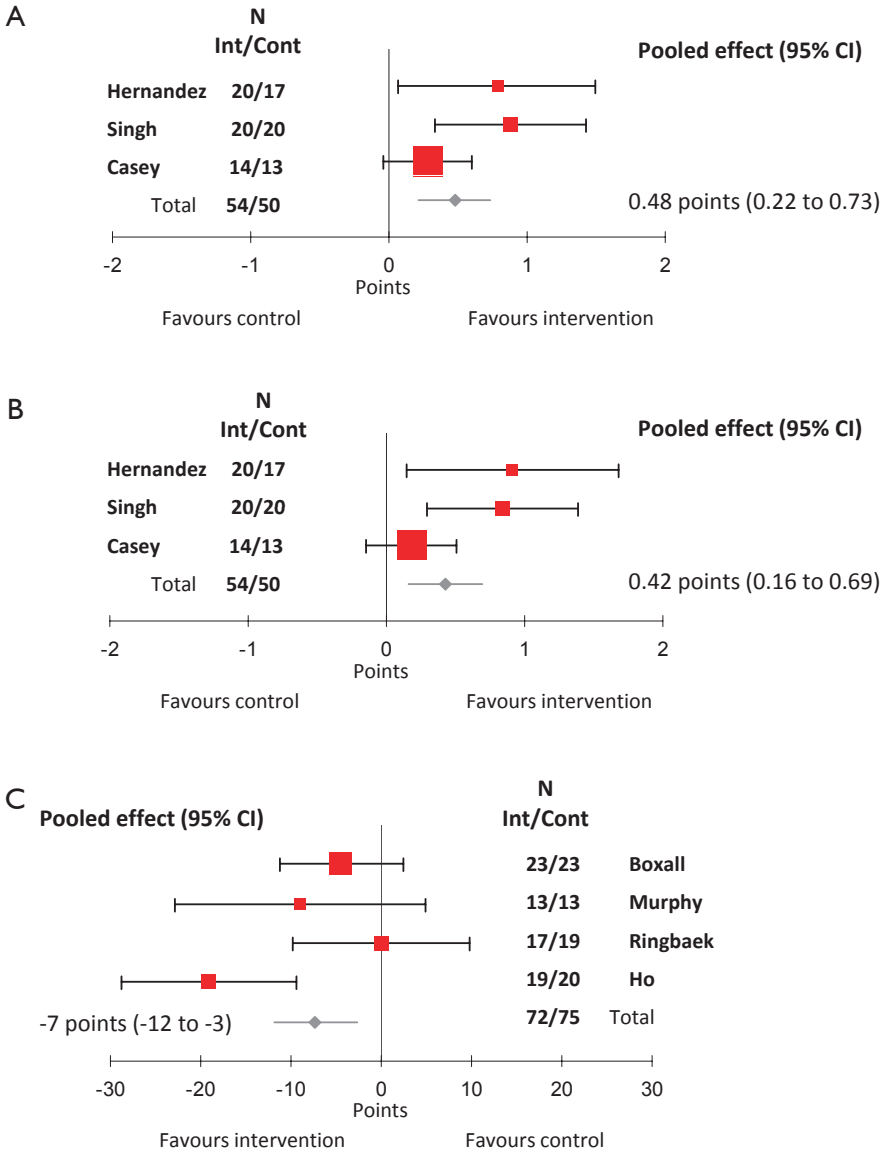

Figure 2 Mean difference (95% confidence interval) for the effect of exercise training using minimal equipment (intervention) compare to no exercise (control) by pooling data from (A) three studies (n=354) that used Chronic Respiratory Disease Questionnaire (CRQ) Dyspnoea as an outcome; (B) three studies (n=354) that used CRQ Fatigue as an outcome and (C) four studies (n=147) that used St George's Respiratory Questionnaire Total Score as an outcome. N, number; Int, intervention; Cont, control.

not require a specific training venue, can be performed without exercise equipment, and promotes aerobic, strength and balance training simultaneously. While there has been a recent systematic review of Tai Chi in COPD the included studies were of low methodological quality (55). Recently, a randomised controlled trial of Tai Chi in COPD with a high methodological quality (Pedro score 8) (56) demonstrated that Tai Chi training resulted in a significant difference in endurance shuttle walk test (ESWT) time and SGRQ Total score in favour of the Tai Chi group compared to the control group (no exercise training) [ESWT mean difference 384 (95% CI: 186 to 510) seconds; SGRQ Total score –11 (95% CI: –18 to –4) points]. These between group differences exceeded the minimum clinically important differences for these outcomes. Balance and quadriceps strength were also significantly increased in the Tai Chi group compared to the control group. Importantly, Tai Chi elicited a VO_2 of approximately 63% VO_2peak

which would be adequate to achieve physiological training effects (54). This study provides some support for Tai Chi as a mode of training to improve exercise capacity and health-related quality of life in COPD.

Further research is needed with larger randomised controlled trials comparing pulmonary rehabilitation programs using minimal equipment with programs using gymnasium equipment. Such studies will help to determine the effects of minimal equipment programs benchmarked against the standard programs. In addition, the effects of minimal equipment on the longer term maintenance of benefits should be evaluated. It is possible that programs using minimal equipment may transfer to the home environment more easily and promote continued exercise and hence maintenance of benefits.

Conclusions

The demand for pulmonary rehabilitation and the lack of available programs requires focus on alternatives to conventional equipment-based exercise training that can be more widely offered. There is growing evidence that exercise training using minimal equipment is effective in improving outcomes of functional exercise capacity and health-related quality of life in people with COPD.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Alison JA, McKeough ZJ. Pulmonary rehabilitation for COPD: are programs with minimal exercise equipment effective? J Thorac Dis 2014;6(11):1606-1614. doi: 10.3978/j.issn.2072-1439.2014.07.45

Review Article

Anxiety and depression—Important psychological comorbidities of COPD

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Abstract: Anxiety and depression are common and important comorbidities in patients with chronic obstructive pulmonary disease (COPD). The pathophysiology of these psychological comorbidities in COPD is complex and possibly explained by common risk factors, response to symptomatology and biochemical alterations. The presence of anxiety and/or depression in COPD patients is associated with increased mortality, exacerbation rates, length of hospital stay, and decreased quality of life and functional status. There is currently no consensus on the most appropriate approach to screening for anxiety and depression in COPD. Treatment options include psychological [relaxation, cognitive behavioural therapy (CBT), self-management] and pharmacological interventions. Although there is some evidence to support these treatments in COPD, the data are limited and mainly comprised by small studies. Pulmonary rehabilitation improves anxiety and depression, and conversely these conditions impact rehabilitation completion rates. Additional high quality studies are urgently required to optimise screening and effective treatment of anxiety and depression in patients with COPD, to enhance complex chronic disease management for these patients.

Keywords: Chronic obstructive pulmonary disease (COPD); anxiety; depression; comorbidities; diagnosis; therapy

Submitted Jun 30, 2014. Accepted for publication Sep 03, 2014.
doi: 10.3978/j.issn.2072-1439.2014.09.28
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.09.28

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease that has significant extrapulmonary effects that may impact the severity of symptoms in individual patients. COPD is a highly prevalent disease worldwide. The prevalence is variable between countries, but overall there is a prevalence rate of around 10% in individuals aged 40 and above (1). In developed countries, COPD is responsible for approximately 4% of all deaths and is the only major condition for which the burden of disease continues to increase, currently being 5th overall in underlying cause of death and 3rd for burden of disease (2).

Anxiety and depression are well-recognized major comorbidities in COPD (3), and consequently there has been a surge in clinical and research interest in reducing the negative impact of these important comorbidities in patients with COPD (4). This review provides an overview of the pathophysiology associated with anxiety and depression in COPD patients, the prevalence and impact of these comorbid conditions, and the strategies for their diagnosis and treatment. Areas of need for future research are also highlighted.

Prevalence of anxiety and depression as comorbidities in COPD

Like other major chronic diseases, COPD has a significant

impact on psychological well-being of people affected. Patients with COPD have a higher prevalence of depression and anxiety than the general population (5) and COPD patients have relative risk of 1.69 of developing depression (6). The rates of both anxiety and depression may even be more prevalent among COPD sufferers compared with other chronic diseases (7).

The reported prevalences of each condition are quite varied, depending on the population surveyed and the tools used to assess depression and anxiety. For patients with stable COPD in primary care settings or respiratory clinics, the prevalence of depression varies widely from 10% to 57% (5,8), and for anxiety, prevalence ranges from 7% to 50% (5,9).

Risk factors for increased rates of depression include living alone (10) and gender. Females have a higher rate of both anxiety and depression (11-13), and rates of depression are more strongly correlated with severity of dyspnoea as compared with males (12). Increasing severity of COPD is associated with higher rates of depression and anxiety (14,15); for example, in patients requiring long-term oxygen, 57% were found to have depressive symptoms and 18% had depression classified as severe (16). End-stage COPD patients undergoing palliative care also have high rates of anxiety and depression (7).

Other important risk factors are patients that have been hospitalized for an exacerbation of COPD or recovering from an exacerbation (17,18), severity of respiratory symptoms especially dyspnoea (19), living alone, and severe impairment of physical functioning (9,10).

Pathophysiological mechanisms for anxiety and depression in COPD

The aetiology of the association between depression and COPD is not fully understood; however the relationship is complex and interactive. The most important risk factor for COPD is smoking. Smoking and depression have a bidirectional interaction. Depressed individuals are more likely to smoke (20), display higher risk to commence smoking (21,22), and find smoking cessation more difficult (20,23). Conversely, smokers are more likely to be depressed (24), which could be caused by activation of nicotinic acetylcholine receptors (25), or direct inflammatory effects of smoking (26).

Although smoking could have some part to play as a causative factor for depression, depression is still more prevalent among COPD patients than smokers without COPD (13). A possible mechanism could be related with 'overspill' of local lung inflammation in the circulation (26,27). It has been speculated that systemic inflammation may play a role in the presence of depression (28). Although there are difficulties in quantification of inflammatory markers in the 'overspill' theory (26), sTNFR-1 has shown a strong association with rates of depression in COPD patients (27), while TNF-α has shown conflicting results (28,29). It is not clear if the presence of systemic inflammation has a causative association with depression or that it is a marker a specific COPD phenotype; such as frequent exacerbators (27).

Hypoxia is an additional factor that may play a role in the development of depression in COPD. Low arterial oxygen saturation has been shown to be associated with periventricular white matter lesions (30), which are present in patients with depression (31). However, the significance of these findings is contentious since the localization of subcortical hyperintensity in depressed patients has been found to be variable due different imaging technologies, lesion definition and measurement techniques (31,32).

Although smoking, inflammation and hypoxia have potential impact on the prevalence of depression in COPD, the strongest predictors of depression among patients with COPD are their severity of symptoms and reported quality of life (13). Functional limitations have been similarly shown to mediate depression in other disorders such as arthritis and heart failure (33). The amount of perceived instrumental support (the need of assistance for activities of daily living) among COPD patients has also been shown to be correlated with depression (34).

Several theories have been proposed to explain the overlap of anxiety and panic attack symptoms with COPD (35). Hyperventilation is defined as the exaggerated breathing in excess of metabolic need, causing lowering pCO_2 and causing respiratory alkalosis (36,37). This pattern of breathing can cause dyspnoea in healthy individuals and consequently panic attacks in those predisposed patients (37).

In panic disorder patients it is possible to evoke symptoms of dyspnoea and chest pain when infusing lactate or inhaling excessive CO_2 (37). These findings are the basis of the carbon dioxide hyperventilation model (35). Areas of the brain with intrinsic CO_2/H^+-sensitive neurons such as the ventrolateral surface of the medulla and locus coeruleus are involved in ventilation, but also play role in panic behaviours. The activation of these areas may concomitantly activate a defensive behavior and precipitate a panic attack (37).

Another important theory is the cognitive behavior

model which is based on the principle that normal bodily sensations are misinterpreted by patients with panic disorder and can consequently cause a panic attack (35). This misinterpretation may be associated with a behavioural sensitization event (trauma), since 20-30% of healthy panic disorder patients had a near-drowning or suffocating past experience (37). COPD patients are at greater risk of a traumatic event caused by an exacerbation, which may lead to an increased risk of developing panic disorders.

The pathophysiology of anxiety and depression among COPD patient is complex and poorly understood. Patients with depression and anxiety are at higher risk of developing COPD due to smoking. Likewise the physical, emotional and social impact of COPD is correlated with development depression and anxiety. This complex interaction between COPD and mental health diseases may cause a self-perpetuating cycle that has a severe impact upon a patient's well-being.

Impact of depression and anxiety on COPD

Depression and anxiety have considerable impact on patients with COPD, in terms of associations with mortality, exacerbations and quality of life.

Effect on mortality

Among COPD patients, depressive symptoms are associated with increased mortality among hospitalized (18,38) and community patients (15,39-41). Some studies of COPD patients have shown an association of anxiety with increased mortality (18,38,42), whereas others have failed to show any association (41). A recent meta-analysis demonstrated that in COPD patients, comorbid depression and anxiety were associated with increased risk of mortality with relative risks of 2.29 and 1.27 respectively (6).

Importantly, a prospective study by Divo and colleagues, from the BODE cohort, has demonstrated that anxiety among female COPD patients was associated with a significant increase in mortality, with a hazard ratio of 13.76 which was more than the risk conferred by coronary heart disease, heart failure, or lung cancer (43). The potential causes of this increased mortality with anxiety are probably multifactorial. One factor is treatment compliance; for example, patients with depression are more likely to not complete rehabilitation (44,45). A meta-analysis has showed that patients with depression and anxiety symptoms are 3 times more likely to be non-adherent to their prescribed medications (46). Alternatively, anxiety may be secondary to the severity of the underlying COPD, and could therefore be a clinical marker of disease severity and risk of death.

Effect on exacerbations

Among COPD patients, exacerbations contribute significantly to morbidity and mortality (47). A systematic review of 20 studies has shown that depression and anxiety increases the risk of hospitalization for COPD patients (48). A meta-analysis by Laurin *et al.* showed that the relative risk of in-hospital treated COPD exacerbation was 1.12 for depression and 1.18 for comorbid depression and anxiety (49). Anxiety and depression symptoms were also associated with increased length of stay in hospital for COPD exacerbations (18,50,51).

