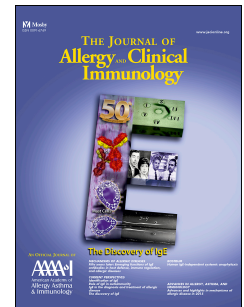


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Journal Allergy & Clinical Immunology Perspective: Clinical potential for imaging in asthma
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Abstract

The ability of lung imaging to phenotype patients, determine prognosis, and to predict response to treatments is expanding in clinical and translational research. The purpose of this perspective is to describe current imaging modalities that may be useful clinical tools in asthma and other lung disorders and to explore some of the new developments in imaging modalities of the lung. These imaging modalities include chest radiography (CXR), computed tomography (CT), lung magnetic resonance imaging (MRI), electrical impedance tomography (EIT), bronchoscopy, and others.

Keywords: Chest Computed tomography, quantitative imaging, lung MRI

Abbreviations

Chest radiograph (CXR)
Chronic obstructive pulmonary disease (COPD)
Computed tomography (CT)
Cystic fibrosis (CF)
Electrical impedance tomography (EIT)
Endobronchial Ultrasound (EBUS)
hyperpolarized noble gas MRI (HP gas MRI)
Magnetic resonance imaging (MRI)
Optical coherence tomography (OCT)
oxygen-enhanced MRI (OE-MRI)
positron emission tomography-computed tomography (PET-CT)

- 47 Single-photon emission computed tomography (SPECT)
- 48 Ultra-short echo time MRI (UTE MRI)

Introduction

Asthma is an extremely common but heterogeneous diagnosis that can cause airflow obstruction from infancy through adulthood¹. For all ages, history, physical exam, and lung function testing are used by clinicians to diagnose and monitor asthma. Clinical and translational researchers aim to expand the diagnostic and prognostic biomarkers available for clinicians. Imaging studies are commonly obtained in the evaluation of patients with asthma, however imaging biomarkers have yet to prove widespread utility as clinical tools or indicators of disease outcome.

Chest radiographs (CXR) are typically acquired for most patients with asthma; however this is to rule out other diseases that could mimic its symptoms or to look for complications^{1,2}. If CXR suggests an abnormality requiring further characterization, then chest computed tomography (CT) is obtained as the gold standard to establish a diagnosis or to evaluate for complications. Chest CT is commonly obtained in difficult-to-treat or severe asthma, in chronic obstructive pulmonary disease (COPD) and emphysema, and in rare diffuse and interstitial lung disease. Clinically, ultrasound may be used to image pneumothorax, pleural effusions, and pneumonia, and flexible bronchoscopy may be used to evaluate airway anatomy.

In translational research, new imaging techniques, including quantitative CT, lung magnetic resonance imaging (MRI), and others, can describe lung pathophysiology. To translate into clinical care, imaging protocols need to be clinically efficient, safe, and repeatable including technical (e.g. radiation) and patient-centered parameters (e.g. depth of inhalation). Local radiologists and clinicians need to accurately and efficiently interpret the image in real time. The benefits to the patient of obtaining the image must outweigh the risks.

With the increasing number of options available to image the lungs, clinicians are tasked to understand how these imaging modalities can help in the care of their patients³. Clinicians must be able to explain the risks and benefits of these procedures to their patients and determine how they will incorporate new care guidelines into their practice. This perspective gives a brief overview of imaging modalities that show promise in their potential to improve personalized clinical care in asthma.

Differences Between Clinical and Research Imaging

Radiological procedures produce images for the direct clinical care of patients. Radiologists interpret these images and give a qualitative written interpretation of the findings present on an image. This work flow typically produces real-time results for clinicians and patients. Although guided by algorithms and protocols, these interpretations, including results and terminology, may be based on the provider's personal and institutional bias.

