Increased pulmonary capillary permeability in smokers as measured by DCE-MRI

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INTRODUCTION

Smoking causes inflammation of the lung airways and interstitium resulting in increased alveolar epithelial permeability as measured by clearance rates of ^{99m}Tc-DTPA (1). Vascular endothelial permeability has been observed to increase in-vitro (2) but to date the only in-vivo studies (using PET) have not demonstrated a change (3). A number of studies have demonstrated the feasibility of estimating pulmonary perfusion using first-pass DCE-MRI according to the indicator dilution theory (4). These methods assume negligible extravasation of contrast agent and cannot therefore be used to probe pulmonary capillary permeability. In this study we aimed to assess the feasibility of acquiring and modelling an extended dynamic time series in order to extract quantitative regional information relating to pulmonary capillary permeability in smokers in comparison with non-smokers.

METHODS

Subjects Ten smokers (4 male, age range 29-57) and ten non-smokers (5 male, age range 23-35) with no previous diagnosis of COPD or other lung condition were recruited. The number of pack years (PY = no. cigarettes smoked per day × number of years ÷ 20) was recorded for the smokers and all subjects had spirometry tests.

Image Acquisition Imaging was carried out using a Philips 1.5T Intera system (Philips, Best, NL). Images were acquired under free breathing. The DCE-MRI protocol consisted of 3D T_1-fast field echo (spoiled gradient echo (GRE)) coronal acquisitions with 20 slices, slice thickness 8mm (16mm over-contiguous) , FOV 375x375mm, matrix size 128x128 (using elliptical k-space sampling), TR 2.4ms, TE 0.82ms. Baseline T_1 was determined using 5 individual acquisitions of each of 3 different flip angles of 2°, 10° and 20° acquired prior to the DCE-MRI time series. The dynamic series consisted of 180 consecutive volumes with flip angle 20° and temporal resolution 1.9s. The imaging parameters were selected to minimise acquisition time for each volume in order to minimise motion artefact and maximise temporal resolution for kinetic model fitting. Contrast agent was administered intravenously at the beginning of the 10th volume by power injector. 0.1 mmol/kg of body weight of Omniscan 0.5 mmol/ml (gadodiamide, GE Healthcare) was administered at a rate of 3ml/s followed by an equal volume of saline flush.

Analysis Individual subject arterial input functions were obtained by manual definition of a region of interest in the pulmonary artery (fig 1). A single posterior slice (chosen to avoid the heart and major vessels) was selected for parameter mapping and linear registration was applied to both the baseline T_1 images and the dynamic time series using a method described previously (5). T_1 maps were generated and used to convert the dynamic series signal intensity to contrast agent concentration. An extended version of the Kety model (6) was fitted to the dynamic data on a voxel-by-voxel basis within the registered lung outlines

$$C_t(t) = v_p C_p(t-\omega) + K^{trans}\int_0^t C_p(t'-\omega)\exp\left(-K^{trans}(t-t')/v_e\right)dt'$$

where $C_t(t)$ is the concentration of contrast agent in the tissue, C_p is the concentration of contrast agent in the blood plasma, K^{trans} is the volume transfer coefficient, v_p is the blood plasma volume fraction, v_e is the volume fraction of the extravascular extracellular space and ω is the time delay between the arterial input function (C_p) and the tissue uptake curve (C_t). The area under the first 60s of the contrast agent concentration curve (IAUC60) was also calculated on a voxel-by-voxel basis.

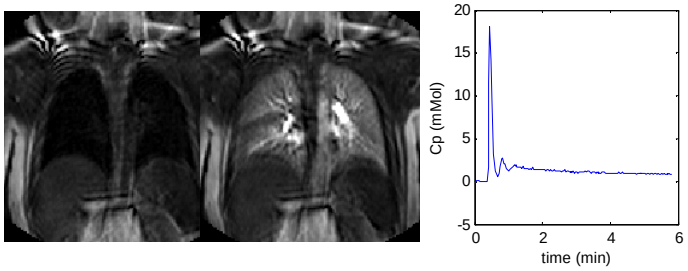

Figure 1 *a) Example images from the dynamic time series, before and after contrast agent injection. Note the signal enhancement throughout the parenchyma. b) Example arterial input function*

