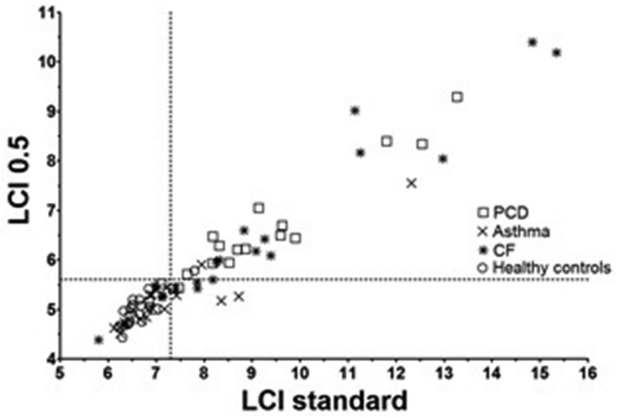

Abstract P205 Figure 1 Correlation between LCI0.5 and LCIstd. Shortened MBW, LCI0.5, correlated significantly with LCIstd with r values of 0.84, 0.96 and 0.92 in asthma, CF and PCD groups respectively. The dotted lines indicate the upper limits of normal: LCI0.5 is 5.6 and LCIstd is 7.3

with LCIstd and change following an intervention were considered.

P206 CHANGES IN INDICES DERIVED FROM MULTIBREATH WASHOUT (MBW) FOLLOWING TREATMENT WITH IVACAFTOR IN PATIENTS WITH CYSTIC FIBROSIS

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Background Lung clearance index (LCI) is a measure of gas mixing inhomogeneity derived from multi-breath wash (MBW) out techniques, which has been shown to be more sensitive than conventional spirometry/ FEV_1. The potentiator, Ivacaftor, led to improvement in LCI in patients with mild cystic fibrosis (CF) lung disease however its utility as an outcome measure in more severe disease requires further investigation. Whilst LCI reflects overall ventilation heterogeneity, analysis of the phase III slopes of successive breaths in the MBW; known as Sacin and Scond; are thought to reflect the ventilation heterogeneity generated at branch points in the acinar and conductive lung zones respectively. This study aimed to explore changes in the indices derived from analysis of MBW following a year of treatment with Ivacaftor.

Method A prospective study was performed between March 2013 and April 2014 on patients with the G551D mutation and eligible for clinically prescribed Ivacaftor. MBW (Innocor SF6 technique) and spirometry were performed immediately prior to commencing Ivacaftor, and at a clinic visit following 9–12 months therapy. FEV_1 is calculated using Stanojevic references and all data are expressed as mean (SD). Paired data were analysed with a Wilcoxon rank sum test and correlations with Spearman's rank correlation. The null hypothesis was rejected at $p < 0.05$.

Results 8 patients were enrolled with ages ranging from 6–27 years. FEV_1 increased from 68.7 (17.2)% before treatment to 80.1 (16.3)% after 9–12 months (p1 and LCI did not correlate with each other.

Discussion Patients prescribed Ivacaftor demonstrated improvements in both conventional FEV_1 and the newer measure of LCI; improvement was not limited to patients with milder disease and was seen throughout the group. In this study, the phase III slope measures did not appear to add further value to the LCI. It is possible that this reflects under powering in this small group; further data will be obtained.

P207 RELIABILITY OF MEASUREMENTS USING INNOCOR BREATH BY BREATH ANALYSER DURING A MAXIMAL EXERCISE TEST IN CYSTIC FIBROSIS PATIENTS

