BRONCHIAL ASTHMA

Mechanisms and Therapeutics
Second Edition

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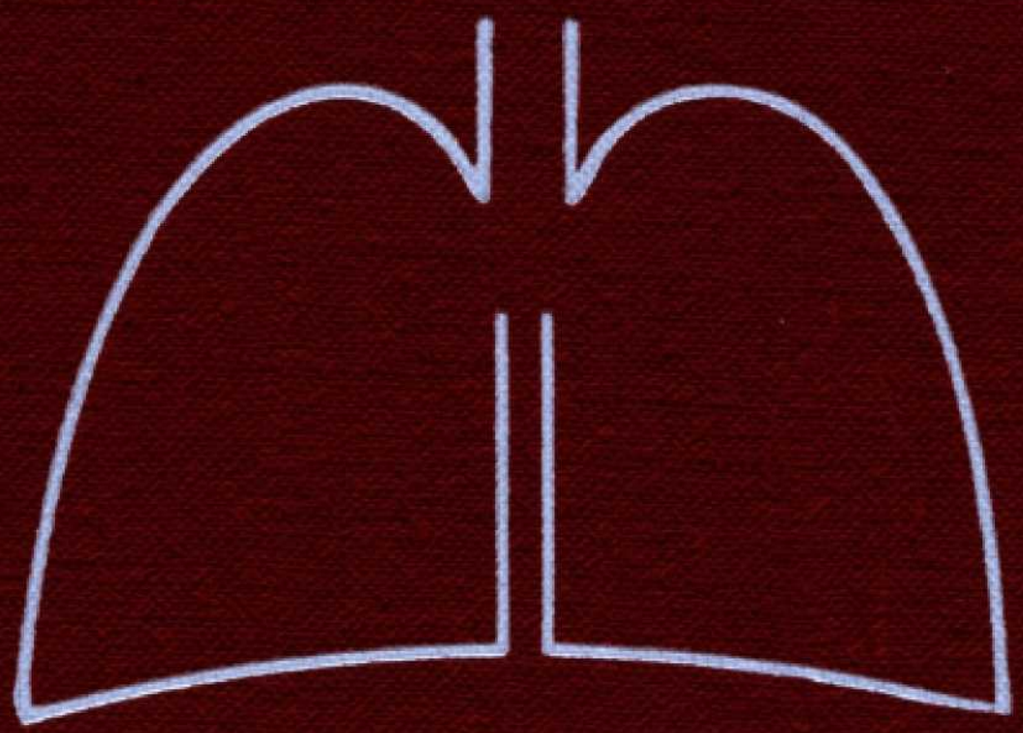

68. STATUS ASTHMATICUS

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Status asthmaticus is the most critical clinical expression of bronchial asthma because its advanced gas exchange defects are life-threatening. Since status asthmaticus is associated with a 1 to 3 percent mortality rate, the diagnosis warrants immediate hospitalization with full supportive measures. The clinical state is essentially defined pharmacologically as an episode of asthma unrelieved by usually effective bronchodilator drugs. This pharmacologic defect is, however, not absolute for it may be partially overcome with parenteral (intravenous) isoproterenol or similar adrenergic drugs. This effect of isoproterenol has been seen largely (but not exclusively) in children and presumably reflects changes mainly in bronchomotor tone, because these patients are more likely to be suffering from a rapidly reversible bronchial muscle contractile component. This contrasts with the more resistant, slowly resolving patterns associated with secretional obstruction, where beta-adrenergic refractoriness seems not to be a problem exclusively of the membrane receptor but one essentially of intraairway mechanical obstruction from glandular secretions and inflammatory matrix. Inasmuch as the majority of affected patients undoubtedly exhibit such secretional airways obstruction, the use of bronchodilator drugs in this context thus becomes a maneuver to identify that such refractory pathomechanical obstruction exists.

What constitutes an adequate trial of effective therapy to fulfill this definition has not been firmly established. It is general clinical practice to administer epinephrine (or another sympathomimetic), theophylline, or both to an acutely ill patient with asthma and to assess the response over the first hour or two of treatment. A favorable response is judged by both subjective clinical features and objective spirometric, peak expiratory flow rate (PEFR), or arterial blood gas measurements. Since these findings may vary among patients and as no absolute data exist that define an appropriate therapeutic trial or parameters of response in such patients, no strict criteria can be provided. Nevertheless, as approximate guidelines in addition to subjective or clinical improvement by the patient, the forced vital capacity (FVC) should improve to at least 1.5 liters; the first-second forced expiratory volume (FEV_1) by 15 percent or more and at least to 1.0 liter; and the PEFR to at least 100 to 120 liters per minute. In addition, an arterial blood gas and pH determination may be required to validate the clinical and spirometric improvement, as some patients may exhibit more subjective or clinical relief than is documented from spirometric or blood gas data; in this context PaO_2 should be at least 60 torr, and $PaCO_2$ 40 to 45 torr or less (room air) (see further discussion later).

Several recent studies, in evaluating the approach to assessment and treatment of the acute asthmatic attack, have provided further guidelines for determining drug refractoriness. Banner et al. [8] found that the need for hospitalization could be predicted by the severity of airways obstruction (initial PEFR $< 16\%$ of normal) and poor response to the initial injection of epinephrine ($< 16\%$ improvement in PEFR in 20 min); either finding alone did not preclude successful ambulatory management. In another report the successful treatment of acute severe asthma in the emergency room was correlated with the duration of treatment and the magnitude of improvement in FEV_1 during treatment but did not correlate well with the initial FEV_1 or with improvement in clinical symptoms and signs [142]. Fischl et al. [79] concluded that the need for hospitalization could be predicted with 96 percent accuracy if four or more of the following were present before therapy was initiated: pulse rate at least 120/min, respiratory rate at least 30/min, pulsus paradoxus at least 18 mmHg, PEFR $\leq$ 120 L/min, moderate to severe dyspnea, accessory muscle use, and wheezing (see Chap. 67). This grading index could also be applied after initial therapy as an indicator of drug refractoriness. Two recent studies employing the Fischl index did not confirm its predictive accuracy regarding relapse or immediate response to therapy in acute asthma [33, 234].

Concerning the therapy of acute asthma, Josephson et al. [135] reported that epinephrine alone was equieffective to a combination of parenteral theophylline and epinephrine. Another evaluation, however, concluded that the combination of a sympathomimetic agent and theophylline was more effective and no more toxic than epinephrine alone for the initial treatment [235].

During the initial presentation the physician must rapidly assess the gravity of the asthmatic attack. A summary of the major indexes of severity of an asthma episode is provided in Table 68-1. These features may also be viewed as guidelines in the decision for hospitalization, particularly when the immediate response to initial bronchodilator therapy is absent or marginal.

For the initial approach the following drug schedules may be considered. Intravenous or subcutaneous therapy is generally preferred for the acute episode in order to ensure the most rapid and complete drug delivery to the sites of the intrinsic airways obstructive processes; however, aerosol therapy is also commonly utilized. The following beta-adrenergic drug schedules may be employed in adults: (1) Epinephrine aqueous (1:1000) 0.3 ml subcutaneously for an adult (70 kg) may be given initially followed by the same dose at 20- to 60-minute intervals, not to exceed 1.5 ml total dose. If the response is suboptimal, avoid repeated dosing and employ another agent. For older (> 40 years) or higher-risk adults (hypertension, cardiac disease) we prefer subcutaneous terbutaline (1 mg/ml) as 0.25 mg subcutaneously, which may be repeated in 30 minutes; maximum dose 0.5 mg q4h, subcutaneously thereafter. (2) Isoproterenol by aqueous aer-

Table 68-1. *Indexes of Acute, Severe, or Life-threatening Refractory Asthma*

Disturbances of consciousness
Cyanosis (central)
Severe respiratory distress or exhaustion
Recurrent acute episodes over a short period (for example, 2–7 days)
Increasing bronchodilator requirement with minimal relief
Profuse diaphoresis
Pulsus paradoxus ≥ 15–18 mmHg
Sternocleidomastoid contraction, intercostal retraction
Wheezing on inspiration (high pitch) or silent chest
Tachypnea ≥ 30/min
Tachycardia ≥ 120/min
PEFR ≤ 100–120 L/min
FVC ≤ 1–1.5 L
FEV_1 ≤ 1.0 L
PaO_2 ≤ 60 torr (room air)
$PaCO_2$ ≥ 40–45 torr (± acidemia)
ECG abnormalities; hypotension
Coexisting pneumonia, pneumothorax, pneumomediastinum

osol (0.5 ml of 1:200 dilution) q 20 min for three doses delivered by a pneumatic nebulizer. Alternatively, the following may be employed: (1) nebulized metaproterenol, 0.25 to 0.5 ml diluted to 2 ml given q4 to q6h; (2) nebulized aqueous isoetharine (1.0%), 0.25 ml to 0.5 ml diluted to 2.0 ml for 2 to 3 doses at 2- to 3-hour intervals per dose; (3) metered aerosol salbutamol, two inhalations initially. Excellent information on the pharmacology of sympathomimetic drugs including dose recommendations may be found in the resource by Ziment [308] and in Chapters 53 through 55.*

When there is no or only limited response to beta-adrenergic drugs within a reasonable time interval (i.e., 10–30 min), theophylline is generally added to the therapeutic program. Initial intravenous loading theophylline doses will depend on the most recent theophylline usage and preferably should be adjusted based on the results of an immediate plasma theophylline measurement. For those not already taking theophylline, Mitenko and Ogilvie [184] recommended an aminophylline loading dose of 5.6 mg/kg body weight diluted and infused over 20 minutes, followed by a maintenance infusion of 0.9 mg/kg/hr. However, Hendeles et al. [111] found that this maintenance dose was likely to result in excessive serum concentrations in many adult asthmatics and therefore recommended a continuous infusion of 0.5 mg of aminophylline/kg/hr in adult nonsmokers without cardiovascular or hepatic disease. Since theophylline clearances can vary widely between patients and even in a single patient for a variety of disparate causes (advanced age, infection, heart failure, liver disease, drug interactions), the maintenance dose in those circumstances should be reduced to 0.2 to 0.4 mg/kg/hr. Thereafter, plasma theophylline levels must be monitored as safe and therapeutic in the 10- to 20-μg/ml range. For those already taking theophylline, if the immediate plasma level is in the therapeutic range, the loading dose is omitted and the patient should receive an appropriate maintenance infusion. If an immediate plasma level cannot be obtained, a single 2.5 mg/kg intravenous dose delivered over 15 to 20 minutes can generally be administered with relative safety, provided the patient has no symptoms of and is monitored for theophylline toxicity. Further details of aminophylline administration are provided in Chapter 56.

The methods for specifying doses of inhaled bronchoactive drugs are not so precise. Aerosol nebulized isoetharine is often preferred to isoproterenol because of fewer cardiac side effects. The adequacy of propellant-delivered aerosol salbutamol in this setting is not fully defined. Interestingly, intravenous salbutamol (not available in the United States) is reported in several studies to be no more effective than inhaled salbutamol [16, 114, 153].

Once initial drug refractoriness to conventional bronchodilators is determined, intravenous corticosteroids should be initiated as 4.0 mg/kg body weight hydrocortisone hemisuccinate (or equivalent preparation) and maintenance doses continued in-hospital [46] (see Chap. 57). While two recent studies conclude that there is no added beneficial role for routine adrenal corticosteroids in acute severe asthma [140, 161], these agents are still currently considered indicated once status asthmaticus is diagnosed (see also Therapy section and Chap. 57).

Finally, while a variety of clinical or quantitative methods are available for determining the initial effectiveness of drug therapy (PEFR, spirometry, arterial blood gases, predictive indexes, etc.), *no single feature or combination of observations can unequivocally predict the need for hospitalization nor can they supplant the meticulous concerns of the involved physician.* In any case of uncertainty as to the course of the patient, hospitalization is safer and is strongly recommended.

If this diagnosis is made, 3 corollaries arise:

1. Bronchial asthma is now life-threatening.
2. Status asthmaticus is a medical emergency: All efforts are to be alerted and intensified.
3. Hospitalization is *required* immediately for diagnostic studies, intensive treatment, nursing care, and elimination of offending agent(s).

Causes

No unique precipitating factor has been incriminated in causing status asthmaticus. The usual incitants are those that may provoke any attack of asthma including allergen exposure, viral respiratory infection, air pollutants, toxic exposure, cold air, and temperature-humidity changes. In many instances the initiating event(s) may not be clini-

*Avoid cumulative dosages in patients with immediate prior use.

cally obvious, and also many factors may interact to intensify or propagate the process. For most patients status asthmaticus begins as any other attack, revealing its true character only as drug resistance develops. Infectious exacerbations may be more common in intrinsic asthma, whereas allergic insults may be more easily incriminated in those with extrinsic atopy.

Concerning allergens, no one incitant appears particularly noteworthy. Inhalant antigens are important by their sheer incidence, but in any given case other allergens can be important and will require eventual identification. Fever, emotional or physical stress, dehydration, and hypermetabolic demands are ancillary factors, but they all are of therapeutic importance. Occupational hazards require consideration (see Chap. 40). Asthma has been associated with exposure to isocyanates, enzyme detergents, baking, plastic wrapping, cotton or flax dust, certain wood dusts, and metal compounds such as nickel or platinum salts [243]. Nonasthmatic occupational toxic insults must be distinguished because acute chemical bronchiolitis can mimic status asthmaticus. Also, cigarette smoking can intensify any insult. However, any incitant is important because *once an attack is precipitated by any cause, it may progress to status asthmaticus in any patient.*

Patients with allergic respiratory diseases exhibit an increased morbidity and mortality during periods of high air pollution with particulates, ozone, oxides of sulfur, carbon monoxide, metals, and photochemicals as well as during periods of temperature inversions and climate changes. In one serious epidemic in Donora, Pennsylvania, about 90 percent of the asthmatic population was affected, compared with 40 percent of the total population [94]. Also, hospital emergency room visits in urban areas increase during periods of air stagnation; common examples cited occurred in New Orleans and Yokohama, "Yokohama asthma" being a nonspecific effect of air pollutants in susceptible persons [262, 287] (see Chap. 38). In other instances wind forces from a city dump were related to similar outbreaks [156]. Status asthmaticus and deaths have occurred with such exposure to industrial pollutants, temperature, and atmospheric or geographic changes, and appropriate protective measures should be encouraged.

Respiratory tract infections may precipitate an asthma episode or in some instances develop secondarily. Viral provocations appear to be commonly incriminated, particularly in children, and include respiratory syncytial virus, influenza, parainfluenza, rhinovirus, and adenovirus. Estimates for a viral etiology range from 10 to 40 percent in children requiring hospitalization, with the variability in incidence arising from differences in age, serologic methods, and patient selection [60, 169]. *Mycoplasma pneumoniae* infection, a common cause of community-acquired pneumonia in children and young adults, has been reported to be associated with exacerbations of asthma [12]. The association between viral infections and subsequent airways hyperreactivity is detailed in Chapter 37.

While bacterial infections are not commonly involved in precipitating asthma attacks in comparison with viral respiratory infections, they may be causative in select instances and need to be identified. Bacterial infection in childhood status asthmaticus is perhaps greater in nonatopic children and in those with an immunologic deficiency, while in adults infective bronchitis or sinusitis may be contributory. There may also be a risk in corticosteroid-treated patients, for in one study an increased infection rate was reported [50, 179]; this risk may not apply to patients on alternate-day schedules [53]. Whether asthma predisposes to subsequent infectious complications is not entirely resolved; in one study 11 percent of asthmatic children experienced recurrent bacterial pneumonias [143]. Other data indicate this to be an infrequent problem, possibly because of the brevity of such attacks [174]. In adults it is becoming clear that routine antimicrobials are not warranted in the management of acute episodes unless specific findings of a bacterial process are present [100] (see Chap. 37).

Drug sensitivity (aspirin) or underuse of necessary medications may amplify the effect of these causative factors.

Mechanisms

A variety of physiochemical and pharmacologic mechanisms have been proposed to explain why patients in status asthmaticus are refractory to therapy (Table 68-2). Some of these mechanisms are discussed below.

Several of the pathomechanical findings observed in the lungs of patients who die in status asthmaticus are apparently of sufficient severity to explain refractoriness. Widespread tenacious mucous plugs obstructing the bronchi may block the entry of inhaled drugs and hence limit the access of aerosolized bronchodilator drugs to the distal or even more central airways; rapid shallow breathing may further reduce aerosol delivery to the peripheral airways. Extensive bronchial wall edema and smooth muscle spasm-hypertrophy may additionally retard the diffusion of drugs from the luminal surface to their site of action (see Chap. 53). Of course, the essential issue is how and why such critical secretory problems arise in status asthmaticus.

Bronchodilator ineffectiveness could hypothetically result from decreased drug absorption, increased drug elimination, or alterations in homeostatic mechanisms. One factor currently being studied extensively in relation to asthma is the so-called down-regulation or subsensitivity to beta-adrenergic agonists, a phenomenon that could contribute to adrenergic refractoriness. Tachyphylaxis to sympathomimetic drugs such as ephedrine, which acts indirectly through the release of norepinephrine from adrenergic nerve terminals, has been known for many years [34]; it results from depletion of norepinephrine stores in the nerve ter-

Table 68-2. *Mechanisms of Pharmacologic Refractoriness (Postulated)*

Limited access of aerosolized drugs
Intense bronchospasm and edema
Secretions
Tachypnea and hypopnea
Inadequate dosages
Relative to pharmacologic need
Increased metabolism of drugs
Drug interactions or clearance changes
Beta-adrenergic receptor abnormalities
Beta-adrenergic blockade
Down-regulation or tachyphylaxis
Metabolite inhibitors
Others
"Epinephrine fastness in acidemia" (?)
Infection
Alpha-receptor, cholinergic influences
Defects in clearance mechanisms
Allergen "load" and mast cell mediator effect
Smooth muscle hypertrophy
Reduced corticosteroid or catecholamine bioavailability

minals. Other sympathomimetic drugs, such as isoproterenol and salbutamol, act directly on membrane receptors of target cells, causing a different form of tachyphylaxis. Studies in isolated tissues and experimental animals have provided evidence that prolonged treatment with such beta-adrenergic agonists decreases the number of functional membrane receptors, thereby reducing the response to a given dose of drug (down-regulation) [86, 185]. For example, Galant and colleagues [86] have shown in vitro that chronic beta-adrenergic therapy leads to a decrease in beta-adrenergic receptor function.

Holgate et al. [118] demonstrated decreased responsiveness to inhaled salbutamol in normal subjects. A decreased response to test doses of salbutamol was observed after 2 weeks of regular salbutamol administration; after 4 weeks the peak response to salbutamol, measured as specific airways conductance, had fallen to 46 percent of control. When regular salbutamol administration was stopped, responsiveness returned over 7 to 10 days. In subjects who had received regular salbutamol for 2 weeks, responsiveness to test doses of salbutamol was completely restored 3 to 5 hours after a single 200-mg intravenous dose of hydrocortisone.

Studies of beta-adrenergic subsensitivity in asthma patients have yielded mixed results [132, 152, 189, 206]. In asthmatic patients the bronchodilator response to a test dose of oral salbutamol was reduced following 1 to 2 weeks of treatment with oral salbutamol, 4 to 6 mg qid [189]. There was no further decrease in response during 1 year of continuous treatment with 8 mg of salbutamol qid. Jenne et al. [132] demonstrated diminished metabolic and bronchial responses to terbutaline, 5 mg orally, in patients with stable asthma or chronic bronchitis who had received oral terbutaline, 5 mg tid, for 1 week or longer. Peak FEV_1 was reduced by 7 percent at 1 week and 15 percent at 2 weeks. Responses returned to pretreatment levels within 2 weeks after discontinuation of terbutaline therapy. Plummer [220] has discussed the possible development of cross tolerance between isoproterenol and terbutaline following chronic adrenergic therapy. In contrast to those findings, eight patients with asthma and/or chronic bronchitis studied by Larsson et al. [152] did not develop resistance to the bronchodilating effects of infused isoproterenol after treatment with terbutaline for 1 year. Resistance to isoproterenol-induced muscle tremor developed within 1 month of the start of terbutaline therapy.