There are multiple possible links between depression and anxiety, and increased rates of COPD exacerbation. The impact of symptoms of depression and anxiety could place patients at risk due to non-adherence with treatment (46,52), and suboptimal success with smoking cessation (18,49). Depression could have direct effects by impairing the immune system and consequently predisposing to infections (53) leading to increased frequency of exacerbations. Worsened perception of dyspnoea may lead patient to seek medical attention unnecessarily and increase hospital admissions; patients with anxiety and depression during admission have worse dyspnoea scores despite having less severe physiological parameters (e.g., pH, partial pressure of oxygen and carbon dioxide) (54). The meta-analysis by Laurin *et al.* has shown that patients with anxiety were at greater risk for exacerbations that required treatment in the community, whereas those with depression were at higher risk for exacerbations requiring treatment in hospital (49). This discrepancy could be explained by "early intervention" among anxious patients that could prevent the need for treatment in hospital (49).

Effect on quality of life

The detrimental impact of COPD on quality of life is well-documented (3). Depression and anxiety symptoms also have significant impact on quality of life and functional status in many chronic diseases (55,56). In general, patients with depression and anxiety perceive their health as poorer than the average population (57). Specifically for COPD, the impact of quality of life and functional status is also evident in several studies, independent of the severity of

COPD or related comorbidities (14,56,58-62). A meta-analysis showed that the presence of depression and anxiety among COPD patients was one the strongest correlations with self-reported health status (63). Comorbid depressive symptoms in patients with COPD are associated with persistent smoking, increased symptom burden, poorer physical and social functioning (18), and difficulty in performing daily activities (64). Low self-confidence or self-efficacy is also common, which may lead to worsened ability to cope with chronic disease (49,56).

Depression and anxiety symptoms are associated with increased perception of dyspnoea (54,65,66). The presence of psychological symptoms (mainly depression and to lesser extent anxiety) has an effect on vital exhaustion, defined as a state characterized by fatigue and lack of energy, worsening irritability and feelings of demoralization (67). Fatigue and especially dyspnoea are independently negatively associated with poor health status (63,68).

The impact of depression and anxiety symptoms are not limited to an individual's lung disease. The presence can influence a person's end of life decisions (69) or may have negative impact upon partners and their respective relationships (70).

Diagnosis and screening of depression and anxiety

The gold standard for the diagnosis of depression or anxiety is based in the criteria listed in the DSM-IV and achieved through structured interviews performed by a psychiatrist or a clinical psychologist. As there is a strong positive relationship between self-reported severe symptoms and the existence of a mental disorder (71,72), screening instruments have also been developed, which are less costly, faster and easier to administer. These instruments can also monitor clinical outcomes of mental health treatments (73,74).

Several screening tools have been validated for use in COPD patients. The Geriatric Depression Scale and its 15-item short form (GDS-15) are validated as depression tools (75), and the Hospital Anxiety and Depression Scale (HADS) and the Geriatric Anxiety Inventory (GAI) have been validated for anxiety in COPD patients (76). Anxiety Inventory for Respiratory (AIR) Disease and Brief Assessment Schedule Depression Cards (BASDEC) are two other scales that have been developed exclusively for COPD (9,77).

There are concerns regarding the use of screening instruments due to the risk of false positives caused by the overlap of symptoms (78), and the uncertainty regarding impact on routine practice (79,80). The Global Initiative for Chronic Obstructive Lung Disease guidelines recommend that new COPD patients should have a detailed medical history including for depression and anxiety (3). However, to date, there is no consensus on the most appropriate screening approach for anxiety and depression (81).

Treatment approaches for anxiety and depression in patients with COPD

Depression and anxiety, when coexisting with COPD, significantly impact quality of life and functional outcomes. In acknowledgement of the biopsychosocial impact of chronic ill health, the World Health Organization has stated that patients with chronic diseases such as COPD should receive integrated care programs which are centered on the patient rather than just the disease (82). Fortunately, interventions targeting these psychological comorbidities are well-established for the general population (83). However psychological care guidelines are less well developed for the specific COPD patient population (84). Where psychological treatments have been used in COPD, these have typically been based on guidelines already in use for depression and anxiety in the wider population (85). Treatments can be divided into psychological [relaxation, cognitive behavioural therapy (CBT), self-management] and pharmacological interventions. Pulmonary rehabilitation, a specific treatment for COPD, also has beneficial effects on anxiety and depression.

Psychological therapies

For patients with a chronic health condition who are also experiencing clinical or sub-threshold depression, the UK's National Institute for Health and Care Excellence (NICE) recommends use of low to high intensity psychosocial interventions depending on the severity of mood symptoms (85). Low intensity interventions may include individual or self-help programs, or online CBT, while high intensity interventions are typically individual or group CBT sessions. These recommendations are based on moderate quality randomized controlled trials and the experience and opinion of the Guideline Development Group (85). While the NICE guideline targets general chronic health presentations, good quality studies are somewhat lacking in COPD-specific populations. Existing studies show mixed results that are difficult to compare, because of factors such as small sample size, varied populations, lack of data on

disease severity and differences in the screening tools used to assess these patients. A recent meta-analysis has described the benefits of the most common psychological interventions—relaxation therapy, CBT and self- management education programs (83).

Relaxation therapy

The aim of relaxation therapy is to promote psychological change through techniques that create a relaxed state. Techniques commonly used range from breathing exercises, hypnoses, meditation, body positioning, sequential muscle relaxation, mild forms of exercise and visualization techniques (86). These methods are used separately or as a element of other psychological treatments or pulmonary rehabilitation (4).

The effectiveness of relaxation-based therapies for COPD was evaluated in a meta-analysis by Devine *et al.*, which showed significant improvements in symptoms of dyspnea and anxiety (87). For patients undergoing a pulmonary rehabilitation program, progressive relaxation techniques administered by tape-recorded classes showed a non-significant improvement in depression and, to a lesser extent, anxiety symptoms at the time of the end of the pulmonary rehabilitation program (88). There have been several smaller studies that have investigated other types of relaxation approaches. One small study using tai chi demonstrated a non-significant improvement of depression, dyspnoea and physical capacity as measured by six minute walk test results (89). A study examining yoga as the intervention showed a significant improvement in six minute walk results and functional performance, non-significant improvement in dyspnoea score and quality of life, but no change in anxiety or depression scores (90). In these types of studies, it is often difficult to determine whether the benefit is due to the physical activity or the relaxation components of the treatment.

Loosely related to relaxation interventions, singing classes have also been used as an intervention in COPD patients. The underlying theory is that singing lessons might improve patient quality of life and/or functional status by offering techniques that address both the sensory component of dyspnoea (e.g., control of respiratory pattern to reduce hyperinflation) and the affective component (e.g., anxiety and low mood around perceived breathlessness) (91). A moderate-sized study employing singing classes showed improvement in anxiety levels and the physical component of a quality of life questionnaire (92). In a further study by the same researchers, the improvements remained after controlling for the incidental beneficial effects of social interaction amongst the participants (93). In regards to these less traditional interventions, there is still a lack of clarity about their applicability, their long-term effectiveness, the active component (physical or psychological), and how they may be incorporated into standard care.

Cognitive behavioural therapy (CBT)

CBT is a type of psychotherapy used in the management of a range of psychiatric disorders. It is based on an information-processing model in which emotional symptoms are thought to be driven by negatively-biased evaluations of the world, the future, or the self (including bodily sensations) (94). Often performed in collaboration between the therapist and the patient, CBT utilizes a number of strategies to correct those biased evaluations and provide skills aimed at controlling their symptoms and consequently improving the management of their illness (4).

The use of CBT has gained traction because of its effectiveness in achieving symptomatic relief for patients with chronic illnesses (56,95). There have been numerous studies of varying quality and sample size that have shown promising results (96-101) (*Table 1*). The studies showed small to moderate improvements in anxiety and depression scores and quality of life; however direct comparison is hampered by the fact that interventions varied in regard to number of sessions, duration of each session and delivery format (group or face to face). The fact that positive impact was demonstrated in most studies, even those with shorter interventions, holds promise for future applicability.

Cost-effectiveness is undoubtedly an important issue, particularly given tightening health budgets, and increasing service imperatives to reduce health care spending. One study has shown that face-to-face CBT is effective and also may be cost neutral when implemented in COPD patients (95). If other less expensive approaches are interchangeable to face-to-face they may be more economically attractive. The use of telephone-based interventions for depression has shown to be just as effective as face-to-face (102-104), and such an approach has also been shown to be beneficial for patients with anxiety and depression associated with other chronic diseases (105,106). A novel alternative approach is the use of an Internet-based intervention, which has been shown to be as effective as face-to-face interventions for depression and anxiety (107-109). CBT-based therapies, particularly tightly manualised therapies for sub-clinical anxiety or depression, may not require a fully trained psychologist for its administration, adding to overall cost effectiveness. A nurse-

Table 1 Major randomized control trials involving cognitive behaviour therapy and COPD for anxiety and/or depression

First author, year	Study design	Patients	Measures	Treatment and comparison	Results
Livermore *et al.*, 2010 (100)	RCT Outpatients Attended pulmonary rehabilitation program Panic attacks and panic disorder were diagnosed with the ADIS-IV	41 patients; 21 CBT, 20 control CBT: Age 73.2±6.4 43% male Control: Age 73.5±8.1 45% male	Primary: Rates of panic attack and anxiety symptoms Panic attacks and panic disorder were diagnosed with the ADIS-IV Secondary: HADS IPBQ SGRQ COPD-related admissions	Intervention: 4 individualized 1 hour sessions and manual (with strategies effective for the prevention and treatment of panic disorder in younger adults) Follow-up: post intervention, 6, 12 and 18 months	ADIS-IV there were significant differences post-intervention and at the 6-, 12- and 18-month No panic attacks in intervention group while no CBT had 35% post intervention tie and 60% at 18 months Significant difference in HADS score at 6-, 12- and 18-month follow-up Significant positive effect on IPBQ No differences in HADS depression scale, SGRQ Significant decrease in hospital admission rate between 6 and 12 months
Hynninen *et al.*, 2010 (97)	RCT Clinically significant anxiety and depression Outpatients Scores >15 BAI and/or >13 on the BDI-II	41 patients; 25 CBT and 26 control 17 participants (33.3%) fulfilled the diagnostic criteria for a mood disorder CBT group: 56% male Age 59.3±7.6 Control group: 42% male Age 62.6±9.9	Primary: BAI BDI-II Secondary: SGRQ PSQI Actigraphy CSQ	Intervention CBT: 7 sessions of 2 hours of group CBT psychology students. Telephone session at 1 and 3 months after Control: telephone contact every 2 weeks for 7 weeks. Call lasted 5-10 minutes Follow-up 8 months	Significant improvement of BAI and BDI-II after treatment and on follow-up Control had no improvement Women had more anxiety and depression, responded more however had more significant anxiety and depression at the end of treatment Treatment was intensive although response was rapid
Kunik *et al.*, 2008 (99)	RCT Outpatients Stable COPD Scores ≥16 BAI and/or >14 on the BDI-II No smoker , low MMSE (<23) or psychiatric disorder	138 patients; 118 to CBT, 120 to control 95% males Education group: 95.8% male Age 66.5±10.4 CBT group 96.6% male Age 66.5±10.1 62.2% had a DSM-IV diagnosis of depression or anxiety	Primary: QoL CRQ SF-36 Secondary: BAI BDI-II 6MWD Use of health services	Intervention: 8× 1 h CBT sessions, group sessions Control: 8× 1 h COPD education sessions Both by same therapist Follow-up: weeks 4 and 8 and months 4, 8 and 12	Both treatments significantly improved QoL with trend favoring CBT group Improvement of SF-36, anxiety and depression (P<0.005) over 8 weeks for both groups No change of 6MWD for either group Follow-up at 8 and 52 weeks showed no change in improvement obtained at end of therapies

Table 1 (*continued*)

Table 1 (*continued*)

First author, year	Study design	Patients	Measures	Treatment and comparison	Results
de Godoy *et al.*, 2003 (101)	Single blinded RCT COPD attending a pulmonary rehabilitation program	32 patients; 14 to CBT, 16 control CBT: 85% male Age 62.1±14.9 Control: 62.5% male Age 58.8±11.8	BDI BAI 6MWD	Intervention: 12 sessions of psychological sessions: Cognitive therapy and logo therapy techniques Both had 12 weeks of rehab with: 24 sessions of physical exercise, 24 sessions of physiotherapy, 3 educational sessions	Significant improvement in BAI, BDI and 6MWD 6MWD improved for both groups, higher improvement in group treated with psychotherapy, although the improvement was not directly related with improvement of anxiety and depression
Kunik *et al.*, 2001 (98)	Single blind RCT Outpatients, from veteran hospital Stable COPD	50 patients; 21 CBT and 29 education group CBT and education: Age 71.3±5.9 83.1% male	SF-36 GDS BAI 6MWD FEV_1	Treatment: same education session lasting 2 hours and 1× 2 h session of group CBT Control and treatment: 1× 2 hour education session focusing on COPD process, etiology and treatment options Weekly calls for 6 weeks for both	Statistical Improvement in BAI and GDS and one measure of SF-36 (mental health question) Non statistical improvement of 6MWD
Emery *et al.*, 1998 (96)	RCT Three groups; Exercise, education and stress management (EXESM), Education and stress management (ESM) and waiting list (WL) Outpatients 79 community-based out-patients	79 patients; 30 EXESM, 24 ESM and 25 WL EXESM: Age 65.4±6.4 50% male ESM: Age 67.4±5.9 41.6% male WL: Age 67.4±7.1 48% male	Anxiety and depression: CES-D The Bradburn Affect-Balance Scale STAI SCL-90-R Health-related quality of life: MHLC SIP Cognitive test battery Pulmonary rehabilitation health knowledge test Bicycle ergometry testing	EXESM: 10 weeks: 37 exercise sessions, 16 education sessions, 10× 1 hour stress management sessions based on CBT and delivered by clinical psychologist ESM: 16 education sessions, 10× 1 hour stress management sessions based on CBT and delivered by clinical psychologist WL: Awaiting to be in study. 25 patients Follow up at 10 weeks	VO_2 max = maximal oxygen consumption during bicycle test – improved only with exercise program. However it was not a predictor of any other outcome. Depression improved with exercise and waiting. No improvement with education and psychology Anxiety reduced more with exercise that without. SIP improved with EXESM and WL Verbal processing improved only with EXESM EXESM and ESM improved health knowledge

BAI, Beck Anxiety Inventory; BDI-II, Depression Inventory-II; SGRQ, St George's Respiratory Questonaire; PSQI, Pittsburgh Sleep Quality Index; CSQ, The Client Satisfaction Questionnaire; Disease-specific and generic quality of life (QoL), CRQ, Chronic Respiratory Questionnaire; 6MWD, 6-minute walk distance; CES-D, The Center for Epidemiological Studies-Depression Inventory; STAI, The State-Trait Anxiety Inventory; SCL-90-R, The Hopkins Symptom Checklist; MHLC, The Multidimensional Health Locus of Control; SIP, The Sickness Impact Profile; IPBQ, The Interpretation of Breathing Problems Questionnaire; ADIS-IV, Anxiety Disorder Interview Schedule. Disease-specific and generic quality of life (QoL), Medical Outcomes Survey Short Form-36 (SF-36).

administered minimal psychological intervention (MPI), based on the principles of CBT and self-management, was used in one study of COPD patients and showed promising results (110).