Clinical and translational imaging research requires the ability to directly compare images across multiple individuals and/or time points. The findings must be manipulated into a numerical or categorical score that can be analyzed using standard statistics. Quantitative imaging is the approach to analyzing medical images that quantifies normal and abnormal findings⁴. Outcomes can be disease scores, generated either by expert readers or automated or semi-automated software programs, or a summary of raw quantified data such as relative density. Expert reader scores are limited because they require training, time, and reader consistency through a research study. Certain scores, like bronchiectasis scores, are quite repeatable, but air trapping scores are prone to inter-reader and intra-

reader variability⁵⁻⁸. Automated scores decrease reader variability and time; however, automated techniques can be affected by image quality, are difficult to generalize due to protocol and scanner differences, and are limited in the number of characteristics that can be assessed^{9,10}. Nevertheless, automated scores may be more clinically useful than qualitative or semi-quantitative scoring systems because of the time limitations of expert visual scorers.

Acquisition of medical images

Protocols to obtain chest imaging are as varied as their indication, however in order to generalize large clinical and translational imaging studies to personalized patient care, protocols must be standardized. Inspiratory images are performed close to total lung capacity and expiratory images are performed close to residual volume¹¹. Spirometry-triggered scans allow better consistency in children and adults who are able to perform adequate spirometry^{12,13}. In infants and patients without the ability to cooperate, protocols to inflate the lungs using an external airway are the best way to consistently image lungs at total lung capacity, and size-specific phantoms and other adaptations to the protocol are also needed to limit radiation dosage and maximize quality¹⁴⁻¹⁶. Research is being performed to understand the utility of images, including chest CT and MRI, performed during tidal breathing¹⁷⁻¹⁹. Chest imaging is commonly performed upright (CXR) and supine (CT and MRI), but other positions including prone and decubitus can also provide useful information²⁰.

Through SPIROMICS (Subpopulations and intermediate outcome measures in COPD study), the National Institutes of Health has sponsored a subcommittee to standardize

acquisition and analysis of imaging data in obstructive lung disease¹¹. This and other worldwide collaborations is a major advance toward standardizing scans, an integral move toward clinical utility⁷.

For radiography, CT, and fluoroscopy, radiation dose can vary between centers and protocols. Promoted by the *Image Gently* Campaign and the Alliance for Radiation Safety in Pediatric Imaging, Radiation dose is as limited as possible while allowing for adequate tissue interpretation²¹⁻²³. Widespread improvements in CT scanners have significantly decreased radiation dose. Current protocols for combined inspiratory and expiratory chest CT are generally below 5 mSv, and many are lower²⁴. New CT scanners use iterative reconstruction algorithms to lower the dose even further. Iterative dose reconstruction utilizes computational techniques to optimize the final image, rather than higher radiation dose²⁵. Although iterative reconstruction allows for lower radiation dose, specific algorithms are proprietary based on manufacturer, which may limit direct comparison of images obtained on different scanners.

Chest Radiography

CXR remains the most commonly used imaging modality to evaluate the airways, lungs, and mediastinum in the majority of respiratory diseases. In asthma, CXR may show nonspecific findings including peribronchial thickening and hyperinflation. Its primary utility is to exclude diagnoses with similar symptoms or to evaluate for complications including infiltrates, pneumothorax, or pneumomediastinum. Studies have shown that CXR results rarely change clinical asthma management^{26,27}; therefore, treatment protocols have aimed at decreasing the number of radiography studies ordered in routine asthma care^{28,29}. In

other lung diseases, radiography plays a larger role as a useful outcome measure in clinical trials and aiding in longitudinal monitoring of disease^{30,31}. In cystic fibrosis (CF), quantitative CXR scores and chest CT scores correlate with the severity of CF lung disease³⁰. Examples include the Brasfield and Wisconsin visual CXR scoring systems, which are used clinically in some CF centers to monitor disease^{32,33}.

Despite its low yield in asthma to date, advantages of CXR include widespread availability, low cost, and minimal radiation. Further research is needed to fully understand if the data contained in these traditional images can be useful for disease monitoring, as has been shown in other diseases.

