Day: *4 June 2015*

My overarching objective is to provide the research evidence related on how to best exploit pulmonary MRI and CT for the evaluation of imaging biomarkers of airways disease and parenchyma tissue destruction (emphysema) common in chronic obstructive lung diseases including chronic obstructive lung disease (COPD), pediatric bronchopulmonary dysplasia and congenital lobar emphysema. In attending, I hope the learners will better understand the advantages of using MRI and CT in these important chronic lung diseases that often require serial imaging over many years.

Specialty area: *Quantitative Biomarkers of Chest Disease: the Role of MRI in a Multimodality Practice*

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Highlights

- Hallmark radiological findings in COPD include CT-derived airway abnormalities including reduced numbers of airways and morphological abnormalities and CT-measured parenchymal abnormalities including emphysema and bronchiectasis.
- Hallmark MRI findings in COPD include ventilation heterogeneity and abnormally elevated apparent diffusion coefficients based on inhaled gas (^{3}He, ^{129}Xe, ^{19}F MRI. Static and dynamic ^{1}H MRI and Oxygen-enhanced ^{1}H MRI also provide quantitative information about ventilation and parenchymal abnormalities in COPD, BPD and CLE.

TALK TITLE: Imaging of Chronic Obstructive Pulmonary Disease (COPD): MRI vs. CT

TARGET AUDIENCE: Respiratory researchers, Pulmonologists, pediatric radiologists, radiologists, imaging scientists, patients and care-givers

OUTCOME/OBJECTIVES:
Learning objectives include:

1) What are the hallmark CT and MRI findings in COPD, BPD and CLE
2) How can imaging methods be used in a complementary fashion to better understand the contributions of both airways disease and emphysema, collateral ventilation and bronchiectasis in COPD, BPD and CLE
3) In what situations is the preferred method of choice CT? MRI?

PURPOSE:

Chronic obstructive pulmonary disease (COPD) affects over 300 million adults worldwide and over 3 million Canadians. COPD is progressive, debilitating and chronic, and the disease course is punctuated by sudden, acute worsening of symptoms or "exacerbation" that require immediate medical care – most often requiring hospital admission. COPD exacerbation or "lung attack" accounts for the vast majority of Canadian urgent hospital admissions[1] and represents a staggering healthcare and societal burden that is under-appreciated. The enormity of this cost becomes apparent by recognizing that, in 2008-2011, 1 of every 4 Ontario hospital beds was occupied by a COPD patient, equivalent to filling 250 of the 1000 hospitals in Canada with COPD patients only. Unfortunately, despite these dismal statistics and alarming costs, there is no reliable way to prospectively identify COPD patients at higher risk of exacerbation and intervene in order to obviate the necessity for hospitalization.

Currently, COPD diagnosis, disease severity and progression are evaluated using the spirometry measurement of the forced expiratory volume in 1s (FEV_1) - a simple and inexpensive measure of airflow limitation. Unfortunately, FEV_1 measurements report global lung measurements that provide no information about the site and pathology responsible for airflow limitation, symptoms and disease worsening.[2,3] Because of this, FEV_1 measurements are weakly predictive of COPD therapy response, progressive worsening, and risk of exacerbations and death. ***To decrease the staggering burden of COPD on patients and the health care system, new tools for monitoring COPD and predicting COPD exacerbations are required. We think that pulmonary structure-function imaging measurements of COPD can be used to address this critical gap and predict COPD exacerbations and then dramatically decrease their number, impact and costs.***

Medical imaging has ***not*** played a large role in the clinical management of COPD and pediatric cases of BPD and CLE, mainly because of the radiation burden and risks associated with serial and longitudinal use of x-ray computed tomography (CT) and nuclear medicine methods such as

positron emission tomography (PET) or single photon emission computed tomography (SPECT). While magnetic resonance imaging (MRI) does not pose such risks, conventional MRI is not used in routine COPD clinical care because of the inherently low pulmonary ^{1}H MRI signal which makes imaging at clinical field strengths very challenging. MRI approaches using inhaled gas contrast agents however have enormous promise because they are rapid (~15s), safe and information-rich.