Not all aspects of CBT therapy may be necessary to produce a therapeutic effect. Purely behavioural interventions can be as effective as CBT for patients with depression (111). They are simpler to administer and theoretically could be used for patients with COPD.

Self-management strategies

Self-management programs aim to improve patient care by providing resources and guiding health behaviour change in ways that empower the individual. This empowerment is thought to increase their ability to carry out medical regimens designed to control their chronic disease, improve well-being and decrease exacerbations (112-114). Many self-management programs incorporate aspects of CBT.

The effects of self-management programs for patients with chronic health conditions are still unclear, and the results have been modest when compared to more specific psychological interventions (83). Jonker *et al.* found improvement in self-efficacy in older people, but no reduction in health care utilization or improvement in quality of life (112). In cardiac patients one study reported a moderate effect of self-management on functional outcomes and depressive symptoms after an acute coronary syndrome (115). For COPD patients, although a review by Kaptein *et al.* reported favourable outcomes for self-management on frequency of hospitalisation, greater exercise tolerance and increased quality of life (116), in the meta-analysis of 29 RCTs by Coventry *et al.*, there was no overall benefit for self-management education alone for anxiety and depression in COPD (83).

A large multicenter randomized trial in COPD patients showed that a self-management intervention reduced exacerbation rates (114). Similarly, a Cochrane review by Effing *et al.* (113) showed a significant and clinically relevant reduction in the number of patients with one or more hospital admissions and a small but significant reduction of dyspnoea scores. Results were inconclusive for anxiety and depression symptoms, doctor and nurse visits, the use of courses of oral corticosteroids and antibiotics, and the use of rescue medication. No effects were seen for ER visits, lung function, exercise capacity, and days lost from work (113). Interestingly, conflicting results for quality of life questionnaires were seen, as a positive trend was seen for the St. Georges Respiratory Questionnaire (SGRQ), but not for SF-36 (113). This last result highlights the need for precision and clarity in the description of the construct being measured (e.g., quality of life) and consistency in the selection of measures. The wide range of measures used across the papers surveyed herein reveals the difficulty in both assessing the effectiveness of interventions within a study, and comparing findings across studies reported in the literature.

Finally, health mentoring is a self-management intervention that uses cognitive behavioural techniques to provide skills to improve self-efficacy and disease management, and to change unhealthy behaviours (117). Nursing-based mentoring has shown conflicting results with one study showing benefit in quality of life for patients with COPD (118), while other studies have failed to show any positive effect on quality of life (119,120) or anxiety and depression symptoms (119). A meta-analysis has shown case management was the least effective intervention for reducing anxiety and depression when compared to CBT, relaxation or self-management intervention (83).

Pharmacotherapy

Pharmacotherapy is a mainstream treatment for anxiety and depression. Although there is some controversy regarding effectiveness, meta-analyses have shown the overall benefit of pharmacotherapy in the treatment of anxiety and depression (121). In standard clinical practice, antidepressants are the main medication used for depression and anxiety. Other less common agents used are benzodiazepines, antipsychotics, anticonvulsants and azapirones (4).

Antidepressants work mainly by increasing synaptic monoamines, dopamine, serotonin and/or noradrenaline. They have similar effectiveness but mainly differ based on type and severity of side effects. The main categories are: selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenaline reuptake inhibitors, tetracyclic antidepressants, tetracyclic analogues of mianserin [sometimes called noradrenergic and specific serotonergic antidepressants (NaSSA)], tricyclic antidepressants (TCAs), reversible inhibitors of monoamine oxidase A (RIMAs), monoamine oxidase inhibitors (MAOIs) and melatonergic antidepressants [summarised in (122)]. Antidepressants are a moderately effective treatment for depression in healthy individuals, more so in cases of greater severity and in melancholia, but there is less certainty in physically ill patients. Among this population with subthreshold

symptoms of depression (symptoms that are below the DSM-IV criteria for major depression) or mild to moderate depression, NICE guidelines advice that antidepressants should not be routinely prescribed (72).

A recent Cochrane review of antidepressants (mostly SSRI and TCA), for the treatment of depression or depressive symptoms among physically ill patients, demonstrated a significant improvement among patients with depression or milder depressive disorder, and a positive trend for depressive symptoms and other depressive disorders (123). This Cochrane review also observed that there was greater long-term improvement for SSRIs compared to TCAs. A study assessing the effects of the SSRI, fluoxetine, in hospitalized patients with depression showed a positive trend towards improvement of depression symptoms specially for those patients that were more severely ill (124).

In contrast to the wider general population or physically ill, at present, the data for efficacy of pharmacotherapy for anxiety and depression are limited for COPD. The main studies have been of SSRIs and TCAs. SSRIs are the first line pharmacotherapy treatment for depression and anxiety (125). For depression, small studies in COPD have shown mild improvements. Two studies of COPD patients using paroxetine showed variably significant improvement in quality of life questionnaires (126,127), and improvement of anxiety and depression scores and physical capacity after 3 months (127) (*Table 2*). A single-blinded open trial study of 57 COPD patients, aiming to assess the acceptability of fluoxetine therapy, showed that over two-thirds of patients declined to use fluoxetine therapy, mostly related to patient biases regarding use of psychiatric medication (128) (*Table 2*).

For TCAs, a number of small studies have been conducted in COPD. A study by Borson *et al*. showed that nortriptyline was effective in reducing depressive and anxiety symptoms and in increasing physical function (131), although a crossover study of similar size failed to show any benefit when using doxepin for patients with symptoms of anxiety and depression (129). In another study using protriptyline, the majority of the patients did not complete the trial because of the anticholinergic side effects (130). TCAs are no longer first line treatment for depression or anxiety, and consequently future trials for this medication class are unlikely (132).

Regarding the treatment of anxiety in COPD patients, a Cochrane review was unable to undertake any meta-analysis due to poor quality of the studies and very small sample sizes (122). Only four studies were analyzed, with two studies using SSRIs, and the other two using a TCA and azapirones. Two studies using SSRI showed a non-significant reduction in anxiety symptoms (122,127). The studies using TCA and azapirones did not show any improvement (129,133).

As was the case for psychological treatment, the overall effectiveness of pharmacotherapy for anxiety or depression in COPD has not been rigorously tested. Studies in COPD have been small, with large heterogeneity of sampling and tools used to assess efficacy of the treatments. In addition, there is limited evidence regarding the impact of side effects of pharmacotherapy, such as dry mouth and sexual dysfunction (123). Some side effects of treatment (such as dry mouth) may compound adverse effects of medications used for COPD, notably the anticholinergic activity of long-acting muscarinic antagonists (134). In addition, there are issues regarding patient refusal to take antidepressants due to misconceptions regarding depression and addiction, stigma associated with the disease, and lack of interest and motivation (132). Clearly, much more work needs to be done to test pharmacotherapy for anxiety and depressive symptoms in COPD, and to undertake head-to-head comparisons with psychological interventions and combinations of treatments (121).

The role of pulmonary rehabilitation

Pulmonary rehabilitation is an essential component of standard care for people who are symptomatic from chronic lung diseases causing breathlessness and functional impairment, such as COPD (135,136). Large observational studies of pulmonary rehabilitation participants have reported the prevalence of anxiety symptoms to range between 25% (137) and 32% (138), and depressive symptoms to range between 17% (137) and 27% (138). The symptoms of anxiety and depression have been associated with program non-completion (137,139), increased dyspnoea, fear of exercise and reduced functional performance both at commencement and completion of pulmonary rehabilitation (140,141). Furthermore, improvement in the symptoms of depression has been associated with improvements in specific domains of health-related quality of life (142). However, it is unclear if the symptoms of anxiety and depression should be addressed prior to entry to a pulmonary rehabilitation program or during the program.

Importantly, the symptoms of anxiety and depression have been shown to improve following completion of

Table 2 Example of studies involving pharmacotherapy and COPD for anxiety and/or depression

First author, year	Study design	Population	Measures	Results
Eiser *et al.* 2005 (127)	Double blinded RCT Initial blinded for 6 weeks After all patients took un-blinded Paroxetine for 3 months Out-patients with moderate to severe, stable COPD Patients screened using HAD and depression further diagnosed by psychiatrist	28 patient were diagnosed with depression 14 patients in each group 14 females and 14 males, mean age 66	HAD BDI Psychiatrist completed MADRS SGRQ 6-minute walking test	6 weeks' treatment produced no significant differences between placebo 5 patients treated with paroxetine developed side effects and medication was changed Three months of un-blinded treatment: Significant improvement in HAD, BDI and MADRS Significant improvement in walking distances (369 to 427 m, P=0.0003) Significant improvement in St. George's Respiratory Questionnaire Total Scores (65 to 58, P=0.033)
Lacasse *et al.* 2004 (126)	Double blinded randomized control trial Treatment was paroxetine for 12 weeks Outpatients with severe COPD, oxygen dependent GDS >11/30	23 patients entered the trial. 82 refused Treatment group (12 patients, 5 males, mean age 71.2 Control group (11 patients, 5 males, mean age 69.8	CRQ SF-36 GDS Side effects Compliance	2 patients on paroxetine did not tolerate maximum dose Clinical and statistical improvement in emotional domain of CRQ Non significant improvement in GDS
Yohannes *et al.* 2001 (128)	Single-blinded (open) study. Paroxetine for 6 months Inpatients with moderate to severe COPD GMS diagnosed depression	57 (25 males and 32 females) Mean age 72 14 accepted treatment with fluoxetine	BPQ, MRADL were done as baseline MADRS	7 subjects completed the trial 4 (57%) responded to fluoxetine therapy 5 subjects withdrew because of side effects
Light *et al.* 1986 (129)	Double-blind crossover study Doxepin or placebo for 14 weeks Outpatients, at least moderately severe COPD	12 patients (all male), 6 patients for each group 3 ceased doxepin due to side effects, 9 completed trial Aged 57 to 69 (mean 61.2)	STAI BDI FEV_1, PaO_2, $PaCO_2$ 12 minute walk test	No improvement in any of the measures (anxiety and depression scores, respiratory function and physical capacity) Worse mean depression score for the treatment group Half ceased therapy due to side effects (drowsiness, blurred vision, nausea and vomiting)
Ström *et al.* 1995 (130)	Double blind randomized trial Outpatients, COPD stable with mild or moderate hypoxaemia Treatment with Protriptyline for 12 weeks	26 patients 14 patients on treatment group and 12 on placebo group Treatment group had 4 males and 10 females. Aged 57 to 75 (mean 66) Placebo group had 4 males and 8 females. Aged 52 to 66 (mean 59)	SIP MACL HAD Dyspnea score Exacerbations Arterial blood gas Respiratory function	No improvement in all measures (arterial blood gas tension, spirometry, quality of life, anxiety and depression score, dyspnea score and exacerbations) 12 of 14 patients on protripyline had side effects. 6 of 12 patients on placebo had side effects

HAD, Hospital Anxiety-Depression; BDI, Beck's Depression inventory; MADRS, Montgomery Asberg Depression Score; St. SGRQ, George's Respiratory Questionnaires; CRQ, Chronic respiratory questionnaire; GDS, Geriatric depression scale; GMS, The Geriatric Mental Status Schedule; MRADL, Manchester Respiratory Activities of Daily Living Questionnaire; BPQ, Breathing Problems Questionnaire; STAI, State-Trait Anxiety Inventory; MACL, Mood Adjective Check List; Hospital Anxiety and Depression (HAD) scale, Medical Outcomes Survey Short Form-36 (SF-36), Sickness Impact Profile (SIP) questionnaire.

comprehensive pulmonary rehabilitation (143,144). In a large randomised controlled trial, participants completing pulmonary rehabilitation were shown to significantly improve symptoms of anxiety and depression when compared to the control group of usual care (144). Studies have also shown that participants with symptoms of anxiety or depression can gain similar improvements in other program benefits arising from pulmonary rehabilitation. For instance, in an observational cross-sectional study, individuals with symptoms of anxiety and depression had similar benefits in exercise capacity and health-related quality of life following pulmonary rehabilitation as participants not experiencing these symptoms (145). Moreover, another observational study reported that participants with greater symptoms of anxiety in fact had a larger improvement from exercise training following pulmonary rehabilitation (146). Therefore, the recent guideline on pulmonary rehabilitation in adults from the British Thoracic Society states that the psychological status of participants is improved with pulmonary rehabilitation when compared with usual care, and recommends that individuals with symptoms of anxiety and depression should not be excluded from pulmonary rehabilitation (147).

