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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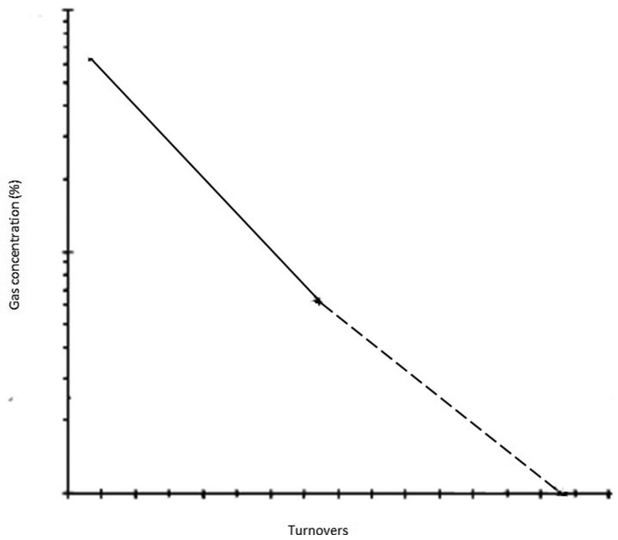
Introduction and Hypothesis In cystic fibrosis (CF), but not in PCD (Am J Respir Crit Care Med. 2013;188:545–549), lung clearance index (LCI) and spirometry are correlated. The difference may be related to differences in small airway disease. To explore this further, the novel MBW analyses Curv, S_{cond*} 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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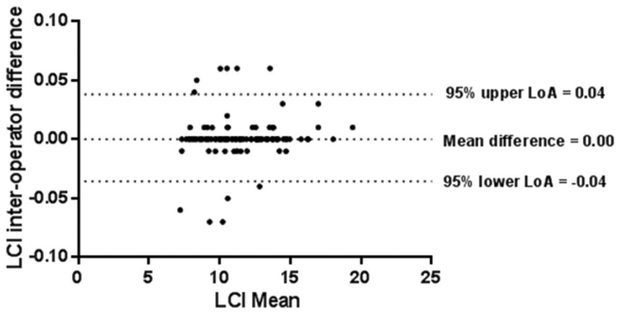
Introduction Lung clearance index (LCI) is a sensitive and repeatable non-invasive measure of ventilation inhomogeneity derived from the multiple breath washout (MBW) technique. It is more sensitive to early lung disease than traditional lung function measurements. Before it can be adopted as a primary 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

customised offline analysis software (SimpleWashout, Igor Pro) by a single operator at each site. To test inter-operator agreement, every seventh MBW from each timepoint was randomly selected, without subject duplication, and used to calculate LCI values by both operators separately.

Results A total of 854 LCIs were performed during the trial, and technically acceptable measurements were achieved in 95.9% and 94.2% of tests at the two sites (mean 94.8%). 118 (13.8%) of LCIs were analysed independently by two operators, with a full range LCI values represented (range 7.24–19.21). The 95% limits of agreement (LoA) for LCI values were -0.04 to 0.04 (mean difference 0.00) and for FRC values were -0.01 to 0.01 (mean difference 0.00).

Conclusions Our results demonstrate that LCI is an achievable outcome measure in a multicentre trial in 94.8% of attempts. Separate offline analysis completed by two operators, with appropriate training and knowledge of the test, produces mean LCI and FRC inter-site differences of 0.00. LCI is feasible and appropriate for use as a surrogate endpoint in multicentre clinical trials using stringent methodology.

P210 AIRWAYS RESISTANCE IN BRONCHIAL CHALLENGE TESTING

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Introduction Measurement of airways resistance is an alternative to spirometry to assess airflow obstruction. This can be measured by the interrupter technique (RInt) using a hand held device. We wished to know how RInt compared to forced expiratory volume in 1 second (FEV1) during a histamine challenge test.