Parker et al. [206] observed that the improvement in PEFR with oral salbutamol, 4 mg qid, was sustained during 4 weeks of treatment in patients with chronic asthma who were receiving maintenance corticosteroids. That the bronchodilator response to catecholamines is similarly enhanced by corticosteroid therapy was demonstrated in some patients with asthma [249]; in one study a single injection of 40 mg of prednisolone appeared to restore responsiveness to inhaled isoproterenol in 8 of 10 asthmatics who were previously unresponsive to catecholamines [69].

Other studies have indicated that beta-adrenergic therapy may induce an apparent loss of the protective effect of a beta agonist against exercise-induced asthma [92], while not affecting the protective effect of inhaled salbutamol against histamine-induced bronchoconstriction [213].

Currently, it would appear that the decline in bronchodilator response to beta-adrenergic drugs, when observed, has generally been small, and its clinical significance in relation to status asthmaticus is yet to be fully clarified.

Relevantly, a recent study examined beta-agonist effectiveness in acute asthma patients self-pretreated with sympathomimetics [236]. Since no drug resistance was identified, it was recommended that beta-adrenergic drugs be utilized in treating acute asthma despite the history of prior sympathomimetic therapy. For patients in status asthmaticus failing to respond to adrenergic therapy, however, the phenomenon of adrenergic refractoriness should be considered in management.

In some patients overusage of inhaled isoproterenol has been implicated or associated with severe refractory asthma and lack of bronchodilator response to isoproterenol, with clinical and spirometric improvement occurring when the isoproterenol was discontinued or reduced in dosage [230, 279]. Therapeutic doses of nebulized isoproterenol have also been reported to induce bronchoconstriction in some patients [141]. Bronchoconstriction following inhaled isoproterenol may result from an irritative effect of one or more of the ingredients in the aerosol, from beta-receptor subsensitivity, or from beta-adrenergic blockade combined with endogenous alpha-adrenergic stimulation; a metabolite of isoproterenol, 3-methoxyisoproterenol, is a weak

beta-receptor antagonist [209]. The role of alpha-adrenergic pathways in asthma is the subject of continuing study. Alpha-adrenergic blocking drugs have been shown to reduce postexercise bronchoconstriction in asthmatics [105, 208]; however, the significance in relation to status asthmaticus is not currently clear.

Another factor possibly contributing to refractoriness is adrenal corticosteroid dependency or resistance. Asthmatic patients receiving continuous systemic steroid therapy may manifest varying degrees of impairment of hypothalamic-pituitary-adrenal axis responsiveness when faced with an asthmatic exacerbation, infection, or other stress. Steroid resistance is characterized by increased plasma clearance of cortisol, decreased eosinopenic response to steroids, and poor asthma control on usually effective corticosteroid doses [245]. Such patients require 2 to 3 times the usual steroid doses for control of an asthmatic exacerbation and require an immediate increase in dosage during any physiologic stress.

Hence, while a variety of factors may contribute to drug refractoriness, and these may vary among patients, the precise mechanism(s) for status asthmaticus is unresolved. Generally, the presence of obstructive airways secretions appears in the first instance to be one, if not the major, problem. Additional biochemical and pharmacologic factors presumably become additive or operative as secondary causes against this background. While drug-induced beta-adrenergic desensitization may decrease beta-adrenergic reactivity, such subsensitivity may in fact be a fundamental feature of atopy and hence directly related to drug refractoriness as recently stressed by Krzanowski and Szentivanyi [148]. That muscarinic cholinergic receptor changes are altered has also been proposed, and the potential role of adrenoceptor interconversion in asthma is presented in Chapter 13 for the interested reader.

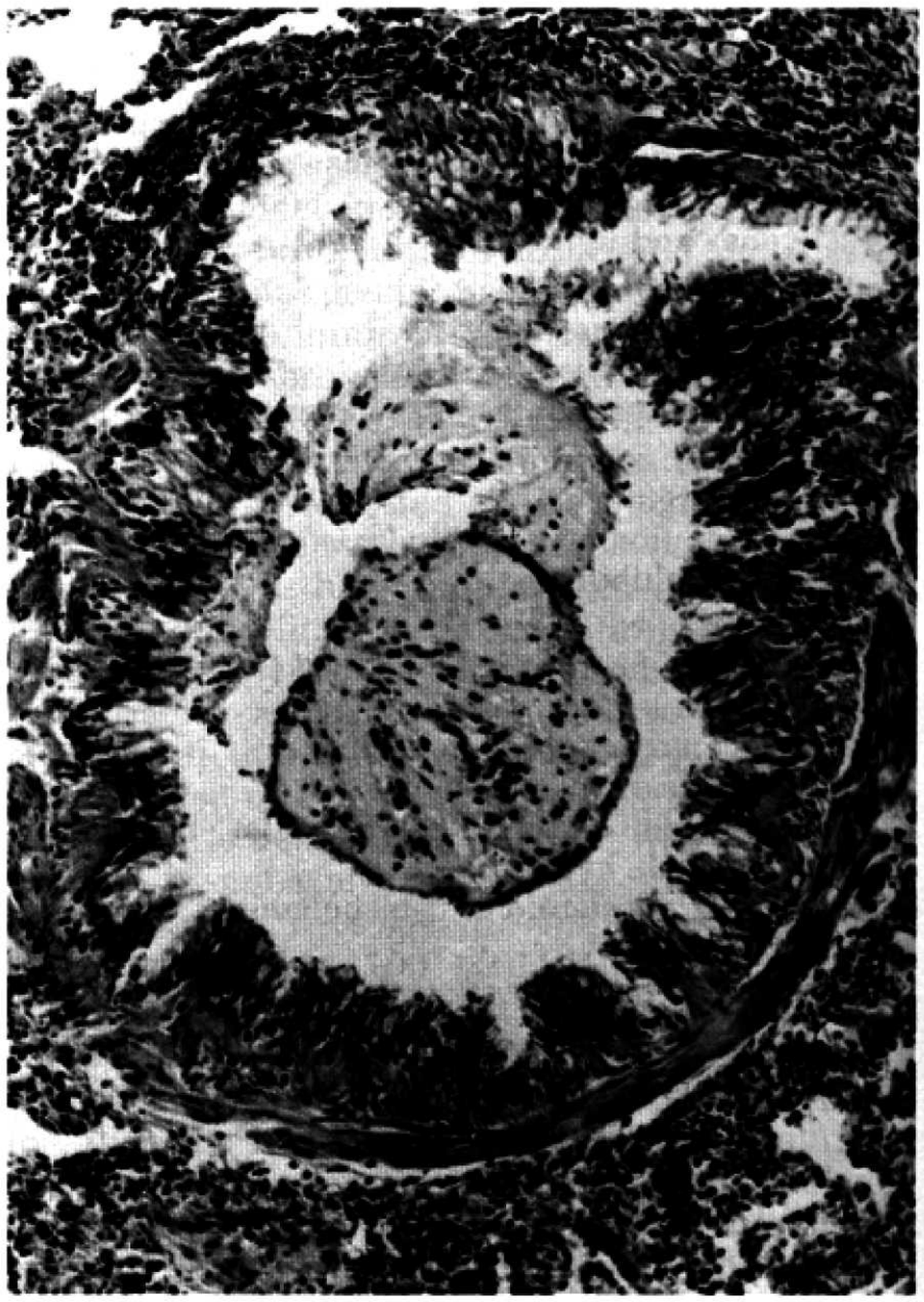


Figure 68-1. *Bronchus from a patient with status asthmaticus. Luminal diameter is reduced by the invagination of the airway, mucous plug in lumen, and muscle hypertrophy and spasm.*

Pathology

Our understanding of the pathologic features of status asthmaticus is derived largely from autopsy examination in fatal cases [29, 120, 121, 178, 294]. The gross and microscopic findings in status asthmaticus were recently reviewed by Thurlbeck [276] and are discussed in Chapter 19.

At autopsy the lungs are markedly hyperinflated and do not collapse when removed from the thorax. A ubiquitous pathologic finding in patients dying with status asthmaticus presumably reflects a predominant cause of refractory airways obstruction, namely, the occlusion of airways by thick, extremely tenacious mucous plugs. These may extend diffusely from upper airways to respiratory bronchioles and coexist with the above-described gross morphologic parenchymal overdistention. In addition to marked compromise of airways by spasm of hypertrophied smooth muscle and epithelial invaginations and evaginations, these inspissated PAS-positive secretions grossly reduce the effective luminal diameter (Fig. 68-1). These plugs are composed of a mixture of mucus and proteinaceous exudate containing large numbers of eosinophils, Charcot-Leyden crystals, and shed airway epithelial cells either singly or in clumps, which are recognized in expectorated sputum as Creola bodies [187]. Additional findings in some patients dying of asthma include areas of atelectasis, subpleural fibrosis, and bronchiectasis [64]. True emphysema, with airspace enlargement and tissue destruction, is seldom seen in fatal asthma [64, 99, 294]. A constellation of other important facets of these secretional phenomena are yet to be clarified in status asthmaticus such as the biochemical changes in such mucus, mucociliary transport, and epithelial mucosal permeability.

Typically, the bronchial mucosa shows extensive goblet cell metaplasia. Large areas of epithelium are sloughed into the lumen, leaving only the basal layer of the epithelium. Thickening of the basement membrane by deposition of increased amounts of collagen on the nonluminal side of the basal lamina is characteristic of asthma but not pathognomonic, as it is also found in other respiratory diseases [49,

241]. Mucous glands are enlarged, and the bronchial wall is heavily infiltrated with eosinophils in patients dying of status asthmaticus. A marked increase in the thickness of bronchial smooth muscle is seen in status asthmaticus, unlike chronic bronchitis, and reflects primarily muscle cell hyperplasia rather than hypertrophy [65, 109, 274]. IgE has been identified by immunofluorescent staining in bronchial epithelial cells, basement membrane, bronchial glands, and intrabronchial mucus in patients with asthma [90].

The classic descriptions of lung pathologic changes in bronchial asthma are based on postmortem features of patients dying of acute asthma or status asthmaticus. Thus, it has only been inferred that lesser degrees of these characteristic findings occur in milder or nonfatal cases. However, a valuable ultrastructural study of the airways in asthmatic children during clinical remission, using tissue obtained from lung biopsies performed for other reasons, has recently been reported [51]. Interestingly, these asymptomatic patients exhibited typical but lesser degrees of mucous plugging, goblet cell hyperplasia, peribronchial smooth muscle hypertrophy, and eosinophilic infiltration. Hence, secretional obstruction seems undoubtedly characteristic of asthma whether mild or severe, in clinical remission or in status asthmaticus. Again, this pathomechanical feature not only limits effective aerosol bronchodilator drug dispersion but appears to be the major cause of initial pharmacologic refractoriness to therapy by any route in this entity.

Epidemiology

According to the National Center for Health Statistics, there were an estimated 8.9 million asthmatics in the United States in 1975. Although adequate statistics on the incidence of status asthmaticus in that population are unavailable, it is apparent that only a small fraction of asthmatics require hospitalization for severe asthma, and the mortality rate in patients who are hospitalized is approximately 1 to 3 percent [18, 66, 138, 246]. Rackemann and Edwards [222], reporting a 20-year follow-up study of 449 patients first seen for asthma before the age of 13, found that only 2 percent required treatment in-hospital, and only 0.8 percent of the entire group died of asthma. Cochrane and Clark [41] estimated that the asthma mortality rate of patients admitted with asthma to Greater London Council hospitals in 1971 was approximately 1 percent in patients aged 35 to 64 years and 1.5 percent in the 55- to 64-year-old group.

Asthma was responsible for 8 percent of admissions to the medical service and 25 percent of admissions to the pediatrics service of a New York City municipal hospital in 1972 and 1973 [139]. Seventy-three percent of adults admitted for refractory asthma were women, in contrast to the 63 percent male predominance among hospitalized children. The mean age of hospitalized patients age 15 and over was 36.9 years. The peak age group for pediatric admissions was under 6 years and for adults 20 to 29 years.

A strong female predominance was also observed among adults hospitalized for status asthmaticus at Colorado General Hospital, where women comprised 80 percent of 811 adults admitted (mean age 42.2 years) [246], and among 70 admissions to a respiratory care unit for status asthmaticus, 83 percent were women [248]. Aggregated data from five series of asthma deaths in-hospital also reveal a 2:1 female predominance [41, 138, 162, 200, 246], but no sex difference was noted in two series of asthma deaths occurring outside the hospital [163, 200]. Fraser et al. [84] obseved a marked male predominance in asthma deaths in patients aged 5 to 14 years and a marked female predominance in the 30- to 34-year-old group. It is not clear whether these data merely reflect a difference in the frequency of asthma in males and females at different ages or whether the case fatality rate in asthma is higher in male children and in female adults.

Mortality

Death from asthma, once thought to be rare, is now known to occur in a small but distressing fraction of the asthmatic population. There are an estimated 2,000 to 4,000 asthma deaths in the United States annually, most occurring in adults. Mortality statistics for asthma are subject to limitations owing to the uncertainty in identifying the cause of death, especially in cases without autopsy examination, and to the changing interpretation of the term *asthma* over the years.

Alexander [1], in reviewing the history of fatal asthma, identified three historic periods. Before 1930 death during an asthmatic attack was almost unknown. Leading medical textbooks of the nineteenth and early twentieth centuries stated that asthma was rarely, if ever, fatal. By 1930 only a handful of autopsy examinations in cases of fatal asthma had been reported. Increasing numbers of asthma deaths were recognized during the next 25 years, and U.S. vital statistics indicate an increase in the asthma death rate from 2.5 per 100,000 population in 1937 to 4.5 in 1951. The third period, beginning in the early 1950s and coinciding with the expanding use of adrenal corticosteroids in treating asthma, saw a sharp decline in the death rate to a level of 2.8 per 100,000 in 1959.

In contrast to the fluctuation in the crude death rate for asthma in the U.S. statistics, Speizer and Doll [259] noted the remarkable stability of the asthma death rate in England and Wales between 1867 and 1961 in persons aged 5 to 34 years.

However, a steady rise in asthma mortality was observed in England and Wales between 1959 and 1966, affecting all ages from 5 to 64 years but especially pronounced in the 5- to 34-year-old group, in which the death rate tripled from 0.7 to 2.2 per 100,000 persons. Mortality began to fall during 1967, and by 1969 was only slightly higher than in 1959. Similar increases were observed during the same

period in Australia, Ireland, New Zealand, and Norway but not in the United States, Canada, the Netherlands, Belgium, and West Germany [268]. Some investigators suggested that the overuse of pressurized aerosols containing sympathomimetic bronchodilators may have been responsible for the excess deaths [127, 260, 261]; especially implicated were nebulizers that delivered a much larger dose of isoproterenol, which were sold to patients in countries that experienced an epidemic of asthma deaths but were not available in countries that were spared the epidemic [268]. That explanation has been disputed by other investigators [87,225], and as yet there is no satisfactory explanation for the increased mortality during those years.

Deaths from asthma in persons aged 5 to 34 years in the United States and Canada remained stable at a rate at or below 0.4 per 100,000 persons throughout the 1960s and 1970s [130]. In New Zealand, however, the reported asthma mortality in that age group rose steeply from 1.4 per 100,000 in 1975 to 4.1 in 1979 [130]. No such increase was observed during that period in the United States, Canada, West Germany, Australia, England, and Wales. As in the earlier epidemic of deaths in several countries in the 1960s, no satisfactory explanation has yet emerged.

Recently, Wilson et al. [301] questioned whether an increased use of oral theophylline in combination with inhaled beta agonists may have led to additive cardiotoxicity. Other observers, however, have disagreed with that explanation [103, 128, 288], and Grant [104] has suggested that other therapeutic practices in New Zealand, including the widespread use of air compressor nebulizers in the home for the self-administration of large doses of salbutamol, may have contributed to the increased mortality. Studies in animals have demonstrated an increased potential for cardiotoxicity (including fatal ventricular dysrhythmias and myocardial necrosis) and death when beta-adrenergic agonists are administered in combination with aminophylline [134]. Fatal myocardial toxicity with histologic confirmation of myocardial necrosis was reported in an asthmatic patient treated concurrently with intravenous isoproterenol, aminophylline, and hydrocortisone [149]. In light of those findings, the U.S. Food and Drug Administration has issued a warning [82] and has proposed additional studies of the potential toxicity of combined beta-adrenergic and methylxanthine therapy [191]. Current information is insufficient to permit an unequivocal recommendation in this matter; however, appropriate caution as well as using proper therapeutic doses and monitoring for side effects of such combined therapy is indicated. The physician will have to consider whether undertreatment of the patient with severe asthma poses more of a risk than prescribing a combined methylxanthine-adrenergic drug program [194].

Despite advances in our understanding of the pathophysiology of asthma and the wider availability of arterial blood gas analysis and mechanical ventilation, patients continue to die of status asthmaticus. Evidence has accumulated in support of the view expressed by Read in 1968 [225] that many asthmatics die because of failure to appreciate the severity of an episode and failure to take appropriate action [21, 41, 84, 200]. Subjective assessment by patients [25, 237] and physical examination by physicians [96] may not reflect the degree of airways obstruction present. Indeed, severe airflow obstruction and marked gas exchange disturbances may be present in patients who appear clinically stable [165, 273]. Such patients may not become symptomatic until the functional derangements are far advanced, and progression from that stage to death can occur rapidly (i.e., within 30 minutes) [55, 163]. Thus, some patients do not survive long enough after the onset of symptoms to reach medical assistance. Others are seen by a physician who fails to recognize the severity of the episode and consequently does not initiate adequate therapy or recommend admission to the hospital [21, 84, 163, 200]. Those factors may help to explain why many asthma deaths take place outside of the hospital and often are regarded as sudden and unexpected [84, 102, 163, 261].

While some outside-of-hospital deaths may be related to causes other than status asthmaticus, evidence to support other mechanisms is generally lacking. Furthermore, such deaths are commonly preceded by a period of poor symptom control [84, 200]. Moreover, autopsy examination, where available, shows identical findings of overdistended lungs and widespread mucous plugging of bronchi in such patients reported to have died suddenly and unexpectedly [9, 30, 67, 163, 210, 261].

Analysis of asthma deaths in-hospital suggests that inadequate patient assessment and/or underuse of therapy, especially corticosteroids, may contribute significantly to mortality. Several studies reveal that objective physiologic assessments, such as PEFR, spirometry, and arterial blood gas analysis, were seldom performed in hospitalized patients who died of asthma [41, 162, 200]. Eight of 19 patients aged 35 to 64 years who died of asthma in one hospital series were not receiving corticoste-

Table 68-3. *Factors That May Contribute to Mortality in Asthma*

Failure to diagnose asthma
Failure of the patient to be properly educated concerning asthma and to seek medical help promptly when symptomatic therapy fails
Failure of the physician to intensify therapy or advise hospitalization when usual therapeutic measures fail
Failure to use objective measurements (PEFR, spirometry, pulsus paradoxus, arterial blood gases) to assess severity of the attack
Failure to use, and in proper dose, bronchodilators and corticosteroids
Failure to monitor hospitalized patients closely and serially with objective and clinical evaluations
Inappropriate use of sedatives or other drugs

roids (or ACTH) at the time of death [41]. Other reports also reveal either a failure to employ corticosteroid therapy or the use of small doses in many instances of fatal asthma [162, 200]. Additional factors thought to contribute to deaths in some series are the administration of sedatives [188] and the use of intermittent positive pressure breathing devices, resulting in pneumothorax [137, 138, 178]. Table 68-3 lists errors in management that have frequently been identified in cases of fatal asthma.

Risk Factors

The continuing problem of deaths in asthma has prompted a search for risk factors that may identify patients with greater susceptibility to life-threatening attacks. For example, a longitudinal study of 1,000 patients indicated that prognosis, in terms of both morbidity and mortality, was worse in patients whose symptoms began after age 16 and in those with continuous rather than intermittent symptoms [196]. It has been the experience of some investigators that severe asthma rarely develops soon after the onset of the illness and that symptoms are usually present for months or years before hospitalization is necessary [18, 296]. Similarly, other studies have suggested that most asthma deaths occur in chronic asthmatics and in persons who have been hospitalized previously with severe asthma [21, 162, 163]. Nevertheless, in a given patient serious asthma can develop at any time. Moreover, one study found that 40 percent of persons who died of asthma outside of the hospital had never been hospitalized [163].

