Functional MRI Ventilation Discriminates Well-controlled Asthmatic and Healthy Subjects: Sensitivity, Specificity and Comparison with FEV_1

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Target Audience: Scientists and clinicians interested in pulmonary functional magnetic resonance imaging (MRI) to quantitatively evaluate asthma.

Purpose: Asthma is commonly diagnosed and monitored using the spirometry measurement of the forced expiratory volume in one second (FEV_1) - a global measurement of lung function made at the mouth that is relatively insensitive to structural and functional changes in the small airways <2mm.[1] Accordingly, there is an urgent need for alternative, non-invasive and regionally quantitative methods to evaluate asthma progression and treatment response. Previous work using hyperpolarized ^{3}He and ^{129}Xe MRI provide a strong foundation for the use of MRI in asthma research and clinical care. However, in order to accelerate clinical translation and regulatory approval, the etiology of MRI ventilation must be determined and validated against clinically-acceptable measurements, such as FEV_1. Therefore, our objective was to evaluate the performance of hyperpolarized ^{3}He MRI ventilation heterogeneity measurements to discriminate asthmatic patients from healthy volunteers. We hypothesized that ^{3}He MRI ventilation measurements before, during and after methacholine challenge – the clinical diagnostic test for asthma would provide sensitivity and specificity that was not significantly different than FEV_1.

Methods: Well-controlled asthmatic patients and healthy volunteers (18-60 years) provided written informed consent to the study protocol approved by the local research ethics board and Health Canada. At a single visit, subjects performed spirometry, plethysmography and MRI at baseline and post-methacholine challenge (at the provocative concentration causing a 20% decrease in FEV_1 (PC_{20}) or the final methacholine dose). Asthmatic patients had a current physician diagnosis of mild-to-moderate disease, with asthma treatment optimized to improve asthma control and with a positive methacholine challenge within the past 5 years. Healthy volunteers had no history of asthma or any other chronic or current acute respiratory illness. Imaging was performed on a whole body 3.0 Tesla Discovery MR750 system (General Electric Health Care, WI, USA). Conventional ^{1}H MRI was performed prior to hyperpolarized ^{3}He MRI as previously described.[2] For hyperpolarized ^{3}He MRI, a polarizer system (HeliSpin, Polarean, NC, USA) was used to polarize ^{3}He gas to 30-40%. Subjects were instructed to inhale a ^{3}He/N_2 gas mixture from functional residual capacity and image acquisition was performed in 8-10s under breath-hold conditions using a fast gradient-recalled echo sequence (14 s breath hold; repetition time (TR) = 4.3 ms; echo time (TE) = 1.4 ms; flip angle = 7 degrees; field of view = 40 x 40 cm; matrix, 128 x 128; 14-17 slices; slice thickness = 15 mm; 0 mm gap). As previously described, ^{3}He MRI static ventilation semi-automated segmentation was performed to generate the ventilation defect percent (VDP).[2] We also generated the ventilation coefficient of variation (VenCOV) as previously described.[3] Receiver operating characteristic (ROC) analysis was used to characterize the performance of FEV_1, ^{3}He MRI VDP and VenCOV as predictors of asthma using clinical diagnosis (Asthma/No Asthma) as the diagnostic threshold. The optimum cut-off point was determined according to the maximum Youden's index value (J=sensitivity+specificity-1) and the corresponding sensitivity, specificity, positive and negative likelihood ratios were calculated. All statistics were performed using GraphPad Prism version 6.02 (GraphPad, Inc., San Diego).

Results: Subject measurements are provided in Table 1 for 26 asthmatics and 9 healthy volunteers. For all subjects ventilation heterogeneity was very minimal as evidenced by very modest ventilation defect percent values. This likely reflected the fact that all asthmatics were well-controlled with treatment optimized in a tertiary care asthma practice. ROC curves for each of the diagnostic measurements (FEV_1, ^{3}He MRI VDP and VenCOV) are shown in Figure 1. Similar to $FEV_1\%_{pred}$ (AUC ± 95% CI =0.82±0.67 to 0.96; p=0.006), ^{3}He MRI VDP (AUC ± 95% CI =0.79±0.63 to 0.95; p=0.01) and VenCOV (AUC ± 95% CI =0.76±0.60 to 0.92; p=0.02) discriminated asthmatics from healthy controls. For each diagnostic measurement, the established cut-off point and the corresponding performance characteristics (sensitivity, specificity, positive and negative likelihood ratios) were: $FEV_1\%_{pred}$: <92%, 68, 89, 6.1, and 0.4; VDP: >1.5% 80, 89, 7.2, and 0.2; and VenCOV: >0.20, 52, 100, ND, and 0.5. Comparison of the diagnostic measurements using their performance characteristics showed that the largest positive likelihood ratio (7.2) and smallest negative likelihood ratio (0.2) at the established cut-off was associated with ^{3}He MRI VDP. Figure 2 shows ^{3}He MRI ventilation images for a true positive asthmatic (36 yr old F, FEV_1=66%$_{pred}$, PC_{20}=0.08mg/mL, VDP=7.8%) and false negative asthmatic (23 yr old F, FEV_1=96%$_{pred}$, PC_{20}=16.89mg/mL, VDP=0.9%) diagnosed using the established cut-off point for VDP. The false negative asthmatic had homogenous ventilation without ventilation defects and normal PC_{20} and FEV_1.

