

Exploring the Distal Lung: New Direction in Asthma

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Abstract

Asthma is an airway disease, yet that airway extends all the way to the alveolar tissue area. Pathohistological as well as physiological and clinical studies have recently documented this aspect of asthma. The implications of this are important for all asthmatic patients, but particularly for those whose asthma is more difficult to control. Many of the inhaled preparations used as therapy for asthma are of relatively large particle size. Thus, the deposition of these medications is mainly in the central and medium sized airways and very little of a given actuation gets to the distal airways. Ultrafine inhaled steroid particles have been shown to reach the more peripheral portions of the airway, and improvement in outcome variables such as air trapping as well as symptomatic outcomes have been demonstrated. This review focuses on anatomic airway changes, physiological changes of the distal airways, clinical outcome data, and particle size of inhaled preparations.

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Asthma is an airway disease. However, the airway extends distally to the alveolar tissue area, which has not been emphasized in textbooks or guidelines. The importance of considering the very distal lung involvement in asthma relates to obtaining better control of asthma in our patients. This article is based on the lecture given at the 2008 Israel Association of Allergy and Clinical Immunology – American College of Asthma Allergy and Immunology (IAACI-ACAAI) meeting held in Jerusalem, December 2008. The article is written in the form of six questions, followed by the answers.

Is there supporting anatomic evidence that the distal airways are involved in asthma and to a different extent than the central airways?

To answer this question we must look at postmortem studies. One such study by Carroll and colleagues [1] measured the outer wall area of a normal control population, asthmatics who died from causes other than their asthma, and those with fatal asthma. Looking at the medium-size airways, 2–4 mm, there was no statistically significant difference between groups. Moving to the more peripheral lung, less than 2 mm, they found significant differences. Both asthma groups had significantly increased outer wall area compared to the control population, but there was no difference between the two asthma groups. This suggests that regardless of the severity of asthma, there are remodeling changes in the airway walls with predominance in the more peripheral areas of the lung.

In a non-published postmortem bronchogram evaluation of

the airways in three individuals – one normal, another whose asthma was “well controlled” during her life, and one with fatal asthma – the way the dye penetrated the airways in all three was very informative. The normal individual had fine branching of the airways with dye penetrating into the alveolar spaces. The “well-controlled” asthma patient during life, who died from causes other than her asthma, had fine branching of the airways but the alveolar “blush” was not demonstrated. The individual who died from his asthma had cutoffs of the major airways and thus no gas exchange could possibly occur. This anatomic evaluation of the airways demonstrated that even in “well-controlled” asthma, abnormalities occur in the very distal lung.

Is there supporting physiological and clinical evidence that the central and distal airways differ in asthma?

A physiological evaluation of peripheral airway resistance via a wedge bronchoscope was performed by Wagner and co-workers [2]. They selected two groups of subjects, mild asthma and normal controls. Figure 1 demonstrates that peripheral airway resistance even in mild asthma is markedly elevated compared to normal controls. Even after bronchodilator therapy, the peripheral airway resistance was still significantly elevated. This study demonstrates that the physiological measurements of distal lung dysfunction are apparent in asthma, even in mild asthma.

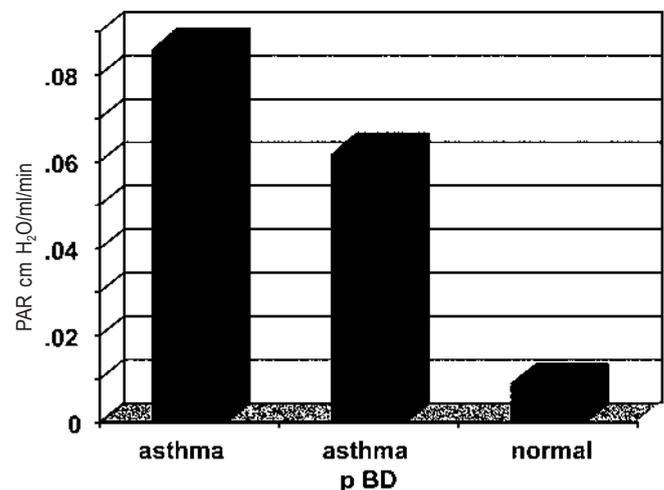


Figure 1. Peripheral airway resistance (PAR) is measured in normal controls and mild asthmatic subjects. Although spirometry was similar between the groups, PAR was markedly elevated in the asthmatic subjects. This held true even for a post-bronchodilator (BD) measurement. [From reference 2]

Using asthmatic children, in't Veen et al. [3] showed that there is a distal airway difference between those children whose asthma is stable throughout the year and those who have exacerbations. The investigators could not find significant physiological differences in forced expiratory volume in 1 second, total lung capacity, functional residual capacity, or residual volume, but they did find significantly elevated closing volume in the unstable asthma group. Although this study was not set up to determine if early closure of the distal airways was specifically the physiological cause for the exacerbations throughout the year, one can deduce that if a child with an elevated closing volume came in contact with a trigger such as an upper respiratory infection or allergen, this trigger could produce closure of the distal airways resulting in an asthma exacerbation.

