West's Pulmonary Pathophysiology

The Essentials

NINTH EDITION

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Wolters Kluwer

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THE ESSENTIALS

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Obstructive diseases of the lung are extremely common and remain an important cause of morbidity and mortality. While the distinctions among the various types of obstructive disease are blurred, giving rise to difficulties in definition and diagnosis, all of these diseases are characterized by airway obstruction.

AIRWAY OBSTRUCTION

Increased resistance to airflow can be caused by conditions (1) inside the lumen, (2) in the wall of the airway, and (3) in the peribronchial region **(Figure 4.1)**:

1. The lumen may be partially occluded by excessive secretions, such as in chronic bronchitis. Partial obstruction can also occur acutely in pulmonary edema or after aspiration of foreign material and, postoperatively, with retained secretions. Inhaled foreign bodies may cause localized partial or complete obstruction.
2. Causes in the wall of the airway include contraction of bronchial smooth muscle, as in asthma; hypertrophy of the mucous glands, as in chronic bronchitis (see Figure 4.6); and inflammation and edema of the wall, as in bronchitis and asthma.
3. Outside the airway, destruction of lung parenchyma may cause loss of radial traction and consequent narrowing, as in emphysema. A bronchus may also be compressed locally by an enlarged lymph node or neoplasm. Peribronchial edema can also cause narrowing (see Figure 6.5).

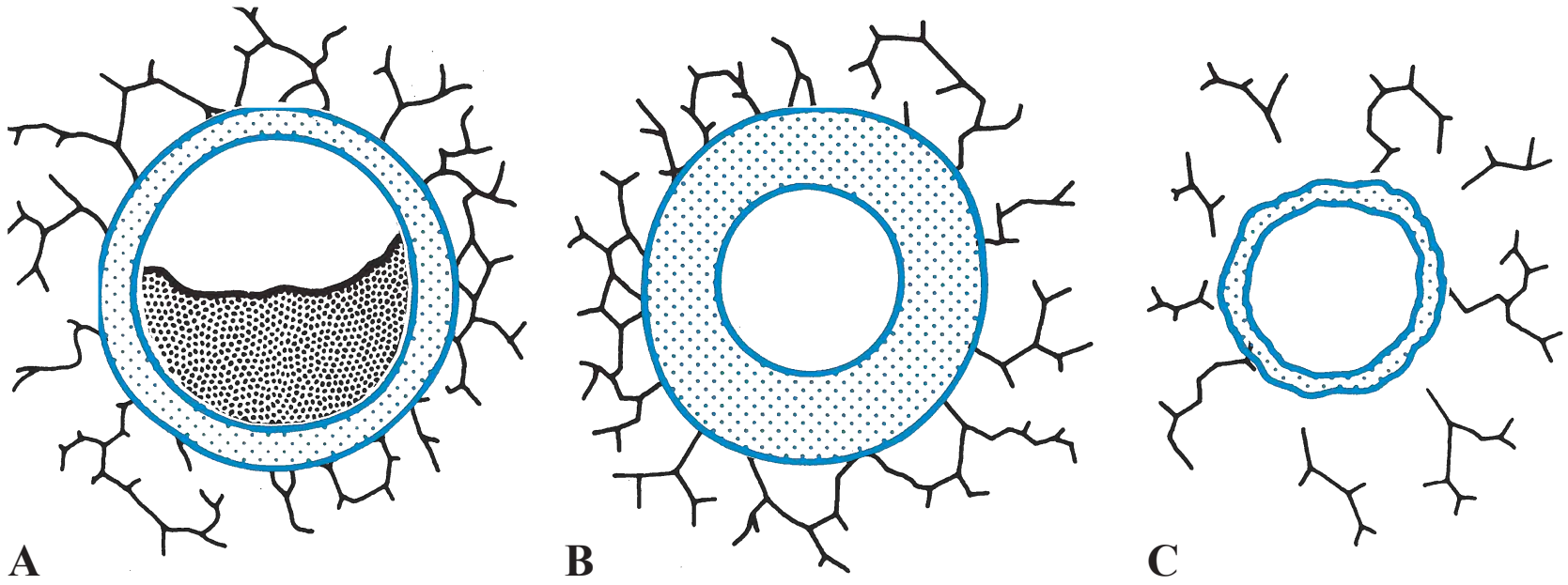

Figure 4.1. **Mechanisms of airway obstruction. A.** The lumen is partly blocked, for example, by excessive secretions. **B.** The airway wall is thickened, for example, by edema or hypertrophy of smooth muscle. **C.** The abnormality is outside the airway; in this example, the lung parenchyma is partly destroyed and the airway has narrowed because of the loss of radial traction.

ASTHMA

This disease is characterized by increased responsiveness of the airways to various stimuli and is manifested by inflammation and widespread narrowing of the airways that changes in severity, either spontaneously or as a result of treatment.

Pathology

The airways have hypertrophied smooth muscle that contracts during an attack, causing bronchoconstriction **(Figure 4.1B)**. In addition, there is hypertrophy of mucous glands, edema of the bronchial wall, and extensive infiltration by eosinophils and lymphocytes **(Figure 4.15)**. The mucus is increased and is also abnormal; it is thick, tenacious, and slow moving. In severe cases, many airways are occluded by mucous plugs, some of which may be coughed up in the sputum. The sputum typically is scant and white. Subepithelial fibrosis is common in patients with chronic asthma and is part of the process called remodeling. In uncomplicated asthma, there is no destruction of alveolar walls, and there are no copious purulent bronchial secretions. Occasionally, the abundance of eosinophils in the sputum gives a purulent appearance, which may be wrongly ascribed to infection.

