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Pneumonia: Treatment and Prognosis

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Oxygen

The concentration of oxygen in the atmosphere has not changed since the turn of the century, and currently predictions are for it to remain constant for the foreseeable future. It does not, however, satisfy the needs of patients with pneumonia. The therapeutic potential of supplemental oxygen was immediately apparent to Priestly when he and his "volunteer" mice experienced the "high" of inspiring the "dephlogisticated air" he discovered 200 years ago. Following a dinner conversation shortly thereafter, Lavoisier subsequently elaborated on his colleague's findings. He demonstrated its uptake in the lungs and its respiratory function with the resultant carbon dioxide production. It was not until 1798, however, after a lapse of 25 years when Thomas Beddoes opened his Pneumatic Institute at Bristol, that the therapeutic potential of oxygen was pursued for a variety of ailments including lung disease. This spa (as well as the residential hotels established for hyperbaric oxygen therapy 150 years later), unfortunately did not prove to be a financially viable endeavor and could not be sustained on its scientific merit alone.

It was not until World War I, When oxygen was used to treat victims of gas poisoning, that it became an acceptable mode of therapy. Over the next 40 years high inspired concentrations of oxygen became firmly established as an essential component of therapeutic stratagems for management of patients with acute cardiopulmonary disease. The subsequent two decades witnessed the concept of high flow-controlled oxygen concentration therapy, which became a routine modification in treatment and, most recently, long-term domiciliary oxygen therapy for hypoxemic patients with chronic lung disease. Controlled studies showing improved survival have confirmed the anticipated benefits of continuous oxygen therapy in such patients. Their clinical response was characterized by increased exercise tolerance, reduction of pulmonary vascular resistance and pulmonary artery pressure, improved cardiac output, and improved neuropsychological function. Similar data regarding the use of oxygen for

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acute lung disease (pneumonia or otherwise), however, is not so readily available. Even the proclaimed benefit from its continuous administration in ambulatory patients with obstructive lung disease has been questioned and attributed not to enhanced oxygenation but to cessation of smoking.

Administration

It was the introduction of the technique of radial artery puncture that allowed assessment of arterial oxygenation in pneumonia.[1] Until this study of the cyanosis associated with pneumonia, only its relation to the saturation of venous blood had been analyzed, which of course made interpretation difficult. The arterial unsaturation (difference between oxygen content and total oxygen capacity) was found to be a valuable prognostic indicator, with fatal cases usually having an arterial saturation of less than 80% and nonfatal cases of greater than 80%.[1] Similarly, the observation was reported that in fatal cases of pneumonia the mean value of the venous unsaturation was 20% higher than in the nonfatal cases. The mechanism of cyanosis was correctly attributed to venous admixture or "incomplete oxygenation of the blood as it passes through the pulmonary capillaries or the passage of but part of the blood thru [*sic*] the lungs (as in congenital heart disease)."[1] Barach and Woodell, Stadie, and Meakins starting during the 1920s instituted the clinical use of oxygen,[2–4] and its value as a therapeutic agent, though initially debated, was subsequently firmly established.[5] It was administered by mask, in an oxygen chamber, and in a ventilated oxygen tent; and each mode was reported to provide a 40–50% inspired oxygen concentration. The arterial hypoxemia was relieved along with the associated cyanosis, dyspnea, tachycardia, restlessness, and delirium; and the life of the pneumonia patients was reported to be prolonged by this therapeutic intervention. The lower mortality rate was attributed to the additional time afforded for the patient to develop an immunity to the causative agent of the pneumonia by the avoidance of fatal hypoxemia.[6] Oxygen administration allowed limited compensation by the body's other organ systems for the lungs' diminution in redundancy resulting from pneumonia.

The development of high-pressure cylinders was stimulated by introduction of the ventilated oxygen tent, the double nasal catheter, and subsequently the double nasal cannula to treat moderately severe hypoxia necessitating a larger oxygen reservoir. The question of dosage considered critical to the administration of pharmacologic agents so as to provide the full therapeutic effect as well as to avoid toxicity is fully applicable but frequently ignored during the administration of oxygen. The observation that along with enhanced oxygenation there was an increase in the patients' carbon dioxide content[6] led to the suggestion that oxygen enrichment with alleviation of the hypoxic drive may depress ventilation.[7] This observation resulted in evolution of the concept of "controlled' oxygen

therapy and led to the widespread practice of inappropriate administration of limited-flow high concentration (nasal cannula) or high-flow fixed inspired concentrations (Venturi masks) that frequently fail to achieve adequate levels of arterial oxygenation.[8]

It became readily apparent that physiologic concepts rather than controlled clinical data would have to serve as therapeutic guidelines, as withdrawal or withholding of oxygen therapy was immediately appreciated as ethically impossible. The benefits of oxygen therapy in the absence of cyanosis, confusion, and cardiovascular collapse are difficult to rationalize physiologically or to document clinically[9] (Table 8.1). Efficacy also depends on the adequacy of the other determinants of oxygen delivery—flow (cardiac output) and distribution—as well as oxygen binding capacity (hemoglobin concentration), the affinity of hemoglobin for oxygen, and finally the enigmatic actual oxygen uptake versus the need concept of pathologic supply dependence.

Availability

An aspect of oxygen transport unique to states of severe hypoxemia associated with dyspnea and alveolar hyperventilation such as pneumonia is the variable left shift in the oxygen dissociation curve caused by respiratory alkalosis. It was found to be an essential feature of effective oxygen transport in the Peruvian Andes and on the summit of Mt. Everest.[10] The advantage of an increase in oxygen affinity is thought to be analogous to the altered position of the oxygen dissociation curve of the blood in the placental circulation where fetal hemoglobin has a higher affinity for oxygen than does maternal hemoglobin, protecting the fetal "arterial" saturation. This adaptation during pneumonia favors oxygen

TABLE 8.1. Effect of oxygen therapy on oxygenation.[a]

Measurement	$PvO_2 > 32$ mm Hg ($n = 12$)			$PvO_2 < 32$ mm Hg ($n = 10$)			
	Room air	O_2	p1	Room air	O_2	p2	p3
PaO_2 (mm Hg)	71.9	124.4	*	65.1	138.8	*	NS
SaO_2 (%)	92.2	95.4	*	87.2	96.9	*	NS
PvO_2 (mm Hg)	35.8	38.2	NS	28.9	34.2	*	*
SvO_2 (mm Hg)	64.1	68.1	NS	54.8	61.9	*	*
Q (L/min)	7.90	7.50	NS	6.30	5.70	NS	NS
$(a-v)O_2$ (ml/dl)	3.82	3.52	NS	4.18	4.40	NS	NS

p1, p2 = oxygen versus room air value within each PvO_2 group; p3 = room air values between groups; NS = $p > 0.05$.

[a]The effects of an enriched inspired oxygen concentration on mixed venous oxygenation: oxygen and hemodynamic profiles in 22 critically ill patients according to the severity of tissue hypoxia.[9] Apparent benefit appears to be due to increased CaO_2 with unpredictable changes in mixed venous saturation.

*$p < 0.05$.

loading in the lungs rather than unloading in the tissues as an otherwise predicted increase in P_{50} would do. This situation stands in contrast to the effect of the reduced oxygen affinity observed under conditions of decreased carrying capacity when arterial oxygenation is adequate, such as with anemia, which serves to improve oxygen delivery to tissues. With other lung diseases as well, because of increased venous admixture from V/Q abnormalities, increased shunting and diffusion limitation of oxygen uptake in the lung, increased oxygen affinity seems appropriate to enhance uptake. Presumably, this advantage is not offset by the resulting impaired tissue unloading caused by excessively low venous PO_2, which reflects the driving pressure to cell mitochondria. Similarly, the benefits of the 2,3-diphosphoglycerate (2,3-DPG) effect for tissue oxygenation in the presence of normal lung function is not applicable in patients with pneumonia.

In addition, the "optimal hematocrit" for oxygen transport in the presence of disease must balance viscosity against oxygen-carrying capacity. In general, increased hematocrit resulting from dehydration increases the vascular resistance to flow, requiring increased blood pressure and left atrial filling pressure until a new homeostatic state is reached. Furthermore, "blood doping" with hypertransfusion is rheologically disadvantageous, leading to a decrease in cardiac output. Humans are unlike the Weddell seal, a mammal with the ability to breath-hold for an hour with a hemoglobin concentration of 27 g/dl. This phenomenon is made possible by maximal cerebral and coronary vasodilation of a magnitude capable of neutralizing the adverse affects of increased viscosity.

Tissue oxygenation utilizing classic parameters, still, even with disease, is a concept that appears simple enough. Difficulty with its application, however, arises immediately with the appreciation that heterogeneity of distribution to organs and to regions within a tissue exists normally and varies in addition as a function of physiologic stress, both normal and pathologic[11] (Table 8.2). It is further exaggerated in the pneumonic lung

TABLE 8.2. Proportion of basal blood flow and $\dot{V}O_2$ to organs in man.[a]

Organ	Blood flow (%)	$\dot{V}O_2$ (%)	COD
Mesenteric viscera	27	23	1.2
Kidney	25	9	2.8
Muscle	18	21	0.9
Brain	15	28	0.5
Heart	4	11	0.4
Other	11	8	1.4

[a] Distribution of blood flow as the percent of basal cardiac output (5.5 L/minute) and oxygen consumption as percent of basal metabolic rate (240 ml/O_2/minute). The ratio of oxygen delivery as reflected by blood flow to oxygen utilization is indicated by the utilization fraction, the coefficient of oxygen delivery (COD).[11]

owing to the reported increase in its metabolic rate caused by the inflammatory response.[12] The vast infiltration of metabolically active cells, particularly polymorphonuclear leukocytes (PMNs), significantly increases the organ's apparent oxygen consumption, found to be as much as 13–15% of whole-body VO_2 in the dog.[12] Moreover, this additional oxygen extraction increases the resulting arterial hypoxemia as well owing to the admixture of pulmonary or bronchial venous blood that is even more desaturated than pulmonary arterial blood.

Delivery

Metabolic inhomogeneity within organs exists normally and may be pathologically exaggerated with hypoxia when loci of critical oxygen pressures arise. In these tissues VO_2 depends on regional PO_2. Tissues such as the cerebral cortex contain regions that in the basal physiologic state operate near their critical PO_2 (approximately 20 mm Hg); the kidneys' medullary thick limb of the loop of Henle has a high metabolic rate of oxygen consumption and may be limited by oxygen availability. These compromised tissue beds are readily apparent by clinical and laboratory manifestations of cerebral (confusion) or renal ("prerenal") dysfunction. Thus it is recognition of the nature as well as the existence of tissue hypoxia that dictates appropriate therapy to increase oxygen delivery. Such therapy might include increasing the arterial oxygenation by increasing FIO_2; increasing the blood's oxygen-carrying capacity with transfusion; or increasing flow (cardiac output) directly with ionotropes or indirectly by influencing its distribution with selective vasoactive agents.

It can be shown mathematically that with severe arterial hypoxemia it is not possible physiologically by simply increasing the cardiac output to raise the oxygen delivery or coefficient of oxygen delivery to a level that prevents a fall in mixed venous oxygen saturation below normal.[11] Similarly, analogous with the critical shortening of pulmonary transit time in the lung, diffusion limitation may also exist at the tissue level, precluding the attainment of gas equilibration. Heterogeneity of capillary lengths (and therefore oxygen release time) impairs unloading; and the effluent blood from these capillaries constitutes a convective shunt (arterial admixture) and contributes to an "elevated" PvO_2. Such "impaired extraction" limits the value of mixed venous oxygen monitoring as a sensitive indicator of the adequacy of tissue oxygenation. Thus oxygen delivery is not synonymous with "oxygen availability" and tissue oxygenation.

Distribution

A further adaptation to hypoxic stress is relaxation of precapillary sphincters and recruitment of capillaries into the perfused network to

shorten the oxygen diffusion path. The recruitment of systemic capillaries brings transit times and rate of oxygen release into balance, similar to the autoregulatory phenomena that are effective in the lung with pneumonia to enhance pulmonary gas exchange in uninvolved areas. The movement of oxygen from capillary to cell is the final step in the oxygen delivery system. Although mitochondria require oxygen tensions of less than 3 mm Hg, a "critical" PO_2 is presumed to exist below which mitochondrial respiration is compromised. It would be affected not only by failure of the delivery system but by an up-regulation of the cells' "oxygen sink" as well (i.e., metabolic rate or tissue oxygen consumption).

When oxygen supply is limited relative to demand, flow is restricted to tissues with low oxygen extraction, such as kidney and mesenteric organs in favor of tissues with high extraction, such as heart and brain. Thus renal and mesenteric blood flow are diminished during exercise and arterial hypoxemia. Flow limitation to these "core" organs, because of impaired coronary or cerebral vessel patency, would defeat these homeostatic mechanisms. Hypoxia alone, in contrast to asphyxia, has a weak effect on the magnitude of splanchnic vasoconstriction and alteration in arterial pressure as a result of systemic vasoconstriction. It may be attributable to local unopposed "prejunctional" effects of adenosine and potassium. Accordingly, just as exercise with hypoxemia induces sympathetic adrenergic stimulation and the release of norepinephrine, the role of the associated release of inflammatory mediators, such as the prostenoids and cytokines in pneumonia patients appears to be critical to the redistribution of blood flow and oxygen availability to different tissue beds.

One report demonstrated an oxygen delivery-independent effect of blood flow on a canine model of diaphragm fatigue.[13] It was suggested that oxygen availability to contracting myocytes is more than the sum of the whole (i.e., a function of total muscle delivery). Such compensatory enhancement of membrane transport (permeability) and local microvascular control with alterations in venous PO_2 serve to maintain tissue oxygenation. In skeletal muscle such regional control is thought to depend on perfusion pressure rather than blood flow (i.e., a more homogeneous flow pattern may increase the proportion of flow directed through nutrient vessels) and the recruitment of new capillary channels, shortening the oxygen diffusion path. Furthermore, intraluminal pressure is a critical determinant, especially in pathologic states associated with increased interstitial pressure for sustaining a transmural pressure adequate to maintain vascular patency.

It is thus integration of a complex series of homeostatic reflex mechanisms and stress factors that is responsible for regional vasoconstriction and the overall conservation of oxygen for focused delivery to the organs most susceptible to hypoxia: brain and heart. Furthermore, intraorgan distribution appears to be a function of perfusion pressure interaction,

with metabolic and endothelial factors controlling the capillary surface area available for oxygen diffusion. Teleologically, the high-flow–low extraction areas of the circulation constitute an oxygen reserve system that may be called on at times of stress. If prolonged, signs of organ ischemia (e.g., renal, mesenteric, and muscle dysfunction) become apparent and are interpreted as stress bleeding, prerenal failure, non-infectious (ischemic) hepatitis, pancreatitis, and diaphragmatic fatigue.

Mechanical Ventilation

Modes of Ventilatory Support

Indications

The evolution of technologic advances in mechanical ventilation has not been accompanied by the necessary scientific support to establish their value. Patients with pneumonia, community-acquired or otherwise, who have respiratory failure with severe refractory hypoxemia are widely believed, on the basis of uncontrolled trials and anecdotal reports, to have increased survival with assisted ventilation. Clinical studies showing still greater advantages of newer ventilatory modes are similarly non-existent. The most apparent examples of these unsubstantiated benefits are the use of positive end-expiratory pressure (PEEP) in patients with acute lung injury syndrome (adult respiratory distress syndrome, or ARDS) and intermittent mandatory ventilation (IMV) and pressure support ventilation for weaning a patient from mechanical assistance. Proposed advantages of IMV over assisted ventilation include eliminating respiratory alkalosis, enhancing hemodynamics, and reducing weaning time, all of which are without substantial support. There is similarly no evidence for the value of PEEP in reducing the incidence of pulmonary oxygen toxicity and increasing survival of ARDS patients. The administration of PEEP has also not been found to be of value, as reflected by increased survival in one report of its use in bacterial pneumonia.[14] Studies have also failed to show the benefit initially reported for the prophylactic use of PEEP to avoid the development of ARDS in predisposing clinical states or to avoid atelectasis or pneumonia in postoperative patients.