Recommendations and future directions in research and practice

Full spectrum anxiety and depression are highly prevalent among patients with COPD and are associated with poorer outcomes. This seems to hold even for milder or sub-threshold levels of anxiety and depression. The first step to improve practice is to achieve earlier and more accurate diagnosis of these psychological comorbidities in COPD. This is important since these conditions are underdiagnosed and consequently undertreated (8,58). Self-reported screening instruments are useful as an initial approach; however validated tools should then be utilized to minimize false positives and standardize care. When and in whom screening should be done is still not clear for patients with COPD. It is also not clear if it should be carried out with all COPD patients or just to those at higher risk of these comorbidities. After the psychological distress screening scale has been performed, high-scoring patients should be referred to a mental health specialist to facilitate access to comprehensive, gold-standard diagnostic assessment (85).

Due to the impact of associated depressive and anxiety disorders and symptoms on COPD patients, determining the best treatment approach is essential. Unfortunately, as highlighted in this review and by others, there is currently a relative scarcity of strong evidence of benefit for any specific pharmacological or non-pharmacological treatment for anxiety and depression in COPD (4). Furthermore, at this point of time, guidelines are based on treatment of depression and anxiety for the general population (3).

Due to the bidirectional nature of the association of COPD with depression and anxiety, an integrated approach that enhances the benefits between mental and physical health would be the most effective. There is extensive evidence of the benefits of pulmonary rehabilitation for patients with COPD and it has shown to significantly reduce symptoms of both anxiety and depression in COPD patients, possibly through improved physical capacity (148). Adding a depression or anxiety targeted treatment to the pulmonary rehabilitation program may have additive therapeutic benefits. This synergistic effect has been alluded to in a study where marked improvement in depression symptoms was shown when brief inpatient pulmonary rehabilitation plus antidepressants were used with COPD patients with major depression (149). Similarly, another study showed a significant improvement in anxiety and depression with improvement of physical capacity, when CBT was provided within a pulmonary rehabilitation program (101).

Future studies should aim to fill the current gaps in knowledge about treatment of psychological symptoms in COPD. First there are no large studies that have definitively assessed the true benefits of psychological, pharmacological or combined treatment modalities in the COPD population. Future studies should also focus on determining the best treatment for specific COPD groups e.g., based on gender, severity of COPD and frequency of exacerbations. There is also uncertainty regarding the cost-effectiveness of targeted treatment of anxiety and depression, and feasibility of restructuring health-care delivery to incorporate care for mood and anxiety disorders as an integral part of high quality, comprehensive chronic disease management of patients with COPD.

Summary

This review has provided an overview of the pathophysiology, prevalence and impact of anxiety and depression in patients with COPD, and has discussed diagnosis and treatment options for these important psychological comorbidities. In COPD patients, the presence of symptoms of anxiety and depression are common and have significant impacts that, adversely affect mortality rate, exacerbation rates,

hospital length of stay, quality of life and functional status. Anxiety and depression are underdiagnosed in patients with COPD, and consequently undertreated. Studies examining specific pharmacological and non-pharmacological treatment of these conditions are limited and generally are comprised of small studies of varying quality. Given the current state of knowledge, many further areas of research are needed in the field of COPD chronic disease management, including in whom to screen for clinically important anxiety and depression, and the most effective and cost-effective treatment approaches for these conditions in COPD patients. A much greater awareness of the clinical importance of mental health comorbidities in COPD is urgently needed.

Acknowledgements

We sincerely thank the patients and staff of the Metro North Hospital and Health Service for their involvement in our research studies. We thank Hugh Walker (psychology intern at The Prince Charles Hospital) for assistance in the literature review.

Funding support: NHMRC Career Development Fellowship 1026215 (IY).

Authors' contributions: All authors contributed to the writing and approved the final version of this review.

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Pumar MI, Gray CR, Walsh JR, Yang IA, Rolls TA, Ward DL. Anxiety and depression—Important psychological comorbidities of COPD. J Thorac Dis 2014;6(11):1615-1631. doi: 10.3978/j.issn.2072-1439.2014.09.28

Review Article

Oxygen therapy for COPD

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Abstract: Chronic obstructive pulmonary disease (COPD) is a leading cause of disability and death globally, characterised by progressive breathlessness, loss of function and, in its later stages, chronic hypoxaemia. Long-term continuous oxygen therapy increases life expectancy in patients with severe resting hypoxaemia. However, there are few data to support the use of oxygen in patients with only mild hypoxaemia and more research is required to determine any benefits of oxygen supplementation in COPD in such individuals.

Keywords: Oxygen; oxygen usage; chronic obstructive pulmonary disease (COPD)

Submitted Jul 07, 2014. Accepted for publication Sep 15, 2014.
doi: 10.3978/j.issn.2072-1439.2014.10.23
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.10.23

Introduction

As we mark the centenary of the First World War, it is opportune to recall that the medical use of oxygen was popularised when Haldane first used it in treating gas inhalation injuries during World War I (1). Physicians before and after Haldane used oxygen intermittently for treatment of a range of conditions, but it was not until the 1950s (2) saw the development of techniques to facilitate point of care arterial blood gas analysis that the use of oxygen and its titration to a measured sample became common place. In the mid-late 20th century two randomised trials were performed almost simultaneously which have had a profound effect on the management of chronic obstructive pulmonary disease (COPD) over the last three decades.

Benefits of long-term oxygen therapy in COPD: review of original trials

In the 1970s physicians in the United Kingdom and the United States conducted two separate but similar studies to determine whether treating hypoxaemia in COPD could improve mortality. These trials, the UK Medical Research Council (MRC) (3) study and the US Nocturnal Oxygen Therapy Trial (NOTT) (4), showed that long-term oxygen therapy when given for greater than 15 hours per day improved survival in patients with COPD and chronic hypoxaemia (PaO_2 ≤55-60 mmHg), with or without hypercapnia. The UK study included 87 hypercapnic patients with PaO_2 40-55 mmHg on two measurements over a 3-week exacerbation-free observation period. Exclusions were co-existent fibrotic lung disease, pulmonary thromboembolism, hypertension and ischaemic heart disease or other life-threatening illness. In this unblinded controlled study, patients received oxygen via concentrator for 15 hours/day or no oxygen at all. No portable oxygen was provided and patients were not excluded if they continued to smoke. Patients were followed for three years or until death (3). The US Nocturnal Oxygen Treatment Trial (NOTT) enrolled 203 patients with stable hypoxaemia (PaO_2 ≤55 or 59 mmHg in the presence of cor-pulmonale, haematocrit ≥55% or electrocardiographic evidence of P pulmonale) on two measurements over a 3-week exacerbation free period (4). The patients received continuous or nocturnal oxygen and were also followed for a period of 3 years or until death. Those on continuous oxygen received portable oxygen as well. In this study the oxygen flow rate provided was sufficient to increase PaO_2 to 60-80 mmHg, with flow rates increased by 1 L/min during sleep and exercise. In both studies the majority of subjects

were male with a mean age of 65 years. In the MRC study mortality at three years was 45.2% in the oxygen treated group and 66.7% in controls. In the NOTT mortality rates at 24 months were 27% for the continuous group and 41% for the nocturnal group, demonstrating a significant survival advantage in the continuous oxygen group, in whom the average oxygen usage was 18 hours per day, compared with the nocturnal oxygen only group.

Because of the many similarities between these two trials, the results came to be considered together to demonstrate that oxygen for 15 hours per day was better than no oxygen (data from the MRC study) and that continuous oxygen had a greater mortality benefit than nocturnal oxygen (data from the NOTT) (3,4). These results significantly altered treatment of hypoxaemic COPD and, to this day, domiciliary oxygen is the only therapy (apart from smoking cessation) that has been shown to reduce mortality in COPD (3-5). As a consequence, most international guidelines for the management of oxygen therapy in COPD recommend that oxygen should be considered for patients with stable COPD, who have an oxygen partial pressure in arterial blood (PaO_2) consistently less than or equal to 55 mmHg (7.3 kPa) at rest when awake and breathing air and for patients with PaO_2 56-59 mmHg (7.4-7.8 kPa) with polycythaemia (haematocrit >0.55) or clinical, electrocardiographic or echocardiographic evidence of pulmonary hypertension and or right heart failure (6-9). At assessment, the patient's condition must be stable and all reversible factors (such as anaemia) should have been treated (9). In the Thoracic Society of Australia and New Zealand Position Statement, it is recommended that assessments should be made at least one month after the patient has stopped smoking, given that gas exchange may improve substantially on ceasing smoking (9,10). However, other guidelines do not necessarily recommend smoking cessation and it is to be remembered that at least one of the two studies on which the recommendations are based included current smokers (3). It is generally recommended that oxygen should be used for as many hours of the day as possible; ideally a minimum of 15+ hours.

These recommendations for oxygen therapy are based on two randomised non-placebo-controlled trials containing fewer than 300 patients, conducted over 30 years ago. The indications for prescription of oxygen therapy were the results of pragmatic decisions by the trial designers and the studies were performed in COPD populations that would not necessarily be representative of today's COPD patients, many of whom are older and have more co-morbidity. There have not been any subsequent, high quality randomised controlled studies of long-term oxygen therapy in severely hypoxaemic COPD. A retrospective analysis of South Australian COPD patients prescribed long term home oxygen from a single centre between 1977 and 1999 found the annual death rate was 20-33% per year—worse than that for the control (no oxygen) group in the UK MRC study (11). Reasons for the differences between the prospective MRC study and this retrospective review may include the older age of the patients being prescribed oxygen, the presence of co-morbidities, continued smoking, inadequate treatment of hypoxaemia, lack of adherence or the fact that this was a real world situation rather than a clinical trial. It would seem important to clarify the true impact of long term oxygen therapy on all-cause mortality in those patients who are currently receiving it, many of whom are elderly with multiple co-morbidities. The introduction of local or national databases aimed at capturing information about patients receiving home oxygen could provide an ideal means of obtaining prospective data on patients currently receiving oxygen therapy. The introduction of such a national database in Denmark was associated with an improvement in adherence to guidelines and slight reduction in mortality (12).

Other benefits of long-term oxygen therapy

There is little convincing evidence from studies to date that long-term oxygen therapy has significant benefits other than on survival. Indeed, the mechanism for the improvement in survival with oxygen therapy still remains unclear, despite the observation of small improvements in some haemodynamic parameters in the NOTT (4). Endpoints in the MRC study were physiological characteristics and mortality (3). In the NOTT, neuropsychological tests were assessed in both continuous and nocturnal oxygen groups at baseline and at six months. Only 42% of patients showed improvements at six months and there were no differences between the continuous and nocturnal groups (13). It should be reiterated that the lack of a control group (intranasal air) makes it difficult to determine whether the improvements in neuropsychiatric function were due to more than placebo effect.

With the potential restriction of movement imposed by long-term continuous oxygen therapy, it is possible that the treatment may only prolong suffering rather than improving quality of life (QOL). Non-placebo-controlled trials differ in showing either no benefit or a small benefit

in health related QOL in subjects commenced on long term continuous oxygen therapy (14,15). Although small improvements in QOL were found in the NOTT (4), the study did not have a placebo (air) arm and thus the presence of a placebo effect is not excluded. Whether oxygen therapy is worthwhile in the context of a particular individual's management should be determined by a comprehensive clinical assessment rather than solely, or mainly, by the increase achieved in PaO_2.

Nocturnal desaturation in COPD: is oxygen therapy indicated?

The clinical consequences of nocturnal hypoxaemia in patients with COPD and daytime PaO_2 ≥60 mmHg (8.0 kPa) are unclear. Although it has been suggested that repetitive transient desaturations throughout sleep may be one mechanism underlying the development of pulmonary hypertension in COPD, the primacy of hypoxia as a driving force in the development of pulmonary hypertension in COPD is now questioned, with systemic inflammation suggested as one of several possible alternative factors. Chaouat *et al.* showed that elevated circulating levels of interleukin-6 correlated with elevations in mean pulmonary artery pressure (16).

C-reactive protein levels have also been shown to correlate with both pulmonary artery pressure and levels of endothelin-1, a potent vasoconstrictor postulated to play a role in vascular remodelling and pulmonary hypertension (17). The issue of the role of inflammation in pulmonary hypertension complicating COPD remains controversial (18). However, *in vitro* animal models of pulmonary artery remodelling related to tobacco smoke studies support such a mechanism (19).

Although a New Zealand study suggested that isolated nocturnal desaturation was very uncommon in a general COPD outpatient population, and that patients with nocturnal desaturation had no worse sleep quality, QOL or daytime somnolence than those without desaturation (20), other studies have reported sleep fragmentation (21) as well as surges in both systemic and pulmonary blood pressure (22) as a consequence of nocturnal desaturation. Fletcher *et al.* suggested that nocturnal desaturation in patients with PaO_2 >60 mmHg occurred in 27% of patients, where desaturation was defined as a desaturation below 90% for five minutes or more, with a nadir saturation of at least 85% (23). Although a small retrospective study by Fletcher *et al*. suggested that patients with nocturnal oxygen desaturation had a poorer survival than those without (24) a subsequent small prospective study by Chaouat *et al.* found that COPD patients with nocturnal desaturation did not develop pulmonary hypertension more than a group of patients without nocturnal desaturation and their prognosis was no different over 6 years of follow-up (25). Whether nocturnal hypoxaemia alone can lead to substantial pulmonary hypertension remains controversial. Fletcher *et al.* demonstrated that nocturnal supplemental oxygen at 3 L/min over three years was associated with a smaller rise in pulmonary artery pressure than in a control group receiving supplemental air (26). However, there was no effect on mortality. A larger 2-year study of patients with COPD and modest daytime hypoxaemia [PaO_2 56-59 mmHg (7.4-7.8 kPa)] who desaturated to a pulse oximeter oxygen saturation (SpO_2) <90% for >30% of the night found no survival benefit in the group receiving oxygen supplementation and no effect on pulmonary haemodynamics (27). There is no international consensus regarding provision of nocturnal oxygen in COPD for patients with daytime PO_2 >60 mmHg.

Episodes of nocturnal hypoxaemia due to hypoventilation or worsening ventilation-perfusion in patients with COPD should be distinguished from those associated with sleep apnoea caused by upper airway obstruction, obesity hypoventilation syndrome or central sleep apnoea. Apnoea syndromes are diagnosed by overnight polysomnography and generally require other forms of therapy (such as continuous positive airway pressure or nocturnal ventilation) rather than supplemental oxygen.

