Development and characterization of pulmonary disease in G551D ferret model on chest computed tomography imaging

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Background: Cystic fibrosis (CF) animal models are needed to develop novel therapies in efforts to cure the condition. The G551D ferret model has shown promise in fulfilling this role but needs sensitive endpoints for physiological assessments. Micro-resolution chest computed tomography (CT) can be used in vivo and in the lungs of euthanized ferrets in situ. We developed a scoring system based on clinical CT scoring to help characterize pulmonary disease in ferrets with CF.

Methods: A semi-quantitative clinical scoring system based upon extent of airway and parenchymal disease in each lobe was developed. This was generally based on Alan Brody CT scoring in humans to help characterize extent and distribution of disease in airways and parenchyma [1]. Multiple in situ scans of ferrets were reviewed to develop understanding of anatomy and lung disease patterns. After this learning phase, a blinded pediatric pulmonologist (TSP) scored available CT scans in a consistent fashion with standard lung window (~1350 to 150 HU) in the axial plane. In situ scans were scored from CF G551D ferrets off ivacaftor for 2 to 3 months, wild-type controls of a similar age, and WT ferrets exposed to intratracheal bleomycin to induce lung injury.

Results: CT scans had substantially more lung disease than WT controls (p<0.01). The extent of parenchymal and small airway disease in CF ferrets was the greatest contributor to total score and was variable among animals. In comparison, bleomycin-exposed WT ferrets had prominent large airway and parenchymal and small airway disease that were more equal in severity (Figure 1). This trend persisted when adding aged bleomycin scores to the bleomycin group, showing a greater difference between percentage contribution to total scores of the parenchyma than the airway in CF ferrets and bleomycin-exposed ferrets (n=5 vs 14, p=0.03).

Conclusions: Ferret chest CT scoring can be helpful in characterizing lung disease. CF CT scans show more-extensive parenchymal and small airway disease, similar to a pattern observed in early lung disease in humans. This contrasted with bleomycin-induced injury, which exhibited a distinct large airway-centric pattern. Analysis of serial in vivo CT scans are in progress. CT imaging of ferrets may be useful in monitoring lung pathology and as an indicator of therapeutic response.

Figure 1. (A) Comparison of combined total computed tomography score of G551D ferrets (n=5) with that of similar age wild-type (WT) controls (n=4) and similar age WT exposed to bleomycin (n=5); (B) percentage of total score attributed to parenchymal and small airway disease and larger airway disease for G551D group and bleomycin group.

Acknowledgements: This work is supported by the Cystic Fibrosis Foundation (POORE2D00), UAB CF Research and Translation Core Center (P30DK072482), and UAB Research and Development Program (CF, ROWE19R0).

Reference

Use of daily home spirometry to predict clinical outcomes in persons with cystic fibrosis

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Background: Use of home spirometry to monitor lung function has been increasing in popularity in persons with cystic fibrosis (PwCF) since the start of the COVID-19 pandemic. Although clinic spirometry is interpreted from validated standards, expected test-to-test variation of home spirometry and how variation during baseline health may relate to clinical changes are unknown. The aim of this study was to determine variation in baseline lung function during daily home spirometry and identify associations with clinical outcomes.

Methods: Subjects were selected based on available spirometry data from a cohort of PwCF enrolled in a long-term airway microbiome study. Subjects were provided with a PiKo-6 hand-held spirometer (nSpire Health, Inc., Longmont, CO) and asked to perform spirometry maneuvers three times per week. Validity of home spirometry (percentage predicted forced expiratory volume in 1 second [FEV1,pp]) was compared with that of clinic spirometry using Bland-Altman plots. Spirometry acceptability across multiple maneuvers in the same day was assessed using the American Thoracic Society (ATS) guidelines, with grade A or B (two or more maneuvers within 150 mL) considered acceptable. Variation in FEV1,pp was assessed by calculating a mean FEV1,pp and coefficient of variation (CoV).

Results: Thirteen subjects (62% female) with a mean age of 28.7 ± 8.3 and mean FEV1,pp of 59.9 ± 8.2% were included. Median study duration was 377 days (range, 65–728 days) of baseline spirometry readings was available for further analysis. Comparing validity of home spirometry with that of clinic spirometry, Bland–Altman plots demonstrated overall good agreement with a slight bias (+0.042 L) toward higher readings for clinic FEV1,pp (95% limits of agreement, −0.26 to 0.34 L). Spirometry quality was graded as acceptable on most study days (mean 90.6 ± 0.4%) in which two or more maneuvers were recorded. Intra-individual variation in baseline FEV1,pp was high, with a mean variation of 17.6 ± 5.9% day to day and 15.2 ± 6.2% week to week. Neither rates of acceptable spirometry grades nor CoV was associated with lung disease severity. Of the 13 subjects, 10 experienced one or more PEx, for a total of 32 PEx during the study. CoV was not associated with time to first PEx (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.51–1.21; p=0.24) or time to subsequent PEx (HR, 0.91; 95% CI, 0.73–1.12; p=0.28) during the study.

Conclusions: Although home spirometry has generally good validity and acceptability, variation in lung function during baseline health is present and often exceeds expected variation in clinic spirometry per ATS standards. Variability may represent normal physiological variation or be related to the home spirometer itself or other factors but did not portend upcoming PEx. Recognition of variation during baseline health provides important context for interpretation of home spirometry.