Since a major characteristic of asthma is airway inflammation, is there physiological evidence of a differentiation between central and distal inflammation?

To answer this question, background information on the nocturnal worsening of asthma needs to be understood as this is used for a model of naturally occurring worsening of asthma. Circadian rhythm in lung function occurs in both normal individuals and asthmatics. In normal individuals, the best lung function is during the afternoon and the nadir lung function occurs during the middle of the night, at approximately 4 a.m. Asthmatics follow the same circadian pattern but can have major decrements in lung function overnight. Thus, reversible airway obstruction occurs naturally in this model. The second characteristic of asthma, bronchial hyperresponsiveness, is also worsened during sleep. The study by Martin and collaborators [4] demonstrated that even an asthma control group highly selected not to have overnight decrements in lung function will still have marked increases in bronchial hyper-responsiveness by approximately twofold [Figure 2]. Of marked importance is the finding that those individuals

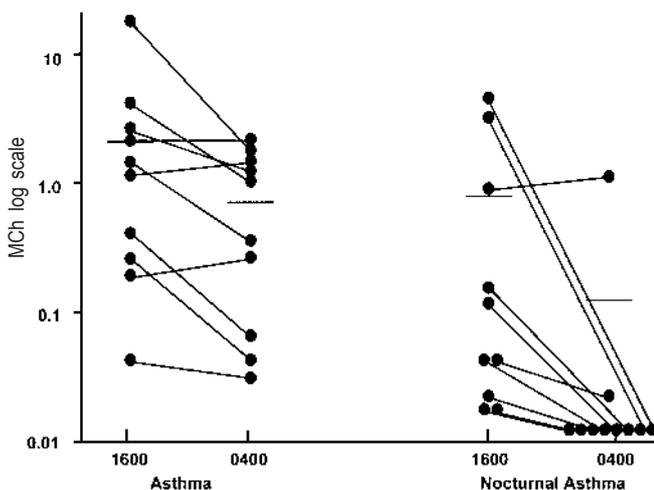


Figure 2. Asthmatic subjects without and with nocturnal decrements in forced expiratory volume in 1 second were evaluated for bronchial hyper-responsiveness (BHR) by methacholine challenge (MCh) at 4 p.m. and 4 a.m. During the night both groups had a significant increase in BHR of two- and eightfold, respectively. [From reference 4]

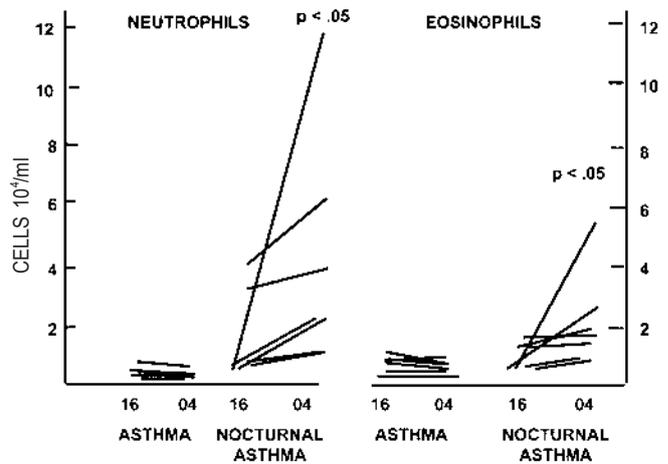


Figure 3. Asthmatic subjects without and with nocturnal asthma had bronchoalveolar lavage performed at 4 p.m. and 4 a.m. The effector cells of asthma, neutrophils and eosinophils increased only in subjects with nocturnal asthma. [From reference 5]

who worsen their lung function overnight have approximately an eightfold increase in bronchial hyper-responsiveness based on methacholine challenge. Thus, this naturally occurring circadian variation, whether in the asthma control group or the nocturnal asthma group, demonstrate the marked pathobiological changes that occur in circadian rhythms in our asthma patients. The third major characteristic of asthma is airway inflammation. This also changes from day to night. The effector cells of asthma increased markedly in the nocturnal asthma group from day to night, but not in the asthma control group [Figure 3] [5].

To answer the question posed above, the physiological uncoupling of lung parenchyma and airways was studied at night [6]. If the volume-resistance curve does not change, i.e., increasing volume does not produce a fall in resistance, then distal

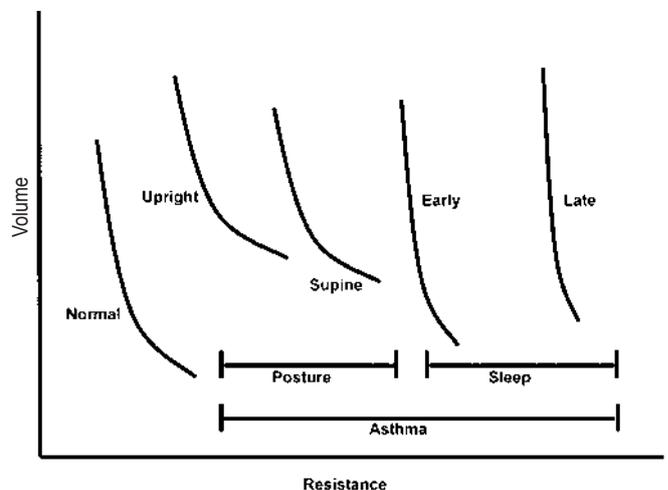


Figure 4. Volume-resistance relationships in normal awake and asthmatic awake (upright and supine) individuals and early and late in sleep. Only during sleep was there loss of this relationship, suggesting distal airway inflammation and edema resulting in uncoupling of the airways and parenchyma. [Adapted from reference 6]