Ambulatory oxygen

In those fulfilling criteria for long term continuous oxygen therapy

Ambulatory oxygen therapy may be used as part of continuous oxygen therapy, in which case its use is aimed at maximising the number of hours per day a person with COPD can use their oxygen for, at the same time as maintaining adequate physical activity including engaging in pulmonary rehabilitation. Pulmonary rehabilitation has been demonstrated to improve exercise capacity and QOL in COPD (28), whilst reduced physical activity is associated with increased risk for hospitalisation and for mortality (29). Patients in the "continuous" arm of NOTT, whose survival benefit was greatest, used both stationary and ambulatory systems in order to enable an average usage of 18 hours per

day (4). Extrapolation from the studies of long term oxygen therapy (3,4) may suggest that using ambulatory oxygen during activity would enhance the benefits of LTOT but there are few data to support this.

In those not fulfilling criteria for long term continuous oxygen therapy

Despite the observation of small, acute benefits of oxygen therapy during laboratory-based exercise tests in COPD (30), the subject of ambulatory oxygen use in patients who do not fulfil criteria for LTOT remains controversial. Ambulatory oxygen is often provided for patients who desaturate with exertion because of such short-term in-laboratory studies which have demonstrated modest improvements in exercise capacity and/or dyspnoea. Interestingly, these small benefits may be noted in patients who do not desaturate on exertion as well as in those who do and have been attributed to reductions in dynamic hyperinflation induced by a hyperoxia-driven reduction in ventilation (31,32). The underlying mechanisms for dyspnoea and exercise limitation in COPD are complex (33). In a study of ten patients with severe COPD and mild hypoxaemia by Somfay *et al.* (34), endurance time on a symptom-limited incremental exercise test was increased whilst breathing increasing concentrations of oxygen up to 50%, with small but statistically significant decreases in dyspnoea score, end-expiratory and end-inspiratory lung volume, minute ventilation and breathing frequency. These authors determined that there was a dose-dependent improvement in exercise endurance and dyspnoea which may be partly related to a reduction in hyperinflation and reduced breathing frequency. Although widely prescribed, usually on the basis of relief of exertional desaturation during a laboratory-based test, the use of domiciliary ambulatory oxygen is not strongly evidence-based. Two studies of cross-over design which examined the impact of portable oxygen therapy on QOL had conflicting findings in terms of QOL and a small multiple n-of-one study found no benefit (35-37). In an adequately powered study of patients with COPD who remained breathless on exertion despite maximal treatment, Moore *et al.* randomised patients without severe resting hypoxaemia to use ambulatory oxygen or ambulatory air at 6 L/min during exertion for 3 months at home (38). Included patients (n=143) had PaO_2 greater than 60 mmHg at rest on room air, with a third desaturating to SpO_2 <88% on exertion. Although there was a trend to improvement in both arms of treatment, there was no difference between supplemental air and supplemental oxygen used during exercise with regards to dyspnoea, QOL or function, and the presence of exertional desaturation was not predictive of outcome. These results suggest a substantial placebo effect from the administration of intranasal gas, possibly relating to the wearing of nasal cannulae (39). Nonetheless, in the study by Nonoyama *et al.*, where investigators performed multiple n-of-1 studies, occasional patients (n=2 out of 27) achieved clinically significant reductions in dyspnoea, so blinded assessments may be useful in selected individuals (37).

Oxygen for pulmonary rehabilitation in COPD

Theoretical reasons to support the use of supplemental oxygen during training include the potential for amelioration of exercise-induced elevations in pulmonary arterial pressure (40,41) and the potential for reductions in minute ventilation and dynamic hyperinflation (34). However, there is no evidence to support this practice.

"Palliative" oxygen

Supplemental oxygen has been used in an attempt to provide symptomatic relief for patients with intractable dyspnoea due to terminal illnesses, including late-stage lung disease such as COPD, even in the absence of hypoxaemia. In the first large, international multi-centre trial examining this question, Abernethy *et al.* randomly allocated 239 patients with life-limiting disease, including COPD (64%) and cancer (16%), to receive oxygen or medical air (42). Both were delivered at 2 L/min through nasal cannulae via a concentrator for seven days. Primary outcomes were impact on breathlessness and QOL. The study found that both medical gases induced small improvements in dyspnoea and QOL, with more severe baseline breathlessness predicting this benefit. They also found that most of the improvement occurred in the first three days. The conclusion was that palliative oxygen had no benefits over medical air for relieving dyspnoea or for improving QOL for the whole population and that there were small improvements with both arms of the treatment. A therapeutic trial of medical air or oxygen over 3 to 4 days was thus proposed as a way of assessing those dyspnoeic patients who might benefit. It is thought that relief of breathlessness with either oxygen or air, as described in the abovementioned study, could be due to stimulation of nasal receptors by gas flow, however, the mechanism by which this occurs is not known. The role of air flow as an intervention has been explored and cold air directed on the face has been shown to

reduce breathlessness induced by inspiratory resistive loading and hypercapnia in normal subjects (39) and in patients with COPD (43). A placebo controlled study using a handheld fan in patients with intractable dyspnoea from different causes showed benefit (44).

Oxygen in moderate hypoxaemia

Despite the mortality benefits from long term oxygen therapy in patients with COPD and severe hypoxaemia, there is no such benefit for continuous oxygen supplementation in patients with milder degrees of hypoxaemia. A trial reported by Górecka and colleagues (45) found that LTOT (oxygen for a mean of 17 hours/day to raise PaO_2 to ≥65 mmHg) had no effect on survival over a mean observation period of 40.9 months in patients with COPD and only moderate hypoxaemia (56-65 mmHg). One hundred and thirty five patients with mean FEV_1 of 0.83 L were included. The overall mortality in this study was 11-12% per annum, which is close to that of patients on continuous oxygen therapy in the NOTT (4). Younger age, better spirometric values and higher body mass index predicted better survival.

Cognitive function, hypoxaemia and driving

Cognitive dysfunction has been described in people with COPD. The frequency of cognitive dysfunction varies depending upon the battery of neuropsychological tests used, with the domains most influenced being memory and attention. COPD diagnosis was linked with an 83% higher risk for developing non-amnestic mental decline in a recent prospective study of aging adults (46). Although hypoxaemia may be one several mechanisms by which COPD induces mild cognitive impairment in COPD there is limited evidence for benefit of long term oxygen therapy on cognition (47). Previous guidelines on fitness to drive in Australia recommended patients on long term oxygen therapy should use supplemental oxygen whilst driving a motor vehicle (48). However, there is no evidence for either improvement in cognition (49,50), or in simulated driving performance with acute oxygen therapy in this patient group (51). Thus, there is currently no recommendation for hypoxaemic patients to use portable oxygen therapy whilst driving in Australia and/or New Zealand (52).

Risks of oxygen in acute exacerbations of COPD

It has been known for decades that patients with acute exacerbations of COPD may develop worsening hypercapnia with the application of supplemental oxygen, particularly at high concentrations. The mechanisms underlying this phenomenon relate to a combination of (I) worsening ventilation perfusion mismatch secondary to attenuation of hypoxic pulmonary vasoconstriction; (II) the Haldane effect which involves displacement of carbon dioxide bound to haemoglobin by increased oxygen concentration; and (III) hypoventilation. The adverse effects of high concentrations of supplemental oxygen were recently confirmed in a study by Austin *et al.* which reported an increase in mortality for patients randomised to receive high concentration oxygen versus those who received low concentration titrated oxygen to a target saturation range of 88-92% when transported via ambulance with acute exacerbation of COPD (53).

Current research and future research needs

Oxygen is a widely used treatment for COPD and a range of other chronic lung diseases. Apart from the demonstrated evidence of mortality benefit with LTOT in patients with severely hypoxaemic COPD and minimal co-morbidities, the evidence for significant benefit with oxygen in a range of other circumstances is lacking.

Currently recruiting studies

Long term oxygen treatment trial (LOTT)

The currently recruiting LOTT is sponsored by the National Heart Lung and Blood Institute and Centers for Medicare & Medicaid Services in the United States. Its stated aims are to determine whether continuous supplemental oxygen increases time to a composite outcome of all-cause mortality or all-cause hospitalisation as well as examining deterioration in QOL. Patients will receive either continuous oxygen for 24 hours/day if they have moderate resting hypoxaemia or supplemental oxygen for sleep and activity for those with exercise desaturation. There will be no placebo (supplemental air) arm which is disappointing given there is clinical equipoise. The reason for the absence of a placebo arm is unclear, but it may relate to the (no doubt significant) costs of supporting such a study. The absence of a placebo arm is extremely disappointing as there are clearly demonstrated placebo effects of intranasal gas flow and such a study would have provided an excellent opportunity to explore the question in detail. The

NOTT was not able to clearly determine any benefits on QOL or cognition because of the lack of a placebo arm.

Supplemental oxygen in pulmonary rehabilitation trial (SuppORT)

This currently recruiting trial sponsored by the Australian National Health and Medical Research Council (NHMRC) is a randomised controlled trial of supplemental oxygen versus medical air in people with COPD aimed at determining whether supplemental oxygen improves the exercise capacity and QOL of patients with COPD who desaturate with exertion.

Studies of oxygen therapy are difficult to undertake because of the severely disabled population of patients involved and the lack of funding sources, however, further studies are needed. Research questions include whether oxygen for exertional use can improve QOL and activity levels if the delivery device is more "user friendly". Although recent studies of exertional oxygen used over medium term durations in COPD have not demonstrated benefits over portable air; it is the case that patients do not use their portable oxygen delivery devices more that about 40 minutes per day. Future studies should try and determine whether the absence of oxygen use relates to the ineffectiveness of the treatment or to the physical properties of the portable device being clumsy or heavy or embarrassing to use and cancelling out any the small magnitude of any potential benefits gained.

A large study to determine whether nocturnal desaturation has short and long term sequelae on sleep quality, pulmonary haemodynamics and QOL is also warranted.

Conclusions

Oxygen therapy is known to improve mortality in patients with severe hypoxaemia and COPD. Patients currently receiving this treatment are often older and have more co-morbidities than the patients who were enrolled in the original long term oxygen studies. Further studies and the development of national and perhaps international registries should allow clarification of the impact of oxygen therapy on COPD patients receiving oxygen therapy currently. Benefits from oxygen in patients with milder degrees of hypoxaemia who may desaturate on exertion or nocturnally are unclear and require further study. Such future prospective studies should include a placebo arm in order to distinguish benefit due to oxygen from placebo effect.

Acknowledgements

Disclosure: The author declares no conflict of interest.

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Cite this article as: McDonald CF. Oxygen therapy for COPD. J Thorac Dis 2014;6(11):1632-1639. doi: 10.3978/j.issn.2072-1439.2014.10.23

Review Article

Advanced therapies for COPD—What's on the horizon? Progress in lung volume reduction and lung transplantation

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Abstract: Advanced chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity. Treatment options beyond conventional medical therapies are limited to a minority of patients. Lung volume reduction surgery (LVRS) although effective in selected subgroups of patients is not commonly undertaken. Morbidity associated with the procedure has contributed to this low utilisation. In response to this, less invasive bronchoscopic lung volume techniques are being developed to attempt to mitigate some of the risks and costs associated with surgery. Of these, endobronchial valve therapy is the most comprehensively studied although the presence of collateral ventilation in a significant proportion of patients has compromised its widespread utility. Bronchial thermal vapour ablation and lung volume reduction (LVR) coils are not dependent on collateral ventilation. These techniques have shown promise in early clinical trials; ongoing work will establish whether they have a role in the management of advanced COPD. Lung transplantation, although effective in selected patients for palliation of symptoms and improving survival, is limited by donor organ availability and economic constraint. Reconditioning marginal organs previously declined for transplantation with ex vivo lung perfusion (EVLP) is one potential strategy in improving the utilisation of donor organs. By increasing the donor pool, it is hoped lung transplantation might be more accessible for patients with advanced COPD into the future.

Keywords: Chronic obstructive pulmonary disease (COPD); lung volume reduction surgery (LVRS); bronchoscpic lung volume reduction; lung transplant

Submitted Jun 24, 2014. Accepted for publication Oct 27, 2014.
doi: 10.3978/j.issn.2072-1439.2014.11.34
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.11.34

Introduction

Chronic obstructive pulmonary disease (COPD) is the 4th leading cause of mortality also conferring significant adverse impact on the quality of life for millions of people world wide (1). Goals of treatment are avoidance of disease progression by cessation of noxious particulate exposure, improving exercise capacity by participation in pulmonary rehabilitation, prescription of pharmacotherapy and reducing exacerbation rate (2). Despite these measures a large proportion of patients continue to experience functional impairment and diminished quality of life with consequential economic and social burden (3). This article will explore advanced therapies and surgical interventions for patients who remain impaired despite optimal medical care. The mainstay of treatment options are:

(I) Lung volume reduction surgery (LVRS);
(II) Lung transplantation.

Although yet to be integrated into widespread clinical practise, bronchoscopic methods of lung volume reduction (LVR) are currently being developed. These potentially represent a less invasive, more accessible treatment option for advanced emphysema.

Lung volume reduction (LVR) practises

Physiological basis for LVR

Airway obstruction and emphysema both cause hyperinflation leading to alterations in both lung and

chest wall mechanics (4). The combination of impaired gas exchange, unfavourable lung mechanics at high volume and respiratory muscle inefficiency (due to the respiratory muscles being placed at a mechanical disadvantage) lead to a substantial (and unsustainable) increased work of breathing. Loss of elastic recoil and dynamic airway closure during expiration cause increases in intrinsic PEEP and gas trapping. In these circumstances greater respiratory effort is required to overcome these loads to achieve similar alveolar ventilation. The resulting hyperinflation further exacerbates the problem by reducing respiratory muscle efficiency through diaphragmatic flattening. These physiological alterations result in symptoms of dyspnoea and reduction in exercise capacity. LVR techniques aim to improve respiratory mechanics by resecting, collapsing or obliterating areas of diseased lung making a poor contribution to gaseous exchange. The remaining lung fills the space restoring elastic recoil, reducing dynamic airway closure and gas trapping. The resulting decrease in residual volume returns the diaphragm to a favourable position for efficient ventilation (5).

