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

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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 devised (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_A 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_{ox} 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_b 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_A is shape is defined by the ventilation time T_{vent} (3). Eqn. 1 was fit to the dynamic oxygen concentration curves to solve for K_{ox}, $E_{ox}F_b$ and T_{vent}. ***Volunteer Recruitment: 12 current smokers and 11 non-smokers were recruited. The smokers had pack-years (number of years or equivalent years in which 20 cigarettes a day was smoked, PY) ranging from 1.6 to 40 PY. No previous diagnosis of COPD or other lung disease was an inclusion criterion and smoking habits and level of exposure to passive smoke were 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 (FEV_1). ***MR imaging:*** All imaging was carried out using a 1.5 T-Philips Intera 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 gas 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_1 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 T_1-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 ml/s, followed by an equal volume of saline flush on the 10th acquisition of the dynamic set. Imaging parameters and conversion of T_1 to contrast agent concentration were as described in (5). ***OE-MRI post-processing:*** T_1 maps at the maximum expiration position were generated using the registration and correction for breathing pattern related technique of (4). T_1 values were converted to changes in oxygen concentration above baseline air breathing ΔPO_2 (or C_w) using the estimated relaxivity of the oxygen in lung tissue (3). ***DCE-MRI post-processing:*** The DCE-MRI slice that best matched the OE-MRI slice position was identified according to position relative to the imaging isocentre and the chosen slice images were registered to the maximum expiration position (2). Whereas in a previous analysis the 'Extended-Kety' model was used (5), this time the adiabatic approximation to the tissue homogeneity (AATH) model (6) was applied to solve for $F\rho$ (blood flow F by tissue density ρ), PS (the permeability surface area product of the exchange vessels), E (the extraction fraction of the tracer), v_p (the fractional blood plasma volume), v_e (the fractional extravascular extracellular space volume), τ (the mean capillary transit time), and K^{trans} (the volume transfer constant). ***Analysis:*** Maps and median values were calculated over both lungs in each slice for the OE-MRI and DCE-MRI data, and permutation test based t-tests (7) (i.e. multiple comparison adjusted) were used to compare median values between lowest risk non-smokers (those with normal spirometry, i.e. FEV_1 (% of predicted) > 80 % and FEV1/FVC > 0.7, previous PY < 1 and not reporting regular passive smoke exposure), all non-smokers, all smokers and smokers with > 20 PY.

$$C_w(t) = \frac{K_{ox}}{v_w}\int_0^t C_A(t')\exp\left(-\frac{(K_{ox}+E_{ox}F_b)}{v_w}(t-t')\right)dt' \quad (1)$$

Table 1: Subgroup Mean (Stdev) values for median parameters

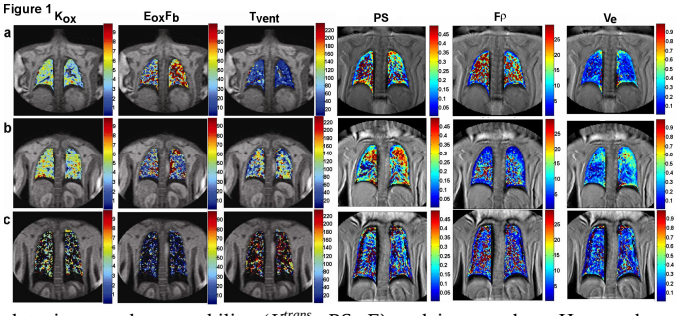
Parameter	LRNS	ANS	AS	S>20PY
T_{vent} (s)	52.7 (19.8)	54.9 (21.4)	74.7 (32.3)	96.4 (33.8)
K_{ox} (ml/min/g)	4.14 (0.33)	4.56 (0.53)	4.66 (0.39)	4.78 (0.33)
$E_{ox}F_b$ (ml/min/g)	56.9 (16.1)	45.5 (24.5)	37.8 (16.1)	27.8 (9.4)
K^{trans} (ml/min/ml)	0.164 (0.039)	0.166 (0.039)	0.238 (0.086)	0.285 (0.085)
$F\rho$ (ml/min/ml)	10.5 (1.9)	9.29 (2.02)	7.31 (2.77)	8.7 (2.8)
v_e (ml/ml)	0.203 (0.008)	0.191 (0.018)	0.244 (0.058)	0.284 (0.053)
E	0.0341 (0.0025)	0.0384 (0.0091)	0.0678 (0.0177)	0.0684 (0.0179)
PS (ml/min/ml)	0.155 (0.041)	0.157 (0.04)	0.229 (0.085)	0.273 (0.084)
v_p (ml/ml)	0.305 (0.058)	0.269 (0.051)	0.231 (0.082)	0.273 (0.08)
τ (min)	0.0585 (0.0053)	0.0611 (0.0055)	0.0669 (0.0123)	0.0637 (0.0054)
Wash-in rate (s)	*98.3 (82.1)*	*56.5 (56.8)*	*53.8 (27.1)*	*78.6 (20.9)*
Enhancement ratio	*1.04 (0.01)*	*1.05 (0.02)*	*1.04 (0.01)*	*1.04 (0.01)*
FEV_1 (% pred)	*102 (12)*	*98.5 (19.5)*	*102 (37.5)*	*83 (24.9)*
FEV_1/FVC	*81 (2.8)*	*76.9 (11.6)*	*67.4 (15.5)*	*64.4 (15.9)*

LRNS: Lowest risk non-smokers; **ANS**: All non-smokers; **AS**: All smokers; **S>20PY**: Smokers with > 20 PY

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 $F\rho$, PS, E, v_e and K^{trans} (see parameters in blue). T_{vent}, K_{ox}, K^{trans},v_e, E and PS were found to increase with PY, whereas $E_{ox}F_b$ and $F\rho$ tended to decrease. In contrast no significant differences were found for either FEV_1 in percentage of predicted or FEV_1/FVC, 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 (21 PY) with abnormal spirometry.

Figure 1



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 $E_{ox}F_b$ and $F\rho$ suggest reduced perfusion, perhaps also due to inflammation of lung tissue, which might also be related to increased permeability (K^{trans}, PS, E) and increased v_e. 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.

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