Physiologic Dysfunction of the Asthmatic Lung What's Going On Down There, Anyway?

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Asthma is a syndrome of lung dysfunction characterized by airflow obstruction, reversibility to bronchodilators, and airways hyperresponsiveness (AHR). There is a growing body of evidence that suggests that the principle defect in asthma is the occlusion of the airway lumen by liquid, fibrin, and mucus. The fall in FEV₁ observed in asthma is best explained by a loss of communicating airspaces and the rise in residual lung volume. Imaging studies in both human patients and experimental animals support this hypothesis. An increased propensity for the airways to close can be a cause of AHR. We conclude that loss of lung volume plays a central role in determining the dysfunction of the asthmatic lung as measured by FEV₁. Together, these recent findings provide a better understanding of the causes of airflow obstruction and AHR, suggesting new avenues for the development of more effective asthma therapies.

Keywords: lung volume; peripheral resistance; FEV₁; airways hyperresponsiveness; airway closure

Asthma as a common syndrome that presents as a physiologic dysfunction of the lung characterized by airflow limitation and airways hyperresponsiveness (AHR). Importantly, patients with asthma respond to β -agonists. A typical example is the patient with asthma who presents to a pulmonary clinic with an FEV₁ of 2 L, or 65% of predicted. After treatment with two puffs of albuterol, the FEV₁ improves significantly to 75% of predicted, consistent with the pretest diagnosis of asthma. The first question one might ask is: "What exactly is the nature of the mechanical defect in the lung that caused this reversible reduction in FEV₁?" This has no simple answer, however, because FEV₁ is a polyvalent measure that is influenced by a myriad of factors, including the volume inspired before forced expiration (i.e., TLC), the level of muscular effort, airways resistance (caliber), airway wall stiffness, and lung elastic recoil (1). Thus, despite being extremely useful from a clinical standpoint (2), FEV₁ is highly nonspecific. This has led physiologists to search for more sensitive and specific measures of lung function. In this review, we will cover the recent investigations using classic physiologic methods and imaging modalities, and discuss how the findings have markedly changed our view of the pathophysiology of the asthmatic lung.

MEASUREMENT OF PERIPHERAL LUNG FUNCTION

A number of studies have directly demonstrated the involvement of the lung periphery in asthma. In 1989, Wagner and coworkers (3) published an investigation that employed the wedged bronchoscope technique to assess peripheral airflow resistance (Rp) in normal subjects and in subjects with asthma, and reported two important findings. First, the magnitude of Rp in subjects with asthma was about an order of magnitude larger than in normal subjects, despite the fact that FEV₁ in the subjects with asthma was within normal limits; saliently illustrating the insensitivity of the FEV₁ to peripheral lung dysfunction. Second, Rp was significantly correlated to AHR as measured by the PC₂₀. We have subsequently extended this line of investigation (4–6), and found Rp to be increased by installation of cold dry air. We also found Rp to be highly variable, very unstable, and correlated to AHR. Even traditional measures of overall lung function implicate the critical role of the lung periphery in asthma. For example, dry gas hypernea increases residual volume (RV) and alters the quasi-static pressure–volume behavior of the lung, only during inspiration (5).

These findings are all highly indicative of loss (derecruitment) of peripheral lung units in asthma (7). In comparing normal subjects, subjects with asthma, and subject with nocturnal asthma, Kraft and colleagues (8) found that Rp increased in direct relation to asthma severity, that the loss of distal lung units was correlated to the increase in Rp, and that Rp was highly correlated to the increase in RV. Further, only 1 subject with asthma out of the 14 studied showed any evidence of proximal airway narrowing. Together, these studies support the hypothesis that the principal event taking place in the asthmatic lung is not central airway narrowing as commonly thought, but rather peripheral airway closure (Figure 1).

IMAGING STUDIES: SEEING IS BELIEVING

Considerable direct evidence now exists for the occurrence of substantial airway closure in the asthmatic lung. Perhaps most convincing are the results of imaging studies showing the inability of tracers to enter or leave distal regions of the lung. For example, King and colleagues (9) used single photon emission computed tomography (SPECT) and inhaled technegas to demonstrate increased areas of poor or nonexistent ventilation in the lungs of individuals with asthma. These ventilation defects were found to be patchy with a basilar prominence. In fact, patterns of patchy inflation can even be seen in CT scans of subjects with asthma taken at the end of a full expiration (10). Dynamic MRI images of hyperpolarized helium-3 also show clear evidence of ventilation defects after exercise or methacholine challenge, and are reversed with bronchodilatation (11, 12). Recently, de Lange and coworkers (12) showed a correlation between the size of imaged ventilation defects and spirometry

