Epidemiology and Pulmonary Physiology of Severe Asthma

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KEYWORDS

• Demographics • Phenotype • Health care utilization • Pulmonary function
• Lung elastic recoil • Ventilation heterogeneity • Gas trapping
• Airway hyperresponsiveness

KEY POINTS

- The definition of severe asthma is still a work in progress.
- The severity of asthma is predictive of higher health care utilization.
- Cluster analysis is useful in characterizing severe asthma phenotypes.
- Airway hyperresponsiveness in severe asthma is a result of abnormal airflow, lung recoil, ventilation, and gas trapping.
- Patients with severe asthma may have a reduced perception of dyspnea.

INTRODUCTION

Severe asthma is a characterized by a complex set of clinical, demographic, and physiologic features. In this article, we review both the epidemiology and pulmonary physiology associated with severe asthma.

DEMOGRAPHICS OF SEVERE ASTHMA

Asthma has long been recognized as a worldwide noncommunicable disease of importance. Within the population of individuals with asthma, there is a subgroup of individuals at high risk for complications, exacerbations, and a poor quality of life.

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These individuals are classified with severe asthma and they account for 5% to 15% of individuals with asthma in the United States and the world.[1,2] Severe asthma, as defined by the American Thoracic Society and European Respiratory Society (ATS/ERS) clinical practice guidelines, is asthma requiring treatment with high-dose inhaled corticosteroids (ICS) and a second controller during the prior year, and/or oral steroids for at least half of the prior year to prevent symptoms from becoming uncontrolled.[1] Severe asthma also can be described as uncontrolled despite reliance on ICS or frequent oral steroid use.[3] Most of these population numbers are based on questionnaires investigating reported symptoms, particularly the presence of wheezing to assess global asthma burden. Wheezing notoriously overdiagnoses asthma, so may create a slightly higher prevalence than the population truly represents. According to information from the Centers for Disease Control and Prevention (CDC) and Environmental Protection Agency, in 2011, there were 25.9 million individuals in the United States, including 7.1 million children, diagnosed with asthma.[4] In a similar effort in 2013, the CDC found asthma prevalence of 7.3% in America with 8.3% prevalence in children and 7% prevalence in adults. In the black population in the United States there was an almost 50% increase in asthma diagnoses over the past 10 years. Epidemiologic research is ongoing to investigate environmental and social influences on race patterns in asthma prevalence.[5] Evidence also shows that although poverty level does not significantly affect the frequency of asthma attacks among children, adults with incomes less than 250% of the federal poverty level were more likely to report asthma attacks than those with incomes over 450% of the poverty level.[6] Asthma also accounts for a significant number of deaths both in the United States and worldwide. In 2007 alone, there were 3447 deaths in the United States attributed to asthma.[7] Data collected in 2010 as part of the National Hospital Ambulatory Medical Care Survey identified asthma exacerbations as the primary visit diagnosis for more than 15 million office visits and outpatient medical center visits along with 2 million emergency department (ED) visits.[8]

In The Epidemiology and Natural history of asthma: Outcomes and treatment Regimens (TENOR) cohort of patients with severe asthma, gender was distributed differently between older and younger populations.[9] For the adult patients, 71% were women compared with 43% of adolescents and 34% of children. This is similar to the findings of Zein and colleagues,[2] who observed that after adolescence there is a shift from male-predominant severe asthma to female.

COHORT CHARACTERISTICS OF SEVERE ASTHMA

Over the past 20 years, there have been large cohorts constructed to observe trends in therapies and patient outcomes related to asthma. These were created to better understand high-risk individuals and what traits may contribute to more severe asthma or difficult to control asthma. The 2 largest studies in the United States are the previously mentioned TENOR cohort,[9] and the Severe Asthma Research Program (SARP).[10] In both studies, most patients were enrolled by specialists rather than by identifying asthma based on questionnaires completed by the patient.