Chest Computed Tomography

Chest CT is a widely used modality for both clinical and research evaluation of lung disease. In general, good quality chest CTs have sub-millimeter resolution and slice thickness, and volumetric inspiratory images paired with either volumetric or intermittent expiratory images. Images are reconstructed using a sharp kernel lung algorithm to improve airway/air interface viewing³⁴⁻³⁶.

The airways, lung parenchyma, and lung density have been extensively studied using quantitative CT imaging in asthma and other lung diseases. Airway characteristics such as wall thickness, lumen area, and airway branching angle have been associated with asthma phenotypes and lung function outcomes, with segmental airway size negatively correlating with lung function (Figure 1)³⁷⁻⁴³. Air trapping on chest CT is quantified by multiple methods to define expiratory lung tissue density, and it defines phenotypes of asthma that may not have measurable airway differences³⁸. Although air trapping on chest

CT and air trapping determined by plethysmography are not identical^{2,44,45}, this characteristic of asthma and COPD may be an important outcome for certain phenotypes and to assess response to specific medications^{39,46}. Since airway disease and air trapping are related but distinct phenotypes in asthma, it remains important to study biomarkers obtained from both inspiratory and expiratory scans.

Many of these measurements can be obtained by semi-automated software programs^{11,47}. These programs vary in cost, user interface, and their adaptability to different scanners and different acquisition protocols⁷. In asthma, a proportion of patients have subtle airway changes that cannot yet be individually interpreted to guide clinical care^{37,46}. Although the majority of semi-automated quantitative imaging programs are aimed at the analysis of chest CT, these analytic principles can be adapted to lung MRI when this modality expands.

Novel CT applications

Lung parenchyma can also be evaluated using texture analysis rather than simply measuring lung density. Texture analysis provides a quantitative pattern analysis of the two- or three-dimensional image, allowing more complex and unique classifications⁴⁸. This method has the potential to classify other structural lung abnormalities including fibrosis and bronchiectasis⁴⁹. The diagnosis of bronchiectasis, which changes treatment in patients with asthma, can be established and monitored longitudinally using multiple automated and semi-automated scoring methods^{9,10}. Although patients with bronchiectasis represent

a subset of all patients with asthma, this structural phenotype is ideal for analysis in large clinical trials aimed at improving bronchiectasis severity, clinical symptoms, and morbidity.

Exciting advances in CT are connecting the structural analysis provided by CT with functional assessment. 4D-CT or cine-CT measures multiple images over the breathing cycle to allow measurements of ventilation using CT^{17,50}. Tracheomalacia, which can lower lung function and likely alters prescribed therapy, can be diagnosed in multiple ways including forced expiratory CT images, cine-CT, flexible bronchoscopy, and clinically⁵¹⁻⁵³.

Functional imaging including computational fluid dynamics methodology allows the mathematical estimation of functional outcomes including airflow and airway resistance from static CT images. Mathematical modeling can create theoretical models to simulate particle deposition within the airways in patient-specific scans⁵⁴. Although the analysis requires sophisticated software and methodology and is therefore available to limited centers, this technology provides the direct vision to unique patient-specific outcomes and guided therapeutic trials^{55,56}.

Models of ventilation and particle deposition can be perfected and validated using nuclear medicine techniques including positron emission tomography (PET)-CT imaging⁵⁷. PET-CT allows for imaging of molecular inflammation in the lungs using different tracers, predominantly fluorodeoxyglucose (FDG). Single-photon emission tomography (SPECT) images tracers that emit gamma rays. SPECT images may also be able to quantify different types of inflammation in asthma and other lung diseases⁵⁸. These modalities, although prevalent in many centers, have not been extensively studied in asthma to determine their applicability as clinical biomarkers.

