

Invited Review

Demonstration of the Heterogeneous Distribution of Asthma in the Lungs Using CT and Hyperpolarized Helium-3 MRI

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Asthma is a chronic inflammatory disease that affects both the large and small airways and results in bronchoconstriction, mucous hypersecretion, smooth muscle hypertrophy, and subepithelial fibrosis. To gain insight into the pathophysiology of asthma, chest computed tomography (CT) has been investigated as a noninvasive method to evaluate airway wall thickness of medium and large airways. Hyperpolarized gas MRI can assess the functional alterations of airflow within the lung resulting from the structural changes in the airways. In this article, we review the application of CT-based techniques and hyperpolarized gas MRI to study structural and functional changes in asthma. From the result of studies with CT and hyperpolarized gas MRI, it is becoming apparent that asthma has a regional distribution within the lung, that is, some areas of the lung are more affected than others. Furthermore, there appears to be some persistence to this distribution which may explain the observed patterns of airway remodeling and provide targets for localized therapies such as local application of anti-inflammatory agents or bronchial thermoplasty. Thus, cross sectional imaging in asthma is providing new insights into the pathophysiology of the disease and has the potential to become essential in the guidance of localized treatments.

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PATHOPHYSIOLOGY OF ASTHMA

Asthma is a chronic inflammatory disease affecting the large and small airways. The pathophysiology of asthma involves airway hyper-responsiveness, mucous hypersecretion, smooth muscle hypertrophy, and subepithelial fibrosis. Studies of airways of people who die from asthma demonstrate thickened airway walls due to several factors, including increased smooth muscle mass, inflammatory cell infiltration, deposition of connective tissue (subepithelial fibrosis), vascular changes, and mucous gland hyperplasia (1–4). Collectively, these pathologic changes are termed airway remodeling. Airway remodeling in asthma has been studied in vivo by performing endobronchial biopsies to obtain tissue from the asthmatic airways that can then be evaluated for structural and inflammatory changes (5–8). Cohen et al found that the epithelium and lamina reticularis thickness on the biopsies was significantly greater in subjects with severe persistent asthma as defined by the Severe Asthma Research Program (SARP) (9) compared with those with mild persistent asthma, normal and diseased controls (chronic bronchitis) (8). The study also found that there was a significant positive correlation between epithelial and lamina reticularis thickness and both indices were inversely correlated with lung function (forced expiratory volume in 1 second [FEV₁] % predicted). This approach is limited by the invasive nature of the procedure and the inability to sample all components of the bronchial wall and the distal small airways. Although generally associated with severe asthma, airway remodeling may be a feature of milder forms of asthma, and may occur in asymptomatic disease in the absence of clinically evident bronchoconstriction (10,11). Remodeling of the airways can result in worsening of airway narrowing, airflow obstruction and may ultimately lead to disease progression (12). The degree to which airway remodeling is reversible and which treatments are effective in accomplishing this is an area of ongoing research.

Computed tomography and more recently three-dimensional reconstruction using airway measuring software algorithms has been applied to noninvasively

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measure airway remodeling to assess disease activity, severity or response to treatment (13). In addition, relatively new gaseous contrast agents for MRI, hyperpolarized noble gases have been used to investigate the regional patterns of airflow obstruction within the lung (14–18). The excellent safety profile of hyperpolarized gases, the lack of ionizing radiation associated with MRI, and the rapid clearance of the gases from the lungs permit repeated evaluation of individual subjects. In asthmatics areas of persistent airflow obstruction demonstrated with hyperpolarized gas MRI may be the precursor and/or the consequence of airway remodeling. In this article we will review the application of CT based techniques to study structural and physiologic changes in asthma, as well as the use of hyperpolarized gas MRI to assess the regional patterns of airflow obstruction within the lung.

AIRWAY REMODELING MEASURED BY COMPUTED TOMOGRAPHY

Computed tomography has been applied to noninvasively study airway remodeling in vivo. Initial descriptions of high-resolution CT findings in patients with asthma included bronchial wall thickening, narrowing of the bronchial lumen, areas of decreased attenuation and vascularity on inspiratory scans, air trapping on expiratory scans, and in some cases, findings of bronchiectasis and emphysema (19–21). Recent efforts have focused on more accurately characterizing the radiographic changes associated with asthma, as well as elucidating the relationship among the radiographic changes, airway pathology and clinical disease activity.