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Figure 1. Conceptual models of the mechanical properties of the lung subtended by the wedged bronchoscope. In *A*, representing the normal subjects, the lung is modeled as a single compartment model with resistance of the proximal airways, compliance of the lung units, and where the major source of resistance are the collateral pathways. In *B*, representing the asthmatic lung, the lung is modeled with increased heterogeneity where airways both in the subtended units or collateral units with airways that are either severely narrowed (long time constants) or more likely closed. (Reproduced by permission from Reference 6.)

in patients with moderate to severe persistent disease. For reasons that are not clear, most imaging studies have shown the defects to predominate in the lower lung zones even though subjects are imaged in the supine posture. Using PET and ^{13}N tracers, Venegas and colleagues (13, 14) have shown similar ventilation defects, and they were able to reproduce this finding in a computational model of a branching airway tree in which closure of a distal airway increased the probability of subsequent nearby closures. They thus established a mechanism whereby the topographical distribution of ventilation defects can exhibit a self-organized patchiness that is reminiscent of other emergent phenomena seen throughout the natural world. Even so, the ventilation defects are not randomly arranged.

The findings from the recent imaging studies mentioned above are consistent with older physiology-based studies that implicate airway closure as a major phenomenon in the patient with asthma (Table 1). On the other hand, an increase in AHR is also a well-known hallmark of asthma. The paradox, given the correlation of indices of airway closure to AHR, is to explain how airway closure causes or contributes to AHR.

LESSONS FROM THE CAGE SIDE

We have previously shown that inhaled methacholine challenge in the allergen-sensitized mouse leads to AHR, as seen in human allergic asthma, and that the mechanical response of the lung seemed to indicate an increase in airway closure with little in the way of evidence for enhanced airway narrowing (15). In support of this, Wagers and coworkers (16) demonstrated an increase in hysteresis of the pressure–volume relationship in the allergically challenged mouse, similar to that observed in humans (5). On the basis of these observations, we postulated that peripheral airway closure, not central airway narrowing, is the major functional defect of the inflamed lung.

We have recently addressed this issue using a well-described mouse asthma system, aided by a computational model-based analysis. Data were collected with a computer-controlled, volume-cycled ventilator for maximum precision of lung func-

TABLE 1. EVIDENCE OF PERIPHERAL AIRWAY CLOSURE IN ASTHMA

- Residual volume is increased.
- Closing volume is increased.
- R_p is increased in correlation to an increase in plateau pressure and fall in peripheral compliance.
- Large breaths increase FVC and cause R_p to abruptly fall.
- The fall in FEV_1 is largely the result of a fall in FVC.
- Increased pressure–volume hysteresis.
- Imaging studies (CT, PET, SPECT, and hyperpolarized helium) show ventilatory defects.

Definition of abbreviations: CT = computed tomography; PET = positron emission tomography; SPECT = single photon emission computed tomography; R_p = peripheral resistance.

tion assessment (17). Using this system, we showed that the AHR that occurs in allergically inflamed mice is of a distinctly different origin than that seen either in A/J mice, a strain that is intrinsically hyperresponsive, or in BALB/c mice treated with polyclonals that compromise the barrier function of the epithelium (18, 19). In particular, the AHR in allergically inflamed BALB/c mice is characterized by a preferential increase in lung elastance rather than airway resistance. Further, this increased elastance is reversed abruptly with a large inflation of the lungs. Incorporating histologic evidence into a computational model of the mouse lung, we were able to deduce the likely mechanisms underlying this AHR (20). First, the model mimics lung impedance measurements from normal mice if the airways follow an appropriate fractional narrowing time profile and if any airway that narrowed to a critical radius of 35 μm (simulating the sudden formation of liquid bridges across the lumen) then closes. However, when we tried to have the computational model fit the impedance data from allergically inflamed mice simply by increasing the degree of shortening of the airway smooth muscle, we were unable to account for the large increases in lung elastance seen *in vivo*. However, all the main features of the experimental data were reproduced when we increased the thickness of the inner lining around the walls of all the airways in the model to represent the epithelial hypertrophy that we observed histologically, along with a modest increase in the critical airway diameter at which closure occurred (20).

To confirm the role of airway closure in allergically inflamed mice, we ventilated mice with pure oxygen before methacholine challenge. When airway closure occurred after challenge, the oxygen trapped behind the points of closure was subsequently absorbed. The resulting atelectatic lung regions were then quantified with whole-body micro-CT (21) (Figure 2). We found that the amount of lung volume that was lost to atelectasis accounted precisely for the measured increases in lung elastance. We also observed that the absorption atelectasis had a basilar predominance reminiscent of that seen in humans, a somewhat remarkable finding given that the mouse has proportionately much larger diameter airways than humans.

