Institute of Child Health, London, UK; [2]Centre for Paediatric Epidemiology and Biostatistics, UCL Institute of Child Health, London, UK; [3]Respiratory Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [4]Department of Paediatric Respiratory Medicine, Imperial College and Royal Brompton and Harefield Hospital NHS Foundation Trust, London, UK; [5]Department of Paediatric Respiratory Medicine, King's College Hospital NHS Foundation Trust, London, UK

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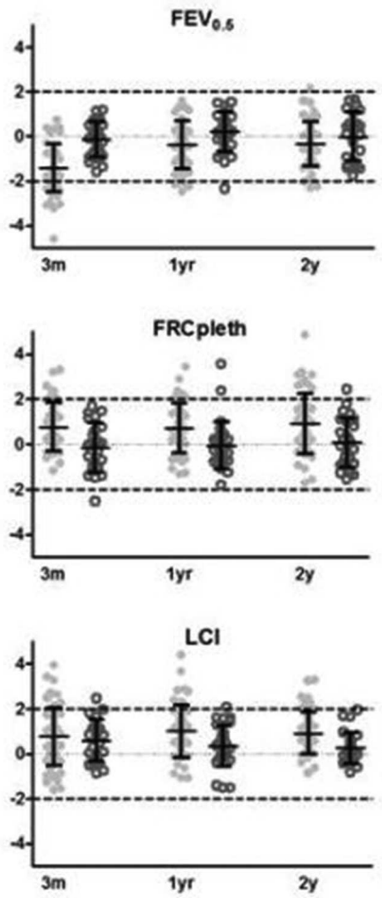
Background In contrast to findings from the Australian AREST-CF study1 infants with cystic fibrosis (CF) diagnosed by newborn screening (NBS) participating in the London CF Collaboration (LCFC) study2 were found to have relatively mild lung disease by 1 year of age when compared to healthy controls.
Hypothesis In NBS CF infants, lung function remains stable to 2 years.
Methods Lung clearance index (LCI), plethysmographic functional residual capacity (FRC) and forced expiratory volume ($FEV_{0.5}$) from the raised volume technique were measured in NBS CF infants and healthy controls at 3months (3m), 1year (1y) and 2 years (2y). Results were expressed as z-scores using equipment-specific equations to adjust for age, sex and body size.
Results To date, 55 CF and 28 control infants have been assessed on all 3 occasions. The mildly elevated LCI and FRC in CF infants identified by 3m when compared with controls remained stable thereafter. The significant reduction in $FEV_{0.5}$ (mean difference (95% CI) -1.26 (-1.73; -0.79) z score) among CF infants at 3m had improved by 1y (see Figure 1). From 1 to 2 years all 3 measurements remained stable with no significant changes in average z-scores for either the CF or control infants. On average, LCI, FRC and $FEV_{0.5}$ only changed by 0.02, 0.16 and 0.06 z-scores respectively amongst CF children between 1–2 years, similar to that observed in controls. Mean (95%CI) group differences (CF-HC) in change of LCI, FRC and $FEV_{0.5}$between 1–2y were 0.02 (-0.61; 0.66), p = 0.94;-0.05 (-0.61; 0.51), p = 0.86; and 0.32 (-0.27; 0.90) p = 0.29, respectively.
Conclusions This is the first study to demonstrate stable lung function to 2y in NBS CF infants managed on standard CF therapy. These results suggest that in many of these infants novel treatments could be deferred beyond infancy when objective outcomes are more easily measured.



Abstract S7 Figure 1. Comparison of change in lung function z-scores between 3m, 1y and 2y in NBS CF infants and healthy controls. Legend: Data are expressed as mean (SD). Closed circles represent NBS CF infants; open circles represent healthy controls. Lung function outcomes were expressed as z-scores which adjusted for age and body size as appropriate. Dashed lines indicate limits of normality(+/-2 z-scores).

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S8 HYPERPOLARISED 3HE MRI IS SUPERIOR TO LUNG CLEARANCE INDEX IN DETECTION OF VENTILATION ABNORMALITIES IN YOUNG CHILDREN WITH MILD CF

[1]H Marshall, [2]A Horsley, [3]L Smith, [3]D Hughes, [1]F Horn, [1]L Armstrong, [1]J Parra-Robles, [4]S Cunningham, [3]I Aldag, [3]C Taylor, [1]Jm Wild; *Academic Radiology, University of Sheffield, Sheffield, UK[1]; Manchester Adult CF Centre, University of Manchester, Manchester, UK[2]; Sheffield Children's Hospital, Sheffield, UK[3]; Child Life and Health, University of Edinburgh, Edinburgh, UK[4]*