Several studies have measured indices of airway wall thickness using semi-quantitative and quantitative techniques. The studies differ in the number of airways measured and the application of semi-quantitative versus an automated, quantitative approach, but have reached similar conclusions: airway wall thickening is increased at the level of the segmental bronchus and is related to disease severity, duration of disease and the degree of airflow obstruction (13,22–25). In addition, airway wall thickening may be partially reversible with inhaled corticosteroid (ICS) treatment in steroid naive patients and may increase in the absence of ICS treatment (26).

CT changes have been correlated with sputum biomarkers of inflammation, specifically matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1). Matsumoto et al in a study of stable asthmatics on inhaled corticosteroid therapy, found that sputum MMP-1 levels were inversely correlated with indices of airway wall thickness (WA%), while sputum TIMP-1 levels were positively correlated with airway wall thickness indices (27). The ratio of MMP-9/TIMP-1 was also inversely correlated with WA%. The investigators conclude that excess TIMP-1 may play a role in the pathogenesis of airway remodeling and airflow obstruction (27). Vignola et al demonstrated that the ratio of MMP-9 and TIMP-1 positively correlated with FEV1 (28).

Investigators have attempted to correlate the CT airway wall changes to histopathologic changes noted on airway biopsies. Subepithelial fibrosis, or thickening of the lamina reticularis (reticular basement membrane) was shown to correlate with airway wall thickening on CT in studies by Aysola et al and Kasahara et al (13,22). Aysola et al, using an automated quantitative MDCT of the airways, found that the airway wall is thickened in patients with severe asthma (using the SARP definition) compared with mild-moderate asthma and healthy controls (Fig. 1). In the study, wall thickness measured by MDCT was inversely correlated with airflow obstruction and response to bronchodilator. Airway wall thickness by MDCT correlated with histopathologic indices (epithelial thickness ratio) of airway remodeling from endobronchial biopsies (13).

In contrast, Kaminska et al, in a study comparing severe asthmatics with and without reversible airflow obstruction reported no significant correlation between the CT-derived parameters (lumen area, wall area percentage) and histopathologic features (airway smooth muscle percentage, reticular basement membrane thickness, epithelial detachment) (29). The severe asthmatics with chronic persistent airways obstruction differed from those with intermittent obstruction in that they had greater percent smooth muscle area. There was no difference between the two groups in regards to reticular basement membrane thickness, epithelial detachment or submucosal fibrosis (although the authors report a trend toward an increase in submucosal fibrosis in the chronic persistent obstruction subgroup) (29).

Gupta et al, in a study of patients with severe asthma, sought to identify changes of bronchiectasis and bronchial wall thickening and clinical characteristics associated with the radiographic findings (30). The study found that bronchiectasis and bronchial wall thickening were present in 40% and 62% of cases respectively, in this cohort of patients with severe asthma. Based on logistic regression analysis, the clinical parameter FEV₁/forced vital capacity (FVC) was the strongest predictor of the CT abnormalities (bronchiectasis and bronchial wall thickening). However, FEV₁/FVC ratio did not reliably differentiate between subjects with severe asthma who had airway wall changes from those who did not. The need for longitudinal studies, standardization of definitions for bronchiectasis and bronchial wall thickening and validation of quantitative CT software analysis for clinical use was highlighted by the authors (30).

