baseline [reference group], n = 259, 13.2%, 95% CI, 8.8–17.7%; 6-month baseline, n = 204, 16.5%, 95% CI, 11.1–21.9%, $p = 0.31$; 12-month baseline, n = 171, 19.8%, 95% CI, 14.0–25.6%, $p = 0.05$), but significantly more acute respiratory event visits (including treated and untreated events) qualified as a 10% or greater worsening in LCI when the baseline was defined as a stable visit 6 months before (n = 109, 44.0%, 95% CI, 34.2–53.8%, $p = 0.008$) or 12 (n = 94, 42.8%, 95% CI, 32.3–53.1%, $p = 0.02$), compared with the reference group of 3 months before (n = 140, 28.7%, 95% CI, 20.7–36.7%).
Conclusions: More frequent LCI testing in clinically stable children does not result in greater detection of significant LCI changes than annual monitoring, although if LCI is being used to define worsening of lung function with acute respiratory events, shorter intervals between tests increase the precision of classifying events with worsened lung function.
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Elexacaftor/tezacaftor/ivacaftor treatment in pediatric cystic fibrosis lung disease reduces ventilation heterogeneity measured using hyperpolarized ^{129}xenon multiple-breath washout magnetic resonance imaging

F. Alam[1,2], B. Zanette[1], S. Braganza[1], R. Jensen[3], M. Dumas[3], F. Ratjen[1,3], G. Santyr[1,2]. *[1]Translational Medicine Program, SickKids Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada; [2]Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada; [3]Division of Respiratory Medicine, Hospital for Sick Children, Toronto, Ontario, Canada*

Background: Sensitive tools to monitor changes in early cystic fibrosis (CF) lung disease in children are needed to assess the efficacy of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA). The lung clearance index (LCI), measured according to multiple-breath washout (MBW), can show treatment effects in pediatric CF [1] but is limited to whole-lung averages of ventilation, thereby missing regional information. Hyperpolarized ^{129}xenon magnetic resonance imaging (Xe-MRI) conducted in a MBW fashion (MBW Xe-MRI) yields maps of fractional ventilation (FV), a measure of percentage gas clearance per breath. The coefficient of variation derived from FV (CoV_{FV}) maps can be used to assess spatial ventilation heterogeneity [2]. By regionally quantifying gas replacement and ventilation heterogeneity, MBW Xe-MRI can potentially provide information about treatment response different from information from LCI. This work assesses the ability of MBW Xe-MRI to capture changes in CF lung disease in children treated with elexacaftor/tezacaftor/ivacaftor.
Methods: Seven children (median age 17, range 14–17.5) underwent two visits each (baseline, 1 month) at which nitrogen MBW and MBW Xe-MRI

