PCD are slowly being unravelled, owing to the multiple phenotypes of the disease and more than 200 different proteins used to construct the ciliary axoneme, it is likely to be some time before such tests and more than 200 different proteins to the multiple phenotypes of the disease PCD are slowly being unravelled, owing to the multiple phenotypes of the disease PCD are slowly being unravelled, owing to the multiple phenotypes of the disease.

The diagnostic service is able to accept appropriate referrals from hospital consultants. However, the service does not extend to providing care for patients diagnosed with PCD. As experience of care for patients with PCD is limited, we would suggest a model similar to that for CF where patients should have access to a specialist paediatric respiratory consultant or thoracic physician with an interest in CF or non-CF bronchiectasis and be followed up regularly for life. The diagnostic service will allow a national database of patients with PCD to be established, facilitating clinical trials to help provide an evidence base for management. An active PCD patient and parent support group has been established which we encourage newly diagnosed patients to contact (www.pcdsupport.org.uk).


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Nevertheless, identifying relevant biomarkers—although the key—is only the first step and thereafter validation becomes critical. Despite this, there is now a profusion of papers looking at both the local and systemic inflammatory processes in COPD, often compared with healthy smokers, patients with COPD who are undergoing exacerbations of their disease (when inflammation increases) and comparing these markers with lung function. This has, however, raised a significant problem of how to interpret such studies.

Although many potential mechanisms have been implicated in the pathophysiology of COPD, the role of proteolytic enzymes has been dominant for over 40 years. This is related to the initial observation that patients with \( \alpha_1 \) antitrypsin deficiency (a genetic deficiency of a key serine proteinase inhibitor) were particularly susceptible to developing emphysema. Since animal models showed that the instillation of enzymes normally controlled by \( \alpha_1 \)-antitrypsin into the lungs produced emphysema, the proteinase/antiproteinase theory of COPD has evolved.\(^7\) This is based on the concept that proteolytic enzymes can produce many of the clinical and pathological features of patients with COPD, and that inflammatory processes lead to the release of proteolytic enzymes within the lungs. Excess release of such proteinases, or a net reduction in the inhibitors required to control them, would lead to persistent enzyme activity and tissue damage producing the features of COPD.\(^7\)

This simple concept initially related to serine proteinases and the serine proteinase inhibitors \( \alpha_1 \)-antitrypsin (produced by the liver) and secretory leucoproteinase inhibitor which is produced locally. However, it has since become clear that such a straight pathway is an oversimplification and a cascade of proteinases and proteinase inhibitors interact, even if the common final pathway is tissue damage caused by neutrophil serine proteinases (fig 1). Furthermore, the use of a series of transgenic or knock-out mice has indicated that this protease cascade is linked to other critical steps in the inflammatory pathway, including TNF\( \alpha \) and its receptor.\(^6\) For this reason, TNF\( \alpha \) itself may be an important biomarker for the link between inflammation and tissue damage, and TNF\( \alpha \) has been implicated in the systemic effects of muscle wasting.\(^7\) However, taking this forward provides a significant challenge of relating a local problem within the lung to a systemic inflammatory process where sampling and co-morbidities create confounding issues. In addition, the validation of biomarkers suffers from the problems of cross-sectional versus longitudinal observations, and whether the markers being identified are predictive or reflective of the disease process being studied.

An ideal biomarker is a direct indicator of the process being studied. It has to be reproducible, easily measured and would have to be sensitive to effective interventions. For instance, TNF\( \alpha \) has been implicated in the pathogenic processes of insulin resistance in humans.\(^7\) This concept is supported by studies of the obese insulin resistant mouse which showed that antagonism of TNF\( \alpha \) leads to the development of insulin sensitivity.\(^7\) TNF\( \alpha \) has also been implicated in osteoporosis,\(^7\) and specific interventions not only lead to an increase in bone thickness but also a reduction in TNF\( \alpha \) production.\(^11\) In vascular disease, several recent studies have indicated that measuring serum C-reactive protein (CRP) predicts future vascular events,\(^12\) and CRP has also been implicated in the pathophysiological pathway leading to atheroma.\(^1\) Studies have also shown that statins not only reduce cholesterol but can reduce CRP,\(^14\) which could account for the subsequent reduction in cardiovascular events.

With this as a background, similar approaches are now being undertaken in COPD. For instance, CRP in the plasma is increased in COPD\(^11\) and can predict the likelihood of future outcomes,\(^12\) although it is difficult to implicate this acute phase protein in the pathophysiology of COPD. Indeed, it is more likely to be secondary as it is known that interleukin (IL)-6 stimulates CRP production in hepatocytes although IL-6 is a pro-inflammatory cytokine, it also has yet to be clearly implicated in the pathophysiological processes in COPD. The dysjunction of this approach has been highlighted recently in a study demonstrating that CRP has predicted mortality in COPD.\(^14\) The accompanying editorial clearly reminds readers that this may not reflect mortality from COPD (and hence pathophysiology of the disease) but, rather, other vascular events.\(^16\)

There have been many studies of numerous other mediators in COPD which relate them to lung function, although often studies apparently showing a correlation almost certainly reflect two populations (ie, healthy smokers with one range for the mediator and patients with COPD who have reduced FEV\(_1\) and a different range).
However, some studies do show a relationship between increasing concentrations of mediators and decreasing lung function. Nevertheless, even with such relationships, the concern regarding whether this is cause or effect remains a key issue.

Lung function in COPD shows progression with time but does not follow a straight line. As the FEV₁ is a measure of airflow within the airways, there has to be a major change in obstruction of the small airways before the FEV₁ is affected. Thus, lung damage in COPD can progress for a long time before the FEV₁ declines, and many subjects with a normal FEV₁ are not at risk.

Once the FEV₁ starts to decline, it does so rapidly in subjects at risk. However, in the presence of severe disease, rapid decliners are less likely to survive and long-term follow-up only relates to patients whose FEV₁ decline has stabilised (the survivor effect). This produces the characteristic sigmoid curve for decline in FEV₁, and this observation has raised questions about the nature of the relationship of biomarkers to lung function. The argument has been that any biomarker that shows an increased value related to FEV₁ in a cross-sectional study is more likely to be easier if the mediator plays a general role in inflammation in COPD, and is likely to be easier if the mediator plays a recognised role in the pathophysiology rather than a general role in inflammation. With this concept in mind, it is difficult to understand or reconcile two recent studies showing that baseline CRP relates to the decline in FEV₁ in mild to moderate COPD but not in population screening. Perhaps, unlike cardiovascular disease, biomarkers in lung disease are only informative once the disease is established. Clearly these recent studies emphasise the complexity of biomarker studies during this period of their infancy.

The study of biomarkers is of major importance in developing new therapeutic strategies for chronic slowly progressive diseases. However, to be valid, the biomarker needs to fulfill several distinct requirements.

- It must be central to the pathophysiological process implicated in the disease.
- It must therefore reflect or be a very clear surrogate of that disease process.
- It must be stable and only vary with events known to relate to disease progression.
- Those at risk with a higher value at baseline must become more prevalent as disease severity or its prevalence increases.
- The biomarker must predict progression.
- The biomarker must also be sensitive to intervention factors that are known to be effective; this may prove the biggest hurdle.

However, once all these boxes are ticked, the biomarker can be used as an early read out of therapeutic efficacy with a reasonable degree of confidence.

In summary, before we get carried away with continued measurements of a multitude of factors that have some link to inflammation in COPD, it is important that we take a deep breath and rethink our concepts of the inflammatory process and design and deliver our studies appropriately and with care.


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Biomarkers in COPD: time for a deep breath

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