Lung volume reduction (LVR) surgery

The National Emphysema Treatment Trial (NETT) continues to be the sentinel research underpinning current LVRS practise, defining patient populations for which the intervention confers benefit (6). Prior to this, case series and small randomised trials had suggested benefit (7,8) although patient numbers were modest. Wider concern was voiced about unacceptable mortality and morbidity associated with the procedure (9). The study was designed in response to these uncertainties (10).

The NETT trial randomly assigned 1,218 patients to either LVRS or best medical treatment using exercise capacity and mortality as primary outcome measures. Inclusion criterion included the presence of severe airway obstruction (FEV_1 <45%), gas trapping (RV >150%) and hyperinflation (TLC >100%). All patients underwent pulmonary rehabilitation prior to trial entry.

The early results from the trial defined a patient population (n=140) at high risk of mortality, reaching 16% at 30 days P<0.001 (11).

- FEV_1 <20% predicted and;
- DLCO <20% or homogeneous emphysema pattern.

The presence of these features continues to be an absolute contraindication to LVRS. Such patients randomised to the control group also had poorer prognosis; these clinical characteristics are therefore used within the current transplant guidelines for selection of appropriate patients.

Even after exclusion of high risk patients, NETT did not demonstrate a survival advantage between patients managed medically and surgically. Mortality results for "non-high risk" patients were dependent on post-hoc subgroup analysis stratified by the pattern of emphysema and patient's exercise capacity. Maximal workload at cycle ergometry was used to define exercise capacity-low exercise capacity being less than 40 Watts for males and 25 Watts for females based on sex specific normal values.

The sub-groups were:

(I) Upper-lobe predominance, low base-line exercise capacity (n=290);
(II) Upper-lobe predominance, high base-line exercise capacity (n=419);
(III) Non-upper-lobe predominance, low base-line exercise capacity (n=149);
(IV) Non-upper-lobe predominance, high base-line exercise capacity (n=220).

Of the four subgroups, only group 1 characteristics conferred a survival benefit during initial follow-up. Over an initial mean follow-up of 29.2 months, these patients undergoing LVRS had a significantly reduced risk of death (P<0.005). No benefit in survival was observed for those patients with non upper lobe emphysema regardless of their exercise capacity. The second primary endpoint of exercise capacity, did favour patients undergoing the procedure. A total of 52% of surgical patients improved exercise capacity defined as any improvement in cycle ergometry from baseline at 6 months compared to 20% of controls (P<0.001). This benefit extended to 24 months although the effect did diminished over time (31% in the surgical group compared to 10% controls had sustained improvement at 24 months).

Long term follow-up of the patient cohorts (12) confirmed the survival benefit to 5 years in the patients with upper-lobe emphysema and low exercise capacity (relative risk 0.67, P<0.003). Again, no survival advantage was demonstrated in the remainder of patients groups. The additional suggestion from this longer term data is the consideration of patients with upper lobe disease and high baseline exercise capacity as a palliative procedure. Significant improvements in quality of life as assessed by the St George's Respiratory Questionnaire (SGRQ) were seen to 5 years.

The long term benefit in the selected patients above must be tempered with shorter term risk of surgery. The original study reported a 90 day mortality of 5.2% in non-high risk patients compared to 1.5% of those patients undergoing

medical therapy. This higher mortality was not seen in the upper lobe predominant low exercise capacity patients for whom the procedure should be considered (2.9 % 90 day mortality *vs.* 3.3% within the control group). Airleak occurred in 90% of patients (median duration 7 days) with 12% persistence at 30 days. Of patients undergoing LVRS, 28.1% remained hospitalised at 30 days. Airleak was universal in those patients not surviving 30 days although the low mortality rate at this time point (3.6%) meant a statistical association was not observed. Nevertheless, higher rates of adverse outcomes (pneumonia, ICU readmission, longer length of stay) were seen in patients with airleak (13). These peri-operative risks and the associated cost implications have contributed to the quest for less invasive bronchoscopic techniques for achieving LVR.

Surgical technique and considerations

The large numbers of patients enrolled in NETT provided an opportunity to compare techniques and outcomes (13,14). Individual centres had the option of using either video assisted thoracoscopic surgery (VATS), median sternotomy or internally randomising patients to either. Of the 552 patients randomised patients who underwent surgery, 69% underwent median sternotomy, with the remainder mostly undergoing a VATS procedure. Choice of operation did not affect mortality outcomes although VATS was associated with shorter ICU and hospital stay with consequential reduced cost (14).

The technique is usually a non-anatomical wedge resection aiming for LVR of 20-30% rather than an anatomical lobectomy (15). Staple lines are a common source of airleak. Prior small non-randomised and randomised studies had suggested that buttressing-reinforcement of stable lines with bovine pericardium or PTFE reduces length of stay (16) and airleak duration (17) with the practise widely applied amongst NETT patients. Patient factors rather than operative technique seemed to have a larger influence on outcome in the NETT cohort. There was no difference in proportion of patients with airleak or its duration when comparing procedure type or buttress material. Longer duration of airleak was associated with lower DLCO and FEV_1, Caucasian ethnicity, use of inhaled steroids, pleural adhesions and upper lobe disease (13).

Non surgical methods for LVR

A number of bronchoscopic interventions have been proposed for non-surgical LVR (18-22). Facilitating LVR bronchoscopically may negate some of the risk associated with surgery, reduce inpatient stay for the procedure and potentially reduce the associated costs. Trial data comparable to the NETT study is not currently available for the majority of these interventions.

For the majority of these techniques, the NETT results have been extrapolated so that patients most likely to benefit can be targeted. Patients identified as 'high risk' by NETT criterion are usually excluded. Likewise most of the existing studies focus on heterogeneous emphysema distribution, usually in the upper lobes. Homogenous emphysema has been addressed with interventions such as airway bypass-endobronchial fenestrations with stenting and LVR coils (LVRCs). The aim of airway bypass is to reduce hyperinflation and gas trapping by creating extra-anatomical airways bypassing expiratory flow limitation utilising stents to maintain patency of the airway created. LVRCs aim to improve these parameters by improving small airway patency by applying traction forces across lung parenchyma thus reducing expiratory airway collapse.

Bronchoscopic interventions can be broadly divided into:

(I) Reversible airway interventions. These include endobronchial valves; LVRCs and transbronchial stents. These may potentially be retrieved if complications occur;

(II) Irreversible interventions inciting an inflammatory/fibrotic response or irreversibly plugging distal airways. These include bronchoscopic thermal vapour ablation (BTVA) and biological LVR (BioLVR).

Of these interventions the largest body of evidence is currently available for endobronchial valves, although as we will see collateral ventilation has limited its overall efficacy and translation to clinical practice. The current focus is on identifying and selecting patients without collateral ventilation for whom the technique may be of benefit. BTVA and LVRCs show promise although large scale randomised trials required to support their widespread use are currently pending or not available. The majority of these techniques rely on analysis of HRCT images via software packages to facilitate precise targeting of the most diseased lung parenchyma.

Endobronchial valves

Endobronchial valves allow unidirectional airflow. When sited in bronchi leading to hyper-expanded, emphysematous

lung parenchyma, air is permitted to escape on expiration with no corresponding inspiratory flow. Lung distal to the stent, assuming no collateral ventilation, will collapse and become atelectatic. Resultant reduction in lung volume should have the same physiological effect to surgical LVR. At present two valve products are marketed (Zephr™ and IBV); despite differences in valve design the physiological principles for action are similar.

Results of the initial large randomised trial (VENT study) (23) were not as encouraging as the preliminary studies (24). A total of 321 patients were randomised to Zephr™ endobronchial valve placement or best medical care with a 2:1 ratio. A sham procedure was not undertaken in this study. Patients all had severe airflow obstruction and radiologically heterogeneous emphysema quantified on HRCT chest. Although the study showed statistically significant improvement in the primary outcomes at 6 months (FEV_1 4.3% increase; 6MWT 9 meters improvement) the magnitude of these changes was deemed unlikely to be clinically meaningful (25). Pre-defined major complications were seen in 4.2% of patients undergoing valve therapy. Although not pre-defined as major complications, 7.9% and 5.6% of patients experienced an exacerbation of COPD requiring hospitalisation or haemoptysis respectively.

The European arm of the VENT trial (n=171) was commenced to support slow recruitment in the American study (26). Target recruitment was eventually achieved hence the European cohort being reported separately. Study design was similar to the American arm. When looking at the study population as a whole, a statistically significant improvement at 6 months was seen in only cycle ergometry (5 watts mean improvement compared to controls; $P<0.05$) and SGRQ. The change in SGRQ (5 points) was again below the threshold considered clinically meaningful. The reported focus on this second paper from the VENT group was the effect of collateral ventilation and complete lobar isolation. Subjects in the treatment arm underwent further evaluation with HRCT 6 months post procedure to assess degree of airway occlusion and volume reduction of the targeted lobe. Forty-four subjects in the treatment group of 111 had a complete fissure suggesting the absence of collateral ventilation. A complete fissure conferred reduction in lobar volume by 55% compared with 13% where the fissure was incomplete. Lobar isolation was seen in 48% of patients at 6 months (assessed by HRCT) indicating most patients continued to ventilate the targeted lobe despite the procedure. Combining these two variables (no collateral ventilation; successful technical isolation) yielded the most encouraging results. Improvements in FEV_1, 6MWT and St George's questionnaire were all clinically and statistically significant in this instance.

Ninane *et al.* tested IBV valves in a sham procedure controlled study (n=73) (27). Upper lobes were targeted although the study design was such that complete lobar occlusion was deliberately avoided to prevent lobar atelectasis which the study author hypothesised may cause adverse events. The primary outcome was proportion of patients responding to treatment by reaching a composite endpoint of change in SGRQ and lobar volume (defined as a 4-point increase in SRGQ, reduction in target lobe volume and 7.5% increase in lower lobe volume at HRCT assessment at 3 months). Although significantly more patients in the treatment group responded (8/33 *vs.* 0/35, $P=0.002$), the majority of patients did not respond to the treatment. The study design and avoidance of lobar atelectasis may account for the low proportion of responders.

The success of endobronchial valves is therefore highly dependent on lobar isolation and collateral ventilation which, as described above, occurs in a significant number of patients. Further techniques have been developed to assess CV (28). The Chartis system allows the targeted lobe to be occluded with an endobronchial balloon with measurement of expiratory airflow and pressure distal to the occlusion. Presence of flow distal to the balloon occlusion is suggestive of CV. This system can be used to determine which patients are more likely to respond to the insertion of endobronchial valves based on the measurement of CV (29). In this cohort of 96 patients undergoing endobronchial valve insertion 35% were assessed as having collateral ventilation present at bronchoscopy utilising Chartis. The system predicted response to insertion of endobronchial valves. Absence of CV conferred mean lobar volume reduction of 751 mLs compared to 98 mLs where CV was present ($P<0.0001$). These figures are clinically relevant as volume reduction in target lobe has been correlated with reduction in BODE index (body mass index, obstruction, dyspnoea and exercise tolerance) at 6 months (30).

The main limitation for using Chartis to assess collateral ventilation and predict which patients stand to benefit is the requirement for bronchoscopy. Patients with CV found at bronchoscopy precluding (or predicting poor response) to endobronchial valve placement would have undergone a procedure with limited potential for therapeutic benefit. At present this must be factored into the risk benefit analysis.

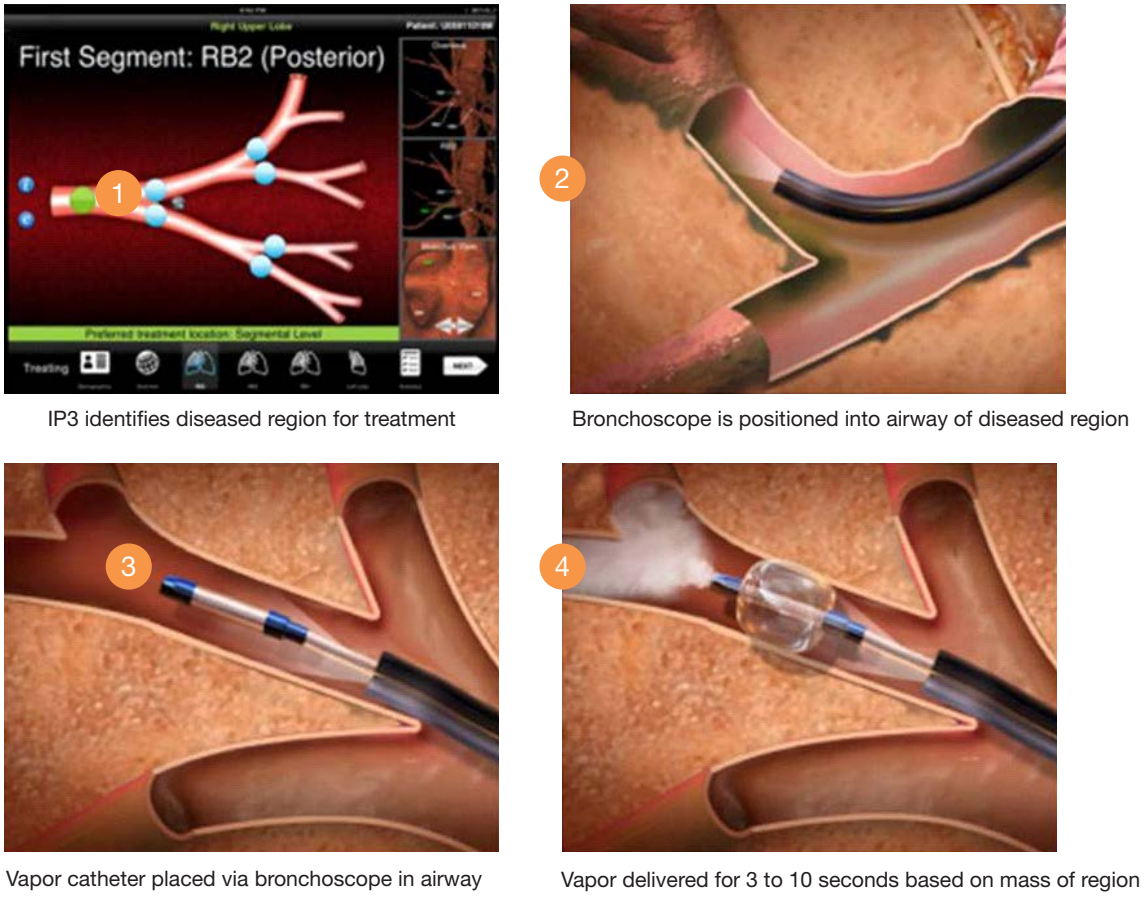

Figure 1 Technical aspects of BTVA-courtesy of uptake medical corporation. BTVA, bronchoscopic thermal vapour ablation.