The presence of hypercapnia during an asthma attack has long been recognized as an index of life-threatening asthma [75, 248]. Williams [296] noted that more than 35 percent of the survivors of an episode of asthma complicated by hypercapnia or the need for intubation had a recurrence of life-threatening asthma and that the risk of recurrence increased further after two or more such episodes. A history of the use of mechanical ventilation for asthma may also be a grave prognostic sign; in one series 8 of 32 patients who survived such an episode eventually died of asthma [293].

Patterns of airways obstruction have also been found to correlate with the risk of fatal asthma. Hetzel et al. [116] identified a subset of asthmatic patients who regularly showed marked decreases in PEFR in the early morning hours; the presence of this pattern was associated with the occurrence of life-threatening ventilatory arrest during hospitalization for asthma, with most episodes occurring between midnight and 6 A.M. [115]. An excess of asthma deaths between midnight and 8 A.M. was also observed in the study of Cochrane and Clark [41] but not in two other series [163, 200]. Westerman and associates [293] analyzed serial FVC and $FEV_{1.0}$ measurements in outpatients who survived mechanical ventilation for status asthmaticus and found that those with markedly labile asthma or gradually deteriorating airways obstruction appeared to be at increased risk of death from asthma when compared with those with relatively constant spirometric values at either normal or subnormal levels. While acute severe asthma commonly precedes death from asthma, patients with more chronic symptoms may have equally severe airways obstruction and not appear acutely ill. Stellman et al. [267] have emphasized that failure to diagnose and treat such patients may contribute to added mortality. Potential risk factors for life-threatening asthma are outlined in Table 68-4.

Table 68-4. *Potential Risk Factors for Life-threatening Asthma*

Long history of asthma (> 20 years)
Continuous and poorly controlled symptoms
Frequent emergency room or office visits for acute treatment
Previous hospitalization for refractory asthma, especially if complicated by hypercapnia or need for mechanical ventilation
Prior or current requirement for corticosteroids
Pattern of early morning decrease in PEFR
Pattern of markedly labile asthma or gradually worsening airways obstruction

Prestatus Asthmaticus

A prodromal period of "prestatus" asthmaticus exists (Table 68-5). This state should be recognized because early recognition and intervention are more likely to abort overt status asthmaticus. Perhaps the well-described British epidemic of asthmatic deaths attributed to an unsupervised excessive usage of concentrated aerosol isoproterenol exemplifies the extreme of the prestatus problem; here, progressive symptoms presumably led to more frequent use of a bronchodilator agent rather than to direct medical care.

It is important for the patient and the physician alike to be able to recognize this period of evolving nonresponsiveness, for it is easier and safer to abort a massive insult than to treat it. In this regard, patient education and the enlistment of the patient as a partner in therapy are essential. Patients should be informed of the purpose of each of their drugs and should be taught to recognize the features of emerging refractoriness. They should be instructed in the importance of continuing prophylactic treatment during asymptomatic periods.

Patients likely to need intermittent oral corticosteroid therapy may be provided with a reserve supply and instructions on when and how to take a short course if immediate physician advice is unavailable. All patients need to know how to obtain prompt emergency assistance at any time, as delay in reaching medical assistance can contribute to asthma deaths [21, 163].

At the same time, physicians should not underestimate the potential for death in status asthmaticus. Since no single observation or group of observations provides absolute, reliable prognostic

Table 68-5. *Clues to Impending Status Asthmaticus*

History
Change in pattern of symptoms
Wheezing: more severe or frequent, particularly at night
Worsening dyspnea: progressive exercise limitations, dyspnea at rest, orthopnea, or fatigue
Cough with tenacious sputum: difficult to expectorate or a substantial decrease in daily volume; changes in sputum color from white to yellow, gray, or green (e.g., purulent)
Refractoriness to drugs: increasing use with less relief from otherwise efficacious drugs
Constitutional: personality changes (irritability, confusion), anxiety, insomnia
Examination
Anxiety, increased respiratory efforts, resting tachypnea
Expiratory prolongation, onset of inspiratory wheeze
Fatigue
Laboratory Data
Falling flow or volume indexes (FVC, FEV_1, FEF 25–75%, PEFR) or reduction in FVC with rising FRC
Limited response to bronchodilator (by spirometry)
Progressive hypoxemia
Hypocapnia (< 35 torr)
X-ray: hyperinflation (or pneumonia or atelectasis)
Eosinophils in blood or sputum: high values or a shift from chronic-state levels
Leukocytosis; purulent sputum

Table 68-6. *Features of Poor Prognosis in Status Asthmaticus*

Persisting refractoriness to all bronchodilators and all other supportive therapy
Use of inappropriate drugs or inappropriate dosages, or delay in initiating therapy
Greater duration of attack
A silent chest reflecting nonmobilization of secretions
Hypercapnia, respiratory ± lactic acidosis
Severe hypoxemia despite full therapy
Cardiac arrhythmias, hypotension
Abuse of sedatives or respiratory depressants
Underlying cardiopulmonary disease

features, all patients must be regarded as having the potential for a serious episode or even mortality. Table 68-6 summarizes selected features associated with a poor prognosis in status asthmaticus.

Physiology

The pathophysiologic features of status asthmaticus include a spectrum of gas exchange defects associated with airways obstruction. This obstruction is widespread but unevenly distributed throughout the lungs and is caused by a variable combination of factors, including intraluminal secretions, airway wall inflammation and edema, glandular hypertrophy, smooth muscle hypertrophy and spasm, and expiratory airway compression. Progressive airways obstruction is associated with hyperinflation, increased work of breathing, and disorders of gas exchange, which in turn are responsible for many of the characteristic symptoms and signs of status asthmaticus.

AIRWAY DYNAMICS AND LUNG VOLUMES. During an acute asthmatic attack the increase in bronchial smooth muscle tone and other factors tend to induce closure of small airways at higher-than-normal lung volumes. Counteracting this tendency, the lung volume is increased, thereby raising the static transpulmonary pressure and resulting in an increased outward radial traction on the airways, which helps to maintain their patency [214]. The more severe the asthmatic attack, the greater is the tendency to airway closure and the higher the lung volume must be to keep the airways open. Tonic contraction of inspiratory intercostal and accessory muscles throughout expiration has been shown to contribute to the increase in lung volume in asthma [171]. That the diaphragm may also be actively involved in maintaining an increased lung volume has recently been reported by Muller et al. [186] during experimental histamine-induced hyperinflation.

This increased lung volume is recognized clinically and radiographically as hyperinflation of the chest. Functional residual capacity (FRC) and residual volume (RV) are usually markedly increased, in some instances by as much as 3 to 5 liters [304]. Total lung capacity (TLC) may be increased or normal [199, 304], and vital capacity (VC) is usually substantially reduced. For example, Stănescu and Teculescu [265] found a mean VC of 67 percent of predicted (range 38–99%) during status asthmaticus. Serial changes in TLC can be used to monitor the course of the asthmatic attack; even with a constant FEV_1 percent, a fall in TLC indicates a lysis of the obstruction [304]. The increase in RV, not specific for asthma, is a primary reason for the observed decrease in vital capacity.

Such increases in residual volume may mimic pulmonary emphysema: a chest radiograph with flat diaphragms and apparently attenuated pulmonary vasculature, physical examination revealing use of accessory musculature (implying a temporary mechanical disadvantage of the diaphragm), low-lying diaphragms, hyperresonance, and diminished intensity of breath sounds caused by the elevated air-tissue ratio. However, destructive emphysema is not present, and these findings are reversible.

Lung volume measured by the helium dilution method may underestimate the true lung volume because of impaired ventilation of air spaces distal to severely obstructed airways. The plethysmographic method, on the other hand, measures the entire thoracic gas volume, whether or not in free communication with the airways, but this method may yield spuriously increased values of TLC in some patients with severe airways obstruction because of incomplete transmission of alveolar pressure to the mouth [255, 264].

Expiratory airflow obstruction is consistently present. Rebuck and Read [228] found a mean FVC of 1.2 liters and FEV_1 of 0.54 liter among 35 patients hospitalized for emergency treatment of asthma. A peak expiratory flow of 80 L/min or less has been shown to correlate with deaths in asthma [295]. The possible role of extrathoracic airway obstruction in some asthmatic patients has been investigated by Lisboa et al. [158].

Asthma can involve both large and small (< 2mm) airways [167], a feature that is extensive in status asthmaticus. Although the major resistances during status asthmaticus are undoubtedly in intermediate or larger airways, a major contribution by small airways is an added critical problem because their large cross-sectional area is now reduced by intraluminal secretions, whose mobilization is arduous but *mandatory* for complete relief.

The nature and distribution of airways obstruction are important in the definition of refractoriness. In asthma a basic requisite is bronchoreversibility, conventionally accepted to be a 15 percent (or greater) increase in FEV_1, mean forced expiratory flow during the middle half of the FVC (FEF25–75%), or airway conductance within 10 to 15 minutes of bronchodilator drug administration. Status asthmaticus by definition does not exhibit this acute reversibility for reasons previously discussed. In addition, drug refractoriness can be exaggerated by the inability of aerosol dilator drugs to reach peripheral airway zones and the obvious inability of such drugs to reverse airways obstruction caused by extensive mucous plugging.

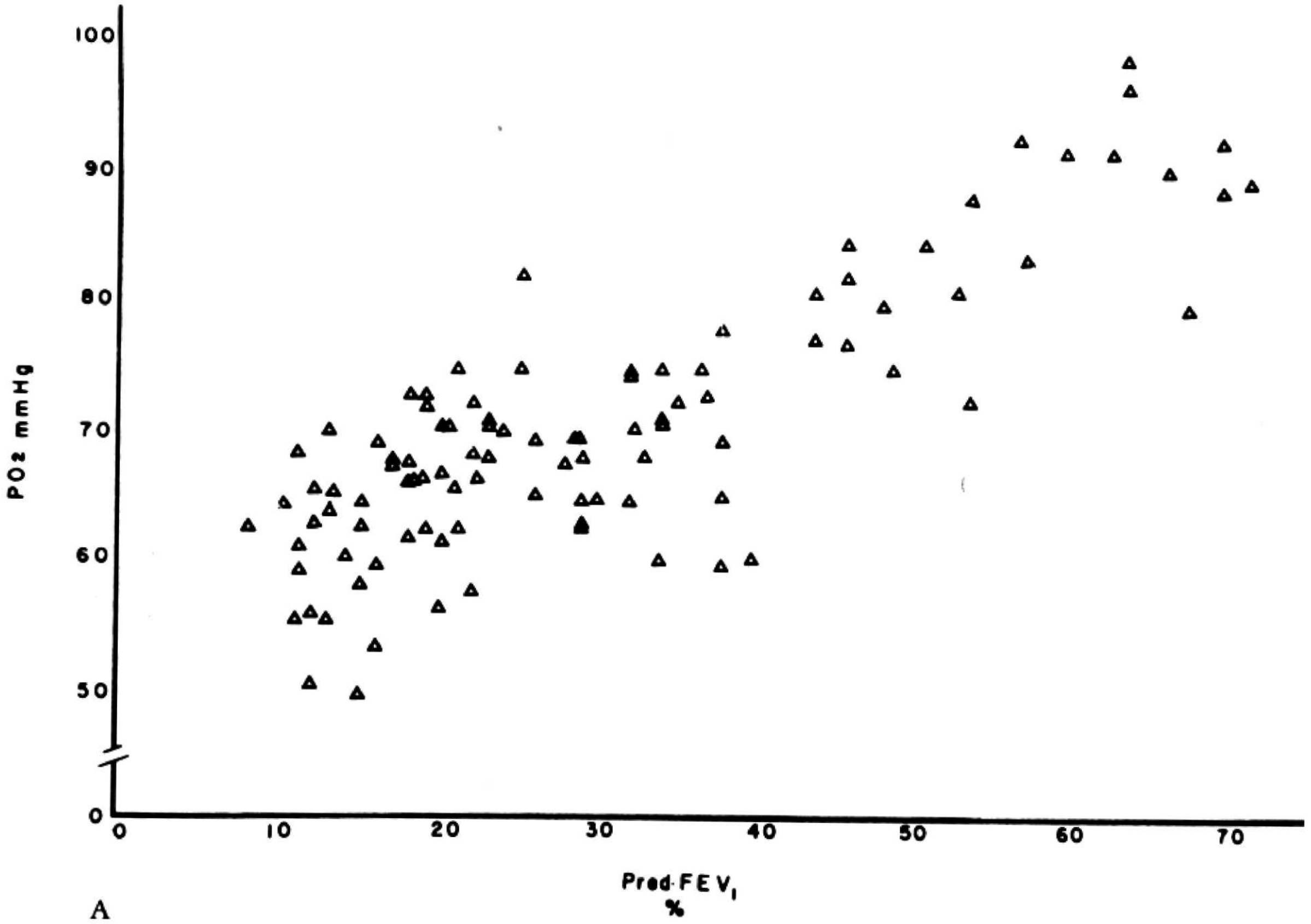
Airflow patterns are also a consideration in advanced asthma. To meet the demands of basal gas exchange as well as those additionally imposed by fever, infection, stress, and the augmented work of the respiratory muscles, total ventilation must be increased. When this state occurs, concurrent increases in airflow are not proportional to higher driving pressures and become alinear, leading to turbulent flow patterns. Energy losses resulting from these increased gas velocities, eddy currents, and gas vortices from bronchospasm, airway secretions, and swollen inflamed mucosa must be then met by greater changes in alveolar pressure by the respiratory muscles. Resistance to airflow over and through intraairway secretions is estimated to occur with viscid sputum and when secretional thickness exceeds 300 μm [40]. These flow patterns are more extreme in larger airways where turbulency is influenced by the gas density. Further, transbronchial pressure gradients are now shifted so that peripheral airways are subject to expiratory airflow limitations earlier than in normal subjects. Also, compression of the trachea and large bronchi may complicate the process when active expiration or cough elevates the intrathoracic pressure [56].

PULMONARY CIRCULATION. In acute asthma blood flow is reduced in poorly ventilated regions of the lung [182]. Ventilation-perfusion lung scans may reveal focal areas of reduced perfusion with corresponding areas of abnormal ventilation [300]. The principal mechanism responsible for the redistribution of flow is probably hypoxic vasoconstriction, but alterations in intraalveolar pressure and other factors may also play a role. This vasoconstrictive response has the effect of reducing the degree of hypoxemia that results from perfusion of hypoventilated lung zones and is at least partially reversible with resolution of the acute attack and with the administration of certain bronchodilator drugs such as isoproterenol [281, 300].

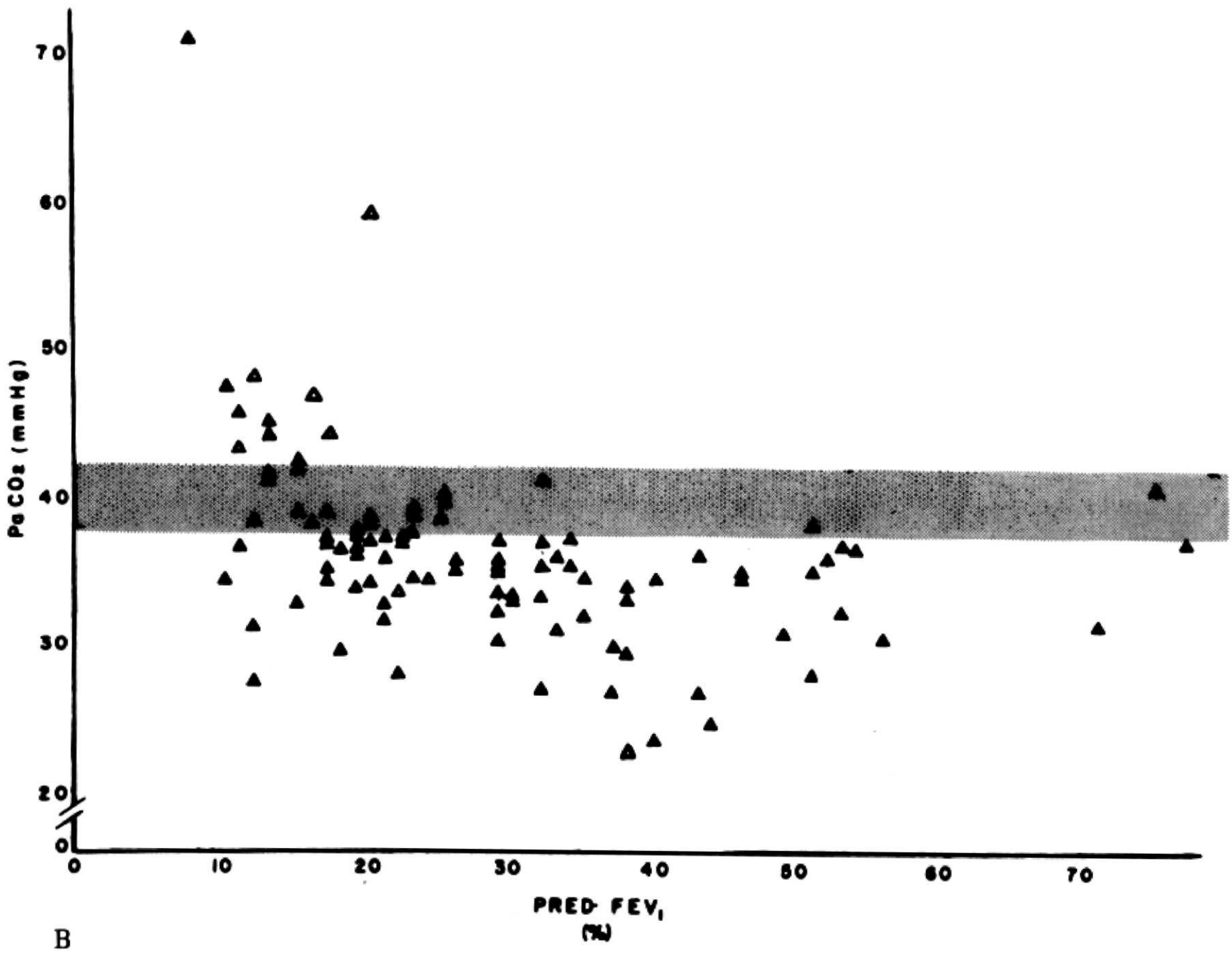
Pulmonary vascular resistance is increased by hypoxemia, acidemia, and the effect of increased transmural pressure on pulmonary capillaries at high lung volumes in acute asthma. Although pulmonary arterial pressure measured relative to atmospheric pressure may be normal, the highly negative intrapleural pressure exposes the outer surface of the heart and pulmonary artery to pressures much lower than atmospheric [214, 263]. Hence, transmural pressures across the heart and pulmonary artery are increased and effectively induce a reversible pulmonary hypertension, as the right ventricle must generate more tension during systole. Permutt [214] reported that the average transmural pulmonary arterial pressure approximately doubled in five subjects during severe asthmatic attacks. The hemodynamic effects of the highly negative intrapleural pressure may be responsible for the reversible P pulmonale observed on the electrocardiogram in severe asthma [89] and have been implicated as a cause of fluid accumulation in the lung in acute asthma [263].

WORK OF BREATHING. The combination of hyperinflation and advanced airways obstruction in severe asthma results in a marked increase in the work of breathing. The elastic work of breathing is increased because the slope of the pressure-volume relationship of the thorax is reduced at high lung volumes [98] and because obstruction of some lung units results in overinflation of nonobstructed units, thereby decreasing dynamic lung compliance. Permutt [214] has pointed out that an increase in FRC of 2.5 liters with a tidal volume of 500 ml would require an 11-fold increase in the inspiratory work of breathing, even if there were no change in compliance or resistance. However, a reversible increase in compliance has been reported in some patients during acute asthma exacerbations in association with an increased total lung capacity; the mechanisms involved are unclear [305]. In addition, hyperinflation impairs the efficiency of the diaphragm. As lung volume increases, the muscle fibers of the diaphragm shorten (reducing their force of contraction), and the radius of curvature of the diaphragm increases, thereby decreasing its ability to exert pressure for a given force of its fibers. The high lung volume at which the asthmatic patient is forced to breathe is probably a predominant cause of dyspnea in the asthmatic attack.