The TENOR cohort demonstrated that the presence of a recent exacerbation within 3 months of introduction to the study was the strongest predictor of future asthma exacerbation in individuals older than 12.[9] This remained high when adjusted for patient demographics. Recent exacerbation was defined as an ED visit or overnight hospitalization. Increased risk also remained significant if patients required oral corticosteroids in the 3 months preceding baseline evaluation (**Box 1**). Other factors suggesting high risk included prior pneumonia, intubation, and postbronchodilator

Box 1
Predictors of asthma severity as demonstrated in Severe Asthma Research Program (SARP) and The Epidemiology and Natural history of asthma: Outcomes and treatment Regimens (TENOR) cohorts

- Emergency visit or hospital stay within prior 3 months
- Use of oral corticosteroids within prior 3 months
- Prior pneumonia or intubation
- Postbronchodilator forced vital capacity (FVC) less than 70% predicted
- Prebronchodilator FEV1 diminished
- Lower than normal level of blood basophils
- Asthma symptoms with routine physical activity
- Fewer number of positive skin tests

Children

- Nonwhite
- More than 3 allergic triggers

forced vital capacity (FVC) less than 70% predicted. Additional predictors of exacerbations in children included nonwhite ethnicity and presence of more than 3 allergic triggers.[11]

In adults older than 65, the older patients had lower health care utilization, better reported quality of life, and fewer control issues despite the presence of worse lung function when compared with those younger than 65. In this study, it was unclear if this was related to better compliance and more extensive medication regimens. Overall, the severe asthma classification primarily included adults older than 18 years, those with weight gain over time, black race, persistent airflow limitation, and aspirin-sensitive asthma.[9]

The SARP cohort was created after the 2000 National Heart, Lung, and Blood Institute workshop on severe asthma to investigate characteristics of those with severe asthma and create more succinct diagnostic criteria.[10] This study enrolled patients from major sites in the United States and from 1 European site. The analysis of this cohort revealed various patterns based on objective (pulmonary function, skin prick testing, and immunoglobulin [Ig]E levels) and self-reported questionnaire assessments. The characteristics that independently increased the likelihood of having severe asthma were the presence of diminished prebronchodilator forced expiratory volume in 1 second (FEV1), which carried a 36% increase in likelihood of severe asthma with every 5% decrease in percent predicted FEV1, history of pneumonia, lower number of blood basophils, asthma symptoms during routine physical activity, and lower numbers of positive skin allergy tests. In the population younger than 12 years old included in SARP, the duration of asthma, baseline lung function, and the number of controller medications required were most consistently predictive of the asthma phenotype.[12]

The most frequently reported symptoms among the severe asthma group in the SARP cohort were cough and shortness of breath. This cohort did show that daily cough, chest tightness, and nighttime symptoms were associated with higher health care utilization, suggesting greater impact on individuals' lives than those with different symptoms.[10]

FINANCIAL IMPACT

Severe asthma accounts for a greater proportion of costs and health care utilization compared with controlled asthma. The TENOR data demonstrated that costs increase directly with number of control issues.[13] This mimics a prospective study done in 1996 in France for 1 year following costs related to asthma and severity of asthma.[14] In the 3 months before enrollment in TENOR cohort, 10% of individuals had at least 1 hospitalization or ED visit for asthma for adults, adolescents, and children. Also reported was 50% of adults and 40% of adolescents had oral corticosteroid bursts and unplanned primary care appointments in that time frame for asthma symptoms. High-dose ICS were used in 56% of children and 26% of adolescents at onset of this study. There were consistently high rates of reliance on the health care system despite use of high-dose ICS in these patients. In the TENOR cohort, 53% of adults and 44% of adolescents who were on long-term controllers required oral corticosteroid (OCS) bursts in the 3 months before study initiation.[11] In this same cohort, patients with controlled asthma had fewer work and school absences, and asthma costs increased directly with number of control problems. In the TENOR group, the average cost throughout the 3-year study for uncontrolled asthma was $14,212 compared with $6452 for controlled asthma per patient.[11] Additionally, according to the CDC, asthma accounted for $56 billion in medical costs including lost school and work days, and early death in 2007; $50 billion of that was accounted for by direct medical costs. Over the span of 2002 to 2007, cost was estimated at $3300 per person per year in health care expenses.[7]

DISEASE HETEROGENEITY OF SEVERE ASTHMA

Asthma is a heterogeneous disease with many potential targets for improvement in control. One set of variables related to severity and control involves environment and exposures. Sheehan and Phipatankul[15] completed a review looking at asthma control and environmental factors. This review showed that children with comorbid severe allergic rhinitis were more likely to have uncontrolled asthma. Additionally, this review highlighted the growing argument that exposure and sensitization to mouse allergen is more predictive of severe asthma than cockroach antigen.[16] It is also interesting to note that although the public limitation of tobacco use has translated to some decreases in childhood hospitalizations related to tobacco exposure, there is also a trend toward increased indoor pollutants as homes become more insulated to promote energy efficiency.[15] Otherwise, tobacco use and exposure are related to more severe symptoms and worse control along with diminished response to ICS.[15] Additional trends shown to be associated with more severe asthma include smoking and second-hand smoke exposure. It is found that those with severe sinus disease, gastroesophageal reflux disease, and obstructive sleep apnea also have a tendency to experience more severe asthma exacerbations. Adults with sensitization to aspergillus have an association with more severe asthma onset as adults.[1]

