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Title

Correlating lung function with quantified mucus densities and locations in healthy and cystic fibrosis subjects

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Hypothesis and Objectives

The goal of this study is to quantify and compare lung function in healthy controls and cystic fibrosis (CF) patients, with pulmonary function tests, multibreath washouts nitrogen (N_2), and MRI studies. While current practices use pulmonary function tests (PFT) and forced expiratory volume (FEV_1) to quantify lung ventilation in CF patients, multibreath washouts (MBW) and MRI studies are more sensitive to mucus build-up, lung function, and disease progression. By determining exactly where the excess mucus is and establishing correlations with lung function, we hope to provide the foundation for physicians to be able to customize treatment for individual CF patients.

Hypothesis: MRI and MBW studies will provide more information about mucus build-up, lung function, and disease progression in CF patients than standard-of-care PFTs alone. The establishment of these correlations may lead to better, more efficient, and more customizable treatment strategies for individual CF patients.

Background

Cystic fibrosis is an inheritable disease with an average life expectancy of 38 years^[1]. Although cystic fibrosis is a multi-organ disease, its most considerable target is the lung with approximately 80% of mortality in CF patients due to cardiopulmonary disease^[2]. CF results from a mutation in the epithelial ion transporter gene, CFTR, which results in excess secretion, production, and buildup of mucus in the lungs, thus preventing the lung from properly clearing out bacteria and cellular debris. This results in chronic respiratory infections, bronchiectasis, and difficulty in breathing. Mucus initially generates an ideal environment for bacterial growth, after which, the body's defense system sends neutrophils to target the bacteria. During this process, the neutrophils leave behind extracellular DNA which exacerbates the already thickened mucus, in addition to remodeling and scarring the airways and decreasing efficient gas exchange. The collected mucus is extremely difficult to dislodge, resulting in chronic coughing and difficult breathing. Mucus buildup locations vary from patient to patient. In some, mucus is seen more in the central conducting airways while in others, it is seen more in the smaller peripheral airways. Although treatment is not differentiated between the two, we hope that our study may change that.

The most widespread measurement of lung function is by performing PFTs and measuring FEV_1 , the volume of air that can be forcefully expelled within the first second of expiration. Although useful, FEV_1 values lack the sensitivity required to chronicle the progression of bacterial accumulation and changes in ventilation inhomogeneities within the lung (such as between central/conducting and peripheral airways). CT imaging is also used to measure lung function but due to the radioactivity, it is impractical to use to follow disease progression.

An alternative way to measure the progression of CF is by MBW studies, which have been used in previous studies to quantify airway impairment due to airway remodeling and/or obstruction in COPD, asthma and CF. This procedure requires that the patient have 25 regular breathing cycles each with approximately 1 L tidal volume beginning from functional residual

capacity (FRC; lung volume at end of a normal expiration) while inspiring pure (100%) oxygen (O₂). When the MBW test was performed on CF adults, studies showed that when compared to control groups, they had overlapping values for ventilation inhomogeneities in the peripheral acinar and elevated values for inhomogeneities in conducting airways^[3,4]. It should be noted that even in CF patients with normal FEV1, the MBW was more sensitive than FEV1 and was able to show ventilation inhomogeneities.

Another alternative way to quantify CF progression is via MRI with T₂* studies that measure lung water density. UCSD has developed a rapid, quantitative MRI imaging that allows for lung water density measurement within a 9 second breath hold. In healthy subjects, this MRI technique detects the water from blood and lung tissue^[4]. In CF patients, these measurements also include water content from excess airway secretions and lung abnormalities^[5] and as such allows for monitoring excess water in the lung. Preliminary data have shown that the distribution of lung density increases in dependent lung regions of healthy subjects at FRC^[4]. In other words, in a healthy subject, the average lung density at FRC will be greater at the bottom than the top of the lung, with a very obvious gradient. In CF patients, however, lung density changes due to relative mucus secretion, tissue scarring, increased FRC (as seen in patients with severe CF), and/or air-trapping.

One of the most difficult aspects of CF treatment is patient adherence. On average, a CF patient spends 60-74 minutes per treatment with an average of 4-6 treatments a day^[7] with some patients requiring up to 8 hours a day^[8] to do chest physiotherapy, hypertonic saline treatments, pulmozyme treatments, albuterol, antibiotic regimes and/or other treatments in attempt to clear and dislodge the mucus from the lungs and prevent chronic respiratory infections^[7]. While treatment time obviously negatively impacts the quality of life of CF patients who must spend the majority of their day treating the disease, it is unknown why the efficacy of each treatment varies from patient to patient. If an airway is blocked, all airways distal to it will not have access to any inhaled medications so it seems reasonable to hypothesize that there may be a correlation between the location of the mucus (such as in the central or peripheral airways) and the efficacy of specific treatments. Thus, it is imperative that physicians be able to correlate specific mucus location and progression with lung function and ventilation to better treat each individual CF patient. If physicians were able to treat patients more effectively, treatment time would decrease daily and hopefully improve patients' quality of life.