The flow-resistive component of the work of breathing also increases markedly in severe asthma,


100
90
80
70
60
50
0
PO2 mmHg
0
10
20
30
40
50
60
70
Pred FEV1
%

A


70
60
50
40
30
20
0
PaCO2 (mmHg)
0
10
20
30
40
50
60
70
PRED FEV1
(%)

B

and expiratory muscle contraction adds further to the work of breathing. Intraluminal secretions impair airflow in inspiration as well as in expiration. Clinicians are familiar with complaints of the inability to inspire or of inspiratory wheezing in status asthmaticus, features that can be explained by the inspiratory obstruction as well as by the increase in FRC, which intensifies elastic work. Thus, the inspiratory airways resistance may be almost as high as the expiratory resistance in patients with asthma, in contrast to patients with emphysema in whom the airflow limitation occurs primarily during expiration [292]. Mean airways resistance values as high as 25 to 56.5 cm H_2O/L/sec (normal 1.4 to 4.0) have been reported in severe asthma, and the work of breathing has been estimated at 5 to 25 times that done by the normal adult at rest [292]. As stated previously, breathing at higher lung volumes provides support to the airways and increases airway diameter, thereby reducing airflow resistance.

Breathing patterns may also affect respiratory work. Theoretically, slow deep breaths reduce turbulent airflow and thereby viscous resistance [110]. However, in acute asthma respiratory frequency is increased by mechanisms that are not yet clearly defined.

As ventilatory demands rise during an attack, oxygen consumption by the respiratory muscles also increases. Faced with these impedances, a given amount of ventilation will consume more oxygen in contrast to normal subjects. As an illustration, if minute ventilation rises to 60 L/min, oxygen consumption of the respiratory muscles may rise to more than 100 to 200 ml per minute with airways obstruction in contrast to only 20 ml/min. in normal subjects. Clinically, fatigue and exhaustion will be obvious when these factors accumulate, as in status asthmaticus. Besides this inefficiency of the oxygen cost, total work may fall below that required to eliminate carbon dioxide, and hypercapnia will ensue. Noelpp et al. [192, 193] demonstrated that in animals with induced bronchospasm the work of breathing against elastic resistance increased 44-fold and the total work of breathing 12.5-fold. Parallel findings in human asthma for both overall elastic work and expiratory airflow resistances were observed by Attinger et al. [3].

Hence, many factors contribute to the increased work of breathing in asthma: The combined effects of marked increases in the elastic and flow-resistive components of the work of breathing, the decrease in dynamic lung compliance, the reduced efficiency of the respiratory muscles, and the need for active expiratory muscle work produce a substantial increase in the oxygen requirements of the respiratory muscles, which can lead to respiratory muscle fatigue and eventual hypercapnic ventilatory failure.

GAS EXCHANGE. Uneven distribution of inspired gas owing to marked variations in time constants of different lung units leads to gross disturbances in ventilation-perfusion ($\dot{V}/\dot{Q}$) ratios characteristic of asthma. These $\dot{V}/\dot{Q}$ disturbances are reflected in alterations of the arterial blood gases [273, 300]. The degree of arterial hypoxemia correlates roughly with the severity of airways obstruction and hence the population of low $\dot{V}/\dot{Q}$ units. For example, Flenley [81] observed that a PaO_2 of less than 60 torr was commonly associated with an FEV_1 of less than 0.5 liters or less than 30 percent of predicted. In another study of 101 patients, the correlation between mean FEV_1 and PaO_2 was as follows: mean FEV_1 59, 35, and 18 percent of predicted; mean PaO_2 of 83, 71, and 63 torr, respectively [168]. These relationships are further depicted in Figure 68-2A. In addition, complete airways obstruction may arise from extensive secretions. In this circumstance added right-to-left anatomic shunting may intensify the hypoxemia induced by simple $\dot{V}/\dot{Q}$ mismatch. Concerning the contribution of venoarterial shunts, Valabhji [278] found a mean PaO_2 of 66 torr during acute asthma attributable mainly to disturbed $\dot{V}/\dot{Q}$ relationships with only a small shunt fraction ($\dot{Q}s/\dot{Q}t$) of 3.7 percent. Also, McFadden and Lyons [168] found an increased ($\dot{Q}s/\dot{Q}t$) in 4 of 30 asthma patients studied during an acute attack; two had hypercapnia and the others had an FEV_1 less than 15 percent predicted. Compensatory pulmonary vasoconstriction may reduce this shunt component by diverting blood flow from nonventilated lung zones. In some instances zones of increased $\dot{V}/\dot{Q}$ ratios occur, resulting in an increase in physiologic dead space, which can increase respiratory work. Diffusion limitations do not appear to contribute significantly to arterial hypoxemia. In fact, while the steady-state carbon monoxide diffusing capacity (D_LCO) has been reported to be reduced in asthma [198], the single-breath D_LCO may be increased owing to a perfusional redistribution to the lung apices [291]. Arterial hypoxemia may be worsened by the administration of certain drugs such as isoproterenol, which act to increase $\dot{V}/\dot{Q}$ inequality by means of an augmented perfusion of underventilated lung units [77]. In severe asthma, including status asthmaticus, dangerous levels of arterial hypoxemia may develop, at times with alarming rapidity, and without hypercapnia. Given the circumstance of an existing marginal PaO_2 level (e.g., 60 torr), a small critical decrease in airways flow could contribute to this phenomenon. Finally, at some point in the asthmatic airways obstructive process, overall or net alveolar ventilation may fall, and hypoventilation, aside from producing hypercarbia, will add its component to arterial hypoxemia.

In a mild asthmatic attack the primary gas exchange defect is hypoxemia accompanied by hypocapnia, the latter reflecting the increased alveolar ventilation induced by hypoxia, anxiety, and other

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Figure 68-2. *A. Percent predicted FEV_1 versus arterial oxygen tension in acute asthma. B. Percent predicted FEV_1 versus arterial carbon dioxide tension in acute asthma. The normal range of $PaCO_2$ is shown by the shaded area. (Reprinted with permission from E. R. McFadden, Jr., and H. A. Lyons, Arterial-blood gas tension in asthma. N. Engl. J. Med. 278:1027, 1968.)*

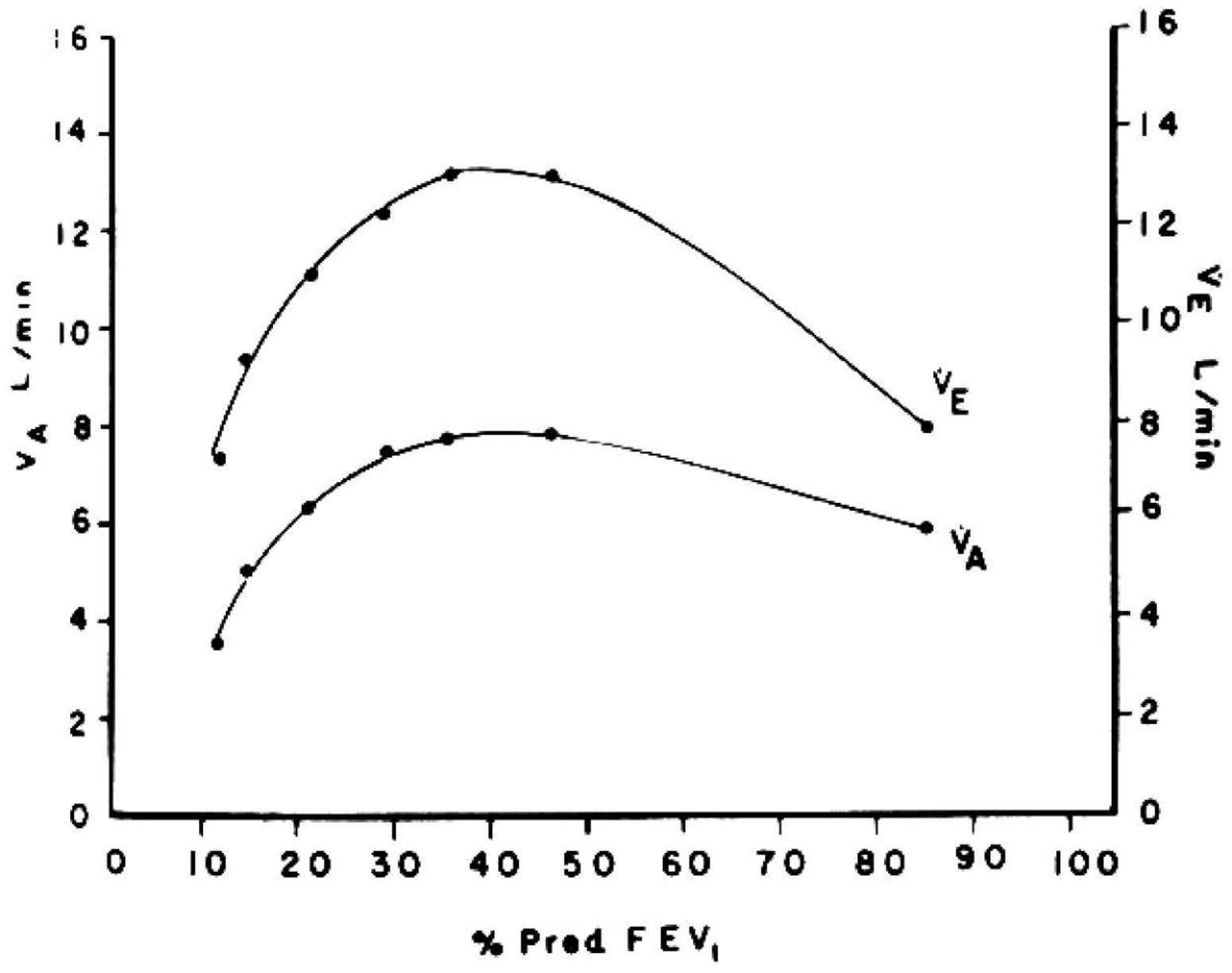

Figure 68-3. *Minute ($\dot{V}_E$) and alveolar ($\dot{V}_A$) ventilation versus percent predicted FEV_1 in acute asthma. (Reprinted with permission from E. R. McFadden, Jr., and H. A. Lyons, Arterial-blood gas tension in asthma. N. Engl. J. Med. 278:1027, 1968.)*

Table 68-7. *Arterial Blood Gas and pH in Asthma*[a]

Stage		PaO_2 (torr)	$PaCO_2$ (torr)	pH	FEV_1	Dyspnea
I	Mild attack or chronic stable	Normal or mild ↓ 65–80	35–42	7.40	>2.0 L	+
II	Mild-moderate attack	55–65	<35	>7.45	~1–2 L	+ +
III	Crossover	45–55 (or normal[b])	≅40	≅7.40	≤1 L	+ + +
IV	Severe	<45 (or normal[b])	>45	<7.35	<1 L	+ + + +

[a] Schema of general range values only.
[b] On therapeutic oxygen.

factors. With progressive airways obstruction, however, effective alveolar ventilation fails, and hypercapnia will supervene (Fig. 68-3). The relationship between FEV_1 and $PaCO_2$ is not linear (see Fig. 68-2B). In a study of acute exacerbations in 101 asthmatics hypercapnia was present in only 11 patients and was not observed until the FEV_1 fell below 20 percent of its predicted value [168]. Similarly, Nowak et al. [195] found hypercapnia ($PaCO_2$ > 42 torr) in 18 of 102 episodes of acute asthma seen in an emergency department; in all hypercapnic patients initial FEV_1 was less than one liter and less than 25 percent of predicted, and the PEFR was less than 200 L/min. While the incidence of hypercapnia is low, prompt identification of this stage is critical because of its high mortality rate and the frequent need for tracheal intubation and mechanical ventilation [204]. Respiratory acidosis develops in only a small number of patients but may be severe when it occurs. Among 101 adults with acute asthma seven had respiratory acidosis, 21 had a normal pH, and 73 had respiratory alkalosis [168]; in children a higher incidence of acidosis may exist [62, 257].

Lactic acidosis may be seen in severe asthma [2, 233]; in a series of 12 patients with severe asthma and metabolic acidosis plasma lactate concentrations ranged from 2.9 to 9.4 mmol/L [2]. Believed to result from a combination of lactate overproduction by the respiratory muscles and lactate underutilization resulting from hypoperfusion of the liver and skeletal muscles, this metabolic derangement reflects severe airways obstruction and possibly impending respiratory failure.

No single pattern of PaO_2, $PaCO_2$, and pH changes is characteristic of status asthmaticus; rather, evolving stages of severity can be arbitrarily categorized (Table 68-7). Because an arterial PO_2 of less than 60 torr may be associated with $PaCO_2$ varying from 30 to 80 torr, and even hypocapnia can exist with FEV_1 values from 0.5 to 1.0 liters, such divergencies require blood gas and pH documentation of ventilatory adequacy and acid-base status. Hence, significant advances in the management of status asthmaticus have emerged by the use of such arterial blood gas and pH profiles, especially with the use of serial observations, since the severity of the gas exchange and acid-base disturbances *cannot* be re-

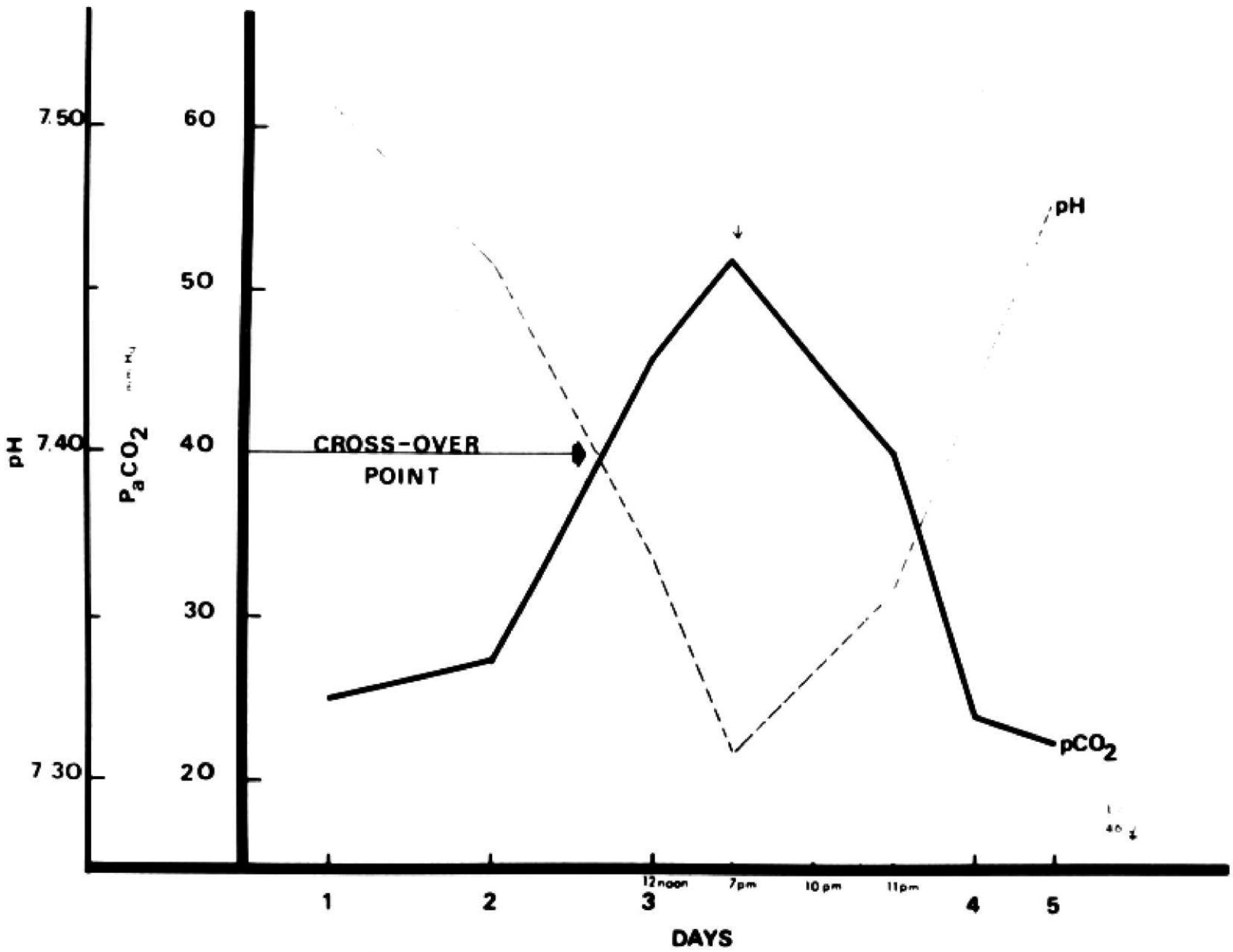

Figure 68-4. *An example of cross-over Stage III. $PaCO_2$ and pH in a 46-year-old woman in status asthmaticus. Note initial hypocapnia and respiratory alkalosis progressing to normal $PaCO_2$-pH relationships as a prelude to frank respiratory acidosis despite full medical therapy. PaO_2 on supplemental oxygen at the cross-over point was 80 torr. The vertical arrow indicates institution of intubation and ventilatory support. The patient fully recovered. Note the rapid development of acidosis; it can occur in an hour. (Reprinted with permission from E. B. Weiss, and L. J. Faling, Clinical significance of $PaCO_2$ during status asthma: The cross-over point.* Ann. Allergy *26:545, 1968.)*

liably judged on the basis of clinical and spirometric data alone.

Stage I, the least severe stage of gas exchange disturbance, is characterized by hypoxemia with mild hypocapnia and respiratory alkalosis. Here $\dot{V}/\dot{Q}$ disturbances are insufficient to produce ventilatory failure, and respiratory work remains effective in eliminating carbon dioxide. Supplementary oxygen and a sound therapeutic program will often suffice to support such patients. In Stage II, which reflects a greater severity of airways obstruction, advanced hypoxemia with augmented hyperventilation is observed; these patients are typically rather tachypneic and dyspneic with frank respiratory distress. Given proper bronchodilator therapy and supportive measures, many of these patients will respond. Disturbingly, other patients will remain refractory to therapy and will progress to graver stages of gas exchange impairment in association with pharmacologic (secretory) resistance.

The next phase, Stage III, is a critical point in the evolution of airways obstruction and refractoriness and is a useful index of progressive respiratory impairment, potentially heralding frank ventilatory failure and respiratory acidosis. The salient feature here is the paradoxically "normal range" values for $PaCO_2$ and pH *despite the obvious continued clinical severity of the episode.* This normalization of $PaCO_2$ and pH reflects progressive failure of effective alveolar ventilation and is in fact a state of relative hypoventilation. This is the "cross-over" phase [290] (Fig. 68-4). This phase is stressed to alert the physician to the possible transition from a hyperventilating Stage I and II to the ensuing phase (IV) of hypoventilation. Since Stage IV, with overt hypoventilation and respiratory acidosis, is most critical in terms of morbidity and mortality and can develop from eucapnia with alarming rapidity, the cross-over phase becomes one of major clinical concern. This stage warrants appropriate clinical and serial blood gas observations as well as modification and/or intensification, if possible, of all therapeutic modalities.

Patients in Stage IV with advanced hypoxemia, hypercapnia, and respiratory acidosis may well exhibit limited responses to brochodilator drugs and other supportive measures. While some patients presenting in Stage IV may be successfully managed

conservatively, as dictated by the individual clinical circumstances, others will require mechanical ventilatory support if they are exhausted, obtunded, and/or have critical PaO_2, $PaCO_2$, or pH values. Irresponsible causes of hypoventilation, such as sedative use, secretory-drying agents, or uncontrolled oxygen administration, must be identified as reversible but contributing factors.

Clinical Considerations

The onset of status asthmaticus can be rapid, often dramatic, with a terribly oppressive air hunger, but for some patients this evolution may take several days or longer. The salient clinical features of status asthmaticus include significant dyspnea, wheezing, and cough. These findings follow a variety of incitant causes as discussed previously, including allergic provocation, infection, nonspecific inhalant-irritant exposure, trigger mechanisms, and drug sensitivity; inappropriate therapy or inappropriate drug schedules will further potentiate the process. The intensity of wheezing relates poorly to the level of ventilation in severe asthma; extensive peripheral airway plugging may remain undetected until alveolar ventilation is severely limited. Inspiratory wheezing reflects a more advanced obstructive process. A relatively silent chest on auscultation with inability to raise secretions is ominous, suggesting possible widespread inspissation of secretions with bronchial plugging.