RESULTS

Example parameter maps for a smoker and a non-smoker (with normal spirometry) are presented in Fig 2. The parameter maps for the smoker show regional elevated K^{trans} and v_e in this individual. Median values for both K^{trans} and v_e were observed to increase with increasing PY (Fig 3) and were significantly higher in the smoker grouping comparison with the non-smoker group (Table 1). No significant differences in IAUC60 were observed between the groups. The blood volume, v_p was lower in smokers compared to non-smokers but this was only statistically significant when comparing the whole group of smokers and no trend with pack years was observed. Only one smoker had significantly reduced lung function by spirometry (PY=21, FEV1<40%).

Parameter	Non-smokers mean	All smokers mean (P-value)	PY>20 mean (P-value)
IAUC60 (mMol.s)	70.6	67.6 (0.5)	64.0 (0.3)
K^{trans} (ml/min/ml)	0.25	0.40 (**0.03**)	0.48 (**0.002**)
v_e	0.21	0.27 (**0.02**)	0.32 (**0.0006**)
v_p	0.27	0.21 (**0.03**)	0.24 (0.4)

Table 1 *Mean across subjects of median parameter values and statistical comparison (t-test) of all smokers vs non-smokers and PY>20 vs non-smokers.*

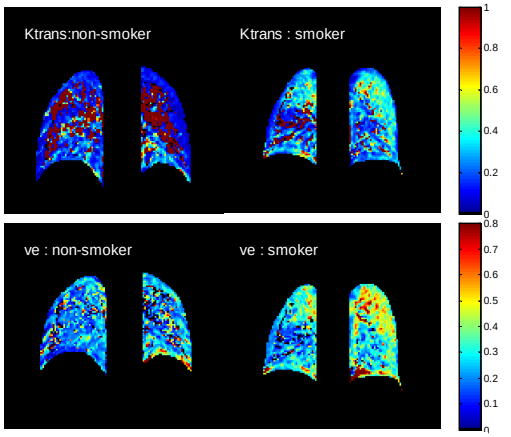

Figure 2 *Example parameter maps show regional elevated K^{trans} and v_e in the smoker*

DISCUSSION AND CONCLUSION

The lungs are highly vascular and extravasation of contrast agent is not flow-limited. We therefore expect K^{trans} to reflect capillary permeability in this study. Our results indicate increased capillary permeability in smokers in agreement with (2). The observed increase in v_e is consistent with the presence of inflammation in smokers. In conclusion, we have demonstrated the feasibility of measuring regional pulmonary capillary permeability in-vivo with DCE-MRI and observe significant increases due to smoking.

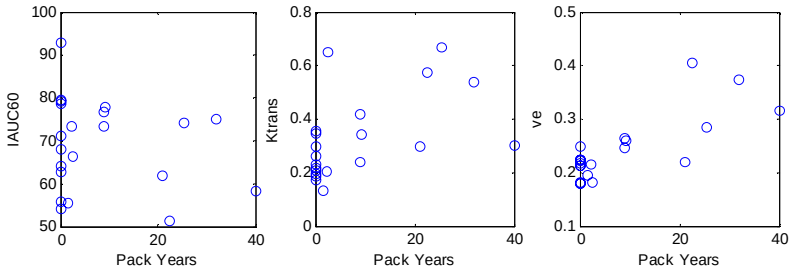

Figure 3 *Median parameter values plotted against pack years*

REFERENCES 1. Jones et al, *Lancet* **1**,66-68 (1980); 2. Holden et al *J Appl Physiol*.**66**, 443-449 (1989); 3. Kaplan et al *Am Rev Respir Dis*. **145**, 712-715 (1992); 4. Hatabu et al *Magn Reson Med* **42**, 1033-1038 (1999), Ohno et al, *J Magn Reson Imag* **20**, 353-365 (2004); 5. Naish et al, Magn Reson Med *Magn Reson Med*, 54, 464-469, 2005; 6. Daldrup et al, *Magn Reson Med* **40**, 537-543 (1998). **Acknowledgements** The study was funded by AstraZeneca.