Recruitment, Derecruitment, Hyperrecruitment

Therapeutic concepts of mechanical support are potentially in conflict in pneumonia patients, complicating the strategies of management if the acute inflammatory process is superimposed on underlying lung disease. The goal of increasing functional residual capacity (FRC) in ARDS patients runs counter to the ventilation goals for obstructive lung disease, as such volume recruitment contradicts the therapeutic concept of avoiding

further or diminishing existing gas trapping and dynamic hyperinflation. Dynamic hyperinflation occurs when insufficient expiratory time is allocated between tidal breathing cycles to reestablish the relaxed equilibrium position between the forces of chest wall expansion and lung recoil. In the nonpassive state increased work is required to halt flow and apply an increased negative inspiratory force with the inspiratory muscles, which because of hyperinflation are at a mechanical disadvantage in generating the pressure necessary to accomplish this work. Thus in the presence of airways obstruction, the peak inspiratory flow rate is maximized to prolong the expiratory time (T_E), whereas with the restrictive disease of pneumonia therapeutic reversal of the inspiratory and expiratory times (T_I/T_E) has been attempted to enhance gas exchange. The actual pattern of inspiratory gas flow is of little consequence for determining uniformity of gas distribution. Inspiratory time is the important factor, especially in the presence of a population of lung units exhibiting long time constants when prolongation of T_E is of importance in order to limit gas trapping.

The use of dual ventilators with a double-lumen endotracheal tube for differential (independent) lung ventilation remains a concept of continuing interest. Here again, although the personal clinical observations showing benefit are well reported, the overall advantages in terms of survival and decreased morbidity have not been substantiated. In the presence of asymmetric lung disease, as with unilateral pneumonia, the logic of treating each lung differently is apparent. Overdistension (hyperrecruitment) of the alveoli of the unaffected lung constricts the vascular elements in their septal walls, increasing vascular resistance, with the consequence of enhancing flow to the involved lung and increasing venous admixture. This gross difference of involvement with unilateral pneumonia is always obvious in lung units at the microscopic level in bilateral bronchopneumonia, and full recruitment with PEEP may be readily achieved, especially during the proliferative stage of ARDS and beyond, with minimal pressure requirement for aerodynamic strutting. Further increases in lung volume, then, tend only to reduce effective compliance, as with unselective inflation the less affected (more compliant) lung units and the chest wall approach their elastic limits. Determination of the best "recruitment" pressure is controversial in part because of the implied suggestion that it has a built-in factor presumed to reflect the number of alveoli being therapeutically recruited. The reality, rather than just the potential, for morbidity to result from barotrauma is becoming more appreciated.

Tracheal Intubation

The use of mechanical ventilation generally requires an endotracheal tube. Intubation, while reducing the normal 72-ml upper airway volume with a 15-ml endotracheal tube, also interjects a tube of 7.5–9.0 mm

internal diameter as a fixed inspiratory and expiratory resistor.[15] Tube resistance at low rates of laminar steady flow is inversely related to the fourth power of the radius and directly to its length. For high flow rates with increased ventilation, not only does the increased flow directly increase the pressure gradient required but when the Reynolds number is exceeded, which is the usual situation, turbulent flow results, further increasing the effective resistance. Bending of the tube and pooled secretions also serve to increase work. The potential advantages of a shorter orotracheal tube over a narrower nasotracheal tube is therefore apparent. However, with all the various determinants involved, there is little if any difference between an endotracheal tube and a tracheostomy tube despite the differences in length and radius. Intubation also serves only to retard the rate of return to FRC; it does not diminish the actual FRC, indicating that the widely held concept of "natural" PEEP is incorrect.[15] It should be expected, as observed not infrequently in the clinical setting, that extubation may allow successful weaning from machine support in certain intubated patients who otherwise would not have been predicted to be able to tolerate the breathing circuit independently.

Hemodynamics

Pulmonary Circulation

The hemodynamic consequences of spontaneous ventilation on "the pump within a pump" may frequently be enhancing, such as with spontaneous hyperventilation; but with mechanical ventilation they are primarily determined by alterations in lung volume and intrathoracic pressure. The pulmonary circulation consists of alveolar and interstitial vascular beds, each influencing the total pulmonary vascular resistance "independently"; but the effect of the alveolar vessels is predominant over the extraalveolar vessels. Lung inflation has a complex effect on pulmonary vascular resistance, as the small vascular elements in the alveolar septa are primarily influenced by alveolar pressure, and alveolar overdistension leads to their occlusion. At low lung volumes alveolar instability is promoted and collapse occurs, which is only in part attributable to the loss of interstitial traction forces. Alveolar vessels then become narrower as a result of alveolar wall collapse or an active process of hypoxic vasoconstriction. In the presence of an acute lung injury syndrome, however, dependence on maintenance of the integrity of such an interactive homeostatic autoregulatory control mechanism seems unlikely.

The extraalveolar vessels are larger, and their patency is a function of interstitial forces, a primary determinant of which is intrathoracic pressure (lung-vascular interdependence). The degree of radial interstitial traction on these vessels is also influenced by the actual lung volume, with the promotion of luminal narrowing and collapse at low lung volumes.

Thus deflating the lung has a complex effect on the pulmonary vascular resistance, which is minimal at normal FRC.

The bronchial vasculature is similarly highly sensitive to the effect of both lung inflation and airway pressure. Increases in bronchial vascular resistance are related to its primary drainage into the pulmonary capillaries and other vessels that connect the peribronchial arterial and submucosal vessels.[16] PEEP has been shown to eliminate virtually all bronchial blood flow, suggesting that patients with ARDS who have occlusive lesions of their pulmonary capillaries are at risk for additional tissue damage and lung infarction with the administration of PEEP.

Ventricular Function

An additional mechanical effect of lung volume is direct compression of the heart between the expanding lungs. The heart is in effect trapped in the cardiac fossa subject to the consequences of overdistension and mechanical heart–lung interaction. This situation may result in significant impairment of ventricular relaxation and filling (preload), especially in states of decreased ventricular "reserve." In patients being mechanically ventilated, the cardiac output, which primarily depends on venous return, may also be decreased as a result of the adverse effect on venous return of increased intrathoracic pressure. The venous return is further impaired with increases in lung volume, which raises pulmonary vascular resistance and the back-pressure to venous blood flow. Fluid resuscitation, preferably transfusion, is the usual means for enhancing venous return, and therefore the hemodynamic status must be carefully monitored with weaning for signs of acute circulatory overload.

The decrease in right ventricular transmural pressure resulting from the increases in intrathoracic pressure associated with positive-pressure lung inflation is unpredictable. It is attributable to the variable effect on juxtapericardial pressure that has been observed and the nonuniformity of its regional distribution over the surface of the heart—which in turn is related to the variety of factors responsible for transmission of the pressure. These factors include lung compliance and mediastinal compression[17] and a tethering effect of diaphragmatic descent on the pericardium,[18] as there are areas of pleural surface contiguous with the pericardium. Moreover, because of the sharing of a common interventricular wall and elastic pericardial compartment (sac) there is interdependence with the left ventricle. In addition, the right ventricular outflow is mechanically coupled to left ventricular inflow via the pulmonary circulation.[17]

Distension of the right ventricle therefore impairs left ventricular compliance and filling. Continuous positive-pressure breathing by increasing the left ventricular surface pressure, however, decreases the left ventricular afterload and may improve left ventricular performance. If this unloading effect is acutely eliminated by weaning, the patient with

borderline "reserve" may experience acute left heart failure as a result of the reinstitution of negative intrathoracic pressure. Further stress on a limited oxygen delivery system is caused by the redistribution of blood flow to a now working, if not overstressed, diaphragm in the presence of an increase in the work of breathing. Another mechanism of lung–heart interdependence exaggerated by ventilator management in the presence of pneumonia is attributable to the inhomogeneous distribution of pulmonary compliance, allowing the overdistended, more compliant lung units to compress juxtaposed alveolar vascular elements. This condition is associated with a decrease in pulmonary blood volume and the usual transfer of blood volume from the right to the left side of the circulation during inspiration being enhanced by positive pressure, with a resultant increase in left ventricular preload and cardiac output.[18]

Peripheral Circulation

Because most deaths associated with respiratory failure are nonpulmonary in nature, the effects of increases in intrathoracic pressure on cerebral, hepatic, renal, and splanchnic perfusion are of great significance[19] (Table 8.3). Increased airway pressure has been implicated as a significant factor responsible for the high incidence of hepatic dysfunction observed in patients treated with positive-pressure ventilation. In one report, 77% of patients had a serum bilirubin higher than 2.5 mg/dl.[20] Descent of the diaphragm increases intraabdominal pressure, in turn increasing portal vein pressure and decreasing portal venous flow. The observed increase in splanchnic resistance and decrease in splanchnic blood flow is directly proportional to the tidal volume with an associated decrease in oxygen delivery to the mesenteric organs. Thus adequate oxygenation depends on the varying abilities of the abdominal viscera to increase oxygen

TABLE 8.3. Effect of PEEP (10 cm H_2O) on distribution of blood flow in dogs.

Measurement or site	Blood flow (% of control)
Cardiac output	53
Mean artrial pressure	80
Heart rate	93
Kidney	55
Brain	106
Adrenal	62
Gastric	40
Liver	57
Pancreas	28
Bronchial	28
Coronary	60

Source: Modified from data of Cassidy and Schwiep.[19]

extraction. Continuous PEEP has, as would be expected, a much greater adverse effect on flow than an intermittent positive-pressure (IPPB) ventilatory mode.

Positive end-expiratory pressure is also associated with decreased urine output and salt and water retention as a result of the release of antidiuretic hormone (ADH) and alterations in the pattern of intrarenal perfusion. This reaction is characterized by weight gain, positive water balance, hyponatremia, and decreased hemoglobin concentration. The distribution of renal blood flow, rather than total renal blood flow, is primarily affected, with preservation of flow to the inner cortex and medullary zones (juxtamedullary nephrons) at the expense of flow to the outer cortex (cortical nephrons). This redistribution of blood flow exaggerates the normal nonhomogeneous distribution of intrarenal blood flow superimposed on nephron heterogeneity to result in renal dysfunction. The antidiuresis and antinatriuresis caused by PEEP may also be the result of a decrease in glomerular filtration rate, which is reversed with fluid administration, and a baroreflex-dependent mechanism that has been demonstrated in animals by its reversal with renal denervation.[19]

The decrease in splanchnic blood flow presumably predisposes to gastrointestinal bleeding from such well recognized entities as "stress" gastric ulcers and ischemic colitis. Another event that is a routine accompaniment of mechanical ventilation, even in the presence of a competent endotracheal tube cuff, is *meteorism*, commonly termed *aerophagia*. If excessive, the intraluminal pressure distends bowel loops to an extent that may be extensive enough to occlude the vascular elements in the bowel wall and cause ischemia in the bowel segments. It is also of interest to speculate on the hemodynamic effects of enteric feeding, as food intake normally increases mesenteric blood flow. Thus during weaning the postprandial increase in blood flow to the gastrointestinal tract may be of significance if it compromises diaphragmatic blood flow.

The increase in intrathoracic pressure acts to impede cerebral venous return, promoting an increase in intracerebral pressure. This tendency for impaired cardiac output and increased intracranial pressure results in a decrease in cerebral perfusion pressure. Thus increased tissue pressure, impeding inflow of a reduced cardiac output with blood having a decreased oxygen tension, sets the stage for cerebral dysfunction and a toxic metabolic encephalopathy due to cerebral hypoxia.

Ventilatory Monitoring

Arterial blood gas determinations remain the standard for respirator management. As with any parameter, it is the absolute value as well as the relative value that is of importance. The PaO_2 is compared to a norm or preceding result using the same or an interpolated PaO_2 for a varying

TABLE 8.4. Derived oxygen exchange indices.

Abbreviation	Index
Q_{Va}/Q_T	Venous admixture (any F_IO_2)
Q_s/Q_T	Shunt flow ($F_IO_2 = 1.0$)
$(A\text{-}a)D_O$	Alveolar-arterial oxygen gradient
PaO_2/PAO_2	Arterial/alveolar oxygen ratio
PaO_2/F_IO_2	Arterial/inspired oxygen ratio
$(A\text{-}a)DO_2/PaO_2$	Respiratory index

F_IO_2 from a nomogram. Other derived parameters of oxygen exchange have been suggested as well (Table 8.4), but PaO_2 remains the standard guide for tissue oxygenation and a reflection of the adequacy of pulmonary gas exchange. Tissue oxygenation is more closely reflected by $P\dot{V}O_2$ and $\dot{V}O_2$ as well as oxygen delivery. The sensitivities of these parameters are frequently seriously compromised and have been shown to be inadequate because of variabilities in the distribution of blood flow and the failure of the actual $\dot{V}O_2$ to be the required $\dot{V}O_2$ to meet the energy demands of all of the transport and metabolic processes of the body's organs. Similarly, arterial oxygenation cannot be equated with oxygen transport, as blood flow is frequently impaired by techniques used to enhance the PaO_2 (i.e., PEEP). When considering the adequacy of oxygen transport, the total hemoglobin concentration must also be closely monitored. Noninvasive and continuous methods to monitor arterial oxygenation (including pulse oximetry and transcutaneous blood gas measurements) have variable accuracy, undetermined clinical usefulness, and unproved savings for cost containment. The accuracy of such measurements of tissue oxygenation in critically ill patients is related to oxygen delivery[21] (Fig. 8.1).

The "amount of ventilator" required to achieve the level of oxygenation and ventilation ($PaCO_2$) desired has prognostic significance, especially if used in a monitored fashion. For a given tidal volume and inspiratory flow rate, the peak inspiratory pressure serves as a measure of the "effective dynamic compliance." With an "inspiratory hold" maneuver, the "plateau," or distending, pressure of the system at end-inflation reflects the static elastic recoil force. The greater the airway resistance, the lower is the dynamic compliance in comparison to the compliance measured at plateau pressure. Finally, the level of auto-PEEP may be determined at end-expiration, and the severity of dynamic hyperinflation and "gas trapping" may be monitored.

Weaning

The concept of partial ventilatory support for weaning from mechanical ventilation evolved from the desire to diminish the work of breathing

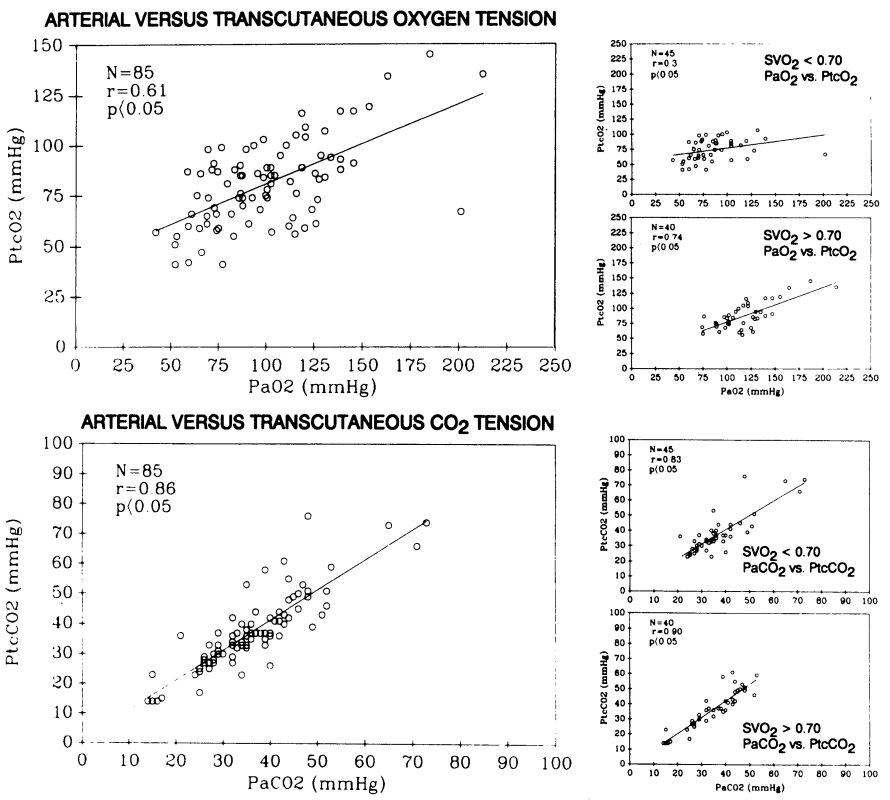

FIGURE 8.1. Transcutaneous (tc) oxygen and carbon dioxide measurements (n = 85) in 26 critically ill patients shown with simultaneous arterial blood gas values (39 on ventilator). Cardiac output and mixed venous blood gases were also determined, allowing calculation of oxygen delivery (OD) and measurement of SO_2. In group with SO_2 < 70% OD = 865 ml/minute and with SO_2 > 70% OD = 1035 ml/minute. (Data from Zaman et al.[21])

through the utilization of interactive modes. Such patient–ventilator interaction has the goal of amplifying patient effort to normalize its relation to ventilatory reward. In keeping with this thesis, yet another "weaning mode" has been described; termed proportional assist ventilation, the pressure delivered to the airway increases in proportion to inspiratory effort. Other noninvasive support techniques, such as nasal continuous and patient-triggered nasal intermittent positive-pressure ventilation, have been anecdotally reported to be successful.