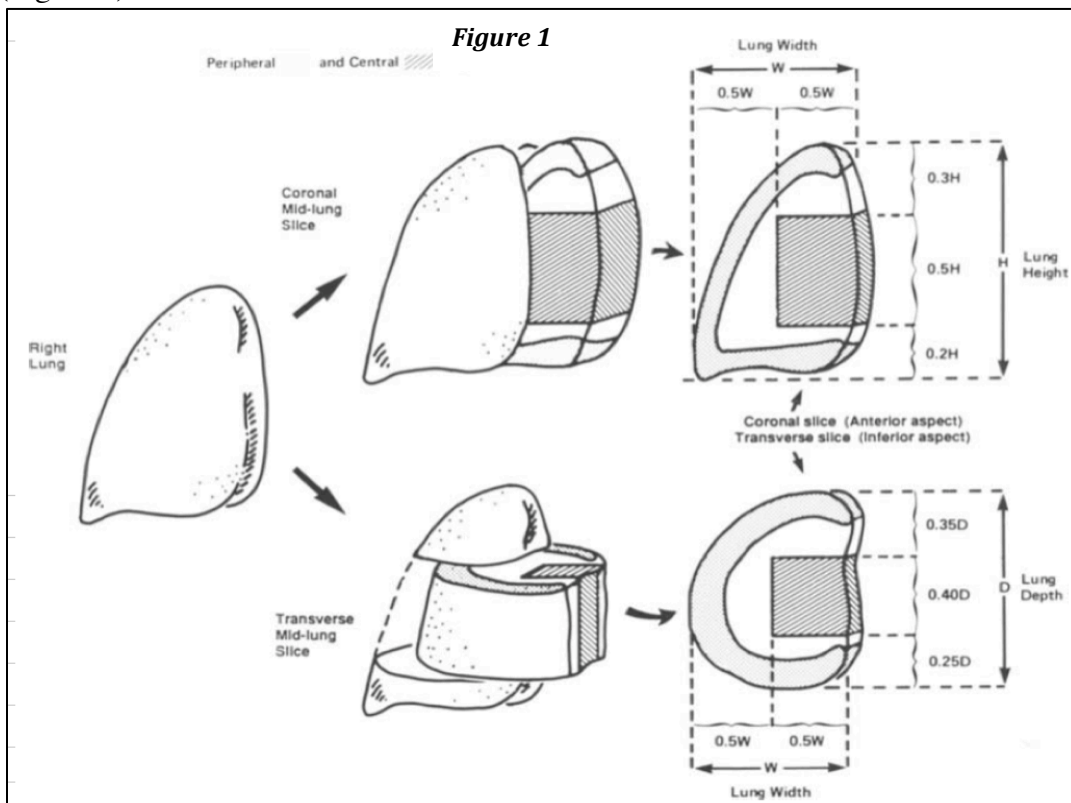
Methods

Twelve CF subjects were recruited from the UCSD Adult CF clinic led by Dr. Douglas Conrad. Eleven healthy controls were recruited from the community at-large. Participating subjects were included without regard to ethnicity or gender. The groups were significantly different in terms of mean weight which may be assumed to be due from the burden of chronic disease in CF patients. Otherwise, there were no other significant differences in demographics between the groups (Table 1). Each subject performed a MRI study and a MBW study, done in random order, followed by a PFT.

Table 1

Subject Demographics			
	CF	Healthy	Unpaired t-test p-value
Total Subjects	12	11	-
Total Male Subjects	5	5	-
Total Female Subjects	7	6	-
Mean age in years (range; std)	28 (23-39;5)	33 (23-44;8)	0.084
Height in cm (range; std)	170 (155-183;9)	172 (160-185;8)	0.5806
Weight in kg (range; std)	63 (49-76;8)	72 (56-90;11)	0.035

MRI. Each subject underwent rapid, quantitative T_2^* MRI studies that measured lung water density within a 9 second breath-hold. Details of the MRI technique can be found in ^[4]. Images were taken at total lung capacity (TLC) and functional residual capacity (FRC) with 12-16 sagittal slices at regular intervals throughout each lung. In a healthy subject, this technique detects water from blood and lung tissue. However, in CF patients, water content from mucus build up and other lung abnormalities is also detected. From these images, we collected quantifiable data for central and peripheral total density and total volume at TLC and FRC for each patient. Central and peripheral total density were delineated post-imaging as described below (Figure 1).