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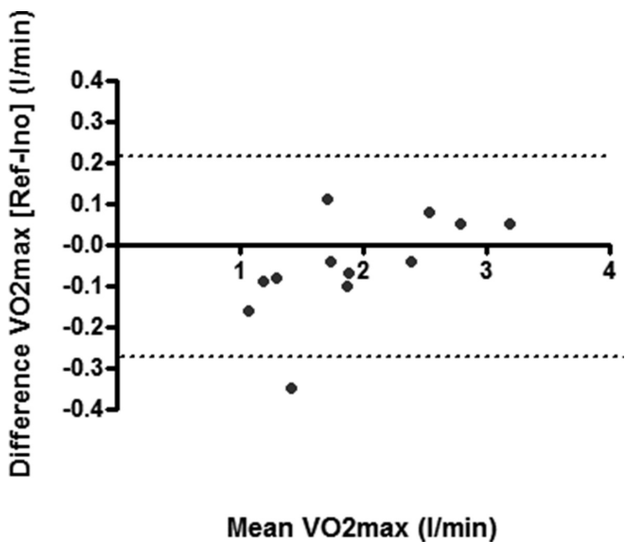
Introduction Cardiopulmonary exercising testing (CPET) is considered the gold standard to study exercise capacity as an endpoint in clinical trials. Originally the UKCFGTC used the shuttle walk test for exercise capacity measurement but this proved inappropriate for mild, fit cystic fibrosis (CF) patients in our trial cohort (FEV_1 50–90% predicted). The Innocor device uses photoacoustic gas detection technology and offers metabolic measurement but has not previously been validated for CPET in CF.

Aim To compare the Innocor with known reliable CPET machines to see if it is suitable to take forward into a multi dose clinical trial of gene therapy.

Methods 12 CF patients (7 Male, 14–47 years) participated in the study recruited from London and Edinburgh sites. They performed two incremental cycle ergometer exercise tests to exhaustion (adapted Godfrey protocol) with breath by breath analysis assessed using a reference system (Jaeger Masterscreen PFT, London; Pulmolink Medisoft, Edinburgh) or the Innocor device. All tests were randomly ordered, completed at least 24 h apart, with no more than two week's separation.

Results VO_2max and V_E max were comparable between the Innocor and reference systems ($p = 0.1790$ and $p = 0.7642$ respectively; paired t tests). For VO2max, Bland Altman analysis showed the mean difference [Reference equipment-Innocor] was -0.026 l/min and the 95% confidence interval was -0.27 to 0.22 l/min (see Figure). In our experience the Innocor heart rate (HR)



Abstract P207 Figure 1 Bland Altman plot: the difference between VO_2max measured by Innocor vs Reference methods.

recording (derived from saturation monitor) was unreliable; reading low during exercise compared to ECG-derived HR.

Conclusions This small study confirms the Innocor device can produce measures of VO_2max comparable (95% confidence interval) with standard calibrated exercise systems in CF patients with mild to moderate lung disease. We found the method for Innocor to derive HR (pulse oximetry) was not reliable compared to reference ECG especially during heavy exercise. We were subsequently able to overcome this problem by interfacing the Innocor device with a separate electrocardiographic heart rate monitor.

P208 ASSESSMENT OF CURVILINEARITY (CURV) AND PHASE III ANALYSIS OF MULTIPLE BREATH WASHOUT (MBW)

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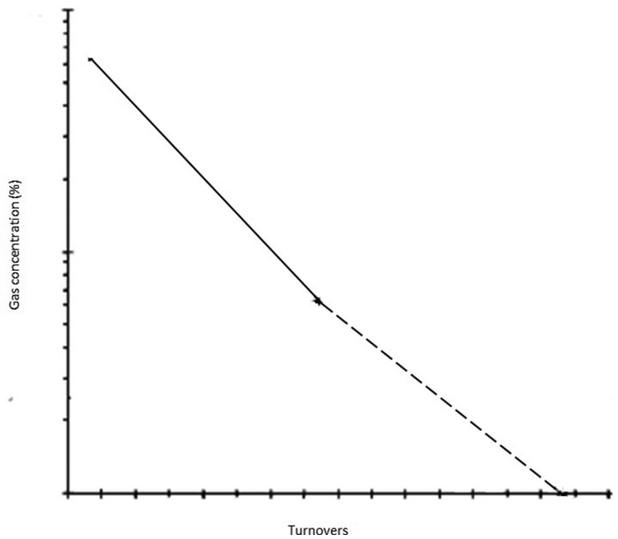
Introduction and Hypothesis In cystic fibrosis (CF), but not in PCD (Am J Respir Crit Care Med. 2013;188:545–549), lung clearance index (LCI) and spirometry are correlated. The difference may be related to differences in small airway disease. To explore this further, the novel MBW analyses Curv, S_{cond*} and S_{acin*} were calculated in PCD and CF (Eur Respir J. 2013;42 (suppl 2):380–388). Curv assesses specific ventilation inhomogeneity calculated as the ratio of the slope of the first half to the second half of the washout, and unlike LCI is not sensitive to deadspace effects. S_{cond} and S_{acin} are not useful in severe obstructive lung disease; S_{cond*} and S_{acin*} are recalculations corresponding respectively to VI in the conducting airways and the acinar region. (S_{cond*} is measured from the slopes of the increase in phase III modified to include the 0–3 lung turnovers and S_{acin*}* is phase III over the first breath of the washout, minus the contribution of S_{cond*}). We hypothesised that these novel indices will differ in PCD compared to CF due to differences in small airways disease.



