Assessment of imaging techniques for evaluating small-airway disease in asthma

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Summary
The imaging techniques used to investigate patients with asthma and to assess the effects of asthma treatments include computed tomography (CT), helium magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), and positron-emission tomography (PET). Only MRI does not involve radiation exposure. Technical improvements in CT, together with the imaging advantages inherent in the presence of air in the lung, have diminished the radiation exposure required for lung CT. High-resolution low-dose lung CT protocols deliver a dose roughly equal to 1 year of natural radiation exposure and can be used even in pediatric patients. To date, CT is the most extensively studied lung imaging method, the simplest to perform, and the least expensive. In patients with asthma, CT may show several structural changes related to small-airway disease including cylindrical bronchiolectasis, bronchial wall thickening, and air trapping; an indirect marker for bronchiolar obstruction. A robust body of evidence indicates that valid CT markers for small-airway disease can be derived from quantitative lung density measurements and that these markers correlate with clinical severity and lung function test results. In addition, these CT markers are sufficiently sensitive to demonstrate therapeutic effects.

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Imaging methods that have been used to investigate patients with asthma and to evaluate asthma treatments include computed tomography (CT), helium magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), and positron-emission tomography (PET).

Computed tomography
Among imaging methods for asthma, CT is the most extensively studied, the simplest to use, and the least expensive. Technical advances, together with the image advantages inherent in the presence of air in the lung, have allowed the development of low-dose CT protocols. High-resolution low-dose protocols deliver doses roughly equal to 1 year of natural radiation exposure and are therefore suitable even in pediatric patients. Normally, the distal airways (lumen diameter smaller than 2 mm in diameter) are not visible by
CT because their walls are below the CT resolution threshold. However, small-airway abnormalities can be identified based on direct or indirect CT findings. Direct signs consist in filled and dilated bronchioles seen as small centrilobular nodules, often with linear branching opacities (tree-in-bud appearance). Indirect signs are mosaic perfusion on images in inspiration and air trapping on images in expiration. Mosaic perfusion is seen as a patchy appearance of the lung parenchyma produced by areas with slight overattenuation adjacent to areas with lower attenuation and decreased vessel caliber. The attenuation differences increase in expiration, indicating air trapping. In patients with bronchiolitis, these CT findings have been demonstrated to correlate with the histopathological findings [1]. Their occurrence rates varied widely across studies of patients studied during the course of asthma. In these studies, cylindrical bronchiectasis, bronchial wall thickening, and air trapping were common [2–5]. Other findings included centrilobular micronodules and mucoid impaction, bronchiolization, and foci of subsegmental atelectasis seen as linear densities.

The indirect signs of small-airway disease are mosaic perfusion and, above all, air trapping, which reflects bronchiole obstruction [6]. The density of the lung in areas without large bronchi or large vessels is the net result of the amounts of air, lung parenchyma, bronchiolar tissue, capillary wall tissue, and intracapillary blood. A change in any of these components produces a change in lung density. In the supine position, the anterior-posterior density gradient increases significantly in expiration, and this increase affects all areas equally except for a few lobules, most notably in the bases and dependent areas of the lung [7]. Focal or diffuse increase of this density increase indicates obstruction of the small airways and produces low-attenuation areas of air trapping. Air trapping reflects obstruction of the distal small airways with accompanying hypoxic vasoconstriction, as well as an increase in the lung volume at which airway closure occurs (Fig. 1).

Air trapping and mosaic perfusion can be assessed visually. Visual detection of these signs is facilitated by post-processing methods such as minimum intensity projection (miniP). In addition, quantitative methods based on lung density measurements are available. After lung contour segmentation, density histograms can be obtained to derive indices such as mean or median lung density and surface area of low-density regions. These methods are more objective and more reproducible [8,9]. However, they require specific software. Furthermore, the indices that should be taken into account are not agreed on. Although software programs for clinical use are available, their design needs to be improved. More specifically, the thickness and surface area of the largest bronchi remain difficult to evaluate, and work is ongoing to develop appropriate software programs. In addition, the detection and measurement of air trapping requires sections acquired in expiration, which are difficult to obtain reproducibly without coupling to spirometry, a procedure that substantially complicates the investigation. In practice, two methods are available for obtaining an end-expiration breath-hold. The patient may be asked to stop breathing at the end of an expiration. The patient must be given detailed instructions and must practice briefly just before the investigation. Alternatively, multi-array CT may be performed during expiration. Although this last method may be more sensitive for detecting air trapping, as it may allow a greater degree of lung emptying, no consensus exists about which method is best [10]. When measurements are to be compared over time, spirometry is helpful to ensure that the same degree of lung inflation is used for all measurements. Several studies showed that concomitant spirometry was feasible but made the procedure considerably more cumbersome [11,12]. Finally, CT studies in asthma patients have documented lung density changes during methacholine-induced bronchoconstriction [13] and salbutamol-induced bronchodilation [14]. In asthma patients evaluated between attacks, methacholine testing shifts the density distribution toward lower densities [13].