Technical advances have not been shown to enhance weaning efforts and decrease the time required for assisted ventilation. Parameters usually monitored on "T-bar trials" include the tidal volume (V_T), respiratory frequency (f), minute ventilation (V_E), vital capacity (VC), maximum

voluntary ventilation (MVV), and maximum inspiratory ($P_I$max) and expiratory ($P_E$max) forces.

Following tracheal intubation, especially if prolonged (>72 hours), complications can ensue with extubation, such as the sudden development of laryngeal (glottic) edema. The edema may be in the supraglottal or subglottal tissue or in the glottis itself. The pathogenesis of this entity is unclear, but several possibilities have been suggested including acute ulceration, acute laryngitis, sudden heart failure, epiglottitis, and even allergy to rubber.[20]

Laryngeal edema is usually readily apparent within minutes after extubation as the patient develops respiratory distress accompanied by inspiratory stridor. Uncontrolled observations have suggested benefit from corticosteroids and racemic epinephrine acutely as well as the administration of a helium-oxygen mixture. A simple comparison of "weaning parameters" before and after deflation of the cuff of the endotracheal tube may be a reliable method for predicting success or failure when weaning[22] (Table 8.5). The greater the entrainment of room air around the cuff, the lower is the PaO_2 and the more unlikely the presence of laryngeal edema.

The smaller the spontaneous V_T (<300 ml) and the greater the f (>25 breaths/minute) the poorer the outlook for successful weaning. Despite

TABLE 8.5. Weaning parameters on T-bar before and after cuff deflation.

Parametir	Entire group		Success		Extubation outcome: fail/not tried	
	Inf	Def	Inf	Def	Inf	Def
No.	55	55	32	32	23	23
pH	7.43	7.41	7.43	7.42	7.42	7.41
$PaCO_2$ (mm Hg)	42	43	40	40	46	47
PaO_2 (mm Hg)	121	101*	140	113*	95	84
HR (beaths/min)	103	105	103	103	104	107
f (breaths/min)	26	28*	24	25	29	31*
BP—syst. (mm Hg)	137	134	139	134	134	134
BP—diast. (mm Hg)	68	68	72	72	63	63
$\Delta PaCO_2$ (mm Hg)	0.8		0.8		0.8	
ΔPaO_2 (mm Hg)	20		26		11	
VC (L)	1.63		1.57		1.78	
V_T (ml)	433		513		334	
V_E (L/min)	10.1		10.7		9.4	
$P_I$max (cm H_2O)	31.5		31.7		31.1	

Source: Data from Zaman et al.[22]

The successfully extubated group had a statistially significant fall in PaO_2 with cuff deflation ($p = 0.001$). The failed/not attempted extubation group did not have a statistically significant decrease in PaO_2 following cuff deflation ($p > 0.05$).

Inf = inflated; Def = deflated; V_T = tidal volume; VC = vital capacity; $P_I$max = maximal inspiratory force.

*$p < 0.05$ in comparison to Inf value.

its ease of measurement (i.e., counting) the breathing frequency has been shown to be a notoriously inaccurate determination, as has the clinical estimation of tidal volume.[23] In general, the respiratory rate is elevated in proportion to the severity of the underlying lung disease, presumably to minimize inspiratory muscle effort. It has been equated with the magnitude of ventilatory muscle load, and the roles of mechanical and irritant receptors have been ignored. It has not been shown that the work or energy cost of breathing is higher in patients who are "weaning" failures. Current theses about weaning depend on the "jogger's mentality" of deconditioned respiratory muscles in the presence of increased respiratory loads. Ventilatory modes are used that theoretically reload the muscles of the respiratory pump in a tolerable, efficient, and synchronous manner.

Compartmental movement as determined by physical examination or technical recordings have also been used to predict weaning failures. Asynchronous motion (respiratory alternans), defining a time lag between the thoracoabdominal compartments and paradoxical motion (abdominal paradox), when the two compartments are completely out of phase and moving in opposite directions, have been suggested to reflect inspiratory muscle fatigue. These parameters are not universally accepted, however. Others have not found them to be reliable or sensitive signs of impending weaning failure, perhaps indicating that they are mere reflections of an increased respiratory work load rather than progressive fatigue.

Most patients who fail a weaning trial do not do so for their lack of effort. They generally display an elevated respiratory drive, as reflected by an increased mean inspiratory flow, tidal volume/inspiratory time (V_T/T_I), or $P_{0.1}$.[24] In general, weaning failure is not due to carbon dioxide retention, reflecting impaired drive, or failure of the diaphragm as a pressure generator. Rarely, carbon dioxide retention presents not from excessive carbon dioxide production resulting from the work of breathing but from therapeutic misadventures, classically with excessive parenteral rather than enteral nutrition, especially with a formula that has a high carbohydrate composition.

It is not difficult to understand the uniform failure of the variety of physiologic indices suggested to predict the success of weaning efforts. The studies use patients not only with varying severity of disease but different underlying causes of respiratory failure, varying durations of mechanical support and preceding weaning attempts, and the general absence of standardized objective criteria of weaning failure. The indices should be used as indicators of how closely to monitor the patient's independent ventilatory efforts not whether to initiate or even terminate them unless they fall within predefined "failure" limits. Whether these indicators should be the same as those used for initiating mechanical ventilatory support is not any clearer than which indicators should be used for initiating support short of complete cardiorespiratory collapse.

The best regimen for controlling a ventilator and then its discontinuation is never starting it in the first place.

Nutritional and Metabolic Support

Nutritional repletion has achieved the exalted status of qualifying as a legitimate "stratagem" in the therapeutic management of respiratory disease. The role of the calorie in the armamentarium of the pulmonary clinician has assumed a significance equivalent to that of spinach for the cartoonist's Popeye cult. The quantitative and qualitative appropriateness of the caloric intake has been enthusiastically, if not discriminately, endorsed as a means of both avoiding and treating respiratory insufficiency. This thesis has been suggested for patients with and without preexisting lung disease. It has been applied to the management of patients being weaned from mechanical ventilators and, more importantly, as a prophylactic measure to avoid the need for such devices by inadvertently precipitating ventilatory failure through "nutritional oversight."

Nutritional therapy for ambulatory, in contrast to hospitalized, patients has as its dual goals enhancement of ventilatory reserve and alleviation of dyspnea. Moreover, infection causes superimposed alterations in host metabolism and anorexia with decreased nutrient intake in the face of an increased metabolic demand due to fever. The need for gluconeogenesis because of carbohydrate depletion and inefficient fat utilization results in proteolysis manifested as myalgia and muscle weakness. This section attempts to correlate and place in perspective proposed effects of observed metabolic phenomena on parameters of respiration and immune function with reported clinical realities.

Respiratory Function

Muscle Strength

The potential benefits of nutritional support in enhancing pulmonary function by increasing the mass, strength, and endurance of the inspiratory muscles have been inferred from the clinical correlates of autopsy studies.[25] The size of the most important muscle of inspiration, the diaphragm, expressed in terms of thickness (centimeters), mass (grams), or area (square centimeters), has been found to be proportional to body weight in normal subjects and in patients who have no evidence of lung disease (Fig. 8.2).

In patients with emphysema, the diaphragmatic weight and total body weight decrease in proportion to the severity of the apparent airway obstruction; but the relative loss of diaphragmatic mass exceeds that of the rest of the body[26] (Fig. 8.3). The implied deterioration of muscle

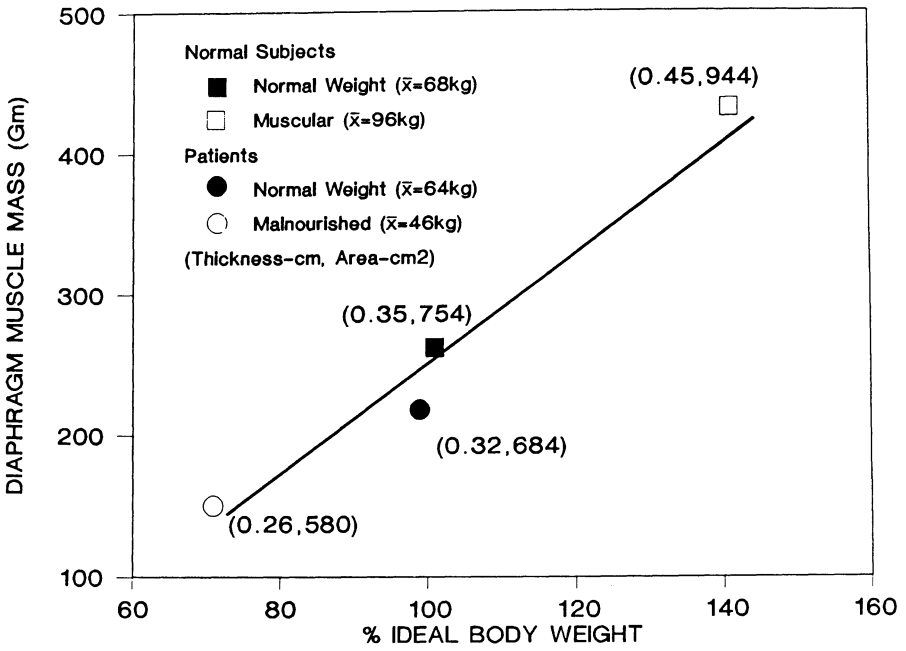

FIGURE 8.2. Mean values of diaphragmatic weight, thickness, and surface area of 33 normal subjects and 37 patients with various nonpulmonary diseases studied at autopsy. They are grouped according to estimates of the state of nutrition as determined from body weight. (Data from Rochester.[25])

performance in relation to nutritional status is also demonstrable in patients without lung disease by objective tests of pulmonary function.[27] The vital capacity (VC), maximum voluntary ventilation (MVV), and maximum inspiratory ($P_I$max) or expiratory ($P_E$max) pressures, inferring muscle strength, endurance, and force-generating capacity, respectively, of the respiratory muscles are reduced in association with weight loss (Fig. 8.4) Just as the loss of diaphragmatic muscle mass has been observed in autopsy studies to be relatively greater than the reduction in total body weight in patients with or without lung disease,[25,26] the impairment of inspiratory muscle strength has been found to be out of proportion to and to exceed that which would be predicted from loss of muscle mass alone, suggesting a superimposed nutritional myopathy.[27]

Ventilatory Control

The ventilatory response to an appropriate stimulus, in the absence of pulmonary or neuromuscular disease, is used as a measure of the chemosensitivity of the respiratory control mechanism. It may, however, be influenced by alterations in muscle strength. Both resting ventilation

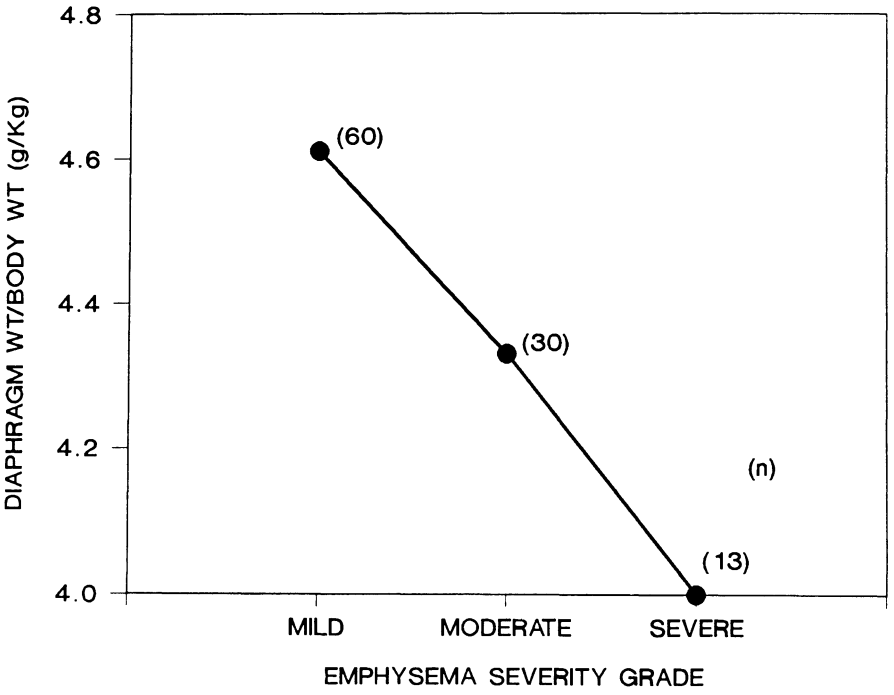

FIGURE 8.3. Mean values of the diaphragmatic/total body weight ratio found at autopsy in 103 male patients grouped according to severity of emphysema as determined by septal destruction and measured flow rates. The number (n) of patients in each group is shown in parentheses. (Data from Thurlbeck[26])

and the hypoxic ventilatory response decrease with caloric deprivation in direct relation to the magnitude of the associated fall in metabolic rate[28,29] (Fig. 8.5). In contrast, the effect of starvation on the ventilatory response to carbon dioxide is variable. This variability in part appears to be related to diet composition (Fig. 8.5).

The relation between the regulation of ventilation and metabolic activity has been previously studied, but only recently have primary alterations in metabolism as a consequence of nutrition been related to the central respiratory controller's "black box." The hypoxic response is readily restored by refeeding. However, calories supplied by amino acids alone, though they may be adequate to sustain nitrogen balance and enhance the ventilatory response to carbon dioxide, do not suffice to normalize chemosensitivity (Fig. 8.5). Normal ventilatory control can be fully restored only if total metabolism ($\dot{V}O_2$) is also returned to normal levels with calorie supplementation from additional sources such as fatty acids.[29]

This linkage of chemosensitivity to metabolism is also apparent with maneuvers inducing hypermetabolic states, as is seen with the thermogenic

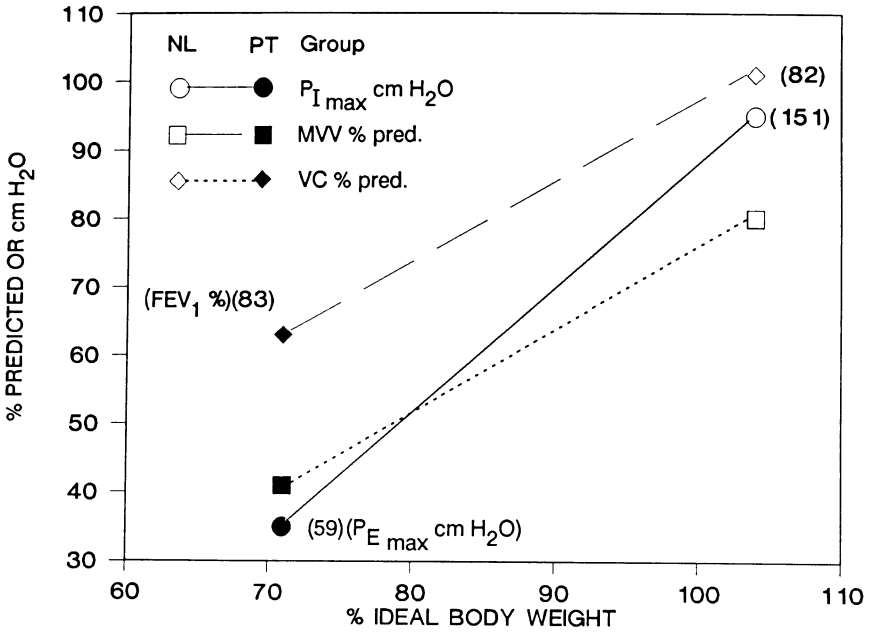

FIGURE 8.4. Mean values of tests of pulmonary function reflecting muscle strength in 16 normal subjects (NL) and 16 poorly nourished patients (PT) without cardiopulmonary disease. PImax (PEmax) = maximum inspiratory (expiratory) force; MVV = maximum voluntary ventilation; VC = vital capacity; $FEV_1\%$ = FEV_1/VC. (Data from Arora and Rochester.[27])

responses to exercise and overfeeding. The resting ventilation and hypoxic ventilatory response are enhanced in proportion to the immediate increases in metabolism induced by either carbohydrate (CHO) or protein administration.[30] However, for isocaloric intake, protein but not CHO enhances carbon dioxide chemosensitivity (Fig. 8.6).