Lung Magnetic Resonance Imaging

Whilst CT of the lungs has had routine use in clinical practice for several decades, MRI is a comparatively novel technology for pulmonary imaging. In contrast to CT scans, whose repeated use is limited by ionizing radiation, MRI has the advantage that it can be utilized for longitudinal imaging without accumulating risk. Historically, the lungs are not visualized on MRI, appearing black due to a near absence of detectable signal; in fact, the presence of obvious signal can be a clear indication of pathologies such as a pneumonia or infiltrative soft tissue process⁵⁹. In conventional MRI, two main challenges limit imaging of the lungs. First, the low tissue density of an inflated lung inherently means that there are fewer nuclei per unit volume that can be detected. Secondly, air-tissue interfaces lead to a decay in signal, and thus the structure of the lung itself causes any signal to vanish rapidly⁶⁰. Despite these challenges, numerous approaches to lung MRI have been developed, often capitalizing on the ability to detect nuclei other than hydrogen to yield a wide range of functional and structural information. Although these techniques can be performed on clinical MRI scanning platforms, some modalities require additional specialized equipment. Therefore, many of the techniques are currently limited to centers with specific expertise in lung MRI.

Other challenges include the inherently slower process of MRI acquisition compared with CT. Although most studies can be performed within a single breath hold, modern CT scanning remains faster. As in CT, protocols evaluating tidal breathing may yield significant advantages for younger children and others who are unable to maintain a breath hold¹⁹.

Proton MRI

Two approaches to imaging with proton MRI have been explored. The first capitalizes on the absence of signal from healthy lung as a way to identify abnormalities. Pulmonary edema and inflammatory infiltrates can be identified by certain proton sequences. As one example, segmental allergen challenge is a procedure in which allergens are instilled by bronchoscopy into individual lung segments, with study results typically obtained by repeat bronchoscopy. Recent work suggests that proton MRI sequences may be a feasible, non-invasive alternative for determining segmental challenge results ⁶¹.

The other approach is to alter the MRI scan sequence itself in order to detect the signal of the lung parenchyma itself before it decays – ultrashort echo time (UTE) MRI. Since the air-tissue interfaces cause a rapid decay in signal, UTE acquires images at echo times below one millisecond, prior to signal decay. UTE methodology has thus far not been utilized in human asthma studies. A mouse model of asthma revealed mucus plugging, bronchial remodeling, and evidence of eosinophilic inflammation on UTE MRI ⁶². In humans, a study in COPD patients demonstrated a strong relationship between MR signal intensity and tissue density (as calculated from Hounsfield units by CT), as well as spatial correlations between UTE MRI and CT identification of emphysema, inflammation, and mucus plugs ⁶³. In CF, UTE MRI has been shown to be sensitive to early disease and perform comparably to CT ⁶⁴⁻⁶⁷. Recent reports of successful free-breathing image acquisition in neonates are expanding the availability of this technology into the youngest patients for diseases such as bronchopulmonary dysplasia^{68, 69}.

Hyperpolarized Gas MRI

The most extensively studied lung MRI technique is hyperpolarized (HP) noble gas MRI, an approach that has been in use for nearly two decades. In HP gas MRI, patients inhale a noble gas, either ^3He or ^{129}Xe , that is “hyperpolarized” in a lab prior to administration. The inhaled gas can have upwards of 40% polarization, which is on the order of 100,000-fold greater than the polarization of nuclei achieved in commercial MRI magnets⁷⁰. The MRI scanner then detects not the lung tissue itself but rather the hyperpolarized gas. Since the gas is inhaled, the resulting images demonstrate ventilated lung. The simplest measures in HP gas MRI are those relating to ventilation defects – regions of the lung where ventilation is decreased or absent (Figure 2). However, HP gas MRI can also reveal lung microstructure by measuring diffusion of gas atoms within the airways.

Initial studies in asthma established that ventilation defects on HP gas MRI correlate with clinical spirometry, disease severity, and can be induced with bronchoconstriction by methacholine⁷¹⁻⁷⁴. More recent work has sought to expand on the relationship between imaging findings and clinical phenotype. Ventilation defects appear to correlate with the degree of bronchial hyper-responsiveness by methacholine challenge, specific airway resistance, and patient dyspnea⁷⁵⁻⁷⁸. HP gas MRI can identify responses to therapies, such as reduction in exercise-induced bronchospasm with montelukast⁷⁷. Recent work also demonstrated a negative correlation between ventilation defects and asthma control as well as quality-of-life scales⁷⁹. Similar findings have been identified in children, with

imaging correlates between numerous spirometric measures as well as disease burden in asthma¹⁹.