Pathogenesis

Two features that appear to be common to all asthmatics are airway hyperresponsiveness and airway inflammation. Research suggests that the hyperresponsiveness is a consequence of the inflammation, and some investigators believe that airway inflammation is responsible for all the associated features

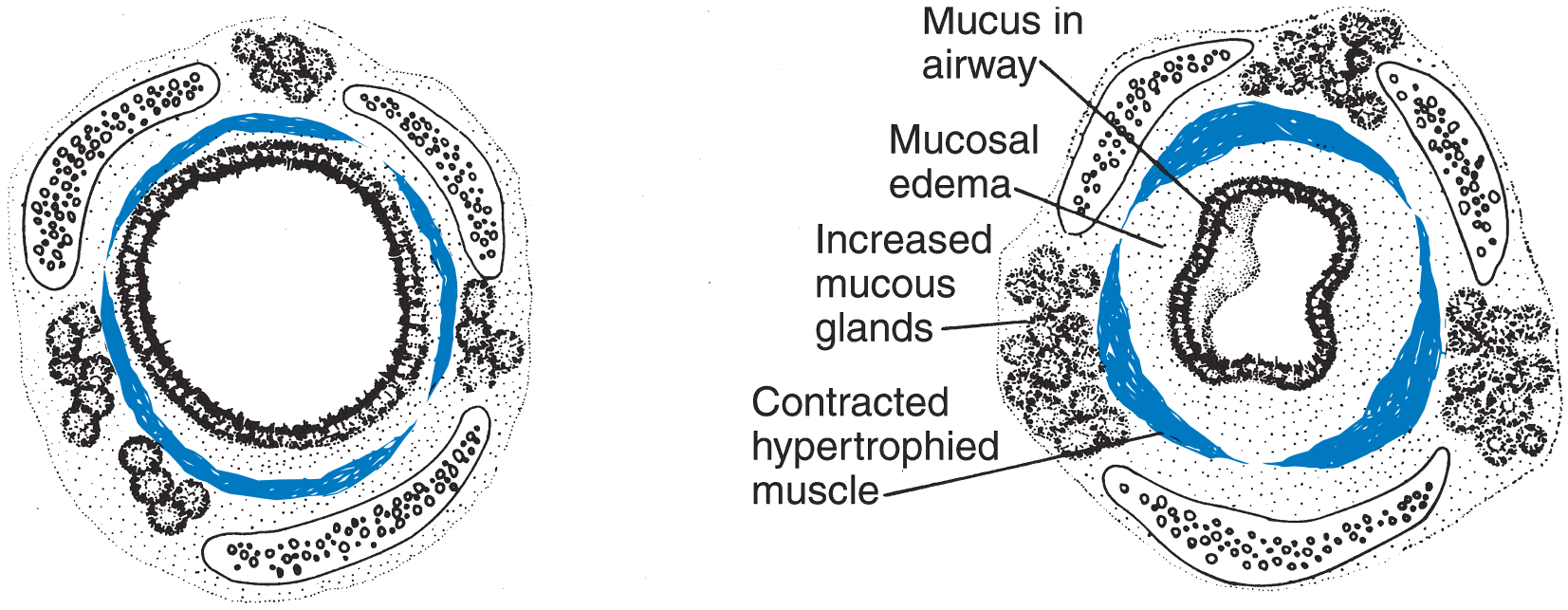

Figure 4.14. **Bronchial wall in asthma (diagrammatic).** Compared to the normal airway **(A)**, the bronchial wall in asthma **(B)** demonstrates contracted smooth muscle, edema, mucous gland hypertrophy, and secretions in the lumen.

