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MRI ventilation abnormalities predict quality-of-life and lung function changes in mild-to-moderate COPD: Longitudinal TINCan study

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RESEARCH LETTER

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ABSTRACT

COPD biomarkers are urgently required for clinical trials of new therapies. We evaluated the longitudinal change and relationship of MRI and CT biomarkers of COPD with St. George's Respiratory Questionnaire (SGRO) and FEV_1 worsening over 30 months. Among imaging biomarkers, only the longitudinal change in MRI ventilation defect percent (VDP) was greater in ever-smoker (n=34/p<0.05) and COPD (n=48/p<0.0001) subgroups compared with never-smokers (n=42). Only the longitudinal change in VDP was correlated with change in SGRQ (r=0.26/p=0.03), and only baseline VDP predicted longitudinal change in SGRQ>minimum clinically important difference (p=0.047) in mild-to-moderate COPD. These data strongly support the use of MRI intermediate endpoints in COPD studies.

Trial Registration Number NCT02723474; Status: Recruiting.

INTRODUCTION

COPD is a growing public health problem projected to overwhelm healthcare systems.[1] This is motivating the development of new, sensitive COPD biomarkers that can be used in clinical trials as intermediate study endpoints.

CT biomarkers of emphysema (15th percentile of the CT density histogram, $HU_{15\%}$) and airways disease (wall thickness of airways with 10 mm internal perimeter, Pi10) have shown promise for providing prognostic information.[2] Although recent data[3] showed that the change in CT emphysema may be used to estimate the efficacy of therapy in patients with α-1-antitrypsin-deficiency, thus far none of the currently developed CT biomarkers have been shown to reflect changes in outcomes that are important to patients with COPD. MRI with inhaled noble gases provide highly sensitive and unique microstructural and functional information in COPD.[4] MRI biomarkers of COPD are highly reproducible,[5] are associated with COPD outcomes[6] and detect changes with greater sensitivity and before disease-related changes can be detected by CT or FEV_1.[7–9]

Here we evaluated longitudinal changes in both CT and MRI measurements of COPD. Based on previous longitudinal results,[8 10] we hypothesised that ^{3}He MRI biomarkers would predict quality-of-life and FEV_1 changes in COPD, and that longitudinal changes in MRI biomarkers would be correlated with changes in COPD quality-of-life measures.

METHODS

The Thoracic Imaging Network of Canada (TINCan) was a single centre, prospective longitudinal study. Participants aged 40–85 years that were never-smokers, current/ex-smokers without airflow