Neither air trapping nor mosaic perfusion is specific of asthma. Both abnormalities were first described in patients with constrictive bronchiolitis obliterans, whose CT features may be indistinguishable from those of asthma. However, mosaic perfusion images are more common and more marked in constrictive bronchiolitis [15]. Air trapping may be found in any disease that affects the small airways, and some degree of air trapping occurs in 50% of individuals who are free of lung disease, being more common in older individuals and in smokers [16]. Several features differentiate normal air trapping from air trapping related to bronchiolar disease. Normal trapping is confined to a few lobules and is most marked in the bases and dependent areas of the lungs. Abnormal air trapping, in contrast, often affects multiple lobules, segments, or lobes and extends beyond the lung bases and dependent lung areas.

Several lines of evidence suggest that CT may be appropriate for evaluating the small airways in patients with asthma, based on the relations linking density, symptoms, and functional abnormalities. That disease severity correlates with changes in lung density was established by Ueda et al. [17]. Lee et al. reported that centrilobular nodules were more numerous in patients with greater disease severity and were partly reversible [18]. Several studies found correlations between the main functional indices of small-airway disease and lung density values [17,19]. These

Figure 1. Computed tomography of the chest in a 35-year-old patient with moderate asthma. This end-expiration section shows two multilobular hypodense areas of air trapping (stars) in the right and left lower lobes, respectively.
correlations were also present in a paediatric population, as well as correlations linking lung density values to small-airway resistance measured using the impulse oscillation technique [20].

Several studies used CT lung density measurements as the primary endpoint for evaluating the efficacy of corticosteroids given by inhalation [12,21,22] or systemically [23]. A 4-week randomized double-blind trial compared two corticosteroid aerosols, one composed of fine particles and the other of conventional-size particles, in patients with mild-to-moderate asthma. The fine-particle preparation was associated with less air trapping before methacholine provocation and with a smaller increase in air trapping after methacholine provocation. Although these differences were statistically significant, they were not accompanied with differences in clinical symptoms, spirometry results, or responses to conventional methacholine testing [21]. Zeider et al. [23] measured air trapping before and after methacholine in patients with asthma allocated at random to a placebo or montelukast. Montelukast was associated with a decrease in air trapping and with improvements in quality of life scores but had no effect on measures of small airway physiology or bronchial hyperreactivity. These studies provide information on the sensitivity of lung density measurements compared to that of lung function testing.

Magnetic resonance imaging

MRI is the only imaging method that involves no radiation exposure. For several reasons, conventional MRI, which images proton concentrations, is of limited usefulness for investigating the lung: spatial resolution is low, the air contained within the lung generates low-intensity signals, and the air-tissue interfaces result in magnetic microfields. However, with appropriate sequences and a polarized gas (usually helium), high-quality static and dynamic images of regional lung ventilation can be obtained [24]. Lung ventilation imaging is a complex technique that is not suitable for routine use at present. MRI holds considerable appeal as an entirely safe procedure that involves no radiation exposure. In symptomatic asthma patients under basal conditions, lung ventilation imaging with polarized helium showed peripheral ventilation defects located at nonposterior sites, which were ascribed to small-airway involvement [25]. Increasing ventilation defects were seen after exercise or methacholine challenge testing [26].

Single-photon emission computed tomography and positron-emission tomography

SPECT, with Technegas inhalation, visualizes the patchy distribution of small-airway disease with tracer accumulation in the proximal airways during methacholine challenge testing [27]. This technique does not enable isolated imaging of the small-airway abnormalities and has low spatial resolution. SPECT with Technegas inhalation is chiefly useful to document the distribution of inhaled particles.

PET has been used in studies of the pathophysiology of asthma. Nitrogen 13 gas (13NN), a marker for peripheral alveolar perfusion and ventilation, can be evaluated during the same procedure. PET is a costly and complex technique that involves substantial radiation exposure. As a research tool, however, PET has allowed the development of theoretical models that explain the heterogeneity of peripheral airway involvement in asthma [28,29].

Conclusion

The various imaging techniques available for patients with asthma have established that small-airway involvement occurs in a patchy distribution. CT is the simplest and most extensively studied method. Lung density values determined using CT correlate with functional indices of small-airway involvement and with asthma severity, and they are sufficiently sensitive to demonstrate treatment effects. Acquisition techniques and density measurement parameters must be standardized.

**KEY POINTS**

- CT is the simplest and most extensively studied method for imaging the lungs in asthma patients. Lung density measurements correlate with functional indices of small-airway involvement and with disease severity. CT is sensitive to changes induced by treatments. Acquisition techniques and density measurement parameters must be standardized.

- MRI of the lungs is the only non-irradiating imaging method but is extremely complex.

- SPECT is chiefly useful for documenting the distribution of inhaled particles.

- PET is a costly and complex procedure associated with substantial radiation exposure. PET is therefore used only for research purposes.

- Computed tomography visualization of air trapping in expiration detects small-airway involvement in asthma with sufficient sensitivity to demonstrate treatment effects.

- Quantitative computed tomography density measurements correlate with functional indices of small-airway involvement and with asthma severity.

- The other imaging techniques, i.e., SPECT, MRI, and PET, have not yet been adequately evaluated.
Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References