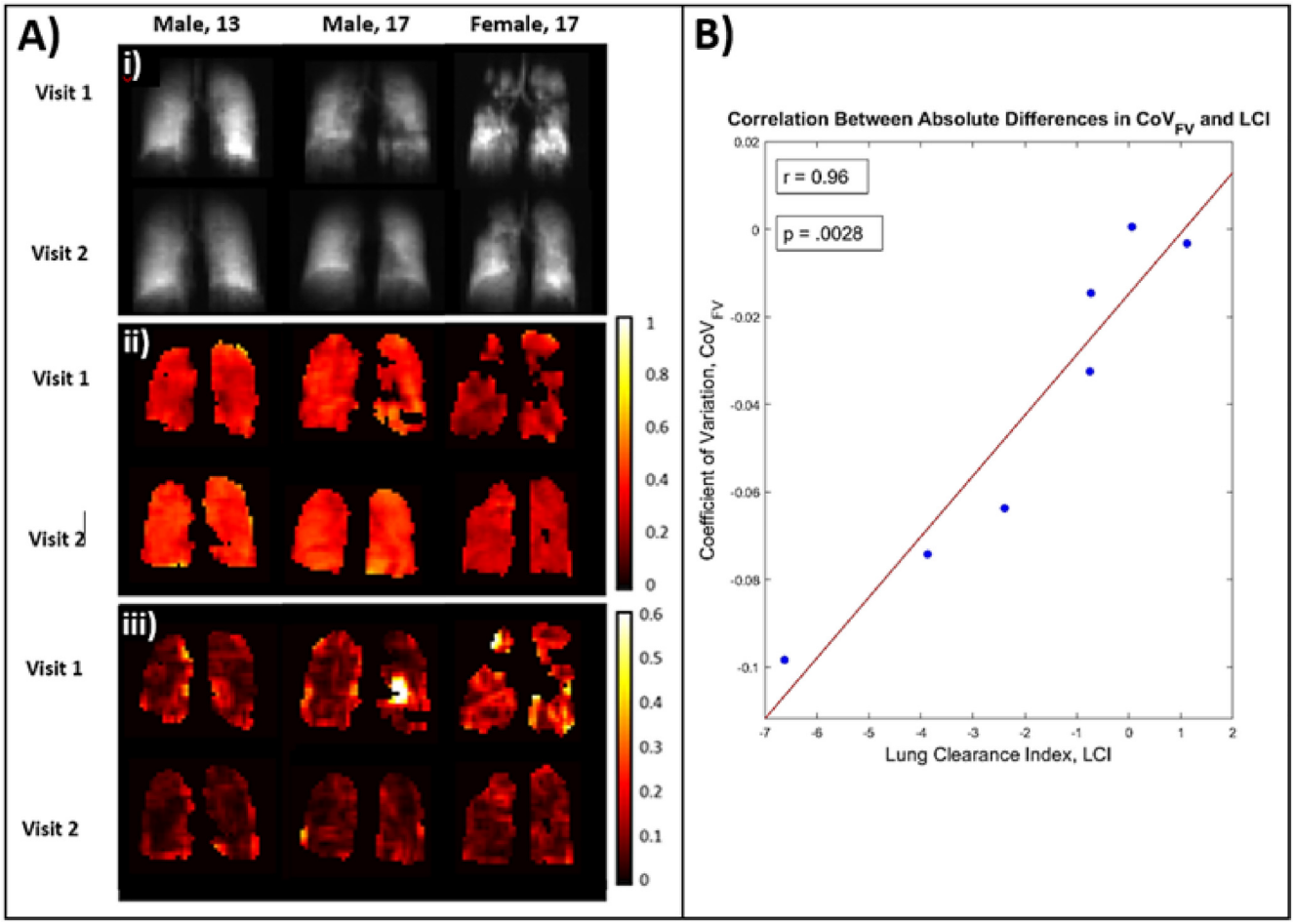

Figure 1 (abstract 177): Sample images and correlation: A) Three sample subject results from visit 1 (baseline) to visit 2 (1 month), with i) signal intensity images from first washout breath, ii) fractional ventilation (FV) maps, and iii) coefficient of variation FV (CoV_{FV}) maps. B) Correlation between absolute differences in CoV_{FV} and lung clearance index (LCI) values before and after treatment

were measured. LCI was measured using an Exhalyzer D MBW device (EcoMedics, Duernten, Switzerland; Spiroware 3.3.1). MBW Xe-MRI was performed as previously described [3], with the ^{129}xenon dose (10% of total lung capacity) was topped with nitrogen to a volume of 1/6th total lung clearance. CoV_{FV} was calculated by comparing the average value of FV in one voxel to that of its nearest neighbors through image kernel convolution and taking the standard deviation over the mean. The Wilcoxon signed-rank test was used to determine significant changes between visits. Correlations between absolute differences in mean FV and CoV_{FV} and LCI were tested with a Spearman correlation.

Results: Xe-MRI (breath = 1), FV, and CoV_{FV} maps for three representative subjects are shown in Figure 1A. The following values are averages from the maps. Median (IQR) CoV_{FV} was significantly ($p = 0.03$) lower at 1 month (median 0.07, interquartile range [IQR] 0.06–0.08) than at baseline (median 0.10, IQR 0.08–0.14). Absolute changes in CoV_{FV} between visits were found to significantly ($p = 0.003$) and highly (r = 0.96) correlate with absolute changes in LCI (Figure 1B). Median FV did not change significantly ($p = .16$) between baseline (0.36, IQR 0.33–0.40) and 1 month (0.41, IQR 0.40–0.44) or correlate significantly with LCI (r = –0.61, $p = 0.17$).

Conclusions: CoV_{FV} detected improvements in ventilation homogeneity 1 month after ELX/TEZ/IVA treatment. Absolute changes in CoV_{FV} correlated with LCI. The ongoing study will help clarify the relationship between this novel measure and other imaging outcomes in capturing treatment response.

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Toward targeted exhaled breath analysis for young children in cystic fibrosis care to detect bacteria in the lungs

D. Mager[1], P. Brinkman[2], B. Manaï[1], W. Karar[1], L. Slimmen[1,3], D. Fenn[2,4], L. Bos[2,5,6], E. Haarman[7], A. Maitland-van der Zee[2], H. Janssens[1]. *[1]Division of Respiratory Medicine and Allergology, Department of Pediatric Medicine, Erasmus MC-Sophia Children's Hospital, Erasmus University Medical Center Rotterdam, the Netherlands; [2]Respiratory Medicine, Amsterdam University Medical Centers, Amsterdam, the Netherlands; [3]Laboratory of Pediatrics, Division Infectious Diseases and Immunology, Department of Pediatric Medicine, Erasmus University Medical Centre, Rotterdam; [4]Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam University Medical Centers, Amsterdam, the Netherlands; [5]Intensive Care, Amsterdam University Medical Centers, Amsterdam, the Netherlands; [6]Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam University Medical Centers, Amsterdam, the Netherlands; [7]Pediatric Respiratory Medicine, Emma Children's Hospital, Amsterdam University Medical Centers, Amsterdam, the Netherlands*