inflammation and edema are the probable cause. In asthmatics the volume-resistance relationship during the awake and upright position is preserved [Figure 4]. That is, as lung volume is increased, airway resistance falls. In the awake but recumbent position the volume-resistance relationship is still maintained. However, early in sleep, after about an hour and a half, a physiological uncoupling begins. With volume being increased during sleep there is very little fall on resistance. Late in sleep, after approximately 3–4 hours, asthma continues to worsen as noted by increasing airway resistance and additionally there is almost a complete physiological uncoupling of the lung parenchyma and airways. No matter how much the lung volume has increased, there is very little change in airway resistance. This leads to the next question.

Does a difference in proximal versus distal inflammation support the nocturnal uncoupling?

In a study of two groups of asthmatics Kraft et al. [7] demonstrated a marked increase in the volume of tissue eosinophils in alveolar tissue area in the nocturnal asthma group. These investigators bronchoscoped an asthma control population who were highly selected not to have worsening asthma at night and those who had nocturnal worsening of asthma. The bronchoscopy occurred at 4 p.m. and 4 a.m. with randomized starting times for the initial bronchoscopy. The locations where endobronchial biopsies were performed were approximately at the fifth generation airway as well as the alveolar tissue area. During the afternoon study, there were no statistically significant differences between groups or locations. However, even at 4 p.m. there was a trend to increased inflammation in the alveolar tissue area in both groups. There was no doubt at 4 a.m. that the volume of eosinophils in the alveolar tissue area was tremendously increased in the nocturnal asthma group. Thus, both uncoupling of the airways and lung parenchyma occur at night and the inflammatory response is greatest in the distal airways.

Is there a non-invasive measure of distal airway inflammation?

At the present time there are no good physiological measurements or biomarkers that adequately represent the distal airway inflammation on a non-invasive basis. However, Berry and co-authors [8] conducted an interesting study in which they considered alveolar nitric oxide levels as a surrogate marker of distal airway inflammation. Alveolar nitric oxide was measured at several different flow rates with the results incorporated into a complex equation to arrive at the measurement. There was no significant difference between a normal control population and mild to moderate asthmatic subjects. However, in the "refractory asthma" group alveolar nitric oxide was significantly elevated compared to the other two groups. It should be noted that the variability of values in the refractory asthma group was large. However, the investigators then doubled the inhaled corticosteroid preparation that the subjects were taking or added oral prednisone as a systemic agent to cover the entire airway. The inhaled steroid preparations were large-particle steroids. The authors found that doubling a large-particle in-

haled steroid did not change the alveolar nitric oxide. However, giving an oral systemic preparation did produce a significant fall in alveolar nitric oxide levels, suggesting a decrease in the inflammatory response in that area. This leads to the next question.

Does particle size of inhaled medication alter lung physiology and inflammation?

Deposition studies of large-particle inhaled steroids show that the medication is mainly deposited in the more central airways and very little gets to the periphery [9]. To determine if particle size of an inhaled steroid can alter air trapping, Goldin et al. [10] looked at the same inhaled steroid, beclomethasone, but two different particle sizes. A chlorofluorocarbon preparation of beclomethasone has a particle size of approximately 4 microns and hydrofluoroalkane beclomethasone has a particle size of 1.1 microns. Using high resolution computed tomography scanning and after 4 weeks of treatment, these investigators demonstrated that the ultrafine particle, HFA beclomethasone, had less air trapping than the larger particle inhaled steroid. Even after methacholine challenge to produce bronchoconstriction and bring out air trapping, there was a minimal increase in the CT measurement with the ultrafine HFA beclomethasone. However, with the CFC beclomethasone there was further increase in air trapping.

A similar type of study examining the same inhaled steroid with two different particle sizes demonstrated that bronchial hyper-responsiveness was partially improved with the ultrafine HFA beclomethasone compared to the large-particle size CFC beclomethasone [11]. Both preparations, compared to baseline, had significant improvement in bronchial hyper-responsiveness.

In summary, there is supporting physiological and clinical evidence that the central and distal airways are different in asthma. Additionally, there is strong evidence to support a differentiation between central and distal inflammation in asthma. The distal inflammation continues all the way to the alveolar tissue area. The major question is – does particle size of inhaled medication alter asthma outcome? There are several open-label studies that suggest this is indeed the case. However, what is needed are double-blind year-long trials with multiple asthma outcomes to definitively mandate an ultrafine particle size inhaled steroid as first-line therapy or add-on therapy. Clearly, the very peripheral airways are important in asthma and should be considered in the treatment paradigm.

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HFA = hydrofluoroalkane
CFC = chlorofluorocarbon

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