Novel measure of lung function for assessing disease activity in asthma

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ABSTRACT

Introduction In asthma, lung function measures are often discordant with clinical features such as disease activity or control.

Methods We investigated a novel technique that provides a measure (cCL) of unevenness (inhomogeneity) in lung inflation/deflation. In particular, we compared cCL with FEV, % predicted (FEV, %pred) as measures of disease activity in the asthmatic lung.

Results cCL correlated modestly with FEV, %pred. However, cCL is not simply a proxy for FEV, %pred as the effects of salbutamol on the two parameters were unrelated. Importantly, cCL reflected disease control better than FEV,.

Discussion We conclude that cCL shows promise as an objective measure of disease activity in asthma.

INTRODUCTION

In asthma, lung function measures, such as spirometry, are often discordant with the clinical assessment of disease activity, as determined by symptoms, exacerbation frequency and response to treatment.1 2 There is no single diagnostic test for asthma, and both clinical assessment of symptoms and objective tests can produce false positives and false negatives.3 Spirometry may be normal in patients with active airways disease, and the diagnosis of asthma, for example, may require multiple measurements over time to demonstrate variable airflow obstruction. In addition, age-related changes in FEV, or fixed airflow obstruction may lead to overdiagnosis or treatment in older people. This disparity, alongside the fact that primary care clinicians may not have access to reliable lung function testing at the point of clinical decision-making, often leads clinicians to adopt a no-test approach to diagnosis and treatment.

Recently, Mountain et al. described a new approach to lung function testing that involved assessing the inhomogeneity of gas exchange in the lung.4 This study is a first look at whether this technique has the potential to provide a better measure of disease activity in the lungs of asthmatic patients than standard spirometry.
Details are given in the study by Mountain (standardised) deadspace across the lung volume. Further \( \sigma \) across the lung volume, respectively. The third measure is standardised alveolar compliance and vascular conductance which are the SDs for the log-normal distributions of (standardised) deadspace across the lung volume at FRC and three measures of inhomogeneity. Two of the inhomogeneity measures are \( \sigma_{\text{CL}} \) and \( \sigma_{\text{Cd}} \), which are the SDs for the log-normal distributions of (standardised) alveolar compliance and vascular conductance across the lung volume, respectively. The third measure is \( \sigma_{\text{VD}} \), which is the SD for the normal distribution for the (standardised) deadspace across the lung volume. Further details are given in the study by Mountain et al.\(^4\) The present study focuses particularly on \( \sigma_{\text{CL}} \) as a measure of unevenness of lung inflation/deflation during breathing.

**Data analysis**

The following analyses were conducted on the data: (1) values for \( \sigma_{\text{CL}} \) and other model parameters were compared between the healthy volunteers and asthma patients; (2) the correlation between \( \sigma_{\text{CL}} \) and FEV\(_1\)\% predicted (FEV\(_1\)\%pred) was calculated; (3) the effects of salbutamol on \( \sigma_{\text{CL}} \) and FEV\(_1\)\%pred were compared; (4) the relationship between symptom severity (as assessed by the patients’ clinicians using the ACQ5 asthma control questionnaire) and \( \sigma_{\text{CL}} \) was explored and (5) the ability of \( \sigma_{\text{CL}} \) versus FEV\(_1\)\%pred to predict overall disease control was examined. A pragmatic approach was used to define disease control based on whether the clinician intended to escalate therapy (‘bad control’) or not (‘good control’), based on their overall assessment.

Pearson correlation coefficients were used to explore relationships/correlation between variables. A Shapiro–Wilk test of normality was performed on the data and Student’s unpaired t-tests were used to compare parameter values between healthy versus asthma groups. Logistic regression analysis was used to explore the predictive power of \( \sigma_{\text{CL}} \) versus FEV\(_1\)\%pred in terms of disease control.

**RESULTS**

Values for \( \sigma_{\text{CL}} \) were significantly larger in asthma patients compared with healthy volunteers (figure 2A). Values for other model parameters and FEV\(_1\)\%pred are provided in the online supplementary file.

There was a significant correlation between \( \sigma_{\text{CL}} \) and FEV\(_1\)\%pred (figure 2B), but the majority of the variance (71\%) in \( \sigma_{\text{CL}} \) was unexplained by FEV\(_1\)\%pred. Following salbutamol, \( \sigma_{\text{CL}} \) fell in the patients with asthma, but the effects of salbutamol on \( \sigma_{\text{CL}} \) were independent of whether the patients showed FEV\(_1\) bronchodilator reversibility (figure 2C,D). Indeed, for patient 1 in figure 2, FEV\(_1\) rose following salbutamol by 193\% while \( \sigma_{\text{CL}} \) hardly changed (0.55 to 0.57), demonstrating that \( \sigma_{\text{CL}} \) is not a surrogate for FEV\(_1\)."
DISCUSSION
The results indicate that σCL is not simply a proxy for FEV₁%pred, but rather that it captures different aspects of the disease’s pathophysiology, beyond airflow obstruction. FEV₁ changes are generally thought to arise from hyper-reactivity of smooth muscle in the large airways resulting in increased airways resistance. In contrast, σCL may preferentially reflect the effects of hyper-reactivity of smooth muscle in the small airways through an effect on ventilation distribution. An alternative hypothesis is that σCL reflects small airways inflammation. Small airways inflammation is associated with localised oedema which increases the stiffness of that part of the lung. As the distribution of disease across the lung tends to be uneven, then so too is the distribution of stiffness. This mechanism can explain an increase in σCL without invoking any change in airways resistance. Indeed, distinct mechanisms of action of salbutamol on σCL (enhanced lung water clearance) and FEV₁ (smooth muscle relaxation in large airways) may explain why the effects of salbutamol on σCL were similar for both FEV₁ responders and non-responders to salbutamol.

