

# Irreversible Airway Obstruction in Asthma

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Asthma is generally characterized by fully reversible airway obstruction. However, a significant proportion of asthma patients demonstrate an incomplete reversibility of airway obstruction (IRAO) despite optimal treatment and the absence of a significant smoking history. Such partially irreversible airway obstruction may be due to residual airway inflammation, particularly of the eosinophilic type, and structural changes. Risks factors for IRAO include reduced pulmonary function early in life, frequent exacerbations, smoking, continuing exposure to a sensitizing agent, and adult-onset asthma. IRAO is associated with increased disease severity and increased asthma-related morbidity and mortality. Optimal asthma control, including prevention of asthma exacerbations, smoking avoidance, and sufficient anti-inflammatory therapy, should be implemented in an effort to avoid an accelerated decline in lung function and the development or worsening of IRAO.

## Introduction

The currently accepted definition of asthma includes the presence of chronic inflammation of the airways; airway hyperresponsiveness; and recurrent episodes of wheezing, breathlessness, chest tightness, and coughing that are associated with variable airway obstruction. Several phenotypes of asthma exist, and severity ranges from mild and intermittent to life-threateningly severe [1–3].

Airway obstruction in most asthma patients can resolve spontaneously or after treatment, as shown by normalization of expiratory flows. This is in contrast to smoking-induced chronic obstructive pulmonary disease (COPD), in which reversal of airway obstruction does not occur, not even with treatment. Nevertheless, a subgroup

of individuals with asthma do not have a significant history of smoking yet have persistent residual obstruction despite optimal treatment [4–7,8••,9].

## Definition of Irreversible Airway Obstruction

No consensus currently exists regarding the criteria that define incomplete reversibility of airway obstruction (IRAO). For example, some authors use a postbronchodilator forced expiratory volume in 1 second over forced vital capacity ( $FEV_1/FVC$ ) ratio of less than 70% [10••] and/or less than 75% at a minimum of two consecutive annual visits [9], whereas others use an  $FEV_1$  that is out of the normal range (eg,  $\leq 75\%$ ) after optimal treatment [9,11].

## Prevalence of IRAO

ten Brinke [8••] has provided an excellent overview of IRAO. The exact prevalence is not clear. Depending on the specific population studied, it varies from 15% to 50% or higher [8••,9,12,13]. In the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, 612 of 1017 patients (60%) showed evidence of persistent airflow limitation as defined by a postbronchodilator  $FEV_1/FVC$  ratio of  $\leq 70\%$  at two consecutive annual visits [14•].

## Mechanisms of Development of IRAO and Natural History

Airway inflammation and structural changes have been documented in asthma and can be responsible for alterations in airway function and the development of variable or persistent airway obstruction [15]. Determinants of expiratory flow include the elastic recoil pressure of the lung (which provides a driving pressure for the expiratory flow), airway resistance, and airway compressibility or compliance [16]. Persistent airway obstruction is associated with loss of elastic recoil, increased airway resistance, and/or increased collapsibility of the airways. These characteristics are almost always found in the most extreme form of airway obstruction—pulmonary emphysema—but also are often present to various degrees in chronic bronchitis and asthma [12,17].

### Persistent airway inflammation

IRAO in asthma can be due to insufficient treatment, which is often related to noncompliance with anti-inflammatory therapy or failure to objectively measure airway obstruction [18]. IRAO also could be due to the persistence of a marked inflammatory process that is not fully responsive to current therapy (eg, if it is more neutrophilic than eosinophilic). Another possibility is that the inflammatory process involves some form of steroid resistance, such as impaired glucocorticoid receptor function or impaired histone deacetylase-2 recruitment [19].

An accelerated decline in lung function over the course of many years often leads to IRAO. There are rare exceptions, such as in reactive airway dysfunction syndrome or irritant-induced asthma, linked to rapid development of fixed airway obstruction. Eosinophilia is an important contributor to this rapid decline [8••,10••,20,21]. For example, in the Childhood Asthma Management Program, sputum and serum eosinophil levels were higher in individuals who had at least a 1% loss in the percentage of FEV<sub>1</sub> predicted per year compared with those with an insignificant fall in FEV<sub>1</sub> [22]. Guerra et al. [10••] also showed that eosinophilia predicts the development of persistent airflow limitation among adults with onset of asthma during their first 25 years of life. Furthermore, ten Brinke et al. [9] reported that sputum eosinophilia is independently associated with persistent airflow limitation. It also has been suggested that persistent levels of nitric oxide in the exhaled air can predict a decrease in lung function [23•].