Phipps, Paul R., Igor Gonda, Dale L. Bailey, Peter Borham, George Bautovich, and Sandra D. Anderson. "Comparisons of the Planar and Tomographic Gamma Scintigraphy to Measure the Penetration Index of Inhaled Aerosols." Am Rev Respir Dis 139 (1989): 1516-523. Fig. 2 – Diagram of Peripheral and central regions and mid-lung slicing.

MBW. The MBW tests were performed using custom-built equipment available in the laboratory of Dr. Darquenne. The test utilizes a bag-in-box system with separate bags for inspired and expired gases where gas flow and concentrations is measured with a pneumotachograph within the apparatus and a rapid-responding mass spectrometer near the lips of the subject, respectively ^[9]. The test consisted of the subject performing about twenty-five regular breathing cycles with a tidal volume of approximately 1 L. Starting at FRC, the subject inspired 100% oxygen while the expired N₂ concentration and respired volume were continuously recorded at the mouth. Test was completed when the mean expired N₂ fell below 2%. The test was repeated three times for each subject. The data from the MBW allowed us to determine the inhomogeneities that existed in CF patients by comparing their lung clearance index (LCI) values to healthy controls. Inhomogeneities were also quantified by analyzing the heterogeneity in the conducting airways (Scond) and ventilating acinar within the lungs (Sacin).

PFT. Standard PFTs were performed with the best test out of three results recorded. Forced expired volume in the first second (FEV₁) values, forced vital capacity (FVC), forced expiratory flow from 75% to 25% of FVC (FEF₂₅₋₇₅) were collected.

Data Analysis:

MRI. MRI lung images were divided into a central and peripheral zone as shown in Figure 1. It should be noted that while most of the large and medium-sized airways are included in the central region, this region also includes a non-negligible portion of the lung parenchyma. Total density and total volume were calculated for both respective zones at TLC and FRC with density expressed as Fractional Lung Density (FLD) ranging from zero (100% air) to 1 (100% water).

MBW. MBW data was used to calculate lung clearance index (LCI), ventilation heterogeneity in the conducting airways (Scond), heterogeneity in ventilating acinar airways (Sacin), and curvilinearity (curv). Calculating Scond and Sacin begins by deriving the normalized regression of a phase III curve. Specifically, N₂ gas concentration is plotted against expired volume for each breath where the regression of the alveolar plateau slope (phase III) is normalized by dividing it by the mean gas concentration. This is then plotted against lung turnover (TO). TO is a better measurement than breath number as it allows for better comparison of subjects with different lung volumes. Scond is the difference in the normalized regression of phase III per TO up to TO=3 given that in severe heterogeneity, the regression approaches a theoretical horizontal asymptote at higher values of TO. Sacin is determined by subtracting the contribution of conductive airways from the normalized regression of phase III in the first breath. A curv value is derived from the curvilinearity of the semilog washout curve which is associated with a specific ventilation heterogeneity. A curv value of 0 indicates homogenous ventilation while a value of 1 indicates an infinitesimally slowly emptying lung. LCI quantifies the inefficiency of gas mixing in the lungs from dead space effects and heterogeneity among intra-acinar and convection-dependent ventilation ^[11,12].

Results and Discussion:

All healthy subjects had normal PFT values ($\geq 80\%$ predicted) while CF patients had FEV₁ values ranging from 23 to 104 %predicted (mean=65 \pm 26 %predicted; p-value=0.001),

FVC values from 24 to 108 %predicted (mean=76 ±24 %predicted; p-value=0.018), FEF₂₅₋₇₅ values from 10 to 110 %predicted (mean=51 ± 37%predicted; p-value=0.003) (Table 2).

