Novel Vascular Manifestations of Chronic Obstructive Pulmonary Disease (NoVasC) Study: Results from Multimodal Cerebral Magnetic Resonance Imaging of Non-Hypoxaemic Stable Chronic Obstructive Pulmonary Disease (COPD) Vs. Smoker Controls Without COPD

C.A. Spilling[1], M-P. K. Bajaj[1], D.R. Burrage[2], S. Ruickbie[2], E.H. Baker[2], P.W. Jones[2], T.R. Barrick[1], J.W. Dodd[3]

[1]Neuroscience Research Centre, Molecular and Clinical Sciences Research Institute, St George's, University of London - London/UK, [2]Clinical Pharmacology, Infection and Immunity Research Institute, St George's, University of London – London/UK, [3]Academic Respiratory Unit University of Bristol – Bristol/UK

Introduction

Cognitive impairment is a common systemic manifestation of chronic obstructive pulmonary disease (COPD) and is associated with higher levels of functional dependence [1], poorer medical adherence [2] and greater mortality [3]. However, its neurobiological causes remain unclear. We have previously reported greater volumes of hyperintense white matter lesions (WML) and widespread white matter (WM) tissue microstructural changes (from Diffusion Tensor Imaging, DTI) in people with COPD [4]. These and findings from other studies, such as hypoperfusion [5][6], hippocampal atrophy [7], localised grey matter (GM) loss [8][9], and presence of cerebral microbleeds [10] are consistent with a vascular pathophysiology. However, several studies, including our own, are confounded by large group differences in smoking history. The Novel Vascular Manifestations of COPD (NoVasC) study was designed to address this limitation through direct comparison of COPD patients and smoking controls.

Methods

Funding: British Lung Foundation Research Grant

Subjects: 27 COPD patients (age 67±8, 41% male, pack years 39±21, FEV_1 58±18% predicted), 23 controls (age 63±9, 48% male, pack years 30±14, FEV_1 101±19% predicted).

Key clinical measures: standard pulmonary function and spirometry testing (inc. blood pressure), Montreal Cognitive Assessment (MoCA) (cognitive screen for dementia and mild cognitive impairment), Hospital anxiety and depression scale (HADs).

MR Image acquisition: 3-Tesla T1-weighted (T1W) and Fluid-attenuated Inversion Recovery (FLAIR) (tissue structure) , pseudo-Continuous Arterial Spin Labelling (pCASL) (cerebral blood flow), Diffusion Tensor Imaging (DTI) (tissue microstructure).

Image analysis

Whole-brain

- T1W data were segmented into GM, WM and cerebrospinal (CSF) tissues-types [11].
- Tissue volumes were calculated and subsequently normalised with respect to total intracranial volume (TIV=GM+WM+CSF).
- Image intensities on FLAIR (hyper-intense) and T1W (hypo/iso-intense) images were used to delineate WMLs. Their number, average size and total normalised volume, were calculated.
- Cortical thickness was computed from T1W tissue segmentation maps.
- Fractional Anisotropy (FA) and Mean Diffusivity (MD) maps calculated from DTI data, provided measurement of tissue microstructure in the GM and WM.
- Cerebral Blood Flow (CBF) was calculated from the pCASL data and CBF values classified as either GM or WM (using a Bayesian Markov Random Field model).
- Histogram parameters (mean, median, standard deviation, interquartile range, normalised peak height , normalised peak values, skew, kurtosis) were used to describe the distribution of cortical thickness, CBF, FA and MD values within each tissue-type (Fig. 1).

Local (voxel-wise)

- Voxel-based analysis of the GM, cortical thickness, WML and CBF maps, and tract-based spatial statistics of the FA and MD maps, was performed.

WM connectivity (networks)

- WM connectivity was modelled as a network 'wiring-diagram', with WM fibres (traced from the DTI using deterministic tractography) forming the connections (edges) and anatomical cortical and deep-GM regions, the network nodes.
- 'Graph' metrics were used to describe the topological organisation of these networks in terms of their connection density, the 'quality' of connections, the importance of particular nodes, and the efficiency of communication both locally and between distributed areas.

Statistical analysis

- For continuous data, group differences were tested using parametric (Gaussian) and non-parametric (non-Gaussian) variants of the general linear model (GLM). For the categorical voxel-wise WML data Liebermeister tests were used.
- All GLM models controlled for the confounding effects of age and gender, with education additionally included in cognitive analyses and TIV, in voxel-wise GM and cortical thickness analyses.
- Additional models were tested controlling for vascular risk factors (pack years and mean arterial pressure), and anxiety/depression (HADs).
- All voxel-wise analyses were corrected for multiplicity.

Results

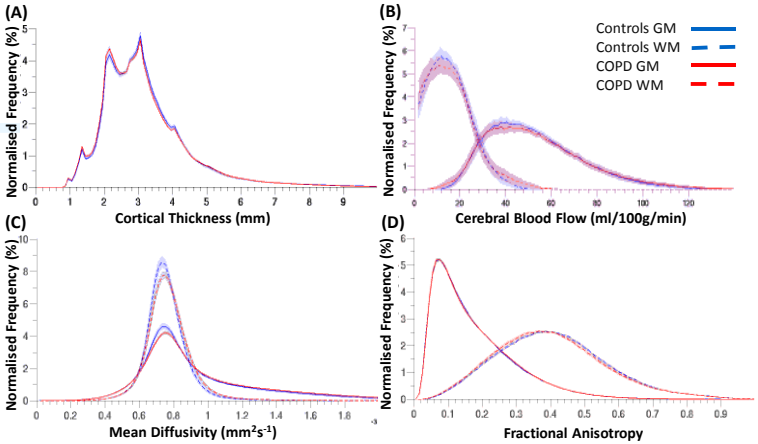
Cognition: neither group met the criteria for dementia. There was a trend toward COPD having lower cognitive function *(p=0.069)* but this was removed following correction for HADs score.