The stimulatory effect of protein on neuromuscular drive, unlike that for CHO or lipid, does not totally depend on a rise in metabolic rate. This dynamic property of protein manifests by enhancing the sensitivity to carbon dioxide, as reflected by a shift of the intercept of the carbon dioxide response curve to the left (decreased threshold or carbon dioxide set-point), and the responsiveness (gain or slope) of the chemoreceptors to carbon dioxide. This effect is further characterized by greater flow rates (V_T/T_I) for a given PCO_2 (slope). The inspiratory timing mechanism (duty cycle), or duration of inspiration, expressed as a percentage of the total respiratory cycle (T_I/T_{TOT}), however, remains unchanged. CHO also tends to decrease the carbon dioxide threshold but less so than a calorically equivalent amino acid meal and without an associated change in flow rates. Thus the ventilatory stimulus of parenteral nutrition is

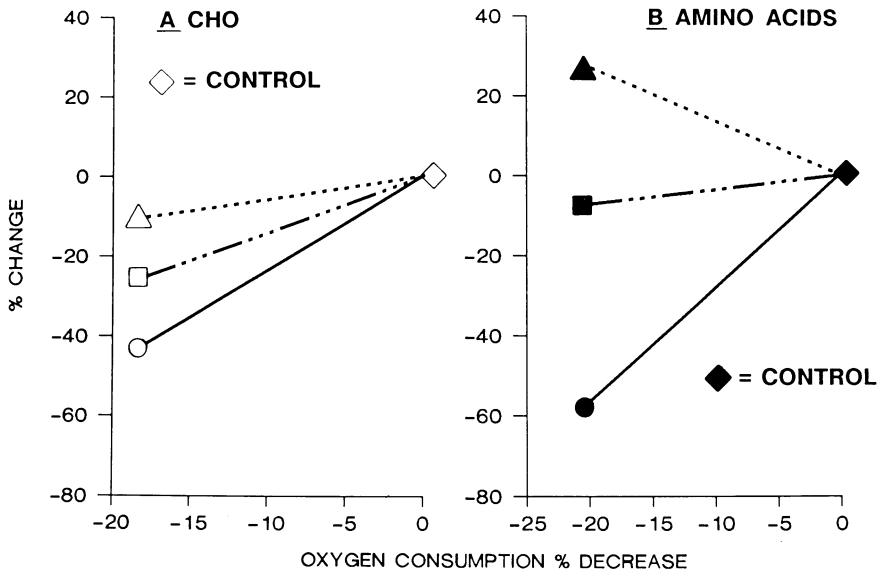

FIGURE 8.5. Mean changes in resting ventilation (□), carbon dioxide (△), and hypoxic (○) ventilatory responses in normal subjects after 10 days of semi-starvation on a daily diet of (A) 500 kcal glucose given daily (n = 7, open figures)[28] and (B) 550 kcal amino acids given parenterally (n = 6, solid figures)[29] in relation to the associated decrease in metabolic rate ($\dot{V}O_2$). (Data from Doekel et al.[28] and Baier and Somani.[29])

primarily due to the neurodynamic action of protein magnifying the ventilatory response to the carbon dioxide and thermogenic loads resulting from the oxidation of CHO.

The ventilatory response to caloric intake represents the efferent limb of a stimulus influenced by a number of factors, including nutrient composition, quantity, rate, and even route of administration. The afferent axis further depends on the subject's preexisting metabolic and nutritional status. The net magnitude of the resulting response is a complex function of the metabolic deposition of the caloric substrate and its intrinsic thermogenic contribution to the metabolic rate. If a given metabolic load is associated with a rise in $\dot{V}O_2$ and $\dot{V}CO_2$, the resulting ventilatory stimulus would be greater than if an increase in only $\dot{V}CO_2$ occurred. The pattern of the observed ventilatory response tends to be frequency-dependent in acutely ill patients but volume (V_T)-dependent in normal subjects and patients with normal lungs and stable metabolic profiles.[30] It may be postulated that the "impaired" neuromuscular drive and metabolic "dumping" associated with starvation serve a teleologic role when pulmonary function is impaired, and the potential adverse consequences of nutritional therapy are heralded clinically by dyspnea initially and, at its extreme, by the dreaded "weaning" failure.

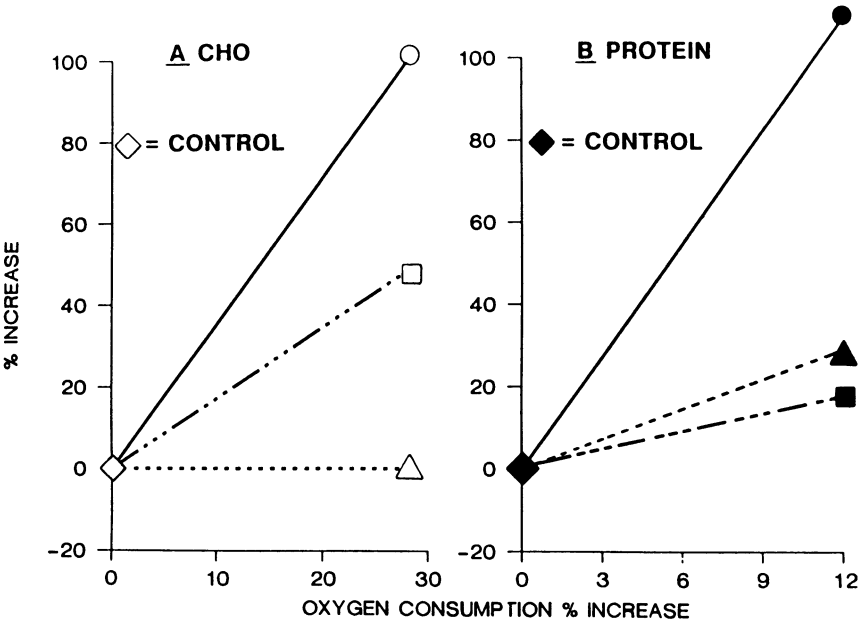

FIGURE 8.6. Mean changes in resting ventilation (□), carbon dioxide (△), and hypoxic (○) ventilatory responses in 6 normal subjects 3 hours after a 1000-kcal enteric bolus of (A) glucose (open figures) and (B) egg albumin (solid figures) in relation to the associated increase in metabolic rate ($\dot{V}O_2$). (Data from Zwillich et al.[30])

Acute Ventilatory Failure

Caloric repletion enhances ventilation in patients with respiratory insufficiency not only by increasing central neuromuscular drive but, if it results in a gain in body mass, by an increase in inspiratory force as well. Thus it has been proposed that the nutritional state of patients with respiratory failure should be optimized to maximize the bellows function of the respiratory apparatus. Others have clarified the important roles of the Mg^{2+} and PO_4^{2-} ions in muscle metabolism. Muscle weakness and respiratory failure may be precipitated by depletion of these ions, as they are essential for synthesis of the high-energy phosphate compounds adenosine triphosphate and creatine phosphate, which serve as sources for the immediate energy requirements of muscle contraction. The stores of both these compounds are depleted from respiratory and nonrespiratory skeletal muscle during episodes of respiratory failure.

The composition of the caloric regimen utilized is also of added significance in ventilatory failure because of the potential carbon dioxide load resulting from CHO metabolism. The burden is greater with CHO

TABLE 8.6. Metabolic pathways and resultant respiratory quotients.

Process	Reaction	RQ
Oxidation	$CHO + 10\ O_2 = 10\ CO_2 + H_2O$	1.0
Oxidation	$Fat + 10\ O_2 = 7\ CO_2 + H_2O$	0.7
Lipogenesis	$CHO + 10\ O_2 = 80\ CO_2 + Fat$	8.0+

relative to fat with complete oxidative metabolism [respiratory quotient (RQ) 1.0 versus 0.7]. The adverse consequences of administering excessive calories in the form of CHO are potentially even greater owing to the potential for "futile cycling" and because a progressively massive carbon dioxide load results, as lipogenesis (with an RQ far in excess of 1.0), rather than oxidation, becomes the predominant metabolic pathway (Table 8.6).

In patients whose ventilation is absolutely or relatively fixed owing to either dependence on mechanical ventilation or intrinsic pulmonary disease, this additional metabolic burden may result in overt respiratory failure or an inability to be successfully "weaned" from a ventilator. The stratagem of maximizing the fat content of nutritional supplementation must, however, also allow for an increase, albeit not as great, in ventilation, as for CHO loads[31] (Fig. 8.7).

In summary, a good deal of information has accumulated pertaining to the effects of nutritional interpositions on ventilation and respiration. Unfortunately, much of the evidence is contradictory and does not clearly indicate the role of nutrition in pulmonary dysfunction. With this approach to treatment, as with others, it is important to appreciate not only the well recognized side effects but the disputed benefits and then attempt to estimate the risk/benefit ratio.

Immunity

Cell and Humoral Mechanisms

Malnutrition is clinically associated with altered immune function (secondary immunodeficiency), increased respiratory tract infections, and increased mortality, yet the scientific relation between the cellular defense mechanisms and nutrition is complex and remains unclear. There is a well recognized linkage between infection and malnutrition, with bronchopneumonia commonly found at autopsy in children dying with severe malnutrition; its frequency correlates with the severity of malnutrition.

Changes in B cell number and function are inconsistent. Humoral immunity is less sensitive than cellular immunity to effects of protein

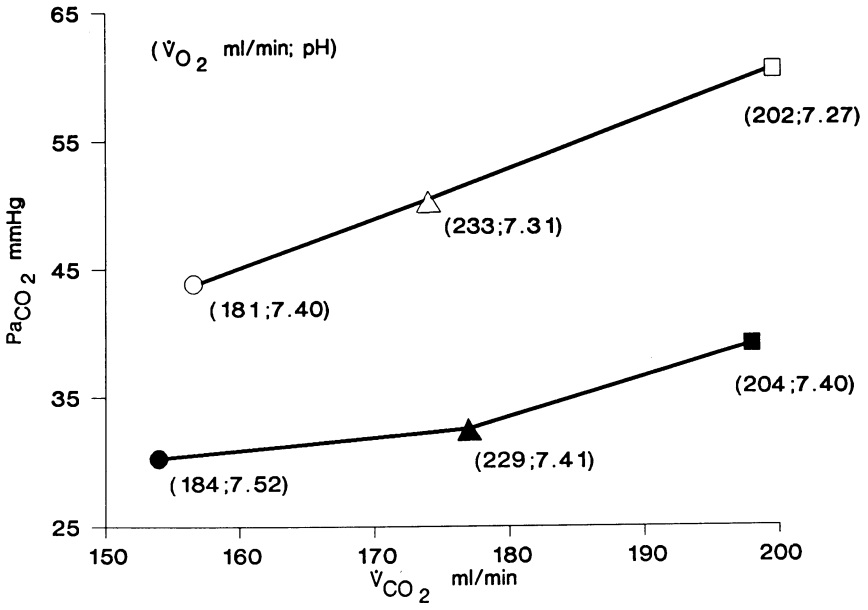

FIGURE 8.7. Mean control values (○) of arterial PCO_2 in 514 patients with COPD on mechanical ventilatory support measured at a fixed V_E of 6 L/minute (open figures) and 10 L/minute (solid figures) and 48 hours after a 1500 ml 50% glucose (2550 kcal/day) (□) or 1500 ml 20% fat emulsion (3000 kcal/day) (△). (Data from Herve et al.[31])

deficiency. Studies tend to indicate that nutritional deprivation decreases the humoral immune response to both viral and bacterial vaccines; the response is variable, however, and refeeding can correct the abnormality. B cell regions in lymphoid tissue are histologically preserved, and normal numbers of circulating B cells are present in the peripheral blood of patients with protein-calorie malnutrition.

Primary and secondary lymphoid tissue is altered with malnutrition. The thymus becomes atrophic, tonsillar size is grossly decreased, and the weight of the spleen can be reduced to one-third normal. Histologic examination of lymph nodes shows diminished cellularity of both germinal centers and the T-cell-dependent paracortical areas, but the latter are more severely affected. Peripheral blood lymphocytopenia with reduction of T4-helper and T8-suppressor lymphocytes and natural killer cells are reported, but there are also reports that lymphocyte populations may be normal, especially circulating suppressor T lymphocytes. Cell-mediated immunity and other T-cell functions have been reported to be impaired. The most consistent finding is impairment of cutaneous delayed hypersensitivity reactions. These abnormalities of cell-mediated immune function

are reversible with nutritional repletion. Although early steps in PMN activation may be impaired, phagocytic activity and bactericidal capacity remain intact.

Repletion

It is difficult to attribute the state of nutrition to infection or reversal of the nutritional state to a return of immune function. It appears that nutritional support, enteric or parenteral, allows protein sparing and decreased infection and mortality in malnourished patients. It has been shown that during infections in protein-deficient patients antibody synthesis is maintained despite the reduction in synthesis of other serum proteins such as albumin. It appears that the quality as well as the quantity of the amino acid content of the protein is also important. Specific amino acid deficiencies (e.g., isoleucine, valine, and other essential amino acids) impair lymphopoiesis and cellular immunologic competence.

Enteric feedings are thought by many to be superior to total parenteral nutrition (TPN) for maintaining gut integrity and preventing septic complications presumably by the mechanism of translocation. Regardless of the route of repletion, few data are available to validate the intuitive benefit of nutritional therapy. This point is particularly pertinent to infections in general and lung infection in particular, which have not been used as clinical endpoints in the human studies that are available. Immunocompetence, though it reveals aberrant parameters in anorexia nervosa, is seldom reported to be impaired to a degree of such severity as to be associated with an impressive increase in infectious disease.

Similarly, perioperative nutritional supplementation (TPN) appears to benefit only those severely malnourished, whereas those identified as having only mild malnutrition (after stratification) have an increased incidence of infection.[32] The increase in bacterial complications are not catheter-related but are wound infections and pneumonia. Although TPN has not previously been shown to be causally related to an increased rate of other than catheter-related infection, concern has been expressed that, rather than supporting host defense mechanisms, TPN might have the opposite effect and in critically ill patients may cause further impairment of the host's defense. Lipids in particular have been suggested to have a possible detrimental effect on the immune system. This suggestion has not been substantiated to date, and questions remain particularly regarding overload of the reticular endothelium system and how the various fatty acids in fat emulsions may adversely modulate immunity. The difficulty of assessing outcomes is the synergistic interaction between nutrition and the immune response to infectious disease. This interaction is bidirectional: Nutritional status influences host immunologic responsiveness, and infectious disease has a detrimental influence on nutritional status.

