Poster Session Abstracts

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QUALITY OF HOME SPIROMETRY IN ADOLESCENT CF AND BRONCHIECTASIS PATIENTS

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Introduction: Spirometry requires maximum patient effort to achieve acceptable and repeatable results. Verbal and visual feedback is given to patients to correct technique and improve quality of spirometry data in outpatient clinics. This is in line with European Respiratory Society/ American Thoracic Society 2005 criteria on acceptability and repeatability. Sophisticated spirometers provide feedback to the patient on test performance and repeatability at home, in order to obtain good quality data in the absence of a physiologist. Our aim is to determine the repeatability of home forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and peak expiratory flow (PEF) data collected using the Air Next device in adolescent patients with cystic fibrosis (CF) or bronchiectasis, and to compare home NuvoAir results with hospital spirometry results.

Method: Thirty patients received an Air Next spirometer (NuvoAir), this study was completed over a 6-week period between 23 April - 4 June 2020. A total of 95 spirometry assessments were completed, patients were virtually instructed how to use and perform spirometry. The repeatability criteria for FEV_1 is based on 3-8 blows with the best two results being within 5% or 100 mL repeatability. We asked patients to perform lung function tests 30 min post-exercise and physiotherapy. We provided an instruction booklet, with reminders of when and how to perform tests. We compared the patients' last clinic visit spirometry when they were clinically stable (using the Vyaire/SentrySuite software) with their independent home spirometry results. If the time between these two periods were greater than 3 months we calculated their predicted heights to correct for their growth, and used these for the Air Next device.

Results: Patient characteristics were (Mean ± SD); Age 13 ± 3 years, Height 152 ± 14 cm, Weight, 45 ± 14 kg, FEV_1% of predicted 77 ± 19%, FVC% of predicted 89 ± 12%, and PEF (L/s) 5 ± 2%. A total of 95 spirometry tests were analysed; of this 48.8% were performed in the morning, the remaining 51.2% were in the afternoon. Seventy-four percent of home tests achieved ATS/ERS 2005 repeatability criteria for FEV_1. The average numbers of manoeuvres recorded were 4 blows per session. The average PEF remained the same, mean difference in FEV_1, and FVC were 4% respectively (Table).

Conclusion: Using the Air Next device, 74% of CF and bronchiectasis patients were able to produce reproducible spirometry at home. The device provides instant feedback which aided patients in the absence of coaching and guidance from trained physiologists. All sessions had FEV_1, FVC and PEF measurements recorded, so the feedback message to the patient to "blow longer" may have aided the expiration time beyond 1 second. However, these 30 patients have had years of experience in performing spirometry in hospital which aided the use of the Air Next device. To validate these findings we would need to test a different cohort of patients, who have less experience performing regular lung function.

Parameter	PEF (L/s)	FEV_1 (%)	FVC (%)
Hospital Spirometry (Mean ± SD)	6 (± 2)	79 (± 19)	90 (± 13)
Home NuvoAir (Mean ± SD)	6 (± 2)	83 (± 19)	94 (± 16)

Table 1: The difference between their last Hospital Vyaire and home NuvoAir spirometry

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DIFFERENCES IN PROSTAGLANDIN E_2 RECEPTOR MEDIATION OF BICARBONATE SECRETION BETWEEN CYSTIC FIBROSIS AIRWAYS AND INTESTINE

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Background: Cystic fibrosis transmembrane conductance regulator (CFTR) mutations result in defective bicarbonate transport and cultivate an acidic pH in cystic fibrosis (CF) airways. Pulmonary exacerbations promote the release of prostaglandin E_2 (PGE_2). Prior studies showed PGE_2 stimulates CFTR-dependent and -independent HCO_3^- secretion in the intestine, the latter of which occurs through PAT-1 mediated Cl^-/HCO_3^- exchange. In contrast, we previously found that this process is entirely CFTR-dependent in the airways.