Limiting Chartis assessment for CV to patients with complete fissures identified at radiology may improve the yield of bronchoscopic assessment identifying subject most likely to benefit from valve therapy. A trial addressing this question is currently recruiting (31). An alternative strategy might be to use an alternative irreversible CV independent technique in patients where CV is identified as described below.

Bronchoscopic thermal vapour ablation (BTVA)

This technique causes a thermal injury via heated water vapour to emphysematous lung to induce an inflammatory response. The resulting atelectasis and fibrosis reduces the volume within the targeted lung segment potentially conferring similar physiological effect to conventional LVRS. Unlike endobronchial valves, the technique is not dependent on collateral ventilation.

Snell *et al.* published a case series of 44 patients undergoing unilateral BTVA (32). Patients with severe airway obstruction (FEV_1 15-45% predicted) were included if heterogeneous upper lobe emphysema was present as defined by lower lobe: upper lobe tissue to air ratios of >1.2 on baseline HRCT scan. This scan was used to plan treatment location and dose using predefined algorithms. In the above trial the 10 cal/gram dose of steam vapour was directed to the most diseased lung parenchyma. The targeted segments are intubated using a catheter directed through the bronchoscope working channel. A balloon is then fed over the guide catheter and inflated to protect the non-treated lung and airways prior to the predefined vapour dose being delivered (*Figure 1*). Follow-up to 6 months demonstrated encouraging results. Significant volume loss was seen in the targeted lobe (mean reduction 715 mL; P<0.001), FEV_1 improved (141 mLs, P<0.001) as did 6MWT distance (46.5 metres, P<0.001). Symptomatic improvement was reported although these improvements must be interpreted with caution given the absence of a control group.

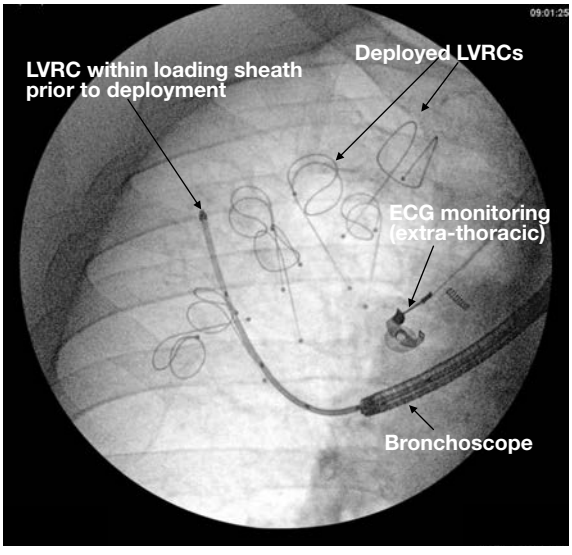

Figure 2 Fluoroscopic appearance of endobronchial coils at bronchoscopy. Seven coils have been sited with the 8th coil remaining within the guide sheath just prior to deployment. Courtesy of PneumoRx Inc.

Given the mechanism of LVR-thermally induced lung injury and inflammation-it is unsurprising that respiratory complications were reported. A total of 25 of 29 adverse events were of a respiratory aetiology (43% of patients). COPD exacerbations and pneumonia were recorded in the 3 months following the procedure. A single death due to 'end stage COPD' was reported at 67 days. Follow-up analysis demonstrates that patients who experienced symptoms attributable to the localised inflammatory response derived greater benefit from the procedure in terms of volume reduction (33). A randomised phase III "Step-Up" trial is currently underway (34), recruiting 69 patients with heterogeneous bilateral upper lobe emphysema randomised 2:1 to either sequential bilateral upper lobe BTVA 3 months apart or best medical therapy. The treatment will clarify the role of this therapy and provide important safety data.

Lung volume reduction coils (LVRCs)

By applying traction forces to lung parenchyma, LVRCs aim to improve hyperinflation and gas trapping by reducing dynamic airway collapse (22). The mechanism of action is again independent of CV and could be applied to emphysema that is homogeneous or heterogeneous (in contrast to BTVA where heterogeneous disease is currently being targeted). The early published data shows promise with larger studies underway (35,36). The technique involves catheterising target lung segments with a guide wire to a distance 3.5 mm to the pleural edge (*Figure 2*). The coil sits within a loading sheath, straightening it prior to deployment. As the sheath and guide wire are withdrawn the LVRC reverts to its prior coiled shape applying traction to the surrounding lung parenchyma. Dynamic expiratory small airway collapse is reduced by application of radial traction thus improving gas trapping and hyperinflation. Up to ten LVRCs can be sited during a procedure initially unilaterally with further scope for a contra-lateral procedure at a later date if tolerated.

The most comprehensive evaluation of LVRCs was published as the RESET trial (35). Forty-seven patients were randomised to either LVRCs or usual care (1:1) with follow up to 90 days. Inclusion criterion included severe airflow obstruction (FEV_1 <45%), emphysema on HRCT, TLC >100% and dyspnoea (MMRC score >2). Primary outcome was SGRQ with secondary outcomes including 6MWT, FEV_1 and MMRC dyspnoea score. Although baseline characteristics were not matched, clinically and statistically meaningful improvements were seen in SGRQ (8.36 between group improvement P=0.04) and 6MWT distance (63.55 metre between group improvement, P<0.001). No improvement in TLC was seen at 90 days. Further studies are required and are currently recruiting to further evaluate this technique in larger cohorts of patients (35).

Biologic lung volume reduction (Bio-LVR)

The principle of bio-LVR is similar to that of bronchoscopic thermal ablation. A fibrinogen based biopharmaceutical suspension containing thrombin polymerises when instilled into targeted airways (20). The resulting biodegradable matrix induces a localised inflammatory response inducing fibrosis and collapse of the targeted segment. Nonrandomised phase II studies evaluating optimal dose and safety demonstrated significantly improved FEV_1, RV/TLC ratio and RV in 22 patients undergoing higher dose (37). The treatment was associated with transient fevers, leukocytosis and COPD exacerbations. Despite promise, phase III trials were not further pursued, presumably due to the development of the alternative preparation Aeriseal® by the study sponsor.

In contrast to bioLVR, the Aeriseal® preparation aims to induce LVR acting at bronchiolar and alveolar levels by sealing airways inducing absorption atelectasis thus leading to reduction in lung volume. The proposed mechanism may also obscure collateral ventilation pathways. Non-randomised

case series have examined the safety of this intervention (38). Magnussen *et al.*'s later case series is the most comprehensive evaluation of the intervention (39). Fifty-four patients with Global Initiative for Obstructive Lung Disease (GOLD) stage III or IV COPD, gas trapping RV >135% (mean 242%) and hyperinflation were evaluated with HRCT to assess for upper lobe emphysema. All included patient were treated with Aeriseal at 2-4 subsegemental sites and followed to 12 weeks. The authors further divided the cohort into patients for whom data with regard to fissure integrity was available. In this subset of 28 patients TLC reduced by 214 and 261 mLs in patients with and without complete fissures respectively. There was no significant difference between the magnitude of change when assessing for the presence of radiologically intact fissures suggesting the treatment is independent of CV. Six-minute walk distance improved by a mean of 31.9 metres with 31% of patients achieving a clinically meaningful improvement of 54 metres. Despite promise the phase III trial was terminated by the study sponsor in November 2013 prior to publication (40). At present the only registered trial recruiting is a phase II study evaluating the role of autologous blood as a biological irritant to induce LVR (41). Given the absence of phase III trials actively recruiting, it is unlikely that biological methods of LVR will implemented into routine clinical practise in the near future.

Endobronchial and extra-pulmonary bypass procedures

Airway bypass procedures have been proposed to reduce gas trapping by directly relieving trapped air in emphysematous lung by creating extra-anatomical airways. Bronchoscopic fenestrations between large airways and diseased lung parenchyma are created to improve expiratory flow. Drug eluting stents are then sited in an attempt to maintain ongoing patency of the novel tracts. The procedure was proposed for those patients with homogenous (diffuse) emphysema. Unfortunately the large (n=315), randomised, sham procedure controlled study evaluating the technique showed disappointing results (42). Improved FVC immediately post procedure was not sustained past 1 month. There was no difference in MMRC dyspnoea scale. Adverse events occurred at higher frequency in the treatment group although serious adverse events were rare. The authors hypothesised that lack of sustained response likely related to occlusion of the stent with mucus or granulation tissue. At present there is no role for the technique-whether changes to stent design might improve long term efficacy remains unevaluated.

An alternative extra-anatomical approach has been suggested and is in early developmental stages (43,44). Expiratory flow rates may be augmented by surgically creating a fistula between the diseased hyper-inflated lung parenchyma and the chest wall thus reducing hyperinflation. The larger calibre bypass airway created is likely to be less prone to occlusion than transbronchial airway stents. The initial case series (six patients) utilised an improvised endotracheal tube to maintain airway patency. Custom designed pneumonectomy catheters-the 'portaero pneumostoma' have subsequently been developed and are under evaluation (45). The risk benefit profile for this method of LVR will require careful evaluation (*Figure 3*).

Lung transplantation

Indications for lung transplantation in COPD

Despite significant symptoms and functional limitation patients with advanced COPD have survival which is variable due, generally, to slow chronic disease progression over years. Median survival of patients with GOLD stage III and IV disease is 6 years (46). After transplantation, patients with COPD have median survival of 5.4 years with 30% of transplanted patients surviving to 10 years (47). Given that goals of transplantation are improvement of symptoms and survival, patient selection and identification of subgroups of patients with poor prognosis is critical. The presence of severe airway obstruction alone is insufficient to predict who might benefit. Whether lung transplantation should be offered to palliate symptoms without improvement in survival benefit is contentious, especially given limited availability of donor organs (48). In general terms, lung transplantation is indicated where predicted survival is less than 2 years in patients with NYHA III or IV symptoms and associated poor quality of life. The presence of absolute or relative contraindications must be considered and factored into clinical decision making when proceeding to transplant (*Tables 1*,*2*) (48).

Patients should ideally be referred to a transplant centre before they are established in the "transplant window"-the time period for which the patient is likely to confer benefit from transplantation prior to becoming too frail to undertake the peri operative rigours and recovery after transplantation. This allows adequate time for assessment, consideration of alternative options (i.e., LVRS as discussed above) and addressing reversible relative contraindications or issues that may impact on the transplant process. Factors

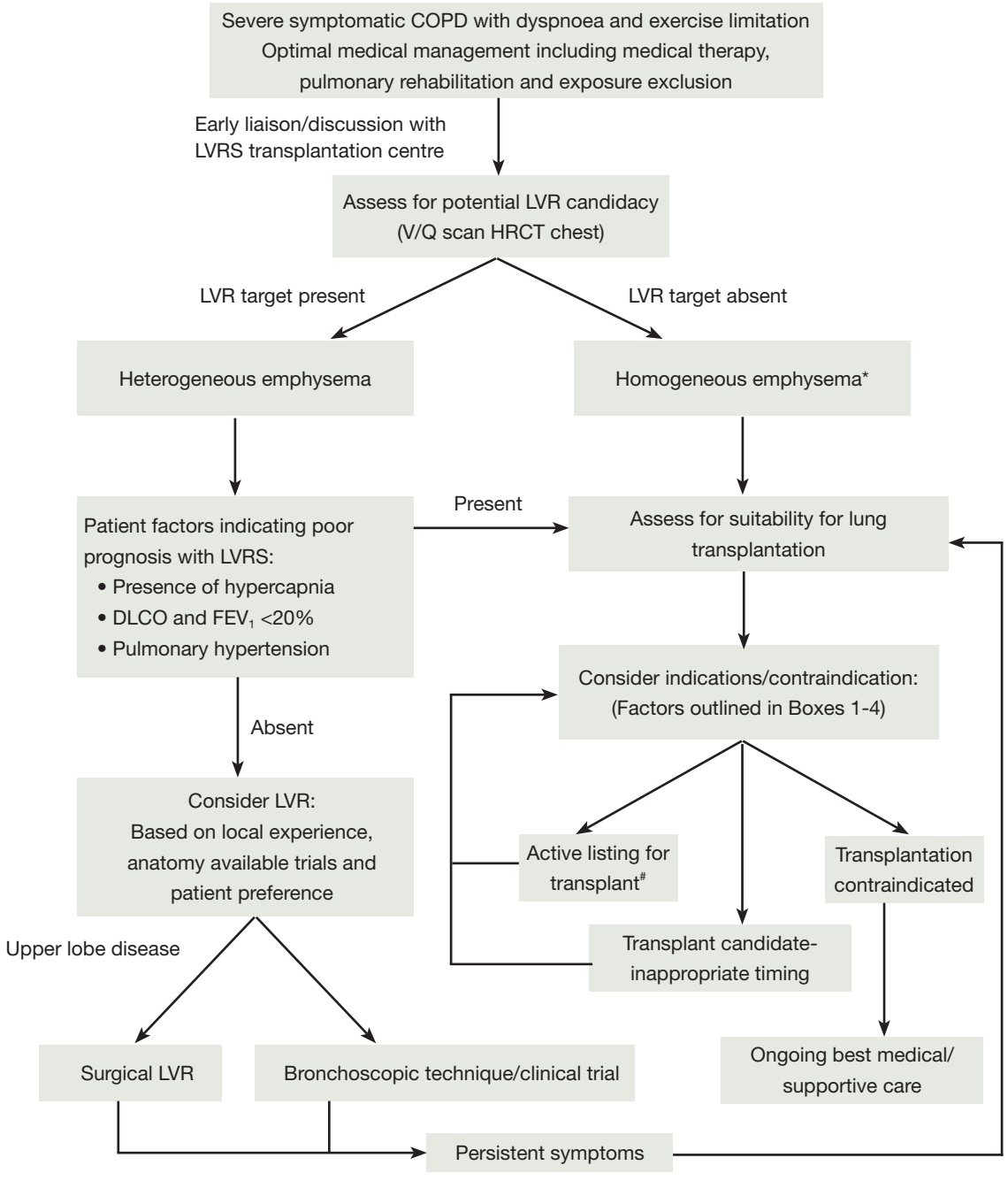

Figure 3 Suggested pathway for management of advanced COPD. *, in selected centres trial may be available for patient with homogenous disease. #, patient active on transplant waiting list require ongoing evaluation. COPD, chronic obstructive pulmonary disease; LVRS, lung volume reduction surgery; LVR, lung volume reduction.

which should prompt referral to a transplant unit in patients considered appropriate are outlined in *Table 3*.

