Dear APSR colleagues

In this issue of the APSR Respiratory Updates, we want to highlight important findings of some recently published papers that are related to quantitative imaging of the respiratory system.

Quantitative imaging has evolved into a useful non-invasive tool for assessing structural changes of the lungs. This evolution results from the development of novel image analysis programs and the advent of advanced technology in computed tomography (CT) and magnetic resonance imaging (MRI). Quantitative imaging has shed new light on the structural-
functional relations in COPD, asthma, idiopathic pulmonary fibrosis, and cystic fibrosis. Measurements generated by quantitative imaging have helped phenotype heterogeneous diseases, predict clinically relevant outcomes, and predict survival. However, more studies are needed to solve problems as pointed out after each selected paper. For example, quantitative imaging-derived phenotypes need to be validated both internally and externally in longitudinal studies. The method of assessing airway remodeling needs to be standardized when using either quantitative CT or MRI.

Yours faithfully,

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Cluster Analysis in the COPDGene Study Identifies Subtypes of Smokers with Distinct Patterns of Airway Disease and Emphysema

Authors: Peter J Castaldi et al.
URL: http://thorax.bmj.com/content/69/5/416

Comment:
This study was conducted to identify subgroups of smokers by applying cluster analysis to data of 10,192 smokers from the COPDGene study. Smokers were classified into four distinct subgroups based on FEV₁ % predicted and quantitative CT measurements: relatively smoking-resistant, mild upper zone-predominant emphysema, airway-predominant, and severe emphysema. Adverse outcomes of COPD (exacerbations, mMRC dyspnea, BODE, and hospitalizations) occurred more frequently in each of the remaining subgroups than in the relatively smoking-resistant subgroup. The four subgroups were also associated with known genetic variants of COPD. Results of this study demonstrate that quantitative CT is useful for classifying smokers. Because the cluster analysis is a data mining method, the subgroups proposed by this study are not suitable for testing a priori hypotheses or for clinical settings.
Hypermorplished 3He Ventilation Defects Used to Predict Pulmonary Exacerbations in Mild to Moderate Chronic Obstructive Pulmonary Disease

Authors: Miranda Kirby et al.
Reference: Radiology. First published online 24 Jun 2014 as DOI: http://dx.doi.org/10.1148/radiol.14140161
URL: http://pubs.rsna.org/doi/abs/10.1148/radiol.14140161

Comment:
In this study, the authors found that $^3$He MRI ventilation defect percentage (VDP) was significantly higher in patients with at least one hospitalization than in patients without hospitalization after following up 91 COPD patients for 5 years. VDP was significantly associated with airway wall area ($r = 0.26$, $P = 0.01$) and low attenuation area percent ($r = 0.61$, $P < 0.0001$) measured by quantitative CT. VDP was significantly associated with the number of hospitalizations in patients with mild to moderate COPD ($RR = 1.19$, $P = 0.01$) after adjusting for other variables. The findings suggest that $^3$He MRI VDP may reflect a mixed airways–emphysema phenotype and help identify patients with mild to moderate COPD who are at risk for hospitalizations due to COPD exacerbations. Because the effect size is relatively small—$RR = 1.19$, the clinical implications of VDP need to be validated in studies with larger sample size.

CT Measurement of Airway Remodeling and Emphysema in Advanced COPD: Correlation to Pulmonary Hypertension

Authors: Gael Dournes et al.
Reference: Am J Respir Crit Care Med. First published online 13 Nov 2014 as DOI: 10.1164/rccm.201408-1423OC
URL: http://www.atsjournals.org/doi/abs/10.1164/rccm.201408-1423OC#.VGvVy_mUfXU

Comment:
The authors hypothesized that airway remodeling measured by quantitative CT may be associated with pulmonary hypertension (PH) in COPD. The airway remodeling was assessed by quantitative CT as the square root of wall area of a hypothetical airway with internal perimeter of 10 mm (Pi10). The authors found that Pi10 was positively associated with mean pulmonary arterial pressure (PAP$_m$) measured by right heart catheterization ($r = 0.62$, $P < 0.001$). Pi10 was an independent predictor of PAP$_m$ after adjustment for other variables. The findings suggest that airway remodeling measured by quantitative CT may predict the severity of PH in COPD. Because this is an observational study, the significant association between Pi10 and PAP$_m$ does not imply that airway remodeling and PH have a causal relationship. The generalization of the findings is limited because the sample size is small ($n = 60$) and includes only patients with advanced COPD.
**Comparison of Spatially Matched Airways Reveals Thinner Airway Walls in COPD. The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study and the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS)**

**Authors:** Benjamin M Smith et al.

**Reference:** Thorax 2014;69:987-996

**URL:** [http://thorax.bmj.com/content/69/11/987](http://thorax.bmj.com/content/69/11/987)

**Comment:**
This study was conducted to answer the question “Are airway walls in COPD thicker or thinner than those in controls?” To that end, the authors compared airway wall areas between the two groups by taking the approach of “spatially matched central airways”, in which airway wall area for each “generation number” was grouped from 5 pre-specified paths. The authors found that mean airway wall areas at generation numbers 3-6 were significantly smaller in smokers with COPD than in smokers without COPD after adjustment for other variables. Therefore, the authors concluded that airway walls were thinner in COPD than in controls. However, we are not sure what the mean airway wall area for each “generation number” reflects because it was adjusted for many variables, while it was not adjusted for important variables such as lumen diameter and the count of airway segments for each “generation number”. More studies are needed to answer the question raised by the authors.