Physical Therapy

Antibiotic regimens are frequently supplemented with adjuvant modes of therapy that are meant to augment the lung's defense mechanisms, enhance gas exchange, and ameliorate symptoms. Their efficacy has been challenged; and as soon as one therapeutic modality has been irrevocably put into disrepute it is replaced by another unproved supportive measure that rapidly becomes a standard of care through usage and intuitivism.

Chest Physiotherapy

Supportive measures in addition to expectorants and mucolytics to improve pulmonary toilet have classically included chest percussion and postural manipulation to enhance gravity drainage. Chest physiotherapy consisting of postural drainage was introduced as a therapeutic intervention at the turn of the century. After World War I, chest percussion and vibration were used concomitantly and subsequently with intermittent positive-pressure breathing (IPPB), which had been developed prior to World War II but was not widely utilized until the 1950s. These modes of therapy, though vigorously advocated, have not been shown to have a beneficial effect on pneumonia patients with respect to mortality, radiologic clearing, duration of fever, or hospitalization.[33]

Even more discouraging are the results of a study in patients with pneumonia that revealed regular chest physiotherapy to be associated with prolonged duration of fever and increased hospital stay when compared to verbal advice on the need for expectoration and deep breathing.[34] Airway obstruction as determined by the forced experatory volume in 1 second (FEV_1) also showed no benefit from therapy. As might be expected, responses from patients who received physiotherapy, when contacted 5 months after discharge, were all "positive" or "very positive" in regard to the value of the physiotherapy for the healing process.[34] The prolonged fever in the treatment group was attributed to the spread of the infectious process; and it was pointed out that in Russia chest physiotherapy is not started in pneumonia patients until the fever has subsided, and it is then thought to give prompter and more complete healing.[34] Similarly, there is also little evidence to suggest benefit of its prophylactic use for preoperative or postoperative management or for any of the wide variety of clinical situations in which it is used. Thus although secretions may be mobilized by chest physiotherapy and there is increased sputum production, it has not been shown to translate into affecting the clinical course or the development of pneumonia.

The uncontrolled mobilization of secretions has the theoretic hazard of spreading the infection to otherwise uninvolved areas of the lung. In the absence of large volumes of secretions in the patient with a normal cough, there is no support for even the teleologic argument for the benefit of

physiotherapy. In such situations, physiotherapy may well be expected to result in deterioration of lung function in patients with airway hyperreactivity, such as asthmatic bronchitis, presumably by inducing bronchospasm such as suction catheters are known to do. Moreover, as with lung inflation devices, several studies have shown that there may be worsening of the hypoxemia. Therefore chest physiotherapy should only be done with oxygen treatment in patients with concurrent arterial desaturation.

Arterial oxygenation has been observed to remain unchanged after chest physiotherapy in patients on mechanical ventilation[35] and to increase immediately after treatment with a mechanical vibrator in critically ill patients with pneumonia.[36] It is postulated that sputum that is thixotropic becomes more liquid upon constant disruption, and increased clearance results if there is an expiratory flow bias (two-phase flow) allowing for its mobilization and the opening of peripheral lung units. Vibrations are also thought to excite the walls of large airways, so secretions detach from the mucosa and are carried away by the oscillatory air flow. It has been suggested that the standard duration of the physiotherapy sessions are inadequate. During this era of resource rationing, such claims require substantial support by objective data to show the value of physiotherapy—not obtained during the nearly 100 years of its documented use—before this mode of therapy, on the wane, is restored to modern therapeutic protocols.

A similar question of dose has been raised most recently for continuous lateral rotational therapy, which has been introduced as a kinetic form of prophylactic therapy against nosocomial pneumonia for use in immobile patients. It involves continuous slow rotation in the longitudinal axis over 124 degrees. Studies have suggested that effective prophylaxis can be achieved, with pneumonia occurring in fewer stroke and trauma patients compared to the standard hospital bed, but the mortality among stroke patients was unchanged. Patients with sepsis and pneumonia had a shorter intensive care unit (ICU) stay compared with controls; but again overall mortality was no different.[37] The prospective medical and economic benefits of prophylactic physical therapy creates pressure for premature acceptance of yet another unproved modality for which pulmonary medicine as other subspecialty areas have a well recognized heritage.

Lung Expansion Devices

The concept of early ambulation classically utilized during the postoperative period to mobilize peripheral blood flow (and thereby prevent phlebitis due to venous stasis) is similarly applied to the bedridden pneumonia patient. Provided this concept in reality is not corrupted into becoming, as it has in phlebology, a state of early angulation, it is probably as effective as any of the growing number of devices available to

alleviate microatelectasis and promote sputum mobilization. Sitting in a chair with the proximal and distal portions of the lower extremities at right angles is not the goal, but the deep breaths that occur as a result of the exertion of getting to the chair and returning to the bed is the presumed therapeutic segment of this maneuver, which is further enhanced by walking. The use of simple devices, such as the classic Dale-Schwartz tube, blow battle, IPPB instrument, and incentive spirometer, has been shown to add little if any therapeutic advantage. Moreover, these devices present potential dangers of worsening hypoxia or barotrauma, or of being the source of nosocomial infection.

Enlarging the physiologic deadspace with a hollow breathing tube without supplemental oxygen may cause dramatic lowering of the alveolar PO_2 in the predisposed patient, despite an autoregulatory attempt by the central respiratory center and peripheral chemoreceptors to maintain the effective alveolar ventilation by hyperventilation. Thus the Dale-Schwartz tube fell into disuse to be replaced by mechanical devices to induce hyperventilation other than by "purposeful" deep breathing. When the ineffectiveness of blow bottles was subsequently demonstrated, it was attributed to the expiratory mode of action, which was suggested to worsen the existing atelectasis by promoting further small airway collapse. A potential beneficial effect results or predominates in some patients from the deep inspiration preceding the blow that is performed to generate a greater expiratory force.

The IPPB instruments were initially introduced not only to expand the lung in the debilitated patient but to deliver medication such as bronchodilators, mucolytics, and antibiotics as well. On the basis of available clinical studies, IPPB remains an accepted valid intervention only in the patient with a chest deformity, such as kyphoscoliosis. The "therapeutic" pressure bolus has been shown to worsen hypoxemia, bronchospasm, and gas exchange with the life-threatening danger of barotrauma as well.

Incentive spirometry remains the most popular and a much utilized mode of therapy, primarily in the postoperative patient. Documentation of its benefits is poor, and most studies have failed to show that it has value. It has been shown to be as "effective" as the previously discredited prophylactic measure of IPPB postoperatively in coronary bypass patients.[38] Its cost aside, patients are frequently given the instructions for its use without being given nasal oxygen during the inspiratory exercise despite being maintained on oxygen by mask.

Continuous positive airway pressure (CPAP) masks have been more consistently shown to result in the desired expansion of lung volume. However, its efficacy as a prophylactic or therapeutic measure for managing microatelectasis does not speak for its role, much less its benefit, in decreasing the incidence or the treatment of established airway collapse or pneumonia. None of these techniques has been shown to alter the severity, duration, or course of an established pneumonia.

Mucology: Expectorants and Mucolytic Drugs

The Bible, the earliest pharmacopoeia that emphasized mucokinetic drugs, was in reality only continuing to give them the prominence already endowed by the preceding ancient Eastern civilizations.[39] The goal regarding pneumonia was, as stated by Hippocrates, to soothe the cough and promote expectoration. The prescription of Maimonides for "highly spiced chicken soup" was for the same purpose: to promote a "gustatory reflex" and productive cough, which because of the vapors (if served appropriately steaming) acts as a mucorrheic agent. Since the nineteenth century therapeutic doses of iodide have been prescribed to make sputum less tenacious; thus iodide has been thought to be of value in refractory cases of pneumonia. These are but two common examples not only of our customary practices without scientific basis that are widespread in mucokinetic therapy but that fail to differentiate between expectorants, antitussives, demulcents, and so on. All of these agents are aggregated under the banner of mucoactive drugs, implying their common endpoint of promoting mucociliary clearance. Many of the most traditional expectorants (e.g., potassium iodide) in therapeutic doses may act on the gastric mucosa, evoking a "gastropulmonary mucokinetic reflex" through the vagus nerve, whereas in toxic doses nausea results via the central vomiting center.

Mucin Structure

Airway mucins are synthesized by both goblet cells of the epithelium and mucous cells in the submucosal glands. Although control is probably complex, these glands appear normally to be under autonomic regulation. The mucins are hydrated on the mucosal surface, forming the mucous gel. Just as a liquid and its gas vapor phase coexist at the boiling point, polymer gels can exist in one of two phases: a condensed phase or an expanded hydrated phase.[40] The transition from the condensed polymer (released by the cells) to its hydrated phase on the surface of the mucosa is reversible and is associated with a several hundredfold volume change.

Rheologically, bronchial mucus forms a complex nonnewtonian viscoelastic polymer gel layer flowing over an underlying serous sol layer, allowing the cilia's oscillatory movements. The rheologic and viscoelastic properties of mucus that enable ciliary transport are primarily conferred by the glycoprotein mucin component. Polymerization creates the high molecular weight (HMW) mucous glycoprotein and gel matrix. The basic unit of the glycoprotein macromolecule is a linear polypeptide backbone from which side chains of carbohydrate extend. The "oligosaccharide clusters" (o-glycans) are joined by o-glycoside bonds to the core protein or apomucin. These side chains are responsible for the high carbohydrate

content (80%) of mucin, as well as its density, hydrodynamic volume, and viscosity.

The bronchial mucus, which is a heterogeneous mixture of HMW glycoproteins, has a tertiary structure of flexible, tortuously coiled, entangled threads. These threads are polydispersed in size from a minute 300 nm to "immense" chains up to 5 μm in length; they have a "bottle brush" structure of amino acid cores with glycoprotein branches.[41] The rheologic properties of the mucous gel are determined by what is termed its tangle density, which rapidly decreases with increasing hydration. Thus the capacity and degree of mucous hydration (swelling) is the main determinant of mucous rheology. The absence of interchain bonds allows dispersion of the tangled polymer network in solution.[40]

The flexible, long, "coiled thread" model proposes one long peptide containing highly protease-resistant glycosylated regions covered by hundreds of heterogeneous glycan chains that are interspersed with poorly glycosylated (naked), protease-sensitive regions.[41] The conformation of mucin macromolecules were formerly thought to be dependent on branched, covalently cross-linked disulfide bridges, but it is their quaternary structure that is now being emphasized as being responsible for the linear conformation of mucin strands tangled in the mucus matrix.

The architecture of the mucin peptide moiety shows extreme polydispersity, and the quaternary structure of carbohydrate chains are heterogeneous. The diversity of carbohydrate chains may undergo subtle but specific modifications during inflammatory processes, possibly reflecting differences in cell origins or disease-induced alterations. The carbohydrate chains are recognized by surface adhesins of microorganisms and represent potential sites for their attachment. This trait allows their trapping on the mucous blanket, their removal by mucociliary elevation, and under normal circumstances swallowing of the raised mucus. Thus the carbohydrate chains play an important role in the pulmonary defense system.[41]

Mucokinesis

The hundreds of oligosaccharide clusters or chains on a single mucin molecule may vary in length between 1 and 20 sugars and may be neutral, sialylated, or sulfated. Mucolytics generally contain a free thiol group thought necessary to interact with the cysteine-SH group, thus breaking the disulfide bond, reducing the viscosity (mucolysis) of the mucous structure, and enhancing mucokinesis. Such an agent, acetylcysteine, has been reported to be an effective mucokinetic agent despite its irritative properties in making pulmonary secretions more easily removed by ciliary action or cough, thereby reducing pulmonary complications and the need for endotracheal aspiration.

Mast cells and neutrophils are sources of inflammatory mediators, especially proteases, such as chymase, elastase, and cathepsin G, which

have been found to be the most potent secretagogues of airway submucosal gland secretion ever described.[42] It has been proposed that the release of these enzymes near glands in inflammatory diseases plays an important role in the pathogenesis of the accompanying hypersecretion. An important strategy for intervention may eventually involve inhibitors of these enzymes. Similar roles have been suggested for several neuropeptides, including substance P, neurokinin A, and the parasympathetic neuropeptide vasoactive intestinal peptide; the therapeutic use of neuropeptidases has also been proposed.

Hypertonic saline given by ultrasonic aerosol has been used to induce sputum; this technique has been adapted for routine use in acquired immunodeficiency syndrome (AIDS) patients to diagnose *Pneumocystis carinii* pneumonia. Impaired mucokinesis in some instances is presumed to be related to a deficiency in depth or an increase in viscosity of the sol layer, preventing the cilia from maintaining an effective coordinated beat with their tips extending into the overlying mucous gel layer. Water and saline solutions have long been used ineffectually in efforts to modify the sol layer and for the hydration of mucus. Similarly, efforts to correct imagined or real systemic dehydration in order to hydrate an often viscous desiccated mucous layer has proved futile, as respiratory tract fluid appears to be resistant to dehydration. Primary mist treatments, encouraged by manufactures rather than suggested on a scientific basis supported by clinical data, is also without benefit in lower respiratory tract infections. Cold humidification of oxygen administered by mask, nasal cannula, or venturi apparatus does not achieve a real increase in humidification. Such adult "cold steamers" palliate the senses, not the bronchial mucosa. Normal saline has no specific mucokinetic action when given orally, intravenously, or by aerosol; although topical administration can induce coughing, its main value in aerosol form is as a vehicle for drug administration rather than as a mucokinetic agent.[43]

In summary, much emphasis has been placed on the therapeutic benefits of enhancing elimination of the purulent material that results from the inflammation of pneumonia, just as it is characteristically pursued for inflammatory airway disease. Although many of the mucologic drugs currently available are ineffectual products of, or direct descendants from, ancient preparations, the current growth spurt in the understanding of mucus—its physiochemical properties, control, and mechanisms of secretion—promises revised therapeutics in the near future.

Steroidal and Nonsteroidal Antiinflammatory Agents

Bacterial Pneumonia

Much discussion if not controversy has been focused on the mechanisms of hypoxemia and diminished perfusion of the consolidated lung associ-

ated with bacterial lobar pneumonia. There are various postulates for the apparent increase in vascular resistance redirecting blood flow to uninvolved lung: intravascular occlusion by active thrombotic or cell aggregative processes; extrinsic vascular compression from the weight of surrounding alveolar and interstitial tissues due to exudative edema-forming processes; necrosis or destruction of parenchymal tissue or vasculature; and vasoactive hypoxic vasoconstriction.[44] Emphasis for therapeutic purposes has been placed on impairing the synthesis of vaso-active prostanoids such as the vasodilators prostaglandin E_1 (PGE_1) and prostacyclin (PGI_2), which have been shown to be capable of increasing the venous admixture of experimental lobar pneumonia.

It has been demonstrated in a dog model that infusion of PGE_1 results in disappearance of the selective perfusion deficit and the redistribution of blood flow to consolidated lung tissue in lobar pneumonia.[44] Thus rather than mechanical control, a pharmacologic "imbalance" of vasoactive dilator and constrictor mediators were postulated, specifically the prostanoids. Subsequently, efforts were initiated to abort the arachidonic acid cascade proximally with inhibition of phospholipase A or more distally at the cyclooxygenase level in order to restore or augment the normal autoregulatory hypoxic pulmonary vasoconstriction mechanisms and homeostasis.

It has been demonstrated that administration of acetylsalicylic acid or indomethacin, potent inhibitors of cyclooxygenase, reduce blood flow to the consolidated lung in dogs with experimental pneumococcal pneumonia, thereby improving oxygenation.[45] It has become apparent that, because of the varying type and intensity of the inflammatory process, the degree of impairment of the responsiveness of vascular elements to vasoconstrictor drugs is unpredictable. Moreover, even if complete blockade can be accomplished, vasoactive mediators other than prostanoids are involved in the inflammatory process, and "appropriate" hypoxic vasoconstriction appears to remain an unachievable goal. Such pharmacologic manipulation therefore may favor not only redirection of the arachidonic acid cascade to the lipoxygenase pathway with the net synthesis of excess leukotriene vasoconstrictors[45] but other, as yet unknown metabolic effects that affect mediators capable of altering vaso-motor responses. Subsequent studies in humans with respiratory failure due to bacterial pneumonia supported the failed hypoxic vasoconstrictor hypothesis by showing clinically significant increases in arterial oxygenation in five patients immediately following oral administration of indomethacin.[46] Efficacy may be expected to be negilgible in diffuse processes and enhanced in localized processes of interstitial or bronchopneumonia because the extent to which blood flow is diverted away from a hypoxic segment (i.e., the strength of the hypoxic vasoconstrictor response) is inversely proportional to the size of the segment.