Because of the heterogeneity across this disease category, clusters of similar characteristics are becoming identified as more descriptive phenotypes to guide management. This may prove to be more helpful in guiding therapy than classification based on level of control alone. From the SARP data set, 5 clusters of asthma were identified as having similar characteristics.[17] The first 2 clusters involved individuals with atopic asthma. Atopic or eosinophilic asthma is currently one of the most commonly recognized asthma phenotypes. As many as 50% to 60% of asthma cases can be attributed to atopy.[18] IgE mediates the allergic response in asthma, and individuals with asthma have higher levels of IgE than their counterparts without asthma. In the TENOR cohort,

IgE levels were found to be higher in men compared with women and in children and adolescents compared with adults and correlated to severity of asthma in younger individuals.[11] IgE levels were also higher in smokers compared with former or never smokers and adults with childhood-onset asthma compared with the adult-onset asthma population. IgE levels were also higher in nonwhite individuals compared with white individuals. When corrected for education level only, there remained a significant difference in IgE levels between black and nonblack groups. Among African American participants in SARP, there was an increase in number of mast cells with higher IgE levels bound to these mast cells.[19] Atopic asthma was divided into younger, mostly female individuals with childhood-onset atopic asthma and normal lung function and older subjects, 66% of whom were women with primarily childhood-onset, atopic asthma. In the older subjects there is a trend of predominantly normal prebronchodilator lung function or lung function that had reversed to normal over the course of the study period. These individuals relied more on medications than the group younger at diagnosis.[17] This phenotype was also described by Haldar and colleagues[20] in a subset of individuals with refractory asthma and poor medication compliance. The early-onset atopic group in this descriptive study also required high doses of corticosteroid therapy similar to the SARP cluster 2.

The third SARP cluster of individuals was predominantly female, older age, and obese, with a body mass index (BMI) higher than 30 kg/m^2. These individuals had late-onset asthma and were less likely to be atopic. Although they have shorter duration of their asthma history, they were more likely to have diminished pulmonary function at baseline.[17] This phenotype has been an increasingly important focus of research and characterized elsewhere. These individuals tend to have worse control, poor response to controller medication, and disease complicated by presence of obesity-related comorbidities and metabolic issues.[21] Obesity-related asthma has also been described to have decreased airway inflammation suggesting adipokines play a role in mediating disease.[22] The exact mechanism of how obesity influences asthma remains unclear but is an important research area.

An additional cluster consisted of individuals with a long duration of disease and a severe reduction in baseline pulmonary function. This was divided into 2 groups based on ability to reverse lung function after bronchodilator, as well as different degrees of atopy and age of onset of disease. Nearly half also required 3 or more OCS bursts over the prior year, with 70% of this cohort having some aspect of daily symptoms and poor quality of life.[17] Additionally, in the TENOR cohort, it was observed that black patients had a higher frequency of ED visits and more problems with asthma control. There was also a pattern of worse quality of life and more reliance on 3 or more control medications. This did not change statistically when adjusted for socioeconomics, disease severity, BMI, allergen sensitivity, or medication adherence. This suggests there is a genetic component trending data this way. As of yet, the exact mechanism remains unclear, but IgE levels and TH2-related alleles are both areas of investigation.[9,23]

PULMONARY PHYSIOLOGY OF SEVERE ASTHMA

Severe asthma includes asthma phenotypes of a wide variety. Although much has been learned about severe asthma from studying large cohorts of patients, we also need to investigate the pathophysiology of severe asthma to help discriminate among the various phenotypes and better understand and address this large public health issue. These physiologic abnormalities can be categorized as alterations in airflow, airway resistance, lung recoil, gas trapping, ventilation heterogeneity, airway

hyperresponsiveness, and perception of dyspnea (Fig. 1). In the following sections we examine each of these areas as they relate to severe asthma.