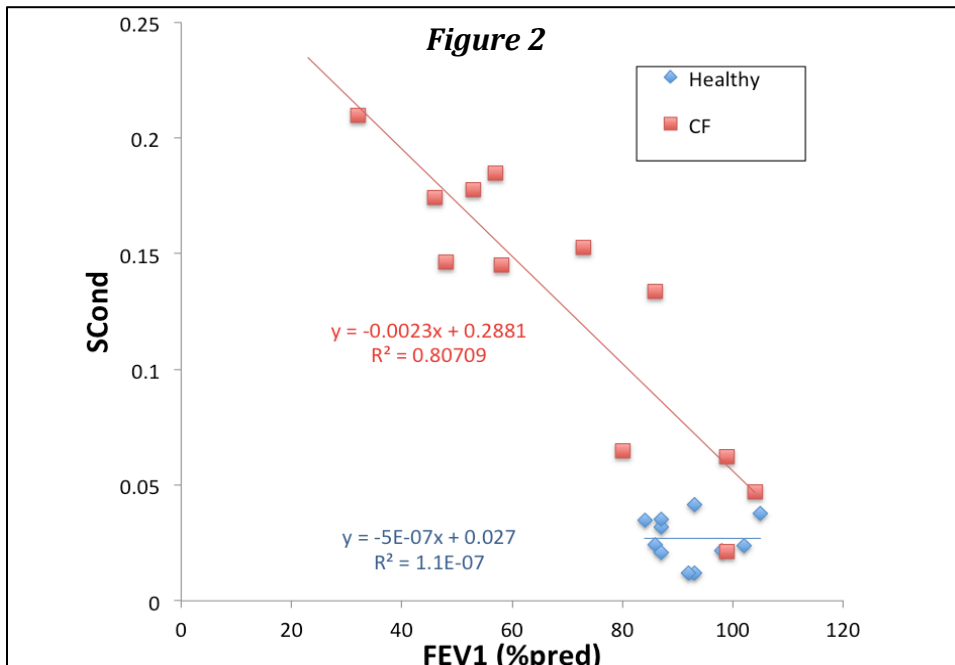
Table 2

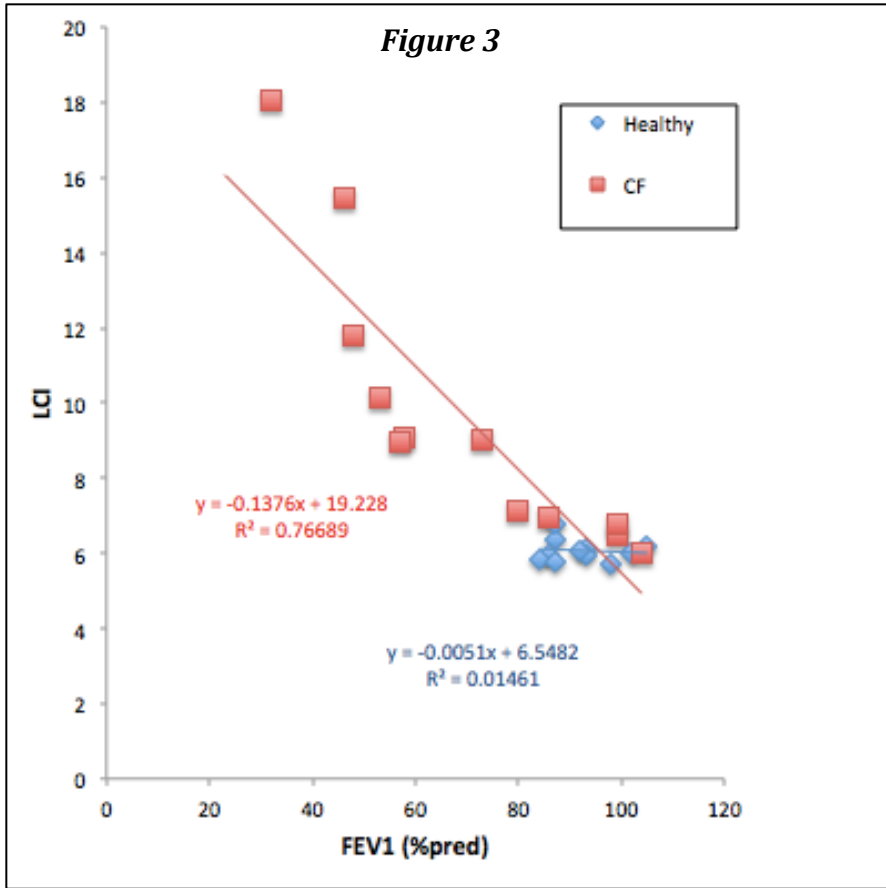
Average %-Predicted PFT Values (range; std)		
	CF	Healthy
FEV₁ (%)	64.6 (23-104; 25.9)	92.2 (84-105; 6.9)
FVC (%)	75.8 (24-108; 23.8)	93.5 (80-107; 8.6)
FEV1/FVC (%)	85.5 (67-102; 13.1)	98.5 (88-105; 6.0)
FEF₂₅₋₇₅ (%)	50.1 (10-110; 37.2)	88.3 (58-121; 18.9)