Sputum is rarely copious at the outset, a paucity reflecting its inspissation and adherence to mucosal surfaces. A commonly used clinical guideline suggests that most attacks will not remit until adequate secretion mobilization occurs, although this does not apply to atopic extrinsic asthmatic patients with pure bronchospasm who respond rapidly to bronchodilator drugs.

Anxiety, tachypnea, tachycardia, monosyllabic speech, diaphoresis, and accessory muscle use with sternocleidomastoid contraction and intercostal muscle retractions are typical findings in severe asthma. Brenner et al. [20] observed that patients who assumed the upright position in bed upon admission generally had more severe asthma attacks, as measured by objective criteria, than those who took a recumbent position; the combination of the upright position and profuse diaphoresis was present in patients with the most severe attacks. Disturbances of consciousness, systemic hypertension, cardiac arrhythmias, and cyanosis are occasionally present. A pulse rate of greater than 130/min may indicate hypoxemia with PaO_2 ranging to less than 40 torr, or it may relate to catecholamine response or arise from adrenergic drugs or a combination of factors [229].

The presence of pulsus paradoxus has been shown to reflect lung hyperinflation combined with wide fluctuations in intrathoracic pressure and is regarded as a valuable clinical sign, indicating the severity of the obstructive process in asthma [95, 145, 227, 228]. Of 76 patients hospitalized with asthma, Rebuck and Read [228] found paradox of 10 mmHg or more in 34, all of whom had FEV_1 of 1.25 liters or less. Significant paradox was found in all patients with FEV_1 of less than 20 percent of their best FEV_1; it often disappeared within hours of starting treatment. In contrast, Shim and Williams [250] observed that pulsus paradoxus was often present with only mild obstruction and often absent in severe obstruction and concluded that pulsus paradoxus is an unreliable guide to the severity of obstruction in asthma.

Evaluation of the patient with an acute asthmatic attack requires an assessment of the severity of the attack and of the response to initial therapeutic measures. Unfortunately, symptoms and physical findings correlate poorly with the degree of airflow obstruction, severity of the gas exchange disturbance, and responsiveness to initial therapy [142, 165, 228]. The asthmatic patient's self-assessment may be more accurate than the physician's examination in estimating the degree of airways obstruction present [253], but asthmatics vary widely in the degree of functional impairment necessary to elicit symptoms, often tolerating increases of more than 50 percent in residual volume and airways resistance before experiencing symptoms [237, 238]. In addition, there is considerable variation among physicians in detecting the physical signs of airways obstruction [96]. A recent study found that the intensity, pitch, and timing of wheezing had a general relationship to the severity of airways obstruction but were not sufficiently reliable to substitute for measurement of PEFR [254].

Rebuck and Read [228] found a considerable overlap of FEV_1 and of VC among three groups of hospitalized asthmatic patients who were divided on the basis of clinical assessment of severity. When McFadden et al. [165] compared symptoms and physical findings with lung mechanics in patients with acute asthma, sternocleidomastoid retraction correlated well with the degree of mechanical impairment, but dyspnea and wheezing did not; when all symptoms and signs had disappeared, marked abnormalities persisted in FEV_1, FRC, and RV. In another study [142] pulsus paradoxus and sternocleidomastoid contraction were the only physical examination variables that reflected the degree of obstruction present, but even in the presence of severe obstruction ($FEV_1 < 1$ L) the absence of those signs was the rule.

Clinical circumstances or failure to respond to therapy may suggest other disorders that may mimic acute status asthmaticus: acute bronchiolitis (infective, chemical inhalational), croup, pulmonary embolism (rare), advanced upper airways obstruction (e.g., tumor), angioedema, pulmonary aspiration, and cystic fibrosis (children) (see Chap. 30). A sweat test or quantitative immunoglobulin assay may be indicated if cystic fibrosis or immune deficiency is suspected. Monophonic wheezing arising from a local obstructive process should not be confused with diffuse asthmatic airways wheezing. In the case of a monophonic sound, the intensity of

the wheeze clearly diminishes with increasing distance from the site of its generation. The presence of basilar rales, cardiac left ventricular S3 gallop, or elevated central venous pressure with diffuse wheezing are signs of cardiac failure, although wheezing can at times be the only presenting sign of cardiac decompensation. If severe hypoxemia and hypercapnia supervene, papilledema, neuromuscular abnormalities (asterixis, irritability), confusion, agitation, cardiac arrhythmias, hypotension, or shock may ensue and add their respective findings; rarely some patients, especially children, may present obtunded. These problems require proper clarification.

Laboratory Procedures

RADIOGRAPHY (see Chap. 50). The principal value of the chest radiograph is to identify the specific coexisting conditions or complications of status asthmaticus with therapeutic implications, such as pneumonia, pneumothorax, pneumomediastinum [54], atelectasis, or mucoid impaction. Marked hyperinflation is commonly present [78, 216, 226], but in uncomplicated asthma, in contrast to destructive emphysema, the hyperinflation is reversible and the symmetric pulmonary vascular pattern is preserved. Transient opacities may be caused by mucous plugs with or without *Aspergillus* or by foci of pneumonia. Pneumomediastinum may be more easily detected on a lateral film [226] and is more commonly observed in asthmatic children than in adults [68]. Radiographic identification of pneumomediastinum and pneumothorax, both of which may be unsuspected on clinical examination, has important therapeutic implications, especially if the use of positive pressure ventilation is being considered. The findings of a foreign body or a hiatal hernia have obvious clinical implications.

Recent studies in children and adults have suggested that chest radiography is not routinely indicated in the emergency room evaluation of asthma [91, 307]. However, other investigators do not agree [93], and in any case the application of those conclusions to patients with status asthmaticus would be unjustified. Eggleston et al. [68] noted infiltrates or pneumomediastinum on admission chest radiographs of 23 percent of 479 children hospitalized with severe asthma. Petheram et al. [216] detected clinically unsuspected pulmonary consolidation or collapse on the admission radiographs of 9 of 117 adults with acute severe asthma. Whenever there is clinical concern that an inciting or complicating process (e.g., pneumonia, pneumothorax, congestive heart failure) might be present, a chest radiograph may be of considerable practical value in management and is recommended.

ELECTROCARDIOGRAPHY. Sinus tachycardia, the most common rhythm disturbance in severe asthma, is influenced both by the pathophysiology of the disease, especially coexistent hypoxemia and acidosis, and by chronotropic drug administration. Other ECG findings in one series included, in order of frequency: right axis deviation, clockwise rotation, right ventricular dominance (R V_1, S V_5 pattern), P pulmonale, ST-T abnormalities, right bundle branch block, and ventricular ectopic beats [228]. These changes reflect not only the presence of hypoxemia, pH shifts, and pulmonary hypertension but perhaps also mechanical factors such as impairment of cardiac output and cardiac compression owing to increased intrathoracic pressure. Many of the ECG changes have been observed to disappear within hours after the initiation of effective asthma therapy [228], but reversion of the ECG to normal may be delayed for up to 9 days [256].

P pulmonale (P wave amplitude $\geq$ 2.5 mV in leads II, III or aVF, axis + 79 $\pm$ 8°) was found in 49 percent of patients with $PaCO_2$ of 45 torr or more and arterial blood pH of 7.37 or less during a severe asthma attack and in only 2.5 percent of asthmatics without hypercapnia and acidosis. P pulmonale persisted for 12 to 60 hours after correction of hypoxemia, hypercapnia, and acidosis and is presumed to result from increased transmural right atrial pressure, which in turn is a reflection of the severity of obstruction in the asthmatic attack [89]. In older patients the stress of hypoxia during status asthmaticus may provoke cardiac ischemia, arrhythmias, or myocardial infarction.

EOSINOPHILIA. Blood eosinophilia may be present in both extrinsic and intrinsic asthma; in adults with intrinsic asthma the degree of eosinophilia has been reported to correlate with the severity of obstruction [119]. The total eosinophil count (TEC), a more accurate index than the percent eosinophils in the differential leukocyte count, is less than about 250/mm^3 in normal populations and ranges from normal values to 2,000/mm^3 or more in allergic asthmatic exacerbations [159]. The TEC may be reduced in acute infections and in patients treated with corticosteroids, epinephrine, isoproterenol, or aminophylline [197]. Corticosteroid-induced eosinopenia ($<$ 100 cells/mm^3) can be a useful index of steroid efficacy in airways obstructive processes and assist in evaluating the adequacy of steroid dosage. Steroid-resistant asthmatics with accelerated plasma cortisol clearances tend to have higher TECs and require higher corticosteroid doses to achieve eosinopenia and clinical remission; in one series TEC fell 77 percent in steroid-responsive asthmatics but only 36 percent in steroid-resistant patients 4 hours after 40 mg of cortisol given intravenously [245]. Sputum eosinophils or Charcot-Leyden crystals have also generally been considered useful clinically in diagnosing allergic asthma. A recent careful investigation has further defined the relationships of sputum and blood eosinophilia during corticosteroid treatment of acute exacerbations of asthma [6]. The conclusions of the study were (1) blood eosinophilia is not a necessary feature of noninfectious asthmatic exacerbations; (2) the numbers of eosinophils in blood and sputum do reflect the response of such an acute noninfectious exacerbation

to corticosteroid therapy; and (3) clinically effective doses of corticosteroids may not necessarily clear eosinophils from the sputum. Finally, with infection, leukocytosis or immature band shift may occur; dehydration, intercurrent steroid use, or metabolic stress may influence this response.

CHEMISTRY. Elevated SGOT, SGPT, and ornithine carbamyltransferase levels during severe asthmatic exacerbations are thought to reflect hypoxic injury to the liver [42]. Increased activities of lactate dehydrogenase isoenzymes LDH-3, LDH-4, and LDH-5 in serum of patients during moderate to severe asthmatic attacks suggest that both lung and liver contribute to the increased total LDH activity; neither total LDH activity nor the isoenzyme pattern correlates with the severity of the attack [277]. Serum creatine phosphokinase (CPK) elevations, derived entirely from the skeletal muscle isoenzyme, have been found in asthmatics; levels correlate with the severity of symptoms and of airways obstruction and probably reflect increased respiratory muscle activity [26]. Rhabdomyolysis with acute renal failure was reported in a patient in status asthmaticus; vigorous respiratory muscle contraction, hypoxia, and dehydration were considered responsible [38].

High plasma levels of antidiuretic hormone (ADH) may be found in patients with status asthmaticus; the levels decrease toward normal with clinical and spirometric improvement [7]. Factors known to influence ADH secretion that may be operative in status asthmaticus include hypovolemia, decreased left atrial filling pressure, stress, and beta-adrenergic stimulation. Hypotonic fluid therapy in asthmatics with elevated plasma ADH levels may result in hyponatremia, water intoxication, and coma. Hyponatremia and an elevated urine-plasma osmolality ratio were noted in 5 of 25 children with acute asthma [117].

SPUTUM. (see Chap. 49) Sputum examination in status asthmaticus may provide useful clues to the endobronchial pathology and even the inciting events. Initial sputum volumes may be scant, presumably because of widespread inspissation and entrapment of thick tenacious secretions rather than hyposecretion. Later or with treatment such sputum becomes thinner and more copious, often containing cylindrical mucous plugs or bronchial casts. On gross examination the sputum may be mucoid, purulent, or a mixture of both. Mucoid sputum is white, gelatinous, and tenaciously adherent to mucosal surfaces (or sputum containers) (Fig. 68-5), making it difficult to expectorate. Purulent sputum may be tinctured yellow, gray, or green and is often thick and voluminous. Curschmann's spirals are thin twisted bronchiolar casts composed of mucinous material surrounding a central thread and containing entrapped cells and cellular debris. They may be visible macroscopically or, more often, microscopically and, while not unique to asthma, are frequently present in sputum during or after the asthmatic attack.

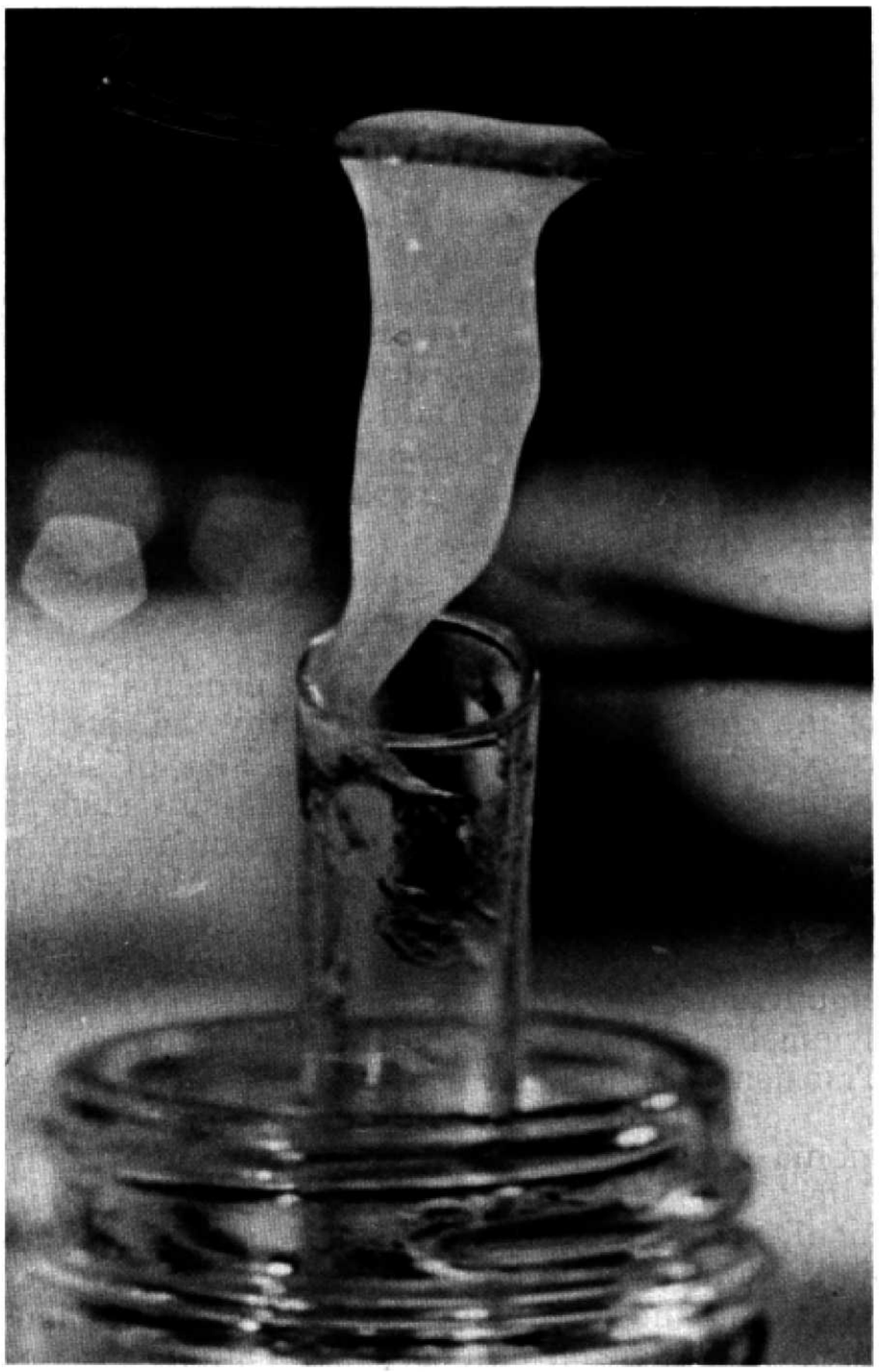

Figure 68-5. *Mucoid sputum exhibits adhesiveness to the test tube and increased viscosity manifested by the tendency to remain as a bolus. The reader is advised to envision this sputum in the airways. (Reprinted with permission from E. B. Weiss et al., Acute respiratory failure in chronic obstructive pulmonary disease: II. Treatment.* Disease-A-Month, *p. 9, November 1969, H. F. Dowling et al. (eds.); copyright © 1969 by Year Book Medical Publishers, Inc., Chicago.*

The Gram stain is important for the detection and tentative identification of bacteria pending results of sputum culture. Golden brown mucous plugs containing mycelia of *Aspergillus* are characteristic of allergic bronchopulmonary aspergillosis.

Cytologic examination of the sputum simply with an unstained wet preparation may reveal evidence of the damage in the airways mucosa and the response of inflammatory cells; such changes may be useful in diagnosis and therapy (see prior discussion of eosinophilia). For example, a predominantly eosinophilic response in sputum indicates an allergic exacerbation, while a prevalence of polymorphonuclear leukocytes suggests irritative or infectious factors. Individual exfoliated bronchial epithelial cells are easily recognized by their elongated columnar shape, basal nucleus, tapering tail,

and ciliated surface. The Creola body, a cluster of such columnar bronchial epithelial cells with intact cilia, implies severe asthma, as intense submucosal edema is presumably required for this cellular dehiscence from the basement membrane. Naylor [187] found Creola bodies in 45 percent of sputum specimens obtained from patients during attacks of asthma and in only 3 percent of specimens from nonasthmatics. The presence of macrophages in sputum generally is felt to indicate an "adequate" cellular defense response.

Sputum eosinophilia may be characteristic but not diagnostic of status asthmaticus; occasionally the number of eosinophils is sufficient to give the sputum a purulent appearance. Corticosteroid-treated asthmatics have a lower proportion of sputum eosinophils than do asthmatics not on steroids, and sputum eosinophilia may decrease with steroid therapy [6, 36]. The release of cytoplasmic contents from degenerating eosinophils gives rise to elongated octahedral Charcot-Leyden crystals, which may be found in large numbers in asthmatic sputum. Recently, the principal proteinaceous constituent of the eosinophil granule, eosinophil major basic protein (MBP), was shown to cause exfoliation and cytotoxic damage to human bronchial epithelium [85]. Markedly elevated sputum levels of MBP are found in asthma in contrast to other respiratory diseases; the levels decline with effective treatment and clinical improvement [85] (see also Chaps. 20, 23, 49).

Therapy

Once as thorough a clinical and laboratory evaluation of the patient with status asthmaticus as is feasible has been performed and the severity of the gas exchange abnormalities determined, therapy should be instituted without delay. The goal of therapy is to support the patient with whatever measures are necessary while the responsible pathophysiologic processes are reversed.

Most patients will respond to conservative but intensive regimens of drug therapy, oxygen, and measures to aid in the removal of bronchial secretions. Others, particularly those with Stage IV gas exchange abnormalities, may require tracheal intubation and mechanical ventilation. It has been reported that the severity of the asthma episode upon admission does not necessarily reflect the subsequent resolution rate [131]. Delayed recovery may be anticipated under the following conditions: age over 40 years, nonatopic asthma, duration of attack before admission of more than 7 days, poor long-term asthma control, use of maintenance corticosteroids, a PaO_2 of less than 80 torr (room air) 48 hours after admission, and failure of PEFR to increase by at least 40 L/min after 6 hours of intensive therapy [11, 131]. During the course of treatment the adequacy of the patient's response to the therapeutic program should be determined by frequent clinical and laboratory assessments, including arterial blood gases and pH. Because status asthmaticus is a life-threatening disease and the clinical deterioration can be precipitous, an aggressive management is best conducted in an intensive care unit with continuous cardiopulmonary monitoring and attentive medical and nursing observation around the clock.