Kurashima et al evaluated the effect treatment with inhaled corticosteroids (ICS) on airway wall thickness in patients with asthma (31). Specifically, the study examined whether the duration of asthma symptoms before the initiation of ICS therapy is an important determinant of the reversibility of airway wall thickening. Airway wall thickness was assessed by CT before initiation of ICS and after 1 year of treatment. The patients were divided into five groups based on the duration of self-reported asthma symptoms (from less than 1 year to greater than 10 years). CT scans were obtained at total lung capacity (TLC) at four selected

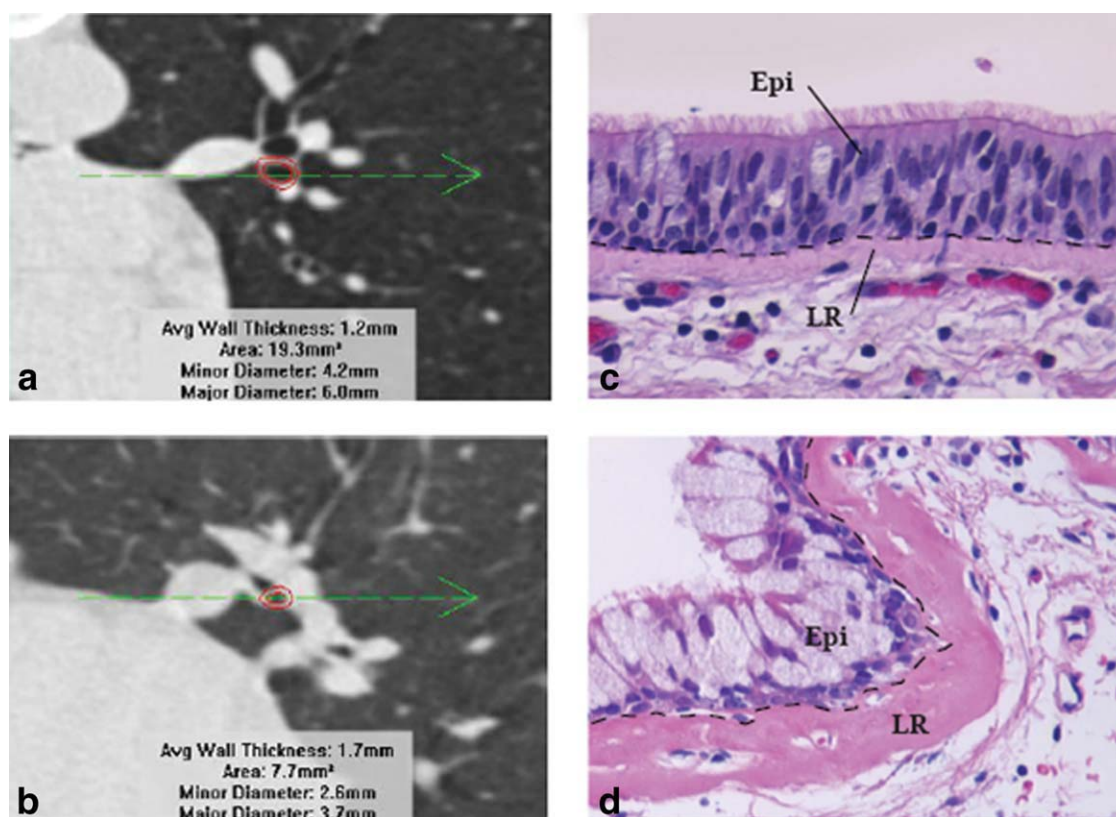


Figure 1. A–D: CT images and bronchial biopsy specimens from healthy subjects (A,C) and patients with severe asthma (B,D). The epithelial layer (Epi), lamina reticularis (LR), and the basement membrane (dashed line) are indicated (C,D). In the normal subjects, note the thin airway wall on CT (A) and the normal thickness LR (C). In the severe asthma patients, the airway wall was thickened on CT (B) and the LR thickened on histology (D). Reprinted with permission from Aysola et al (13).

anatomic levels, sampling the lung apex, upper lobes, superior and inferior lower lobes. Airway wall thickness was measured semi-quantitatively. The investigators found that the degree of airway wall thickness at the start of the study was increased in direct relation to the duration of asthma symptoms. There was no difference in the degree of airway wall thickening among the groups of patients who had asthma symptoms for greater than 3 years. There was a significant decrease in airway wall thickness after 1 year of treatment with ICS in patients who experienced asthma symptoms for less than 5 years. Additionally, this study found that patients experiencing asthma symptoms for less than 1 year had mild but statistically significant airway wall thickening when compared with controls after 1 year treatment with ICS. Of interest, the investigators found that asthma control improved even in the patients with longer duration of disease despite the lack of change in airway wall thickness and spirometry (31).