Not all AHR in mice is due to enhanced airway closure, however. Computational modeling of impedance measurements from mice treated with the cationic protein poly-L-lysine showed that the AHR induced by this treatment is due entirely to enhanced shortening of the airway smooth muscle because the methacholine now reaches the muscle unimpeded (19). Intriguingly, when both epithelial thickening and increased smooth muscle shortening are included in the computational model of the mouse, one predicts that the effects of methacholine challenge will be catastrophic, a result we recently confirmed experimentally (22). This suggests that we should focus on the ways in which multiple mechanisms can synergize to

Figure 2. Micro-CT images taken from allergen-challenged mice after ventilation with 100% oxygen and subsequent methacholine challenge. The CT images were inverted and digitally filtered to show only air-containing spaces. Areas of black are those lung units that have undergone reabsorption atelectasis due to proximal airway closure (red arrows). The cobblestoned pleural surface suggests that closure also occurs at the alveolar or alveolar duct level (white arrows). Scans have 47 μm resolution. (Reproduced by permission from Reference 21.)

produce a degree of AHR that is vastly more severe than any one mechanism on its own. In any case, it is clear that abnormalities in the smooth muscle itself can, as traditionally thought, play a role in the AHR of asthma. The speed of contraction has been found to be increased in allergically inflamed airway smooth muscle (23). The reasons why speed of muscle contraction should matter are less obvious than the implications of increased force. Anafi and Bates recently used a computational model to show that accelerated airway narrowing may affect the topographic pattern of airway closure throughout the lung and cause closure of larger airways (24).

Together, these investigations in mice and associated computational modeling studies lead us to conclude that AHR can occur through a number of very unrelated mechanisms that include hypercontractility of the airway smooth muscle, disruption of the epithelial barrier, and enhanced peripheral airway closure. Nevertheless, our work in animals and patients with asthma supports the conclusion that the mechanism of enhanced airway closure best explains the AHR observed in humans with asthma.

MECHANISMS OF AIRWAY CLOSURE

Our attention is thus now focused on airway closure as perhaps the key phenomenon underlying AHR in asthma. There seem to be several mechanisms by which enhanced closure might arise. An obvious possibility is mucus plugging. Agrawal and coworkers (25) showed that treatment with a MARCKS-related peptide that blocks the release of mucin can ameliorate AHR in allergically inflamed mice. Presumably other components of the inflammatory exudates that accumulate in the airspaces of the asthmatic lung could also contribute to blockage of airways.

One such possible player in airway closure is fibrin. Wagers and colleagues (26) reported finding that fibrin accumulates within the airway lumen in asthma (Figure 3), that fibrin

formation is associated with AHR, and that enzymatic dissolution of fibrin ameliorates AHR. Fibrin is known to be a potent inactivator of surfactant (27), which would result in increased formation of liquid bridges across the airway lumen. Indeed, surfactant disruption has been previously reported in the airways of individuals with asthma. Jarjour and coworkers (28) showed a correlation between surfactant dysfunction and eosinophilia after sequential antigen challenge. This work has recently been extended by Hite and colleagues (29), who showed that surfactant aggregates in BAL from individuals with asthma were correlated to FEV₁. Associations of polymorphisms in the genes that encode surfactant proteins to asthma (30) also strongly support a key role for surfactant dysfunction (31) and suggest a potential therapeutic role for surfactant replacement therapy (32). Further, it has recently become apparent that β -agonists, as well as relaxing smooth muscle, may also cause release of surfactant molecules into the air-liquid interface, thereby reducing surface tension within the lungs and stabilizing airways. Thus, β -agonists may improve spirometric measures of lung function by more than a single mechanism.

ROLE OF DEEP BREATH

Nadel and Tierny first observed that the importance of the bronchodilating effects of a deep breath (33), an observation that was extended by Fish and coworkers (34) to show that this bronchodilation was impaired in the individual with asthma. More recently, Skloot and colleagues (35) reported that the inhibition of large breaths during a methacholine challenge in normal people leads to a degree of AHR that is remarkably similar to that observed in individuals with asthma. Subsequently, Togias and coworkers illustrated in a series of studies how a deep breath can induce both bronchodilation and bronchoprotection, the latter referring to the phenomenon

Figure 3. (A) Scanning electron micrograph of an alveolar duct of an allergen (OVA)-challenged and -sensitized mouse. (B) The extravasation of red blood cells, white blood cells, and both monomeric and polymeric fibrin are visible. Magnification bars on bottom right are 100 and 10 μm , respectively.

whereby a deep breath before methacholine challenge ameliorates the subsequent degree of bronchoconstriction. Bronchodilation is reduced (36) to a degree related to severity (37), but bronchoprotection is diminished even in mild airways disease (38), suggesting that the mechanisms for the two effects of deep breaths may not be the same. Both bronchoprotection and bronchodilation are improved by treatment with inhaled corticosteroids (39).

