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


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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 hypointense 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 hyperperfusion [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
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Subjects: 27 COPD patients (age 67±8, 41% male, pack years 39±21, FEV1 64.1±19% predicted). These and findings from other studies, such as hyperperfusion [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.

Key clinical measures: standard pulmonary function and spirometry testing (inc. blood pressures), 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) (structure tissue), 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 (hypoo-isointense) 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).
• The present study found no evidence for greater WM atrophy, severity of WMLs, cortical thickness, and hippocampal volume [7] in COPD. However, these studies found specific foci of change that were not replicated in this study.
• For continuous data, group differences were tested using parametric (Gaussian) and non-parametric (non-Gaussian) versions of the general linear model (GLM). For the categorical voxel-wise WM/AML data Lieberman tests were used.
• Additional models were tested controlling for confounding factors of age and gender, with education educationally included in cognitive analyses and TIV, in voxel-wise GM and cortical thickness analyses.
• All voxel-wise analyses were corrected for multiplicity.

Table 1: Whole-brain measures

<table>
<thead>
<tr>
<th></th>
<th>Controls (N=23)</th>
<th>Patients (N=27)</th>
<th>Difference</th>
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<tbody>
<tr>
<td>N</td>
<td>(Median)</td>
<td>SD (IQR)</td>
<td>(Median)</td>
</tr>
<tr>
<td>Grey Matter Volume (% TIV)</td>
<td>42.96</td>
<td>1.42</td>
<td>41.71</td>
</tr>
<tr>
<td>White Matter Volume (% TIV)</td>
<td>28.21</td>
<td>2.57</td>
<td>27.98</td>
</tr>
<tr>
<td>Tissue Volume Ratio</td>
<td>0.71</td>
<td>0.03</td>
<td>0.70</td>
</tr>
<tr>
<td>WML Volume (% TIV)</td>
<td>(0.21)</td>
<td>(0.27)</td>
<td>(0.24)</td>
</tr>
<tr>
<td>WML Number</td>
<td>(27)</td>
<td>(20)</td>
<td>(23)</td>
</tr>
<tr>
<td>WML Average Size (mm³)</td>
<td>(94)</td>
<td>(103)</td>
<td>(126)</td>
</tr>
</tbody>
</table>

Key terms: GM, cerebral (GM), white (WM) and cerebrospinal (CSF) tissues:

WML 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.

Whole-brain and network:
• There were no localised differences in WML frequency which are consistent with a vascular pathophysiology.

Whole-brain:
• For continuous data, group differences were tested using parametric (Gaussian) and non-parametric (non-Gaussian) versions of the general linear model (GLM). For the categorical voxel-wise WM/AML data Lieberman tests were used.
• All GLM models controlled for the confounding factors of age and gender, with education educationally included in cognitive analyses and TIV, in voxel-wise GM and cortical thickness analyses.
• Additional models were tested controlling for confounding factors of pack years and mean arterial pressure, and anxiety/depression (HADS).
• All voxel-wise analyses were corrected for multiplicity.

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 hyperperfusion 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.

Figure 1: Voxel histograms of whole-brain measures

(A) GM Density Controls Controls COPD COPD GM COPD WM

(B) Cortical Thickness

(C) Cerebral Blood Flow

Figure 2: Voxel-wise GM maps

(A) GM Density Left lateral Right lateral Left medial Right medial

Figure 3: Group average WML maps

(A) Controls Controls COPD Controls COPD WML

References