AIRFLOW

The most important hallmark of the physiologic definition of asthma is variable and reversible airflow limitation. Of all the pulmonary function tests, FEV1 is the most reliable indicator of the severity of airflow limitation, but it correlates poorly with severity of disease.[24] Although asthma is characterized as severe when FEV1 is less than 60% predicted,[25] other criteria can define severe asthma even with normal lung function.[10,26] Patients with severe asthma may have incomplete or poorly reversible airflow limitation,[27] and reversibility does not appear to influence survival.[28] When reversibility does occur, it appears to be due mainly to an increase in FVC, suggesting a reduction in gas trapping.[29] A recent study has shown that gas trapping (elevated residual volume/total lung capacity (RV/TLC)) was present in 48% of patients with poorly controlled asthma.[30] Severe asthma is also characterized by reduced fluctuations in low lung function (peak flow), suggesting less ability of the airway tree to respond to therapy.[31] Patients with severe asthma have accelerated loss of lung function over time compared with patients with mild to moderate asthma and healthy controls, which is related to increased airway wall thickness by computed tomography (CT) imaging.[32]

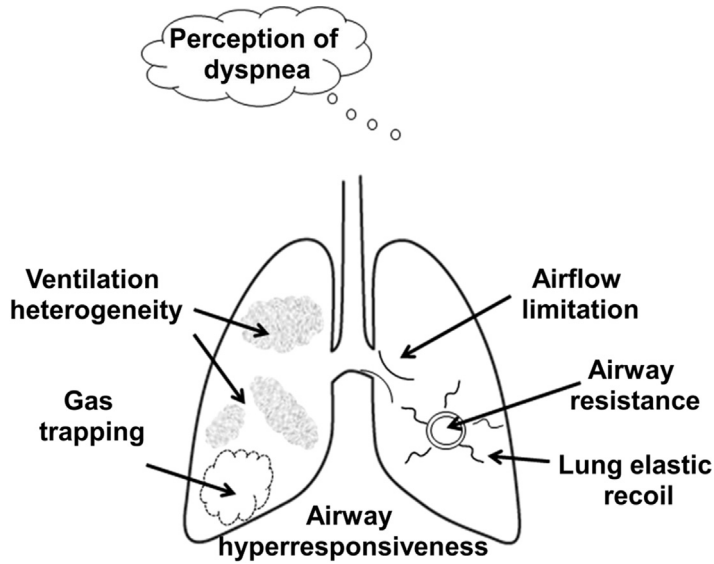

Fig. 1. Physiologic abnormalities in severe asthma. Multiple physiologic abnormalities occur in severe asthma. Like all asthma, severe asthma is characterized by airflow limitation that may be reversible. Airflow limitation is caused by variable contributions of increased airway resistance and reduced lung elastic recoil. In addition, airway narrowing results in ventilation heterogeneity throughout the lung, which may become extreme and result in airway closure with consequent gas trapping. All of these factors may contribute to the development of airway hyperresponsiveness. In addition, patients with severe asthma or poorly controlled asthma that have had near fatal events also have a reduced perception of dyspnea, making it extremely dangerous for them to develop severe lung dysfunction without sufficient awareness in time to seek medical care.

AIRWAY RESISTANCE

The fundamental mechanisms behind airflow limitation are loss of elastic recoil and increased airway resistance upstream from the equal pressure point that occurs during forced expiration.[33,34] Airway resistance (Raw) is increased by any process that narrows the airway lumen, which may include airway smooth muscle constriction, airway wall thickening, luminal mucus and inflammation, and loss of elastic recoil.

Raw is usually measured clinically during body plethysmography; however, measuring overall Raw may not detect subtle abnormalities in the lung periphery, where the total cross-sectional area of the airways is so large that this area only contributes approximately 10% of total airway resistance.[35] One method that may yield insight into this "silent zone" is the forced oscillation technique (FOT), which, because it probes the lung across different frequencies of imposed airflow, is able to differentiate proximal from distal contributions to lung mechanics and measure the contributions to lung impedance by resistance and reactance.[36]

The FOT has revealed that small airway dysfunction plays a crucial role in the pathophysiology of severe asthma.[26,37] For example, Lutchen and colleagues[38] showed that the response to methacholine in asthma results in a heterogeneous constriction pattern, which derives from airway closure that is poorly responsive to deep inflation. Alfieri and colleagues[39] evaluated the response to methacholine in patients with asthma by using FEV1 and FOT. Small airway dysfunction by FOT was more associated with excessive bronchoconstriction (fall in FVC), than with sensitivity to methacholine (fall in FEV1), implicating small airway closure in the response. Shi and colleagues[40] showed that indexes of peripheral airway dysfunction by FOT are more common in children with poor asthma control, and may predict loss of control. In adults, asthma control is associated with changes in lung reactance, reflecting residual peripheral airway dysfunction related to ventilation heterogeneity, airway closure, and gas trapping.[41]