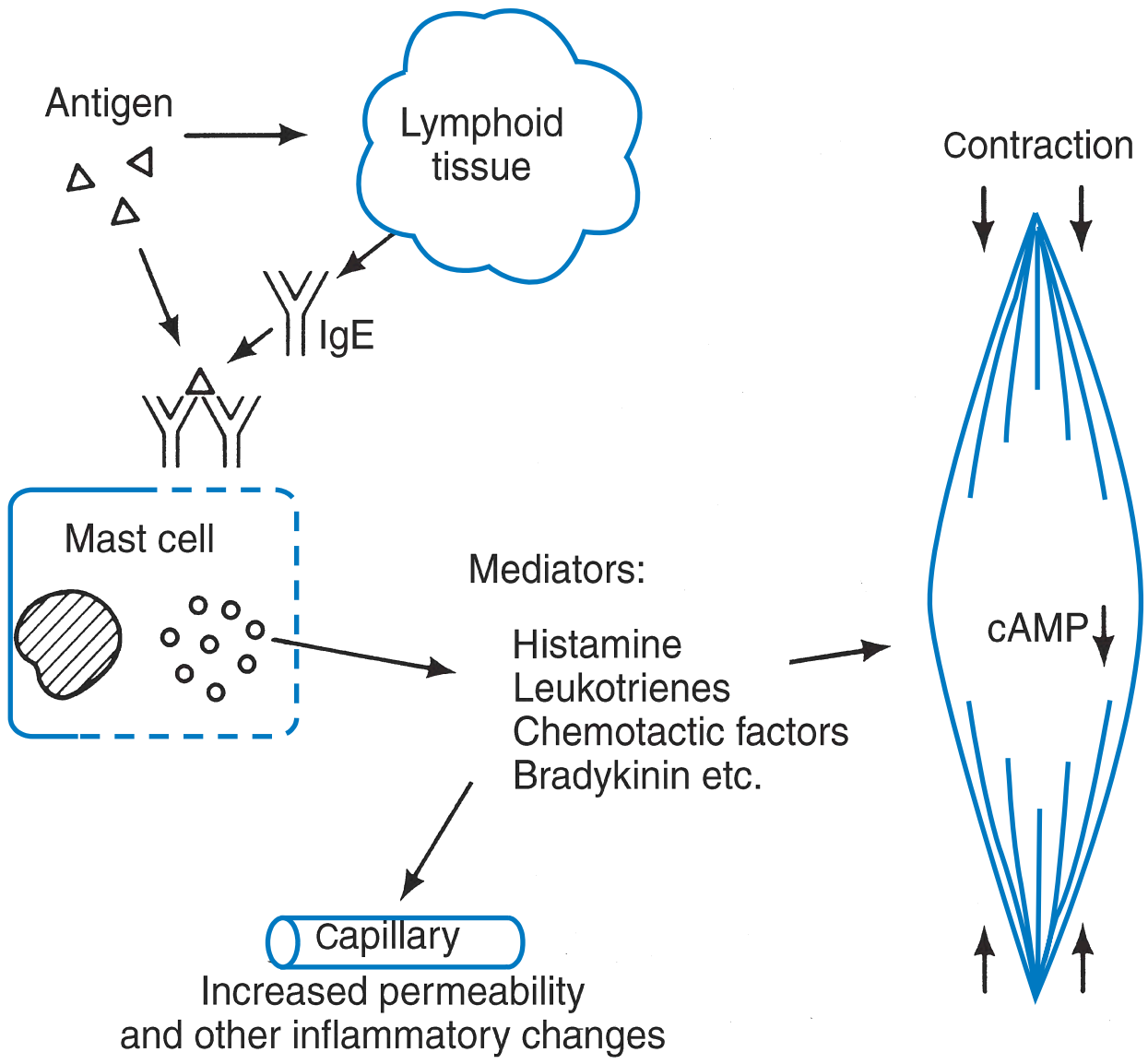

Figure 4.15. **Some pathogenic changes in allergic asthma.** (See text for details.)

of asthma, including the increased airway responsiveness, airway edema, hypersecretion of mucus, and inflammatory cell infiltration. However, a fundamental abnormality of airway smooth muscle or regulation of airway tone is possible in some patients.

Epidemiologic studies indicate that asthma begins in childhood in the majority of cases and that an allergic diathesis often plays an important role. However, environmental factors appear to be important and may be responsible for the increase in the prevalence and severity of asthma over the last 20 to 40 years in modernized, affluent western countries. Frequent exposure to typical childhood infections and environments favoring fecal contamination are associated with a lower incidence of asthma. These observations and others have led to the "hygiene hypothesis," which suggests that children in a critical stage of development of the immune response who are not frequently exposed to typical childhood infectious agents may more frequently develop an allergic diathesis and asthma. Other hypotheses have also been proposed to explain the increases in prevalence including obesity, poor physical fitness, and exposure to pollutants.

The trigger for the development of airway inflammation cannot always be identified. It is well recognized in some instances, as in the case for some antigens in persons with allergic asthma **(Figure 4.15)**. However, in other types of asthma, such as exercise-induced asthma or asthma following a viral respiratory tract infection, the trigger is not recognized. Atmospheric pollutants, especially submicronic particles in automobile exhaust gases, may also play a role.

A single inflammatory cell type or inflammatory mediator does not appear to be responsible for all manifestations of asthma. Eosinophils, mast cells, neutrophils, macrophages, and basophils have all been implicated. There is also evidence that noninflammatory cells, including airway epithelial cells and neural cells, especially those of peptidergic nerves, contribute to the inflammation. Some investigators believe that eosinophils play a central effector role in most cases of asthma. There is also evidence that lymphocytes, especially T cells, are implicated, both because they respond to specific antigens and because they have a role as a modulator of inflammatory cell function.

Many inflammatory mediators have been identified in asthma. Cytokines are probably important, particularly those associated with Th-2, helper T-cell activation. These cytokines include interleukin-3, IL-4, IL-5, and IL-13. It is believed that these cytokines are at least partly responsible for modulating inflammatory and immune cell function and for supporting the inflammatory response in the airway. Other inflammatory mediators that probably play a role, particularly in acute bronchoconstriction, include arachidonic acid metabolites, such as leukotrienes and prostaglandins, platelet-activating factor (PAF), neuropeptides, reactive oxygen species, kinins, histamine, and adenosine.

Asthma also has a genetic component. Population studies show that it is a complex genetic disorder with both environmental and genetic components. The latter is not a single gene trait but is polygenic. Associations of asthma with a variety of chromosomal loci through linkage analysis have been demonstrated.

