

**SMOKING CESSATION AND FUNCTIONAL CT ASSESSMENT OF PULMONARY
ARTERIAL DYSFUNCTION IN SMOKING ASSOCIATED EMPHYSEMA**

Short title: Smoking Cessation and Functional CT Assessment

Principal Investigator(s):

Eric A. Hoffman, Ph.D.

Medically Accountable Investigator(s):

Alejandro Comellas, MD

Sponsor:

National Institute of Health

NCT03382106

Grant Number: R01HL130883

11 September 2017

STATISTICAL ANALYSIS PLAN

Statistical Analysis Method

Image Quantitation and Outcome Measures: Lung density histogram-based measures of parenchymal characteristics and PBV parameters extracted using the Siemens software for material decomposition will serve as the primary metrics in this project. Regional PBV will be expressed as a percent of the total lung PBV. The primary outcome measure in this study will be CV of PBV and regional ventilation along with neutrophil accumulation assessed by SPECT. The primary measure used to assess lung parenchyma in the non-contrast scans will be the percent of lung falling below -950 HU. Secondary measures include the position of the lower 15th percentile point on the lung density histogram (P15) and “Alpha” negative of the slope of the log-log plot of the number of holes plotted against hole size (44) with holes defined as connected voxels < -950 HU. In all of the volume scans we will extract the lungs, lobes, sub-lobe segments, airway tree out to two generations beyond the segmental airways as outlined in (1) in addition to assessing CV of PBV and ventilation (from image matching) and lung density measures for completeness of lung characterization. From the image matching, we will have lung density on a region-by-region basis at an acinar level of detail. Based upon density changes within a known regional volume of lung, we have a measure of regional ventilation. In the Sildenafil study, change in DLCO (pre and post Sildenafil) will serve as a secondary outcome measure with the expectation that as inflamed lung regions are perfused, DLCO will drop but that this will recover in the smoking cessation follow-up and will correlate with a drop in total lung density on the TLC scans. In addition to evaluating CV of PBV and ventilation, we will warp pre and post hypoxia and Sildenafil PBV image sets and test whether the regions of highest PBV remain high under hypoxia in the emphysema susceptible smokers and whether the regions of low PBV increase with Sildenafil. This test will significantly strengthen the link back to our primary hypothesis. Image matching software developed in house (53, 55-59) will be used to correlate data from the non-contrast volume scan and the PBV DECT scan. Heterogeneity of PBV will be assessed using our in-house PASS software. All other analysis will be assessed via VIDA’s (Software derived from our laboratory and now commercialized and FDA 510K cleared) Apollo software. The VIDA software together with PASS has analyzed over 50,000 CT data sets from a growing number of multi-center investigations. Details of analysis approaches are given in (1). Segmentation results are passed between Apollo and PASS. In PASS, we are able to use the vascular tree extracted by Apollo to identify the vascular paths that serve to define the sub-lobe segments. We will use these lobar and sub-lobe demarcations as the basis for evaluating PBV heterogeneity and lung density metrics in the emphysema susceptible and emphysema-free normal smokers.

Statistical Analysis

For outcome variables that meet a normal distribution error assumption (or are suitable to normalization through a transformation) our statistical analysis for Aims 1-4 will be primarily based on general linear models with identity link and normality of errors. Specifically, we will look at increasing/decreasing trends of the outcome variable as well as pair-wise comparisons across groups. These pair-wise comparisons will be obtained as orthogonal contrasts within the linear models. For those variables that do not meet the assumptions of the general linear models

we will use generalized additive models (GAM). These regression models allow for exploration of nonparametric relationships of an outcome variable with a number of independent variables simultaneously and identify associations when the response variable is not normally distributed or equal variance assumptions are not met. PBV measures will also be assessed using Bland-Altman methods, with adjustment for heteroscedasticity if present. For comparisons that involve an intervention (e.g., hypoxia and Sildenafil), differences between study groups will be estimated by a time (pre/post)*group interaction term in linear models with generalized estimating equations.

All models will be adjusted for covariates. Covariates will be considered for inclusion into regression models based principally on plausible evidence and secondarily on evaluation of statistical associations in the dataset. Data from multiple scans of the lung of a subject are generally spatially and/or temporally correlated; we will account for such correlation in the analysis, e.g. as random effects in a linear mixed model (113) Since a major interest in this study is to investigate differences between ordinal groups we perform pair wise comparisons between groups. To control the experiment-wise type I error (“multiple comparisons”), we use the Holm step-down procedure, an improved version of the Bonferroni criterion. Subject dropout and resultant missing data in the smoking cessation project will use the Generalized Estimating Equation GEE to impute the missing values for our generalized linear model analysis of the data.