Acute Lung Injury Syndrome

Because CPAP was shown to be an ineffective means of prophylactic therapy for ARDS, despite favorable early reports, other therapeutic interventions, particularly antiinflammatory agents, steroidal and nonsteroidal, have been proposed. Early reports of PMN-aggregation-induced ARDS preceded by complement activation and successful prophylaxis with corticosteroid treatment, presumably acting to inhibit complement activation, led to their use in clinical trials. In such studies of patients with septic shock, corticosteroids did not affect the development of ARDS,[47,48] and no correlation was found with complement levels and the development of ARDS.[47] Moreover, corticosteroid treatment seemed to be associated with an increased incidence and severity of ARDS with a greater mortality, which may be attributed to a higher incidence of secondary infections.[48] It has also been shown that once ARDS is established corticosteroid administration has no beneficial effect on outcome when it is considered in terms of reversal of the respiratory failure of ARDS (characterized by chest roentgenoram, lung mechanics, arterial oxygenation, or associated mortality).[49]

Animal studies suggest that for corticosteroids to effectively ameliorate increases in pulmonary microvascular permeability they must be given prior to or within 30 minutes of the induction of endotoxemia. Therefore it was suggested that once ARDS is present it is too late; previous studies did not carefully assess the effect of corticosteroids, when given early, on parenchymal lung injury associated with sepsis short of ARDS. Once again, even when the immediacy of administration was stressed, it was found that neither mortality nor even lesser degrees of parenchymal lung injury were ameliorated by corticosteroid treatment.[50] Thus corticosteroids were again not found to decrease the incidence of ARDS in the presence of sepsis. Additionally, a high dose of corticosteroid was not found to affect the time interval between the clinical suspicion of septic shock and the onset of ARDS or the time to resolution of ARDS from its onset. However, it is difficult to diagnose septic shock readily enough for truly early intervention; and the process of parenchymal lung damage leading to respiratory insufficiency has already been initiated during the initial interval of time devoid of the critical clinical manifestations of sepsis that would allow early diagnosis. In contrast to these negative results, others have reported benefit from a sustained (3 weeks), rather than short (24–48 hours), course of corticosteroid treatment in patients with established ARDS in whom the primary process that produced ARDS was controlled.[51]

Finally, several studies have suggested that corticosteroids might be of benefit in human immunodeficiency virus (HIV)-positive patients with *Pneumocystis* pneumonia. It was concluded that the early use of such

adjunctive therapy in patients with moderate to severe pneumonia decreases the magnitude of the Herxheimer type of initial deterioration in oxygenation, progressive respiratory failure, and death associated with antimicrobial treatment.[52,53] These conclusions and recommendations, noted in a consensus statement, have created a number of questions, including the role of shorter pulse therapy, the risk of superinfection especially with tuberculosis, the pathophysiology of deterioration in oxygenation, and the apparent unique mechanism for therapeutic efficacy with this type of pneumonia. Additionally, all studies have not found benefits for survival. Because of the lack of initial response and the early recurrence of complicating secondary infection, corticosteroids as "rescue therapy" in a clinical state perhaps more synonymous with "true" ARDS has not been shown to be of value.[53] Similar apparent benefit from such adjuvant therapy has also been reported for the treatment of severe tuberculosis infection in both HIV-positive and HIV-negative patients.

Because of the eventual disappointments for which steroids have been historically responsible when definitive studies have followed up on the initial positive accounts of therapeutic responses, it is difficult to become a strong believer in the current favorable reports regarding *Pneumocystis* pneumonia. It does seem reasonable, however, that higher dosage and longer durations of treatment at different stages of disease for different etiologic agents, pathogenesis, and pathophysiology might well produce different results.

Fluid

The long recognized relation and coexistence of pulmonary edema and pneumonia, seen both clinically and at autopsy, led to warnings nearly 40 years ago regarding the potential adverse consequences of parenteral fluid therapy.[54] Terms such as serous pneumonia, satellite and localized pulmonary edema, and congestive atelectasis were subsequently assimilated into the semantics of the acute lung injury syndrome. The synergistic interactions between hydrostatic pressure, vascular permeability, oncotic pressure, and impaired lymphatic fluid resorption are largely ignored in attempts to "hydrate" the pneumonia patient. These attempts at "early hydration" are in fact due to the clinician's innocent acts of "early drowning."

Numerous studies utilizing animal models of noncardiogenic pulmonary edema have demonstrated that changes in left ventricular filling pressure within the normal range affected the rate and amount of lung water accumulation. Vasodilator and diuretic treatment of aspiration pneumonia in dogs was observed to decrease lung water accumulation and reduce venous admixture while maintaining cardiac output despite a decrease in left ventricular filling pressure.[55] In contrast, volume expansion in a

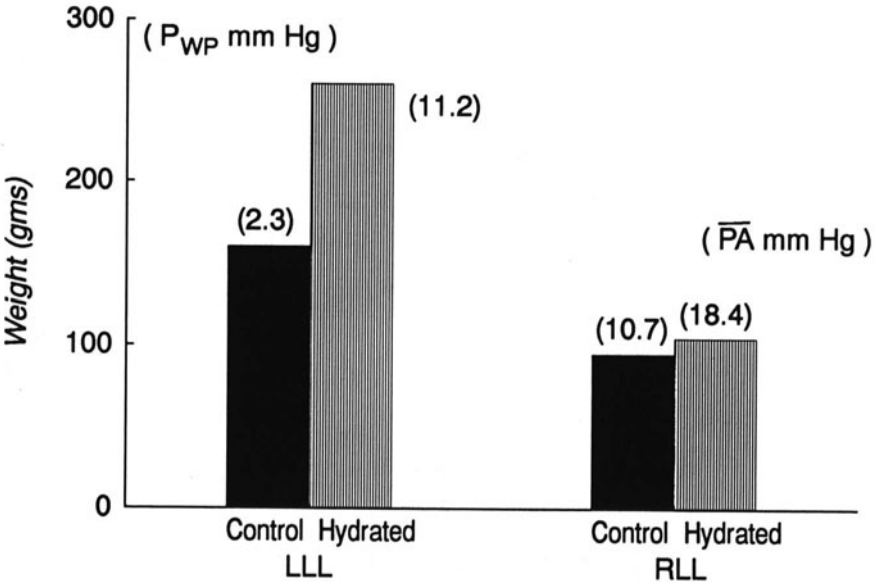

FIGURE 8.8. Mean values of lung weight 48 hours after the induction of pneumococcal pneumonia in the left lower lobe (LLL) of 14 dogs (RLL = right lower lobe). The hydrated group (n = 7) were made hypervolemic for 3 hours prior to being sacrificed and were compared with the control animals (n = 7) who were not volume-loaded. The mean values of pulmonary capillary wedge pressure and mean pulmonary artery pressure in both groups are indicated. (Data from Cooligan et al.[56])

canine model of pneumococcal pneumonia has been shown not only to increase lung water (Fig. 8.8) but to enhance spread of the infection to the contralateral lung as well.[56]

Approximately one-third of patients with bacterial pneumonia have evidence of ventricular dysfunction and demonstrate a hypodynamic circulatory response to the acute infection and its metabolic stress. It has been attributed to ventricular interdependence as well as to a circulating myocardial depressant factor such as reported for sepsis.[57] The response of pneumonia patients to volume infusion is thus diminished (Fig. 8.9). Therefore unless there is evidence of impaired regional blood flow to a level inappropriate for metabolic needs, volume expansion is poorly handled hemodynamically and serves to enhance fluid accumulation in the lung.

In a canine experimental model of pneumococcal pneumonia, the clinical concept that dehydration delays the appearance or decreases the extent of radiologic infiltrates has also been assessed. It was found that dehydration did not alter the radiologic picture or time of appearance of infiltrates.[58] Similarly, a retrospective study of dehydrated patients with

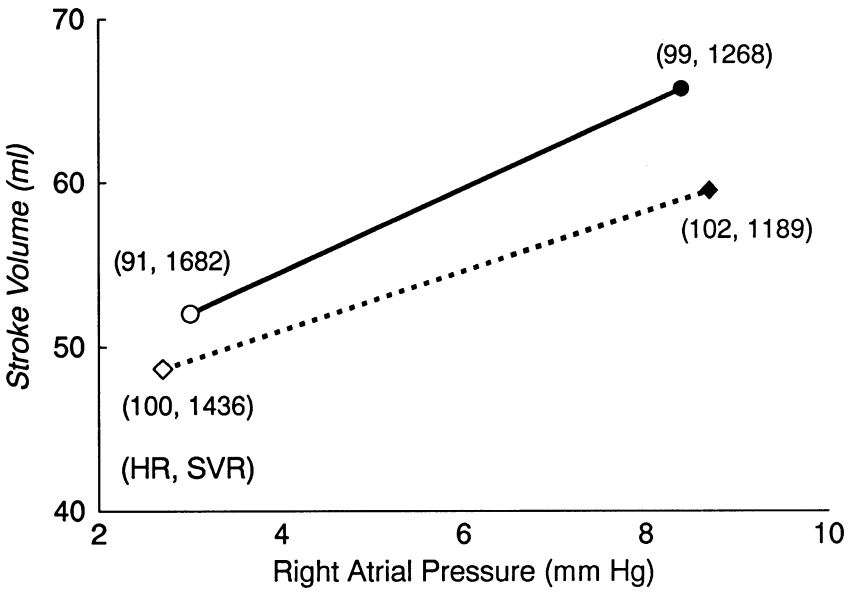

FIGURE 8.9. Ventricular function curves in acute pneumonia (diamonds) and the immediate convalescent period (circles). Mean values in 5 patients (4 pneumococcal, 1 *Klebsiella*) prior to (open figures) and following (solid figures) volume expansion with dextran or saline (hematocrit decreasing 5.7%). The metabolic rate (VO_2) decreased from 290 to 236 ml/minute with recovery and was unaffected by volume infusion. The mean values of heart rate (HR) and calculated systemic vascular resistance (SVR) in both groups are indicated. (Data from Kumar et al.[57])

pneumonia did not support the concept of delayed or diminished radiologic manifestations.[58] The effects of hypohydration in normal subjects has been studied,[59] and improved lung function (hyperinflation and increased flow rates with change in the DLCO) was found to be associated with volume contraction (Fig. 8.10). It was related to a decrease in airway resistance due to loss of interstitial lung water (bronchovascular sheath) or pulmonary vascular volume in contrast to the peribronchial fluid collection or mucosal edema observed with pulmonary edema. Lung volumes may also increase as a result of the associated increase in lung compliance. Thus perhaps dehydration should be a therapeutic goal in pneumonia patients.

Weight loss and favorable fluid balances[60] and a strategy aimed at decreasing lung water[61] have been reported to be correlated with improved survival in patients with ARDS. This balance may not be easy, as the kidneys of patients with mechanical ventilation and pneumonia have difficulty clearing free water. Acute infectious pneumonia appears to cause a resetting of the vasopressin osmostat, impairing renal water excretion.[62] This defect varies in proportion to the severity of the pneu-

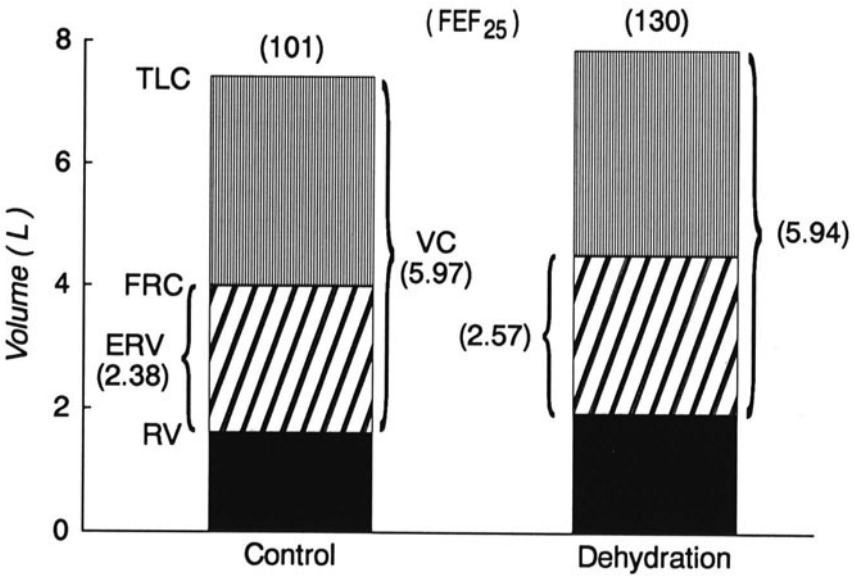

FIGURE 8.10. Effects of acute dehydration (hemoglobin 15.7–18.2 g/dl) after 48 hours of diuretic administration to 6 normal male subjects. Changes in mean values of lung volumes are shown with weight loss of 2 kg. TLC = total lung capacity; RV = residual volume; FRC = functional residual capacity, ERV = expiratory reserve volume, VC = vital capacity; FEF_{25} = flow rate in terminal 25% of vital capacity. (Data from Javaheri et al.[59])

monia and persists until the pneumonia resolves. In a report of a dog model of acid aspiration, plasmapheresis has been suggested as a particularly effective therapeutic alternative to effect a negative fluid balance in order to reduce pulmonary vascular pressures.[63] On the basis of the linear correlation between lung water and the measured pressures, it was concluded that the "leak" occurs predominantly from extraalveolar vessels, and the reduction of pulmonary pressures allows vascular derecruitment, thereby decreasing the number as well as the size of the pulmonary vascular leak sites.[63]

In summary, the cumulative clinical experience suggests that outcome after severe pulmonary edema can be affected by judicious fluid management. When pulmonary artery catheterization is used to maximize diuresis and fluid restriction in patients with nonhydrostatic (permeability) pulmonary edema, extravascular lung water significantly decreases as do ventilator and ICU days.[64] There is an ever-increasing database in support of increasing and perhaps maintaining cardiac output and oxygen delivery by the use of inotropic and vasoactive drugs, rather than by intravascular volume expansion.

Prophylaxis and Prevention

Pneumococcal Vaccine

The pneumococcus is still the major cause of community-acquired bacterial pneumonia. Moreover, the limited epidemiologic evidence available suggests that although mortality from pneumococcal infection has declined during the antibiotic era attack rates have not. Current estimates are that 15–30% of pneumonia cases requiring admission to the hospital are caused by *Streptococcus pneumoniae*. Morbidity data on pneumococcal disease are sparse and mortality figures often unreliable. Among bacteremic patients, mortality is approximately 20%, with 60% of deaths occurring within 5 days of "onset" despite antibiotic treatment. These early deaths are presumably due to irreversible physiologic injury in the face of an antibiotic infectious "cure." The presence of chronic systemic illness and age over 50 years, increases mortality to almost 30%. Therefore prophylaxis appears to be the only alternative in high risk groups to lower the unacceptable high mortality rates (Table 8.7).

The immunogenicity of the pneumococcal capsular polysaccharides provide a vaccine efficacious in preventing type-specific pneumonia. Such vaccines have been available for about 50 years. The continued morbidity and mortality even in the face of effective antibiotic therapy led to the revival of interest in pneumococcal vaccines. Polyvalent vaccines of purified capsular polysaccharides were developed and have been in general use since their licensing in 1977. Pneumococcal vaccine currently contains the capsular carbohydrate antigens of the serotypes (polyvalent, $n = 23$) most commonly found in bacteremic infections (88%) in the United States. A single injection usually induces an antibody response in adults (poor response in infants) that lasts at least 3 years and probably more than 8 years. There is little or no secondary response to a later injection. The efficacy of the vaccine remains controversial, particularly in the elderly. The cumulative weight of evidence indicates that the vaccine is safe and approximately 60% effective against bacteremic disease in immunocompetent persons.[65] The vaccine is significantly less effective in immunocompromised patients, with increasing age, and with increasing time since vaccination.[65] Because of the difficulty of determin-

TABLE 8.7. Recommendations for pneumococcal vaccination in adults.