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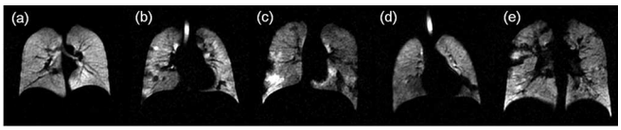
Introduction Hyperpolarised ^{3}He MRI provides high resolution images of lung ventilation and is more sensitive than spirometry to early changes in lung ventilation in cystic fibrosis (CF). Lung clearance index (LCI) is a global measure of ventilation heterogeneity which is also sensitive to early changes in the lungs in CF before spirometry. The aim of this study was to investigate the capability of hyperpolarised ^{3}He MRI and LCI to detect ventilation changes in children with mild CF.
Methods 4 CF patients (FEV_1 78–110% predicted) and 4 healthy volunteers have been assessed so far. ^{3}He ventilation images were acquired at breath-hold following inhalation of hyperpolarised ^{3}He, with 2.7x2.7x10mm resolution and full lung coverage using a 1.5T MRI system. The percentage of lung ventilated (VV%) was calculated as ^{3}He ventilated volume divided by total lung volume segmented from ^{1}H MR images. LCI was measured using 0.2% SF6 and a modified Innocor gas analyser. LCI was performed sitting and repeated supine to mimic the position adopted for MRI scanning. Spirometry and plethysmography were also performed. Gas trapping was calculated as% difference in plethysmographic versus washout FRC.
Results Healthy volunteers had a mean (standard deviation) age of 8.8(1.5) years, FEV_1% predicted = 97(10) and gas trapping = 4.4(9.1)%. LCI sitting was 6.9,7.3,6.6 and 6.9, LCI supine was 7.3,7.5,6.8 and 6.4. Healthy volunteers had homogeneous ventilation in ^{3}He ventilation images e.g. Fig1(a), and VV % = 94.5(2.8). CF patients had an age of 11.8(2.9) years, FEV_1% predicted = 95(13), and gas trapping = 8.7(11.0). LCI sitting was 7.7,6.6,6.6 and 9.1, LCI supine was 7.8,7.3,7.1 and 11.8. Ventilation abnormalities were observed using ^{3}He MRI in all four CF patients scanned (Fig 1(b-e), with order

corresponding to the LCI values given), and VV% = 89.2(2.6). 2 of the 4 CF patients had normal sitting and supine LCI and 2 of 3 had no evidence of gas trapping, but ^{3}He MRI showed clear focal ventilation defects in all patients (b-d).

Conclusions High quality ^{3}He MRI images can be produced in young children. Preliminary results suggest that hyperpolarised ^{3}He ventilation MRI may be more sensitive to early ventilation changes in CF than LCI or conventional lung function tests.

Acknowledgements CF Trust funding



Abstract S8 Figure 1. Ventilation images from (a) a healthy volunteer and (b-e) patients with mild CF.

S9 SIFT-MS ANALYSIS AS A NON-INVASIVE DETERMINANT OF PSEUDOMONAS AERUGINOSA INFECTION IN PATIENTS WITH CYSTIC FIBROSIS

[1]R Pabary, [2]S Kumar, [2]J Huang, [3]EWFW Alton, [1]A Bush, [2]GB Hanna, [3]JC Davies; *Royal Brompton and Harefield Hospital Foundation Trust, London, United Kingdom[1]; Department of Cancer and Surgery, Imperial College, London, United Kingdom[2]; National Heart and Lung Institute, Imperial College, London, United Kingdom[3]*

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Background There is evidence that *Pseudomonas aeruginosa* (Pa) produces volatile organic compounds (VOCs) such as hydrogen cyanide (HCN) and 2-aminoacetophenone (2-AA). VOCs in exhaled breath are therefore proposed as potential biomarkers of infection. We hypothesised that selective ion-flow mass spectrometry (SIFT-MS) breath analysis might allow discrimination of CF patients with (CF + Pa) and without Pa (CF-Pa).

Methods 79 adults (31 CF + Pa, 22 CF-Pa and 26 healthy controls) provided starved, single tidal exhalation breath samples into Nalophan^{TM} bags. Quantification of 15 VOCs was performed within two hours on SIFT-MS. All results are presented as (median parts-per-billion by volume [IQR]).

Results 2-AA was significantly higher in CF + Pa than CF-Pa (5.0 [3.4–7.1] vs. 1.3 [0.0–3.2], p <0.01). However, there was significant overlap and median co-efficient of variation was 35.41%; clinical utility is therefore questionable.

Dimethyl disulphide was also significantly higher in CF + Pa (95.2 [41.3–211.2 vs. 35.5 [22.1–79.8], p < 0.01). When combined with 2-AA, area under ROC curve was 0.867.