Aim: To determine if differential PGE_2 receptor and/or Cl^-/HCO_3^- exchanger expression and/or activation can explain the difference in HCO_3^- secretory mechanisms between airways and intestine.

Methods: Primary human bronchial epithelial cell cultures (HBECs) and patient-derived human duodenal enteroid cell cultures (both differentiated and undifferentiated) were used. Anion secretion was measured by short-circuit current (*Isc*) while HCO_3^- secretion was measured by pH-stat. mRNA expression was determined by qPCR.

Results: PAT-1 mRNA expression was similar between HBECs, undifferentiated enteroids, and differentiated enteroids (n=4-5). We next examined EP receptor expression between the airways and intestine. In HBECs EP_4 receptor predominated with a relative expression profile of EP_4>>EP_1>>>EP_2/EP_3 (n=3). EP receptor subtype specific agonists (10 μM), identified EP_4 as the primary receptor responsible for PGE_2-stimulated Cl^- secretion (EP_4: 11.31 ± 4.13 ΔμA/cm^2, n=3 vs PGE_2: 10.58 ± 0.88 ΔμA/cm^2, n=3). EP_1 and EP_2 agonists stimulated Cl^- secretion to a lesser degree (EP_1: 4.0 ± 0.79 ΔμA/cm^2, n=5; EP_2 : 5.36 ± 1.36 ΔμA/cm^2, n=5), and EP_3 agonist only caused a minimal elevation in *Isc* (n=6). PGE_2-stimulated Cl^- transport in HBECs was inhibited by both PKA (~41% inhibition) and Ca^{2+} (~56% inhibition), both downstream effectors of EP_4 and EP_1, respectively. PGE_2 stimulated Cl^- and HCO_3^- secretion in duodenal enteroids. Duodenal enteroids exhibited a different EP receptor profile than HBECs with predominant expression of EP_3 and EP_4 (EP_3≈EP_4>>EP ≈EP_2 ; n=3). EP_3 receptor expression in enteroids was >100-fold increased over EP_3 receptor expression in HBECs.

Conclusions: Comparable PAT-1 expression levels between airways and intestines suggest this Cl^-/HCO_3^- exchanger is not responsible for differing HCO_3^- secretory responses between CF intestine and airway. The functional agonist data in HBECs matches its mRNA expression profile and is further supported by the PKA and Ca^{2+}-mediated inhibition observed, suggesting that EP receptor mRNA availability is in fact tied to EP receptor activity. Differences in EP_3 receptor expression between HBECs and enteroids indicate that this receptor may be responsible for CFTR-independent HCO_3^- secretion in intestine and the lack of CFTR-independent HCO_3^- secretion in airways. Ongoing experiments are aimed at stimulating HCO_3^- secretion in enteroids using specific EP receptor agonists to further examine this process. If true, promoting EP_3 receptor activity in the airways may correct the acidic pH in CF lungs through increased HCO_3^- secretion, improving clearance of pulmonary infections.

Acknowledgment: Supported by the CF Foundation (SELLER16L0).

CFTR

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WHOLE GENOME SEQUENCING OF INDIVIDUALS WITH CYSTIC FIBROSIS REVEALS UNEXPECTED LEVELS OF HOMOZYGOSITY ENCOMPASSING THE ENTIRE *CFTR* GENE

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Introduction: Variation in *CFTR* is a major determinant of disease severity in individuals with CF but is typically limited to description of single variants. To explore the role of intragenic modifiers, we performed detailed analysis of the region surrounding *CFTR* in 5,058 individuals with CF who underwent whole genome sequencing. We report here the unexpected finding of a severe reduction in the number of heterozygous DNA variants (region of homozygosity; ROH; defined using BCFtools (Narasimhan, et al. 2016)) surrounding *CFTR* in 1.4% of the cohort.

Methods: Individuals recruited by the CF Genome Project from Johns Hopkins Univ (CF Twin and Sibling Study and CFRD Study), the Univ of North Carolina (Genetic Modifier Study and the Genetic Modifier Study of