Clinical Features

Asthma commonly begins in children but may occur at any age. The patient may have a previous history to suggest atopy, including allergic rhinitis, eczema, or urticaria, and may relate asthmatic attacks to a specific allergen, for example, ragweed or cats. Such a patient is said to have allergic asthma. Many such patients have an increased total serum IgE, increased specific IgE, and peripheral blood eosinophils. If there is no general history of allergy and no external allergen can be identified, the term "nonallergic asthma" is used.

In all asthmatics, there is general hyperreactivity of the airways, with the result that nonspecific irritants, such as smoke, cold air, and exercise, cause symptoms. The hyperreactivity (or hyperresponsiveness) of the airways can be tested by exposing the patient to increasing inhaled concentrations of methacholine or histamine and measuring the FEV_1 (or airway resistance). The concentration that results in a 20% fall in FEV_1 is known as the PC_{20} (provocative concentration 20). This can also be tested by measuring spirometry before and after specially designed exercise protocols and demonstrating a decrease in FEV_1 in the postexercise period.

Exacerbations, often referred to as "asthma attacks," may follow changes in air quality, viral infections, or exercise, especially in a cold environment, but

can also occur without obvious triggers. Aspirin ingestion is a cause in some individuals because of inhibition of the cyclooxygenase pathway. This may have a genetic component. During an attack, the patient may be extremely dyspneic, orthopneic, and anxious and complain of chest tightness. The accessory muscles of respiration are active. The lungs are hyperinflated, and musical rhonchi are heard in all areas. The pulse is rapid, and pulsus paradoxus may be present (marked fall in systolic and pulse pressure during inspiration). The sputum is scant and viscid. The chest radiograph reveals hyperinflation but is otherwise normal. *Status asthmaticus* refers to an attack that continues for hours or even days without remission despite bronchodilator and corticosteroid therapy. There are often signs of exhaustion, dehydration, and marked tachycardia. The chest may become ominously silent, and vigorous treatment is urgently required.

Depending on the severity of their disease, some patients lack symptoms and have a normal exam and spirometry between exacerbations. Other patients, however, remain symptomatic even when not in an exacerbation and require daily medications for disease control.

Bronchoactive Drugs

Drugs that reverse or prevent bronchoconstriction play a major role in the treatment of patients with asthma.

b-Adrenergic Agonists

β-Adrenergic receptors are of two types: β_1 receptors exist in the heart and elsewhere, and their stimulation increases heart rate and the force of contraction of cardiac muscle. Stimulation of β_2 receptors relaxes smooth muscle in the bronchi, blood vessels, and uterus. Partially or completely β_2-selective adrenergic agonists have now completely replaced nonselective agonists, with the most commonly used agents being albuterol and levalbuterol. These agents have an intermediate duration of action. Long-acting agents, such as formoterol and salmeterol, are also available for daily use but should always be used in combination with inhaled corticosteroids. All these drugs bind to β_2 receptors in the lung and directly relax airway smooth muscle by increasing the activity of adenyl cyclase. This in turn raises the concentration of intracellular cAMP, which is reduced in an asthma attack (Figure 4.15). They also have effects on airway edema and airway inflammation. Their anti-inflammatory effects are mediated by direct inhibition of inflammatory cell function via binding to β_2 receptors on the cell surface. There is some polymorphism in these receptors that affects the responses.

These drugs are delivered by aerosol, preferably using a metered-dose inhaler or a nebulizer. Frequent administration during an asthma attack can be associated with tachyphylaxis. This issue is not generally seen, however, with chronic administration in stable patients.

Inhaled Corticosteroids

Corticosteroids appear to have two separate functions: they inhibit the inflammatory/immune response, and they enhance β receptor expression or function. Because asthma is an inherently inflammatory disorder, inhaled corticosteroids are now the primary controller medication (i.e., routine daily use) in all patients with persistent disease of any severity. This is in contrast to COPD, where inhaled corticosteroids are reserved for those with more severe disease. Current guidelines recommend inhaled corticosteroids for patients with symptoms more than twice a week, inhaled β-agonist use more than twice a week or frequent nighttime awakenings due to asthma symptoms. A wide variety of inhaled corticosteroids are now available and, when used as directed, result in minimal systemic absorption of corticosteroid with almost no serious side effects. In many cases, patients use combination inhalers that deliver both a corticosteroid and a β_2-agonist.

Bronchoactive Drugs for Asthma

b-Adrenergic Agonists
Selective β_2 types are now exclusively used.

Long-acting forms are useful in chronic disease management but should only be used in conjunction with inhaled corticosteroids.

Short-acting forms are reserved for rescue.

Inhaled Corticosteroids
These are given by aerosol and are often indicated except in the mildest cases of asthma.

Auxiliary Drugs
Antileukotrienes, methylxanthine, and cromolyn may be useful adjuncts.

Anticholinergics

While anticholinergics are used extensively in management of patients with COPD, they are generally not part of the treatment regimen in the majority of asthma patients. This is despite some evidence that the parasympathetic system plays a role in asthma pathophysiology. Some recent evidence suggests the long-acting anticholinergic tiotropium may have benefit in patients with persistent symptoms despite intensive therapy with inhaled corticosteroids and β_2-agonists, but this is not presently standard practice.