OXYGEN. The marked gas exchange disturbances resulting from impaired ventilation-perfusion relationships, right-to-left intrapulmonary shunting, and alveolar hypoventilation, if present, make hypoxemia a universal finding in severe asthma. Extreme hypoxia induces a variety of adverse sequelae including pulmonary hypertension and impairment of myocardial, cerebral, and other vital organ functions and has been implicated in sudden deaths in asthma. *Thus, arterial oxygen tensions sufficient to provide adequate tissue oxygenation must be maintained continuously from the outset in all patients.*

It should be stressed, however, that the arterial oxygen tension does not in itself provide a direct assessment of the adequacy of tissue oxygenation. Blood hemoglobin concentration and its oxygen affinity, cardiac output, and tissue perfusion significantly influence oxygen delivery. Clinical evaluation of individual organs (e.g., brain, heart, kidneys) may afford some indication of the adequacy of their oxygenation, provided consideration is given to other toxic, metabolic, inflammatory, and infectious factors. Elevation of blood lactate concentration may be utilized as an index of tissue hypoxia, but its value may be limited by its late occurrence. Despite certain limitations, mixed venous oxygen tension ($P\bar{v}O_2$) or saturation ($S\bar{v}O_2$) is commonly employed to assess overall tissue oxygenation. While a very low $S\bar{v}O_2$ probably reflects impaired tissue oxygenation, a normal value does not assure that vital organs are being adequately oxygenated [136]. Hence, a constellation of clinical and laboratory findings in addition to PaO_2 should be employed to assess the effectiveness of tissue oxygenation in status asthmaticus. Provided that red blood cell mass, P_{50}, cardiac output, and tissue perfusion are sufficient to meet tissue demands, a PaO_2 of 80 to 100 torr provides a margin of safety from the potentially adverse hypoxic effects of suctioning and of bronchodilator drugs [88]. In many instances this level is achieved easily with inspired oxygen concentrations of 30 to 50 percent, delivered by nasal cannula, face mask, or mechanical ventilator. Since oxygen sources are absolutely dry, supplemental humidification should be provided to minimize bronchial irritation and secretional desiccation. Higher oxygen concentrations are needed in the presence of large right-to-left shunts, as may occur with extensive airways secretions or atelectasis. The proper use of therapeutic oxygen requires periodic determination of arterial blood gases, a need that is not supplanted by spirometry or clinical observations.

Oxygen-induced suppression of ventilatory drive is seldom encountered in acute asthma [168, 278].

However, caution should be exercised in administering oxygen to patients with chronic or evolving hypercapnia, coexisting metabolic alkalosis, or inappropriate sedative use. In such cases low-flow oxygen delivery by nasal cannula or controlled delivery by Venturi mask may permit alleviation of arterial hypoxemia without marked increases in $PaCO_2$. Inability to provide or maintain adequate oxygenation because of ventilatory suppression is an indication for mechanical ventilation. Extracorporeal membrane oxygenation (ECMO) has been successfully employed in a patient with status asthmaticus and refractory respiratory failure unresponsive to the usual forms of therapy [164].

Inhalation of low-density mixtures of helium and oxygen has been employed in the treatment of status asthmaticus in an attempt to decrease airflow resistance and thereby increase flow rates and reduce the work of breathing. These advantages, however, depend on the site of obstruction within the airways, which is variable in asthma [57]. Thus, the efficacy and practicability of helium use in status asthmaticus remain to be fully delineated.

BRONCHODILATOR AGENTS. Bronchodilator drugs are fundamental in management and should be administered at once. Their primary effect is upon a labile or reversible bronchial smooth muscle contraction, with presumably little action on the inflammatory processes and secretions, which are more fixed and slower to resolve. The relative contribution of these inflammatory and secretory elements varies from case to case, a difference that should be appreciated in evaluating therapeutic effectiveness [133]. Although experimental evidence indicates that both methylxanthines and beta adrenergics are capable of enhancing mucociliary clearance [83, 270, 282], the clinical significance of that effect is presently unclear. In addition, aminophylline has been shown to improve the contractility of the diaphragm and to render it less susceptible to fatigue, actions that may contribute to its therapeutic efficacy [4].

The evaluation of bronchodilator response in status asthmaticus includes assessments of clinical improvement and changes in spirometry, PEFR, arterial blood gases, and pH. However, by definition immediate responses are precluded, and the effectiveness of such drugs is deduced from studies in the stable state and less severe stages of disease. Responses may also be influenced by drug complications, such as induced hypoxemia or, less commonly, a delayed bronchoconstrictive effect from isoproterenol, which can contribute to refractory obstruction [141]. *Thus, bronchodilator drugs must be properly prescribed with established effective dosage schedules and the patient observed for both benefits and adverse effects.*

Theoretical considerations and in vitro studies [154, 271] suggest that methylxanthines and beta agonists may act synergistically on bronchial smooth muscle; however, most clinical studies of such combined therapy have failed to demonstrate synergy either in stable [107, 252, 302] or in acute asthma [70, 72, 135, 235]. Indeed, several studies showed no significant difference in expiratory flow rates between patients who received combined therapy and those treated with a beta-adrenergic agent alone [72, 107, 135, 252]. The latter findings seem to indicate that in many asthmatics the bronchodilating effect of a potent beta-adrenergic agonist is sufficiently great alone that little additional benefit is derived from the addition of a methylxanthine [72]. However, as none of the cited studies was limited to patients with status asthmaticus, the same conclusions may not apply to such patients, especially in the presence of beta-adrenergic subsensitivity or in patients with the most severe airways obstruction. Rossing et al. [235] found that combined therapy with intravenous aminophylline and either subcutaneous epinephrine or inhaled isoproterenol improved FEV_1 more than did epinephrine alone and that the advantage of combined therapy was most apparent in patients with the most severe airways obstruction ($FEV_1 < 1.0$ liter). At present it would appear that both classes of bronchodilator drugs are indicated in the treatment of status asthmaticus.

METHYLXANTHINES. Aminophylline, the ethylenediamine salt of theophylline, contains 79 to 87 percent anhydrous theophylline by weight. It is a potent, rapidly acting, and relatively long-acting bronchodilator drug with an average half-life of 312 ± 84 minutes in normal adults. Its primary advantage is its presumptive continued activity despite epinephrine fastness.

In severe asthma aminophylline is administered intravenously as a loading dose followed by a continuous infusion. Dosage recommendations are provided in the introductory section of this chapter, and further details are found in Chapter 56. In order to avoid the acute toxicity resulting from high local concentrations, the drug should never be given by rapid intravenous injection and should be infused into a peripheral vein and never into a centrally placed venous catheter. Because of their uncertain absorption, oral or rectal preparations are not indicated in status asthmaticus.

The plasma concentration of theophylline should be maintained in the therapeutic range of 10 to 20 μg/ml, although some bronchodilation is achieved at levels as low as 5 μg/ml [184]. When the plasma concentration exceeds 20 μg/ml, some patients begin to experience adverse effects including anxiety, headache, anorexia, nausea, vomiting, and diarrhea. At higher plasma levels cardiac arrhythmias, seizures, and death may occur and may not be preceded by any of the milder side effects, thus making serial monitoring of plasma theophylline concentration mandatory [310]. It must be emphasized that patients vary considerably in their tolerance to the drug.

Few well-designed studies of methylxanthine therapy in status asthmaticus have been published. Jackson et al. [129] were able to correlate sympto-

matic response and improvement in pulmonary function tests with serum theophylline concentrations after a single dose of an oral theophylline preparation in patients that had acute exacerbations of asthma. Nicholson and Chick demonstrated that the bronchodilator effect of intravenous aminophylline had a direct relationship to the whole blood theophylline concentration within the range of 2.0 to 8.0 μg/ml [190]. In a double-blind, placebo-controlled trial of intravenous aminophylline in children hospitalized for status asthmaticus, an aminophylline-treated group had a greater increase in FEV_1 and FVC after 1 and 24 hours of treatment compared with a control group [218]. Adults treated for acute exacerbations of either asthma or chronic obstructive pulmonary disease with a high-dose continuous intravenous aminophylline infusion (mean serum concentration 19.0 μg/ml) demonstrated a greater improvement in FEV_1 and FVC and required a shorter duration of aminophylline therapy than those who received a low-dose infusion (mean serum concentration 9.7 μg/ml) [280].

Parenteral aminophylline in doses sufficient to maintain a therapeutic plasma concentration should be administered throughout the treatment period of status asthmaticus. Studies in patients not in status asthmaticus indicate that tolerance to theophylline apparently does not develop with prolonged use [15]. Finally, oral therapy is resumed once the patient is clinically stable.

SYMPATHOMIMETIC DRUGS. Adrenergic bronchodilator agents are available for administration orally, subcutaneously, intravenously, and by aerosol inhalation from metered-dose inhaler or nebulizer. The optimal route of administration in treating status asthmaticus remains controversial, reflecting the competing therapeutic goals of rapidity of onset, efficacy, ease of administration, and avoidance of adverse effects.

Aerosol inhalation has the advantages of a rapid onset, prolonged action, and minimal side effects. The metered-dose inhaler (MDI) delivers a small dose of drug per inhalation, and its use requires careful attention to the technique of administration [251], which may be difficult in patients with severe respiratory distress. Those limitations may be overcome by the use of the compressor-driven nebulizer, in which drug delivery is less dependent on a controlled breathing pattern and the more prolonged administration permits delivery of a larger total dose. However, as with the MDI, drug distribution and delivery to distal airways may be limited by airways secretions and obstruction. Isoetharine, a short-acting, relatively $beta_2$-selective catecholamine, may be administered by nebulizer every 2 to 4 hours in a dose of 0.25 to 0.5 ml of a 1% solution diluted 1:3 with saline. Metaproterenol, which has a longer duration of action, is given every 4 hours in a dose of 0.2 to 0.3 ml of a 5% solution diluted in 2.5 ml of saline. A solution of salbutamol for administration by nebulizer is available in other countries but not in the United States.

The use of intermittent positive pressure breathing (IPPB) for the administration of bronchodilator drugs to patients with acute severe asthma is controversial. Webber et al. [285] found only marginal benefit, and two randomized crossover studies [28, 76] found no advantage in the use of IPPB rather than simple nebulization to deliver salbutamol to patients with acute severe asthma. Furthermore, IPPB therapy has been associated with the occurrence of fatal pneumothorax in patients with severe asthma [137, 138]. Despite those observations, the administration of a bronchodilator by IPPB may be justified in selected patients, particularly those with very severe airways obstruction who cannot take a deep enough breath to derive full benefit from a simple nebulizer, although scientific evidence to support such use is lacking. The role of IPPB in asthma is discussed further by Stein and Gelbard [266] and in Chapter 76.

The subcutaneous route of administration delivers adrenergic agents systemically to obstructed bronchi and combines the advantage of an onset of action nearly as rapid as that of intravenous therapy with the disadvantage of a high potential for side effects. In the initial therapy of acute asthma, aqueous epinephrine 1:1000 (adult dose, 0.3 ml) may be administered subcutaneously and repeated once or twice at 30-minute intervals; if there is no response, it should be discontinued. Epinephrine has potent alpha, $beta_1$, and $beta_2$ effects, and in the presence of beta-adrenergic receptor blockade its alpha-adrenergic effect could theoretically intensify bronchospasm. In general, epinephrine should not be employed in the elderly and in patients with hypertension, cardiovascular disease, or marked tachycardia. In one study of acute asthma three 0.3-ml doses of epinephrine given subcutaneously at 20-minute intervals (total dose = 0.9 mg) was as effective a bronchodilator as a total of 0.96 mg of epinephrine given by metered-dose inhaler at 10-minute intervals over 50 minutes. However, the subcutaneously administered drug was more effective in patients with severe airways obstruction (PEFR $\leq$ 120 liters/min) but was associated with a higher incidence of palpitations and tremulousness [219]. Terbutaline, which is more $beta_2$-selective and has a longer duration of action than epinephrine, may be administered subcutaneously to adults in a dose of 0.25 mg, repeated after 15 to 30 minutes if necessary (maximum dose, 0.5 mg every 4 hours). Pang et al. [205] obtained a good clinical response to subcutaneous terbutaline in 9 of 10 children in status asthmaticus who were refractory to subcutaneous epinephrine and intravenous aminophylline. In another study of subcutaneous adrenergic therapy in acute asthma, 1 mg of terbutaline produced equivalent bronchodilatation to 0.5 mg of epinephrine, but terbutaline, despite its reputed $beta_2$ selectivity, caused a substantially greater increase in heart rate [258].

The intravenous route for adrenergic drug administration provides rapid onset of action but is accompanied by a high rate of adverse effects,

especially tremor and tachycardia. The use of a continuous intravenous infusion of isoproterenol in patients with impending respiratory failure resulting from status asthmaticus has been suggested as a means of gaining time, during which bronchodilator and corticosteroid therapy may become sufficiently effective to avert intubation and mechanical ventilation [144]. Seventeen of 19 children with status asthmaticus and hypercapnic respiratory failure responded with a fall in $PaCO_2$ to 48 torr or less following continuous intravenous infusion of isoproterenol in doses ranging from 0.08 to 2.7 μg/kg/min [303]. The treatment was accompanied by significant increases in pulse rate, and one child developed ventricular tachycardia. In another study a favorable response was observed in 27 of 34 children in status asthmaticus who were treated with intravenous isoproterenol when their $PaCO_2$ exceeded 40 torr despite conventional therapy [207]. Intravenous isoproterenol did not appear to reduce the proportion of such patients who required mechanical ventilation but was felt to have decreased the duration of severe respiratory distress. Complications included rebound bronchospasm upon sudden interruption of the infusion as well as one episode of nodal tachycardia and two instances of adverse effects resulting from acute mobilization of copious secretions. In seven adult asthmatics not in status asthmaticus who received an intravenous infusion of isoproterenol, maximal dose-dependent bronchodilatation occurred within 2 to 5 minutes, accompanied by prompt relief of dyspnea and a decrease in PaO_2 [144]. Thus, use of intravenous isoproterenol requires concomitant oxygen administration and continuous electrocardiographic monitoring for arrhythmias or signs of myocardial ischemia [173]. In addition, patients receiving such therapy must be carefully observed to determine whether airways obstruction and gas exchange are improving satisfactorily and complications are not developing.

Based upon current information, *intravenous isoproterenol should be reserved for use in children and young adults and should not be employed in any patient with a history of cardiac disease*. The cardiotoxicity of isoproterenol may be enhanced by severe hypoxia and possibly by concurrent administration of aminophylline [43, 134]. In addition, animal studies suggest potentiation of isoproterenol cardiotoxicity by pretreatment with corticosteroids [106].

The method employed by Wood et al. [303] for administering intravenous isoproterenol to children in status asthmaticus is as follows:

1. Continuous electrocardiographic monitoring is begun and a radial artery is cannulated for continuous arterial pressure monitoring and periodic sampling of arterial blood.
2. Isoproterenol, diluted to a concentration of 4 to 12 μg/ml, depending upon the size of the child, is administered intravenously by infusion pump at a starting dose of 0.1 μg/kg/min.
3. The dose is increased stepwise at 10- to 15-minute intervals in increments of 0.1 μg/kg/min until the heart rate approaches 200 beats/min or until the $PaCO_2$ and clinical status begin to improve.
4. Arterial blood gases are determined every 15 to 30 minutes during the early phase of therapy and then at 2- to 4-hour intervals after a satisfactory response has been achieved.

During this procedure hypoxemia must be corrected and a margin of safety in PaO_2 provided before starting the infusion of isoproterenol, since this drug may induce worsening of hypoxemia. Adrenergic aerosols should be discontinued during the intravenous isoproterenol therapy. If concurrent intravenous aminophylline is continued, close monitoring of plasma theophylline levels is necessary because of the potential for enhanced toxicity with use of isoproterenol and aminophylline. When a satisfactory clinical and blood gas response has occurred, the isoproterenol dose may be decreased by 0.1 μg/kg/min at 1-hour intervals. Here, clinical status and $PaCO_2$ should be monitored carefully, since bronchospasm can intensify if the drug is withdrawn too rapidly [113].

Intravenous salbutamol (not presently available in the U.S.) has been studied extensively in status asthmaticus (see Chap. 55). Fitchett et al. [80] treated 11 patients in status asthmaticus with 100 to 300 μg of salbutamol given by bolus injection and found a mean increase in PEFR of 44 percent at 5 minutes and 34 percent at 40 minutes. The pulse rate rose transiently by a mean of 22 beats per minute; there were no significant changes in arterial blood gases. In another study of acute severe asthma no difference was observed in response measured by airflow rates and arterial blood gases in patients treated with either 900 μg intravenous salbutamol or 10 mg salbutamol by nebulizer, both administered over 45 minutes [153]. Mean pulse rate rose in the intravenously treated group and fell in the nebulizer group; among nine patients treated intravenously, two had no subjective improvement, and two others had adverse effects requiring abandonment of the trial. In another study 500 μg of salbutamol, given intravenously by infusion over 1 hour, increased PEFR at least as much as 500 mg of aminophylline in patients with severe asthma and had a lower incidence of side effects [299]. Comparing intravenous and aerosol salbutamol, Williams and Seaton [298] found that only 2 of 10 patients in status asthmaticus responded to 5 mg of salbutamol given by IPPB, but 9 of 10 responded to a subsequent 200-μg intravenous dose of salbutamol. Responsiveness to the aerosol drug was restored in all patients after 1 to 3 days of corticosteroid therapy. The onset of responsiveness to the aerosol corresponded closely with the beginning of sputum production, suggesting that secretional airways obstruction inhibited the response to aerosol but not to intravenous salbutamol. These studies illustrate the efficacy of intravenous salbutamol and support the impression that it may be a useful adjunct in the treatment of

status asthmaticus, particularly since at appropriate doses it appears to have less cardiotoxicity than isoproterenol [48].

OTHER BRONCHODILATORS. The antimuscarinic agents atropine and ipratropium bromide are effective bronchodilators, with a predominant effect on central airways [112, 126]. In children with stable asthma, bronchodilatation was sustained for 5 hours after treatment with nebulized atropine sulfate, 0.1 mg/kg; all patients experienced dryness of the mouth [31]. Ipratropium bromide, a quarternary ammonium derivative of atropine (not currently available in the U.S.), is administered by metered-dose inhaler or nebulizer. The drug is poorly absorbed through the gastrointestinal tract, has minimal systemic antimuscarinic effects, and, unlike atropine, does not impair mucociliary clearance [211]. Its action is additive to that of $beta_2$ stimulants and theophylline [146, 157]. In 28 patients with acute asthma 500 μg of nebulized ipratropium bromide was as effective as 10 mg of nebulized salbutamol, and the two drugs given in sequence 2 hours apart produced greater bronchodilatation than either used alone [284]. Currently, further studies are necessary to clarify the role of antimuscarinic drugs in status asthmaticus (see Chap. 63). Antihistamines have little documented effect and may be detrimental because of a desiccant action on secretions; they cannot be generally recommended.

Halothane anesthesia has been administered to patients with status asthmaticus who were unresponsive to other therapy [97, 201]. Halothane has potent bronchodilator properties and does not stimulate respiratory secretions, but its use is limited by its side effects: myocardial depression, arrhythmias, and increase in intrapulmonary right-to-left shunting. We do not feel rectal ether has any role in this disorder.

CORTICOSTEROIDS. Corticosteroids are widely used in the treatment of status asthmaticus, although their exact mechanism(s), optimal dosing, and end points are not fully clarified. Chapter 57 reviews the rationale for their use in asthma in general. The controlled trials of the British Medical Research Council [175] as well as considerable clinical experience established the presumed advantages of glucocorticoids in life-threatening asthma. The specific target cells and mechanisms of action of glucocorticosteroids in asthma are uncertain; known effects that may contribute to their action include antiinflammatory properties, alteration in immunologic mechanisms, and effects on chemical mediators, catecholamines, and adrenergic function [46]. One effect of corticosteroids that may be of particular importance in status asthmaticus is their potentiation of the bronchodilator response to exogenous (and presumably endogenous) catecholamines [249]. In addition, Ellul-Micallef and Fenech [69] observed a restoration of responsiveness to inhaled isoproterenol after a single intravenous injection of 40 mg of prednisolone in 8 of 10 stable chronic asthmatics who were previously unresponsive to catecholamines.

However, the concept that corticosteroids are essential in acute severe asthma has recently been challenged in studies involving both children and adults. Pierson et al. [217] treated 54 children hospitalized with status asthmaticus and unresponsive to subcutaneous epinephrine with either placebo or one of three intravenous corticosteroid drugs. All children received bronchodilators and supportive therapy. There were no significant differences in the first 24 hours of therapy between the placebo and steroid groups with respect to clinical score, FEV_1 improvement, and $PaCO_2$. The steroid-treated patients had a significantly greater increase in PaO_2 after 24 hours of therapy than the placebo group, suggesting that steroids had a beneficial effect other than by relief of large airways obstruction. In another study of 19 children not on chronic steroid therapy who were hospitalized with status asthmaticus, Kattan et al. [140] found no difference in clinical score, PEFR, and response to inhaled salbutamol and intravenous aminophylline during 36 hours of treatment with or without intravenous hydrocortisone, 7 mg/kg every 6 hours. Changes in PaO_2 were not reported. In these children, therefore, corticosteroids did not increase the rate of recovery from status asthmaticus nor was there an increased responsiveness to aminophylline and salbutamol.