Counter to our sputum results, there was no difference in HCN between CF + Pa and CF-Pa (8.1 [5.0–11.9] vs. 6.9 [4.4–11.0], n/s) or between all CF patients and healthy controls (7.8 [4.9–11.5] vs. 7.0 [4.6–11.5], n/s).

Our early *in vitro* data showed decreased butanol above Pa cultures, suggesting consumption. This was replicated in breath with lower levels in CF + Pa vs. CF-Pa (37.4 [24.3–87.6] vs. 91.7 [46.9–143.7], p < 0.05).

Of VOCs likely to be of host origin, isoprene was increased in CF vs. controls (108.0 [83.4–195.5] vs. 69.6 [46.9–89], p < 0.01) with no difference between CF + Pa vs. CF-Pa. Acetone was reduced in CF (269.9 [161.9–356.4] vs. 324.9 [236.7–598.9], p < 0.01).

Conclusions 2-AA is a potential biomarker of Pa infection but clinical applicability is uncertain. Dimethyl disulphide and butanol also show promise. Mouth-exhaled HCN assessed by SIFT-MS does not appear to fulfil its promise as a Pa biomarker. Other VOCs assessed were either similar between Pa groups or different between healthy controls and CF, but unable to differentiate between Pa status. This study provides proof-of-concept for the development of a non-invasive tool with which to screen for lower airway bacterial infection in CF though a clinically applicable test remains some way off.

S10 LUNG CLEARANCE INDEX (LCI) AND PSEUDOMONOUS AERUGINOSA IN ADULTS AND CHILDREN WITH CYSTIC FIBROSIS (CF)

[1]K O'Neill,[2]J M Bradley, [3]I Bradbury, [1]E Johnston, [4]A Reid, [4]J McCaughan, [4]JE Moore, [1]MM Tunney, [1]JS Elborn; *[1]Queen's University Belfast, CF & Airways Microbiology Research Group, Belfast, United Kingdom; [2]Centre for Health and Rehabilitation Technologies, University of Ulster., Belfast, United Kingdom; [3]Frontier Science Ltd, Scotland, United Kingdom; [4]Belfast Health and Social Care Trust, Belfast, United Kingdom*

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Introduction LCI obtained from multiple breath washout (MBW) is a sensitive measure of ventilation inhomogeneity in CF. Persistent colonisation with *P. aeruginosa* is associated with a decline in LCI in children (Kraemer *et al*. 2006). Further research is required to investigate the relationship between airways infection and LCI in adults.

Objective To investigate the sensitivity of LCI to *P. aeruginosa* in adults and children compared with FEV_1%pred and $FEF_{25–75}$% pred.

Methods Stable CF patients from adult & paediatric Northern Ireland CF centres were recruited. LCI was derived from MBW, using 0.2% SF_6 and a modified Innocor^{TM}device. *P. aeruginosa* status was determined from routine diagnostic culture of a sputum sample or deep throat swab. Patients categorised as having *P. aeruginosa* infection met the criteria of chronic infection as defined by the Leeds criteria (Lee *et al*. 2003).

Analysis Receiver-operator characteristic (ROC) curves and area under the receiver operating curves (AUC_{ROC}) indicate the level of sensitivity and specificity where 1.0 = perfect discrimination considering sensitivity and specificity.

Results Sixty-seven adults were recruited (39M), median (IQR) age 27 (16) years. Mean (SD) FEV_1%pred 71.8 (20.3), median (IQR) $FEF_{25–75}$%pred 40.0 (46.7) and mean (SD) LCI 10.3 (3.0) lung volume turnovers. 49% had *P. aeruginosa* infection.

Forty-three children were recruited (24M), mean (SD) age 11.7 (3.4) years. Mean (SD) FEV_1%pred 85.2 (16.6), mean (SD) $FEF_{25–75}$%pred 66.0 (27.6) and mean (SD) LCI was 7.8 (1.8) lung volume turnovers. 16% had *P. aeruginosa* infection

Compared to FEV_1%pred and $FEF_{25–75}$%pred, LCI had the greatest sensitivity and specificity to discriminate between CF patients with and without *P. aeruginosa* in both adults and children. Adult AUC_{ROC} (SE) for LCI = 0.82 (0.05), p < 0.0001, compared with FEV_1%pred = 0.66 (0.07), p = 0.021 and $FEF_{25–75}$%pred = 0.64 (0.07), p = 0.044 (Figure 1). Child AUC_{ROC} (SE) for LCI = 0.85 (0.10), p = 0.004, compared with FEV_1%pred = 0.80 (0.12), p = 0.014 and $FEF_{25–75}$% pred = 0.67 (0.13), p = 0.152.

Conclusion LCI is more sensitive and specific to the presence of *P. aeruginosa* airways infection across the age groups in CF compared with spirometry.

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