The evidence is somewhat equivocal with respect to the role of undertreatment in the development of IRAO. Bumbacea et al. [20] found that some asthma patients had IRAO despite receiving very high doses of inhaled corticosteroids, suggesting that the IRAO was not due to undertreatment. However, some of these patients may not have been compliant with therapy. In a report from ten Brinke et al. [9], patient use of 1600 µg of inhaled corticosteroids daily and/or oral corticosteroids in addition to long-acting bronchodilators for more than 1 year did not prevent or correct IRAO, although the authors posited that a more vigorous treatment could have further improved the patients' pulmonary function. This hypothesis was given credence by a study of 22 patients with stable severe asthma who had persistent sputum eosinophilia despite extensive antiasthma treatment [24]. A 2-week treatment with triamcinolone was associated with almost complete disappearance of sputum eosinophils and significant improvement in asthma symptoms, suggesting that patients with severe asthma may need additional or alternative anti-inflammatory treatment [25].

### Airway remodeling and lung parenchyma alterations

IRAO also may be—at least in part—a consequence of structural airway changes. This remodeling can be defined as alterations in the content, quantity, and type of structural elements of the airways [15]. Airway wall changes in asthma—which can include subepithelial fibrosis, deposition of proteoglycans, angiogenesis, glandular hyperplasia,

and many other changes—may result in an alteration of the airways' functional properties and a thickening of the airway walls. Patients with asthma have more eosinophilia and subepithelial airway fibrosis than individuals with smoking-induced COPD given the presence of a similar degree of irreversible airway obstruction in both diseases [24,26,27]. Therefore, airway remodeling can contribute to the development of IRAO in various ways [15,28,29,30•].

Lung parenchyma changes also may be involved in the development of IRAO. Emphysema-like changes in the lung parenchyma have been reported in asthma, although in only a minority of individuals [17]. Loss of parenchymal support may contribute to airway obstruction, but emphysema is not always found in patients with IRAO [8••]. Furthermore, people whose asthma is severe or who smoke may have a reduced diffusion capacity and peripheral airway spaces distention detected on high-resolution CT [31]. Other observations related to lung and airway remodeling include that elastin, a major component of the airway's extracellular matrix, can be disrupted in asthma, and increased elastase levels have been reported in asthma [32]. This can contribute to the many features of airway wall remodeling and to altered elastic recoil and lung elasticity.

### The link between airway inflammation and remodeling in IRAO

The preponderance of evidence suggests that eosinophilia is the main link among airway inflammation, airway remodeling, and IRAO due to the provoking of an intense or abnormal repair response [32–35]. For example, a 1-year follow-up of 582 asthma patients showed that a post-treatment FEV<sub>1</sub> of less than 75% predicted is associated with elevated levels of sputum eosinophils, as well as nonatopic status, longer asthma duration, emphysema on high-resolution CT, and elevated age and body mass index [21]. Bumbacea et al. [20] also examined the clinical characteristics and risk factors associated with IRAO in a cohort of individuals with difficult-to-treat severe asthma and a control group of people with asthma but near-normal pulmonary function (ie, FEV<sub>1</sub> > 80% predicted). Eosinophilia and airway wall thickening on high-resolution CT were the only two parameters independently associated with the irreversible component of airway obstruction.

### Factors Associated With the Development of Persistent Airflow Limitation

Many factors may contribute to the development of IRAO in any given patient. In the TENOR study, risk factors for persistent airflow limitation were male gender, black ethnicity, current or past smoking, aspirin sensitivity, older age, and longer asthma duration [14•]. Other factors associated with IRAO include specific genetic polymorphisms, reduced pulmonary function in infancy, frequent exacerbations, occupational exposure to sensitizers, respiratory infections, airway hyperresponsiveness, and adult onset of asthma [8••].

### Genetic factors

Some polymorphisms of the *ADAM33* (A disintegrin and metalloprotease 33) gene, which is involved in lung growth and repair, are associated with a decline in lung function [36]. A genetic predisposition to development of IRAO is probable but still needs to be documented.

### Early-life reduction in pulmonary function

IRAO appears to be associated frequently with development of airway dysfunction before they have fully matured. For example, one group of investigators demonstrated that individuals with low levels of pulmonary function in infancy have lower expiratory flows during childhood than their peers [37] and lower FEV<sub>1</sub>/FVC levels by age 22 years [38•]. These same investigators concluded from the 2552-patient Tucson Epidemiological Study of Airway Obstructive Disease that among people with onset of asthma before the age of 25 years and persistent airflow limitation in adult life, the alterations were established before the age of 25 [10••].

These and other studies indicate that insufficiently treated asthma in childhood or another early-life insult to the airways, such as respiratory infections or genetic developmental defects, could lead to reduced airway caliber [39–42].