Two studies of corticosteroid effect in adults with acute asthma showed no significant effect on PEFR [45] or on lung mechanics [166] up to 6 hours after a single intravenous dose of hydrocortisone. In contrast, another study of 20 adult patients hospitalized with acute asthma and unresponsive to 8 hours of intensive bronchodilator therapy demonstrated that treatment with intravenous hydrocortisone (2 mg/kg bolus, then 0.5 mg/kg/h for 24 h) resulted in a greater resolution of airways obstruction than placebo treatment [73]. In the steroid-treated group there was a delay of at least 6 hours before airways obstruction began to remit; at 24 hours FEV_1 had improved significantly by 118 percent in the steroid group versus 36 percent with placebo ($p < .025$). PaO_2 did not change in either group. Similarly, in a study of oral corticosteroid therapy in adult patients with asthma, improvement in FEV_1 did not occur until after at least 6 hours of therapy, and maximal improvement required at least 6 days of therapy [249]. Hence, the available data suggest that the response to corticosteroids in asthma may be delayed for 6 hours or longer after the start of therapy.

In another trial Luksza [161] evaluated the use of corticosteroids in 90 adult patients hospitalized with acute severe asthma as follows: no corticosteroids, 400 mg intravenous hydrocortisone daily, or 1200 mg intravenous hydrocortisone daily. No obvious differences in recovery rate (measured by PEFR, symptoms, or heart rate) were found among the three groups. He concluded that corticosteroids are ineffective once severe asthma is established. Of interest is the observation that 53 percent of the

patients had not received corticosteroids before being hospitalized, suggesting that the patient at risk was not being identified early enough for corticosteroid therapy to be initiated and become effective before the attack of asthma became serious or life-threatening. Overall, the above-cited studies suggest a need for further controlled trials of corticosteroids in acute severe asthma. However, Grant [101] believes such trials to be unethical in view of prior available data.

At present, it would appear that once bronchodilator refractoriness is established, corticosteroids should be administered immediately, even though their effects may not be manifested for 6 hours or more. The risks associated with short courses of corticosteroids are small; on the other hand, failure to treat with steroids or to employ an adequate dose has been implicated in asthma deaths [21, 41, 162, 200]. Corticosteroid therapy should be initiated without delay in patients currently or recently on maintenance steroids and in patients with a history of similar attacks requiring steroids for lysis.

While the dose of corticosteroids necessary to achieve a therapeutic response in status asthmaticus has not been firmly established, some studies have addressed this issue. For example, Britton et al. [22] treated patients with acute severe asthma unresponsive to their usual medications including inhaled salbutamol with one of three corticosteroid regimens providing a total dose equivalent to 36.2, 61.2, or 175.5 mg per kilogram of hydrocortisone over 10 days. The rate of recovery, indexed by PEFR, FEV_1, and pulse rate, was generally not different among the three groups, and no advantage of using high-dose corticosteroids was observed. In another study of 10 adults in status asthmaticus no difference was found in the rate or magnitude of spirometric improvement after 7 days of treatment with bronchodilators plus either 20 or 125 mg of methylprednisolone intravenously every 6 hours [275]. In contrast, Haskell et al. [108] randomized adult patients with status asthmaticus to a dose of either 15, 40, or 125 mg of intravenous methylprednisolone every 6 hours for 3 days in addition to bronchodilators. They found that the medium and high-dose groups had an earlier and greater improvement in FEV_1 than the low-dose group and furthermore that patients receiving the 125-mg dose every 6 hours improved slightly faster than those treated with 40 mg every 6 hours.

We prefer to treat with intravenous methylprednisolone sodium succinate, which has a negligible mineralocorticoid effect, in doses of 100 to 200 mg initially, followed by 50 to 100 mg every 6 hours for the first 24 to 48 hours. Thereafter, 50 to 100 mg may be given every 8 to 12 hours until definite resolution has begun. Alternatively, a regimen of intravenous hydrocortisone hemisuccinate, beginning with a loading dose of 4 mg/kg body weight and continued with doses of 3 mg/kg every 3 hours or with a continuous infusion delivering 3 mg/kg over 6-hour periods, may be employed. Patients with steroid resistance may require considerably higher doses. *The proper dosage is one that is clinically effective*, and this effect must be estimated by clinical and physiologic end points (including FVC and FEV_1) and by biologic effectiveness. Total eosinophil counts may be utilized as an added guide. In general, effective steroid dosages will yield values of $100/mm^3$ or less within 24 to 36 hours; higher counts may indicate a need for increased steroid dosages.

Concerning the method of corticosteroid administration, Collins et al. [44] found that the total daily dose of hydrocortisone required to attain a given plasma cortisol level was less when given by continuous intravenous infusion compared with intermittent infusion. However, the available data at present do not clearly indicate any advantage of either mode of administration in status asthmaticus. Although plasma cortisol levels are low in some patients admitted to the hospital with status asthmaticus, such levels do not correlate with the severity of the attack as measured by pulse rate, FEV_1, or PaO_2, nor with the total dose of corticosteroid required for treatment [32]. In practice, the usefulness of plasma cortisol levels in management is limited. The use of ACTH is not recommended because of the uncertainty of adrenal cortical responsiveness; however, Collins et al. [44] observed that patients with acute asthma who were not previously on steroid therapy responded well to daily depot tetracosactrin.

When clinical improvement is sustained, steroids can be gradually tapered by approximately 50 to 70 mg prednisone a day or by about 25 percent every 2 or 3 days. For those not previously on chronic therapy the drug can be lowered to 15 to 20 mg prednisone daily, then to alternate days, and finally discontinued. During this process, steroid doses are best titrated against clinical symptoms and signs and spirometric-physiologic values. Any relapse may require a temporary increase in dosage. Patients previously on alternate-day schedules are tapered to their previous maintenance levels (see Chap. 57) and/or to their effective aerosol steroid dosage schedule. Finally, evaluation of hypothalamic-pituitary-adrenal axis function may be conducted during remissions to identify liabilities in anticipation of such stresses as surgery or exacerbations of asthma. The use of simple ACTH stimulation and other tests is described in Chapter 58.

Complications of brief, high-dose corticosteroid therapy appear to be minimal [217]; for a full discussion see Chapter 57. In light of the apparent association of corticosteroid therapy and peptic ulceration [177], antacids should generally be administered, titrating the dose to a gastric pH above 3.5. Acute psychotic reactions and other mental changes may occur and must be distinguished from abnormalities related to hypoxia or alterations in pH. Sodium and fluid retention and particularly hypokalemia following large doses of corticosteroids require monitoring and correction; hypokalemic alkalosis with muscle weakness and hypoventilation is an unnecessary complication. Nosocomial infection is a serious concern, especially in the intubated

mechanically ventilated patient. Fatal disseminated aspergillosis has been reported in a patient treated for status asthmaticus with mechanical ventilation and a brief course of high-dose corticosteroids [150]. The use of meticulous aseptic techniques during tracheal suctioning, frequent changing of ventilator tubing [47], and periodic culturing of sputum and tracheal aspirates are indicated in all patients, especially those at higher risk from the concurrent use of corticosteroids. Accelerated corticosteroid metabolism in patients treated with phenobarbital or phenytoin may require an increase in corticosteroid dosage until clinical resolution occurs.

ANTIMICROBIAL AGENTS. The frequency of bacterial respiratory tract infections as a cause of acute exacerbations of asthma has probably been exaggerated in the past, resulting in an overuse of antimicrobial therapy. However, numerous respiratory tract viruses are associated with exacerbations of asthma, and are implicated in a higher proportion of exacerbations in children than in adults. In three studies in children a viral or a mycoplasmal infection was found in from 32 to 42 percent of exacerbations of asthma [12, 169, 181]. Among 63 adults hospitalized with severe asthma 19 percent of admissions were associated with a viral or mycoplasmal infection [123]. Hudgel et al. [122] found in 19 adult asthmatic patients that viral but not bacterial respiratory tract infections were increased during wheezing exacerbations; interestingly, these authors noted that both viral and bacterial infections could occur without inducing an exacerbation of asthma. Viral infection was present in 11 percent of exacerbations and bacterial infection in 9 percent. Similarly, Clarke [39] found evidence of bacterial or viral infection in only 10.8 percent of asthmatic exacerbations in adults. In another study transtracheal aspirates from adults with acute asthma did not yield significantly different bacterial or fungal growth from aspirates obtained from controls [13].

The routine administration of a broad-spectrum antibiotic in 44 children with status asthmaticus who did not have signs of bacterial infection was assessed in a double-blind protocol comparing hetacillin (which is hydrolyzed in vivo to ampicillin) with a placebo [247]. Since the hospital course, length of hospital stay, and complications were similar in the treated and control groups, the authors concluded that there was no obvious advantage of *routine* antibiotic therapy in such patients. A comparable study in 60 adults hospitalized with acute asthma and treated with either amoxicillin or placebo also disclosed no difference in the rate of improvement in symptoms, length of hospital stay, or pulmonary function at the time of discharge [100].

Thus, the available data do not support the use of antimicrobial agents in patients with status asthmaticus unless there is evidence of bacterial infection. The diagnosis of bacterial lower respiratory tract infection in status asthmaticus may be difficult. Large numbers of eosinophils may impart a purulent appearance to the sputum. While eosinophils cannot be distinguished from neutrophils on a sputum Gram stain, a wet mount or Wright stain does permit correct identification. Infiltrates on the chest radiograph may be caused by mucoid impaction and atelectasis rather than pneumonia, and leukocytosis may be present in status asthmaticus without infection. The diagnosis of bacterial infection is supported by the presence of large numbers of neutrophils in the sputum, especially when accompanied by one or two types of bacteria in heavy concentration, and by fever, chills, increased numbers of immature neutrophils in the peripheral blood, or a compatible chest radiograph. Antimicrobial therapy should be based initially on the suspected pathogens and later modified according to the results of drug susceptibility studies of pathogens isolated from sputum or blood.

HYDRATION AND SPUTUM MOBILIZATION. In status asthmaticus hyperpnea, diaphoresis, fever, and reduced fluid intake may contribute to systemic dehydration. The severity of the fluid deficit may vary considerably and is difficult to assess clinically, since many of the signs of dehydration (e.g., dry mouth, tachycardia, reduced jugular venous pressure) are found during acute asthma in patients who are in normal fluid balance. As in any dehydrated patient, correction of systemic fluid deficits is indicated in order to restore normal cardiovascular and cellular function. Although adequate systemic hydration is also thought to have a beneficial effect on respiratory tract secretions, evidence of such an effect is scanty [5, 37]. In mild asthma adequate hydration may be achieved orally, but in status asthmaticus the intravenous route is preferred to assure a sufficient intake. Fluid therapy should be guided by the estimated state of hydration and the initial serum electrolyte concentrations and modified thereafter as clinically required. Careful observations of fluid intake and output, body weight, and serum and urine sodium concentrations will aid in fluid management and early recognition of fluid retention in susceptible patients (children, the elderly, and those with underlying cardiac disease). Stalcup and Mellins [263] have expressed concern that excess fluid administration combined with the markedly negative intrapleural pressures in severe asthma may enhance fluid accumulation in the lung.

Straub et al. [269] observed a variable degree of hypovolemia in nine patients during status asthmaticus. Four patients experienced a rise in pulse rate and fall in blood pressure at the time of relief of airways obstruction. Infusion of 500 to 1500 ml of plasma led to immediate circulatory improvement. The authors speculated that a combination of hypovolemia and vasodilation in response to hyperventilation may result in circulatory collapse, which in turn may contribute to some of the unexpected deaths in asthmatics. Elevated plasma antidiuretic hormone (ADH) levels have been found in some patients with status asthmaticus during the acute phase; they returned to normal with resolu-

tion of the attack [7]. Administration of hypotonic fluids to such patients could result in water intoxication.

Since airways secretions are a major factor in precipitating, intensifying, or perpetuating the acute asthmatic state, mobilization of secretions is vital. Under normal conditions inspired air is warmed and saturated with water vapor in the upper respiratory tract and major airways. If this mechanism is impaired or if the upper airway is bypassed by the use of a tracheal tube, it is possible that secretions may desiccate and become thickened, tenacious, and thus more difficult to raise. In addition, mucociliary clearance may be impaired, further favoring secretional stasis. Therapeutic oxygen, if not properly humidified, can contribute to such desiccation; unheated bubble humidifiers produce only 20 percent of the required humidification.

Humidification devices and mist therapy are commonly employed to assist in the mobilization of bronchial secretions. Clinical experience suggests that those measures may be beneficial in selected cases; nevertheless, there is limited evidence to indicate that airways humidification by currently employed devices has any effect on mucociliary clearance in asthma (see Chap. 64). Studies of the effect of ambient humidity on the viscosity of sputum in vitro have yielded conflicting results [63, 231]. Although aerosols of water or hypertonic saline have been reported to increase clearance of secretions in patients with chronic bronchitis [203, 212], evidence of their efficacy in asthma is presently inconclusive [283]. Furthermore, ultrasonic nebulization of distilled water or saline solutions can induce bronchospasm and may not be tolerated by patients during acute asthma [35, 244].

Mucolytic agents, such as acetylcysteine, reduce the viscosity of sputum in vitro. However, aerosol administration of acetylcysteine in asthmatics induces bronchospasm and worsens hypoxemia [14, 224] and therefore is not generally recommended. Direct intrabronchial instillation of a mixture of 3.0 to 5.0 ml of 10 percent acetylcysteine with 0.25 ml of 1:200 isoproterenol through a tracheal tube or bronchoscope followed by suctioning can be effective in removing mucoid impactions [61]. The role of fiberoptic bronchoscopy and bronchial lavage is discussed in Chapter 77.

The efficacy of expectorant drugs, such as iodides and guaifenesin, has not been convincingly demonstrated in asthma (see Chap. 64). Antitussives should be avoided, as their action is contrary to the goal of sputum removal. Once coughing becomes productive, physical measures such as chest percussion and postural drainage can be of value, although there is some evidence that they may induce bronchospasm [27] and worsening of hypoxemia [124]. Chest physiotherapy, accompanied by supplemental oxygen and preceded by aerosol bronchodilator therapy, should be continued if sputum production is enhanced and bronchospasm is not exacerbated.

ACID-BASE CONSIDERATIONS. The most common acid-base disturbance in status asthmaticus is respiratory alkalosis caused by hyperventilation; it is treated by relief of the underlying asthma. Metabolic acidosis stems from overproduction or impaired clearance of lactic acid [2] or from complicating metabolic conditions such as ketoacidosis. Metabolic alkalosis may result from intravascular volume depletion, from potassium and chloride deficiency owing to vomiting, gastric suction, diuretics, or corticosteroids, or from the administration of bicarbonate. Alkalosis can depress ventilation, decrease cardiac output, induce ventilation-perfusion mismatching, and lower the seizure threshold and should be corrected by appropriate replacement of electrolytes and intravascular volume or by alleviation of the primary cause.

The most serious acid-base disturbance in status asthmaticus is respiratory acidosis resulting from progressive hypercapnia; it may be complicated by a metabolic (lactic) acidosis in severe hypoxemic status asthmaticus. Because of the rapidity with which hypercapnic respiratory failure may develop, compensation by renal mechanisms may be inadequate, and severe degrees of acidemia can be seen. The definitive treatment of hypercapnic respiratory failure unresponsive to conservative measures is mechanical ventilation, the indications for which are discussed below. If the degree of acidemia is severe (pH $\lesssim$ 7.15) and especially if there is a delay in instituting mechanical ventilation or if cardiac or respiratory arrest has occurred, 45 to 90 mEq of sodium bicarbonate (in children, 1 mEq/kg) may be infused slowly over 10 to 20 minutes, the required dose titrated to a blood pH of about 7.25. It should be noted, however, that little increase in blood pH will occur unless the carbon dioxide produced from the infused bicarbonate can be eliminated by the lungs [202] and that bicarbonate infusion in acute asthma may result in a fall in PaO_2, presumably by increasing the perfusion of underventilated lung regions [180]. Acid-base relationships in severe asthma are depicted in Figure 68-6.

SEDATIVES. Fear, restlessness, and agitation frequently accompany the acute asthma attack and may prompt the physician to administer sedative drugs. Sedated patients, however, impart a false sense of security to themselves and to the physician, as physiologic derangements may continue to worsen without evoking the usual intensity of symptoms. Equally important is the depression of ventilatory drive that various sedatives can induce. In normal subjects hypoxic and hypercapnic ventilatory responses were depressed by moderate doses of morphine [286], meperidine [147], and diazepam [151, 223]. Other adverse effects of sedative agents are their tendency to suppress cough, thereby impairing the removal of bronchial secretions, and the enhanced metabolism and consequent reduced effectiveness of corticosteroids when given to patients receiving barbiturates [23].

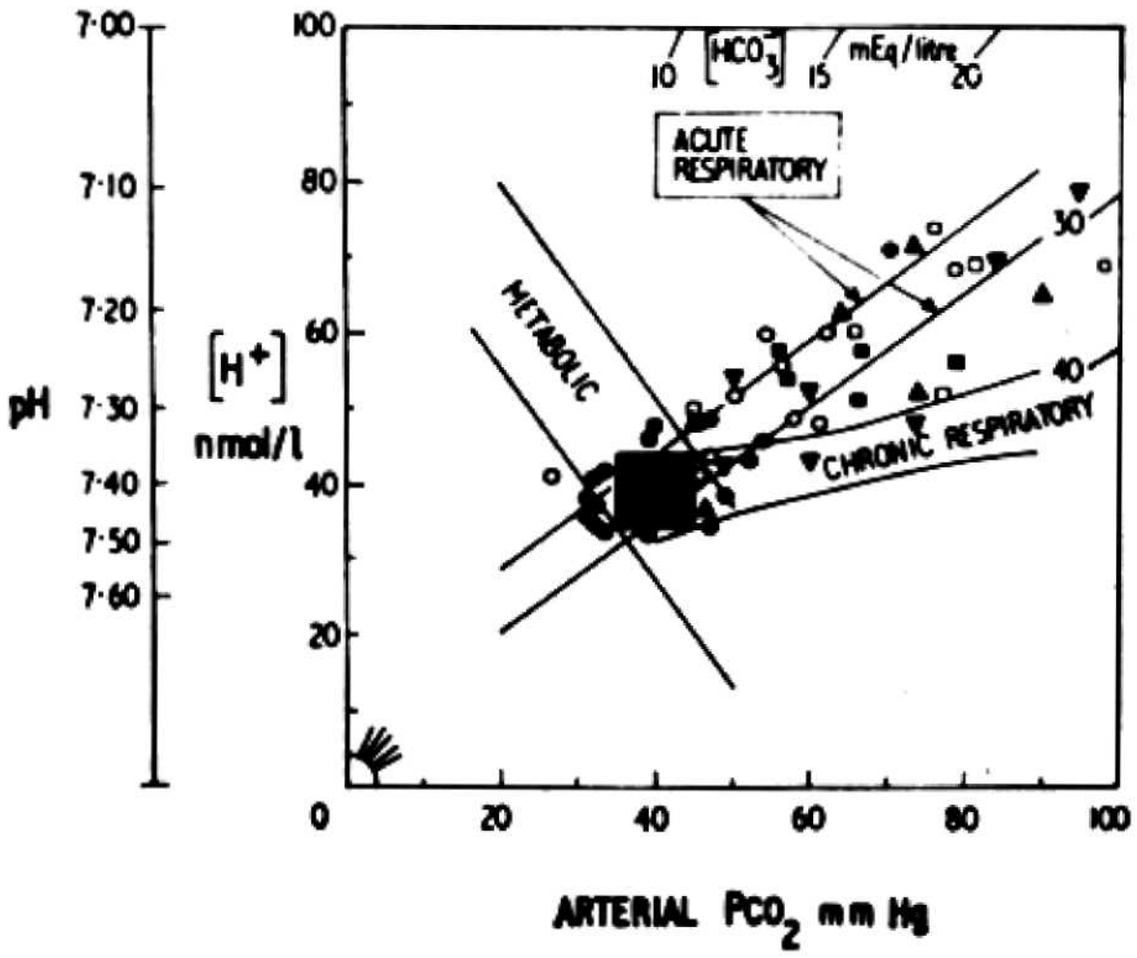

Figure 68-6. *Acid-base relationships in severe asthma. Closed symbols are from adults, open symbols from children in various series of severe asthma. Ninety-five percent confidence limits of these relationships in pure metabolic acid-base disturbances and in acute and chronic respiratory disturbances are shown. (Reprinted with permission from D. C. Flenley, Blood gas tensions in severe asthma.* Proc. R. Soc. Med. *64:1149, 1971.)*

Sedative use has been identified as a risk factor for respiratory failure with the attendant morbidity of mechanical ventilation in status asthmaticus [170, 246, 272, 293] and has been cited as contributing to asthma deaths [24, 66, 188].

