Compartmental Model Analysis of Oxygen-Enhanced MRI and DCE-MRI Detects Pre-morbid Lung Damage in Smokers

D. M. McGrath1, J. H. Naish1, S. S. Young2, L. E. Olsson3, C. E. Hutchinson4, J. Vestbo5, J. C. Waterton5, C. J. Taylor1, and G. J. Parker1

1Imaging Science and Biomedical Engineering, School of Cancer and Imaging Sciences, University of Manchester, Manchester, United Kingdom; 2AstraZeneca, Loughborough, United Kingdom, 3AstraZeneca, Mölndal, Sweden; 4School of Translational Medicine, Respiratory Research Group, University of Manchester, Manchester, United Kingdom; 5Department of Cardiology & Respiratory Medicine, Hvidovre University Hospital, Hvidovre, Denmark; 6AstraZeneca, Macclesfield, United Kingdom

INTRODUCTION

Spirometric measures for the diagnosis of chronic obstructive pulmonary disease (COPD) provide global lung function measures that are poorly sensitive to early stage disease. Oxygen-enhanced MR imaging (OE-MRI) has been proposed to determine regional lung ventilation, using dissolved molecular oxygen as a contrast agent (1, 2). Previous workers have analyzed OE-MRI either through visual determination of heterogeneity, ratios of enhancement or time to maximum contrast (1, 2). However these measures give non-specific information on regional lung health and are without specific insight into underlying physiological processes. A compartmental analysis of OE-MRI has been devise (3) that provides biomarkers specifically of regional airway ventilation, diffusion of oxygen at the alveolar membrane, and perfusion within alveolar capillaries. We sought to assess the impact of smoking on these biomarkers, together with perfusion biomarkers from tracer kinetic modeling of dynamic contrast enhanced MRI (DCE-MRI) data, in comparison with spirometry.

METHODS

OE-MRI Compartmental Model: The two-compartment model was derived from the Kety equations (3), where the first compartment term $C_v$ is the increased oxygen concentration in the alveolar gaseous space (mmHg); the second compartment term $C_w$ the increased oxygen concentration in the alveolar membrane; interstitial space between the membrane and pulmonary capillaries and the plasma within the capillaries, i.e. ‘w’ for water, (mmHg); $v_w$ the fractional volume of blood plasma and tissue water per gram of MRI visible tissue (ml/g); $K_{pd}$ is a term describing the diffusing capacity of the alveolar membrane (ml/min/g); $E_{ox}$ is the extraction fraction of oxygen from the tissue water and capillaries (no units); $F_{v}$ is the effective rate of blood flow in the capillaries (ml/min/g) (see eqn. 1), which is also influenced by haemoglobin uptake of molecular oxygen. The input function $C_i$ is defined by the ventilation time $T_{vent}$ (Eqn. 1). $F_{v}$ was fit to the dynamic oxygen concentration curves to solve for $K_{pd}, E_{ox}$ and $T_{vent}$. Volunteer Recruitment: 12 current smokers and 11 non-smokers were recruited. The smokers had pack-year histories of 10 years or more and had all quit smoking for more than 6 months. No previous history of smoking other than passive smoke was recorded. Also any candidate who reported suffering from a cough or chest infection within the 8 weeks prior to participation was excluded.

Spirometry tests: Immediately prior to the imaging evaluation, standard lung function tests were carried out to assess forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1). MR imaging: All imaging was carried out using a 1.5 T-Philips Interia MR system (Philips Medical Systems, Best, Netherlands), while free-breathing (without triggering or gating) and using the body resonator for RF transmission and reception. OE-MRI: Medical air (21% oxygen) and 100% oxygen was delivered via an anesthesia mask at 15 l/min. A single coronal slice image position in the posterior mediastinum was imaged using snapshot FLASH (Fast Low Angle Shot) with radiofrequency (RF) spoiling (4), which allowed $T_{vent}$ mapping of oxygen wash-in and -out at a high temporal resolution of 6 s for a total of 180 time points (i.e. air for 3 mins, oxygen for 9 mins followed by air for 6 mins). The imaging parameters were as in (4). DCE-MRI: The DCE-MRI acquisition was carried out immediately subsequent to the OE-MRI while the volunteer lay in the same position on the scanner bed. A 3D T1-weighted radiofrequency spoiled fast field echo (FFE; spoiled gradient-echo) method with variable flip angles (5) was employed. 0.1 mmol/kg gadodiamide (Omniscan, GEHC, Amersham, UK) was administered as a bolus using a power injector at a rate of 2 mls, followed by an equal volume of saline flush on the 10th acquisition of the dynamic set. Imaging parameters and conversion of $T_{vent}$ to contrast agent concentration were as described in (5).

RESULTS

Significant differences (p < 0.05) were found between median parameters (table 1) for at least 1 comparison of non-smoking and smoking groups for each of the OE-MRI parameters and for the AATH parameters $F_p$, $P_s$, $E$, $v_w$, and $K_{ox}$ (see parameters in blue). $T_{vent}$, $K_{ox}$, $v_w$, $E$ and $PS$ were found to increase with PY, whereas $E_v$, $F_p$ and $P_s$ tended to decrease. In contrast no significant differences were found for either FEV1 in percentage of predicted or FVC/VVC, or for the OE-MRI parameters used by other workers (enhancement ratio and exponential wash-in time), see table 1. Furthermore, the maps of smokers demonstrated increased heterogeneity above those of non-smokers. In figure 1 row (a) is a low risk non-smoker, row (b) a smoker (40 PY) with normal spirometry, row (c) a smoker with pulmonary emphysema.

DISCUSSION AND CONCLUSION

Our analyses revealed smoking related changes in lung physiology that were not detected by either spirometry or the OE-MRI parameters used previously. Increased $T_{vent}$ in smokers may reflect airway inflammation and/or loss of elasticity. Increased $K_{ox}$ may indicate inflammation or edema at the alveoli. Decreased $E_v$, $F_p$ and $P_s$ suggest reduced perfusion, perhaps also due to inflammation of lung tissue, which might also be related to increased permeability (Ktrans, PS, E) and increased $v_w$. Hence, the compartmental model analysis of OE-MRI and the AATH analysis of DCE-MRI provide insight into the early stage impact of smoking, and pre-morbid development of COPD, as well as a potential biomarker for disease progression and therapeutic intervention.

REFERENCES