In addition to the quantity of ventilation defects, several groups have noted that the size of defects may reflect asthma phenotypes, with larger focal defects appearing only in more severe disease^{19, 71}. Heterogeneous ventilation, including defects and over-ventilation, is also increased in asthma^{19, 76, 78}. Subtler differences in imaging texture, as opposed to frank defects in ventilation, have also been suggested to be of importance in describing ventilation changes⁸⁰.

Changes of ventilation defects over time have been explored in numerous studies, showing that the specific location of ventilation defects within an individual can vary over time, but generally the total burden of ventilation defects is fairly constant^{72, 74, 78, 81}. In fact, one study indicated less intra-individual variability in ventilation defects than spirometric measures between two study visits⁸².

Importantly, HP gas images can be obtained in the same imaging sessions as other techniques such as UTE MRI. The combination of ventilation images by hyperpolarized gas and parenchymal definition through UTE allows for characterizing both lung structure and function in a single imaging session.

Challenges in HP gas MRI are several-fold. Because HP gas decays, or loses its polarity, very quickly, imaging centers need to have an on-site polarizer to create the HP gas. Limited availability of ³He, due to multiple factors, has led to increased development of protocols with hyperpolarized Xenon. Limited data directly comparing the two gases suggests they are similar although not identical in the images generated, and that Xenon may be more sensitive for ventilation defects^{83, 84}.

Oxygen-enhanced MRI

Uniquely suited to the lungs, oxygen-enhanced MRI (OE-MRI) is a novel MRI technique in which paramagnetic $^{16}\text{O}_2$ is imaged. Since inhaled oxygen dissolves in tissue, OE-MRI can demonstrate ventilation-perfusion relationships with delivery of oxygen into tissue. It also allows for measurement of regional changes in PO_2 , which, when assessed for a period of minutes, can describe the variability of local oxygenation throughout the lungs over time. The results of OE-MRI are consistent with HP gas approaches, with both greater heterogeneity of measurements and evidence of delayed wash-in effect that correlates with asthma severity^{85,86}.

Other Imaging Modalities

Chest Electrical Impedance Tomography

Chest electrical impedance tomography (EIT) data is gathered by measuring the voltage across electrodes placed around the circumference of the chest after applying a defined current (Figure 3). Conductivity, a measure of impedance, is calculated for pixels in the cross-sectional plane of the electrodes, and an estimate of continuous ventilation and perfusion in an axial plane of a patient's chest is produced^{87,88} (Figure 3). Frerichs et al. measured improvement in ventilation after bronchodilator therapy in patients with asthma

⁸⁸, proving that EIT can give meaningful clinical outcomes. EIT is a noninvasive imaging modality that does not require cooperation from the patient, has no radiation exposure, and can obtain continuous data over multiple breaths. The primary boundaries to dissemination of this technology include limitations in labs equipped with this technology and the amount of specialized computing time required to interpret the bioimpedance output data.

Bronchoscopy Applications

Flexible bronchoscopy is currently recommended for specific indications in evaluation and treatment of asthma and obstructive lung disease over the life span, including the wheezing infant ⁸⁹⁻⁹². Innovative imaging techniques combined with flexible bronchoscopy are currently available in many centers to diagnose and treat other lung diseases. Endobronchial ultrasound (EBUS), which has clinical applicability in lung cancer, can be used to assess bronchial wall thickening and airway smooth muscle, yielding measurements comparable to those obtained from CT ^{93, 94}. The lack of small EBUS probes limits its use in small children, while the risk of repeated bronchoscopies more broadly limits the use of EBUS to estimate airway remodeling. Further study is needed to determine if EBUS can help monitor and guide asthma therapy.