Cromolyn and Nedocromil

Although their precise mechanism of action remains unclear, these two drugs are thought to prevent bronchoconstriction by stabilizing mast cells **(Figure 4.15)** and other broad ranging effects. Their use is generally limited

to prophylaxis in situations known to provoke symptoms such as prior to exercise in cold, dry conditions, or visiting an environment with a known trigger for the particular patient such as a home with a cat.

Methylxanthines

Methylxanthines, including theophylline and aminophylline, inhibit phosphodiesterases in bronchial smooth muscle, leading to bronchodilation. While used more extensively in the past, they are used little in current practice because of modest anti-inflammatory and bronchodilatory activity relative to corticosteroids and β_2-agonists, risk for toxicity, and the need for monitoring serum concentrations on a regular basis.

Leukotriene-Modifying Drugs

Because leukotrienes C4, D4, and E4 have increasingly been recognized to mediate part of the allergic response in asthma, leukotriene receptor antagonists (e.g., montelukast, zafirlukast) and 5-lipoxygenase inhibitors (e.g., zileuton) are now used in some individuals. In well-selected patients with mild to moderate disease, they can be used in lieu of inhaled corticosteroids, while in more severe forms of disease, they may provide benefit when added to existing treatment with inhaled corticosteroids. They may be of particular use to patients whose asthma is exacerbated by aspirin and other nonsteroidal anti-inflammatory drugs.

Anti-IgE Therapy

A monoclonal antibody to IgE, omalizumab, is now available for use in patients with moderate to severe asthma who are inadequately controlled with high doses of inhaled glucocorticoids and have elevated serum IgE levels and evidence of allergen sensitization. Use has been limited by difficulties predicting which patients respond to therapy, the very high cost and the risk of hypersensitivity reactions including anaphylaxis.

Pulmonary Function

As was the case with chronic bronchitis and emphysema, the changes in lung function generally follow clearly from the pathology of asthma.

Ventilatory Capacity and Mechanics

During an attack, all indices of expiratory flow rate are reduced significantly, including the FEV_1, FEV/FVC, $FEF_{25–75\%}$, $\dot{V}max_{50\%}$, and $\dot{V}max_{75\%}$. The FVC is also usually reduced because airways close prematurely toward the end of a full expiration. Between attacks, some impairment of ventilatory capacity can usually be demonstrated, although the patient may report no symptoms and have a normal physical exam.

The response of these indices to bronchodilator drugs is of great importance in asthma **(Figure 4.16)**. They may be tested by administering 0.5% albuterol by aerosol for 2 minutes or several puffs from a metered-dose

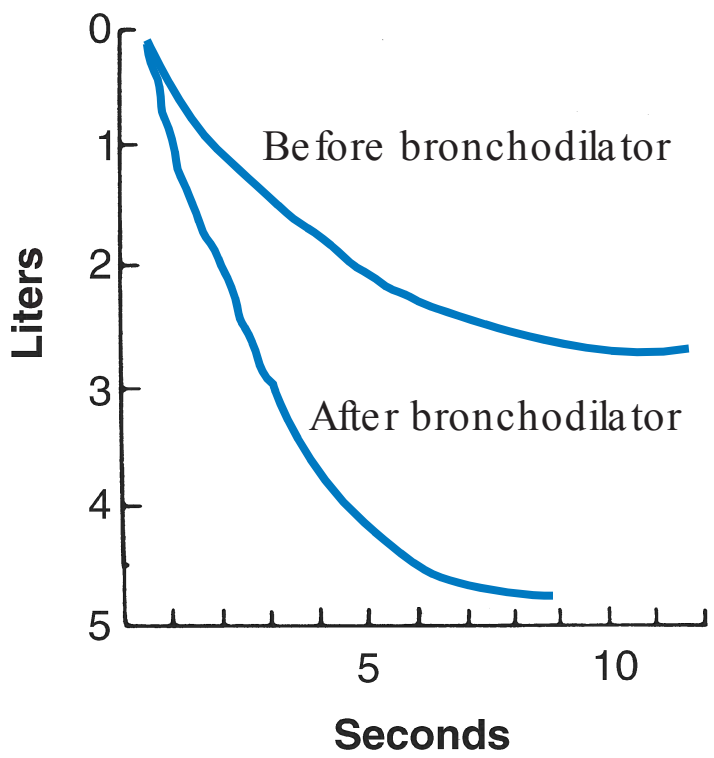

Figure 4.16. **Examples of forced expirations before and after bronchodilator therapy in a patient with bronchial asthma.** Note the striking increase in flow rate and vital capacity. (From Bates DV, Macklem PT, Christie RV. Respiratory Function in Disease. 2nd ed. Philadelphia, PA: WB Saunders, 1971.)

inhaler. Typically, all indices increase substantially when a bronchodilator is administered to a patient during an attack, and the change is a valuable measure of the responsiveness of the airways. The extent of the increase varies according to the severity of the disease. In status asthmaticus, little change may be seen because the bronchi have become unresponsive (although pulmonary function tests are rarely measured during such acute presentations). Again, patients in remission may show only minor improvement following bronchodilator administration, although generally there is some.

There is some evidence that the relative change in FEV_1 and FVC after bronchodilator therapy indicates whether the bronchospasm has been completely relieved. During an asthma attack, both the FEV_1 and FVC tend to increase by the same fraction, with the result that the FEV/FVC remains low and almost constant. However, when the tone of the airway muscle is nearly normal, the FEV_1 responds more than the FVC, and the FEV/FVC approaches the normal value of approximately 75%.

