Characterization of acinar airspace involvement in asthmatic patients by using inert gas washout and hyperpolarized ^{3}helium magnetic resonance

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Background: The multiple-breath inert gas washout parameter acinar ventilation heterogeneity (S_{acin}) is thought to be a marker of acinar airway involvement but has not been validated by using quantitative imaging techniques in asthmatic patients.
Objective: We aimed to use hyperpolarized ^{3}He diffusion magnetic resonance at multiple diffusion timescales and quantitative computed tomographic (CT) densitometry to determine the nature of acinar airway involvement in asthmatic patients.
Methods: Thirty-seven patients with asthma and 17 age-matched healthy control subjects underwent spirometry, body plethysmography, multiple-breath inert gas washout (with the tracer gas sulfur hexafluoride), and hyperpolarized ^{3}He diffusion magnetic resonance. A subset of asthmatic patients (n = 27) underwent quantitative CT densitometry.
Results: Ninety-four percent (16/17) of patients with an increased S_{acin} had Global Initiative for Asthma treatment step 4 to 5 asthma, and 13 of 17 had refractory disease. The apparent diffusion coefficient (ADC) of ^{3}He at 1 second was significantly higher in patients with S_{acin}-high asthma compared with that in healthy control subjects (0.024 vs 0.017, $P < .05$). S_{acin} correlated strongly with ADCs at 1 second ($R = 0.65$, $P < .001$) but weakly with ADCs at 13 ms ($R = 0.38$, $P < .05$). ADCs at both 13 ms and 1 second correlated strongly with the mean lung density expiratory/inspiratory ratio, a CT marker of expiratory air trapping ($R = 0.77$, $P < .0001$ for ADCs at 13 ms; $R = 0.72$, $P < .001$ for ADCs at 1 second).
Conclusion: S_{acin} is associated with alterations in long-range diffusion within the acinar airways and gas trapping. The precise anatomic nature and mechanistic role in patients with severe asthma requires further evaluation. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Asthma, small airways, acinus, physiology*

Asthma is a chronic inflammatory airway disease characterized by variable airflow obstruction, airway hyperresponsiveness, and structural remodeling in both the large and small airways.[1] Understanding the site and nature of small-airways disease in asthmatic patients is important because it might allow the development of therapies that target this region of the lung or better application of existing therapies, such as extrafine-particle inhalers.[2]

Although it is known that inflammatory and structural changes in asthmatic patients occur in the smaller conducting airways,[3-7] it is not known whether the lesion extends to the more distal intra-acinar airways. The acinar airways of the lung constitute the majority of the airway surface area and comprise the respiratory bronchioles, alveolar ducts, and alveoli.[8] Understanding the role and contribution of the acinar airways to asthma is important because currently available inhaled therapies are not designed to provide penetration to this compartment.[9] A number of tools are available to noninvasively probe the structure of the acinar airways in asthmatic patients. These include the physiologic assessment of gas mixing by using multiple-breath inert gas washout (MBW),[10] measurement of gas diffusion by using hyperpolarized noble gas magnetic resonance techniques,[11] and computed tomographic (CT) densitometry to evaluate expiratory air trapping.[12] However, to date, there has not been a comprehensive assessment of the acinar airways in asthmatic patients using these approaches together.

There are thought to be 2 independent mechanisms of gas-mixing inefficiency in the lungs, namely convection-dependent inhomogeneity (CDI) and diffusion-convection–dependent inhomogeneity (DCDI).[13,14] CDI arises because of unequal convective ventilation between relatively large lung units subtended by conducting airways. DCDI is a more complex mechanism that occurs because of an interaction between convective and diffusive gas flows at the convection-diffusion front, the region of the airway tree at which these flows are of approximately equal

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Abbreviations used
ACQ: Asthma Control Questionnaire
ADC: Apparent diffusion coefficient
CDI: Convection-dependent inhomogeneity
CT: Computed tomography
DCDI: Diffusion-convection–dependent inhomogeneity
FRC: Functional residual capacity
GINA: Global Initiative for Asthma
^{3}He-MR: Hyperpolarized ^{3}helium diffusion magnetic resonance
ICS: Inhaled corticosteroid
Kco: Carbon monoxide transfer coefficient
MBW: Multiple-breath inert gas washout
MLD E/I: Mean lung density expiratory/inspiratory ratio
OCS: Oral corticosteroid
P_{15}: Fifteenth lower percentile of the inspiratory lung attenuation curve
RV: Residual volume
S_{acin}: Acinar ventilation heterogeneity
S_{cond}: Conductive ventilation heterogeneity
SF_6: Sulfur hexafluoride

magnitude. The MBW parameters conductive ventilation heterogeneity (S_{cond}) and acinar ventilation heterogeneity (S_{acin}) were proposed by Verbanck et al[15] as measures of CDI and DCDI, respectively. Because in health the convection-diffusion front is thought to be located within the pulmonary acinus, S_{acin} was proposed as a putative physiologic marker of acinar airspace disease. However, the precise location of the convection-diffusion front is heavily dependent on the molar mass of the inert tracer gas being used, with heavier gases, such as sulfur hexafluoride (SF_6) probing more distal regions of the pulmonary acinus than lighter gases, such as N_2.[10] Increases in S_{acin} have been observed in asthmatic patients, leading to the suggestion that this condition is characterized by a specific structural abnormality in the pulmonary acinus.[16] However, the precise nature of this structural abnormality has not been elucidated.