Abstract P208 Figure 1 Gas concentration (y axis, log scale) over the course of an MBW, plotted against turnovers (x axis). Solid line shows gradient of line from start to LCI/2, dotted line shows gradient of line from LCI/2 to full LCI. Cury is expressed as the ratio of these two slopes. In health, slopes are similar and Cury is approaching zero, in disease, doffed slope is increasingly flat, giving an increased Cury value approaching 1

Methods 38 PCD (14 male, group mean (range) age 21.8 (7.2–59.1) years, FEV1 Z score -3.18 ((-6–0.17)) and CF (14 male, group mean (range) age 10.9 (6.8–19.1) years, FEV1 Z score -2.72 ((-5.4–0.9)) patients matched for P. aeruginosa status and 24 healthy controls recorded spirometry and MBW. LCI, Curv, Scond* and Sacin* were calculated.

Results There was no difference in LCI, FEV_1 and Curv between the patient groups. LCI was correlated with S_{cond*} (CF $p = 0.0006$, $r = 0.5$, PCD, $p = 0.03$ $r = 0.3$), S_{acin*} (CF $p < 0.0001$, $r = 0.7$, PCD $p < 0.0001$, $r = 0.6$) and S_{acin} (CF $p < 0.0001$, $r = 0.7$, PCD $p = 0.0003$, $r = 0.5$), whereas S_{cond} was not. There was no difference in S_{acin*}* between the groups, but S_{cond*} was significantly lower in PCD, approaching that of healthy controls.

Conclusions Curv is similarly impaired in PCD and CF. S_{cond*} is nearly normal in PCD but not CF, supporting the hypothesis that there are differences in distal airway disease between these conditions. Finally, the results suggest that the new indices may be better discriminators between diseases in severe obstructive lung disease.

P209 STANDARDISATION OF LUNG CLEARANCE INDEX IN A MULTICENTRE CLINICAL TRIAL

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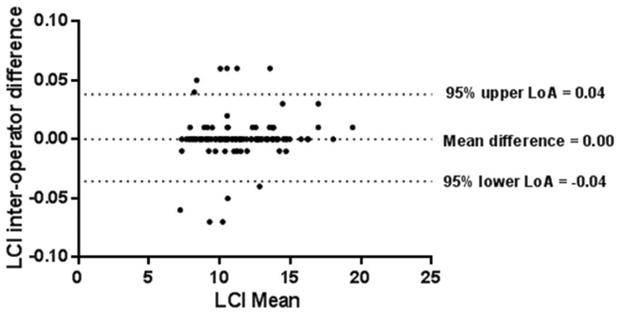
Introduction Lung clearance index (LCI) is a sensitive and repeatable non-invasive measure of ventilation inhomogeneity derived from the multiple breath washout (MBW) technique. It is more sensitive to early lung disease than traditional lung function measurements. Before it can be adopted as a primary endpoint in multicentre trials, it must be demonstrated that it can be applied with minimal inter-operator variability. LCI is a major secondary outcome in our gene therapy multidose trial.

Aim To assess LCI achievability and intra- and inter-site agreement.

Method 136 CF patients at two sites with FEV_1 50–90% predicted were randomly allocated on a 1:1 basis to receive 12 monthly nebulised doses of active gene therapy product or placebo. LCI was performed in triplicate on seven occasions for each subject using a MBW technique completed on an Innocor™ device using 0.2% SF_6. Stringent quality control criteria have been developed, including offset calculations and minimal acceptable differences between tests. LCI was calculated using



Abstract P209 Figure 1 Bland-Altman plot of LCI inter-operator difference