The flow–volume curve in asthma has the typical obstructive pattern, although it may not exhibit the scooped-out appearance seen in emphysema (see Figure 1.8). After a bronchodilator, flows are higher at all lung volumes, and the whole curve may shift as the TLC and RV are reduced.

Static lung volumes are increased, and remarkably high values for FRC and TLC during asthma attacks have been reported. The increased RV is caused by premature airway closure during a full expiration as a result of the increased smooth muscle tone, edema and inflammation of the airway walls, and abnormal secretions. The cause of the increased FRC and TLC is not fully understood. However, there is some loss of elastic recoil, and the pressure–volume curve is shifted upward and to the left (see Figure 3.1). This tends to return toward normal after a bronchodilator has been given. There is some evidence that changes in the surface tension of the alveolar lining layer may be responsible for the altered elastic properties. The rise in lung volume tends to decrease resistance of the airways by increasing their radial traction. The FRC measured by helium dilution is usually considerably below

that found with the body plethysmograph, reflecting the presence of occluded airways or the delayed equilibration of poorly ventilated areas.

Airway resistance as measured in the body plethysmograph is raised, and it falls after a bronchodilator. It is likely that the bronchospasm affects airways of all sizes, and the relationship between airway conductance and elastic recoil pressure is significantly abnormal (Figure 4.10). Narrowing of the large- and medium-sized bronchi can be seen directly at bronchoscopy.

Gas Exchange

Arterial hypoxemia is common in asthma and is caused by ventilation–perfusion ($\dot{V}_A/\dot{Q}$) inequality. There is ample evidence of uneven ventilation, and measurements with radioactive gases show regions of reduced ventilation. Marked topographical inequality of blood flow is also seen, and typically, different areas show transient reductions at different times. Both physiologic dead space and physiologic shunt are generally abnormally high.

An example of a distribution of ventilation–perfusion ratios in a 47-year-old asthmatic is shown in **Figure 4.17**. This patient had only mild symptoms at the time of the measurement. The distribution is strikingly different from the normal distribution shown in Figure 2.8. Note especially the bimodal distribution with a considerable amount of the total blood flow (approximately 25%) to units with a low $\dot{V}_A/\dot{Q}$ (approximately 0.1). This accounts for the patient's mild hypoxemia, the arterial P_{O_2} being