Acute COPD exacerbations with associated hypercapnia (PCO_2 >50 mmHg) confer a poorer prognosis with associated 2-year median survival of 49% (49). This study was performed prior to NIV becoming routine for exacerbations associated with hypercapnia. A total of 89% of the study cohort survived the index admission which suggests that such exacerbations may be a marker for progressive disease and death.

Table 1 Absolute contraindication to lung transplant
Malignancy within last 2 years
Advanced untreatable disease of another major organ system
Non-curable extra-pulmonary infection
Chest wall deformity
Non-adherence with existing medical therapy
Lack of reliable social support
Substance addiction or abuse

Table 2 Relative contraindications to lung transplant
Age >65
Critically unwell (i.e., mechanical ventilation or extra-corporeal membrane oxygenation)
Limited functional status
Obesity (BMI ≥30)
Osteoporosis (particular caution with history of low impact fractures)
Colonization with resistant organisms
Presence of medical conditions which may impact on post transplant course

Table 3 Factors indicating deterioration which should prompt referral to transplant centre
Progressive disease despite optimisation of pharmacotherapy, pulmonary rehabilitation and exposure cessation
FEV_1 <30% predicted
BODE index >5
No suitable target for LVRS
Acute exacerbation with associated hypercapnia
Pulmonary hypertension despite oxygen therapy
LVRS, lung volume reduction surgery.

Scoring systems may also have a role in identifying patients with poor prognosis (50). The BODE score further uses body mass index (B), degree of obstruction (O), dyspnoea (D)-MMRC dyspnoea scale, and exercise capacity (E)-6 minute walk test (6MWT) to stratify which patients have poorer prognosis. Scores of 7-10 confer median survival of 3 years indicating patients are symptomatic, functionally limited and are likely to have a survival benefit from transplantation. The NETT trial also identified a subgroup of patients with poor prognosis. Subjects who did not undergo LVRS (control group) with low FEV_1 (<20%), and either low DLCO (<20%) or homogenous emphysema survived for a median of 3 years although this was significantly better than similar patients undergoing LVRS. Patients with refractory pulmonary hypertension despite oxygen therapy should also be considered given high waiting list mortality (51).

In appropriately selected patients, lung transplant is associated with significant improvements in quality of life and exercise capacity (52,53). Despite COPD being the leading indication for lung transplantation accounting for 33.5% of procedures worldwide, it remains a highly limited resource. The 12,602 procedures have been performed for this indication worldwide between 1995 and 2012. In the United States the lung allocation score (LAS) was introduced to objective prioritise patients on the transplant waiting lists at highest risk of mortality (54). Whilst this intervention has improved waiting time and mortality for patients with idiopathic pulmonary fibrosis, conversely COPD patients can expect to wait longer for lung allocation (55). The main barriers limiting transplantation to a minority of patients are donor organ availability and cost. Increasing the numbers of organs available for transplant can be achieved either by:

(I) Increasing the percentage of eligible donors identified or consenting to transplant. Large variation in organ donation rates worldwide reflect legal, cultural and organisation differences and has been comprehensively reviewed elsewhere (56);

(II) Changing retrieval techniques and practises. The emerging practise of donation after circulatory death (DCD), in addition to the more conventional brainstem death donors;

(III) Improving utilisation rates of organs offered for transplantation using novel technologies such as *ex vivo* lung perfusion (EVLP).

Donation after circulatory death (DCD)

DCD is not a new concept, reintroduced clinically in 1995 (57), but not widely practised due to concerns about prolonged warm ischaemic time and inferior organ assessment opportunity. Donation after brain stem death (DBD) has been the traditional source of donor lungs. Over the last decade, DCD has emerged as a significant pool of donor organs enabling an increase in transplant volume. Since the 2006 introduction of lung DCD programmes in Australia, 12.4% of organs have been acquired from DCD (58). By 2010 this represented an extra 28% of donors being utilised. The Maastrict classification established in 1995 describes the different circumstances whereby DCD organ donors may be procured (59). Briefly, Maastrict categories I and II refer to uncontrolled deaths in patients deceased

Table 4 Conventional criterion for acceptance of lung donors
Age <55
PaO_2 >300 mmHg (5 mmHg PEEP FiO_2 100%)
Clear chest X-ray
Less than 20 pack years smoking
Absence of chest trauma
Absence of prior thoracic surgery
Absence of aspiration or sepsis

on arrival at hospital or with unsuccessful resuscitations attempts respectively. Category III-death after controlled withdrawal of supportive treatment (usually in an intensive care unit) describes the majority of DCDs in Australia, USA and Europe (excluding France and Spain where category II donors are more common) (60). Categories IV and V refer to circulatory collapse after brainstem death and inpatient cardiac arrests respectively-these are not common modes of organ procurement.

Clinical outcomes of patients receiving DCD lungs are comparable to that of conventional lung donors (58,61,62). The Australian DCD collaborative is the largest reported series of exclusively Maastrict III donors (58). Short and long term DCD outcomes are similar to that of DBD patients over the same time period. Among 72 patients receiving DCD lungs, 1 and 5 year survival was reported at 97% and 90% respectively (90% and 60% for 503 patients undergoing DBD during the same time period). Incidence of primary graft dysfunction (PGD) and bronchiolitis obliterans syndrome was similar between groups. This supports the notion that group III DCD donors which otherwise meet conventional acceptance criterion (*Table 4*) should not be considered 'marginal'. This is in contrast to practise in other centres where EVLP has been routinely employed for all DCD lungs (63).

Ex vivo lung perfusion (EVLP)

Lung transplantation is dependent on the availability of organs from suitable donors. Respiratory complications in potential lung donors contribute to a low proportion of organs proceeding to transplantation. Common donor mechanisms of death-chest trauma, aspiration, ventilator associated pneumonia, barotrauma and systemic inflammatory response syndrome all impact on organ utility. Transplant physicians exercise caution when assessing potential donor lungs to minimise the risk of morbidity and mortality from PGD-a condition associated with inferior short and long term outcomes (64). It is seen more frequently in patients where there is deviation from traditional donor acceptance criterion (*Table 4*) (65). These parameters will minimise the risk of PGD but lead to a low proportion of potential donors converting to transplant. Of organs offered for transplant a low proportion—15% to 20%—are utilised (66). Strategies to safely increase the number of "marginal" donors-those organs with clinical features/parameters deviating from traditional acceptance-will have an impact on numbers of patients able to undergo transplantation. Reported results from some larger transplant centres suggest those traditional acceptance criterions are overly stringent (67) with transplantation being safely undertaken where the donor does not fully adhere to this criteria. Recognition that these criteria are not absolute may be contributing to recovery of a higher proportion of organs (68). EVLP is a further tool that has potential to further improve this trend.

EVLP is used in the assessment and reconditioning of donor lungs. The technique was first introduced by Steen *et al.* in 2001 for graft assessment after Maastrict II DCD (69). The Toronto group recognised the potential of the technique for addressing donor respiratory complications. Refinement to the process means that lungs previously discarded can be reconditioned, re-assessed and if suitable transplanted (70). Potential indications for the use of EVLP although not standardised reflect deviation from traditional acceptance criterion (63,71):

(I) PaO_2/ FiO_2 <300 mmHg with PEEP 5 cm H_2O;
(II) Infiltrates on CXR (pulmonary oedema/pneumonic consolidation);
(III) Poor lung compliance or PEEP dependent donor lungs;
(IV) Questionable aspiration history;
(V) Logistical difficulties resulting in anticipated prolonged cold ischaemic time.

As outlined above, procurement of DCD donors has been used as an indication for EVLP (63) although other centres have demonstrates satisfactory DCD outcomes without this additional assessment (58). Controversy exists with regard to EVLP in where it should be employed. As mentioned above, a proportion of marginal donors can be utilised without EVLP assessment without compromising outcomes (67); given this more work is required to redefine the boundaries of donor conventional donor acceptability. Such studies may define where marginal lungs could be utilised without EVLP-without this information there is a

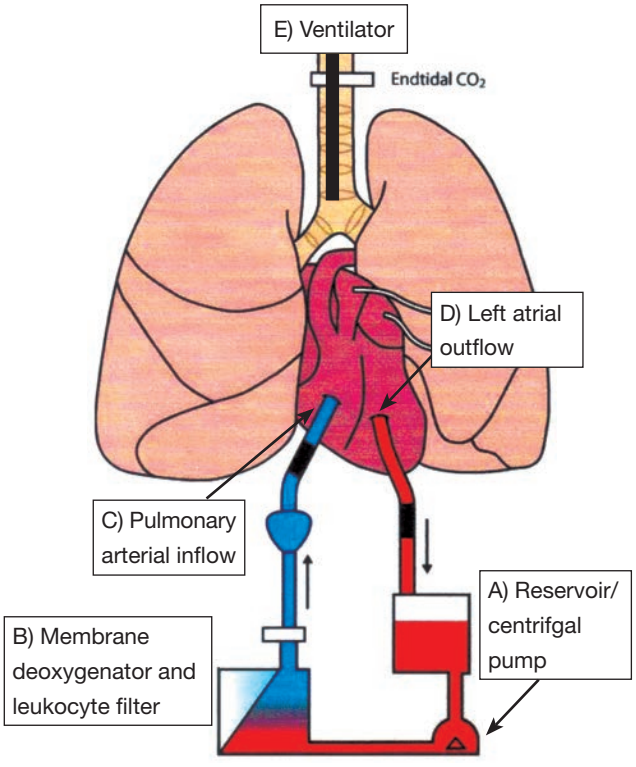

Figure 4 Summary diagram of the EVLP circuit: (A) steen solution™ and blood are circulated via a centrifugal pump; (B) a membrane de-oxygenator allows assumption and regulation of gas pressures equivalent to mixed venous blood. The leukocyte filter minimised leukocyte mediated tissue injury; (C) the pulmonary artery is cannulated. Pulmonary arterial pressure is monitored and flow rate regulated to prevent oedema; (D) left atrial outflow is sampled allowing graft assessment; (E) gentle ventilation commences at a temperature of 32 ℃ full ventilation at 37 ℃ prior to graft assessment. EVLP, ex vivo lung perfusion.

risk that the technique could become standard of care prior to these limits being clarified.

The EVLP circuit consists of a sterile chamber housing the donor lungs, centrifugal pump circulating the perfusate, leucocyte filter and membrane de-oxygenator (*Figure 4*). Two differing protocols are currently used and referred to as Lund protocol (72) and Toronto protocol (64), although the general principles are common to the two methods. The perfusate provides above normal oncotic pressure and inhibits endothelial leucocyte interaction, generation of reactive oxygen species and thrombogenesis. Gradual warming of the solution occurs to 37 ℃ allowing restoration of cellular metabolic pathways permitting return to physiological conditions at normothermia. Antibiotics can be administered and interstitial oedema improved via hyperosmolar perfusate mediated fluid shifts. Lungs are connected at an initial perfusate temperature of 15 ℃; at a temperature of 32 ℃ gentle ventilation is commenced with recruitment manoeuvres enabling re-expansion of lobar or segmental collapse. Bronchoscopy may also be performed to assess for and remove secretions from the tracheo-bronchial tree.

Initial data suggests that outcomes with EVLP are similar to conventional lung transplants (63,71,73,74). The HELP study prospectively assessed the role of EVLP in a non-randomised clinic trial (63). A total of 306 donor offers were assessed; 111 donors proceeded directly to transplant whilst 23 underwent EVLP management having met pre-defined high risk criterion. Of these EVLP conditioned donor lungs 20 were successfully transplanted (3 EVLP assessments were deemed unsatisfactory for transplant). No significant differences in PGD or mortality were seen to 30 days compared with control subjects undergoing standard transplantation procedure. The same group report later reported EVLP conditioned lungs accounting for 20% of their transplant activity-significant given these organs would otherwise not be utilised (71). Larger multicentre trials are currently underway aiming to confirm these preliminary findings—that EVLP can be safely used to increase donor number (75).

Conclusions

Despite the high prevalence of advanced COPD, current therapeutic options in medically optimised patients are available to a minority. For LVRS, the NETT trial showed that patient selection is critical to outcome and limits the availability to those patients with heterogeneous upper lobe disease. The procedure comes with a risk of morbidity and mortality which has led to the development of less invasive methods of LVR. With time, these may improve accessibility for patients. At present the evidence is insufficient to firmly recommend bronchoscopic LVR methods. Endobronchial valves, the most comprehensively evaluated technique, require lobar isolation and CV to be absent. Work is currently underway to further develop patient selection pathways to prospectively predict who may benefit. Non CV dependent techniques (BTVA and LVRCs) are promising, but require larger randomised trials to confirm efficacy and their safety. In patients for whom LVR is not an option due to absence of an LVR target or contraindications, lung transplantation may be considered.

Its widespread application is limited by cost, rigorous selection criterion and organ availability. Work is underway to improve the accessibility of this limited resource. EVLP is an emerging technique which may assist with this by increasing the proportion of potential donors utilised with early data suggesting such transplants comparable to conventional procedures. Further work is required to define indications for EVLP and conversely circumstances where conventional organ acceptance criterion can be confidently extended.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Trotter MA, Hopkins PM. Advanced therapies for COPD—What's on the horizon? Progress in lung volume reduction and lung transplantation. J Thorac Dis 2014;6(11):1640-1653. doi: 10.3978/j.issn.2072-1439.2014.11.34