Optical coherence tomography (OCT) can be combined with flexible bronchoscopy to create a three-dimensional micrometer-resolution image of small airway walls by capturing scattered near-infrared light (Figure 4). OCT use has recently expanded and Kirby et al. showed airway changes after bronchial thermoplasty in a 2-year prospective

study and suggested phenotyping patients for therapy based on airway parameters⁹⁵. Similar to many imaging modalities, limitations based on reproducibility and reliability of both the technique and analysis of images are being studied and improved^{96,97}. The widespread availability of flexible bronchoscopy in combination with early translational success may result in an adoption of these modalities into clinical care practices in the next five years.

Conclusion

The current era of chest imaging research is transitioning toward longitudinal prospective studies to define age and disease-specific biomarkers and to determine feasible and repeatable protocols to allow collaboration and comparison between clinical centers. However, differences in scanners and imaging protocols remain short-term limitations to generalize quantitative imaging research. Clinical centers that already follow strict guidelines to limit radiation will need to follow more stringent guidelines and protocols in order to allow many of these techniques to become clinically useful, while modalities that avoid ionizing radiation may require expansion of imaging capabilities at many centers. The risk and benefits of imaging modalities including traditional and novel CT techniques, adapted MRI protocols, and other novel and established techniques must be evaluated for each patient based on the expertise of the clinician and the imaging center. Studies that use imaging biomarkers to guide therapeutics are still needed but continue to progress rapidly, with promises of greater understanding of pathophysiology and novel ways to monitor disease progression and response to treatment.

At the present time, use of imaging studies in asthma is primarily limited to assessing for complications or the exclusion of alternate diagnoses. However, there is substantial promise of numerous imaging techniques as biomarkers for personalized asthma care in the future.

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Figure Legends

Figure 1. Quantitative CT in a patient with severe asthma has airway narrowing (B) and increased low attenuation areas, a marker of hyperinflation (D), compared to a healthy subject (A and C) ³⁹.

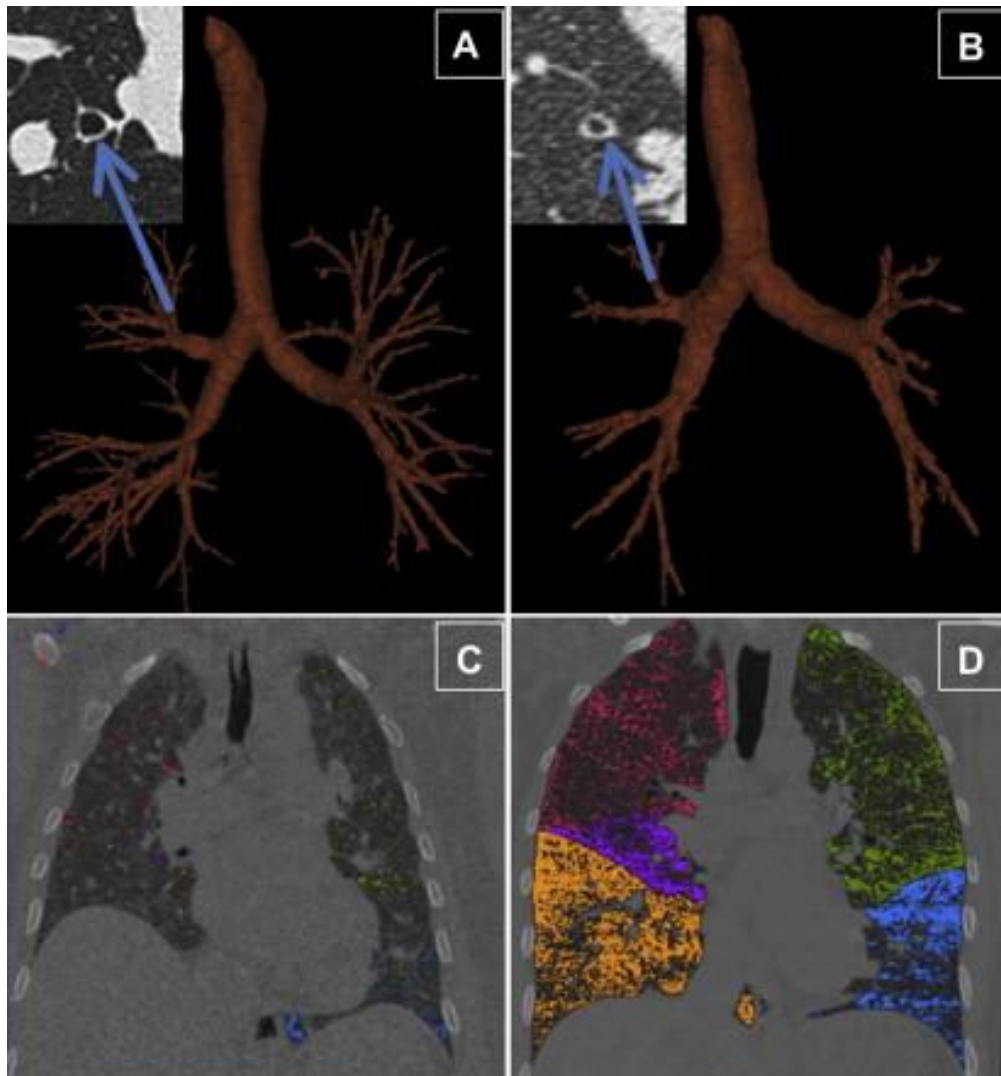
Figure 2. HP gas MRI images can reveal lung ventilation changes before and after medical or surgical interventions, without the concern for repeated radiation exposures; shown here are images obtained from a patient at baseline and 3 months after undergoing bronchial thermoplasty⁹⁸.