Discussion: MRI ventilation measurements discriminated asthmatic patients from healthy controls with accuracy not significantly different from FEV_1, a clinically-accepted measurement of disease. Estimated likelihood ratios suggested that the most accurate diagnosis of asthma was generated using ^{3}He MRI VDP.

Conclusions: ^{3}He MRI measurements of ventilation significantly discriminated asthmatic patients from healthy controls and this is a necessary step towards clinical translation and regulatory approval. Because it is well-understood that ^{129}Xe MRI is more sensitive to ventilation abnormalities in asthma than is ^{3}He MRI[4], next steps include validation of ^{129}Xe MRI ventilation measurements in asthmatics before, during and after methacholine challenge.

Table 1. Subject measurements for asthmatic patients and healthy volunteers.

Parameter (±SD)	Healthy (n=9)	Asthma (n=26)
Age yrs	34 (11)	35 (11)
Male Sex	5	11
BMI kg/m^2	22 (3)	26 (5)
$FEV_1\%_{pred}$	101 (9)	84 (15)
VDP %	1.4 (0.4)	3.3 (3.1)
VenCOV	0.19 (0.01)	0.20 (0.02)

SD=Standard Deviation, BMI=Body Mass Index, FEV_1=forced expiratory volume in 1 second; VDP, ventilation defect percent; VenCOV, ventilation coefficient of variation.

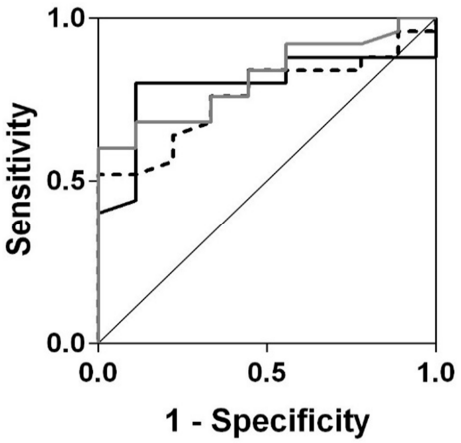

Figure 1. Receiver operating characteristic curve for the diagnosis of asthma using forced expiratory volume in one second (FEV_1, grey solid line), ^{3}He MRI ventilation defect percent (VDP, black solid line) and ventilation coefficient of variation (VenCOV, black dashed line). The areas under the curve ± 95% confidence interval and associated p-value were: FEV_1, 0.82±0.67 to 0.96, p=0.006; VDP, 0.79±0.63 to 0.95, p=0.01; VenCOV, 0.76±0.60 to 0.92, p=0.02.

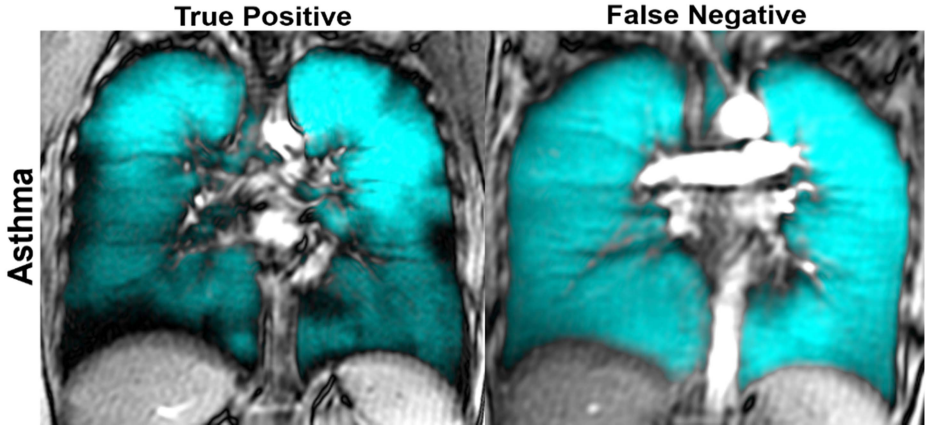

Figure 2. ^{3}He MRI ventilation for two well-controlled asthmatics under treatment. The true positive is a 36 yr old F, FEV_1=66%$_{pred}$, PC_{20}=0.08mg/mL, VDP=7.8% and the false negative is a 23 yr old F, FEV_1=96%$_{pred}$, PC_{20}=16.89mg/mL, VDP=0.9%. It is worth noting that for the false negative, the clinical findings including FEV_1 and PC_{20} are also not diagnostic of asthma.

References:

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