### Airway hyperresponsiveness

The presence of airway hyperresponsiveness, particularly when severe, has been associated with an accelerated decline in lung function [8••,13,43]. However, this loss may be due to underlying airway inflammation, often resulting from continuing exposure to sensitizing agents responsible for this increased responsiveness.

### Frequency and rate of asthma exacerbations

In an 11-year asthma study, Bai et al. [44••] demonstrated that a higher rate of asthma exacerbations is associated with an increased rate of decline in pulmonary function. Furthermore, in a recent analysis of the Inhaled Steroid Treatment as Regular Therapy study, O'Byrne et al. [45•] showed that in patients who have had persistent asthma for less than 2 years, severe exacerbations are associated with a more rapid decline in lung function.

### Occupational exposures

We have previously shown that occupational asthma without a latency period is associated with significantly reduced reversibility of airway obstruction compared with more classical forms of occupational asthma [46]. Prolonged exposure to sensitizers at work is also associated with persistent airflow limitation [47].

### Smoking

The most common factor associated with the development of IRAO is smoking. Approximately 25% of people with asthma smoke regularly, a prevalence that is relatively similar to that seen in the general population [48,49]. We have shown that cigarette smoking is associated with early signs of COPD and, in people with asthma, seems to move the

**Table 1. Risk factors associated with development of persistent airflow limitation**

|                                                         |
|---------------------------------------------------------|
| Genetic predisposition (eg, <i>ADAM33</i> polymorphism) |
| Early-life reduction in pulmonary function              |
| Asthma exacerbations                                    |
| Occupational/sensitizing exposures                      |
| Smoking                                                 |
| Respiratory infections                                  |
| Increased age                                           |
| Female gender                                           |
| Late age at onset of asthma                             |
| Duration of asthma                                      |
| Comorbid chronic obstructive pulmonary disease          |

inflammation toward a more neutrophilic type [31,50•]. This may lead to a reduction in response to inhaled and oral corticosteroids that in turn could contribute to the development of IRAO [51,52]. It is worth noting that people with asthma who smoke do not always have fixed airway obstruction, but they do tend to have a lower airway caliber.

Guerra et al. [10••] found cigarette smoking to be the strongest risk factor for persistent airflow limitation among people without asthma and among individuals with asthma onset after age 25 years (Table 1). Surprisingly, in the Bumbacea et al. [20] study, no difference was noted in the smoking history between patients with or without IRAO; however, each group had only a few current smokers or people with more than a 10-pack-year smoking history. Not surprisingly, exposure to secondhand smoke in young children is associated with altered airway function [53]. Lange et al. [54] reported an accelerated fall in lung function in asthmatic individuals compared with non-asthmatic individuals, with such a fall being worse among smoking asthmatics. Burrows et al. [55] also reported that nonsmoking asthmatics who had moderate to severe airflow limitation had a slower decline in FEV<sub>1</sub> than smoking asthmatics who had similar airflow limitation.

### Respiratory infections

*Chlamydomphila pneumoniae* isolates have been detected in people with newly diagnosed nonatopic asthma [56]. It is possible that viruses and bacteria may also trigger airway remodeling and a decline in pulmonary function, leading in turn to the development of IRAO.

### Age, gender, body mass index, age at onset, and duration of asthma

Increased age is associated with a loss of lung elastic recoil and the development of progressively more irreversible airway obstruction. For example, age was strongly associated with flow limitation in individuals with and without asthma in the Guerra et al. [10••] study. Also, in a study by Jang et al. [21], persistent airway obstruction was associated with higher age and body mass index.

Moreover, severe asthma is more common in women than in men, and women generally show a faster decline in lung function and a lesser benefit from corticosteroids than men [9]. The factors at play likely include a hormonal influence and smaller airways in women. Asthma is frequently observed in association with obesity [57,58]. However, obesity is usually not associated with a restrictive pattern or a significant fall in expiratory flow in individuals with a body mass index of less than 40 kg/m<sup>2</sup> [59].

Age at onset of asthma may influence its outcomes. Asthma beginning in adulthood is usually more severe and steroid dependent than asthma seen in younger patients and is associated with an accelerated decline in pulmonary function [9,60]. Furthermore, duration of asthma has been associated with persistent airway obstruction [16,21,61].

### Comorbid COPD

It is not always easy for the practitioner to differentially diagnose asthma and COPD, particularly in patients who have a significant smoking history. Patients may have both asthma and COPD, in which case IRAO is usually present [62].

