Hyperpolarized gas MRI illuminates lung function

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Historically, hope has been scant for catching any chronic occlusive pulmonary disease, including asthma and emphysema, early enough to treat and reverse, or at least stabilize, the condition.

Today, optimism is being renewed that MR imaging with hyperpolarized noble gases will help diagnose lung airway disease at a treatable stage, assist in monitoring therapeutic progress, and help pharmaceutical companies develop better treatment drugs.

Hyperpolarized (HP) MRI is a technique whereby the lung airspaces are visualized after the inhalation of a polarized gas, generally helium-3 or xenon-129. In patients with severe asthma, for example, the hyperpolarized gas contrast medium will show ventilation defects, places where the disease obstructs passage of the gas. Patients with emphysema have demonstrated a greater apparent diffusion coefficient, an indication that the tiny airspaces in the lungs have lost their elasticity. These changes have been demonstrated in asymptomatic smokers, giving researchers hope they can better understand the beginning stages of the disease.

"The ADC measurement probes the microstructure of the lung, down to the individual alveoli," said Dr. Warren Gefter, chief of thoracic imaging at the University of Pennsylvania. "We didn't have a clinical imaging scanner that could get to that spatial resolution. This is well below what we can see even on a high-resolution CT."

While routine clinical use of HP MRI is years away, investigators are using the method to unlock key mysteries about pulmonary diseases. One recent study by researchers at the University of Wisconsin-Madison suggests that a separate classification for severe asthma is appropriate. Many clinicians say that severe asthma is merely a progressed state of mild or moderate asthma. But some clinicians now agree that a severe asthma phenotype exists that is likely characterized by more severe airway remodeling and perhaps some level of persistent inflammation due to infectious agents such as respiratory viruses, said Sean Fain, Ph.D., an assistant professor of medical physics at UW.

Fain and colleagues studied several dozen subjects with asthma, comparing ventilation defects on He-3 MRI with CT-based measures of airway structure including wall thickness, eccentricity, lumen area, and parenchymal density. Several features went into classifying subjects as having severe asthma, but the most significant feature was whether they were receiving 1000 microg or more per day of corticosteroids, which help to open airways. The researchers also took fluid samples to evaluate inflammatory cell markers specific to sites of ventilation defects. Fain presented the study at the 2006 International Functional Lung Imaging Workshop held at the University of Pennsylvania. The investigators found lung regions that showed air trapping that persisted over a period of six weeks to several months. These more permanent regions of air trapping are not considered a common feature of typical asthma. The finding suggests underlying airway structure change, which would indicate a severe asthma phenotype, Fain said.

They also found inflammatory markers at sites that corresponded with ventilation defects on MRI. Although inflammation is considered a common feature in asthmatic patients, its overall significance in the disease remains subject to debate. The fact that the inflammation corresponded to the ventilation defects supports the idea that persistent airway changes in severe asthma are possibly due to inflammation and infection.

"The results are compelling, but the study is too small to be conclusive," Fain said. Nevertheless, the findings hold promise that HP MRI might one day be used to triage patients to more effective therapy. People with severe asthma are much more resistant to conventional treatments than those with mild to moderate asthma. Knowing the status of asthma cases beforehand will save time, money, and patient frustration, he said.

Dr. Eduard E. de Lange, director of body MRI at the University of Virginia Health Sciences System, Charlottesville, and colleagues found that HP He-3 MRI revealed regional changes of airflow obstruction in patients with asthma that correlated with disease severity (Chest
As the ventilation defect size increased, so did the severity of the asthma, even within subgroups. The differences were most pronounced between patients with mild-intermittent and mild-persistent asthma and those with moderate-persistent and severe-persistent asthma. Researchers concluded that HP MRI could be used to better understand asthmatic patients who are resistant to treatment.

NOBLE GASES

Both He-3 and Xe-129 have advantages and disadvantages as an MRI contrast medium. He-3 offers a stronger signal and is easier to polarize than Xe-129. The supply of He-3 is limited, however, because it is a byproduct of bomb-making. (While He-3 is abundant in the Moon's atmosphere, there are no plans to harvest that supply.) Xe-129, on the other hand, is freely available in the Earth's atmosphere. Unlike helium, xenon crosses into the bloodstream and can have anesthetic effects such as dizziness if given in an inappropriate quantity. An advantage associated with xenon's ability to enter the bloodstream, however, is the potential to measure perfusion as well as diffusion, in other organs such as the brain and kidneys.

Researchers at Harvard Medical School have conducted extensive functional brain experiments with Xe-129, according to Mitchell Albert, Ph.D., formerly with Harvard and now director of MRI research at the University of Massachusetts Medical School. Albert and colleagues at Harvard have demonstrated signal enhancement in certain parts of the animal brain in response to functional stimuli. These xenon signals are up to 80% stronger than those currently attained with conventional proton blood oxygen level-dependent functional MR imaging, said Albert, an early pioneer of HP MRI. The group is also researching xenon's ability to deliver spectroscopic data, which could, for example, distinguish between the brain's white and gray matter. Clinical applications for Xe-129 brain imaging include helping to diagnose and treat multiple sclerosis, Alzheimer's disease, schizophrenia, and other neurodegenerative diseases.

