

Editorials

Polarized helium: Changing our view of asthma

Key words: Asthma, hyperresponsiveness, airway closure, polarized helium

Unlike easily definable diseases, asthma is more a syndrome representing a cluster of diseases. Efforts to disentangle this cluster of diseases are hamstrung by the fact that our best means of characterizing the lung—pulmonary function testing—must be done at the airway opening, which is located far from the complex structure that makes up most of the lung. It is like studying a tree by limiting yourself to making measurements only on the trunk. What we need are better, more direct means of studying and characterizing the entire lung in its complexity.

In this month's issue of the Journal, Samee et al¹ report on an emerging technique for studying the lung: polarized helium imaging. This article is the first work to report on this imaging technique in a large group of individuals with asthma. The authors show that magnetic resonance imaging of lungs in patients with asthma who have inhaled polarized helium demonstrates ventilation defects that are well correlated with lung function and worsen with challenge of either methacholine or exercise. The defects occur heterogeneously throughout the lung and do not immediately resolve. These findings establish polarized helium imaging as a potentially important imaging technique for asthma. Previous work has been done with radiolabeled gases such as Technegas,^{2,3} but those imaging techniques did not have the high degree of resolution that is seen with polarized helium.

The limitation of the report by Samee et al¹ is that the sample size for the challenge studies is small, particularly for the methacholine challenges. If we are going to truly characterize asthma with this technique, many more patients will have to be imaged. And a number of questions remain: What happens to the observed ventilation defects after a deep inflation? What are the effects of treatment on these observed defects? Much more work obviously needs to be done, but polarized helium imaging is currently limited by economic, logistic, and regulatory constraints. Nevertheless, it is safe to assert that we now have a new technique for characterizing asthma.

Why do we need a better way to characterize asthma? Spirometry is far and away the most frequently used measure of lung function in asthma, but it has limitations. Because spirometry is done at the airway opening, it is a summated measure, in that it reflects the sum of airflow and pressure in all of the airways distal to the airway opening. It is impossible to say what is happening in the lung when spirometry changes. Certainly FEV₁/forced vital capacity (FVC) is a measure of airflow obstruction—or rather of airflow limitation—but we do not know what is physically occurring at the level of the airway. Is it airflow *obstruction*—meaning a complete cessation of flow—or is it airflow *limitation*—meaning a diminished flow? Both FEV₁ and FVC can diminish when airways narrow, when the lung is smaller (after a resection), or when parts of the lung have closed and are no longer communicating with the airway opening. Changes in FEV₁ can be directly mirrored by changes in FVC, as evidenced in patients who exhibit so-called “reversible restriction.” There have been several case reports of patients with restrictive spirometry that reverses with a bronchodilator,⁴ and this might in fact be the case in as many as 10% of patients with restrictive spirometry.⁵ Polarized helium imaging steps around these difficulties, which are inherent in spirometry, and gives us a visual representation of what is occurring beyond the airway opening.

Polarized helium imaging provides a new kind of information, but how can we use this information? First, it is important to discuss what polarized helium imaging suggests about the pathophysiology of asthma. Most of us conceive of asthma, and more specifically the response to methacholine, as a result of increased airway smooth muscle tone and subsequent airway narrowing. Although this undoubtedly happens to some degree, given that methacholine is a smooth muscle agonist, the ventilation defects shown by Samee et al¹ suggest that airway closure is also occurring to a greater degree in individuals with asthma. Some would argue that this was established long ago; indeed, work dating back to the 1960s demonstrates that individuals with even mild asymptomatic asthma have an enhanced degree of airway closure.⁶⁻⁹ More recent work, involving the use of wedged bronchoscopes, has suggested that this closure is largely occurring in the very distal lung,¹⁰⁻¹² and this has also been implicated as the cause of “reversible restriction.”⁴ The segmental defects seen with polarized helium imaging suggest that either larger airways are closing or groups of smaller airways are closing. Work in animal models has also demonstrated the importance of airway closure; in fact, there is some suggestion that airway closure is the predominant effect of

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aerosolized methacholine in mice.^{13,14} Collectively, these findings are compatible with either airway narrowing to the point of closure or the complete obstruction of airways, as would happen if they filled with mucus or were blocked by liquid bridging between airway walls. Because the phrase “airway closure” evokes the image of complete airway constriction and because we do not have enough evidence to state absolutely that this is what is happening, a more appropriate term than *airway closure* would be *lung derecruitment*. The finding that the ventilation defects seen with polarized helium imaging persist over hours to days suggests a defect in the ability to rerecruit these derecruited lung segments and further supports this choice of terminology. Accordingly, polarized helium imaging visually demonstrates what decades of physiologic research have been suggesting—namely, that lung derecruitment is a major part of the pathophysiology of asthma.

The knowledge that individuals with asthma have an increased tendency toward lung derecruitment reminds us that we need also to consider mechanisms other than airway narrowing in our efforts to understand the pathophysiology of asthma. Airways hyperresponsiveness is likely the result of at least 3 processes: airways undergoing exaggerated narrowing, airways collapsing or filling with mucus, and airways not rerecruiting easily. All 3 of these processes need to be addressed in our ongoing research efforts. This is particularly relevant to work in transgenic mice, because (as mentioned above) airway hyperresponsiveness in mice might largely be the result of exaggerated lung derecruitment. Thus, we need to continue ongoing efforts that are focused on understanding the mechanisms of mucus hypersecretion and airway instability (ie, surfactant dysfunction) as well as pursuing the causes of exaggerated airway narrowing.

How will polarized helium imaging be used in clinical practice? As Samee et al¹ suggest, polarized helium imaging has the potential to improve our ability to subcategorize asthma, or resolve the syndrome of asthma into its component diseases. It might be that some patients have a disease that is dominated by airway narrowing whereas other patients, such as those with “reversible restriction,” have a disease that is dominated by lung derecruitment. Most patients will likely prove to have a mixture of airway narrowing and lung derecruitment, but different therapies might impact preferentially on one or the other of these processes. Nevertheless, as mentioned above, more work remains to be done before

we can herald polarized helium imaging as the new standard for characterizing asthma.

In general, in this report Samee et al¹ make a significant contribution to our understanding of asthma and our future ability to explore the mechanisms responsible for the pathophysiology of asthma. We should all look forward to more work on this exciting technique that improves our “view” of asthma.

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Correction

With regard to the March 2003 editorial entitled “Dietary prevention of allergy, atopy, and allergic diseases” (2003;111:467-70), reference 2 should have appeared as follows: von Berg A, Koletsko S, Gruebl A, Filipiak-Pittroff B, Wichmann HE, Bauer CP, et al. The effect of hydrolyzed cow’s milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study (GINI), a randomized double-blind trial. *J Allergy Clin Immunol* 2003;111:533-40.