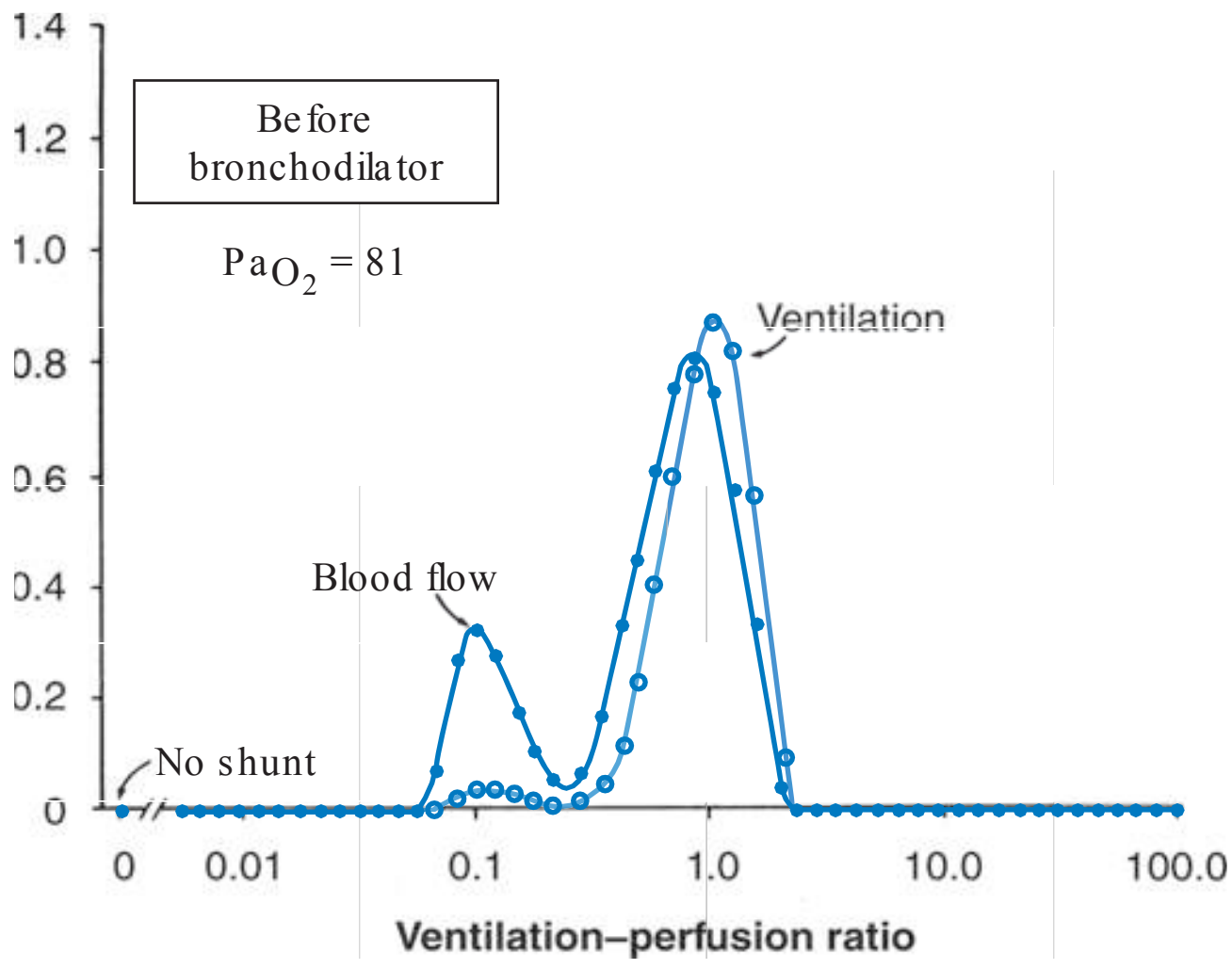

Figure 4.17. **Distribution of ventilation–perfusion ratios in a patient with asthma.** Note the bimodal appearance, with approximately 25% of the blood flowing to units with ventilation–perfusion ratios in the region of 0.1.

81 mm Hg. There is no pure shunt (blood flow to unventilated alveoli), a surprising finding in view of the mucous plugging of airways, which is a feature of the disease.

When this patient was given the bronchodilator isoproterenol by aerosol, there was an increase in $FEF_{25–75\%}$ from 3.4 to 4.2 L/sec. Thus, there was some relief of his bronchospasm. The changes in the distribution of ventilation–perfusion ratios are shown in **Figure 4.18**. Note that the blood flow to the low $\dot{V}_A/\dot{Q}$ alveoli increased from approximately 25% to 50% of the flow, resulting in a fall in arterial P_{O_2} from 81 to 70 mm Hg. The mean $\dot{V}_A/\dot{Q}$ of the low mode increased slightly from 0.10 to 0.14, indicating that the ventilation to these units increased slightly more than their blood flow. Again, no shunt was seen.

Many bronchodilators, including isoproterenol, aminophylline, and terbutaline, decrease the arterial P_{O_2} in asthmatics. The mechanism of the increased hypoxemia is apparently relief of vasoconstriction in poorly ventilated areas. This vasoconstriction probably results from the release of mediators, like the bronchoconstriction. The fall in P_{O_2} is accompanied by increases in physiologic shunt and dead space. However, in practice, the favorable effects of the drugs on airway resistance far exceed the disadvantages of the mild additional hypoxemia.

The absence of shunt—that is, blood flow to unventilated lung units—in Figures 4.17 and 4.18 is striking, especially because asthmatics who come to autopsy have mucous plugs in many of their airways. Presumably, the explanation is collateral ventilation that reaches the lung situated behind completely closed bronchioles. This is shown diagrammatically in Figure 1.11. The same mechanism probably exists in the lungs of patients with chronic bronchitis (see, e.g., Figure 4.12).