Neither FEV₁%pred nor σCL correlated significantly with symptoms. Patient 2 (figure 3) had a very high symptom score but had normal values for σCL and FEV₁%pred (0.53 and 91%, respectively). On review of these patients’ clinical records, their symptoms appeared to have a multifactorial origin including significant nasal/upper airway symptoms, breathlessness from hyperventilation/dysfunctional breathing, depression and fibromyalgia. This patient demonstrates the value that an objective measure of disease activity within the lung could
Figure 3  σCL reflects disease activity more tightly than FEV, % predicted (FEV, %pred). (A) and (B) FEV, %pred and σCL as a function of ACQ5 asthma control questionnaire score, respectively. Neither variable correlated significantly with symptoms (Pearson’s r=−0.27, p=0.40 and r=0.43, p=0.15 for FEV, %pred and σCL, respectively). The patient labelled (2) is considered further in the Discussion. (C) and (D) FEV, %pred and σCL by physicians’ assessment of ‘disease control’, respectively. ‘Good control’ was defined as therapy either unchanged or reduced at clinic visit, ‘bad control’ was defined as therapy increased at clinic visit. There was no significant difference in FEV, %pred between the two groups (p=0.81 Student’s t-test). σCL was significantly higher in the ‘bad control’ group compared with the ‘good control’ group (p<0.05). Red symbols and lines represent means and SD, respectively. (E) and (F) Logistic regressions to predict ‘disease control’ using FEV, %pred or σCL as predictors, respectively. σCL was the better predictor, as judged by the probabilities for individual patients (left panels) and area under the curve of the receiver–operator plots, which were 0.540 for FEV, %pred and 0.802 for σCL. Data illustrated are pre-salbutamol. Post-salbutamol data are similar and are given in the online supplementary file.

have in managing asthma. Apart from this patient, the four patients with the highest symptom scores also had the highest σCL values. Indeed, without this outlier, the correlation between σCL and symptoms would have been significant (p<0.02 and p<0.01, pre-salbutamol and post-salbutamol, respectively). Unlike FEV, σCL predicted whether the physician deemed an escalation of therapy necessary. This is consistent with the hypothesis that σCL reflects small airways disease, which is increasingly recognised as associated with severe refractory asthma.6 7

The technique used in this study was developed to quantify physiological aspects of lung function that cannot be obtained through standard lung function testing. To achieve this, the novel measurement technology was used to provide continuous, highly precise measurements of molar gas flows at the mouth. This precision, combined with the principles of mass balance, enables measurements of gas flow at the mouth to be linked via a computational model to the underlying physical properties of the lung, including the distribution of compliance.

Other physiological techniques that assess small airway function, including oscillometry and single or multiple exhaled breath analyses, have been used in the research setting for some years, and more recently evaluated specifically in asthma, but none has yet been adopted into routine clinical practice. This may reflect the considerable variability that has been associated with these alternative measures. The novel highly accurate gas analysis underlying our approach improves accuracy and reproducibility and allows the provision of indices that directly relate to underlying physiological properties of the lung. Although technically sophisticated, the test is simple to undertake for both the operator and the patient, with no forced breathing manoeuvres required. It is non-invasive,
does not involve ionising radiation and does not require expensive equipment and reagents such as MRI scanners and scarce isotopes. Consequently, it is well suited to clinical use. While the current study involved only a small number of participants and is preliminary, the results are promising and suggest that the method may provide a powerful new objective measure of disease activity in the lung. To determine whether this early promise is fulfilled, and if so, whether the measurement is useful in the management of asthma, will require larger studies across different patient populations using longitudinal and interventional designs and further comparisons with other available lung function techniques.

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Contributors PAR conceived the study. NMJS, NPT and NP collected the data. NMJS, JC, CJF and GR supported the data collection and analysis. NMJS, NPT, GH, IP, GADR, PAR and NP contributed to data interpretation. NMJS, PAR and NP drafted the manuscript. All authors contributed to manuscript revision and review.

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Competing interests Oxford University Innovation, a wholly owned subsidiary of the University of Oxford, owns the IP and holds/has filed patents in relation to the technology. JC, GH, GADR and PAR have an interest in one or more of these patents/filings.

Patient consent for publication Not required.

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