Unpolarized xenon has been used for years in CT imaging, and physicists argue that the molecular structure of the gas does not change during the polarization process. Nevertheless, the FDA will not approve the use of polarized gases (either helium or xenon) without long and expensive trials, a fact that keeps the technique from entering routine clinical practice. Researchers estimate that some 5000 scans have been performed without any serious adverse events. Without reimbursement for the procedure, research is expensive: He-3 costs about $150 a liter, enough for three doses. Most research with HP MRI is being done on 1.5T scanners, but high field strength is not essential. In conventional MRI, field strength provides the scanner with the ability to polarize hydrogen atoms. Since the gases used in HP MRI are already polarized, the magnet strength is irrelevant. In fact, it would be possible to design an inexpensive scanner with very low field strength that is compact and portable enough to go to a patient's bedside. A group at Harvard led by Albert has demonstrated lung imaging with both He-3 and Xe-129 at 15 mT, or 0.015T.

Albert suggests that smaller, cheaper portable scanners could be developed for use in physician offices or rural communities. Low-field-strength open magnets could also be used to image patients in a variety of postures, addressing the postural component to the distribution of gas in lung imaging. Ross Mair, Ph.D., a staff scientist at the Harvard-Smithsonian Center for Astrophysics, presented a study at the Penn workshop showing that a second-generation open-access human MRI system at 6.5 mT produced clear images of the lungs with He-3 while subjects were supine and vertical. Albert's group, with funding from the National Aeronautics and Space Administration, is evaluating the potential for lightweight low-field MRI technology in space. Unfortunately, funds for the project have been drastically cut as NASA steers its focus toward other space initiatives.

GOING DEEPER

The initial excitement sparked by HP MRI revolved around having a noninvasive technique with high spatial resolution that did not subject patients to radiation exposure. The first studies essentially documented defects seen in gas distribution in patients with asthma and emphysema. After that, researchers sought to use the technique to define the cause of those defects and to learn about lung physiology from the hyperpolarized agents. One way of quantifying lung function is by measuring the diffusion of the gas within the airspaces, as increased ADC corresponds to emphysematous airway enlargement.

The ADC of He-3 can detect changes in lung microstructure and has been shown in animals to correlate directly with the peripheral airspace size. Barnaby Waters, Ph.D., and colleagues at the University of Nottingham in the U.K. examined the sensitivity of ADC in human lung morphometry as a result of aging, exposure to cigarette smoke, and lung inflation (Am J Respir Crit Care Med...
2006;173:847-851). They found that in healthy subjects who had never smoked, the ADC increased as a function of age. For active and passive smokers, the ADC increased by up to 40% compared with never-smokers, with mean diffusion values significantly higher.

Fain and colleagues at the University of Wisconsin using ADC measurements also found underlying structural changes associated with natural aging. A recent study showed a correlation between changes in microstructure at the alveolar level and smoking history (Radiology 2006;239[3];875-883). They concluded that smokers demonstrated emphysema-like changes double those of normal aging. The correlations between mean ADC values and pulmonary function test measurements for diagnosing emphysema were statistically significant, according to the researchers. They also noted that many changes seen with HP MRI were not reflected in the CT data. "Although He-3 is not approved by the FDA for clinical use, the results are encouraging that regional emphysematous changes can be identified at an early stage when there are no clinical symptoms," wrote de Lange in an accompanying editorial.

Global function

Conventional lung function testing, such as spirometry and FEV1 (forced expiratory volume in one second), determines global lung function. One of HP MRI's advantages is its ability to measure regional lung function. De Lange noted that an abnormal lung function test result is not necessarily specific for emphysema, while HP MRI can be very specific. Because a certain degree of alveolar damage must have occurred before changes in pulmonary function become noticeable, it is possible that the ensuing airspace enlargement may be detectable with diffusion-weighted He-3 MR imaging before the lung function becomes abnormal.

At the Penn workshop, Dr. James Hogg, a world-renowned pulmonary pathologist from Vancouver, said that the HP He-3 ADC measure could discriminate normal from emphysematous lung better than even his pathological samples. "That's not to say it's seeing something that pathologists can't see," said workshop program cochair Gefter. "But it has the advantage of mapping through the entire lung, whereas pathologists have to sample limited amounts of the lung."

Several years ago, Amersham Health had begun preparations for multicenter clinical trials with HP He-3 MRI with an eye to winning FDA approval. When GE Healthcare bought Amersham, the process stalled. GE has become active again in hyperpolarized MRI research, with several ongoing academic and pharmaceutical collaborations, according to Michael Wood, general manager of MR research collaborations for the company. One initiative is studying hyperpolarized carbon-13, which gives structural and real-time metabolic information. This approach has implications beyond lung imaging, according to Gefter.

Klaes Golman, Ph.D., from the department of experimental research at Malmo University Hospital in Sweden, showed at the Penn workshop cardiac cine images of an HP C-13 molecule making its way through the Krebs cycle. While it's early to predict clinical uses for HP C-13 MRI, Gefter ventured a few guesses. It could be used in cardiac imaging to determine if the myocardium in an ischemic event is truly infarcted or undergoing anaerobic glycolysis. Another application could be in radiation oncology to determine whether tumor activity is hypoxic and to monitor response to therapy. "This is looking at cellular physiology. We're taking functional imaging to cellular imaging," Gefter said.

Mr. Kaiser is news editor of Diagnostic Imaging.

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