Inflammatory mediators may activate sensory nerves, resulting in reflex cholinergic bronchoconstriction or release of inflammatory neuropeptides. Inflammatory products may also sensitize sensory nerve endings in the airway epithelium such that the nerves become hyperalgesic. Neurotrophins, which may be released from various cell types in airways, including epithelial cells and mast cells, may cause proliferation and sensitization of airway sensory nerves. Airway nerves may also release neurotransmitters, such as substance P, which have inflammatory effects.

Airway Remodeling Several changes in the structure of the airway are characteristically found in asthma, and these may lead to irreversible narrowing of the airways. Population studies have shown a greater decline in lung function over time than in normal subjects; however, most patients with asthma preserve normal or near-normal lung function throughout life if appropriately treated.

The accelerated decline in lung function occurs in a smaller proportion of asthmatics, and these are usually patients with more severe disease. There is some evidence that the early use of ICS may reduce the decline in lung function. The characteristic structural changes are increased airway smooth muscle, fibrosis, angiogenesis, and mucus hyperplasia.

Physiology Limitation of airflow is due mainly to bronchoconstriction, but airway edema, vascular congestion, and luminal occlusion with exudate may contribute. This results in a reduction in forced expiratory volume in 1 second (FEV_1), FEV_1/forced vital capacity (FVC) ratio, and peak expiratory flow (PEF), as well as an increase in airway resistance. Early closure of peripheral airway results in lung hyperinflation (air trapping) and increased residual volume, particularly during acute exacerbations and in severe persistent asthma. In more severe asthma, reduced ventilation and increased pulmonary blood flow result in mismatching of ventilation and perfusion and in bronchial hyperemia. Ventilatory failure is very uncommon, even in patients with severe asthma, and arterial PCO_2 tends to be low due to increased ventilation.

Airway Hyperresponsiveness AHR is the characteristic physiologic abnormality of asthma and describes the excessive bronchoconstrictor response to multiple inhaled triggers that would have no effect on normal airways. The increase in AHR is linked to the frequency of asthma symptoms, and, thus, an important aim of therapy is to reduce AHR. Increased bronchoconstrictor responsiveness is seen with *direct* bronchoconstrictors such as histamine and methacholine, which contract airway smooth muscle, but is characteristically also seen with many *indirect* stimuli, which release bronchoconstrictors from mast cells or activate sensory nerves. Most of the triggers for asthma symptoms appear to act indirectly, including allergens, exercise, hyperventilation, fog (via mast cell activation), irritant dusts, and sulfur dioxide (via a cholinergic reflex).

CLINICAL FEATURES AND DIAGNOSIS

The characteristic symptoms of asthma are wheezing, dyspnea, and coughing, which are variable, both spontaneously and with therapy. Symptoms may be worse at night, and patients typically awake in the early morning hours. Patients may report difficulty in filling their lungs with air. There is increased mucus production in some patients, with typically tenacious mucus that is difficult to expectorate. There may be increased ventilation and use of accessory muscles of ventilation. Prodromal symptoms may precede an attack, with itching under the chin, discomfort between the scapulae, or inexplicable fear (impending doom).

Typical physical signs are inspiratory, and to a greater extent expiratory, rhonchi throughout the chest, and there may be hyperinflation. Some patients, particularly children, may present with a predominant nonproductive cough (cough-variant asthma). There may be no abnormal physical findings when asthma is under control.

DIAGNOSIS

The diagnosis of asthma is usually apparent from the symptoms of variable and intermittent airways obstruction, but must be confirmed by objective measurements of lung function.

Lung Function Tests Simple spirometry confirms airflow limitation with a reduced FEV_1, FEV_1/FVC ratio, and PEF (Fig. 309-6). Reversibility is demonstrated by a >12% and 200-mL increase in FEV_1 15 min after an inhaled short-acting β_2-agonist or in some patients by a 2- to 4-week trial of oral corticosteroids (OCS) (prednisone or prednisolone 30–40 mg daily). Measurements of PEF twice daily may confirm the diurnal variations in airflow obstruction. Flow-volume loops show reduced peak flow and reduced maximum expiratory flow. Further lung function tests are rarely necessary, but whole-body plethysmography shows increased airway resistance and may show increased total lung capacity and residual volume. Gas diffusion is usually normal, but there may be a small increase in gas transfer in some patients.

Airway Responsiveness The increased AHR is normally measured by methacholine or histamine challenge with calculation of the provocative concentration that reduces FEV_1 by 20% (PC_{20}). This is rarely useful in clinical practice, but can be used in the differential diagnosis of chronic cough and when the diagnosis is in doubt in the setting of normal pulmonary function tests. Occasionally exercise testing is done to demonstrate the postexercise bronchoconstriction if there is a predominant history of EIA. Allergen challenge is rarely necessary and should only be undertaken by a specialist if specific occupational agents are to be identified.

Hematologic Tests Blood tests are not usually helpful. Total serum IgE and specific IgE to inhaled allergens (radioallergosorbent test [RAST]) may be measured in some patients.

Imaging Chest roentgenography is usually normal but in more severe patients may show hyperinflated lungs. In exacerbations, there may be evidence of a pneumothorax. Lung shadowing usually indicates pneumonia or eosinophilic infiltrates in patients with bronchopulmonary aspergillosis. High-resolution computed tomography (CT) may show areas of bronchiectasis in patients with severe asthma, and there may be thickening of the bronchial walls, but these changes are not diagnostic of asthma.

Skin Tests Skin prick tests to common inhalant allergens (house dust mite, cat fur, grass pollen) are positive in allergic asthma and negative

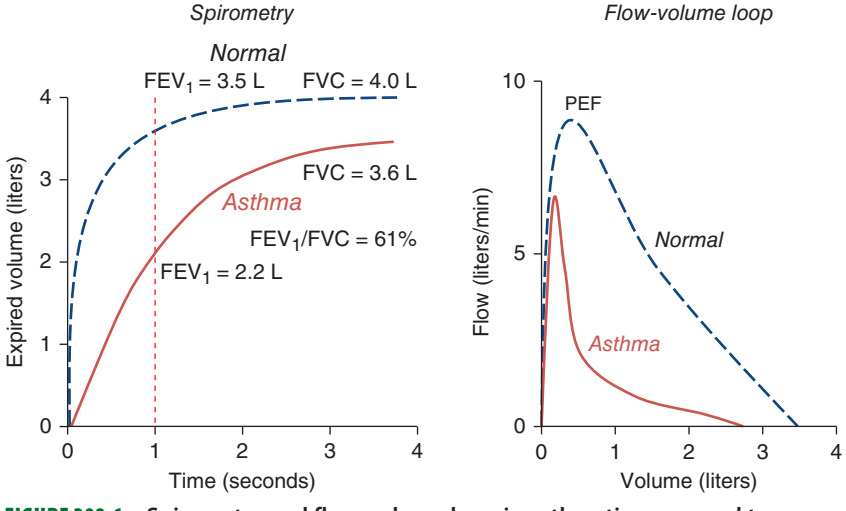

FIGURE 309-6 Spirometry and flow-volume loop in asthmatic compared to normal subject. There is a reduction in forced expiratory volume in 1 second (FEV_1) but less reduction in forced vital capacity (FVC), giving a reduced FEV_1/FVC ratio (<70%). The flow-volume loop shows reduced peak expiratory flow and a typical scalloped appearance indicating widespread airflow obstruction.