Hyperpolarized ^{3}helium diffusion magnetic resonance (^{3}He-MR) is a technique that allows microstructural changes at the level of the alveoli and acinar airways to be examined noninvasively under resting physiologic conditions.[11] The apparent diffusion coefficient (ADC) of ^{3}He within the pulmonary acinus can be measured across a wide range of timescales, from 1 ms to 10 seconds. Short or intermediate timescales of the order of a few milliseconds correspond to diffusion within a single alveolus or a single acinar airway, respectively, whereas long timescales of the order of seconds correspond to diffusion within several acinar airways,[11] as illustrated in Fig 1.[17] ^{3}He-MR has been extensively validated against histology in both human subjects and animal models of disease. Several studies have shown that short-timescale ^{3}He or ^{129}Xe ADCs are increased in both patients with emphysema[18-24] and animal models of emphysema[25-28] in comparison with values obtained in healthy lungs. Moreover, in a number of these studies, ADCs were found to correlate with quantitative histologic measures of emphysema, such as the mean linear intercept, mean alveolar internal area, and mean chord length.[21,23,25-28] Air trapping can be assessed by using physiologic measurements of lung volumes[29] or with imaging techniques, such as quantitative CT densitometry.[12] Indeed, we have recently identified CT imaging phenotypes of asthma using these approaches and identified that air trapping is a feature of all CT imaging clusters and is associated with more severe disease.[30]

We aimed to use ^{3}He-MR at multiple diffusion timescales and quantitative CT densitometry to determine the structural correlates of the multiple-breath washout marker S_{acin} in asthmatic patients using SF_6-MBW. We hypothesized that (1) asthmatic patients with an increased S_{acin} would manifest altered long-range diffusion suggestive of intra-acinar airway disease and (2) the degree of acinar involvement in asthma would be independent of lung hyperinflation.

METHODS

Thirty-seven patients with asthma and 17 age-matched healthy control subjects were recruited. All of the patients within this study were recruited from our secondary care asthma center (Glenfield Hospital, Leicester, United Kingdom). The center primarily evaluates patients at Global Initiative for Asthma (GINA) treatment steps 3 to 5 to optimize their disease control and any potential comorbidities (eg, rhinosinusitis) and treatment nonadherence. Some of these patients (steps 4-5) were evaluated in a difficult/complex asthma clinic that evaluates treatment-refractory populations. Therefore our recruited population was representative of a secondary care asthmatic population in the United Kingdom and included patients with treatment-refractory disease.

Patients were seen in the stable state, with no changes having been made to their regular inhaled or oral asthma therapy within the preceding 6 weeks. All participants were never smokers or exsmokers with a smoking history of less than 10 pack years. Asthma was diagnosed in a secondary care setting according to British Thoracic Society guidelines.[31] The study was approved by the National Research and Ethics Committee (East Midlands, Leicester, United Kingdom), and all participants provided written informed consent.

Patients with asthma completed the 6-point Asthma Control Questionnaire (ACQ-6)[32] and the Standardized Asthma Quality of Life Questionnaire.[33] Participants were administered 200 μg of salbutamol through a metered-dose inhaler and spacer to minimize the confounding effects of airway smooth muscle tone on physiologic and imaging assessments. Spirometry, body plethysmography, and measurement of carbon monoxide diffusing capacity were performed according to American Thoracic Society/European Respiratory Society guidelines.[34-36] Predicted values and standardized residuals (z scores) were derived by using the Global Lung Function Initiative (2012) equations for spirometry[37] and the European Community for Steel and Coal (1993) equations for lung volumes and carbon monoxide transfer coefficient (Kco).[38] Induced sputum inflammatory cell counts were obtained in asthmatic patients by using a previously published method.[39]

MBW was performed according to current guidelines[40] by using the SF_6 wash-in method described by Horsley et al.[41] SF_6 was chosen as the inert tracer gas because of its heavy molar mass and based on previous simulation data from Dutrieue et al[17] suggesting that phase III slope sensitivity to SF_6 is maximal at the level of the alveolar duct (generations 20-21, Fig 1). Participants wore a nose clip and breathed an air mixture containing 0.2% SF_6, while respiratory flows and exhaled breath SF_6 concentrations were monitored with an Innocor photoacoustic gas analyzer (Innovision A/S, Odense, Denmark). Participants maintained a steady respiratory rate of approximately 12 breaths per minute and a constant tidal volume of 1 L throughout the test by using a real-time visual display of inspired volume as a guide. Once inhaled and exhaled SF_6 concentrations had equalized, participants were switched to breathing room air during an expiration. The test was terminated when the end-tidal concentration of SF_6 in exhaled breath decreased to less than 1/40th of the original concentration for 3 consecutive breaths. Lung clearance index,[10] S_{cond}, and S_{acin}[15] were calculated by using custom software written with TestPoint (Measurement Computing Corp, Norton, Mass).

^{3}He-MR was performed with a 0.15-T permanent magnet system (Intermagnetics General Corp, New York, NY) and a Surrey Medical Imaging Systems console (Surrey, United Kingdom). Participants were scanned in the supine position and inhaled 600 mL of a ^{3}He/^{4}He mixture from functional residual capacity (FRC), followed by a breath-hold lasting between 2 and 10