Individuals 64 years of age
Immunocompetence with chronic disease: heart, lungs, diabetes, alcoholism, cirrhosis, cerebrospinal fluid leak
Immunocompromised: Hodgkin's disease, lymphoma, multiple myeloma, chronic renal failure, nephrotic syndrome, organ transplantation with immunosuppressive therapy, splenic dysfunction (including sickle cell disease)
HIV infection
Residents of institutional care facilities

ing causative organisms in pneumonia patients, efficacy studies are limited to bacteremic cases; the efficacy of the vaccine against nonbacteremic pneumonia is unknown. Even though there appears to be reduced efficacy in men, there is still a substantial cost savings supporting the cost-effectiveness of a vaccination for patients predisposed to developing pneumonia or those over 50 years of age.[66]

Pneumococcal polysaccharide vaccine has been recommended for use in all people 65 years of age and older. Although lowering the age for universal vaccination has been suggested, only about 10% of this already recognized high-risk population has been immunized.[67] Achieving the national goal of vaccinating 60% of the noninstitutionalized elderly and 80% of the institutionalized elderly is far off.

Influenza Vaccination

Influenza and AIDS are the most significant pandemic killers worldwide. Influenza-related illnessess in the United States causes 10,000–40,000 deaths annually and in excess of as many as 100,000 during pandemic years. Mortality due to epidemic influenza is, as with other pneumonias, increased in the elderly; and vaccination is thus advised for their protection. Presumably due to immunologic senescence, the serologic response to vaccination is decreased with advanced age, but protection against bronchopneumonia is conferred and infection successfully restricted to the "upper" respiratory tract. As a result of annual antigenic drift, susceptibility returns to a strain with a new antigenic subtype. Heterotypic immunity does not prevent infection but may speed recovery and decrease severity. Thus vaccination offers only short-term protection with no definite long-term advantage. How to bring patients at risk in contact with the medical care system for annual prewinter revaccination with reformulated vaccine remains uncertain. Much the same population, with the important addition of pregnant women who have high-risk medical conditions, should be vaccinated for both influenza and pneumococcal infection as there is no viremia induced by the inactivated vaccine (Table 8.8).

Vaccination reduces clinical infection by only about 30% in elderly institutionalized patients, but serious morbidity and mortality from

TABLE 8.8. Recommendations for influenza vaccination in adults.

Individuals >64 years of age
Those who are immunocompetent with chronic disease: diabetes, renal, pulmonary cardiac, anemia
Immunoincompetent persons
Residents of institutional care facilities
Persons in contact with those at high risk
Pregnant women with a high risk medical condition

respiratory infections are probably cut by about 50% and 70%, respectively. Pneumococcus and influenza vaccines can be given at the same time if injected at different sites. As with pneumococcal vaccine, the chief problem with the influenza virus vaccine is the failure to use it. Each year fewer than 30% of the target population of 45 million to 50 million persons receive the vaccine.[68] As with other preventive medicine programs, physicians' recommendations for vaccination have been strongly associated with receipt of the vaccine. Vaccination rates up to only 39% have been achieved among enrollees in a large health maintenance organization and a slightly higher rate of 55% among patients older than 65 years in a private practice setting. In one study, the major reason for nonvaccination was patient refusal.[69] Almost one-half of patients refusing vaccination when it is offered do so for fear of a reaction despite the evidence available showing no increased incidence of side effects other than a sore arm with the highly purified vaccines now available. Others refuse on the basis that they think it does not work or that it was not suggested the previous year; finally, there is the mistaken perception that the medical provider had not recommended it.[69]

A strategy for inpatient "flu shots" have been increasingly advocated, and one such program utilizing ward nurses, patient-oriented educational intervention, and emphasis on other administrative and organizational components, such as a walk-in clinic for inpatients, has proved successful.[70] Despite the fact that since 1984 the Centers for Disease Control has recommended influenza immunization of physicians treating high risk patients, compliance among this group has been estimated to be among the lowest.[71] As a result of the growing awareness of the need to regard each contact with health care providers as an opportunity for vaccination, a particularly successful effort using a mobile vaccine cart has been reported by offering vaccine to medical house staff and students in clinics and conferences, as had been done with other hospital personnel.[71]

Chemoprophylaxis

The use of antiviral agents as a supplemental strategy in the prevention of viral pneumonia in susceptible patients has focused primarily on influenza. Nonimmunized or suboptimal immune responses in immunocompromised individuals including the elderly has been generating growing interest in the potential use of additional drug-related prophylactic measures. Amantadine and its closely related analog rimantadine are approximately as effective as influenza virus vaccine in preventing influenza A. Simultaneous administration with the vaccine does not suppress the antibody response and can afford protection during the 2- to 3-week interval required for a serologic response. Influenza B or other respiratory viruses are not affected by either drug. Prophylactic use of amantadine has been advised for certain high risk groups, such as residents of

institutional care facilities where there is an outbreak of influenza A infections. It may be used as an adjunct to immunization in unvaccinated residents and for seasonal chemoprophylaxis for high risk (immunocompromised) groups.

Transplantation patients have presented challenging problems for the development of strategies to prevent lower respiratory tract infection. Pneumonia is a major cause of morbidity after transplantation with an incidence as high as 40–60% and a comparably high mortality rate. Viruses have been suspected; and specific agents, such as cytomegalovirus (CMV), respiratory syncytial virus (RSV), and uncommonly adenovirus and influenza, have been subsequently identified as causative agents in previously diagnosed idiopathic pneumonias. Parainfluenza has also been identified as a cause of serious lower respiratory tract involvement in bone marrow transplant recipients, illustrating the relation between the expanding spectrum of causative agents and advances in laboratory technology.[72] Treatment for parainfluenza is relatively unsatisfactory, the diagnosis elusive, and nosocomial transmission the most probable mode of infection. Aerosolized ribavirin, a broad-spectrum antiviral agent that has been approved for the management of severe RSV infection in children and reported to be successful in adults as well, has been suggested as a potentially useful agent, similar to amantidine for influenza, if initiated within the first 48 hours of the onset of symptoms. This approach to management clearly rides the line between prophylactic preventive versus empiric treatment.

Cytomegalovirus pneumonia is one of the most serious infections in transplant patients. Ganciclovir has been found to reduce the incidence of CMV pneumonia in asymptomatic bone marrow transplantation recipients with evidence of viral shedding, seen by bronchoalverlar lavage (BAL). Prophylactic ganciclovir administration after heart transplantation in CMV-seropositive patients also is effective in reducing the incidence of pneumonia and in suppressing CMV shedding as observed in bone marrow transplant patients.[73] Also with respect to bone marrow transplant patients, fluconazole, in contrast to ketoconazole, has been found to effectively reduce the incidence of systemic candidiasis and the number of deaths due to fungal infection.

In patient populations predisposed to *Pneumocystis* pneumonia (PCP), both trimethoprim-sulfamethoxazole (TMP-SMX) or dapsone orally and pentamidine by aerosol have been used for prophylaxis. The agents are used for both primary prophylaxis (those with significantly enhanced probability of infection) and secondary prophylaxis (after a course of therapy for an episode of PCP). There are few studies comparing PCP prophylactic regimens in HIV-infected patients, though experience suggests that TMP-SMX is superior to dapsone or pentamidine.

An intravenous form of concentrated immune globulin is now available for therapeutic purposes as a result of chemists learning how to prevent

its aggregation and denaturation while undergoing processing for purification and stabilization. The use of intravenous immune globulin as an adjuvant agent in patients with secondary, compared to primary, immunodeficiency disorders does not appear to be indicated with the possible exception of HIV-infected children. There is controversy regarding its benefit, which appears limited to invasive pneumococcal infections in patients with depressed CD4 counts (but more than 0.2×10^9/L) and IgG levels (<2 g/L). Immune globulin has been anecdotally reported to have prophylactic benefit against fatal CMV infection in transplant (especially bone marrow) patients. Neither the value nor the cost-effectiveness of this expensive therapeutic tool has been demonstrated for other pneumonias in immunosuppressed hosts.

Selective Decontamination

Aerosolized antibiotics have been shown to decrease the incidence of gram-negative oropharyngeal colonization and nosocomial pneumonia. Mortality, however, is not reduced, attributed in part to finding resistant organisms in those infected. Other topical regimens of antimicrobial prophylaxis, including oral mucosal antibiotic pastes, have been proposed to affect the oropharyngeal colonization of critically ill patients, especially those being mechanically ventilated. Effective pneumonia prophylaxis has been demonstrated in an animal model of ARDS, but the value of this stratagem in patients remains controversial.

In addition, poorly absorbed enterically administered drugs are also used as part of this protective intervention in order to selectively decontaminate the lower digestive tract as well. Because the indigenous anaerobic flora of the gut are thought to play an important role in the protection against gram-negative bacillary (and perhaps fungal) colonization at these sites, agents are used that leave this flora intact. Beneficial effects have been reported to be variable, and some regimens have therefore included the use of antifungal agents and systemic antibiotics to prevent primary pneumonia due to indigenous flora.[74] Although colonization and infections with gram-negative bacilli are reduced in patients undergoing selective decontamination, altered survival is uncertain. Metaanalysis of studies comparing patients treated by such regimens with untreated controls show at best a limited protective effect.[75] Mortality benefit was less clear, in part attributable to the problems involved in making the diagnosis of pneumonia in ventilated patients.

Comparisons between trials are difficult because of differing regimens, the small number of patients involved in each study, and the unblinded nature of the studies.[76] A multicenter, randomized, blinded, placebo-controlled European study was carried out in 445 mechanically ventilated patients (>48 hours) utilizing prophylactic topical antifungals and non-absorbable antibiotics effective against gram-negative organisms in naso-

oropharyngeal preparations and through a nasogastric tube. The overall incidence of pneumonia was not affected by treatment, but there were more staphylococcal and fewer gram-negative infections in the treated group. Survival was similar in the treatment and placebo groups, with no significant difference in any specific subgroups, as determined by physiologic scores.[76] Most of these patients had preexisting disease, in contrast to other studies involving surgical or trauma patients; the incidence of pneumonia in the placebo group was low, only 15%, presumably reflecting the strict diagnostic criteria utilized.

It has been suggested that failure to demonstrate that a reduction in respiratory tract infections has an effect on overall mortality is due to the severity of the underlying diseases which are responsible for mortality rather than nosocomial pneumonia. It was further suggested that patients acquire pneumonia only as a marker of terminal illness.[75]

Morbidity and Mortality

Community-Acquired Pneumonia

Although mortality due to pneumonia decreased dramatically with the introduction of antibacterial agents, during the 1980s pneumonia and influenza regained some of their lost public health stature and became the fifth leading cause of death in the United States. Moreover, between 1979 and 1987 the death rate in the United States attributable to these two diseases increased by 19.3%, one of only 4 of the 15 leading causes of death to increase. Pneumonia-induced mortality is not uncommon and, along with hospitalization rates, increased in the elderly. A population-based study showed a mortality of 6.7% in the 65- to 69-year-old group, with an increase to 20.5% in the age 85+ group.[77] The mortality rate increases further and survival is greatly diminished with age in patients requiring mechanical ventilation.

Clinical characteristics with prognostic significance with respect to both mortality and morbidity that have been demonstrated for pneumococcal pneumonia are bacteremia, multilobar involvement, concomitant disease (especially alcoholism), and leukopenia.[78] Moreover, the day of the disease on which effective antibiotic therapy was started shows no significant correlation with mortality or complications.[78] In a prospective study, however, none of the 37 patients with pneumococcal pneumonia who received antibiotics prior to admission died, whereas 7 of 114 not treated with antibiotics before admission died ($p = 0.13$).[79] Thus although antibiotic therapy greatly improves the outcome of pneumococcal pneumonia, it does not eliminate the significance of adverse clinical parameters or their additive effect on both mortality and morbidity.[78]

Other studies have shown that the only prognostic factors of predictive value for death due to primary community-acquired pneumonia is an

admission respiratory rate of 30 breaths/minute or more, a diastolic blood pressure of 60 mm Hg or less, and a BUN of more than 7 mmol/L (19.6 mg/dl).[79,80] No deaths occurred among patients without tachypnea at admission (respiratory rate < 20 breaths/minute) or with a BUN of less than 7 mmol/L at admission.[79]

The presence of any two of these three criteria of physiologic derangement is associated with a 21-fold greater risk for death.[79,81] In addition, although mortality has not been related to the etiologic agent, the combination of influenza A virus and *Staphylococcus aureus* infection appears particularly lethal.[79]

It has been reported that mortality due to pneumococcal pneumonia is not influenced acutely by antibiotic therapy or admission to the ICU in those with bacteremia. This report has led to the suggetion that death due to pneumonia is predetermined and that intensive care merely prolongs the interval before death. Mortality rates associated with pneumococcal pneumonia continue to be reported as 45% in adults with bacteremia and about 5% in adults without bacteremia during the antibiotic era. However, identification of these high risk patients on admission influences immediate triage to the ICU, which has been suggested to enhance prognosis in a population that has otherwise accounted for 70% of the deaths that occurred within 24 hours of admission.[82] This high risk group requires more aggressive monitoring, as well as diagnostic and life support strategies, including arterial and pulmonary artery catheterization, percutaneous lung aspiration, bronchoscopy, and "routine" ventilator management or vasopressor therapy in an effort to "forestall" death and allow time for the antibiotics to take effect.

The hospital stay of survivors in a British study averaged 10.8 days; after 6 weeks, 79% were able to participate in normal activities.[79] Hypoalbuminemia and age were associated with prolonged hospital stay and delayed returns to fitness. At the time of discharge, only 15% of chest films had cleared (Table 8.9); and although resolution was delayed in the elderly (Table 8.10), there was complete resolution in 55% of patients at 6 weeks.

Nosocomial Pneumonia

Nosocomial pneumonia is the second most frequent hospital-acquired infection, but among the various types of nosocomial infection it is the leading cause of mortality. Various factors have been associated with adverse prognosis[83] (Table 8.11), which significantly worsens in patients being mechanically ventilated.[83,84] The mortality rate is variable but in general is reported to be higher than 30%. Additional adverse prognostic factors in mechanically ventilated patients are a longer than 5-day interval of mechanical ventilation preceding the pneumonia and being a non-

TABLE 8.9. Resolution of chest radiograph with community-acquired pneumonia.

Time from admission (days)	Patients with normal radiograph (%)
Discharge	15
42	55
100	75
157	83

Source: Research Committee of the British Thoracic Society and the Public Health Laboratory Service.[79]

TABLE 8.10. Community-acquired pneumonia: time to baseline radiograph in 50% of patients, by age group.

Age group (years)	Normal chest radiograph (days)
15–32	22
33–53	29[a]
54–64	44
64–74	68

a = also the mean for all ages.
Source: Research Committee of the British Thoracic Society and the Public Health Laboratory Service.[79]

TABLE 8.11. Adverse prognostic factors for nosocomial pneumonia.

Fatal underlying disease
Inappropriate antibiotic therapy
Noncardiac surgery patient, i.e., ICU or medical patient
Presence of shock
Preceding mechanical ventilation of more than 5 day's duration
Age >60 years
"High risk" organism (i.e., *Pseudomonas*)
Polymicrobial infection
Bilateral involvement
Development, or worsening, of respiratory failure

cardiac surgery patient, both factors suggesting the importance of an absence of severe underlying disease.[84]

Although underlying disease is important, there are significant differences for specific diseases, such as between types or severity of immunosuppression. The virulence of different pathologic agents, be they gram-positive or gram-negative, also varies independent of their antibiotic resistance. *Pseudomonas* and *Staphylococcus aureus*, which are generally considered to be associated with the highest mortalities, are also associated with more frequent bacteremias, seeming to combine the factors of virulence with bacterial load in the lung. Mortality is variable and may be increased to as much as 60% in selected populations (e.g., the elderly, patients whose pneumonia is complicated by bacteremia, and

those who acquire their infection in the ICU). Numerous scoring systems to determine severity of illness have been used with varying success for predicting mortality. They include the Acute Physiologic and Chronic Health Evaluations (APACHE II), the Simplified Acute Physiologic Score (SAPS), Mortality Prediction Model (MPM), and the Therapeutic Intervention Scoring System (TISS), among others.