Background: Children with cystic fibrosis (CF) are prone to bacterial infections, which can be associated with lung function decline. Consequently, detection of bacteria plays an important role in CF care, but culture-dependent diagnosis of such infections is a challenge in children because of limited sample availability and quality. Exhaled breath analysis measuring volatile organic compounds (VOCs) might be a promising noninvasive, culture-independent tool to identify bacteria. Several explorative studies have suggested that VOCs can differentiate between bacterial species, although these results are not always consistent. The next step for exhaled biomarkers would be to move from discovery studies to hypothesis-driven targeted analysis, an essential step for clinical application. *Staphylococcus aureus* is a common bacteria found in children with CF. We aimed to test the feasibility of targeted exhaled breath analysis in children with CF in a proof-of-concept study for the detection of *S. aureus* using previously identified VOCs and whether this could discriminate between *S. aureus*–positive and –negative cultures.

Methods: Children with CF aged 1 to 6 were included. Exhaled breath samples were tored in thermal desorption tubes and analyzed using gas chromatography–mass spectrometry (GC-MS). Microbiological cultures were collected on the same day. After a literature review to identify *S. aureus*–related VOCs, targeted peak detection using AMDIS (v.2.68) was performed on the GC-MS dataset, and the resulting peak intensities were used for multivariate modeling using sparse partial least squares discriminant analysis (sPLS-DA), after which the predicted outcomes (*S. aureus* positive or negative) were compared with the actual microbiological outcomes. Statistical analyses were performed in R-Studio (v.1.3).

Results: Exhaled breath collection was attempted in 24 children with CF, and was successful in 83% (n = 20, median age 4, interquartile range 2–6). Of nine patients who had a positive culture for *S. aureus*, six were taken by a nasopharyngeal swab, two from sputum, and one from bronchoalveolar lavage fluid. Two patients had a positive culture for *Haemophilus influenzae* and one for *Moraxella cattharalis.* Eight patients had a negative culture. We identified five VOCs associated with *S. aureus* from the literature review (≥2 consistent notations), which were used to predict culture positivity for *S. aureus,* resulting in accuracy of 70%, specificity of 89%, and sensitivity of 55%. The positive predictive value of the test was 86%, and the negative predictive value was 62%.

Conclusions: Targeted analysis of MS-driven exhaled VOC profiles appears to enable detection of pathogens in exhaled breath. We showed that noninvasive breath collection for targeted exhaled breath analysis is feasible in young children and that VOCs associated with *S. aureus* were detectable. One of the limitations of this study is the small sample size and that most microbiology cultures were taken using a nasopharyngeal swab, which may explain the low sensitivity of the model. More research should be done to evaluate this promising methodology in larger cohorts, preferably using more-sensitive microbiological sampling methods.

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Inflammation-based scoring systems and ratios to identify people with cystic fibrosis at risk for intravenous antibiotic therapy

R. Reitmeier[1], J. Walter[1,2], J. Behr[1,2], P. Mertsch[1,2]. *[1]Department of Medicine V, University Hospital, LMU Munich, Munich, Germany; [2]Comprehensive Pneumology Center Munich, German Center for Lung Research, Munich, Germany*

Background: Pulmonary disease in cystic fibrosis (CF) is characterized by chronic bacterial infection with recurrent pulmonary exacerbations (PEx), which are associated with high systemic inflammatory marker levels. Because PEx are associated with higher morbidity and mortality, prevention is an important therapeutic goal in the treatment of people with CF (PwCF). Identifying patients at risk for future PEx can be challenging in clinical practice. The objective of this study was to compare established and novel markers of chronic inflammation and their ability to predict the need for intravenous antibiotic therapy (nIVT) as a surrogate marker for PEx or decline in pulmonary status in PwCF.

Methods: Individuals aged 18 and older treated between 2014 and 2018 in the adult CF center of the university hospital Munich, Germany, who had at least two pulmonary function tests per year for a 3-year period were included in this retrospective, longitudinal study. Baseline was defined as the first year after the first measurement. The follow-up period was time between baseline and end of follow-up. Neutrophil/lymphocyte ratio, lymphocyte/monocyte ratio, C-reactive protein (CRP)/albumin ratio, Glasgow prognostic score, and CF-Able score of patients with and without nIVT during follow-up were compared. In the univariate analysis, we used chi-square and Fisher exact tests to compare categorical scores and t-tests to compare numerical scores. In the multivariate analysis, we used