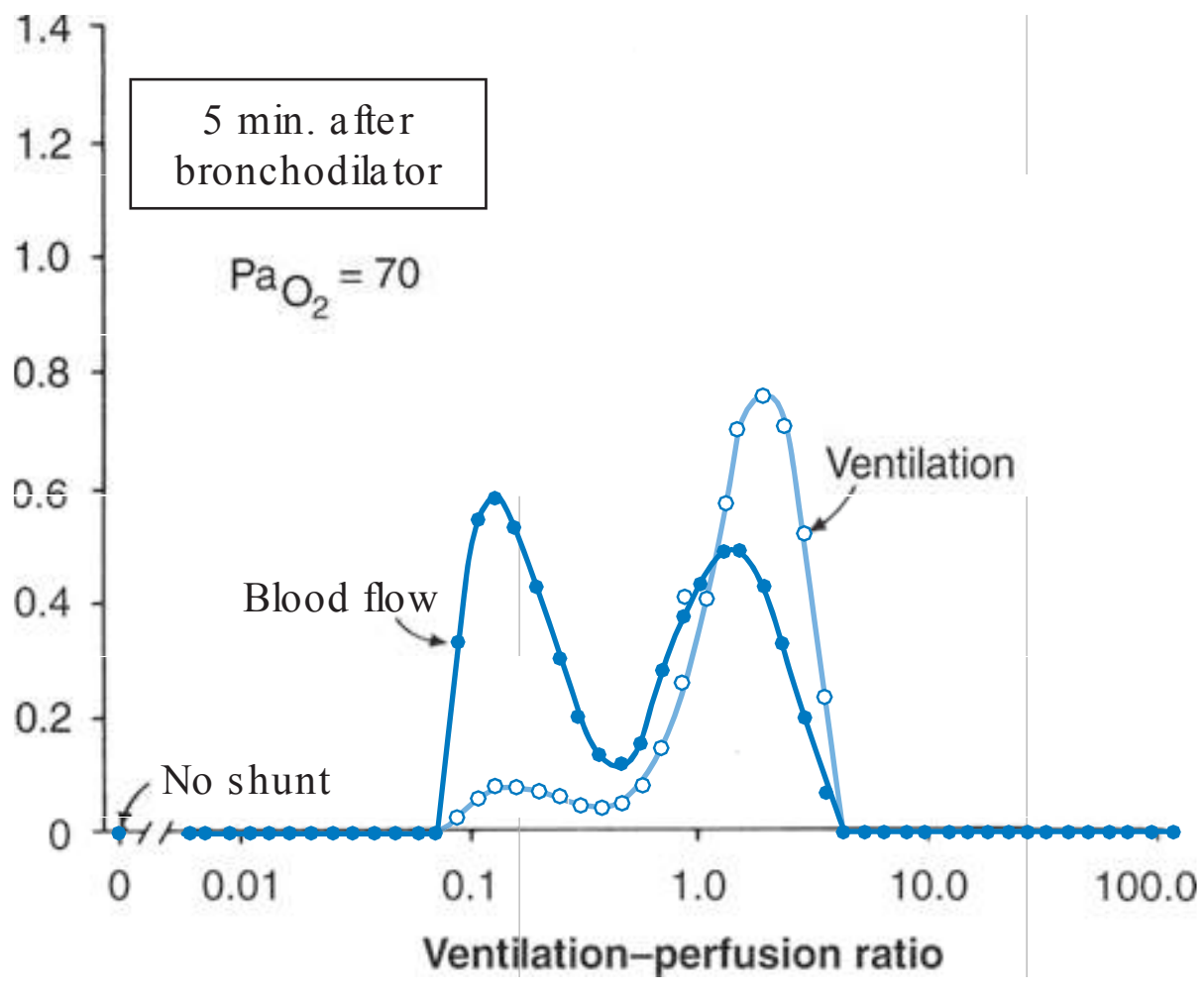

Figure 4.18. **The same patient as in Figure 4.16 after the administration of the bronchodilator isoproterenol by aerosol.** Note the increase in blood flow to the units with low ventilation–perfusion ratios and the corresponding fall in arterial P_{O_2}.

The arterial P_{CO_2} in patients with asthma is typically normal or low, at least until late in the disease. The P_{CO_2} is prevented from rising by increased ventilation to the alveoli in the face of the ventilation–perfusion inequality (compare Figure 2.9). In many patients, the P_{CO_2} may be in the middle or low 30s during an exacerbation, possibly as a result of stimulation of the peripheral chemoreceptors by the mild hypoxemia or stimulation of intrapulmonary receptors.

In status asthmaticus, the arterial P_{CO_2} may begin to rise and the pH to fall. This is an ominous development that denotes impending respiratory failure and signals the need for urgent and intensive treatment, including possibly mechanical ventilatory support (see Chapter 10). Death can occur in severe asthma exacerbations, often as a result of respiratory failure, because the severity of the disease was not sufficiently appreciated and the patient was initially undertreated.

The diffusing capacity for carbon monoxide is typically normal or high in uncomplicated asthma. If it is reduced, associated emphysema should be suspected. The reason for the increased diffusing capacity is probably the large lung volume. Hyperinflation increases the diffusing capacity in normal subjects, presumably by increasing the area of the blood–gas interface.

LOCALIZED AIRWAY OBSTRUCTION

So far, this chapter has been devoted to generalized airway obstruction, both irreversible, as in emphysema and chronic bronchitis, and reversible, as in asthma. (Some chronic bronchitis may show some reversibility.) Localized obstruction is less common and associated with varying degrees of functional impairment depending on the nature and severity of the obstruction. Obstruction may be within the lumen of the airway, in the wall, or as a result of compression from outside the wall (Figure 4.1).

Tracheal Obstruction

This can be caused by an inhaled foreign body; stenosis after the use of an indwelling tracheostomy tube; intraluminal masses; or compression from extraluminal masses, such as an enlarged thyroid or massive mediastinal lymphadenopathy. There is inspiratory and expiratory stridor, abnormal inspiratory and expiratory flow–volume curves (see Figure 1.9), and no response to bronchodilators. Hypoventilation may result in hypercapnia and hypoxemia (see Figure 2.2).

Bronchial Obstruction

This is often caused by inhalation of a foreign body, such as a peanut or marble. The right lung is more frequently affected than the left because the left main bronchus makes a sharper angle with the trachea than does the right.

Other common causes are bronchial tumors, either malignant or benign, and compression of a bronchus by enlarged surrounding lymph nodes. This last cause particularly affects the right middle lobe bronchus because of its anatomic relationships.

If obstruction is complete, absorption atelectasis occurs because the sum of the partial pressures in mixed venous blood is less than that in alveolar gas. (See *West's Respiratory Physiology: The Essentials*. 10th ed. p. 168.) The collapsed lobe is often visible on the radiograph, and compensatory overinflation of adjacent lung and displacement of a fissure may also be seen. Perfusion of the unventilated lung is reduced because of hypoxic vasoconstriction and also the increased vascular resistance caused by the mechanical effects of the reduced volume on the extra-alveolar vessels and the capillaries. However, the residual blood flow contributes to hypoxemia. The most sensitive test is the alveolar–arterial P_{O_2} difference during 100% O_2 breathing (see Figure 2.6). Infection may follow localized obstruction and lead to lung abscess. If the obstruction is in a segmental or smaller bronchus, atelectasis may not occur because of collateral ventilation (see Figure 1.11). Long-standing unresolved bronchial obstruction can lead to infection and bronchiectasis distal to the obstruction.