Assessing remodeling by CT measurements of airway wall thickness alone is limited due to the inability to accurately measure the distal small airways (typically <2 mm diameter) with current CT resolution. The degree of relative air trapping detected when comparing inspiratory and expiratory scans is an indirect measure of small airways obstruction. The development of quantitative lung densitometry applied to CT

images has led to an additional tool to noninvasively study airway remodeling in asthma.

LUNG DENSITY MEASUREMENTS

Quantitative measurement of lung density using automated lung parenchymal analysis software has been used to analyze air trapping in asthmatic subjects. Air trapping is measured on CT by determining the percentage of lung parenchyma that is less dense than normally aerated lung (percentage low attenuation areas (LAA) defined as <−850 Hounsfield units, in some studies <−950 or −960 Hounsfield units) and mean lung density (MLD). Comparison of %LAA and MLD at full exhalation (functional residual capacity) versus inspiration (TLC) is a radiographic index of air trapping.

Ueda et al, in a study of 29 patients with asthma, investigated the relationship between %LAA, MLD, and expiratory to inspiratory (E/I) ratios on CT to disease severity and pulmonary function measures of airways obstruction, air trapping, airways inflammation and bronchial reactivity (32). The group found that %LAA and MLD values at both inspiratory and expiratory phases correlated with FEV₁/FVC. Of interest, greater degrees of air trapping were noted at the lower lung levels (32).

A recent multivariate analysis by Busacker et al measured air trapping by quantitative CT in a cohort of severe asthmatics from SARP (33). The study found that subjects with air trapping measured by quantitative CT were more likely to have a history of asthma-related hospitalizations, intensive care unit (ICU) visits and/or mechanical ventilation compared with subjects without air trapping; characteristics associated with severe asthma. Subjects with air trapping also demonstrated greater airflow limitation measured by spirometry (decreased FEV₁ and FVC percentage predicted, and decreased FEV₁/FVC ratio). They also tended to be older, male, with longer duration of disease. Interestingly, they were also more likely to report a history of pneumonia and atopy. The multivariate analysis ultimately demonstrated that the risk factors associated with air trapping include duration of asthma, airflow limitation measured by spirometry (FEV₁, FVC), atopy and neutrophilic airways inflammation (33).

Mitsunobu quantitatively evaluated CT lung density between unstable asthmatics (those in the midst of an asthma exacerbation), control subjects and stable asthmatics to determine whether there were changes in lung density associated with disease activity, treatment and resolution (34). In a subset of the subjects ($n = 17$), longitudinal analysis of CT lung densitometry before and after treatment with systemic corticosteroids was also evaluated. Decreased lung attenuation was estimated using a standardized scoring system. Weighted MLD was significantly decreased in unstable asthmatics versus both stable asthmatics and control subjects. There was no significant difference in MLD and %LAA between stable asthmatics and control subjects. Additionally, they found that in patients with unstable asthma, the MLD was significantly decreased and the %LAA was significantly increased in the middle and lower levels versus the upper levels of the lung. Patients with stable asthma also demonstrated increased %LAA in the middle and lower levels compared with the upper levels. Treatment of asthma exacerbation with systemic corticosteroids resulted in significant increase in MLD and significant reduction in %LAA. The improvement in CT lung density measurements mirrored concomitant improvements in spirometry and lung volumes. Changes in FEV₁ and RV showed significant correlation with both the weighted MLD and %LAA (34).

Lee et al compared CT findings in patients with near fatal asthma, chronic asthma, and control subjects (35). Repeat CT analysis was also performed in the near fatal asthma cases. A total of 16 patients with near fatal asthma were studied. CT scans were evaluated for the presence of bronchial wall thickening (bronchial wall index), prominence of centrilobular branching linear structures and nodules (suggestive of bronchiolar obstruction and inspissated mucous), air trapping on expiratory scans, bronchiectasis, emphysema, and ground glass opacities. The radiographic changes were semi-quantitatively analyzed with excellent inter-observer agreement. Subjects with asthma of all severities had significantly greater airway wall thickening than normal control subjects.