The greatest correlation (as defined by the greatest R² value; Table 3) in CF patients was between Scond and FEV₁ (Fig. 2). When comparing Scond, 42% of CF subjects (N= 5) fell within the normal ranges of FEV1 (80 to 120% predicted) but had substantially higher Scond values compared to healthy controls (control (N=11): Scond=0.027 ± 0.010; CF (N=5): Scond=0.066 ± 0.013; p-value< 0.0001). This indicates much more heterogeneity and thus, likely much more disease progression than could be detected by FEV1 values from PFT alone. This result was also seen when comparing LCI with FEV1 (control (N=11): LCI = 6.073 ± 0.296; CF (N=5): LCI = 6.667 ± 0.028; t-test P-value = 0.0006) (Fig. 3). This may suggest that FEV1 values obtained from PFTs may not be sensitive enough for early detection of disease progression, with Scond and LCI appearing to be more sensitive parameters.

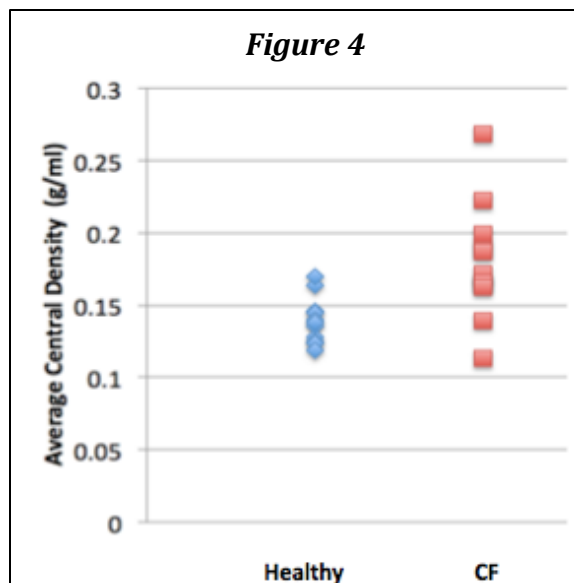
Table 3

R ² Values for CF Subject Comparison								
	FEV ₁ (% pred)	FVC (% pred)	FEV ₁ /FVC (% pred)	FEF ₂₅₋₇₅ (% pred)	Avg Central Density at FRC (g/ml)	Avg Peripheral Density at FRC (g/ml)	Avg Central Density at TLC (g/ml)	Avg Peripheral Density at TLC (g/ml)
Scond	0.8071	0.724	0.53876	0.73455	0.00004	0.15542	0.48797	0.2285
Sacin	0.421	0.272	0.50036	0.36151	0.2338	0.44207	0.0006	0.00591
LCI	0.7669	0.695	0.61561	0.61308	0.02444	0.10593	0.17083	0.01172
Curv	0.7426	0.593	0.63805	0.70003	0.14105	0.41725	0.07345	0.02119
Avg Central Density at FRC (g/ml)	0.0153	0.01	0.00439	0.01067	-	-	-	-
Avg Peripheral Density at FRC (g/ml)	0.2085	0.018	0.63143	0.3105	-	-	-	-
Avg Central Density at TLC (g/ml)	0.3898	0.538	0.07575	0.32923	-	-	-	-
Avg Peripheral Density at TLC (g/ml)	0.2115	0.467	0.00022	0.10306	-	-	-	-





Our other finding showed that average central density at TLC (Fig. 4) was statistically greater in CF than in healthy subjects ($p < 0.009$). There was no significant difference in TLC volume between controls and CF patients (control (N=11): Total TLC volume= 3734.223 ± 689.887 ; CF (N=12): Total TLC volume= 3663.313 ± 811.310 ; p -value=0.824). The increasing density during TLC with no significant differences in lung volume suggests that in subjects with lower FEV₁ values (and therefore lower lung function), mucus and other debris (which increases density) prevents air from reaching the entire lung during maximum inhalation attempts.



Conclusion:

Although FEV1 values from PFTs did correlate fairly well with most measures of lung function, MRI studies and MBW were able to provide more specific information about lung function and excess waters location. Importantly, the use of MBW indices (i.e. Scond, LCI, and Sacin) may potentially allow for a better detection of early CF disease than PFT alone. Also, given that MRI densities are significantly higher in CF patients at TLC than in healthy controls, this technique may be a promising tool detecting and monitoring progression of CF with spatial information.

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