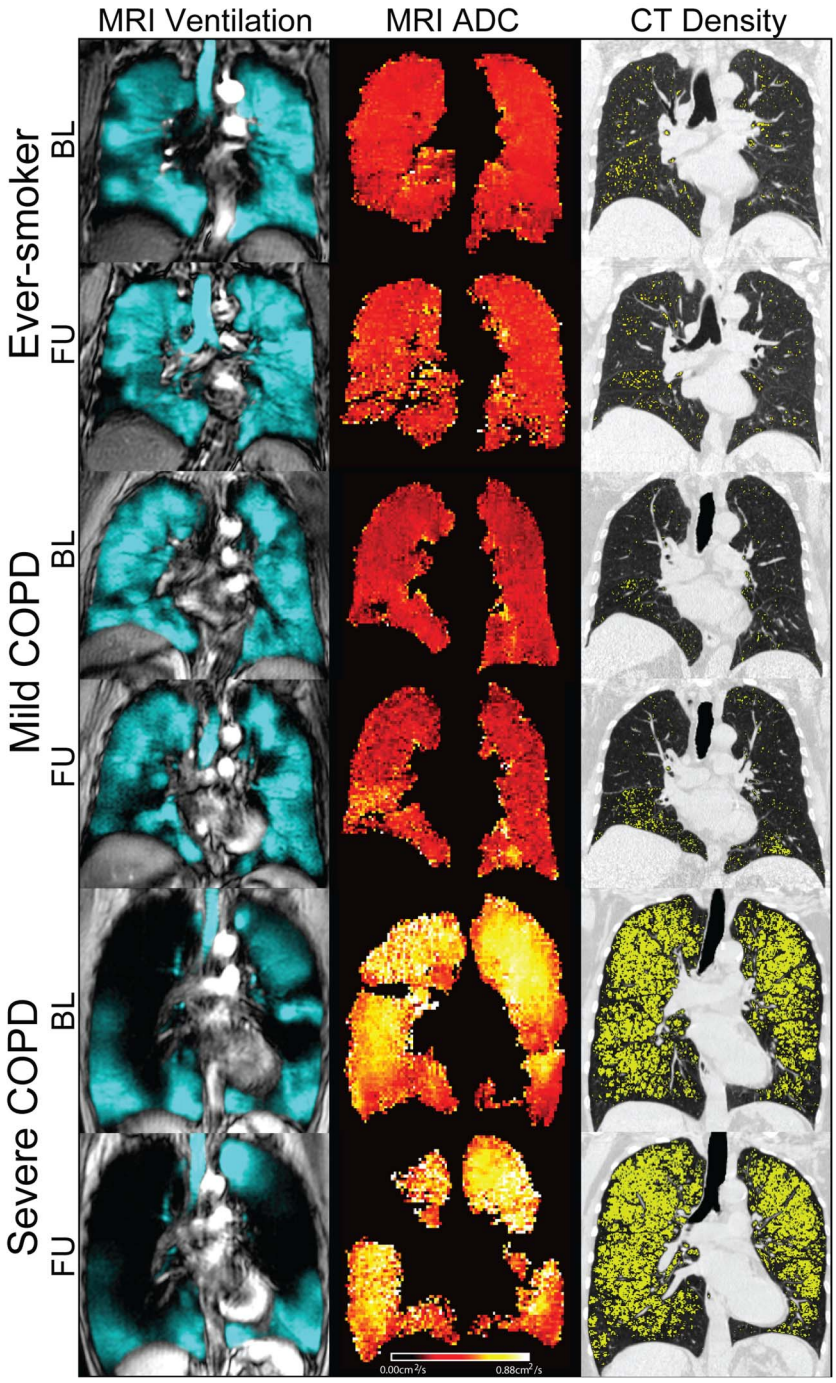

Figure 1 MRI ventilation and apparent diffusion coefficient (ADC) maps as well as CT density masks (<−950 HU in yellow) for representative ever-smoker, mild (GOLD I) and severe (GOLD III) COPD participants at baseline and follow-up. Ever-smoker (BL/FU): 72/75-year-old female ex-smoker, FEV_1=96/94%$_{pred}$, FEV_1/FVC=88/85%, DL_{CO}=54/62%$_{pred}$, VDP=5/6%, ADC=0.34/0.35 cm^2/s, LAA_{950}=1/2%, $HU_{15\%}$=−899/−901 HU. Mild COPD (BL/FU): 76/78-year-old male ex-smoker, FEV_1=77/75%$_{pred}$, FEV_1/FVC=57/58/%, DL_{CO}=70/87,VDP=8/14%, ADC=0.30/0.32 cm^2/s, LAA_{950}=2/3%, $HU_{15\%}$=−895/−914 HU. Severe COPD (BL/FU): 67/69-year-old female ex-smoker, FEV_1=37/33%$_{pred}$, FEV_1/FVC=38/39%, DL_{CO}=21/28%$_{pred}$, VDP=34/44%, ADC=0.51/0.52 cm^2/s, LAA_{950}=33/37%, $HU_{15\%}$=−974/−978 HU. BL, baseline; FU, follow-up; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; VDP, ventilation defect percent.

limitation (ever-smokers) and COPD were enrolled. All participants underwent two visits prospectively planned 2.5 years apart. Details regarding the study participants, pulmonary function tests, imaging acquisition/analysis and statistical analysis are provided in online supplementary panel S1.

RESULTS

Baseline demographic and clinical characteristics for all 124 participants (n=42 never-smokers, n=34 ever-smokers and n=48 patients with COPD of which n=38 were mild to moderate) are provided in online supplementary table S1 and described in online supplementary panel S2. The mean time between baseline and follow-up for all participants was 29±5 months.

Figure 1 shows representative baseline and follow-up MRI ventilation and apparent diffusion coefficient (ADC) maps as well as CT density masks for an ever-smoker, and patients with mild and severe COPD. The longitudinal changes in imaging biomarkers are described in online supplementary panel S3 and summarised in online supplementary table S2 and figure S1; all COPD subjects and the mild-to-moderate subgroup were evaluated separately. The magnitude of the longitudinal change was greater in ever-smoker ($p<0.05$), mild-to-moderate ($p=0.001$) and all COPD ($p<0.0001$) subgroups than in never-smokers for ventilation defect percent (VDP), but not for ADC, $HU_{15\%}$ or Pi10.

The relationship between the longitudinal change in SGRQ and FEV_1 with the change in imaging measurements is shown in online supplementary table S3. The longitudinal change in SGRQ was significantly correlated with the longitudinal change in VDP ($r=0.26$, $r^2=0.09$, $p=0.03$), but not for ADC, $HU_{15\%}$ or Pi10.

Although the magnitude of the SGRQ change was not significantly greater at follow-up in any of the subgroups investigated (see online supplementary figure S1), the longitudinal SGRQ change>minimum clinically important difference (MCID) was reported in several COPD participants (24%). Table 1 and online supplementary table S4 show the results of multivariate modelling for baseline imaging predictors of SGRQ change >MCID, as well as the annual and accelerated change in FEV_1. In mild-to-moderate COPD, only baseline VDP significantly predicted the longitudinal change in SGRQ>MCID ($p=0.047$). Both MRI and CT biomarkers significantly predicted annual (VDP/$p=0.003$; ADC/$p=0.02$; Pi10/$p=0.02$) and accelerated FEV_1 change (VDP/$p=0.009$; ADC/ $p=0.004$; $HU_{15\%}$/$p=0.01$; Pi10/$p=0.03$).