Whole-brain and network: COPD had significantly lower normalised GM volume (Table 1), which survived correction for pack years, HADs score and mean arterial pressure. There were no other significant differences in whole-brain volume, histogram or network measures.

Table 1: Whole-brain measures	Controls (N=23)		Patients (N=27)		Difference	
	Mean (Median)	SD (IQR)	Mean (Median)	SD (IQR)	*F*	*P*
Grey Matter Volume (% TIV)	42.96	1.43	41.71	1.46	6.91	**0.01***
White Matter Volume (% TIV)	28.21	2.57	27.98	2.11	0.22	0.64
Tissue Volume Ratio	0.71	0.03	0.70	0.03	1.44	0.24
WML Volume (% TIV)	(0.21)	(0.27)	(0.24)	(0.35)	0.03[1]	0.86[1]
WML Number	(27)	(20)	(23)	(27)	0.01[1]	0.99[1]
WML Average Size (mm^3)	(94)	(103)	(126)	(165)	0.04[1]	0.85[1]

[1]Permutation general linear models (10000 perms.)

Figure 1: Group histograms of whole-brain measures



Voxel-wise: neither the GM nor the cortical thickness maps showed significant foci of GM loss, instead there was a pattern of generalised sub-significant reduction in GM across the whole brain (Fig. 2). There were no localised difference in WML frequency (Fig. 3), CBF (Fig. 2) or tract-based FA and MD values.

Figure 2: Voxel-wise GM maps

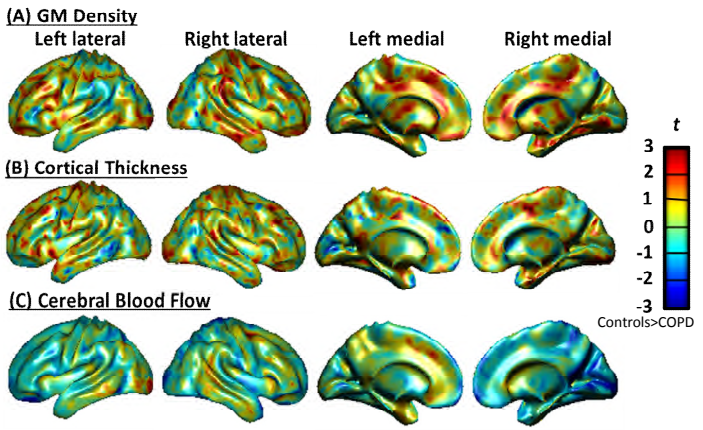
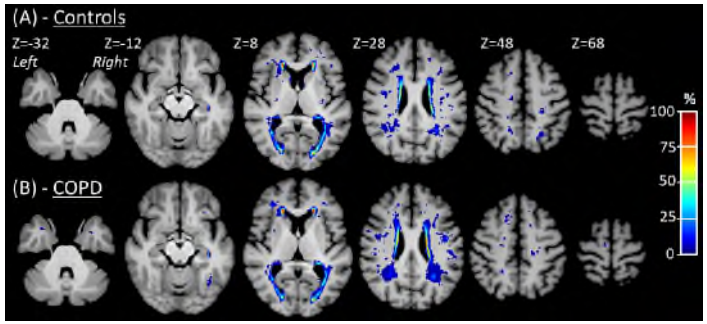


Figure 3: Group average WML maps



Discussion

- COPD patients showed evidence of cerebral atrophy – significant reductions in normalised whole-brain volume.
- Voxel-wise GM density and cortical thickness analyses did not identify any specific focus for this GM loss, instead suggesting a cumulative effect of subtle generalised GM reduction across the brain.
- These results are broadly consistent with previous reports of reduced GM density [8][9], cortical thickness [12], and hippocampal volume [7] in COPD. However, these studies found specific foci of change that were not replicated in this study.
- The present study found no evidence for greater WM atrophy, severity of WMLs, microstructural tissue damage, disruption of WM connectivity, or hypoperfusion in COPD patients when compared to smoking controls.
- This conflicts with previous reports of greater WM damage [4] and perfusion abnormalities [5][6] in COPD. However, these previous findings were obtained through comparison of COPD patients with healthy controls without statistical correction for smoking history. Consequently, they may be indicative of a smoking-related effect. However, this does not account for the cerebral atrophy observed in the present study.

References

[1] Incalzi et al., *J Clin Exp Neuropsychol.* **2008**; 30, 141-150.
[2] Incalzi et al., *Chest.* **1997**; 112, 1506-1513.
[3] Stump et al., *J Am Geriatr Soc.* **2001**; 49, 934-940.
[4] Dodd et al., *Am J Respir Crit Care.* **2012**; 186, 240-245.
[5] Ortapamuk & Naldoken. *Ann Nucl Med.* **2006**; 20, 99-106.
[6] -Incalzi et al., *J Neurol.* **2003**; 250, 325-332.
[7] Li & Fei. *Respir. Res.* **2013**; 14, 1-9.
[8] Zhang et al., *BMJ Open.* **2013**; 32, e000844.
[9] Esser et al., *Chest.* **2016**; 149, 426-434.
[10] Lahousse et al., *Am J Respir Crit Care.* **2013**;188, 783-788.
[11] Lambert et al., *NeuroImage Clin,.* **2015**; 9 194-205.
[12] Chen et al. *Brain Imaging Behav.* [Internet] **2015**; Available from: http://link.springer.com/10.1007/s11682-015-9403-7.