Therefore, in this lecture we directly compare pulmonary MRI and CT and identify the strengths and weaknesses of both approaches. We discuss previous expertise in respiratory MRI and CT, image processing developments that enable high-volume patient-based research. We try to answer the following questions: *How do quantitative ^{1}H MRI measurements compare with CT and ^{129}Xe MRI measurements in COPD patients? Can ^{1}H MRI be optimized to provide measurements of clinically-relevant disease changes over time as COPD progresses? Can ^{3}He and ^{129}Xe MRI measurements be used to phenotype COPD patients to predict and prevent COPD exacerbations?*

There are two major pathological phenotypes in COPD - *emphysema* and *airways disease.* Emphysema is defined histologically as an abnormal permanent enlargement of the lung parenchyma beyond the terminal bronchioles. Recently, Hogg and co-workers showed using histology and micro-CT, the presence of tissue destruction in the respiratory bronchioles (manifested as *emphysema*), and tissue proliferation in the airways (manifested as *airways disease*), these findings separated by only a few micrometers.[3] In a similar manner, clinical CT has been exploited in COPD because it provides quantitative and regional measures of both tissue destruction and airways disease. For example, regional CT measurements of the cross-sectional area of the airway wall (WA%) and the percentage of low attenuation areas (LA%), a

measure of emphysema, explain COPD pulmonary function abnormalities. However, CT does not provide direct measurements of pulmonary function (ie. ventilation), and radiation dose certainly limits its use. Hyperpolarized ^{3}He and ^{129}Xe MRI however, provide measurements without radiation risk of those regions of the lung that participate in ventilation and those that do not (Figure 6 and 7). ^{3}He ventilation defects can be regionally quantified as the ventilation defect percent (VDP) and we recently showed that ventilation defects stem from both airway wall abnormalities and emphysema in COPD. In addition to measuring ventilation, MR methods can be used that are sensitive to gas *self-diffusion*, providing an apparent diffusion coefficient (ADC), a measurement that is dependent on the Brownian motion of the gas atoms. In COPD patients, MRI ADC provide a surrogate measurement of emphysema that has been validated using histology.[49,50] Similar to cardiovascular disease, where the deposition of atherosclerotic plaque is not random, nor homogeneous, in COPD, both airways disease and emphysema are heterogeneously and non-randomly distributed throughout the lung. Until now however, measurements of COPD have relied mainly on global lung volumes and airflow measurements made at the mouth. Such airflow measurements vastly under-estimate the extent of disease because flow is dominated by the major airways that remain patent until disease is far-advanced. Therefore, there is growing consensus that for COPD, quantitative regional measurements provided by imaging are critically needed to evaluate therapy response, progressive worsening and to improve outcomes.

Recent cohort studies[4,5] have prospectively investigated CT phenotypes as a way to predict COPD exacerbations. In one cohort study[6], the frequency of COPD exacerbations was related to the presence of both emphysema and airways disease. Another study[7] also showed that patients with a mixed emphysema and peribronchial thickening had more frequent exacerbations.

Similar to thoracic CT, pulmonary functional MRI provides a way to generate independent emphysema and airways disease COPD phenotypes.[8] MRI ventilation defects are also strongly predictive of COPD exacerbations in patients with mild disease in whom other imaging and clinical measurements were not. This work provides the first evidence that MRI can be used to predict exacerbations in COPD patients in whom all other imaging and clinical measurements were not helpful.

METHODS

We will discuss CT, functional CT, ^{1}H MRI static and dynamic methods and inhaled gas MRI approaches.

RESULTS and DISCUSSION

Example results will be provided for early or subclinical COPD and advanced COPD as well as pediatric bronchopulmonary dysplasia and young adult bronchopulmonary dysplasia and congenital lobar emphysema.

CONCLUSION

In Ontario alone, approximately 850,000 COPD patients account for 24% of all emergency department visits and hospital admissions, 30% of home care visits and 21% of physician visits. The development of pulmonary structure-function CT and MRI methods stems from the recognition of these alarming statistics and the potential for imaging to provide quantitative pulmonary measurements to improve patient outcomes.

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