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. We investigated a novel technique that provides a measure (cCL) of unevenness (inhomogeneity) in lung inflation/deflation. In particular, we compared cCL with FEV₁ % predicted (FEV₁%pred) as measures of disease activity in the asthmatic lung.

Methods We investigated a novel technique that provides a measure (cCL) of unevenness (inhomogeneity) in lung inflation/deflation. In particular, we compared cCL with FEV₁ % predicted (FEV₁%pred) as measures of disease activity in the asthmatic lung.

Results cCL correlated modestly with FEV₁%pred. However, cCL is not simply a proxy for FEV₁%pred as the effects of salbutamol on the two parameters were unrelated. Importantly, cCL reflected disease control better than FEV₁.

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

Key messages

- In asthma, spirometric measurements associated with airways resistance are often discordant with other clinical features of disease activity or control.
- This study demonstrates that a novel technology measuring the evenness of lung expansion and contraction can reflect these clinical features better than spirometry.
- A reliable, objective measure of disease activity in asthma would be very valuable for both patient management and clinical research.

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. There is no single diagnostic test for asthma, and both clinical assessment of symptoms and objective tests can produce false positives and false negatives. 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 FEV₁, or fixed airflow obstruction may lead to over-diagnosis 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. 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.

METHODS

Patient and public involvement

Research into novel diagnostics for asthma is one of the research priorities for a leading UK asthma patient group. Our experimental protocol was designed after obtaining feedback from patients during pilot studies in order to optimise tolerability and acceptability during testing and in future clinical practice. Informal feedback was obtained from all participants in the current study to inform future experimental design.

Experimental methods

Seventeen patients with asthma, recruited from a hospital-based asthma clinic, and 17 healthy volunteers were studied (see online supplementary file for details). Each participant underwent standard forced spirometry and a lung inhomogeneity test before and 30 min after bronchodilation with inhaled salbutamol (400 μg via a spacer).

The lung inhomogeneity tests were performed using molecular flow sensing technology that uses laser absorption spectroscopy and provides highly precise molar flows for oxygen, carbon dioxide and nitrogen at the mouth. Participants breathed air for 10 min and then pure oxygen for 5 min through a mouthpiece connected to the molecular flow sensing device.


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A computational model of an inhomogeneous lung was fit to the gas-exchange data \(^4\) (figure 1). Briefly, the model is comprised of a ‘lung’ with 125 lung units, each with an equal share of the total volume at functional residual capacity (FRC), but differing in their fractional share of total lung compliance, of total pulmonary vascular conductance and of total deadspace. The process of fitting the model to the data is based on the principle of mass balance and provides estimates of anatomical deadspace, alveolar volume at FRC and three measures of inhomogeneity. Two of the inhomogeneity measures are \(\sigma_CL\) and \(\sigma_CD\), 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 \(\sigma_VD\), 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 \(\sigma_CL\) as a measure of unevenness of lung inflation/deflation during breathing.

Data analysis

The following analyses were conducted on the data: (1) values for \(\sigma_CL\) and other model parameters were compared between the healthy volunteers and asthma patients; (2) the correlation between \(\sigma_CL\) and FEV\(_1\)% predicted (FEV\(_1\)%pred) was calculated; (3) the effects of salbutamol on \(\sigma_CL\) 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 \(\sigma_CL\) was explored and (5) the ability of \(\sigma_CL\) 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 \(\sigma_CL\) versus FEV\(_1\)%pred in terms of disease control.

RESULTS

Values for \(\sigma_CL\) 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 \(\sigma_CL\) and FEV\(_1\)%pred (figure 2B), but the majority of the variance (71%) in \(\sigma_CL\) was unexplained by FEV\(_1\)%pred. Following salbutamol, \(\sigma_CL\) fell in the patients with asthma, but the effects of salbutamol on \(\sigma_CL\) 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 \(\sigma_CL\) hardly changed (0.55 to 0.57), demonstrating that \(\sigma_CL\) is not a surrogate for FEV\(_1\).