Prominence of centrilobular structures was noted in all subjects with near fatal asthma, and to a lesser degree in subjects with mild and moderate-severe asthma. Normal control subjects did not demonstrate prominence of centrilobular structures. The authors point out that prominence of centrilobular structures, which is thought to represent bronchiolar obstruction and inspissated mucous, has not been routinely assessed or quantified in other CT studies of asthma. Airway wall thickening was inversely correlated with FEV₁. Follow-up CT scans were obtained in a subset of the patients when they were symptom free at 7 to 24 months from the initial scans. The investigators found that the airway wall thickening and prominence of centrilobular structures were significantly decreased in the mild persistent and moderate to severe asthma groups compared with baseline values. Despite the decrease, airway wall thickening was still higher in the mild persistent and moderate-to-severe asthma groups compared with controls. In the NFA group, airway wall thickening was decreased significantly, however, there was no significant change in the prominence of centrilobular structures or air trapping. Of interest, none of the groups demonstrated significant change in the degree of air trapping. They note that patients in the NFA group exhibited more severe prominence of centrilobular structures than their moderate-to-severe asthma cohorts despite similar FEV₁, wall thickening and air trapping parameters (35). The prominence of centrilobular structures may indicate lung regions prone to air-trapping due to a local "ball-valve" effect thereby increasing the risk of respiratory failure.

VENTILATION HETEROGENEITY

Increased heterogeneous airway narrowing and regional ventilation in the asthmatic patient compared with the healthy control has been demonstrated radiologically using several positron emission tomography (PET), MR, and CT based techniques (36–40). PET based computational modeling studies have also demonstrated that asymmetric bronchoconstriction can predispose to significant compromise in overall lung ventilation (41). In 2007, Downie et al conducted a physiologic study evaluating airway inflammation with exhaled nitric oxide and airway hyperresponsiveness by methacholine challenge (42). Ventilation heterogeneity was determined using multiple breath nitrogen washout and calculation of regional ventilation (42). Asthma patients were measured before and three months after treatment with ICS. The investigators found that baseline ventilation heterogeneity correlated strongly with severity of airway hyperresponsiveness, particularly in the large airways, in asthma patients with a range of disease severity. Interestingly, the relationship between ventilation heterogeneity and airway hyperresponsiveness persisted despite treatment with ICS and improvement in airway inflammation. Although, there was a significant reduction in ventilation heterogeneity after treatment with ICS; consistent with a therapeutic anti-inflammatory effect,

the residual ventilation heterogeneity was most likely due to airway remodeling. King et al measured the heterogeneity of airway narrowing in normal and asthmatic patients in response to methacholine using CT measurements of airway diameter (40). They found that the large airways of normals and asthmatics narrow heterogeneously and that the degree of heterogeneity of narrowing was greater in the asthmatic group.

HYPERPOLARIZED GAS MRI

Hyperpolarized gases are used as inhaled contrast agents for MR imaging of the lung and provide images of the lung airspaces with high spatial resolution. Helium-3 and xenon-129 are nonradioactive isotopes that can be polarized (14,17,18,43–45). When the hyperpolarized gas is inhaled the airspaces are filled, and when subsequently MR images are obtained, the changes in the regional ventilation resulting from air-flow obstruction are depicted. Because no ionizing radiation is required, hyperpolarized gas MRI has an advantage over CT that scanning of the lungs can be repeated, either at short or long time intervals, without exposing the subject to the risks of excessive radiation exposure. As a result, the temporal changes of the regional ventilation within the lungs of asthmatics can be more safely assessed.