**Computed Tomographic Measures of Airway Morphology in Smokers and Never-Smoking Normals**

**Authors:** George R Washko et al.

**Reference:** J Appl Physiol 2014;116:668–673

**URL:** [http://jap.physiology.org/content/116/6/668](http://jap.physiology.org/content/116/6/668)

**Comment:**
Wall area percent (WA%) increases in COPD because wall area (WA) increases or lumen area (Ai) narrows or both. In this study, the authors found that smokers with lower FEV₁ tended to have narrower Ai and smaller WA measured by CT at segmental and sub-segmental bronchi. Therefore, the authors concluded the fact that WA% increased across COPD stages was not due to the increased WA, but rather due to the narrow Ai. Reasons for the narrow Ai should be investigated in other longitudinal studies. The unresolved questions of this study is that “why did nearly half of the smokers with COPD have their sub-segmental bronchi undetected by the software?” If these smokers were excluded from the statistical analysis as a result of their increased WA, the results of this study would be biased. This study once again reminds us about the limitation of WA% and the lack of standardized indices of airway dimensions to reflect airway remodeling.
Variation in the Percent of Emphysema-like Lung in a Healthy, Nonsmoking Multiethnic Sample: the MESA Lung Study

Authors: Eric A Hoffman et al.
URL: http://www.atsjournals.org/doi/full/10.1513/AnnalsATS.201310-364OC#.VHvE9zGUfXU

Comment:
This study was conducted to provide normal reference equations of emphysema percent measured by quantitative CT. Emphysema percent at two threshold levels (%LAA_{950} and %LAA_{910}) was measured from 3137 participants, including 854 healthy never smokers. The authors found that emphysema percent was associated positively with age, height, male gender, and Whites race; it was associated negatively with body mass index. The authors then presented the reference equations of emphysema percent for former and never smokers as one group and current smokers as another. These equations are able to account for covariates and help define abnormal values for emphysema percent. However, these equations should be validated in other cohorts and should not be applied directly to studies using different CT scanning protocols.

Quantitative Computed Tomography–Derived Clusters: Redefining Airway Remodeling in Asthmatic Patients

Authors: Sumit Gupta et al.
Reference: J Allergy Clin Immunol 2014;133:729-38
URL: http://www.sciencedirect.com/science/article/pii/S0091674913014887

Comment:
In this study, the authors found that wall volume percent (WV%) of the apical segmental bronchus of the right upper lobe (RB1) was significantly greater in patients with asthma than in healthy control subjects because its lumen volume was significantly smaller in asthma than in control, while its wall volume was not different. By using cluster analysis, patients with asthma were classified into 3 novel phenotypes. While FEV_{1} % predicted and RV/TLC significantly differed, clinically relevant outcomes such as disease duration, symptom score, and severe exacerbation frequency did not differ among the 3 phenotypes. One should be cautious when interpreting the results of this study because the method of calculating lumen volume and wall volume has not been validated in human bronchial tree. The relevance of the asthma phenotypes described here is another concern because they were generated by a data mining method and based on too many input variables—11 CT indices.
Automated Quantification of Radiological Patterns Predicts Survival in Idiopathic Pulmonary Fibrosis

Authors: Fabien Maldonado et al.
Reference: Eur Respir J 2014; 43:204–212
URL: http://erj.ersjournals.com/content/43/1/204.long

Comment:
The authors developed novel software called CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) to measure volumes of normal lung, ground-glass opacities, reticular abnormalities, honeycombing, and emphysema on HRCT in patients with idiopathic pulmonary fibrosis (IPF). They found that every SD increase in total volume of interstitial abnormalities (the volumetric sum of total ground-glass opacities, reticular abnormalities, and honeycombing) was associated with 1.70-fold increase in mortality (95% CI, 1.19 to 2.43) after adjustment for sex, pack-years of smoking, baseline FVC % predicted, baseline DL_{CO} % predicted, and time between CTs. Therefore, volumes of lung parenchymal abnormalities measured by quantitative CT may complement FVC and DL_{CO} in monitoring patients with IPF. However, the software should be refined and validated in future studies, given that the levels of agreement between CALIPER and radiologists were only mild to moderate.
Automated CT Scan Scores of Bronchiectasis and Air Trapping in Cystic Fibrosis

Authors: Emily M DeBoer et al.
Reference: CHEST 2014;145:593–603
URL: http://journal.publications.chestnet.org/article.aspx?articleid=1750230

Comment:
The authors developed and validated CT image analysis software to count visible airways on inspiratory CT images and to measure air-trapping on expiratory CT images in children with cystic fibrosis. The authors found that airway counts and air-trapping were significantly higher in children with cystic fibrosis than in control subjects. In children with cystic fibrosis, airway counts were associated positively with bronchiectasis scores evaluated by two observers, negatively with FVC and FEV$_1$, and positively with sputum neutrophil elastase concentration. Air-trapping measured by the software was associated positively with air-trapping scored by the two observers. Therefore, airway counts and air-trapping quantified by the software may be useful surrogates for bronchiectasis and air-trapping in children with cystic fibrosis. However, the software should be validated in longitudinal studies and in adults with bronchiectasis; should be refined to not only count visible airways, but also measure the size and wall thickness of dilated bronchi.

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