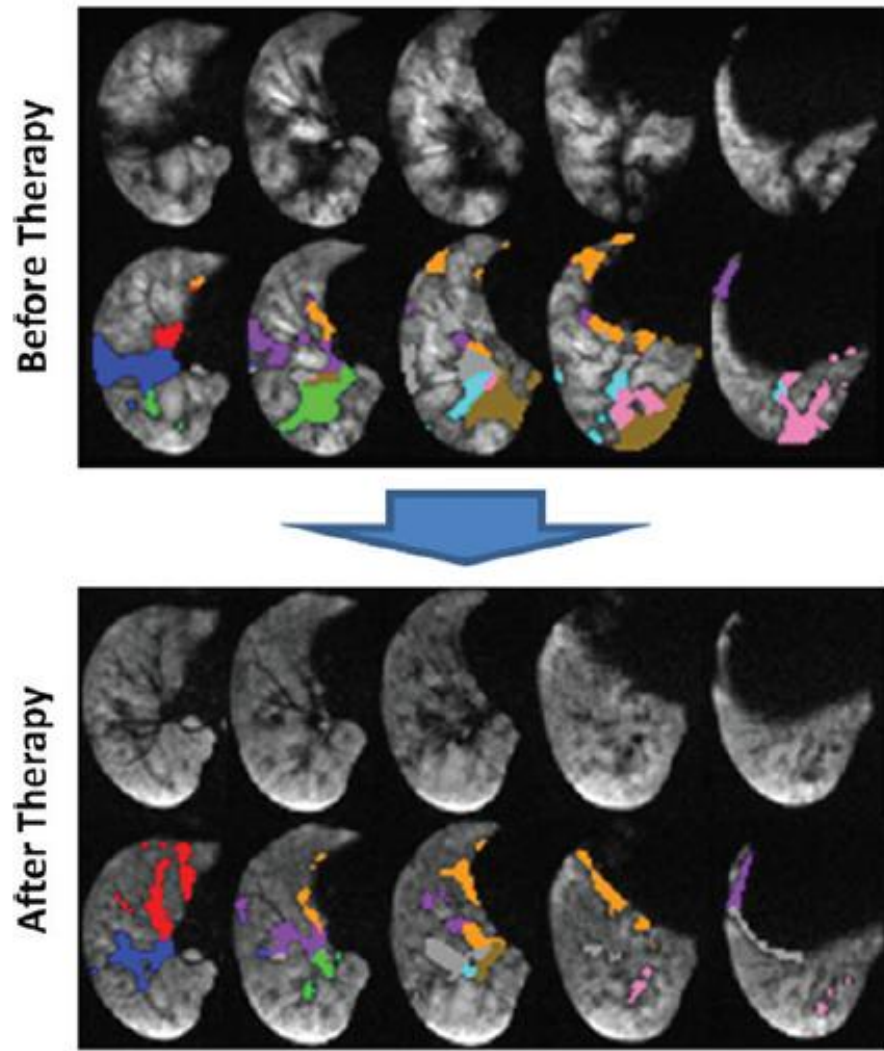
Figure 3.