Figure 3A,B illustrates that neither FEV\(_1\) nor \(\sigma_CL\) correlated significantly with symptom severity in the patients. For an index of ‘disease control’, we defined control as ‘bad’ if the physician at the clinic visit before measurement deemed that an increase/escalation in therapy was necessary (either increased therapy on the day or referred further for biologic therapy). Control was defined as ‘good’ in all other patients, where the physician felt no therapy escalation was needed and either decreased or left unchanged a patient’s therapy. There was no significant difference in FEV\(_1\)%pred between patients with ‘good control’ versus those with ‘bad control’ (figure 3C). In contrast, \(\sigma_CL\) was significantly higher in patients with ‘bad control’ than those with ‘good control’ (figure 3D). Consistent with this, ACQ5 score was 1.17±0.85 (mean±SD) in the ‘good control’ group and 2.94±1.50 in the ‘bad control’ group (p<0.05).

Figure 3E,F illustrates an analysis using logistic regression which demonstrates that \(\sigma_CL\) is a better predictor of disease control than FEV\(_1\)%pred.
DISCUSSION

The results indicate that $\sigma_{CL}$ is not simply a proxy for FEV$_1$%pred, but rather that it captures different aspects of the disease’s pathophysiology, beyond airflow obstruction. FEV$_1$ changes are generally thought to arise from hyper-reactivity of smooth muscle in the large airways resulting in increased airways resistance. In contrast, $\sigma_{CL}$ 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 $\sigma_{CL}$ 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 $\sigma_{CL}$ without invoking any change in airways resistance. Indeed, distinct mechanisms of action of salbutamol on $\sigma_{CL}$ (enhanced lung water clearance) and FEV$_1$ (smooth muscle relaxation in large airways) may explain why the effects of salbutamol on $\sigma_{CL}$ were similar for both FEV$_1$ responders and non-responders to salbutamol.

Neither FEV$_1$%pred nor $\sigma_{CL}$ correlated significantly with symptoms. Patient 2 (figure 3) had a very high symptom score but had normal values for $\sigma_{CL}$ and FEV$_1$%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 2 $\sigma_{CL}$ is not a proxy measurement for FEV$_1$% predicted (FEV$_1$%pred). (A) $\sigma_{CL}$ values for healthy controls and patients with asthma. The average value for $\sigma_{CL}$ is higher in the asthma group than in the control group (0.762±0.241 vs 0.447±0.084, respectively, mean±SD, p<0.001 Student’s t-test). (B) Relationship between $\sigma_{CL}$ and FEV$_1$%pred for the asthma group. The correlation is significant (Pearson’s r=−0.54, p<0.05) but it leaves 71% of the variance in $\sigma_{CL}$ unexplained. (C) Effect of bronchodilation with salbutamol on FEV$_1$ in asthma. The asthma patients have been divided into ‘responders’ and ‘non-responders’ based on their degree of bronchodilator reversibility (responders exhibit an effect size greater than 12% with a minimum increase in FEV$_1$ of 200mL). The patient labelled (1) is discussed in the Results. (D) Effect of bronchodilation with salbutamol on $\sigma_{CL}$ in asthma. The asthma patients have again been divided on the basis of their FEV$_1$ response, as described in (C). Note that salbutamol reduces $\sigma_{CL}$ in both groups, but the effects do not differ between ‘responders’ and ‘non-responders’. In keeping with this finding, there was an absence of significant correlation (r=0.10, p=0.70) between the effect size of salbutamol on FEV$_1$ and the effect size on $\sigma_{CL}$. For (A), (C) and (D), red symbols and lines represent means and SD, respectively. For (A) and (B), data are pre-salbutamol; post-salbutamol data are similar and are given in the online supplementary file.
σCL reflects disease activity more tightly than FEV₁% predicted (FEV₁%pred). (A) and (B) FEV₁%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 FEV₁%pred and σCL, respectively). The patient labelled (2) is considered further in the Discussion. (C) and (D) FEV₁%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 FEV₁%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 FEV₁%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 FEV₁%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 FEV₁, 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 technology4 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,8 but none has yet been adopted into routine clinical practice. This may reflect the considerable variability that has been associated with these alternative measures.9,10 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 and PAR 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.

Ethics approval This study was approved by the South Central Oxford A Research Ethics Committee (17/SC/0172).

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REFERENCES
3 BTS/SIGN. British guideline on the management of asthma, 2019.