The image quality with helium-3, until recently, was better than with xenon-129 because the gyromagnetic ratio of helium-3 is significantly higher than that of xenon-129, and higher polarization rates could be achieved with helium-3 than with xenon-129. In addition, helium-3 is nontoxic and inert, it lacks anesthetic effects, and it is virtually not absorbed (46). As a result, helium-3 has been used most commonly for human studies, including the investigation of the regional lung ventilation in patients with asthma. However, the availability of helium-3 is limited, which has become a particular problem recently due to a marked increase in demand for use of the gas in areas other than medical imaging. Fortunately, advances in polarizer technology for xenon-129 gas now provide polarizations that are substantially higher than previously possible, allowing the acquisition of high quality images of the lungs (47). Because of these developments, it is likely that many future investigations involving hyperpolarized gases will be performed with xenon-129; however, because both gases are inhaled and distribute within the lung when inhaled, it can be assumed that most of the information obtained previously with helium-3 is also applicable to xenon-129. Both gases are classified as investigational drugs by the Food and Drug Administration, and as such, all imaging with these contrast agents is regulated by this agency. The following is a review of the observations that have been made thus far in asthma using hyperpolarized gas MRI. Particular attention is given to the changes in the regional lung ventilation over time, an aspect of the disease that is not easily assessed with CT due to the risks of excessive radia-

tion exposure associated with scanning the patients multiple times.

In a young healthy subject, inhaled helium-3 gas distributes evenly throughout the airspaces producing uniformly high signal throughout the lung on the MR images (48,49). When there is focal reduction in air-flow, the airspaces distal to the area of obstruction do not fill with the gas and appear dark on the images, depicted as a so-called "ventilation defect." Focal ventilation defects have also been found in a variety of other obstructive lung diseases such as chronic obstructive pulmonary disease and cystic fibrosis, and are, therefore, not specific to asthma (50–57). It is likely that multiple different factors such as mucus plugging, and airway narrowing, closure or breakdown from a variety of etiologies can cause ventilation defects on hyperpolarized gas MRI.

Ventilation defects are common in asthmatics on hyperpolarized gas MRI and their size and extent are thought to reflect the regional severity of airway closure/narrowing. In a recent study, the relationship between the extent of the defects and disease severity was assessed in 58 asthmatics who were imaged at their clinical baseline (58). The study also included 18 age-matched healthy subjects. The subjects ranged from 14 to 38 years of age (mean, 23.5 years), had no other lung disease, and had never smoked. Spirometry was obtained in each subject immediately before imaging. It was found that the number and size of ventilation defects as assessed by human readers who were blinded to all clinical information correlated well with clinical measures of disease severity, as well as with the findings on spirometry. In particular, the mean number of ventilation-defects-per-image slice for the asthma group was significantly greater than that of the healthy subjects (0.99 versus 0.26 [$P = 0.004$]), and an increasing number of defects were found with increasing severity of asthma. Ventilation-defects-per-image for the asthmatics with moderate and severe persistent disease was significantly greater than that for the group with mild intermittent and mild persistent disease (1.37 ± 0.24 versus 0.53 ± 0.12 ; $P < 0.001$). Of interest, there were some subjects with persistent symptoms who had few ventilation defects, and there were others with mild symptoms and nearly normal spirometry who had many defects, indicating that hyperpolarized helium-3 MR imaging and spirometry may be assessing different aspects of airflow obstruction within the lungs of these patients.

Another study of hyperpolarized helium-3 MRI in 21 asthmatics of which 6 (29%) had severe disease as defined by the criteria of SARP (9) found a moderate correlation between the number of ventilation defects and FEV1 % predicted ($r = -0.76$), but there was no significant difference in defect score between severe and nonsevere asthmatics (59). There was no significant correlation between the total number of ventilation defects and whole lung inflammatory markers (% neutrophils and total neutrophils) on bronchoalveolar lavage. However, a regional analysis revealed that lobes in which there was a greater percentage of lung that was not ventilated ($>10\%$) had elevated absolute

