Lung Clearance Index (LCI) is Stable in Most Primary Ciliary Dyskinesia (PCD) Patients Managed in a Specialist Centre

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Lung clearance index (LCI) is stable in most primary ciliary dyskinesia (PCD) patients managed in a specialist centre: a pilot study

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Abstract
PCD is a condition in which abnormal cilia structure or function leads to reduced mucociliary clearance and obstructive lung disease. 29 patients had LCI measured in 2009 and we attempted to perform a 5 year follow up. Only 12 patients could be re-recruited, but in this small group LCI was stable over the 5 years, which confirms previous data showing spirometry is also stable in these patients over the medium term. The two patients with the highest LCI in 2009 had since died, despite one having relatively preserved spirometry at the time. This data may be used to inform sample size calculations of future studies.

Introduction

PCD is a rare, inherited condition where defects in the structure or function of the cilia cause reduced mucociliary clearance leading to repeated infection and inflammation and subsequently bronchiectasis. PCD is a heterogeneous condition caused by mutations in many different genes [1, 2].

PCD airway disease and its treatment show similarities with cystic fibrosis (CF). However in PCD the rate of decline in spirometry is less than in CF, if it occurs at all [3, 4].

Spirometry is abnormal in CF and PCD in cross sectional studies[5–7], but lung clearance index (LCI), derived from the multiple breath washout (MBW) test, is more sensitive, and is the first lung function test to become abnormal in longitudinal studies in CF[8, 9]. Longitudinal changes in LCI in PCD have not been reported. Here, we report on a small cohort of PCD patients who had MBW and spirometry in 2009-10 and five years later to investigate which measure changed more over time. We hypothesised that, as with CF, LCI would decline more rapidly than spirometry.

Methods

29 PCD patients were recruited from adult and paediatric PCD clinics at the Royal Brompton, and had a confirmed diagnosis of PCD by either genotype or ultrastructural abnormality on electron microscopy, in accordance with ERS diagnostic guidelines [10]. 13/29 patients had situs abnormalities. Patients had their first MBW in 2009-10. 12 had repeat measures five years later in 2014-15. Seven patients declined to take part, two had died and eight were lost to follow up from our centre. Median age at first visit was 14 years (range 3 to 53), 9 were males, median LCI at first visit was 11.37 (range 7.24 to 14.98) and median initial one second expired volume (FEV_1) z score was -2.93 (range -0.01 to -6.08). MBW and spirometry were performed using identical equipment and methods at both visits. MBW was carried out using a photoacoustic gas analyser (Innocor, Innovision, Denmark) in an open circuit washout using sulphur hexafluoride tracer gas, as described previously[6, 11]. LCI was calculated as the mean of at least 2 acceptable tests. All patients completed at least 2 acceptable manoeuvres.

All patients performed spirometry acceptable within ATS/ERS guidelines, except the youngest patient in the cohort (age 3 at first measurement), who is only included in the LCI analysis. Measurements were compared using the Wilcoxon matched pairs test.

Results

There was no significant difference in age, ethnicity or lung function between those re-recruited and those lost to follow up. There was no significant difference between the results in 2010-2015 (Figure) for LCI or FEV_1 z score. There was a mean difference in LCI -0.3 units (4%, p=NS); there was a mean difference in FEV_1 difference of 0.4 z scores (16%, p=NS). There was no correlation between LCI and FEV_1 z score at either visit, or change in LCI and FEV_1 z score. One patient had a 63% improvement in LCI and a 21% improvement in FEV_1, following treatment for concurrent asthma. One patient had a 34% worsening of LCI, following a clinical decline and the development of bronchiectasis; this was the youngest patient who could not perform acceptable spirometry at first visit. If these patients are removed from both analyses (LCI and FEV_1) this does not alter the conclusions and there remains no significant change.

The 2 patients who had died had the highest LCIs, including those that were lost to follow up or who declined to take part; one deceased patient also had poor spirometry (LCI 17.63 FEV_1 -5.3) but spirometry was relatively preserved in the other (LCI 18.69, FEV_1 -2.3) at the first visit.

Discussion

In this small cohort, there was no significant change in LCI or FEV_1 over 5 years, suggesting that LCI may not offer any advantage over spirometry. Highly anecdotally, a very high LCI may be a bad prognostic sign, and LCI may be more treatment-responsive than spirometry, although both need to be confirmed by a prospective study.

The chief weakness of this study is small sample size. Although 29 patients had tests in 2009-10 fewer than 50% were re-recruited. Also, as most of the patients had shared care arrangements with local hospitals, full treatment and medication history over the 5 year period is not available. Our findings should be confirmed in a larger prospective cohort study.

Our stable spirometry confirm previous studies suggesting in tertiary centres[3]. Contrary to our hypothesis, LCI did not change either, suggesting that using LCI as an end-point in long-term longitudinal studies may not offer any advantage over spirometry in PCD. However, the respective roles of spirometry and MBW in short-term intervention trials of treatment merits further study; certainly in CF, using LCI as an end-point allows sample size to be reduced[12]. These results may better allow sample sizes for larger studies to be generated.

Figure - 5 year stability of lung function measurements in PCD. There is no significant difference in LCI or FEV1 z score between the years. Patients marked "x" are have only one set of measurements. Patients marked □ and ○ have died. Dotted lines show the limits of normality.

Conflict of Interest: None

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