LOSS OF ELASTIC RECOIL

In addition to increased Raw, airflow limitation may also be due to loss of elastic recoil. This has usually been associated with emphysema, but the loss of lung recoil has been noted in previous studies of patients with asthma.[42,43] Typically, the pressure-volume curve of the lung in individuals with asthma is shifted up, but has a normal slope, reflecting that the elastic properties of the lung are normal.[43] Yet some studies have shown that patients with asthma have a loss of elastic recoil when compared with healthy subjects.[44] This is in the absence of any abnormalities by CT imaging or diffusing capacity of the lung for carbon monoxide (DLCO) to suggest the presence of emphysema, and has been dubbed "pseudophysiologic emphysema."[42] The mechanism for the loss of recoil is unknown, but recently autopsy examination has revealed mild centrilobular emphysema not apparent by CT.[45] Loss of recoil would have profound consequences for airway narrowing, as the loss of interdependence between airways and parenchyma would allow excessive airway narrowing during bronchoconstriction.[44] This has been seen in near-fatal asthma[44] and in patients with asthma–chronic obstructive pulmonary disease overlap syndrome.[45] The mechanism of the loss of interdependence is unknown, but may be due to peribronchial inflammation,[46] remodeling of the outer airway wall,[47] or loss of surrounding alveolar attachments,[48] all of which may uncouple the airway wall from the tethering forces of the lung tissue and allow unopposed airway narrowing or closure.

Another interesting aspect of lung function in asthma related to lung recoil is the response to deep inhalation. Healthy subjects and individuals with asthma exposed

to an acute bronchoconstricting stimulus typically bronchodilate in response to a deep breath.[37] However, in spontaneous obstruction of patients with asthma, a deep breath results in bronchoconstriction.[37] The mechanisms involved in these effects are unclear, but may relate to relative hysteresis of airway and lung parenchyma, airway smooth muscle contractile properties, and altered forces of interdependence.[49] The ability to bronchodilate in response to a deep breath is less with increasing severity of asthma,[50] and failure of a deep breath to protect against bronchoconstriction is associated with airways hyperresponsiveness.[51] The failure to bronchodilate in response to a deep breath may be a fundamental defect in severe asthma that inhibits the ability of deep breaths to defend against severe airway narrowing.[52]

GAS TRAPPING

In addition to the FEV1 being a key indicator of airflow limitation, the FVC also is important in asthma. First, because the FVC is measured during a forced expiration, it may be reduced by gas compression and early airway closure. In severe asthma, Wenzel and colleagues[53] showed that there is a reduced FVC/slow vital capacity (SVC) ratio in a group of individuals with severe asthma with persistent eosinophilia who were at higher risk for near-fatal events, suggesting a higher propensity to airway closure during forced expiration. Gibbons and colleagues[54] described how falls in FVC following methacholine reflect excessive bronchoconstriction, reflecting extreme airway narrowing or airway closure in the lung periphery. Sorkness and colleagues[29] further developed this concept, evaluating the FVC as a surrogate for gas trapping, and the FEV1/FVC ratio as a marker of airflow limitation in individuals with severe and nonsevere asthma. They found that compared with individuals with nonsevere asthma, individuals with severe asthma had lower FEV1, lower FVC, and higher RV/TLC, even if no airflow limitation was seen on spirometry, reflecting a higher degree of gas trapping in the severe asthma group. Using the single breath nitrogen washout technique, airway closure has been shown to be associated with recurrent exacerbations in severe asthma.[55] In addition, airtrapping on CT imaging is also associated with severity of asthma, asthma-related hospitalizations, and need for mechanical ventilation among patients with severe asthma.[56]

In addition to an elevated RV/TLC and consequent lower FVC, patients with severe asthma may have an elevated functional residual capacity (FRC),[30] which may be due, in part, to gas trapping. In addition, as FRC relates directly to the balance of recoil forces between lung and chest wall, the mechanism may also relate to a prolonged respiratory system time constant from increased airway resistance, with a consequent reduction in the time available for the lungs to empty.[57] There is also evidence for increased inspiratory muscle activity during expiration, resulting in a higher FRC that allows for tidal breathing at a lower airway resistance.[57,58]