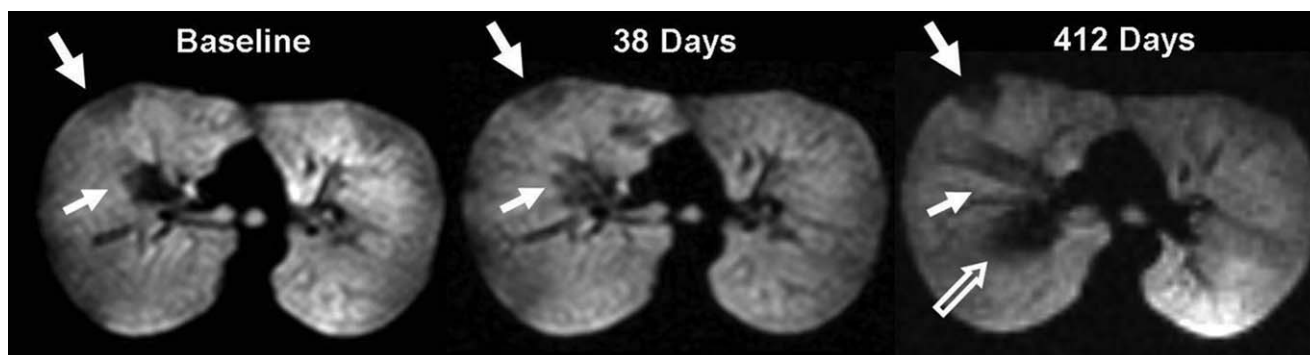


Figure 2. Long-term variability of ventilation defects in an asthmatic. **A:** Large (arrow) and small defect (small arrow) are shown at baseline. **B:** The defects are unchanged in location and size (arrow) 38 days later. **C:** The large defect is also unchanged at 412 days (arrow). The small defect (small arrow) has slightly decreased in size, and a new central defect (open arrow) has developed. Reprinted with permission from de Lange et al (60).

and percentage neutrophils as compared to lobes with relatively preserved ventilation. This suggests that the inflammation in the lung differs regionally and that ventilation abnormalities on hyperpolarized gas MRI are associated with regions of greater inflammation.

Because the regional airflow obstruction in asthma is reversible and is expected to vary with time, it is important to understand the time course of this variability, both at short and long term intervals, as was recently demonstrated in a study using hyperpolarized helium-3 MR imaging (60). The short-term variability was assessed in 26 asthmatics (6 mild intermittent, 5 mild persistent, 8 moderate persistent, and 7 severe persistent) who each underwent helium-3 MR imaging twice within 42–82 min time span. In these patients, it was found that the number of defects at baseline was similar to that seen at repeat scanning, with 75% of defects remaining in the same location, and 71% of these not changing in size. Thus, over the course of approximately 1 h, the ventilation defects, and thus the focal regions with airflow obstruction, were relatively stable with respect to their size and extent.

The long-term variability of ventilation defects in asthma was assessed in 17 patients (1 mild intermittent; 4 mild persistent; 9 moderate persistent; 3 not classified) who were imaged on 3 different days (scan 1, 2, 3), with intervals ranging between 1 and 476 days (60). It was found that there was relatively little variation in total number of defects between the 3 days, and no association was found between the time interval (in days) between scans and the change in the number of defects, or change in spirometric values. However, when the location of the defects within the lung was considered, there was a gradual interval decrease in the number of defects that persisted in the same location, with 67% of defects persisting on the scan obtained with a median scan interval of 31 days, 43% with a 41-day interval, and 38% with a 85-day interval (Fig. 2). This trend was the same regardless of asthma severity or whether the patients used medications for treatment of their disease. Hence, despite the decrease over time, a considerable number of defects remained unchanged in location indicating that the narrowing of the airways persisted to the

same degree over time. Although it is possible that the defects disappeared or changed in size between scans, and then re-occurred to the same degree as on the preceding scan, it seems more plausible that the defects persisted over time and were related to the persistent regional airflow changes that occur as a result of remodeling, that is, the development of structural changes in the airway walls that may occur in the lungs of asthmatics; however, this has yet to be confirmed.

Another study investigated whether there is preference for certain bronchi to constrict with methacholine or whether this effect occurs randomly, i.e. affects certain airways on 1 day and other airways on a different day. The study involved 10 asthmatics who were imaged on two different days before and immediately following methacholine challenge. The days were 7–476 days apart with a mean interval of 185.3 ± 37.2 days (61). On both days, the methacholine dose was the same. The images of day 1 were compared with those of day 2, and determination was made whether there was a change in location or size of the ventilation defects. On each day, it was found that there was marked increase in the number of ventilation defects after methacholine, as expected. A striking finding was, however, that almost 70% of the defects that developed on the first day also occurred in the exact same location on the second day, and of those $43\% \pm 5\%$ had the same size. Hence, a large proportion of airways appeared to have responded to the same degree on each day, suggesting that the bronchoconstriction triggered by the methacholine involved only certain airways and spared others, lending support to the hypothesis that asthma is a regional disease within the lung, perhaps even in the absence of airway remodeling.