The lack of effectiveness of a deep breath in asthma presumably represents a failure to either dilate narrowed airways or reopen closed lung units, and conceivably could result from

either stronger airway smooth muscle or a change in the biophysical properties of the liquid within the airspaces. The effects of a deep breath are mediated by the forces of airway–parenchymal interdependence, which suggests that these forces are altered in asthma. Indeed, it is known that airway–parenchymal interdependence is reduced as a function of severity and asthma activity (40). Alterations in interdependence have also been shown theoretically to affect the topographical distribution of airway closure and may explain the patchiness of ventilation defects that have been observed with various imaging modalities (13, 21).

Figure 4. The changes in the divisions of lung volume and capacities as asthma increases in severity. The dotted band represents the variable nature of the maximal physical limits of maximal lung volume. See text for further discussion.

In aggregate, these findings, together with the well-known effects of asthma on spirometrically determined lung volumes, lead to the conclusion that the key physiologic defects in asthma involve mechanisms related to changes in lung volume (41).

SO WHAT CAUSES FEV₁ TO FALL IN ASTHMA?

Let's return to our patient who presented with a low FEV₁. In light of the foregoing, it should now be apparent that we also need ask whether the patient's FVC fallen as well. In fact, the FVC of this patient was 64% of predicted, giving an FEV₁/FVC ratio that is normal. Brown and colleagues (42) found that the fall in FEV₁ in most patients with asthma is due to a fall in FVC secondary to a rise in FRC, TLC, and in particular RV. They also found that the change in FEV₁/FVC after bronchodilator treatment is related to the diameter of only the large (> 13 mm) airways (43), and that FVC (or FEV₁) only falls if TLC fails to rise. Consequently, it appears as if the rise in TLC commonly seen in patients with asthma can be viewed as a compensatory mechanism to preserve the functional range of lung volume (i.e., FVC) (43). This also illustrates why FEV₁ lacks sensitivity for detecting peripheral airways obstruction (3).

There is a well-known, and somewhat variable, rise of TLC in asthma (43, 44), but the mechanism of this rise still remains poorly understood. However, a clue to the mechanism underlying this phenomenon comes from, of all places, observations in competitive breath-hold divers (45, 46). A technique known as volume packing used by these divers to increase breath-hold times is associated with a profound increase (1 L) in TLC and an increase in static elastic recoil pressures of greater than 80 cm H₂O! Eventually, as lung volume increases, a mechanism to prevent over-distention of the chest wall must be activated, likely involving strong inhibitory reflexes from the respiratory muscles. Alternatively, this postulated reflex is not active during an exacerbation, thus allowing the TLC to rise until the maximum limit of chest deformation is reached. Up until this maximal deformation point is reached, TLC increases in direct proportion to the degree of airway closure that occurs; hence chest wall hyperinflation defends the FVC and in turn the FEV₁ (46). Once the limit of chest wall expansion has been reached, however, further increases in RV due to lung decruitment will result in falls in both FVC and FEV₁ (Figure 4).

CONCLUSIONS

Investigations into the pathophysiology of asthma over the past 10 years have led to profound changes in our thinking about this common and insidious disease, particularly with regard to the link between airflow and volume. It now appears that the AHR of asthma predominantly reflects the closure of small airways, rather than large airway narrowing. The difficulty of opening closed airways in the inflamed lung may also account for the failure of a deep breath to reverse bronchoconstriction in subjects with asthma. Finally, the associated protective increase in TLC that accompanies the closure-related increase in RV in asthma also explains, at least in part, why FEV₁ has remained rather nonspecific in its ability to elucidate the link between structure and function. This underscores the need for more specific measures of lung function that are based on a firm understanding of the physics underlying pressure, flow, and volume relationships in the lung.

This change in our understanding of the asthmatic lung has therapeutic implications. It may well be that β -agonists work not by relaxing airway smooth muscle but by reopening closed airspaces. It also suggests that penetration of drugs to these

airspaces beyond the point of airway closure may be problematic. In this regard, the recent study by Kraft and coworkers (47) is germane because they report that treatment with the oral medication Montelukast resulted in falls in RV and correlated to improvements in wheeze and chest tightness. Accordingly, we speculate that these new insights into the pathophysiology of the patient with asthma have the potential to provide us with a better understanding of both the present and future asthma therapies.

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