VENTILATION HETEROGENEITY

Ventilation heterogeneity refers to the unevenness of ventilation seen by gas distribution tests, frequency dependence of resistance or reactance by the FOT, and by imaging studies. Ventilation heterogeneity likely contributes to severe asthma because of the increased work of breathing expected, the derangements in gas exchange, and its association with airway hyperresponsiveness (AHR).[59,60] Increased ventilation heterogeneity, as reflected by an elevated Phase III slope during a single breath nitrogen washout, is seen in patients with poorly controlled asthma.[61] Studies performing multiple breath nitrogen washout (MBNW) have revealed that severe asthma is characterized by ventilation heterogeneity in the lung periphery measured by abnormalities

in the convection (conducting airways) and diffusion-dependent (acinar airways) components of the Phase III slope. In severe asthma, Thompson and colleagues[62] found that FEV1 correlated with acinar ventilation heterogeneity. However, neither acinar nor conductive ventilation heterogeneity was associated with gas trapping, which the investigators hypothesized was therefore due to widespread airway closure in many parts of the lung. Similarly, Farah and colleagues[63] showed that poor asthma control is associated with small airways disease by MBNW and treatment with ICS improves these abnormalities and asthma control.

Imaging studies also evaluate ventilation heterogeneity in the lung. Xenon ventilation CT and hyperpolarized xenon or helium lung MRI ventilation are 2 techniques that can be used to quantify ventilation heterogeneity. For example, Samee and colleagues[64] and Altes and colleagues[65] showed that patients with severe asthma have more ventilation defects, as seen by hyperpolarized MRI. In an elegant correlative study, Gonem and colleagues[66] demonstrated that acinar ventilation heterogeneity by MBNW corresponds to acinar ventilation defects by hyperpolarized MRI and airtrapping by CT, especially in individuals with severe asthma.

AIRWAY HYPERRESPONSIVENESS AND PERCEPTION OF DYSPNEA

Perhaps the most important physiologic characteristic of asthma is AHR, which develops as a consequence of multiple mechanisms.[67] Because severe asthma is associated with these mechanisms, including reduced FEV1, increased airway resistance, loss of recoil, gas trapping, and airway closure, it is no surprise that patients with severe asthma tend to have more AHR,[68] although the relationship between severity of AHR and asthma is variable.[69]

There is a subgroup of patients with severe asthma with marked AHR who are at greater risk of fatal bronchoconstriction. This group has been described as brittle asthma, and is often constituted by highly atopic, young, female patients with a predominant neutrophilic response, in whom symptoms appear to develop suddenly in a matter of hours.[70] Another group of patients with near-fatal asthma is characterized by a predominant eosinophilic inflammatory response that develops over days. This group, which constitutes 80% to 85% of patients with severe asthma, appears to have a decreased perception of dyspnea.[71] Kikuchi and colleagues[72] showed that patients with a history of near-fatal asthma had a decreased perception of dyspnea to both resistive loaded breathing and to hypoxia. Magadle and colleagues[73] demonstrated that patients with asthma with a low perception of dyspnea were older, more often women with a longer duration of asthma, had low daily use of B2 agonist, and more ED visits, admissions to hospital, and death. To date, different mechanisms have been proposed for poor perception, either genetic or acquired, such as adaptation to chronic hypoxic states and blunted respiratory response to hypoxemia.[70,72–74]

The FOT has also been used to explore the relationship between mechanical lung impedance and the sensation of dyspnea in response to bronchial provocation. A study performed by Antonelli and colleagues[75] revealed that dyspnea to methacholine had 2 distinctive patterns depending on the level of bronchoconstriction. With mild bronchoconstriction, dyspnea was associated with measures of airway narrowing and loss of bronchodilation to deep breath, whereas with moderate to severe bronchoconstriction, it was related to ventilation heterogeneity and lung volume recruitment. These responses perhaps suggest a more proximal effect of mild bronchoconstriction, and a more peripheral effect of moderate to severe bronchoconstriction. In support of this, Van der Wiel and colleagues[76] showed that small airways dysfunction, as assessed by FOT, was associated with an increase in dyspnea during

methacholine challenge, and with the severity of bronchoconstriction as assessed by the dose response slope.

SUMMARY

Asthma involves multiple abnormalities in the physiologic function of the lung. It appears that severe asthma is particularly characterized by changes in the lung periphery that result in increased airway closure and gas trapping, loss of airway parenchymal interdependence, and increased ventilation heterogeneity, all of which contribute to increased AHR. In addition, severe asthma associated with near-fatal events is characterized by reduced perception of dyspnea. All of these components may contribute to not only the baseline severity of asthma, but also the propensity for loss of asthma control and near-fatal exacerbations.

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