There is no evidence that sedative or tranquilizing drugs reverse the pathophysiologic features of status asthmaticus. In view of their depressant effect on ventilation and their other adverse effects *sedatives should not be used in status asthmaticus* except in patients who are receiving mechanical ventilation. The patient's anxiety should be allayed by calm and repeated reassurance offered by the physician and other medical attendants and by prompt efficient application of therapeutic and supportive measures. Faling [71] has recently reviewed this subject in detail.

THE AIRWAY. Maintenance of a patent airway at all times is essential in management. Patients who are unable to mobilize secretions adequately or who are obtunded, comatose, or in respiratory failure need immediate tracheal intubation. An oral or nasal tracheal tube should be inserted as soon as this need is determined and sufficiently early in the course to avoid the complications associated with emergency intubation. Anxious dyspneic patients are often difficult to intubate and may struggle during the process, with resulting aggravation of bronchospasm. Hence, intubation should be performed deftly and expeditiously, with care taken to preoxygenate the patient and to avoid the complication of gastric aspiration [240]. The use of a low-pressure cuff with the minimal cuff pressure necessary to occlude the airway, proper positioning of the tube, avoidance of undue torsional stresses, gentle, aseptic suctioning technique, and meticulous nursing care are necessary to minimize the complications of intubation. Since tracheal intubation in asthma is seldom necessary for more than a few days, tracheostomy can usually be avoided.

MECHANICAL VENTILATION. Mechanical ventilation is indicated when the patient's ventilatory efforts are insufficient to maintain adequate gas exchange. Concurrently, controlled oxygen therapy and suctioning of secretions can be accomplished through the cuffed tracheal tube. Ventilatory failure can be detected by a rise in $PaCO_2$ and can be anticipated by the clinical observation of a marked increase in respiratory effort, a common precursor of fatigue. Since, as we have stressed, $PaCO_2$ is usually reduced during acute asthma, a $PaCO_2$ level at or above the normal range is cause for concern. A steadily rising $PaCO_2$, especially during optimal therapy and when accompanied by incipient or overt respiratory muscle fatigue, is the major indication for mechanical ventilation. Both premature and delayed intubations have their respective hazards. The exact point at which to institute mechanical ventilatory support is determined on the basis of careful longitudinal clinical and gas exchange assessments, observing trends rather than relying on rigid criteria.

From a variety of clinical reports it appears that only a small proportion of patients require mechanical ventilation for status asthmaticus. For example, ventilator therapy was instituted in 21 of 811 patients (2.6%) admitted to Colorado General Hospital for status asthmaticus from 1967 to 1975 [246] and in 16 percent of 111 patients admitted to a respiratory intensive care unit in Los Angeles with status asthmaticus from 1968 to 1977 [242]. In both these series a decline in recent years was noted in the number of asthmatic patients requiring mechanical ventilation. Presumably, early and aggressive therapy can reduce the requirement for mechanical ventilation in some patients. Patients with evolving hypercapnia may be admitted to an intensive care unit for aggressive therapy where facilities for intubation, ventilation, and monitoring may be more readily available.

When frank ventilatory failure occurs or is imminent despite the intensive therapy described previously, continuous ventilation is imperative. Clinical guidelines, although suggestive, are not reliable or quantitative indexes of effective alveolar ventilation, and hypercapnia in acute asthma bears a poor correlation with spirometry until far-advanced obstruction exists. These observations reemphasize the need for measurements of $PaCO_2$ and pH for proof of ventilatory failure. The following are *guidelines* for ventilatory support in status asthmaticus:

1. Respiratory arrest—apnea.
2. Rising $PaCO_2$ greater than 40 to 50 torr, with ob-

vious patient distress, despite complete and aggressive therapy. A rise in $PaCO_2$ of 5 to 10 torr per hour or more is a poor prognostic sign when associated with acute respiratory (and lactic) acidosis.

3. Absolute $PaCO_2$ of 50 to 55 torr or more, with acute respiratory acidosis (pH ≤ 7.20).
4. Refractory hypoxemia despite oxygen administration; or oxygen-induced suppression of ventilation.
5. Other physiologic data (confirm with blood gases):
   a. Vital capacity less than 10 ml/kg.
   b. FEV_1 less than 1.0 liter.
   c. V_D/V_T of 0.6 or more (limited value).

These physiologic and clinical observations should obviate emergency ventilator intervention as a desperate, hasty decision. Even though presentation in an advanced or near terminal state can occur in some instances, in most circumstances mechanical ventilation can be introduced at an appropriate point in a deteriorating patient.

Because airways resistance is high and often quite variable in status asthmaticus, a volume-cycled ventilator capable of generating high peak inspiratory pressures (> 50–60 cm H_2O) should be employed. Practical aspects of mechanical ventilation and the features of some of the commonly employed ventilators were recently reviewed by Bone and Stober [19]. Initial ventilator settings must take into account the large inspiratory airways resistance and obstruction to expiration and in adults may include a rate of 12 to 15 breaths/min, tidal volume 10 to 15 ml/kg, inspiration to expiration (I:E) ratio of 1:3, and FIO_2 of 0.5, with subsequent adjustments made according to serial arterial blood gas values. Some patients may be ventilated effectively and comfortably with the use of assisted ventilation (patient-initiated breaths). Ventilator adjustments, such as changes in inspiratory flow rate, I:E ratio, or tidal volume, may be necessary for patient comfort and ventilator efficacy. A low inspiratory flow rate has the advantages of permitting a more homogeneous distribution of inspired gas and reducing the pressure necessary to deliver a given tidal volume; avoiding high tidal volumes will also decrease the ventilator pressures. Expiratory time should be sufficient to permit adequate exhalation through markedly obstructed airways. These requirements can sometimes be met only by ventilation at a lower rate than the patient's spontaneous respiratory rate and therefore necessitate the use of controlled ventilation. Additional indications for sedation and controlled ventilation include confusion, anxiety, inordinate tachypnea, and the inability to coordinate with the ventilator. Controlled ventilation eliminates excessive respiratory work, reduces metabolic demands, and relieves respiratory muscle fatigue while providing time for other therapeutic measures to reverse the acute airways obstructive processes.

Diazepam, in an initial adult dose of 5 to 10 mg intravenously, may be given to achieve the desired degree of sedation, with additional small doses administered as required. Although the use of either morphine sulfate or meperidine may be limited by their histamine-releasing properties, the clinical significance of that effect is unclear [17, 306]. If sedation alone does not result in adequate control of ventilation, respiratory muscle paralysis may be induced by a neuromuscular-blocking drug such as pancuronium bromide, in an initial dose of 0.04 mg/kg, repeated if necessary in 5 minutes. Subsequent dosage must be individualized on the basis of response. Prior administration of inhalational anesthetics or succinylcholine may increase the intensity and duration of action of pancuronium. Neonates are especially sensitive to pancuronium and should first be given a test dose of 0.02 mg/kg to assess response. Pancuronium is superior to *d*-tubocurarine or gallamine in that it has no histamine-releasing properties and no significant effects on heart rate and blood pressure [155]. However, simultaneous administration of pancuronium and aminophylline may cause serious arrhythmias [10]. In any use of neuromuscular blocking agents prior sedation of the patient is highly desirable. An adequate, secure airway is mandatory. The requirement for additional dosing may be reduced once effective controlled ventilation is achieved.

The technique of intermittent mandatory ventilation (IMV) has gained wide acceptance as a form of mechanical ventilation and has been alleged to reduce weaning time, prevent asynchronous breathing, decrease oxygen consumption, maintain respiratory muscle function and coordination, minimize the adverse cardiovascular effects of positive pressure ventilation, and decrease ventilator-related complications. However, the data supporting such claims are inconclusive [160], and controlled studies evaluating the role of IMV as a mode of ventilation and weaning technique have not been performed in patients with status asthmaticus. Similarly, the importance of nutritional factors and the indications, if any, for high-frequency ventilation, positive end-expiratory pressure (PEEP), and continuous positive airway pressure (CPAP) in the management of patients with ventilatory failure in status asthmaticus remain to be delineated. Recently, the use of high-level PEEP (17–25 cm H_2O) was reported to have reduced the markedly elevated peak airway pressures and gross overinflation of the lungs in two moribund patients receiving mechanical ventilation for status asthmaticus [221]. A study in eight asthmatic subjects with histamine-induced bronchospasm indicated that the application of CPAP (mean 12 cm H_2O) increased ventilation, decreased inspiratory work per liter of ventilation while increasing expiratory work, and improved the efficiency of the inspiratory muscles [172]. The relevance of those findings to the treatment of respiratory failure in status asthmaticus remains to be determined.

Arterial blood gas tensions should be determined 20 to 30 minutes after every change in ventilator

settings. Hypercapnia should be gradually reduced by 5 to 10 torr per hour in order to prevent the emergence of post hypercapnic alkalemia resulting from a prior compensatory (or complicating) metabolic alkalosis. Throughout the period of mechanical ventilation efforts to mobilize and eliminate bronchial secretions must be continued. If secretions are very viscid or inspissated, tracheal instillation of sterile saline or a mucolytic agent such as N-acetylcysteine, administered with a bronchodilator as previously described, or performance of bronchial lavage, as outlined in Chapter 77, may be considered [289]. As airways obstruction is relieved in response to therapy, improvement will be observed as a progressive decrease in the peak inspiratory airway pressure to less than 30 cm H_2O. Full monitoring of all vital physiologic and ventilator parameters is important during the period of mechanical ventilatory support.

Once resolution of the asthmatic process is evident by clinical and laboratory assessments, weaning from mechanical ventilation can begin. Criteria for the decision to discontinue mechanical ventilation include an alveolar-arterial PO_2 difference measured at $FIO_2 = 1.0$ of less than 300 to 350 torr or an adequate PaO_2 at FIO_2 of 0.4 or less; a vital capacity of at least 10 to 15 ml/kg of body weight; a normal range $PaCO_2$ in association with a minute ventilation of less than 10 liters/min; and the ability to generate an inspiratory negative pressure numerically greater than -30 cm H_2O [74, 239]. Clinical findings must support these data. Hence, obvious improvement in auscultatory findings, the very important observation of mobilization of secretions, and resolution of obvious contributing factors (e.g., pneumonia, atelectasis, heart failure) should exist.

Most patients can be successfully weaned from mechanical ventilation when the above criteria are met. Difficulty in weaning may be encountered in patients with respiratory muscle weakness resulting from prolonged mechanical ventilation, a deficiency in total body potassium or phosphate, or continued use of neuromuscular-blocking drugs. Ventilatory drive may be reduced by metabolic alkalosis or by the lingering effects of sedatives. Some patients develop a psychological dependence on the ventilator; in such cases weaning may be facilitated by the use of intermittent mandatory ventilation. When mechanical ventilation has been discontinued, the adequacy of ventilation should be assessed during several hours of spontaneous breathing before extubation.

Complications of mechanical ventilation in status asthmaticus include pulmonary barotrauma, impairment in cardiac output, and infection in addition to a variety of ventilator and tracheal tube malfunctions encountered during mechanical ventilation (Table 68-8). The incidence of barotrauma, including pneumothorax, pneumomediastinum, and subcutaneous emphysema, is increased by the high peak inspiratory airway pressures that are often necessary to ventilate patients with severe asthma [215]. Tension pneumothorax may be manifested by a sudden increase in respiratory distress, cyanosis, and absence of breath sounds on chest auscultation. It must be immediately recognized and relieved by insertion of a large-bore needle or chest tube into the pleural space. In a series of 21 episodes of mechanical ventilation for status asthmaticus, pneumothorax occurred in 33 percent and was associated with decreased survival [246]. In that study pneumothorax, pneumonia, alveolar hypoventilation, tracheal tube malfunction, and ventilator failure occurred at a higher rate during mechanical ventilation in patients with status asthmaticus than in patients receiving mechanical ventilation for other causes (Fig. 68-7). A recently proposed strategy for reducing the high peak inflation pressures during mechanical ventilation for status asthmaticus combines the infusion of large doses of sodium bicarbonate with mechanical ventilation at a lower tidal volume and respiratory rate [176]. This approach maintains a physiologic pH (despite elevation of $PaCO_2$) while reducing peak inflation pressure.

The increase in mean intrathoracic pressure resulting from high airway pressures may impair systemic venous return and cause cardiac output to fall. The problem may be aggravated by hypovolemia and by the use of drugs that increase venous capacitance, such as morphine and diazepam, and can be minimized by maintaining an adequate intravascular fluid volume and by shortening the inspiratory phase of ventilation.

Table 68-8. *Complications of Assisted Ventilation*

Complications attributable to intubation and extubation
Prolonged intubation attempt
Intubation of right mainstem bronchus
Premature extubation
Self-extubation
Complications associated with endotracheal/tracheostomy tubes
Tube malfunction
Nasal necrosis
Complications attributable to operation of the ventilator
Machine failure
Alarm failure
Alarm found off
Inadequate nebulization or humidification
Overheating of inspired air
Medical complications occurring during assisted ventilation
Alveolar hypoventilation
Alveolar hyperventilation
Massive gastric distention
Pneumothorax
Atelectasis
Pneumonia
Hypotension

Source: C. W. Zwillich, et al., Complications of assisted ventilation: A prospective study of 354 consecutive episodes. *Am. J. Med.* 57:161, 1974. Reprinted with permission.

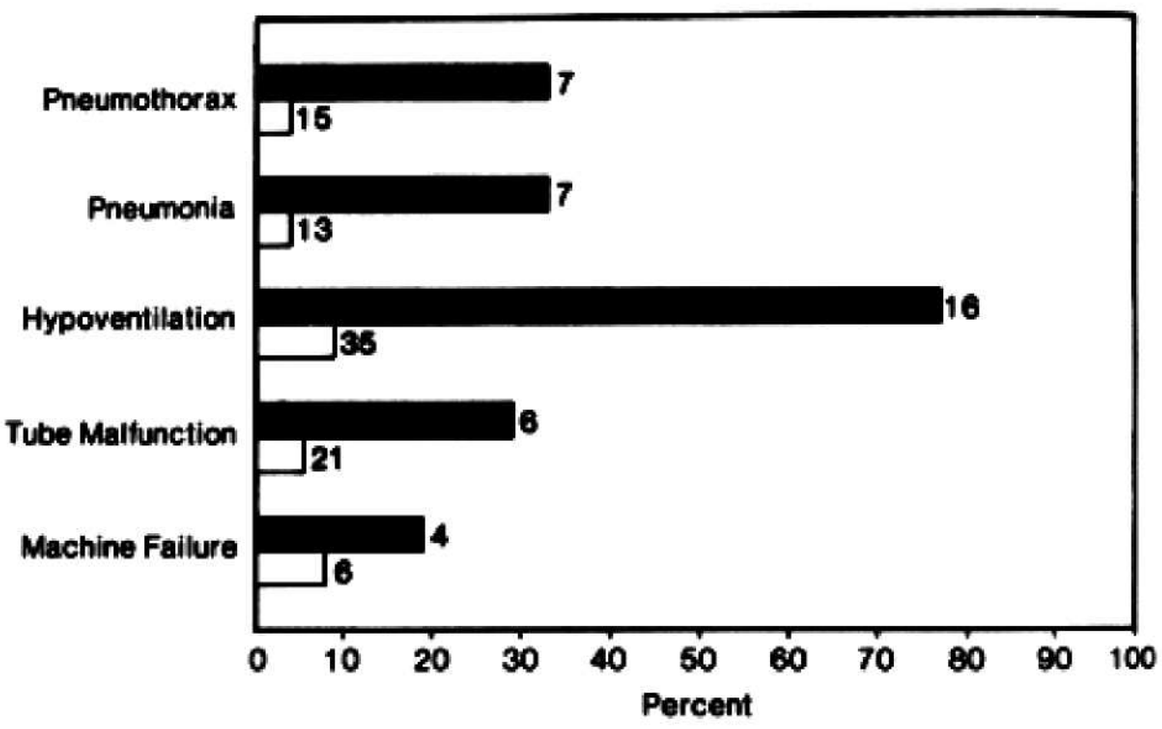

Figure 68-7. *Significantly increased ($p < .05$) occurrence of specific complications during mechanical ventilation in 21 patients with status asthmaticus* (black bars), *compared with rates in 354 patients receiving mechanical ventilation for all other causes* (white bars). *Data from C. W. Zwillich et al. [309]. (Reprinted with permission from C. H. Scoggin, S. A. Sahn, and T. L. Petty, Status asthmaticus: A nine-year experience.* JAMA *238:1158, 1977. Copyright 1977, American Medical Association.)*

The incidence of nosocomial respiratory tract infections in intubated and mechanically ventilated patients may be reduced by careful attention to proper technique during airway care and suctioning and by changing ventilator tubing every 48 hours [47]. Prophylactic antimicrobial therapy is not indicated and may, in fact, predispose to infection with resistant bacteria.

Considering the gravity of the attendant pathophysiologic changes, the survival rate in status asthmaticus complicated by ventilatory failure is rather good. An aggregate short-term survival rate of 87 percent was achieved in 10 published series comprising 206 adults treated with mechanical ventilation for status asthmaticus (Table 68-9).

Since only an occasional patient with severe asthma requires intubation and supportive mechanical ventilation, the identification of such high-risk asthma patients could provide clues to preventing this problem. Accordingly, Westerman et al. [293] analyzed their retrospective experiences with 39 patients requiring mechanical ventilation for status asthmaticus. The following features were identified as risk factors: patient delay in seeking medical attention, incomplete medical assessment, inadequate preadmission use of corticosteroids, and sedative abuse. Follow-up of the survivors of this study also indicated that clinical patterns characterized by significantly labile asthma or chronic deterioration in airways obstruction were associated with an increased risk of sudden death from asthma. A major point to be stressed from this and other studies [84, 163] is that patients must be educated by the physician to seek early medical attention for all acute episodes failing to respond to the usual therapy. It is hoped that this will substantially decrease the need for mechanical ventilation with its attendant morbidity.

Table 68-9. *Short-Term Survival in Status Asthmaticus Supported with Mechanical Ventilation*

Date	Reference	Percent Survival
1966	170	79
1966	183	100
1967	232	82
1968	272	100
1968	297	89
1969	125	86
1972	248	91
1977	246	62
1979	293	90
1980	242	100

AFTER-CRISIS CARE. Once the acute asthmatic attack is controlled, all possible contributing causes must be investigated and a proper program of symptomatic control established. The long-term goal is to eliminate offending causes and to minimize recurrences. The establishment of an effective relationship between patient and physician is an important aspect of management. The knowledge that advice and care are readily available in the event of an emergency provides the patient with a strong measure of reassurance. Patients should be informed of the nature of the problem and the purposes and risks of therapy. It should be stressed that the long-term prognosis is good (see Chap. 82).

Patients may manifest a variety of reactions to the experience of status asthmaticus. As with other life-threatening crises, recollection of the episode may evoke anxiety, even terror. This response may influence the patient's perception of the severity of later asthmatic attacks, thereby influencing medication usage and the frequency of rehospitalization [52, 58, 59]. In contrast, other patients adopt denial as a defense mechanism; by minimizing their symptoms they may permit a subsequent attack to intensify without seeking appropriate medical attention [59] (see Chap. 78). Both of these responses are maladaptive and require patient education and counseling to emphasize that asthma can be well controlled with optimal management and to encourage a realistic perception of the disease. At the same time, there is no place for complacency in the management of these patients, as there is no reliable guide for predicting their course. Throughout management, it is mandatory that careful observations support a rational therapeutic program.

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