Methods Twenty-nine (13 male) patients, aged 48.9 (SD 15.3) years, referred for a histamine challenge test were enrolled. Patients had measurement of RInt then FEV1 after administration of saline and following doubling concentrations of histamine from 0.06 mg/ml to 8 mg/ml. Extrapolation of the log dose-response curve was undertaken to calculate the concentration (Provocation Concentration – PC) causing an increase airways resistance of 20, 40, 60, 80, 100, 120, 140 and 160% (RInt PC1.2 to RInt PC2.6) and a reduction in FEV1 by 20% (FEV1 PC20). The number of patients with a negative challenge (i.e. PC > 8 mg/ml histamine) was calculated for FEV1 and each change in airway resistance. Patients assessed their procedure provoked symptoms of breathlessness, dizziness and tiredness on a 100 mm visual analogue scale.

Results Geometric (SD) PC20 for FEV1 was 1.87 (0.5) mg/ml with 11 patients having a negative challenge. A RInt PC2.0 had the best agreement with FEV1 PC20 (Kappa 0.39 (p = 0.024)). There is a significant negative correlation between RInt and FEV1 (r = -0.94). The respective mean (SD) breathlessness, dizziness and tiredness scores for RInt were 26(4) mm, 18(3) mm, 22(4) mm and for spirometry were 40(4) mm, 27(5) mm, 31(5) mm. There was a significant (p < 0.05) difference for breathlessness.

Conclusion RInt was tolerated better than spirometry. A doubling of airways resistance had the best agreement with PC20 FEV1.

P211 FEV1/FIV1 INDEX IN AMYOTROPHIC LATERAL SCLEROSIS PATIENTS

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Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive, presently incurable, neurodegenerative disorder that causes muscle weakness, disability, and eventually death. The ALS Functional Rating Scale (ALSFRS-R) is a validated rating instrument for monitoring the progression of disability in patients with ALS. The ALSFRS-R incorporates questions for the assessment of dyspnoea, orthopnea, and the need for ventilatory support. However, studies on the relationship of ALSFRS-R with objective measurements of respiratory function are scanty. Therefore, we set out to investigate the relationship of ALSFRS-R with respiratory function indices in ALS patients.

We studied 33 consecutive, ambulatory, Caucasian patients (21 men) with ALS. Seventeen patients had bulbar involvement. Two patients did not satisfactorily perform the lung function testing and they were excluded. ALSFRS-R was assessed. Routine lung function tests, maximum static expiratory (Pemax) and inspiratory (Pimax) mouth pressures were measured. Respiratory muscle strength (RMS) was also calculated.

ALSFRS-R (mean±SD) was 35 ± 9. Patients had: age, y=60 ± 10, FEV_1,%pred=83 ± 18, FVC,% pred=86 ± 20, TLC,% pred=94 ± 11, and DL_{CO},% pred=92 ± 18. Pemax,% pred was 80 ± 28, Pimax,% pred was 73 ± 31, and RMS,% pred was 77 ± 27. These pressures were below the normal limits in 15, 20, and 17 patients, respectively. ALSFRS-R was significantly correlated with Pemax%pred, RMS%pred, and FEV_1/FIV_1 (r = 0.46, p < 0.01; r = 0.38, p = 0.035; n = 20, r=-0.71, p < 0.001, respectively).

Abstract P210 Table 1

Measure	Fall in FEV_1 of 20% (FEV_1 0.8)	RINT increase 20% (1.2)	RINT increase 40% (1.4)	RINT increase 60% (1.6)	RINT increase 80% (1.8)	RINT increase 100% (2.0)	RINT increase 120% (2.2)	RINT increase 140% (2.4)	RINT increase 160% (2.6)
Geom mg/ml	1.88	0.90	1.05	1.47	2.10	3.18	4.29	2.00	1.46
(SEM)	0.51	0.37	0.39	0.48	0.63	0.80	0.87	0.82	0.72
PC20 >8mg/ml (number of patients)*	11	13	12	13	14	16	19	21	23
Kappa (p)		0.15 (0.41)	0.21 (0.26)	0.29 (0.11)	0.37 (0.039)	0.39 (0.024)	0.24 (0.149)	0.24 (0.149)	0.24 (0.149)

FEV1: Forced expiratory volume in 1 second, RInt airways resistance using the interrupter technique, Geom: geometric mean, mg; milligram, ml: millilitre, PC: provocation concentration (the concentration of histamine required to produce the desired effect), * The number of patients with a PC more than 8mg/ml i.e. deemed not to have asthma.