In another study, using a texture-based analysis of the hyperpolarized helium-3 MR ventilation images, a greater heterogeneity of ventilation was found at baseline in asthmatics ($n = 10$) as compared with normal subjects ($n = 6$), similar to prior studies looking at focal ventilation defects (62). After methacholine challenge both the asthmatic and normal subjects experienced an increase in ventilation heterogeneity although the normal subjects received a much higher dose of methacholine than the asthmatic subjects.

Following deep inspirations, there was greater reversal of methacholine-induced ventilation heterogeneity in the normal subjects than the asthmatics. This study again shows the potential utility hyperpolarized gas MRI to provide new information about the dynamics of focal airflow obstruction in lung by being able to safely image repeatedly following various interventions.

Another investigation included a study in which the findings of CT were compared with dynamic hyperpolarized helium-3 MRI findings during forced expiration (63). The study included 10 subjects, with 8 of these having asthma, 1 normal subject, and 1 subject with a pulmonary artery aneurysm. Focal regions of low attenuation on CT were considered areas of air trapping, and areas of persistent MRI signal with expiration were also presumed to be related to air trapping. There was a general concordance between the areas of air trapping on the two imaging modalities, however there was some discordance even in some moderate sized areas. This discordance could be explained by a change in the distribution of air trapping between the two scans but alternative explanations include a relative insensitivity of MRI for detecting some causes of air trapping or inaccuracy of the prevailing concept of air trapping as the single cause of focal hyperlucency on CT in asthma.

In asthma, it can be assumed that the regions of absent or decreased airflow demonstrated with hyperpolarized gas imaging are caused by early closure or narrowing of the bronchi. Many of the ventilation defects have the tendency to persist over time, or occur in the same location and to the same degree after bronchoconstriction is induced using methacholine. The same heterogeneous appearance of the defects over time indicates that the bronchi leading to the areas of decreased airflow have a preference to close when stimulated, while others do not show evidence of decreased airflow, suggesting that the bronchi are heterogeneously involved, with some areas more than others, and perhaps even some not at all. Therefore, the findings from the studies using hyperpolarized helium-3 MRI suggest that asthma is a disease that involves the airways focally rather than diffusely. This may explain why, in asthmatics, some airways undergo remodeling while others do not.

CONCLUSION

Chronic inflammation in the asthmatic airways can lead to airway remodeling, which if unchecked, can lead to progressive decline in lung function. Imaging based techniques are being developed to noninvasively measure airways remodeling and response to treatment. CT based techniques, including measurements of airway caliber, regional ventilation, and lung density, depict asthma as a regional, heterogeneous process resulting in focal airway wall thickening and hyperinflation. The severe asthma phenotype emerges with radiographic features of airway wall thickening, air trapping, regional hyperinflation, and peripheral airways obstruction, which together reflects airway

remodeling and the progressive nature of this disease. As our understanding of the CT-based changes occurring in asthma expands, we must also weigh the risks associated with exposure to ionizing radiation, particularly when studies are obtained longitudinally to follow the course of the disease or to monitor the effects of treatment. The risks of repeated radiation exposure associated with medical imaging is a topic that has received substantial attention recently, both in the scientific community and the general media (64,65). Hyperpolarized gas MR imaging which requires no ionizing radiation forms an attractive alternative modality for assessing the affected airways in asthma.

An interesting focus of ongoing research in patients with asthma is to identify individuals whose pulmonary function is declining because of progressive airway remodeling. These patients could benefit from imaging as it would potentially allow the use of a disease modifying therapy (such as a monoclonal antibody) or the targeting of specific airways that have increased remodeling so that therapy can be applied locally such as aerosolized anti-inflammatory agents or bronchial thermoplasty. However, the imaging modality that would be most clinically helpful is yet to be determined. It is possible that the combination of the structural information from CT and the functional information from hyperpolarized gas MRI will become a powerful tool for guiding treatment in asthma.

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