### Role of atopic status in the development of IRAO

IRAO is more common in severe asthma, whereas atopy is less common in severe asthma than in milder forms of the disease [63]. However, at least one study showed no correlation between atopic status and IRAO [20].

### Consequences of IRAO

Patients with chronic persistent asthma who develop IRAO have more markers of disease severity and mortality risk than individuals with chronic asthma who do not develop IRAO [55,64,65]. Furthermore, IRAO is linked to more severe asthma and to increased morbidity and mortality [9].

We have demonstrated that patients with IRAO have more severe airflow obstruction and hyperinflation than those without residual airflow limitation, but we also found that the two groups have similar lung compliance and carbon monoxide diffusion [11]. In addition, we determined that overall health care use is similar in the two groups, but those with IRAO have greater global asthma-related discomfort and increased diurnal variation of airflow obstruction and use higher doses of inhaled corticosteroids than those without IRAO.

Furthermore, Bumbacea et al. [20] found similar quality-of-life scores in patients with and without IRAO, but others have reported a negative relationship between quality-of-life scores and lung function.

### Management of Asthma With IRAO: Current Therapy and Perspectives

Current guidelines suggest that asthma with IRAO should be managed similarly to asthma without IRAO [1]. However, the first step in managing asthma with suspected IRAO is to determine whether the airflow limitation is truly irreversible.

Adjustment of treatment and proper monitoring—sometimes with a trial of systemic corticosteroids—may help to confirm whether IRAO is present. In addition, the clinician should carefully check the patient's compliance with treatment and ideally should order an induced sputum analysis to check the severity and nature of residual airway inflammation.

We may think that increased loss of pulmonary function and IRAO could be prevented by environmental measures or medications that may act on airway inflammation and/or remodeling. In this regard, the influence of asthma medications on airway remodeling has been reviewed recently [15,66]. Inhaled corticosteroids have been shown to reduce the rate of lung function decline. For example, in a 23-year follow-up study of patients with moderate to severe asthma, inhaled corticosteroid use was associated with a reduction in the decline in pulmonary function only in men who had smoked for less than 5 pack-years [67]. O'Byrne et al. [45•] showed that regular use of low-dose inhaled corticosteroids by patients with a recent diagnosis of persistent asthma resulted in a less rapid decline in lung function after asthma exacerbations.

In some asthma patients with IRAO, the changes in airway structure that led to irreversible obstruction may have occurred early in life. In these cases, we can only try to ensure that optimal asthma control is achieved. In most patients, however, smoking and/or uncontrolled underlying airway eosinophilia is the cause of the IRAO. Suppression of airway eosinophilia has been shown to reduce the number and severity of asthma exacerbations in people with IRAO and has the added benefit of producing excellent asthma control [68,69]. Indirect evidence also suggests that avoiding asthma exacerbations may reduce the rate of decline in lung function and prevent the development of IRAO [45•,67].

In all cases of IRAO in asthma, it is important to follow current guidelines to ensure proper asthma control. This should ideally include regular, noninvasive monitoring of airway inflammation; appropriate anti-inflammatory therapy; avoiding contact with proinflammatory environmental hazards and focusing on relevant indoor allergens and workplace sensitizers; encouraging smoking cessation; and treating and preventing respiratory infections. The role of therapies acting on airway structure that are being developed (eg, bronchothermoplasty) remains to be determined [70].

### Conclusions

IRAO is observed in some individuals with moderate to severe asthma and is associated with increased morbidity and mortality. It may be due to an airway insult early in life, uncontrolled airway inflammation (particularly of the eosinophilic type), smoking, and other triggers and contributing factors to airway remodeling. The clinician should strive for optimal asthma control and prevention of asthma exacerbations in all individuals with moderate to severe asthma to try to avoid an accelerated decline in lung function and the development of IRAO.

## Disclosure

Dr. Boulet has served on advisory boards for AstraZeneca Pharmaceuticals, Altana, GlaxoSmithKline, Merck Frosst, and Novartis; received lecture fees from 3M, Altana, AstraZeneca Pharmaceuticals, GlaxoSmithKline, Merck Frosst, and Novartis; received sponsorship for investigator-generated research from AstraZeneca Pharmaceuticals, GlaxoSmithKline, Merck Frosst, and Schering-Plough; received research support from 3M, Altana, Astmatx, AstraZeneca Pharmaceuticals, Boehringer Ingelheim, Dynavax Technologies, Genentech, GlaxoSmithKline, IVAX, MedImmune, Merck Frosst, Novartis, Roche, Schering-Plough, TOPIGEN Pharmaceuticals, and Wyeth; and received support for producing educational materials from AstraZeneca Pharmaceuticals, GlaxoSmithKline, and Merck Frosst.

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