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Title: Alternative multiple breath washout outcomes for clinical trials in cystic fibrosis

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Body: The Lung Clearance Index (LCI) is a sensitive marker of early lung disease. and LCI, but not spirometry, was able to detect treatment effects of hypertonic saline in CF patients with mild disease (Amin et al; Thorax 2010). We used data from this interventional trial to investigate whether any other outcomes of the multiple breath washout could detect treatment effects similar to LCI. Using a cross-over design, patients were randomized to either hypertonic saline or isotonic saline in a randomized sequence, separated by a 4 week washout period. MBW was measured in triplicate by mass spectrometry (AMIS 2000; Innovision A/S, Odense, Denmark) using a gas mixture containing 4% SF_6, 4% He, 21% O_2 and balanced N_2. The current analysis includes 15 subjects for whom the following additional outcome measures could be assessed: normalized concentration of end tidal tracer gas (Cnet) at 6 turnovers (6T0), moment ratios (M1M0, M2M0) and LCI measured by helium. No significant treatment effects were observed for LCI measured with helium as a tracer gas. For $SF_{6,}$ unlike the LCI, Cnet at 6TO was not able to detect a treatment effect of hypertonic saline. Moment ratios showed different results depending on the ratio chosen; M1M0 was significantly lower for hypertonic saline at $1/40^{th}$ the starting SF_6 concentration, whereas both M1M0 and M2M0 demonstrated a significant treatment effect when 6TO was used as the washout end point. These findings suggest that moment ratios, which may be less sensitive to variations in respiratory rate and tidal volume, may provide a complementary outcome to the LCI in clinical trials. Supported by the Sellers Chair for Cystic Fibrosis.