DISCUSSION

FEV_1 is still the most commonly used endpoint in COPD clinical trials which often require large sample sizes and long follow-up times to enable the detection of significant responses to therapy. Moreover, in clinical trials using CT, which may provide a more direct measurement of COPD pathology, there are a lack of studies showing that currently developed CT biomarkers reflect changes in patient-relevant outcomes. This motivated the development of TINCan—the first prospective study to longitudinally investigate both functional MRI and CT biomarkers as predictors of clinical outcomes in patients with COPD.

As might be expected due to the small sample size, the change in FEV_1 was not

Table 1 Regression models for annual and accelerated FEV_1 change and change in SGRQ>MCID

	Ever-smoker n=34		Mild-to-moderate COPD n=38		All COPD n=48	
	Standardised estimate	p Value	Standardised estimate	p Value	Standardised estimate	p Value
A. Change in SGRQ>MCID						
Model 1: VDP	−69.28	0.41	0.82	0.047	0.97	0.02
FEV_1	−12.28	0.46	0.07	0.89	0.15	0.72
Model 2: ADC	0.56	0.26	1.08	0.07	0.53	0.11
$FEV_1\%_{pred}$	−0.88	0.32	−0.72	0.14	−0.30	0.35
Model 3: $HU_{15\%}$	−0.99	0.11	−2.83	0.06	−1.89	0.01
$FEV_1\%_{pred}$	−0.87	0.30	0.02	0.97	0.06	0.89
Model 4: Pi10	0.40	0.36	0.03	0.95	−0.13	0.65
$FEV_1\%_{pred}$	−0.78	0.31	−0.63	0.18	−0.45	0.16
B. Annual change in FEV_1						
Model 1: VDP	−0.03	0.89	−0.58	0.003	−0.56	0.006
FEV_1	−0.44	0.17	−0.45	0.04	−0.44	0.04
Model 2: ADC	0.25	0.31	−0.40	0.02	−0.43	0.007
$FEV_1\%_{pred}$	−0.45	0.14	−0.15	0.44	−0.23	0.16
Model 3: $HU_{15\%}$	0.15	0.47	0.23	0.27	0.32	0.09
$FEV_1\%_{pred}$	−0.41	0.19	−0.11	0.61	−0.17	0.32
Model 4: Pi10	−0.01	0.95	−0.43	0.02	−0.35	0.03
$FEV_1\%_{pred}$	−0.45	0.15	−0.19	0.34	−0.17	0.31
C. Change in FEV_1>40 mL/year						
Model 1: VDP	−0.34	0.16	1.26	0.009	0.98	0.007
FEV_1	0.42	0.24	0.65	0.11	0.59	0.08
Model 2: ADC	−0.15	0.58	1.07	0.004	0.75	0.007
$FEV_1\%_{pred}$	0.29	0.39	0.20	0.53	0.17	0.50
Model 3: $HU_{15\%}$	−0.45	0.09	−1.12	0.01	−1.12	0.006
$FEV_1\%_{pred}$	0.19	0.58	0.19	0.55	0.27	0.31
Model 4: Pi10	0.02	0.91	0.55	0.03	0.38	0.07
$FEV_1\%_{pred}$	0.28	0.39	0.05	0.85	0.07	0.76

Models adjusted for age, sex, body mass index, smoking status and pack-years.
ADC, apparent diffusion coefficient; MCID, minimum clinically important difference; VDP, ventilation defect percent.

significantly different between patient subgroups, nor was the change in CT measurements. The finding that the change in ADC was not significantly different between subgroups was also not surprising, and was likely related to the fact that ADC can only be measured in well-ventilated lung; this means that lung regions without inhaled gas (ie, ventilation defects) cannot report ADC values and this can drive an inherent bias towards more normal ADC measurements at follow-up.

VDP was the only imaging biomarker in which the longitudinal change was greater in patients with COPD than never-smokers. This is consistent with previous work[8 10] and suggests that only MRI ventilation abnormalities differentiated disease-related worsening from age-related decline. MRI ventilation abnormalities and their worsening over time likely reflect lung regions that trap gas via a fixed obstruction or have long time constants for filling/emptying. Taken together with other studies,[7–9] our findings suggest that MRI ventilation abnormalities are visualised and detected *before* CT structural changes—an important observation that can reduce the size and duration of COPD clinical trials.

In order for a biomarker to be validated as an intermediate endpoint, regulatory authorities require that changes in biomarkers correlate with changes in clinical outcomes. Remarkably, VDP was also the only imaging biomarker for which the longitudinal change was correlated with the longitudinal change in SGRQ. Perhaps more importantly, in the patients with mildest COPD, only MRI biomarkers provided prognostic information and predicted the longitudinal change in clinically relevant quality-of-life measures.

A very important limitation in this study is that only two time points were evaluated. Including a third time point would add strength to our study and to the conclusions drawn. Other limitations of our study are described in online supplementary panel S4.

The growing burden of COPD and dearth of new treatments demands aggressive and targeted development of more sensitive COPD intermediate endpoints. Our findings show that the change in MRI ventilation defects over time may represent a 'canary in the coal mine' that signals future changes in clinical outcomes, even in mild patients and even when FEV_1 and CT biomarkers cannot detect these occurrences. As in coal mining, COPD treatment trials might consider the utility of a 'canary' to serve as an intermediate endpoint.

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