a) Chest electrical impedance tomography (EIT) data is gathered by measuring the voltage across electrodes placed around the circumference of the chest after applying a defined current.

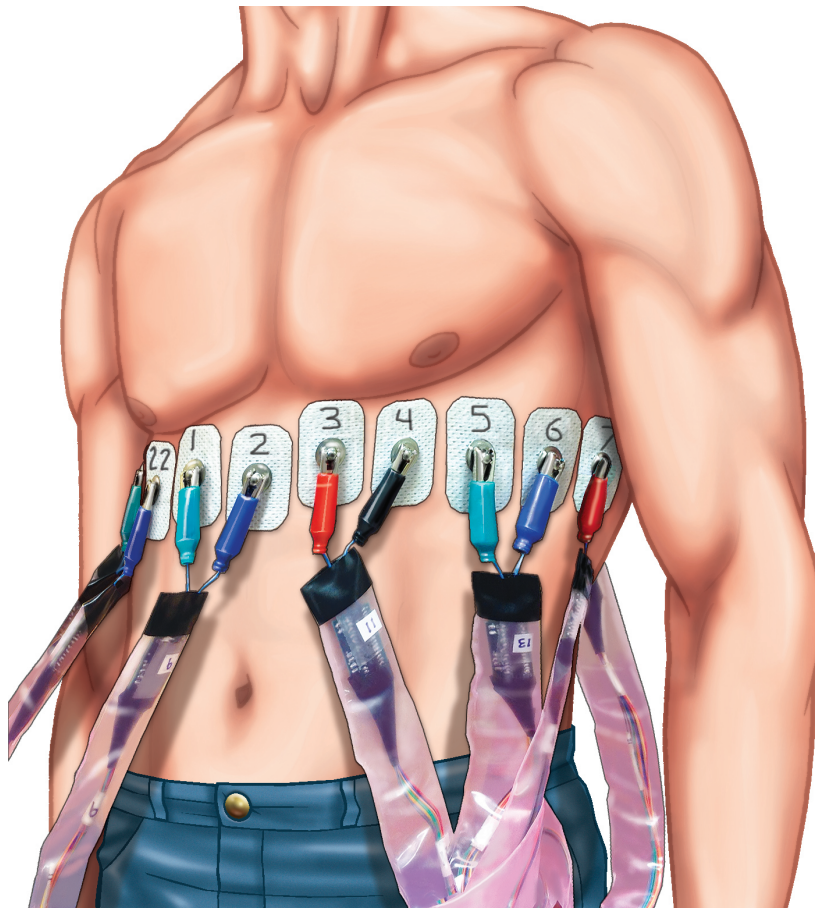
b) Conductivity, a measure of impedance, is calculated for pixels in the cross-sectional plane of the electrodes, and an estimate of continuous ventilation and perfusion in an axial plane of a patient's chest is produced.

Figure 4. Optical coherence tomography (OCT) combined with flexible bronchoscopy can visualize microscopic airway characteristics including epithelium (EPI), basement membrane (BM), and smooth muscle (SM) ⁹⁵.





A.



B.