Pneumocystis carinii *Pneumonia*

Pneumocystic carinii pneumonia (PCP) is the most common pulmonary manifestation of AIDS, with 50–80% of patients surviving their initial episode. Although the duration of presenting symptoms (fever, dyspnea, cough), physical findings (rales), and initial mean leukocyte and lymphocyte counts do not have prognostic significance, the severity of respiratory distress on presentation does. The more severe the impairment in gas exchange (low initial PaO_2) and the higher the respiratory rate, the worse is the prognosis. The adverse prognostic implication of an elevated serum lactate dehydrogenase level (LDH) may reflect the severity of lung parenchymal damage.[85] Those patients with PCP requiring mechanical ventilatory support have a mortality rate of 60–80%.

Factors predictive of hospital survival are the initial presence of metabolic acidosis, a continued need for more than 10 cm H_2O PEEP after 96 hours of ventilator management, and the requirement of an escalating FIO_2.[86] In those patients who require mechanical ventilatory support there is no prognostic significance to the initial severity of impairment of oxygenation, nor are there significant differences in radiographic grades between survivors and nonsurvivors at the time of hospital admission. The mean duration of survival after discharge from the hospital is just over 1 year.[86] Additionally, patients requiring ICU admission demonstrate an inverse relation between length of ICU stay and survival.[87] It has been observed to drop continuously from 39% at the time of ICU admission to 17% at the end of 1 week, with survival not observed after 2 weeks of intensive care.

Adult Respiratory Distress Syndrome

The underlying disease, if not the cause and pathogenesis of the insult leading to the episode of ARDS, and the age of the patient have been reported to be important prognostic factors. Thus an acute lung injury syndrome associated with bone marrow transplantation for patients with malignancy carries 95% mortality.[88] Risk stratification for the development of respiratory failure and mortality in these patients is the same. Such factors include receptor of an HLA-nonidentical donor marrow, an active phase of malignancy, and older age (>21 years).[88] Even if the patients survive the initial episode of respiratory failure, recurrence is common,

and no patient who requires repeat mechanical ventilatory support survives to hospital discharge.[88] None of the long-term survivors in the largest cohort of marrow recipients reported for respiratory failure required ventilatory support for longer than 9 days or had a respiratory infection documented as the precipitating event.[88] Survival rates are thus lower in infected patients than in patients with other conditions predisposing to ARDS.

To enhance quantification of lung injury and to assess prognosis, standardized scoring systems for assessment of pulmonary and nonpulmonary organ dysfunction have been created. These select indicators of severity include (1) acute lung injury: radiologic involvement (quadrants), impairment of oxygenation (PaO_2/FiO_2), lung compliance, and magnitude of PEEP required; (2) parameters of extrapulmonary organ dysfunction; and (3) pathogenesis. It is hoped that more careful stratification utilizing these considerations may clarify the observed varying mortality and morbidity. How one differentiates dysfunction from failure of a particular organ (i.e., lung in the presence of sepsis versus multiorgan failure) is frequently unclear. When systematically and prospectively evaluated, however, only pesistent metabolic acidosis and the presence of fewer than 10% band forms on the initial peripheral blood smear have been demonstrated to have a significant association with increased mortality.[89] The poor prognostic outlook of acidemia is common to sepsis-like syndromes, including pneumonia, and reflect the associated multiorgan dysfunction. The diminished number of band forms mobilized from the bone marrow implies failure of at least that organ to have an appropriate response. Of interest is the difficulty showing prognostic significance of the initial severity of impairment of gas exchange, pulmonary mechanics, and systemic hemodynamics.

There is ongoing debate on the significance—and the existence—of supply-dependent oxygen uptake on survival of ARDS patients. Various groups have reported that delivery and utilization of oxygen is greater in survivors than nonsurvivors. This factor is thought by some investigators to be critically facilitated by an increased stroke volume due to increased ventricular compliance allowing for an increased ventricular end-diastolic volume or preload in the presence of a normal or decreased afterload, which in turn is dependent on the presence of a sepsis-like myocardial depressant factor.[90] The intuitive relation implied between such hemodynamic and derived "oxygen profile" indices and the development of a metabolic acidosis is more apparent than real. The classic association of an increased lactate concentration secondary to the presumed anaerobic tissue environment has been only inconsistently demonstrated at best.

Death of patients with ARDS is characteristically a septic picture with nonpulmonary organ system failure, the lungs having achieved a chronic, stable degree of dysfunction. The development of a complicating infection, which is most commonly pneumonia, in contrast to the precipitating

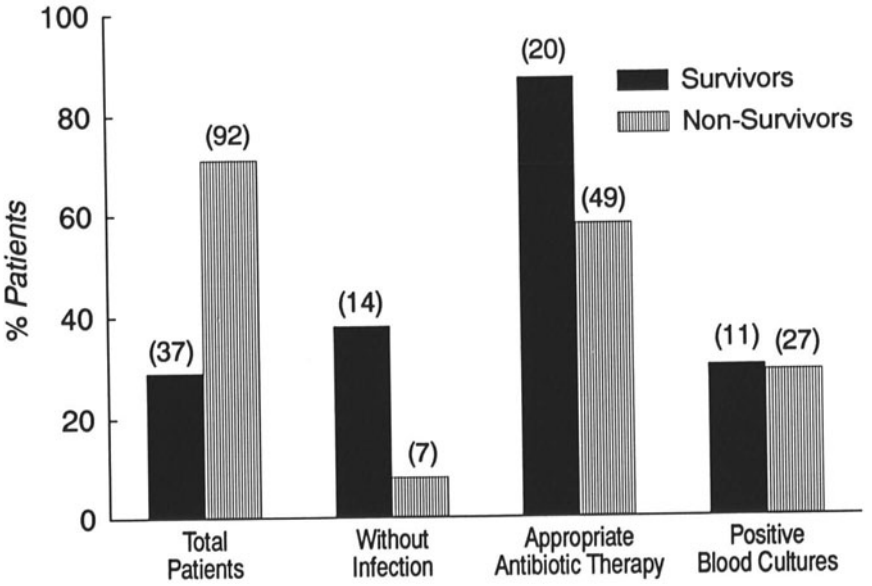

FIGURE 8.11. Clinical and autopsy diagnosis of infection in patients with ARDS (n = 129) who survived (n = 37), of whom 14 were without evidence of infection. The use of adequate antibiotic therapy is also shown (n = 69) in all patients with infection with site unknown (n = 82). Appropriate antibiotic therapy was more frequent in survivors; and although the incidence of documented bacteremia was the same in survivors and nonsurvivors, the site of the infection was identified in all of the survivors but in only 18 of 27 nonsurvivors. The numbers in parentheses indicate the number of patients in each group. (Data from Seidenfeld et al.[91])

infection, is the most apparent adverse prognostic factor. The importance of proper treatment of the infection is most clearly illustrated by an observed 100% mortality in patients with a positive blood culture if the site of the primary infection cannot be identified.[91] When infection is a complicating factor, adequate antibiotic therapy, if not a critical factor for determining survival, is associated with a greater survival rate. Although only 29% of infected patients treated with appropriate antibiotics survived, of the 23 survivors with infection 20 (87%) were treated appropriately[91] (Fig. 8.11). This situation is reminiscent of the apparent lack of effect of antibiotics on the immediate mortality due to primary pneumonia, where the degree of initial physiologic injury appears to predetermine response to therapy and survival.

Survivors of ARDS have varying degrees of impaired pulmonary function that in general has been reported to be of little clinical significance (Fig. 8.12). It has proved difficult to maintain adequate follow-up of patients, which would allow relating pulmonary sequelae to the course or severity of the episode of ARDS. As with survival, there is no evidence

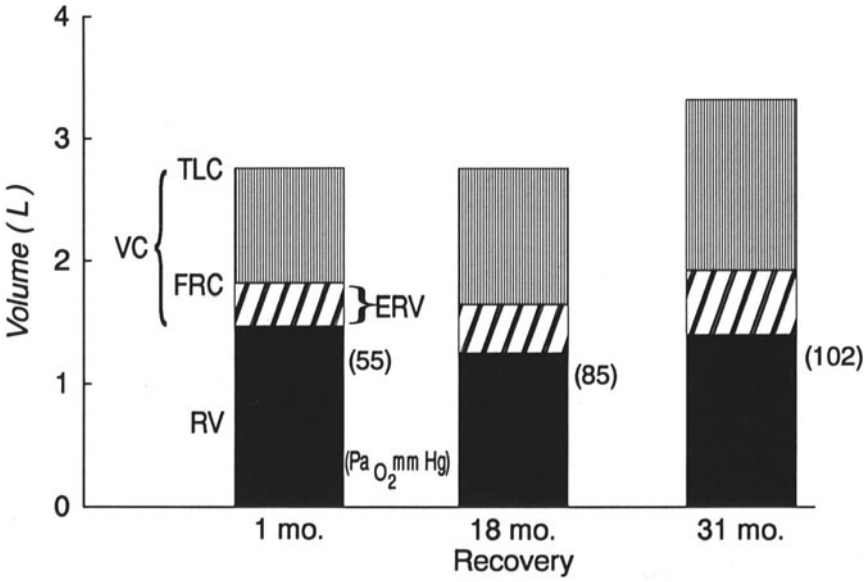

FIGURE 8.12. Pulmonary function tests after a peripartum episode of noncardiogenic pulmonary edema (ARDS) in a 23-year-old woman without a history of previous lung disease. (See Table 8.12) TLC = total lung capacity; VC = vital capacity; FRC = functional residual capacity; RV = residual volume; ERV = expiratory reserve volume.

TABLE 8.12. Exercise values after 18 months recovery.[a]

Index	Rest	W_{MAX} (40 watts)
V_E (L/min)	12.0	34.2
f (b/min)	26	41
V_T (ml)	462	834
V_E/MVV (%)	29	81
V_T/VC (%)	27	48
$\dot{V}O_2$ (ml/min)	230	830
$\dot{V}CO_2$ (ml/min)	180	680
R	0.78	0.82
DLCO (% pred)	45	

Endurance at 25 watts (2.5 minutes)

Index	Rest	2 minutes
Q (L/min)	3.9	7.8
CI (L/min/m^2)	3.3	4.0
SV (ml)	71	64
SVI (ml/m^2)	48	43
PA (mean mm Hg)	14	23
PAWP (mm Hg)	7	12
PvO_2 (mm Hg)	44[b]	30

[a] The measurement were done in a 23-year-old woman with a peripartum episode of ARDS.
[b] Mixed venous PO_2.

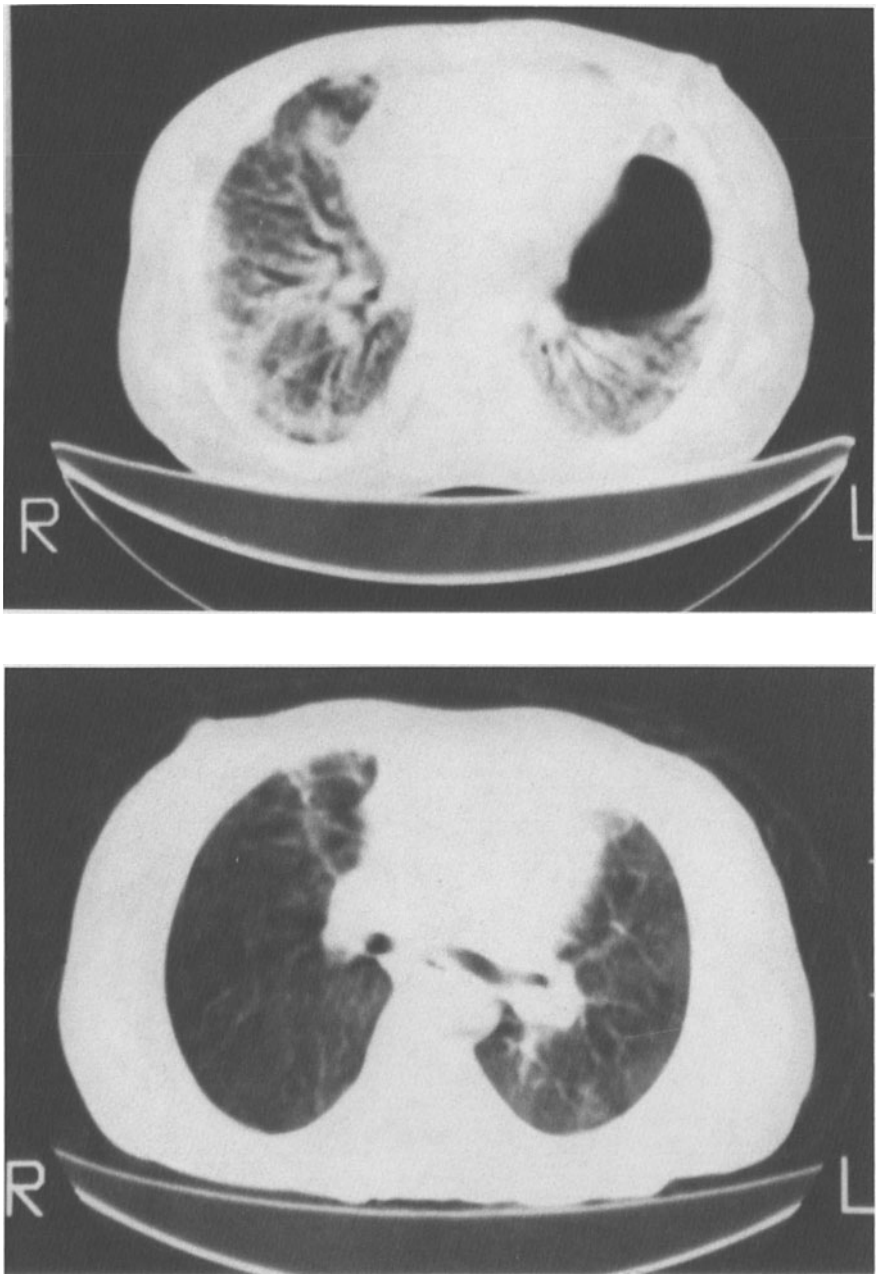

FIGURE 8.13. CT scans showing resolution of ARDS associated with pneumococcal pneumonia. (A) Pneumonia and resulting ventilator-induced barotrauma in an 18-year-old woman with sickle cell anemia. (B) Repeat chest CT scan 11 months after recovery.

that long-term pulmonary function differs according to the precipitating cause, apparent severity of the episode, or (as shown in animal studies) the occurrence of secondary pneumonia. Lung function continues to recover during the months following the acute episode but "classically" plateaus by 6–12 months with little apparent reversibility thereafter (Fig. 8.13). Glottal damage from long-term intubation may also resolve with time. A reduced diffusing capacity is the most commonly observed persistent abnormality, and it has been attributed to destruction of the pulmonary vascular bed. Survivors generally do not complain of dyspnea but have a restrictive ventilatory defect, a decrease in exercise capacity (Wmax), and exercise-induced arterial desaturation (Table 8.12). Therapeutic residua have been suggested for the level of PEEP, the duration of ventilation support, and the degree of enhancement of the inspired oxygen concentration ($FIO_2 > 0.6$), but correlation with pulmonary function values in ARDS survivors has been variable.[92] Finally, the importance of minimizing barotrauma during mechanical ventilation has been supported by reports correlating high inflation pressures, rather than initial PaO_2 and Q_S/Q_T, with long-term morbidity, thus emphasizing the value of therapeutic strategies of low PEEP to minimize long-term pulmonary sequelae.

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